Beyond the tissue: the relationship between structure, function, and pain in Achilles tendinopathy

Beyond the tissue: The relationship between Structure, Function, and Pain in Achilles Tendinopathy

By

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DECLARATION

My submission as a whole is not substantially the same as any that I have previously made or currently am making, whether in published or unpublished form for a degree, diploma, or similar qualification at any university or similar institution. I am the author of this doctoral thesis and the principal author of the five articles, which form its core.

Signature: 

Seán Mc Auliffe

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Can ultrasound reliable measure tendon dimensions? systematic review and clinical implications. Authors: Sean Mc Auliffe, Dr Karen Mc Creesh, Dr Helen Purtill, and Dr Kieran O'Sullivan. International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT), Glasgow. (2016)

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ABBREVIATIONS

MT: Musculotendinous

AT: tendinopathy

OA: Osteoarthritis

Ach: Acetylcholine

CNS: Central nervous system

PNS: Peripheral nervous system

SP: Substance P

UL: Upper Limb

LL: LL

US: Ultrasound

MRI: Magnetic Resonance imaging

PF: Plantarflexor

SSC: Stretch shortening cycle

PT: Peak torque

HSR: Heavy slow resistance

CSA: Cross-sectional area

SEM%: % standard error of the mean

CV%: Coefficient of variation

ICC: Intraclass correlation coefficient

UTC: Ultrasound tissue characterization

95% C.I.: 95% Confidence interval

SEM: Standard error of the mean

CV: Coefficient of variation

LOA: Limits of agreement

MDC: Minimal detectable change

RMSD: Root mean square difference

RR: Relative risk

C.I: Confidence interval

LBP: Low back pain

JH: Jump height

CT: Contact time

PPT: Pressure pain threshold

NRS: Numerical rating scale

FABQ: Fear avoidance belief questionnaire

MCIC: Minimal clinical important change

EIH: Exercise induced hypoalgesia

COREQ: consolidated criteria for reporting qualitative research

MSK: Musculoskeletal

QST: Quantitative sensory testing

MOM: Mature organism model

dCMJ: Drop Countermovement Jump

PF: Plantarflexor

CASP: Critical appraisal skills programme

QST: Quantitative sensory testing

OR: Odds ratio

GRF: Ground reaction force

MVC: Maximal voluntary contraction

RFD: Rate of force development

ACL: Anterior cruciate ligament

PT B/W: Peak torque per bodyweight

BW%: Percentage bodyweight

CERT: Consensus on exercise reporting template

ABSTRACT:

Introduction: Achilles tendinopathy (AT) is a highly prevalent, disabling and often-persistent musculoskeletal complaint, commonly affecting athletic and non-athletic populations. To date, attempts to explain the pathoaetiology of tendinopathy have utilised theoretical models and paradigms, predominantly focusing on the contribution of structural factors, or changes in the physical properties of the tendon. Although structural factors may play an important role in the mediation pain associated with AT, the persistent nature of AT suggests that it is a multifactorial disorder, involving a complex interaction of numerous interlinking variables. Understanding the relative contribution of structure, function and pain, and the possible relationship between these factors may improve our understanding of AT. The aims of this doctoral thesis are to investigate if alterations in tendon structure are associated with the development of pain, examine the relationship between pain and function in AT, and explore the factors associated with clinical improvements following a 12 week loading intervention.

Methods: In the first part of the thesis (Chapter 2), two systematic reviews were completed. Study I investigated the reliability and degree of error associated with quantifying tendon size using ultrasound imaging. Study II reviewed the literature exploring the relationship between alterations in tendon structure and the development of future Achilles or patellar tendinopathy. The second part of the thesis, (Chapter 3) explored the degree and nature of functional deficits in AT by performing a systematic review and meta analysis. The final part of the thesis, (Chapter 4) outlines the results of a pilot intervention study investigating the factors associated with clinical outcomes following a 12 week loading intervention. Finally, a qualitative study explored the beliefs and experiences of people with AT.

Results: Study I demonstrated that US imaging displays good-excellent inter and intra-rater reliability, as well as demonstrating a low degree of measurement error in quantifying tendon size throughout a range of upper and lower limb tendons. A systematic review and meta-analysis performed in study II demonstrated tendon abnormalities were associated with a 5 fold increased risk of developing Achilles or patellar tendinopathy in asymptomatic athletes. In Chapter 3, a systematic review and meta-analysis highlighted people with AT display altered strength profile across the entire strength spectrum using a range of outcome measures. Results from a pilot intervention in Chapter 4 suggest clinical improvements in pain and function following 12-week loading intervention may be attributed to change in a range number of factors. The remaining study in Chapter 4 highlighted the impact of AT on psychosocial factors.

Conclusion: The finding of this doctoral thesis indicates that AT is a multifactorial musculoskeletal disorder, involving a complex interaction between structure, function, and pain. The relative contribution of each factor may vary between individuals. Results of the included studies appears to suggest that future research should investigate the pathoaetiology, prediction and designing of interventions in AT from a multifactorial perspective.

GENERAL INTRODUCTION:

The aim of this doctoral thesis is to investigate the relationship between structure, function and pain in AT. AT is often a persistent or chronic musculoskeletal complaint. To date attempts to explain the pathoaetiology of AT have focused on structural, or peripheral tissue based paradigms. Although these factors undoubtedly contribute to the pathoaetiology of AT, the persistent nature of AT suggests that similar to other MSK complaints, AT should be considered a multifactorial musculoskeletal disorder, involving a complex interaction of numerous peripheral and central mechanisms. Understanding the relative contribution of structure, function and pain, and the possible relationship between these factors may improve our understanding of AT. In order to provide the reader with some context for the chosen topic, the thesis will begin with a general introductory chapter which will cover; epidemiology of AT, current models to explain the pathoaetiology of AT, proposed risk factors for the development of AT, pain concepts in AT, and the role of loading interventions in AT. It is hope that this introductory piece will identify gaps in the literature, which the current thesis aims to investigate. Following the introduction the thesis is split into three distinct sub chapters with each of the relevant chapters formatted as papers throughout. The first chapter of the thesis seeks to investigate the relationship between structure and pain in AT. In order to achieve this, two systematic reviews have been undertaken, the first investigates the reliability of ultrasound imaging in visualising tendon structure. The second study investigates whether alterations in tendon structure are associated with the development of future symtoms of tendinopathy. The next chapter of the thesis investigates the relationship between function and pain by investigating whether AT is associated with alterations in individuals strength profile by performing a systematic review and meta analysis of the available literature. The review will discuss the impact and clinical implications of findings for health care practitioners as well as highlighting further areas of research. Finally the third chapter seeks to investigate the multifactorial response of loading

interventions in AT. The first study in this chapter, an uncontrolled pilot intervention study seeks to investigate the degree of change and correlates of change following a heavy load rehabilitation program in AT. The concluding study in this chapter, a qualitative study seeks to investigate and highlight the psychosocial aspects of AT. The thesis concludes with a comprehensive discussion chapter, which outlines the relevance and clinical significance of findings for clinical practice as well as highlighting potential areas of research for the future.

CHAPTER 1: INTRODUCTION

Tendon anatomy

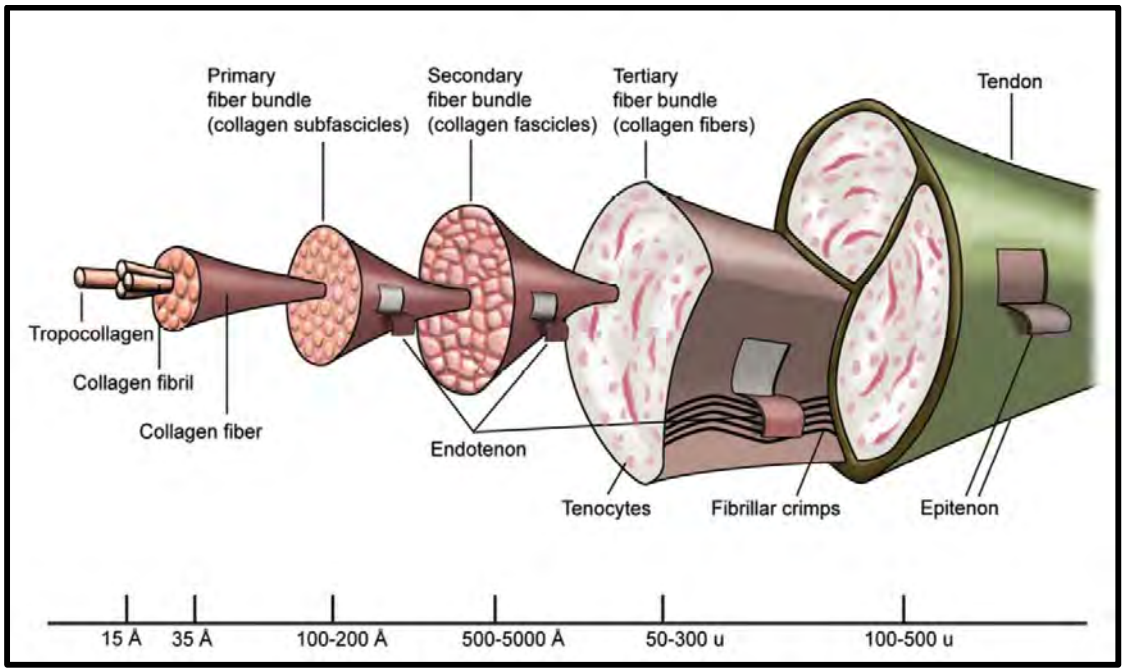
The primary function of a tendon is to connect muscle to bone, thus forming a crucial component of the overall musculotendinous unit (Ash *et al.* 2008). Tendons transmit forces from muscle to bone in order to produce joint motion, and ultimately movement (Saltzman and Tearse 1998, O'Brien 2005). Consequently, tendons perform the role of shock absorbers and energy storage sites throughout the body with the ability to withstand both tensile and compressive forces of up to 17 times body weight (Kader *et al.* 2002). Of these tendons, the Achilles tendon is the largest, thickest, and strongest tendon in the body (O'Brien 2005, Bjur et al. 2005). The Achilles tendon serves as the conjoined tendon for the gastrocnemius and soleus muscles and is also referred to as the calcaneal tendon, tendo calcaneus or the triceps surae tendon (Harris and Peduto 2006).

Collagen bundles, cells and extracellular matrix make up the basic components of tendons (Kader *et al.* 2002). The main role of collagen (predominately type I collagen; 65-80%) is to provide the tendon with the strength to tolerate high tensile and compressive loads (Abate *et al.* 2009). Structural support for the collagen and regulation of the assembly of procollagen into mature collagen is provided by ground substance, which consists mainly of 60-80% water, proteoglycans and glycoproteins (Abate *et al.* 2009). Collagen is arranged in levels of increasing complexity, from basic tropocollagen into fibres, fascicles, and tertiary bundles until it finally forms the tendon itself (Figure 1).

The epitenon, a connective tissue sheath that surrounds the tendon contains vascular, nervous and lymphatic structures. The epitenon is in turn surrounded by paratenon which contains predominantly type 1 and type 3 collagen fibrils, with both the epitenon and paratenon often referred to as the peritendon (Khan *et al.* 1999, Bjur *et al.* 2005).

In relation to the cellular components of tendons, the majority of the cellular elements of a tendon are made up of tenocytes (specialised fibrocytes) and tenoblasts (90-95%). The remaining 5–10% of the cellular components are made up of chondrocytes, vascular cells, synovial cells and smooth muscle cells (Doral *et al.* 2010).

Figure 1: Tendon Ultrastructure



Nerve supply to the tendon is provided by sensory nerves from the overlying superficial nerves or from nearby deep nerves. The nerve supply is mainly afferent, located near the MT junction (Ash *et al.* 2008), either on the surface or in the tendon itself (O'Brien 2005). There are 4 types of receptors in the tendon, type I-IV.

- Type I are pressure receptors, which are sensitive to stretch, are known as Ruffini corpuscles.
- Type II receptors, known as the Vater-Pacini corpuscles, are stimulated by movement.
- Type III, are mechanoreceptors, known as Golgi tendon organs. These are unmyelinated proprioceptive receptor organs, which are sensitive to changes in muscle tension.
- Type IV receptors are the free nerve endings that act as receptors thought to be involved in the modulation of pain (Kader *et al.* 2002).

The MT junction is the area between the muscle and tendon and contains a host of nerve receptors. The MT junction is subjected to high mechanical stress during the conduction of

muscular force from the muscle to the tendon. The osteotendinous junction, also known as the 'enthesis', is located where the tendon inserts into the bone (Abate *et al.* 2009). The transition of tendon to bone at this junction is a gradual process and microscopically there are 4 visible zones; (i) tendon (ii) fibrocartilage (iii) mineralized fibrocartilage and (iv) bone (Khan *et al.* 1999). Finally the blood supply of tendons originates from three sources: the MT junction, the enthesis and via vessels in surrounding connective tissue and the osteotendinous junction (O'Brien 2005).

Given the purpose of the current thesis aims to investigate the Achilles tendon, the remaining aspects of the introduction will be focused on this tendon.

Terminology in Achilles tendon disorders

Much debate exists in relation to the terminology surrounding Achilles tendon disorders. Prior to the 1990's pain associated with the Achilles tendon was referred to as tendinitis, with the premise being inflammation was the primary driver responsible for the pathological process (Khan *et al*. 2002). This view was both widely accepted and adopted throughout the medical literature at the time. However, the emergence of microdialysis studies in tendons demonstrated that there was no increase in prostaglandin E_2 levels in chronically painful tendons compared with asymptomatic tendons, suggesting that inflammation was not the primary driver of Achilles tendon disorders (Alfredson *et al.* 1999b, Alfredson *et al.* 2001). As a result, the term tendinosis was adopted during the course of the first decade of the 21st century to reflect the 'non-inflammatory' or 'degenerative' theories, which abounded at the time. Ironically tendinosis terminology has now become engrained in the medical literature despite a shift away from the degenerative model to explain tendon pain. In recent decades the term tendinopathy has become the widely accepted term to represent symptomatic Achilles tendon disorders. Tendinopathy is an umbrella term used to describe the clinical presentation of localised tendon pain with loading, tenderness to palpation, and impaired function (Abate *et al.* 2009, Cook and Purdam 2009). Consequently for the purpose of this thesis, the term Achilles tendinopathy will be the term used to describe pain in the Achilles tendon.

A brief summary of the definitions utilised in tendon disorders to date is outlined below.

- *Tendinitis:* in which the primary driver of pain is an inflammatory response within the tendon (Järvinen *et al.* 1997).
- *Tendinosis:* a degeneration of the tendon without clinical or histological signs of an inflammatory response in the tendon or its paratenon.
- Tendinopathy: an umbrella term commonly used to describe the clinical presentation of localised tendon pain with loading, tenderness to palpation, and impaired function (Cook and Purdam 2009).
- *Paratenonitis:* an inflammation of the outer layers of the tendon (paratenon). The term paratenonitis also covers the clinical entities of 'peritendinitis',' tenosynovitis.

Tendon Healing and repair

The natural healing process of tendons is poorly understood with a lack of detailed molecular and histopathological studies limiting knowledge in the topic (Docheva *et al.* 2015). Consequently much of the proposed mechanisms of tendon healing have been obtained from animal models using experimentally induced acute tendon damage (Docheva *et al.* 2015). From these models three distinct phases have been proposed as a model of tendon healing and repair following acute injury.

Phase 1: Initial Inflammatory Stage

The inflammatory phase commences with the formation of a haematoma at the site of the injury leading to the attraction of erythrocytes and inflammatory cells, particularly neutrophils (Docheva *et al.* 2015). A vascular network is also created through a process of angiogenic secretions in order to act as a blood, and primarily oxygen supply to maintain the survival of the immature fibrous tissue forming at the location of the injury (Docheva *et al.* 2015). Elastic fibrils also begin to form in this stage, with their filaments measuring 10–12 mm in diameter, without elastin deposition (De Palma *et al.* 2006). The acute inflammatory phase lasts for up to 3 to 7 days after injury (Abate *et al.* 2009).

Phase 2: The Proliferation Stage

The second phase is also known as the proliferation or hypercellular phase characterised by neovascularization, subsequent fibroblast proliferation and synthesis of the disorganized matrix (De Palma *et al.* 2006). Fibroblasts produce collagen, which slowly increases the mechanical strength of healing tendon, so that loading can lead to elastic deformation (Abate *et al.* 2009). Following this phase, the tissue has became more compact and the majority of tenocytes and collagen fibres are arranged longitudinally (De Palma *et al.* 2006). This phase commences a few days after the initial injury, and lasts between 5 and 21 days (De Palma *et al.* 2006).

Phase 3: The Remodeling Stage

This phase begins approximately 6-8 weeks post injury and includes two sub-stages:

1. The consolidation stage – Characterised by a reduction in cellular permeability and the tissue within the tendon, leading to the tendon becoming more fibrous with Type III collagen fibres being replaced by Type I fibres.
2. The maturation stage: This phase is characterised by the commencement of the crosslinking of collagen fibrils and is where the formation of mature collagen tissue begins which remains ongoing for periods beyond the timelines associated with an acute injury (Docheva *et al.* 2015).

Despite the contribution of these proposed models in improving our understanding of tendon healing and repair, these processes are based on the premise of an acute tissue injury. Although acute tendon injuries often occur in the Achilles tendon, the persistent and even chronic nature of AT suggests that the healing and repair processes outlined above may not be sufficiently comprehensive in explaining the pathoaetiology of long standing AT.

Epidemiology of Achilles Tendinopathy

AT as a musculoskeletal disorder affects both athletic and non-athletic populations with athletic populations up to thirty times greater risk of developing AT than their sedentary counterparts (Brukner and Khan 2007). In athletic populations AT is commonly associated with strenuous physical activities, which expose the Achilles tendon to high loads such as running and jumping. Consequently, the occurrence of Achilles tendinopathy is highest among individuals who participate in middle- and long-distance running, orienteering, track and field, tennis, badminton, volleyball, and soccer (Kujala *et al.* 2005). The prevalence appears highest in running populations, with elite long-distance runners reported to have a lifetime risk as high as 52%, while it has also been reported that 1 in every 2 runners will experience AT before the age of 45 (Kujala *et al.* 2005). Chronic Achilles tendon disorders are more common in older athletes than in young athletes (Tenforde et al., 2011). In terms of incidence, an incidence of 2.98 has been reported in the military population (Clement et al 1984) with an annual incidence of 7% and 9% reported in top-level runners (Johannsen and Gam 2010).

Although epidemiological research to date has focused primarily on athletic populations, there is a growing recognition of AT in non-athletic populations (Jarvinen *et al*.1997). In terms of prevalence, it has been reported that 1 of 3 patients with AT is not active in sports (Ackermann and Renström 2012), with a suggested a prevalence of 2.01 per 1,000 in a study of Dutch general practice (de Jonge *et al.* 2011). In the same study a comparable incidence rate was reported of 1.85 per 1,000 registered patients. The minor difference between the incidence and prevalence rate suggests that most patients only visit their GP once with their Achilles tendon problems. This might be because of a short duration of symptoms or that the patients go to a physiotherapist or sports physician afterwards (de Jonge *et al.* 2011). It may be plausible the incidence and prevalence of AT is even higher in non-athletic populations, however the lack of consensus in terms gold standard diagnosis of AT may result in an under estimation or inaccurate diagnosis of AT. Unfortunately no other comparable epidemiological research are available at present in terms of incidence and prevalence of AT in non-athletic populations highlighting the need for future research.

Burden and impact of AT in the general population

In comparison to other chronic musculoskeletal (MSK) disorders such as osteoarthritis (OA) and low back pain, economic evaluations on the socioeconomic burden of tendinopathy, particularly lower limb (LL) tendinopathies are lacking. However, a review by Hopkins *et al.* (2016) has sought to address this by performing a critical review on the socio-economic impact of tendinopathy. The authors suggest that the burden placed on daily activities cannot be ignored, with one study highlighting the difficulty patients with tennis elbow (epicondylitis) reported during activities such as dressing, carrying objects, driving, and sleeping. Furthermore the indirect costs as a result can reach great amounts in terms of productivity loss and worker's compensation. Up to 5% of patients with lateral epicondylitis have claimed sickness absence with an average duration of 29 days in a year. Additional the direct outpatient medical costs were reported as ranging from $430/patient for corticosteroid injection to $921/patient for physical therapy, for lateral epicondylitis (currency in 2004). Repeated medical visits are also a concern as lateral epicondylitis is recurrent, and almost half of those affected have seen their general practitioner within the past 12 months. Unfortunately the majority of studies included in this review included UL tendinopathies with a scarcity of LL and by extension AT studies. Consequently although comparisons can be made given similar aetiologies caution is advised when interpreting the burden and impact in non-athletic AT populations.

Burden and impact in athletic populations:

Despite the potential limitations in evaluating the burden of tendinopathy in the general population, it is possible to make observations in relation to the burden and impact of AT in athletic populations by evaluating injury patterns in athletic populations. In team sports such as basketball and professional football, injury is associated with an inverse relationship with percentage of games won and goals scored (Hägglund *et al.* 2013, Podlog *et al.* 2015). Additionally loss of training time due to injuries and illnesses is a major determinant of success or failure in elite athletes competing in international athletics (Raysmith and Drew 2016). In light of this finding it may be postulated that a prevalence as high as 52% in elite long-distance runners, and with recurrence rates as high as 27% this may lead to frustration and a significant psychological burden as well as significantly interfering with athletes chances of participation or

success in athletic pursuits (Knudsen et al 2013).

Risk Factors

Risk factors for the development of AT may be classified as either intrinsic (within the body) or extrinsic (outside the body) (Reinking 2012). AT is a complex disorder and given its slow and often gradual onset it is possible that risk factors may give inconclusive results when using a single-risk factor analysis approach (Bittencourt *et al.* 2016). It is conceivable that an injury endpoint does not arise from a single identifiable factor but from multiple factors working together to cause eventual transition to symptomatic AT (Lorimer and Hume 2016). Consequently the risk of developing AT is likely as a result of a complex interaction of many proposed intrinsic and extrinsic risk factors, which in general are still relatively unknown.

Intrinsic Factors

An ever-growing body of literature has highlighted the potential association between **metabolic disorders** and the increased risk of developing tendinopathy. Metabolic disorders such as adiposity (Gaida *et al.* 2009), diabetes (Ranger *et al.* 2015) and atherosclerosis (Rechardt *et al.* 2010) have all been associated with an increased risk of developing AT. A systematic review by Gaida *et al.* (2009) indicated that individuals with alterations in tendon structure, tendon pain, tendon rupture, or those who did not respond to conservative management had significantly higher levels of adiposity than their respective controls. A review by Ranger *et al.* (2015) reported that people with diabetes had more than three times the odds of tendinopathy compared to controls. Nevertheless, the findings of these respective studies must be interpreted in the context that association does not necessarily infer causation, with the majority of these studies utilizing cross sectional study designs in mainly non athletic populations, making it difficult to infer direct cause and effect.

Genetic factors are thought to be associated with the risk of developing tendinopathy (Kannus

and Natri 1997, September *et al.* 2007). A heritability as high as 40% for the development of lateral epicondyle tendinopathy has been reported in a twin study by Hakim *et al.* (2003). In addition, the genetic sequence variants that encode for several tendon extracellular matrix proteins associated with tendinopathy have also been cited in the literature (Raleigh *et al.* 2009). New evidence suggests that one or more genes proximal to the ABO gene on chromosome 9 may be a causal factor in the development of tendon pain (Leppilahti *et al.* 1995). However the concept of genetic factors is an extremely complex one and is still relatively new in the area of tendinopathy.

Studies investigating **sex** as a risk factor for the development of AT have reported conflicting results. One prospective cohort study (Owens *et al.* 2013) and one cross-sectional study (Longo *et al.* 2009) examined the association between sex and the risk of AT. Neither of these studies found a significant difference in the rate of AT between men and women. However confidence intervals were wide and overlapping, limiting the strength of these findings.

The concept of **muscle strength** as a risk factor for the development of injury has been investigated extensively in other peripheral musculoskeletal (MSK) disorders with research into hamstring injury suggesting that lower levels of eccentric hamstring strength increased the risk of subsequent hamstring injury (Opar *et al.* 2014). It would seem logical to hypothesize given the high incidence of AT in athletic populations that strength may be an important factor in the development of AT. A prospective study by Mahieu *et al.* (2006) appears to highlight this hypothesis when they reported that reduced PF strength was associated with the development of future AT. Unfortunately this study contained a small sample size (n=10) and was performed on a specific population of army cadets limiting the generalisability of the findings.

Biomechanical factors have also been associated with the development of AT. Alterations in **running style** and mechanics, particularly increased **laterally-directed force** and decreased **displacement of the center of force** (van Ginckel *et al.* 2009) have been associated with the development of AT. Additional biomechanical risk factors cited in the literature include decreased **ankle dorsiflexion** (Rabin *et al.* 2014) and decreased **knee flexion** (Azevedo *et al.* 2009). However similar to many studies involving risk factor analysis in AT, these studies utilised cross-sectional study designs limiting a cause and effect relationship.

Extrinsic Factors

The risk of developing AT has been associated with the use of certain **medications**. The association between **fluoroquinolone antibiotics** and the risk of developing AT or **fluroquinolone tendinopathy** has attracted increasing attention in the past number of years (Van der Linden *et al.* 2002, Barge-Caballero *et al.* 2008). Fluoroquinolone antibiotics are used to treat a range of infections affecting the respiratory systems and those causing prostatitis, skin soft tissue infections, and sexually transmitted diseases (Lewis and Cook 2014). Furthermore low-dose corticosteroids in isolation have been implicated in Achilles tendon rupture (Newnham *et al.* 1991). Concurrent use of **corticosteroids** with fluoroquinolones appears to potentiate this adverse effect (Lewis and Cook 2014). Statins, used in the treatment of hypercholesterolemia, have also been implicated with an increased risk of developing tendinopathy, however the strength of this is association is relatively small with more research needed (Marie *et al.* 2008).

Many researchers acknowledge the importance of running as a potentially important extrinsic risk factor. Thus, "**training errors**" have been suggested as an important cause of running related injuries (Taunton *et al.* 2003, van Gent *et al.* 2007). Unfortunately many of the studies investigating the effects of training errors on the risk of developing injury have looked at running related injuries in general. Despite this, given the high prevalence of AT in running, it would seem plausible that a large proportion of these findings may be interpreted in the context of AT. Clinically and anecdotally sudden alterations in training variables (changes in speed, volume, surface, footwear) are often reported by patients around the onset or prior to developing AT. A weekly **running volume** that is being changed (in this case increasing) or an absolute training volume above 40 miles per week has been suggested to increase the risk of developing injury/pain, however this finding appears to be conflicting with studies suggesting a link in most studies (Jacobs and Berson 1986, Macera 1992), but not in all (Renström 1992, Colbert *et al.* 2000). The conflicting evidence highlights the inaccuracies with investigating risk association between a single training variable without accounting for the confounding or modifying effect of other training variables. For example it may be possible to reduce your running volume but to increase your speed at which you run which has also been associated with injury development (van der Worp *et al.* 2011). Since volume, duration, and intensity all affect one another it may be

relevant to measure and analyze all three variables (Oestergaard Nielsen *et al.* 2012). Another potential extrinsic risk factor is **running experience**. Studies suggest that experience is an important factor for injury risk, because high running experience may diminish the risk of injury (Marti *et al.* 1988, Jakobsen *et al.* 1994). This finding may appear to contradict the previously highlighted risk factor of running volume. However, recent research proposed by Gabbett (2016) suggests a training-injury paradox, which suggests that repeated exposure to high loads over long periods of time can actually be preventative for the avoiding injury compared to those that rarely (or suddenly) expose themselves to high load running/training. Unfortunately this association is under researched in running and AT fields. However, these findings must be considered in light of several methodological factors. The majority of studies are based on cross-sectional study designs making it difficult to infer causation with prospective evidence lacking. Furthermore, the lack of a control group or the comparison of injured populations with a control group does not allow distinct causes for the development of AT to be identified. Consequently, prospective studies investigating the interaction of multiple factors are essential to define possible intrinsic and extrinsic risk factors or a combination of different factors for developing AT, and to clarify the principle of cause and effect.

Theoretical models and paradigms in AT

Although the stages of tendon healing and repair provide an insight into the potential mechanisms of healing at a physiological level, the healing and repair process is based upon experimentally induced tendon damage in animal models. Although animal models of healing and repair may provide a start point, they provide us with little information on the pathoaetiology or clinical manifestation of AT in human populations. To address this, various models have been proposed in the literature in order to explain the pathoaetiology of tendinopathy, the most

popular of these include Cook and Purdam's continuum model (Cook and Purdam 2009) (Figure 2), Abate's Iceberg theory (Abate *et al.* 2009) (Figure 3), Arnoczky's Aetiopathogenesis of tendinopathy (Arnoczky *et al.* 2007) (Figure 4) and Fu's failed healing model (Fu *et al.* 2010) (Figure 5). A summary of the main events of these models is provided in the accompanying appendix 1.

Figure 2: Cook and Purdam Continuum Model

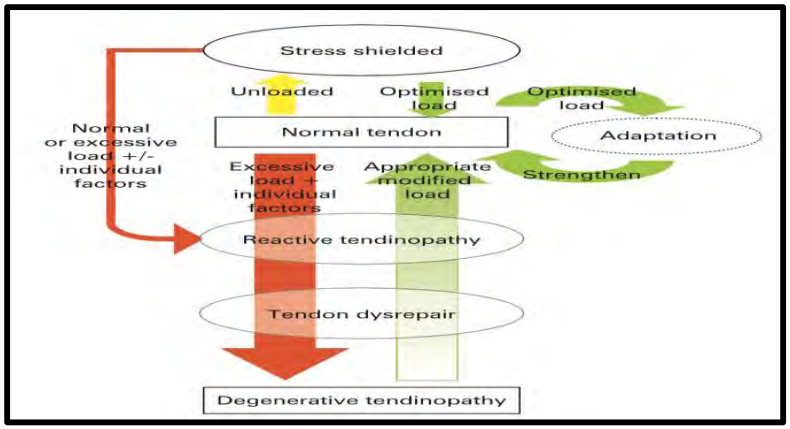


Figure 3: Abate's Iceberg Theory

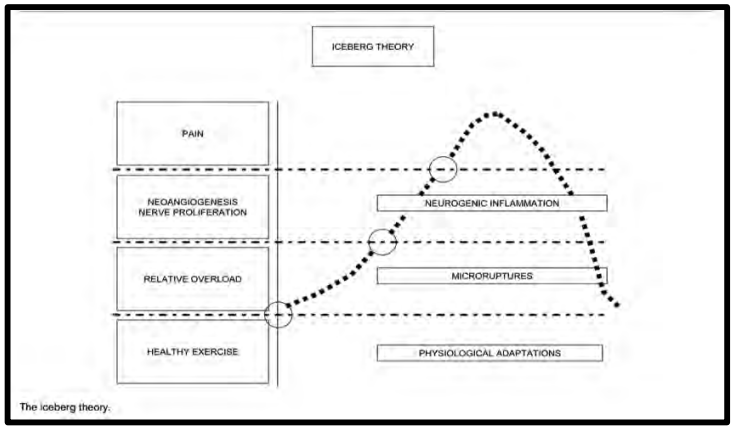


Figure 4: Arnoczky mechanobiological aetiopathogenesis

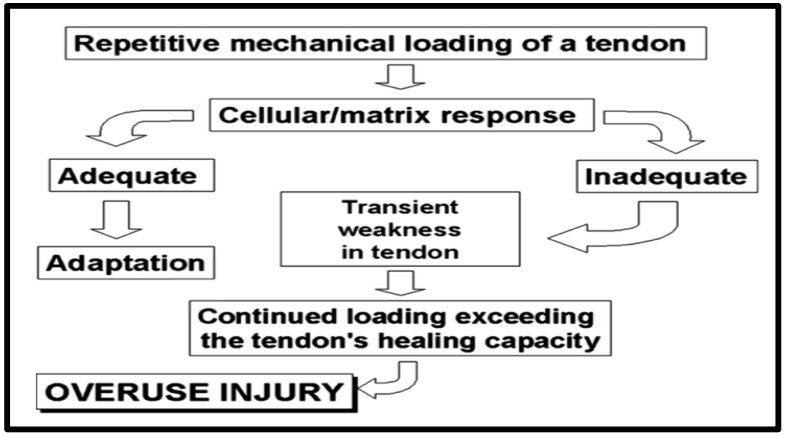
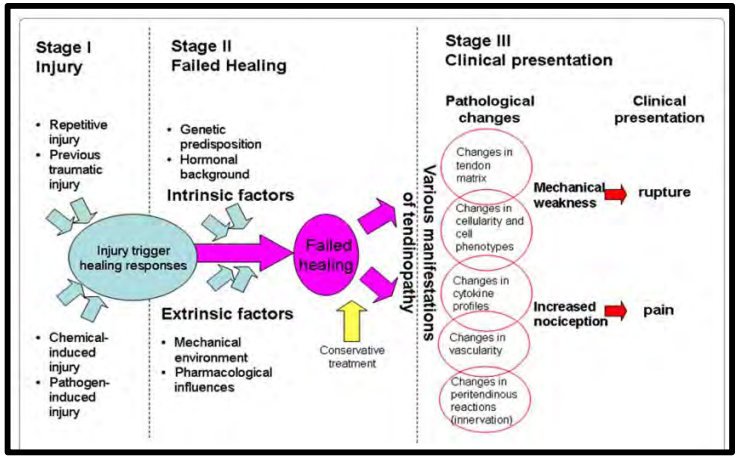


Figure 5: Fu's Failed Healing Response



Broadly speaking, depending on the primary or key event in the pathology 'cascade', these models can be categorized into three paradigms; (1) collagen disruption/tearing, (2) inflammation or, (3) tendon cell response (Cook *et al.* 2016) (Figure 6).

Structural/collagen disruption paradigm

The collagen tearing or disruption model is the oldest and most commonly cited paradigm in tendinopathy. The paradigm is built on the premise that under normal physiological conditions, loading and exercise increases the strength of a tendon. However if the individual threshold of the tendon is exceeded and overcome, micro-damage may occur. If the tendon is given adequate time to recover, in good local conditions of blood flow and nutrition, the healing process will prevail with complete repair (Fu *et al.* 2010). However, it is suggested that if the recovery time is too short and blood flow is inadequate, the repetitive strain will lead to micro-damage inside the tendon resulting in significant extracellular matrix disruption, separation and breakdown. This is mainly attributed to cell proliferation, mainly chondrocytic, as well as some myofibroblasts, resulting in a marked increase in protein production (proteoglycan and collagen) (Cook *et al.* 2016). Erythrocytes, fibrin and fibronectin deposits are often seen around the micro tears (Järvinen *et al.* 1997). Although the collagen tearing or separation theory has primarily focused on a failed healing and degeneration response in chronic overload, the paradigm also proposes a similar pathological process in chronically under loaded tendons (stress-shielded) (Cook *et al.* 2016).

Inflammatory paradigm

As indicated previously, the term tendinitis to describe tendon pain was widely accepted and deeply engrained in the medical community for many decades. The premise of this concept and terminology was based on the suggestion that an inflammatory process was primarily responsible for tendon pain. This paradigm was reflected in the early management strategies in tendinopathy with a heavy reliance on anti-inflammatory medication or corticosteroid interventions (Chan and

Fu 2009). The intervening years saw a shift away from this paradigm due to evidence demonstrating alterations in tendon structure in the absence of any increase in inflammatory prostaglandin E_2 levels compared with asymptomatic tendons using microdyalsis (Alfredson *et al.* 1999b, Khan *et al.* 1999, Alfredson *et al.* 2001). This shift away from an inflammatory model was summarised by Khan *et al.* (2002) in an editorial for the BMJ where he encouraged health care practitioners "to accept the irrefutable evidence that the term tendinitis must be abandoned to highlight a new perspective on tendon disorders". Although it is plausible that inflammation may not be the primary driver in tendon pain, conclusively discounting any contribution of inflammatory mediators and substances appears to be unsubstantiated. Evidence in the past number of years suggests that inflammatory mediators do indeed play some role in contributing to tendon pain (Rees *et al.* 2013), with recent advancements in immunohistochemistry and gene expression improving our ability to investigate inflammatory mechanisms in tendon pain.

To highlight this Schubert *et al.* (2005) have reported that people with chronic AT demonstrate inflammatory mediators T and B-lymphocytes. While other studies have demonstrated the increased presence of inflammatory chemicals such macrophage-derived interleukin-1 (IL-1) (Gotoh *et al.* 1997), cyclooxygenase (COX)-1 (Sullo *et al.* 2001), COX-2 (Zhang and Wang 2010), IL-6 (Legerlotz *et al.* 2012), and isoforms of transforming growth factor-β (TGF-β) (Fenwick *et al.* 2000). Furthermore hypertrophy and hyperplasia of tenocytes are an often cited process in tendinopathy (Scott *et al.* 2007). Tenocytes are known to proliferate and increase metabolic activity in response to cytokines and growth factors that are associated with the inflammatory response (IGF-1 and TGF-β), thus providing indirect evidence of the potential role of inflammatory mechanisms in tendinopathy.

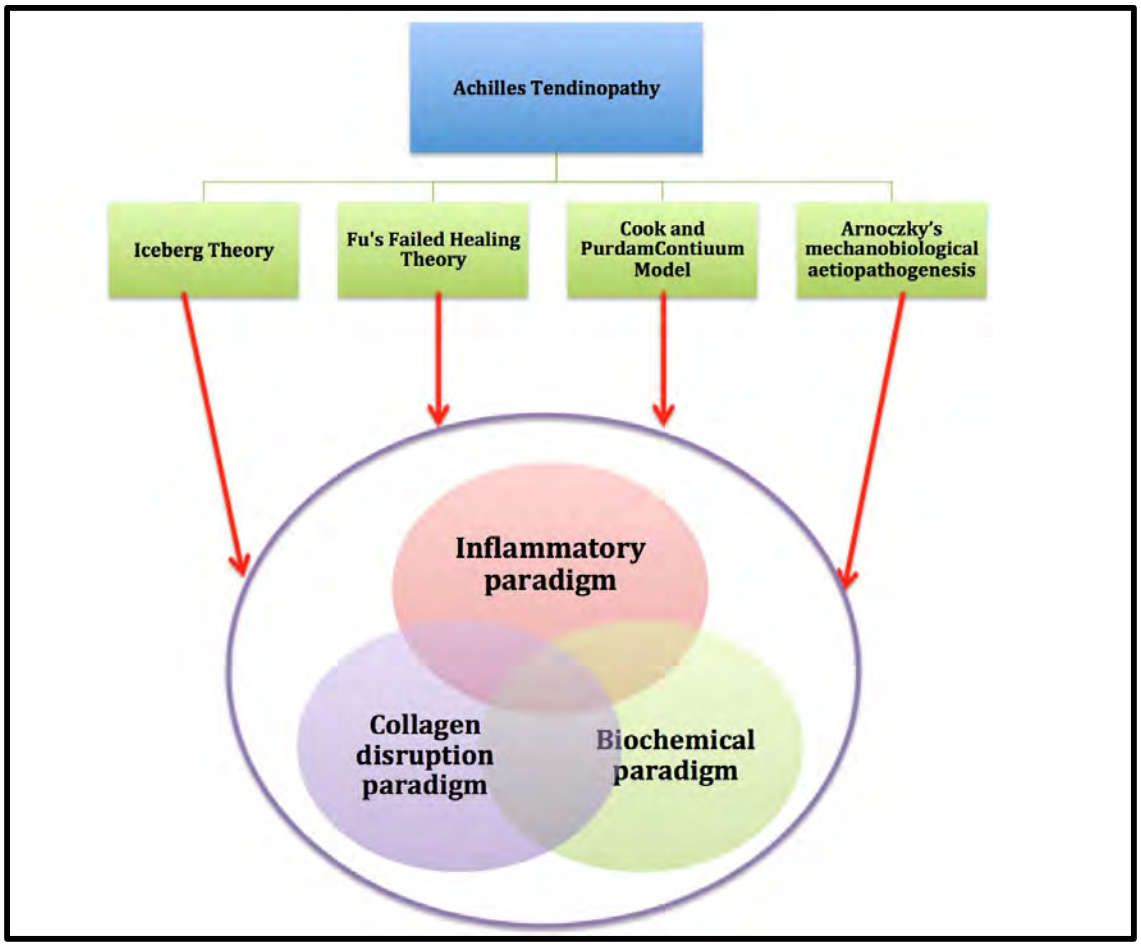
Tendon cell response/Biochemical paradigm

Tenocytes are primarily responsible for maintaining the extracellular matrix in response to the environment (Cook *et al.* 2016). The tendon cell response theory proposes that local, non-neuronal tenocyte production of neuropeptides and neurotransmitters (ACh) occur following activation of tenocytes as a result of overload or sudden changes in loading. Production of these

substances may lead to alterations in tissue, vascular regulation and/or pain processing through peripheral nocioception and signaling. Acetylcholine (ACh), a neurotransmitter in the central nervous system (CNS) and peripheral nervous system (PNS) that is produced by activated tenocytes (Danielson *et al.* 2007), is capable of modulating nociceptive input, influencing collagen production, as well as inducing cell proliferation and regulating vessel tone (Vogelsang *et al.* 1995).

Additionally imaging of tendons using ultrasound power Doppler imaging has demonstrated increased vascularity (measured as augmented blood flow), in close relation to the area with structural changes in some cohorts of people with tendinopathy (Alfredson and Öhberg 2005). Therefore, it has been speculated that the locally produced signal substances might play a role in the differences seen in vasoregulation in tendinopathy (Danielson 2009). Neuropeptides such as substance P (SP) have also been proposed to play an important role in this tendon cell response theory. Binding of SP to its receptor has been linked to the transmission nociception (Levine *et al.* 1993). The expression of SP may lead to a process known as neurogenic or peptidergic inflammation, which is characterized by vasodilation and protein extravasation in surrounding tissue (Rio *et al.* 2014). The concept of biochemical mediators in tendinopathy was first proposed by Khan *et al.* (2000) and built on later through the work of Danielson (2009). Previously it was thought that these biochemical substances were only produced by nerve fascicles. However, recent research has emerged confirming the presence of non-neuronal tenocytes which may play a role in the expression of signal substances (SP, AcH, catechoamines) which may contribute to tendon pain (Rees *et al.* 2013).

Figure 6: Theoretical paradigms associated with tendinopathy models



The complexity of normal tendon structure, and the multifactorial nature and magnitude of the tendon's response to injury has resulted in a difficulty in creating an experimental model that mimics load-related tendon pathology in humans (Cook *et al.* 2016). There are key arguments for and against the existing models, as well as commonalities among models.

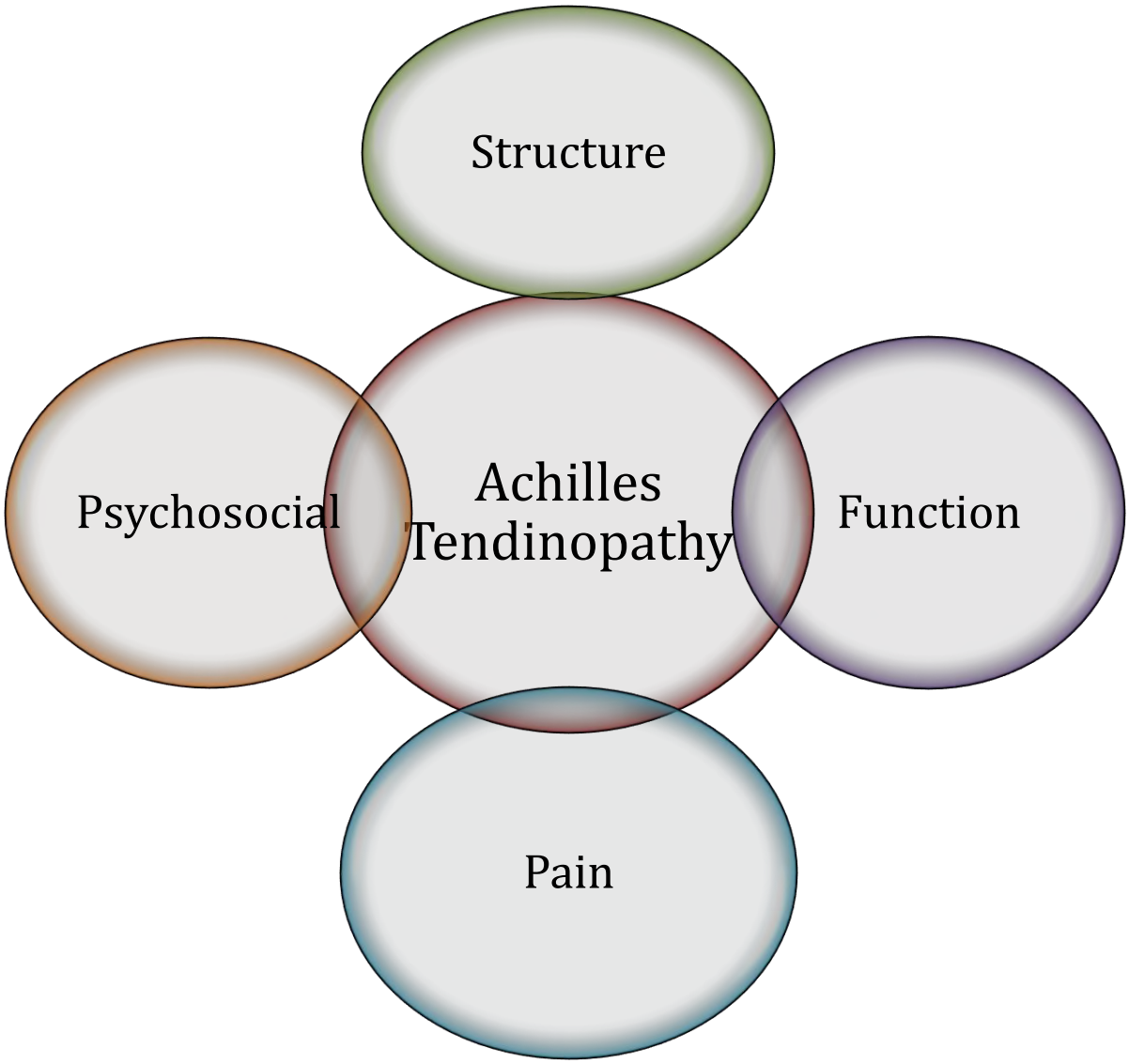
- Alterations in tendon **structure** have been reported in a large percentage of asymptomatic individuals, with studies suggesting that alterations in tendon structure are present as in many as 59% of asymptomatic populations (Khan *et al.* 1997, Cook *et al.* 2000, Fredberg and Bolvig 2002, Lian *et al.* 2005, Gisslen *et al.* 2007, Fredberg *et al.* 2008a), suggesting the relationship between **structure** and **pain** is unclear.
- Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are commonly prescribed in the treatment of tendinopathy in the context of an assumed inflammatory paradigm. NSAIDs are prescribed in attempt to reduce **pain** by inhibiting the production of pro-inflammatory prostaglandins. Although there is some evidence to suggest that NSAIDs may be beneficial in the short term (Green *et al.* 2001), there is little evidence to support the use of such medications in the long term. Additionally, the use of corticosteroid may increase risk of spontaneous ruptures and may even affect healing through deleterious effects on tendon structure (Koester *et al.* 2007).
- Numerous studies suggest that alterations in tendon **structure** may lead to increased hysteresis or strain on the Achilles tendon, which may lead to impaired **functional** performance as a result of the inability to dissipate forces during SSC loading activities (Muraoka *et al.* 2005, Arya and Kulig 2010, Child *et al.* 2010). However, a large percentage of asymptomatic athletic populations display alterations in tendon **structure,** often with no deleterious effect on **function.**
- There has been a growth in the use of autologous blood and autologous blood products (principally platelet-rich plasma, PRP) in the treatment of tendinopathy. The suggestion is that the cells and growth factors (such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1)) in PRP, or other components of these preparations 'repair' the pathological or **structurally** abnormal tendon (Kaux *et al.* 2011). However, evidence suggests that PRP or that altering tendon **structure** is a prerequisite for improving **pain** associated with AT (de Vos *et al.* 2010).
- The premise that tendinopathy is an overuse injury, strictly caused by chronically overloading a tendon does not appear to hold true, given that symptomatic tendinopathy is present in non-athletic populations, particularly in those with associated metabolic

disorders (Van der Linden *et al.* 2002, Marie *et al.* 2008, Gaida *et al.* 2009).

- The majority of histopathological studies to date have investigated responses in animal models. Limited weight can be placed on outcomes in animal studies; given animal tendons do not directly translate to humans.
- Studies to date have predominantly focused on cross-sectional study designs making it difficult to determine whether pathological changes in tendon structure are a causative process in tendinopathy or merely a by-product of the disease.

It is clear that AT is a complex and disabling musculoskeletal disorder, often resulting in persistent **pain** and reduced **functional** ability in both athletic and non-athletic populations. Attempts to explain the pathoaetiology of tendinopathy to date using theoretical models and paradigms have focused on the contribution of **structural** factors or changes in the physical properties of the tendon. Although **structural** factors may play an important role in the **pain** associated with AT, the persistent nature of AT suggests that it is a multifactorial disorder involving a complex interaction of numerous interlinking variables (Figure 7). Understanding the relative contribution of structure, function and pain and the possible relationship between these factors may improve our understanding of AT. In light of this, the remaining aspects of introduction will discuss these factors further as well as identifying the gaps in the literature to be addressed by the current thesis.

Figure 7: Multifactorial aspects in AT



Pain in AT: tissue injury, tissue sensitivity or both?

Pain is the cardinal feature of AT. However, very few of the theoretical models and paradigms have offered insight regarding the underpinning pain mechanisms associated with AT. The assumption inferred from many of these models and paradigms appears indicate the contribution of a local tissue pathology-pain model following actual or impending tissue injury. Although local structural or peripheral physiological processes may potentially contribute to the pain experience in tendinopathy, there is an increasing body of evidence highlighting the potential presence of ongoing tissue sensitivity as a result of alterations in the central nervous system in AT (Rio *et al.* 2015b, Tompra *et al.* 2015). Given the persistent or chronic nature of AT, it has been suggested that similar to other MSK pain disorders, AT may be associated with alterations in the central nervous system via somatosensory or motor cortex changes (Rio *et al.* 2014, Littlewood *et al.* 2013). In order to improve our understanding of AT it is perhaps necessary to discuss the relative contributions of the various pain mechanisms in AT.

Tissue Injury

Biochemical and structural paradigms suggest that tendon pain occurs as a result of peripheral pain processing or "nocioception" in the presence of chemical mediators (Fu *et al.* 2010, Rees *et al.* 2013). It is hypothesized that following matrix disturbance, or alterations in tendon structure due to repetitive micro trauma or acute overload, an activated cell response occurs. This process leads to the proliferation of chemical or inflammatory mediators including bradykinin, histamine, or neovascular substances (Dean *et al.* 2013). These substances alter the excitation threshold of the peripheral nocioceptors, which increases the responsiveness to mechanical, thermal or chemical stimuli in the area, also known as hyperalgesia. Hyperalgesia refers to the decreased threshold and enhanced responsiveness of nocioceptors to stimuli (Sandkühler 2009). Primary

nociceptors have their proximal synapse in the dorsal horn of the spinal cord where they communicate with spinal nociceptors using glutamate or SP (Rio *et al.* 2014). The spinal nociceptor projects to the thalamus and then onward to access the network of cortical and subcortical areas (Apkarian *et al.* 2005). The thalamus is a key structure in pain processing and has ascending projections to multiple areas including the primary and secondary somatosensory cortices, the anterior insular cortex and the cingulate cortex (Tracey and Dickenson 2012). The increased sensory input from the periphery is also influenced by a complex interaction of the above areas in the thalamus, which sample and evaluate inputs from the periphery as well as other areas in the CNS leading to the production of a pain output (Melzack 1996). This type of pain is often referred to as 'physiological nociceptive pain'. The increased responsiveness of the peripheral nociceptors to stimuli or peripheral sensitisation may be considered a helpful warning sign of potential or impending tissue damage, and where appropriate is considered to be of evolutionary importance (Rio *et al.* 2014) because it triggers adequate avoidance reactions following acute tissue damage (Schaible *et al.* 2011).

Tissue sensitivity

The tissue injury or peripheral nociceptive model of pain suggests that peripheral sensitisation should resolve following a necessary healing and repair process as a result of an acute tissue overload or injury. However the pain associated with AT is often persistent or chronic in nature (Longo *et al.* 2009), remaining long beyond the timeframes associated with normal healing and repair highlighting the possibility of other pain mechanisms in AT. The concept of peripheral nocioception as the primary driver of tendon pain reflects the "dualistic" theory of pain based on the Descartian model. The Descartian model suggested that the amount of tissue damage is directly correlated to the amount of pain experienced through the stimulation of specific pain receptors in the brain (Melzack 1996). Within this paradigm, pain is simply a symptom and reflects the degree of damage to the musculoskeletal structure and associated biological responses locally in the tendon through biochemical mediators, or alterations in the tendons structural properties as indicated previously. However, modern pain science suggests that pain that persists beyond expected recovery times, should be evaluated within a framework that

recognises the potential for altered processing and modulated output of the CNS, rather than solely a product of peripherally driven nociception secondary to persistent tissue abnormality (Littlewood *et al.* 2013). Theoretical models that attempt to integrate the research in pain all emphasise the multifactorial nature of pain and the complex and bidirectional interactions that occur between the state of the body and pain. The involvement of central processes in tendinopathy is still relatively unclear. The spreading of pain to areas remote, or away from the primary area of complaint is referred to as widespread hyperalgesia; or central sensitization, and is a commonly cited complaint in chronic MSK disorders (Latremoliere and Woolf 2009). It has been reported that tendinopathy is associated with widespread hyperalgesia also as a result of altered somatosensory profile in the central nervous system (Plinsinga *et al.* 2015). However these findings are based mainly on upper limb (UL) tendinopathies with the evidence in relation to the presence of widespread hyperalgesia in LL tendinopathy is conflicting (Skinner *et al.* 2014, Tompra *et al.* 2015). The concept of hyperalgesia whether local or widespread is similar to other MSK disorders in patients with shoulder impingement (Hidalgo-Lozano *et al.* 2010), patellofemoral pain syndrome (Jensen *et al.* 2008), and groin pain (Drew *et al.* 2016). However hyperalgesia is only one aspect of CNS sensitisation, and absence of widespread hyperalgesia in AT does not necessarily exclude the involvement of the CNS. The involvement of central processes in tendinopathy have also been investigated altered motor output manifesting in strength deficits in the contralateral limb of people with unilateral tendinopathy, despite no apparent pain or injury in this contralateral side, (Slater *et al.* 2005, Coombes *et al.* 2011, Chourasia *et al.* 2012, Chimenti *et al.* 2014). In addition, the odds ratio of rupturing the other Achilles tendon after a unilateral rupture is higher, when compared with the general population (6 % of the participants ruptured the contralateral tendon (Årøen *et al.* 2004)). This may be due to high bilateral loads, but may also indicate central drivers to pathology and/or pain or systemic or genetic factors (Rio *et al.* 2014). Bilateral tendinopathy in both the loaded and unloaded limb of baseball pitchers would support this (Miniaci *et al.* 2002). Furthermore motor output has been investigated in patellar tendinopathy using single-pulse transcranial magnetic stimulation (TMS), with evidence to suggest alterations in cortical inhibition in symptomatic participants (Rio *et al.* 2015b). These findings highlight the potential role of central factors in the pain associated with

tendinopathy.

Pain is a subjective experience, and although it is certainly related to a complex variety of physiological processes (Littlewood *et al.* 2013), persistent or chronic musculoskeletal pain is influenced by a host of psychosocial factors also. Psychosocial variables such as fear avoidance beliefs, anxiety and hypervigilance have been investigated extensively in other MSK disorders (Ross 2010, Kromer *et al.* 2014), and are reported to influence potential outcomes following exercise interventions (Vlaeyen and Linton 2000, George and Stryker 2011). As a result it has been suggested that CNS modulation might be influenced by a range of intrinsic inputs, for example beliefs about the meaning of pain, or extrinsic inputs, for example societal context (Littlewood *et al.* 2013). Qualitative studies in other peripheral MSK disorders have provided an appropriate platform to investigate these concepts by outlining the substantial insight into the psychosocial aspects associated with persistent knee (MacKay *et al.* 2014), shoulder (Jones *et al.* 2013), and back pain (Bunzli *et al.* 2015). ***However, despite a recognition of the value of qualitative research in understanding patients' pain experience, there is a distinct lack of qualitative studies investigating the contribution of psychological variables in AT (Beaton and Clark 2009).***

The role of imaging in evaluating tendon structure

Conventional imaging in the form of X-ray remains the most popular method of visualising bone and joint structures in peripheral MSK disorders. However, radiography does not utilise soft tissue contrast, leading to insufficient information about soft tissue structures such as tendons (Bleakney and White 2005). Consequently, grey scale ultrasound (US) imaging and magnetic ressonance imaging (MRI) (Chourasia *et al.* 2012) have greatly expanded the capacity for accurate musculoskeletal diagnosis in sports medicine (Rasmussen 2000). US has numerous potential roles in the management of tendon disorders.

- Firstly, imaging with US may identify the presence of pathology in the tendon in the clinical setting (Rudavsky and Cook 2014), by confirming the presence and location of structural alterations in tendon size or other associated findings in conjunction with clinical examination (Syha *et al.* 2007, van Schie *et al.* 2010, Scott *et al.* 2013).

- Secondly, US technology may potentially be utilised as a screening tool to identify 'at risk' athletes at baseline to guide interventions or modify training load (Comin *et al.* 2012).

- Finally, US visualisation of tendon structure may be useful in assessing tendon response to numerous interventions (Kongsgaard 2007, Seynnes 2009).

US and MRI

US imaging has gained increasing popularity amongst musculoskeletal practitioners (Bjordal *et al.* 2003) (Figure 8). US offers the advantages of being minimally invasive, portable, and allows for dynamic visualisation of the tendon compared to MRI (Lian *et al.* 2005, Chang and Miller 2009)

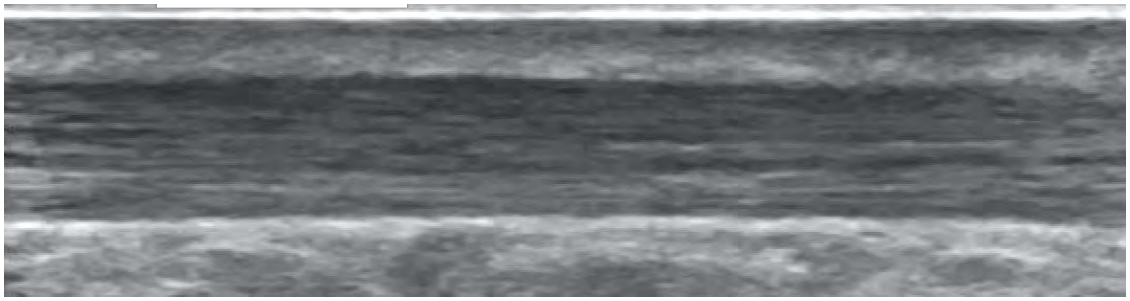
MRI on the other hand offers the advantages of multiplanar imaging with excellent soft tissue contrast, with sagittal and axial planes, the most commonly using a combination of T1 and T2 imaging sequences (Bleakney and White 2005). MRI may provide additional benefit in terms of providing a global assessment of the region of concern, whereas US is generally focused on a particular area (Chang and Miller 2009).

Figure 8: Grey scale ultrasound scanner

Pathological features of tendons using imaging

Under US, the Achilles tendon will display a parallel, striated collagen arrangement consisting of dense largely type I collagen. This will be represented by a bright echogenic pattern due to the fibrillar structure being strongly reflective of sound waves (Rasmussen 2000) (Figure 9).

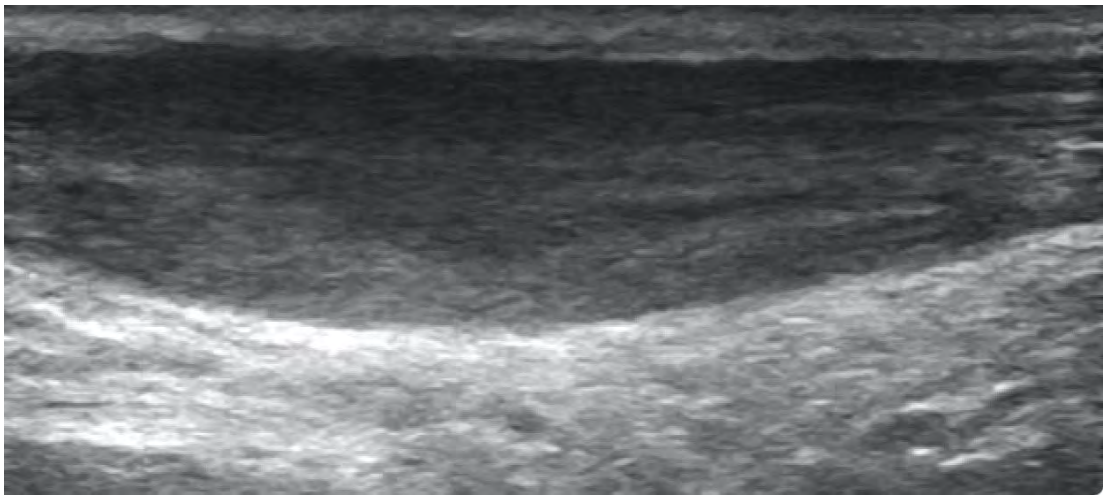
Figure 9: Normal tendon using ultrasound imaging



Alterations in tendon structure are also referred to as tendon abnormalities, include diffuse tendon thickening, hypoechogenicity and neovascularization.

Diffuse tendon thickening is thought to represent altered arrangement of proteoglycans throughout the tendon (Corps *et al.* 2006). Increased tendon thickness is often used as diagnostic criterion of AT (Joensen *et al.* 2009). The current paradigm of tendinopathy describes a continuum of pathological changes, with diffuse thickening thought to represent a "prepathological" state (Cook and Purdam 2009). Previous studies have reported tendon thickness ranging from 7-16mm in patients with a clinical diagnosis of tendinopathy (Fornage 1986), while previous studies have reported symptomatic tendons to be 78% thicker that the asymptomatic side in an athletic population (Maffulli *et al.* 1987) (Figure 10).

Figure 10: Diffuse tendon thickening using ultrasound imaging



Focal hypoechoic areas in a tendon within the normally echobright tendon are suggested to represent areas of tendinopathic lesions. Hypoechoic areas can be attributed to separated collagen fibres, hypoxic tenocytes, or increased ground substance (Józsa and Kannus 1997).

Neovascularisation refers to the increased numbers of blood vessels or neural ingrowth in the tendon visualised using a doppler setting on grey scale US (Bleakney and White 2005). The enhancement of colour and power doppler US has allowed for the non-invasive study of blood flow and vascularity (Bleakney and White 2005), in order to identify this feature in tendons. Studies on chronic AT have indicated a cross-sectional association between pain during tendon loading activity, and the occurrence of neovascularisation in the area with tendon changes (Öhberg *et al.* 2001, Gisslen and Alfredson 2005).

Despite the additional benefit of US in identifying tendon abnormalities, structural abnormalities have been reported in a large percentage of asymptomatic athletic populations (Cook *et al.* 2000, Lian *et al.* 2005). Hypoechoic changes are observed in 10–30% of asymptomatic tendons, and hypoechoic areas can resolve, remain unchanged or expand (Khan *et al.* 1997, Cook *et al.* 2000, Fredberg and Bolvig 2002, Lian *et al.* 2005, Gisslen *et al.* 2007, Fredberg *et al.* 2008a). In terms of neovascularity, Koenig *et al.* (2010) concluded that intratendinous doppler activity should not

be considered pathological given evidence of intratendinous blood vessels in asymptomatic subjects with morphologically normal Achilles tendons. Similar findings were demonstrated by Hirschmüller *et al.* (2012), who reported increased vascularity in more than 30% of asymptomatic long-distance runners. This finding emphasizes the non-linear relationship between **structure** and **pain** in tendinopathy, thus highlighting caution when visualising tendon structure using US.

Is imaging of tendons trustworthy?

The clinical applicability of imaging techniques must always be considered in terms of its validity and reliability to ensure its appropriateness as a measurement tool. Previous research has established that US imaging is comparable to MRI in accurately detecting tears of the rotator cuff or biceps tendon pathologies (Vlychou *et al.* 2009, Fischer *et al.* 2015). Unfortunately to date, there is no agreed gold standard in terms of diagnostic criteria for tendinopathy. Consequently there is a huge variation in the literature in terms of a comparative "gold standard", with surgical comparison, clinical examination, or MRI findings all cited previously (Reiman et al. 2014, Khan et al. 2003, Adams et al. 2010). Therefore, although MRI or US may be effective in terms of accuracy, determining the accuracy of imaging is dependent on how valid the gold standard is. With that yet to be ascertained, caution is advised when assessing the accuracy of imaging in detecting clinical tendinopathy (Docking *et al.* 2015).

Although there is literature reporting the accuracy and sensitivity of US and MRI, little is known about the reliability of US, another fundamental component of any measurement tool.

Reliability

Reliability refers to the reproducibility of measurements (Lexell and Downham 2005) between the same people at two time points, or between two different persons. In comparison to MRI, US is perceived to have a lower level of reliability or higher risk of error, when evaluating tendon structure, due to factors such as operator inexperience, non-standardised imaging protocols and variations in transducer positioning (Gellhorn and Carlson 2013).
Despite these concerns little consensus appears to exist as to whether US imaging displays satisfactory reliability, within or between users. The use of clinically reliable tools is necessary to ensure accurate diagnosis of a condition; to formulate an effective treatment plan based on the obtained information, and also for effective evaluation of the clinical outcomes acquired from the chosen intervention (Kharate and Chance-Larsen 2012). Furthermore, although knowledge in relation to test retest reliability is important, so too is the degree of error or precision involved in the measurement of tendon dimensions. This information has potentially important implications in terms of clinical significance. Clinical significance refers to the practical or applied value or importance of the effect of an intervention - that is, whether the intervention makes a real (e.g., genuine, palpable, practical, noticeable) difference in everyday life to the clients or to others with whom the clients interact (Kazdin 1999).

Are alterations in tendon structure associated with the development of tendinopathy?

AT is associated with lengthy rehabilitation periods, often associated with mixed outcomes and recurrence of symptoms (Sayana and Maffulli 2007, Jonsson *et al.* 2008b, Kongsgaard *et al.* 2009). Consequently, implementation of injury prevention strategies to offset the negative and frustrating consequences of AT, may be beneficial. Alterations in tendon structure identified using US (tendon thickness or hypoechoic areas) have previously been associated with an increased risk of developing future symptoms of tendinopathy, when compared to structurally

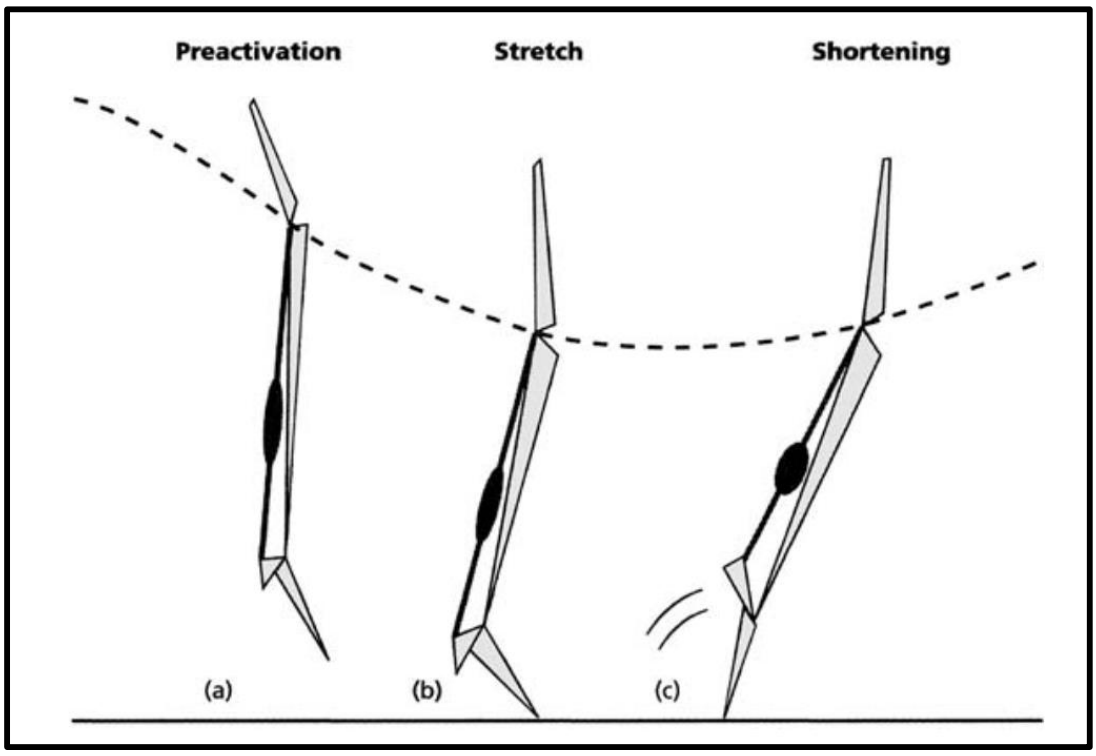
"normal" tendons (Fredberg *et al.* 2008a, Giombini *et al.* 2013). Identification of those tendon abnormalities at baseline which may predispose an athlete to the development of future tendinopathy, may potentially identify asymptomatic high risk athletes and allow introduction or modifications to their training regimen, and/or prophylactic interventions (Comin *et al.* 2012). However, as indicated previously, tendon "abnormalities" have also been identified in a large percentage of asymptomatic athletic populations, with hypoechoic areas, increased thickness and neovascularisation present in as many 59% of asymptomatic individuals (Khan *et al.* 1997, Fredberg and Bolvig 2002, Brasseur *et al.* 2004, Hirschmüller *et al.* 2012, Leong *et al.* 2012, Giombini *et al.* 2013). In addition, the cross-sectional design of many studies investigating tendon structure has led to uncertainty whether structural abnormalities on imaging precede and predict future symptoms, or whether they are just a normal morphological response to specific sporting demands, unrelated to the risk of future symptoms. The lack of clarity in this area has led to considerable uncertainty in the management of sporting populations with a high prevalence of tendon related pain. As a result, medical professionals face a dilemma whether to modify an athletes training regime and/or intervene using preventative strategies based on US imaging. ***This suggests the need to critically evaluate the available evidence investigating the relationship between structure and pain in predicting tendinopathy.***

The role of strength in evaluating tendon function

The Achilles tendon is the largest and strongest tendon in the body (Arya and Kulig 2010). During running and jumping activities, the Achilles tendon is subjected to loads as high as 6–12 times body weight (Schepsis *et al.* 2002, Arya and Kulig 2010). The high loads placed through the Achilles tendon require sufficient accompanying strength of the plantarflexor (PF) muscle and MT unit to ensure optimal functional performance during running, jumping, walking. Tendon function or functional performance in this context refers to the ability of the muscle to

repeatedly generate appropriate force which enables the tendon to store and release energy for athletic movement (Cook *et al.* 2016). The SSC is a combination of an eccentric muscle action (with lengthening of the muscle) immediately followed by a concentric muscle action (shortening of the muscle)(Komi 2008). During walking, hopping and running movements, there are considerable impact loads during ground contact (eccentric phase). This requires preactivation from the LL extensor muscles before ground contact to make them ready to resist the impact (a) and the active braking phase (b). This lengthening phase is followed by the concentric shortening action (c) (Figure 11).

Figure 11: Illustration of the stretch shortening cycle



Individuals with AT often report impairments in functional performance or ability to engage in SSC dominant activities (Paavola *et al.* 2000). One possible explanation for this inability of the MT unit to perform and withstand SSC activities may relate to altered strength profile or persistent weakness as a consequence of AT (Alfredson *et al.* 1998, Mahieu *et al.* 2006,

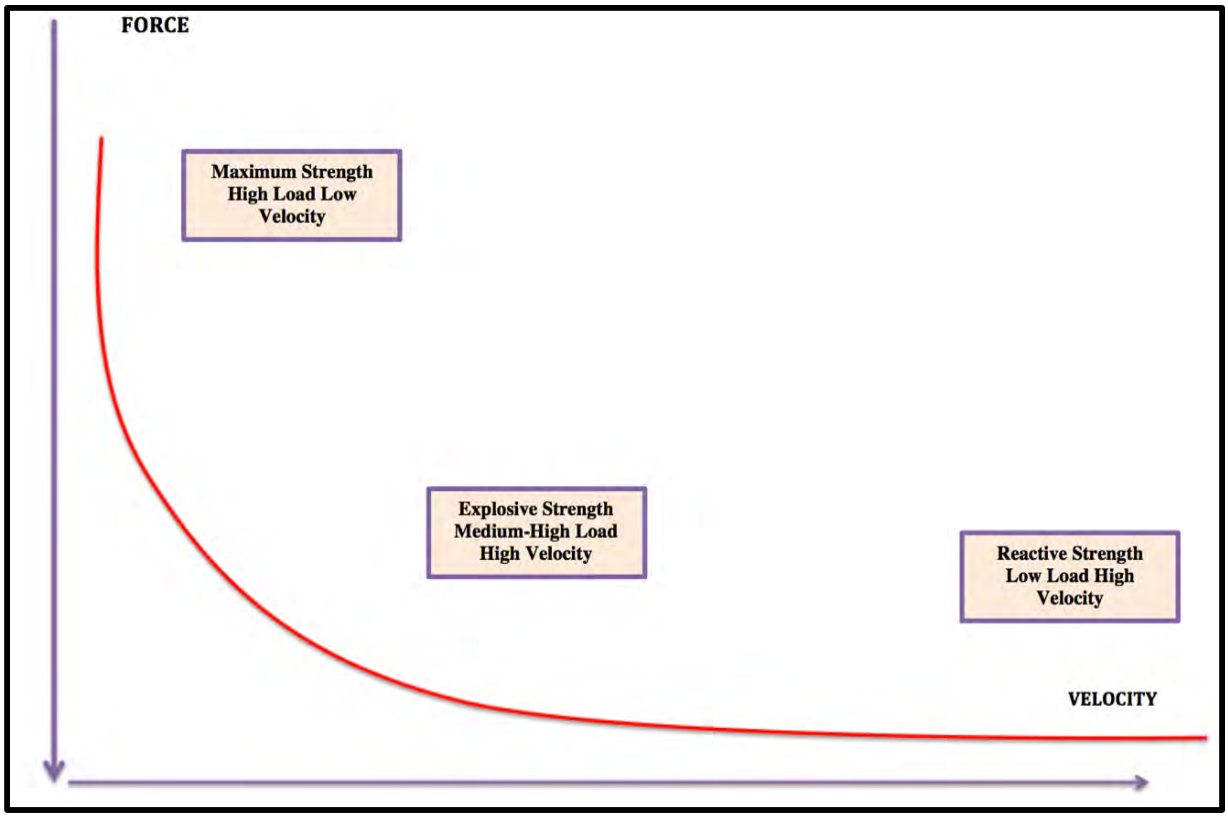
Silbernagel *et al.* 2007c). Presumably, altered strength profile would result in a reduced function of the MT unit to absorb high forces associated with these movements. Additionally persistent strength deficits in AT may reflect a failure of traditional tendon rehabilitation to assess and adequately address the entire strength spectrum or force velocity curve (Beattie *et al.* 2014).

The force velocity curve

The force-velocity curve is a physical representation of the inverse relationship between force and velocity, and can be displayed on an x-y graph (Figure 12). The x-axis (i.e. horizontal axis) indicates velocity, represented by muscle contraction velocity, or velocity of movement (measured in meters per second). Whilst the y-axis (i.e. vertical axis) indicates force, for example, usually through muscle contractile force, or the amount of ground reaction forces produced (measured in Newton's). The interaction between force and velocity, and their influences on assessment and exercise selection may crucial in improving our understanding of tendon function, and ultimately outcomes in AT. Three main strength categories constitute the strength spectrum or force velocity curve: maximum strength, explosive strength and reactive strength.

- ***Maximum strength:*** focuses on maximal force development through high-load, low-velocity movements.
- ***Explosive strength****:* focuses on producing force at high-velocity (rate of force development (RFD) through medium- to high-load, high-velocity movements
- ***Reactive strength:*** focuses on movements that target musculotendinous stiffness and SSC function through low-load, high-velocity exercises (Beattie *et al.* 2014).

Figure 12: Illustration of the force velocity curve



Assessment of function in AT

Tests of muscular strength and power have been applied in order to assess MT function, to provide normative values for various groups of subjects, to predict performance in relevant functional movement tasks, to evaluate the success of training and rehabilitation procedures, or to guide injury prevention strategies (Mirkov 2013, Opar *et al.* 2014).

In a clinical setting, clinicians commonly favour the calf-raise test to assess the functional performance of the PF MT unit in AT (Silbernagel *et al.* 2001, Haber *et al.* 2004, Möller *et al.* 2005, Madeley *et al.* 2007). The test generally involves repetitive concentric-eccentric muscle action of the PF in unipedal stance and is quantified by the total number of raises performed (Lunsford and Perry 1995). Given the popularity of eccentric loading interventions in AT and its similarities to the calf-raise test, the test is frequently used to determine the treatment effects of

loading or exercise interventions (Kountouris and Cook 2007). The test is therefore not only used in the initial assessment of Achilles tendon disorders, but is also used during rehabilitation to quantify treatment outcomes and to monitor evolution of these conditions (Silbernagel *et al.* 2001, Möller *et al.* 2002, Wyatt 2002, Neeter *et al.* 2003). Despite its popularity in clinical practice, anatomical or physiological evidence to support its use is limited (Bruyère *et al.* 2016). The preference for using the number of raises as prime outcome measurement may be attributed to its practical and "user-friendly" clinical application. Although this may encourage a common language amongst researchers and clinicians, valid justification for using the number of raises as outcome measureme is not backed up by scientific literature, calling into question its appropriateness for clinical practice (Hébert-Losier *et al.* 2009).

In research settings to date, the majority of studies investigating functional performance of the PF MT unit in AT have quantified PF peak torque (PT) variables using isokinetic dynamometry through variety of speeds and modes of contraction (Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998, Alfredson *et al.* 1998c, McCrory *et al.* 1999, Öhberg *et al.* 2001). Despite the popularity in the research domain, isokinetic dynamometry is time consuming, expensive and requires specialist training to carry out assessment, which may limit its clinical applicability (Mirkov 2013).

It is clear that functional assessment in AT to date has primarily focused on maximal strength outcomes, or endurance variables in the form of heavy slow contractions, expressed during a heel raise test or during isokinetic dynamometry. However, these strength variables may not provide sufficient assessment of power capabilities in the Achilles MT unit during rapid SSC maneuverers (Rio *et al.* 2015a), where single-joint, isolated assessment may bear little resemblance to running or jumping movements which require considerable amounts of muscle power (Mirkov 2013). ***Unfortunately there is an absence of research to date investigating the relationship between pain and functional ability in AT, by evaluating the role of muscle strength in AT across the strength spectrum.*** Consequently, in the absence of systematic evaluation of the evidence, uncertainty exists in relation to the appropriate methods of assessment, which may inform rehabilitation in clinical practice.

Tendon mechanical properties

Although outside of the traditional strength variables associated with the strength spectrum or force velocity curve, mechanical or structural properties of the Achilles tendon may provide additional information as regards MT function. The most important of these mechanical properties is the mechanical stiffness and strain of the tendon. Stiffness, is the ratio of force applied to the tendon and its elongation in response to the force (Arya and Kulig 2010). Athletes with increased MT stiffness have been shown to have enhanced ability to utilise the SSC (Butler *et al.* 2003, Harrison *et al.* 2004), most likely due to increased energy storage ability in the MTU and increased reflex activity during lengthening, thus minimizing the energetic costs of locomotion (Furlong 2014). It is postulated that decreased tendon stiffness as a result of AT may lead to increased hysteresis or strain on the Achilles tendon which lead to ongoing recurrence of symptoms due to an inability to dissipate forces during SSC loading activities (Muraoka *et al.* 2005, Arya and Kulig 2010, Child *et al.* 2010). Despite the relative importance of tendon mechanical properties to SSC functioning, little is known how AT influences these parameters.

Loading interventions in AT: a multifactorial response?

Exercise or strengthening interventions in AT are often referred to as "loading interventions", and are regarded as the conservative treatment of choice in the management of AT (Malliaras *et al.* 2013). Of these interventions, eccentric loading has become the most popular method in AT to date. Eccentric exercises involve a lengthening contraction of the MT unit. Eccentric loading interventions in tendinopathy originated through the work of Stanish and Curwin 1986 (Stanish *et al.*1986). The authors reported a 44% resolution and 43% marked improvement in 200 participants with AT using an eccentric loading intervention. The authors suggested that the greater mechanical load during eccentric exercises compared to concentric exercises would result in greater remodeling of the tendon. However, this study displayed weak methodological quality, with no comparative control subjects. Despite the methodological issues, the work of Stanish and Curwin (1986) encouraged others to build on their hypothesis of eccentric loading in AT, which later led to the hugely popular "heel drop" programme (Alfredson *et al.* 1998). Alfredson *et al.* (1998) performed the first controlled study examining the effect of eccentric loading in those with AT, compared to a control group, who underwent surgical intervention. The eccentric heel drop programme involved twice daily, every day eccentric loading for 12 weeks. The protocol was shown to improve pain and function in study participants with 100% success rate. Consequently, these results have gone on to influence clinical management of AT, with the prescription of eccentric loading for chronic AT becoming a mainstay of conservative treatment (Malliaras *et al.* 2013).

Eccentric training in AT: does it do what it is proposed to do?

One of the frequently cited benefits of eccentric training in AT, is the progressive strength training nature of the intervention. The suggestion is that eccentric training is more specific and provides a greater load via the force velocity curve, compared to concentric loading (Allison and Purdam 2009). However evidence to support these claims appears tenuous, with a number of counterarguments to challenge the proposed supremacy of eccentric interventions. In terms of basic strength and conditioning principles, hypertrophy programmes would normally utilise a

lower number of repetitions (commonly three sessions per week), and would not prescribe sessions twice a day, 7 days a week for 10+ weeks (Allison and Purdam 2009). Furthermore, despite the alleged high load benefit of an eccentric programme, which involved a huge volume of daily repetitions (up to 180 per day), when compared to lower-repetition volume protocol no differences in outcomes have been found (Stevens and Tan 2014). A further argument favouring eccentric loading is in relation to its specificity, which suggests that eccentric loading is specific to the SSC and optimizes the SSC (Allison and Purdam 2009). However, evidence to support this appears unfounded given the fundamental role of the concentric aspect of SSC movement. The potentiation of the concentric phase of the SSC is a combination of neurological potentiation and elastic recoil, and is a vital component of the SSC. Thus, isolated eccentric exercises specifically avoid a concentric action, thereby intentionally negating any concentric potentiation of the SSC, which may dampen the SSC response (Allison and Purdam 2009). Additionally, it is argued that in terms of the force velocity curve, greater loads can be achieved with eccentric strengthening than concentric. Yet, there is no clear evidence to suggest that tension in the tendon is greater during the eccentric lengthening process than a concentric action (Rees *et al.* 2008).

Comparison to other loading interventions

A lack of evidence to substantiate and support the proposed mechanisms behind eccentric interventions has seen a shift in the last number of years towards mixed contraction interventions, in the form of progressive loading programmes (Silbernagel *et al.* 2007b), isolated concentric programmes (Mafi *et al.* 2001), and heavy slow resistance training (HSR) (Kongsgaard *et al.* 2009, Beyer *et al.* 2015). Of these loading interventions, HSR appears to be the most popular. HSR involves combined concentric and eccentric muscle contractions with the addition of progressive load. HSR programmes are associated with comparable improvements to eccentric training in terms of pain and effect on VISA-A outcomes, however, it is postulated that HSR may be more likely to achieve tendon adaptation and may be better suited to some patient groups (e.g. less irritable or degenerative tendon symptoms, high-load demands such as athletes) (Malliaras *et al.* 2013). Despite this hypothesis, interpretation is advised when generalising these findings due to the fact that the concept of HSR is relatively new, and has only been investigated

in a small number of studies (Kongsgaard *et al.* 2009, Beyer *et al.* 2015).

What changes following loading interventions: structure, function or pain?

A common perception pertaining to loading interventions in AT is the belief that improvements are as a result of alterations in the structural properties of the tendon. The proposed rationale suggests that tendons are regarded as being mechanically sensitive, or mechanosensitive (Maffulli and Longo 2008, Khan and Scott 2009). The term mechanotherapy has been used to describe how the body coverts a mechanical stimulus into a cellular response, which may reverse tendon deconditioning (Khan and Scott 2009). It is suggested that the loading forces applied to the tendon will help stimulate the remodeling of the abnormal tendon structure through altering fluid and blood flow (Ohberg 2004, Wearing *et al.* 2011). However, the assumption that alterations in tissue structure are associated with the improved clinical outcomes is unclear. A recent systematic review by Drew *et al.* (2014) concluded that structural change does not adequately explain the response to loading interventions in tendinopathy. In light of the complex and multifactorial nature of pain in tendinopathy, it would appear feasible that the clinical improvements associated with loading interventions may be associated with a number of factors, which may not exclusively be related to structural change alone. Unfortunately studies investigating the effects of loading interventions in AT to date have focused on unidimensional outcome measures, primarily utilising measures of pain or function using VAS, return or VISA-A (Silbernagel *et al.* 2007c, Silbernagel *et al.* 2007a, Kongsgaard *et al.* 2009, Beyer *et al.* 2015). Undoubtedly these outcome measures provide insight into the effectiveness of a given intervention, however they provide little information in terms of the mechanism of action to explain response or non-response. ***Hence, the mechanism associated the underlying efficacy of therapeutic loading remains unclear. Identification of the factors associated with improved clinical outcomes following loading interventions may shed light on a complex topic, as well as ensuring that rehabilitation interventions are targeted to individual patient deficits.***

Key points from Chapter 1

- AT is a complex, multifactorial MSK disorder, with literature to date mostly focusing on structural paradigms to explain the pathoaetiology of AT.
- Despite the contribution of these paradigms, the persistent nature of AT suggests that it is a multifactorial disorder, involving a complex interaction between structural, functional, and pain related factors.
- Ultrasound imaging is a commonly used in clinical practice to visualise tendon structure, to help aid diagnosis, as well as serving as an outcome measure to assess efficacy of loading interventions.
- One of the most commonly cited criticisms of US relates to its proposed inferior reliability, compared to other imaging modalities such as MRI. Furthermore, little is known in relation to the reliability of US of tendon structure, or the degree of associated measurement error.
- It has been hypothesised that alterations in tendon structure are associated with the development of future AT, in asymptomatic athletes. Despite this, there is an absence of conclusive evidence to prove, or disprove this hypothesis.
- As a result, medical professionals face a dilemma whether to modify an athletes training regime and/or intervene using preventative strategies based on US imaging.
- Individuals with AT often report impairments in functional performance or ability to engage in SSC related activities. It has been proposed that this impairment in functional performance is associated with persistent PF strength deficits as a result of AT.
- Unfortunately there is an absence of research to date investigating the relationship between pain and functional ability in AT, by evaluating the role of PF muscle strength in AT, across the entire strength spectrum.
- Loading interventions are the conservative treatment of choice in the management of AT, and appear to be relatively effective in improving pain and disability in AT.
- Despite the relative effectiveness of loading interventions, individuals with AT continue to experience altered MT function, and suffer recurrence of symptoms. There is an

absence of research in relation to the factors associated with improved clinical outcomes following loading interventions, with studies to date focusing mainly on unidimensional outcomes.

- Identification of the aforementioned factors may shed light on a complex topic, as well as ensuring that rehabilitation interventions are targeted to patient deficits, potentially improving clinical outcomes.
- Psychosocial variables such as fear avoidance beliefs, anxiety, and hypervigilance have been investigated extensively in MSK disorders using qualitative methodologies, and are reported to influence outcomes in exercise interventions.
- Despite recognition of the value of qualitative research in understanding patients' pain experience in MSK research, there is a distinct lack of qualitative studies investigating the contribution of psychosocial variables in AT.

Aims of thesis

A review of the literature highlights the lack of clarity and understanding in relation to the relationship and interactions between structure, function and pain in AT. This doctoral thesis aims to provide a deeper insight into the complex and multifactorial relationship between these factors.

This will be done through five interlinking studies:

1. Systematically review the literature on the reliability of ultrasound imaging in measuring tendon size.

2. Systematically review the literature on the ability of US imaging to predict the future development of Achilles and patellar tendinopathy.

3. Systematically review the literature regarding the presence and degree of strength deficits in AT.

4. Investigate the factors associated with improved clinical improvements following a 12-week loading intervention in AT.

5. Qualitatively explore the experiences and perceptions of pain in people with AT, using semi structured telephone interviews.

CHAPTER 2: Are alterations in tendon structure associated with pain?

STUDY I: A systematic review of the reliability of ultrasound imaging in measuring tendon size: is the error clinically acceptable?

ABSTRACT: US imaging is a commonly used imaging modality for visualising tendon structure and morphology in tendinopathy. US has gained increasing popularity amongst healthcare practitioners in a clinical setting due to its ease of use, portability, and dynamic interpretation in comparison to other imaging modalities. However, in comparison to MRI, US is perceived to have a higher risk of error when evaluating tendon size due to factors such as operator experience, variation in measurement protocol, and measurement interpretation. Furthermore, little is known as regards the degree of measurement error associated with US imaging in tendons. In order to address this concern, a systematic review was performed to assess the evidence regarding the intra-rater and inter-rater reliability and degree of error in US measurement of tendon size.

Eight electronic databases were searched using an agreed set of keywords. Studies which investigated the reliability of tendon size (thickness or cross-sectional area) using US were eligible. Risk of bias was assessed using the Quality Appraisal of Reliability Studies (QAREL) checklist. A total number of 22 studies involving 889 participants were included in the review. Only five studies included symptomatic. Eleven studies investigated both inter-rater and intra-rater reliability; another seven studies investigated intra-rater reliability only, while the remaining four studies investigated inter-rater reliability only.

Combined Inter-rater and Intra-rater ICC values for tendon thickness ranged from 0.45-0.99. Combined Inter-rater and Intra-rater ICC values for tendon cross-sectional area (CSA) ranged from 0.58-0.92. Overall Intra-rater ICC values (0.59-0.99) were marginally higher than Inter-rater values (0.45-0.99) across all tendon sites. Percentage co-efficient of variation (CV%) for tendon thickness and CSA ranged from 0-35% across all tendons. Percentage standard error of the mean SEM% values for tendon thickness ranged from 3.33-7.39%.

The findings of this review suggest US measures of tendon size are reliable, both in terms of relative and absolute reliability. However, the findings must be considered in light of the presence of tendon abnormalities in a large percentage of asymptomatic populations.

1.0 Introduction

Tendinopathy is a term commonly used to describe the clinical presentation of tendon symptoms which includes localised tendon pain with loading, tenderness to palpation and impaired function (Cook and Purdam 2009). It is a highly prevalent musculoskeletal condition affecting both athlete and non-athlete populations, commonly affecting the Achilles, patellar, rotator cuff and wrist extensor tendons (McCreesh and Lewis 2013). AT is the most prevalent lower extremity tendinopathy, with a 5.9% frequency in sedentary people and approximately a 50% frequency in elite endurance athletes (Fredberg *et al.* 2008, Scott *et al.* 2013). Patellar tendinopathy is highly prevalent in participants of jumping and impact type sports with a prevalence of 14.2% (Lian *et al.* 2005). Regarding the UL, the incidence of rotator cuff tendinopathy reportedly ranges from 0.3% to 5.5% (Littlewood *et al.* 2014).

Tendinopathy is often accompanied by alterations in tendon structure, such as degeneration and disordered arrangement of collagen fibres, presence of hypoechoic areas, or an increase in vascularity (Khan *et al.* 1999). Despite these findings there appears to be no correlation between these tendon structural changes and pain. However there appears to be differences in size between symptomatic and asymptomatic tendons for the Achilles tendon (Syha *et al.* 2007, van Schie *et al.* 2010) and the supraspinatus tendon (Joensen *et al.* 2009). MRI and US are imaging modalities of choice when visualising tendon size, morphology and pathology (Brushoj *et al.* 2006). In particular grey-scale US has gained increasing popularity amongst musculoskeletal practitioners and recent technical advancements have made US more affordable and accessible (Bjordal *et al.* 2003). Grey-scale US permits visualisation of the internal architecture of the tendon thus allowing visualisation of fibrillar disorganization or hypoechoic areas, which are common features in tendinopathy. US offers the advantages of being minimally invasive, quick and feasible to use in the community or even the sports field (Lian *et al.* 2005). Recently, this technique has further been supplemented by doppler US and ultrasound tissue characterization (UTC) (Karanicolas *et al.* 2009). UTC captures contiguous transverse ultrasound images over the length of the tendon and semi- quantifies the stability of the echotexture over the length of the tendon into four echotypes (van Schie *et al.* 2010), while doppler quantifies the degree of vascularity using a grading system. Although imaging techniques such as US may confirm the presence of abnormalities within a tendon, this does

not necessarily equate to symptoms. However, tendon abnormalities have been identified in a large percentage of asymptomatic sporting populations, with hypoechoic areas, increased thickness and neovascularisation present in as many 59% of asymptomatic individuals (Khan *et al.* 1997, Fredberg and Bolvig 2002, Brasseur *et al.* 2004, Leung and Griffith 2008, Hirschmüller *et al.* 2012, Giombini *et al.* 2013). However despite this finding, differences in tendon size between symptomatic and asymptomatic tendons have been reported for the Achilles tendon (Syha *et al.* 2007, van Schie *et al.* 2010) and supraspinatus tendon (Joensen *et al.* 2009).

Diagnosing tendinopathy often involves the measurement of tendon size using MRI or US, therefore it is paramount that US is reliable. Reliability refers to the reproducibility of measurements (Lexell and Downham 2005) between the same person at two time points or between two different persons (intra and inter). In comparison to MRI, US is perceived to have a lower level or reliability or higher risk of error when evaluating tendon size due to factors such as operator inexperience, non-standardised imaging protocols and variations in transducer positioning (Gellhorn and Carlson 2013). The reliability analysis used in many studies (Mannion and Troke 1999, Ng *et al.* 2001) has been criticized since the level of association between the data is assessed and no information on the level of agreement between measures is provided (Bland and Altman 1986). Tendon thickness and size measurements are continuous data, such that ICC and pearson's correlation coefficients are commonly used as measures of correlation. For the purpose of this review such measures will be termed *"relative reliability".* However, estimates such as the ICC can be difficult to interpret in the context of an individual score, such that an estimate of precision (e.g. 95% confidence intervals (C.I.), standard error of measurement (Ram *et al.* 2013), coefficients of variation (CV), limits of agreement (LOA) are important for judging the degree to which measurements vary for an individual (Moloney *et al.* 2012). Such measures of precision will be termed *"absolute reliability"* for the purpose of this review. Lucas *et al.* (2010) have recommended that appropriate statistical analysis should utilise a measure of relative reliability (e.g., ICC) as well as a measure of absolute reliability (e.g. minimal detectable difference (MDC) or SEM). Therefore, the aim of this review was to systematically assess the evidence regarding the Intra-rater and Inter-rater reliability of US measurements of tendon size and to interpret the degree of measurement error with reference to studies of clinical populations.

2.0 Methods

2.1 Search strategy

The review was registered on the PROSPERO database (CRD42013004659) and has been reported in accordance with the PRISMA statement (Moher *et al.* 2009). The following databases were searched Academic Search Complete, AMED, Biomedical Reference Collection, Cinahl, Medline, SportsDiscus, Web of Science and Embase databases. The strategy had four components which were combined: (1) tendon AND (2) size AND ultrasound AND (4) reliability. One reviewer (SMA) conducted the database searches independently. The exact search strings utilised are shown in Figure 13. Two independent reviewers (SMA and KOS) assessed the potential studies retrieved from the databases, with any disagreements mediated by a third reviewer (KMC). Once duplicates were removed, titles and abstracts of the studies were screened for eligibility.

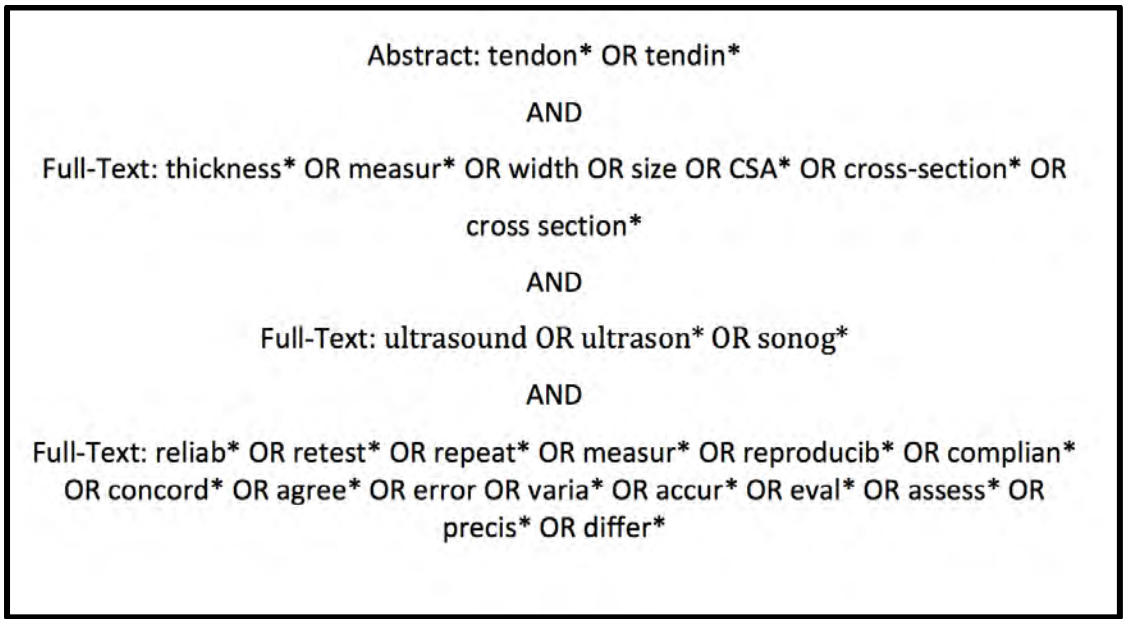
2.2 Inclusion Criteria

- Published as full reports before December 2014.
- Investigated the reliability of US measures.
- Published in English.
- Human participants.
- Investigated either symptomatic or asymptomatic subjects.

2.3 Exclusion Criteria

- Studies investigating thickness of fascia or muscle thickness tears only.
- Studies assessing the use of US in diagnosing tendinopathy who did not provide a measure of reliability.

Figure 13: Study I Literature search strategy



2.4 Quality assessment

Risk of bias was assessed using the Quality Appraisal of Reliability Studies (QAREL) checklist (Appendix 10). The QAREL checklist has previously been tested for validity (Lucas *et al.* 2010) and has been used in numerous studies of test re-test reliability (Moloney *et al.* 2012, Sanjeeva Gupta *et al.* 2012). It consists of 11 items that evaluate seven methodological domains of reliability studies with items graded 'yes', 'no', 'unclear' or 'not applicable' (Gellhorn and Carlson 2013). An outline of the 11 included questions is outlined in appendix 10. One point was awarded for each 'yes' answer; no point was awarded for a 'no' answer. A total score was generated from the amount of 'yes' scores. Using the standards outlined by Van Trijffel *et al.* (2005) studies were considered to be of high quality if they received a yes score on at least 50 percent of checklist items which could be applied to a study. Prior to rating the chosen studies, a consensus regarding the appropriate application and interpretation of rating each variable was reached between the two reviewers by performing a pilot appraisal of two studies not shortlisted for this review. Subsequent to this both reviewers (SMA, KMC) graded each study independently and subsequently discussed the results until a consensus was agreed.

2.5 Data extraction

One author (SMA), extracted information on (1) characteristics of trial participants (sex, age), (2) Characteristics of observers (experience, degree and training), (3) reference landmarks for scanning chosen landmarks (4) tendon investigated, (5) timeframe between repeated measures, (6) type of reliability as well as (7) relative and absolute reliability values.

2.6 Data analysis

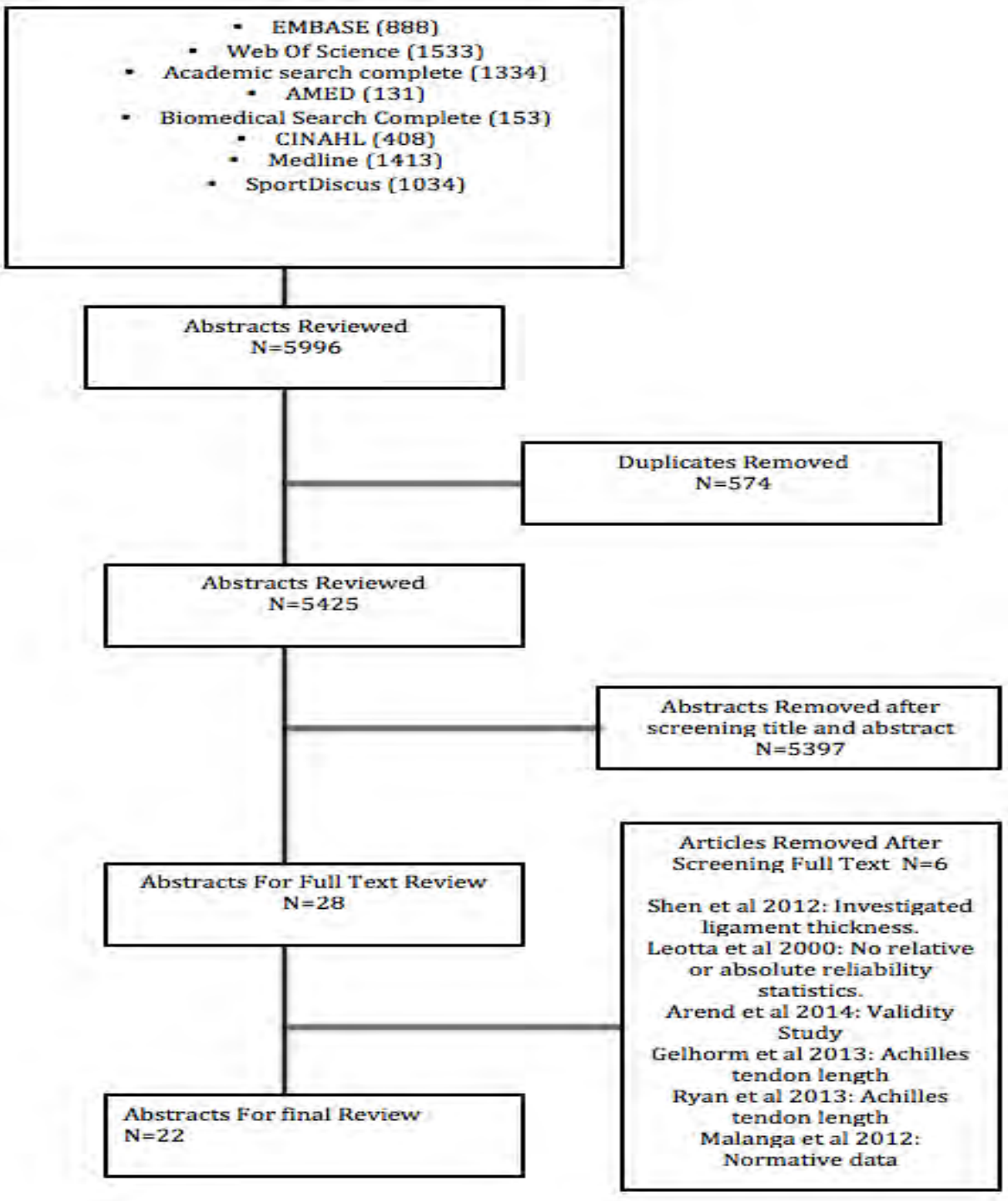
Meta-analysis was not possible due to the heterogeneity of tests, participants and statistical methods used. Hence a descriptive analysis was utilised for the chosen studies. Interpretation of the reliability data presented by each study was done in accordance with the recommendations set out by Lexell and Downham (2005). Relative reliability statistics such as ICC values were interpreted as follows: >0.75 was excellent, 0.40-0.75 was fair to good and <0.40 was poor (Shrout and Fleiss 1979). Pearson's correlation coefficient values were interpreted as follows: 0.00-0.30 negligible correlation, 0.30-0.50 low correlation, 0.50-0.70 moderate correlation, 0.70-0.90 high correlation and 0.90-1.0 very high correlation (Hinkle *et al.* 2003). Absolute reliability statistics in the form of variation and measurement error were interpreted by comparing the variation to test values within the literature. In addition, SEM% was calculated where possible from the information provided in the studies using provided or calculated SEM values. The SEM quantifies the precision of individual scores on a test with most references estimating the SEM using the following formula: $SEM = SD \sqrt{1 - ICC}$ (Weir, J. 2005). The SEM% indicates the typical variation expressed as a percentage value and can be used to interpret the results of an improvement after an intervention. It is calculated using the following formula SEM%= (SEM/Mean) x100 (Lexell and Downham 2005).

3.0 Results

3.1 Search strategy yield

Figure 14 represents the shortlisting of articles through the review process. The search resulted in a total of 5,996 potentially relevant papers. After removal of duplicates (n=574) 5425 articles remained. Screening the title and abstract of each article, 28 full-text articles were identified by both reviewers independently. The reference lists of the included articles were searched for any additional papers, with no additional papers identified. Six articles were excluded (Leotta and Martin 2000, Malanga *et al.* 2012, Shen and Li 2012, Gellhorn 2013, Ryan *et al.* 2013, Arend *et al.* 2014) after screening the full text of the identified articles. The final number of articles included in this review was 22.

Figure 14: Study I Flow Diagram



3.2 Quality assessment

The risk of bias for all included studies is presented in table 1. Three of the 22 studies (Fredberg *et al.* 2008, Özçakar *et al.* 2011, Krogh *et al.* 2013) were deemed to have a high risk of bias, with the remaining 19 studies deemed to have a low risk of bias. With respect to internal validity details concerning the blinding of examiners and randomisation of the test procedures were the main weaknesses, with the majority of studies interpreted as "unclear" for these two scores.

Table 1: Quality Appraisal for Reliability Studies (QAREL) results

Author	1	2	3	4	5	6	7	8	9	10	11	Total	Risk Of Bias
Bjordal *et al.* 2003	Y	Y	N/A	Y	N/A	N/A	Y	UN	Y	Y	N	6	Low
Brushoj *et al.* 2006	Y	UN	Y	Y	N/A	N/A	Y	UN	Y	Y	N	6	Low
Collinger *et al.* 2010	Y	Y	Y	Y	N/A	Y	Y	UN	Y	Y	N	8	Low
Dudley *et al.* 2010	Y	Y	Y	Y	N/A	N/A	Y	UN	Y	Y	Y	8	Low
Ekizos *et al.* 2013	Y	UN	Y	UN	N/A	N/A	Y	UN	UN	Y	Y	5	Low
Fredberg *et al.* 2008	Y	UN	N/A	UN	N/A	UN	Y	UN	UN	Y	N	3	High
Kharate *et al.* 2012	Y	Y	N/A	Y	N/A	N/A	Y	UN	Y	Y	N	6	Low
Klauser *et al.* 2004	Y	Y	Y	UN	N/A	N/A	Y	UN	UN	Y	N	5	Low
Krogh *et al.* 2013	Y	Y	UN	UN	UN	UN	Y	UN	UN	Y	Y	5	High
Lee *et al.* 2010	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	N	9	Low
Leong *et al.* 2012	UN	Y	N/A	UN	N/A	N/A	Y	UN	N	Y	Y	4	Low
O'Connor *et al.* 2004	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	8	Low
Ozcakar *et al.* 2011	UN	Y	UN	UN	N/A	UN	Y	UN	UN	N	Y	3	High
Reaiche *et al.* 2001	Y	Y	N/A	N/A	N/A	N/A	Y	UN	UN	Y	N	4	Low
Schmidt et al. 2004	Y	Y	UN	UN	N/A	N/A	Y	N/A	N	Y	N	4	Low
Sconfienza et al. 2011	Y	Y	Y	N/A	N/A	N/A	Y	UN	UN	Y	N	5	Low
Skou and Aalkjaer 2013	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	9	Low
Syha *et al.* 2007	Y	Y	UN	UN	N/A	Y	Y	UN	UN	Y	N	5	Low
Syha *et al.* 2014	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	8	Low
Toprak *et al.* 2012	Y	Y	N/A	Y	N/A	Y	Y	Y	UN	Y	N	7	Low
Van Schie *et al.* 2009	Y	UN	Y	N/A	N/A	Y	Y	N/A	Y	Y	Y	7	Low
Ying *et al.* 2002	Y	UN	Y	N/A	N/A	N/A	Y	N/A	Y	Y	UN	5	Low

Y=Yes; N=No; N/A=Not applicable; UN=Unclear 1. Was the test evaluated in a sample of subjects who were representative of those to whom the authors intended the results to be applied? 2. Was the test performed by raters representative of those to whom the authors intended the results to be applied? 3. Were raters blinded to the findings of other raters? (inter-rater studies only) 4. Were raters blinded to their own prior findings of the test under evaluation? 5. Were raters blinded to the subjects' disease status or the results of the accepted reference standard for the target disorder? 6. Were raters blinded to clinical information that was not intended to form part of the study design? 7. Were raters blinded to additional cues? 8. Was the order of examination varied? 9. Was the stability of the variable being measured taken into account? 10. Was the test applied correctly and interpreted appropriately? 11. Were appropriate statistical measures of agreement used?

3.3 Description of included studies

A total number of 22 studies involving 889 participants were included in the review. Only five studies included symptomatic populations (Syha *et al.* 2007, van Schie *et al.* 2010, Lee *et al.* 2011, Leong *et al.* 2012, Krogh *et al.* 2013). Eleven studies investigated both inter-rater and intra-rater reliability (Klauser *et al.* 2004, O'Connor *et al.* 2004, Schmidt *et al.* 2004, Brushoj *et al.* 2006, Syha *et al.* 2007, Collinger *et al.* 2009, Dudley-Javoroski *et al.* 2010, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013, Syha *et al.* 2014), another seven studies investigated intra-rater reliability only (Reaiche *et al.* 2001, Bjordal *et al.* 2003, Fredberg *et al.* 2008b, Özçakar *et al.* 2011, Kharate and Chance-Larsen 2012, Leong *et al.* 2012, Toprak *et al.* 2012), while the remaining four studies investigated inter-rater reliability only (Ying *et al.* 2003, van Schie *et al.* 2010, Lee *et al.* 2011, Sconfienza *et al.* 2012). In relation to the tendon characteristics assessed, five studies investigated both tendon thickness and CSA (Ying *et al.* 2003, Brushoj *et al.* 2006, Dudley-Javoroski *et al.* 2010, Lee *et al.* 2011, Toprak *et al.* 2012), one study investigated CSA only (Ekizos *et al.* 2013), while the remaining 16 studies investigated tendon thickness only. Of the 22 studies reviewed, 11 of the 22 studies provide information on the experience or training of each of the investigators (Klauser *et al.* 2004, Collinger *et al.* 2009, Dudley-Javoroski *et al.* 2010, Lee *et al.* 2011, Özçakar *et al.* 2011, Leong *et al.* 2012, Sconfienza *et al.* 2012, Toprak *et al.* 2012, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013). The time between successive testing sessions ranged from 30 minutes to 12 days, with many studies allowing some variation within this. A detailed description of the included studies is provided in table 2.

Table 2: Description of included studies

Study	Sample N (M/F)	Age (mean and range unless stated; years)	Population	Performed by: level of experience	Reference Landmarks	Tendon/Site	Type of Reliability	Timeframe between measures
Bjordal *et al.* (2003)	10 (5M/5F)	Mean 38.7 Range (20-60)	Asymptomatic	One examiner (Trained Physiotherapist): experience N/R	Standardised and stated	Achilles Patellar Common wrist extensor (elbow) Supraspinatus	Intra rater	1 Day
Brushoj *et al.* (2006)	11 (11M)	Mean 17.5 Range (17-18)	Asymptomatic football players	Two examiners: experience N/R	Standardised and stated	Achilles Tibialis Anterior Tibialis Posterior	Inter and Intra rater	Later that day (duration N/R)
Collinger *et al.* (2009)	20 (17M/3F)	Able Bodied: Mean 43.8 Range N/R Manual Wheelchair users: Mean 43.5 Range N/R	15 Able Bodied 5 manual wheelchair users	Two examiners: Three years of experience.	Standardised and stated	Biceps Supraspinatus	Inter and Intra rater	30 mins
Dudley-Javoroski *et al.* (2010)	23 (15M/8F)	Spinal Cord Injury Group: Mean 32.8 Range (27-45) Control Group: Mean 26	7 Spinal Cord Injury 16 healthy controls	Three examiners: Two novice examiners with 6.5 hours of training and one experienced examiner with	Standardised and stated	Achilles Patellar	Inter and Intra rater	N/R

		Range (19-37)		>500 hours experience				
Ekizos *et al.* (2013)	14 (11M/3F)	Mean 29 Range N/R	Asymptomatic	Three experienced observers: experience N/R	Standardised and stated	Patellar	Inter and Intra rater	1 week
Fredberg *et al. (*2007)	47 Achilles 45 Patellar (actual number of participants N/R) All male.	Normal Achilles: mean 26.6 Abnormal Achilles: Mean 28.8 Normal Patellar : Mean 26.2 Abnormal Patellar: Mean (26.3) Range N/R	Elite footballer players Symptom status not reported	N/R	Standardised and stated	Achilles Patellar	Intra rater	5 days
Kharate *et al.* (2012)	25 (14M/11F)	Mean age 25 Range (18-30)	Asymptomatic	N/R	Standardised and stated	Achilles	Intra rater	30 mins
Klauser *et al.* (2004)	20 (12M/8F)	Mean: 29 Range (23-38)	Asymptomatic	Two Examiners: Five and three years' experience respectively	Standardised and stated	3rd Finger Flexor	Inter and Intra rater	N/R
Krogh *et al.* (2013)	18 (sex N/R)	Mean N/R Range N/R	Asymptomatic (n=9) Symptomatic: Lateral Epicondylitis (n=9)	Two Rheumatologists: experience N/R	Standardised and stated	Common wrist extensor (elbow)	Inter and Intra rater	N/R
Lee *et al.* (2011)	111 (26M/85F)	Symptomatic Group:	Symptomatic Lateral	Examiner: (musculoskeletal	Standardised and stated	Common wrist extensor	Inter rater	N/A

		Mean 48.3 Range (34-66) Asymptomatic controls: Mean 48.3 Range (39–63)	Epicondylitis (n=48): Asymptomatic controls (n=63)	radiologist): Seven years experience Measurement: two readers: Six and three months experience respectively.		(elbow)		
Leong *et al.* (2012)	37 (15M/22F)	Mean 21.5 Range (18-25)	24 volleyball players (15 asymptomatic; 9 with Sub Acromial Impingement syndrome) 13 Healthy controls	Examiner: (Sonographer) : 10 years experience Measurement: Physiotherapist: attended training course and extensive supervised practice with experienced sonographer for three months	Standardised and stated	Supraspinatus	Intra rater	N/R
0'Connor *et al.* (2004)	11 (11M)	Mean 38.4 Range (23-53)	Asymptomatic	Two experienced musculoskeletal radiologists; experience N/R	Standardised and stated	Achilles Patellar Triceps Extensor pollicis longus Flexor carpi radialis Supraspinatus	Inter and Intra rater	At least 1 week
Ozcakar *et al.* (2011)	20 (sex N/R)	Mean N/R	Asymptomatic	Novice sonography physicians: supervised by physiatrist with more than 10	N/R	Achilles	Intra rater	1 day

				years' experience				
Reaiche *et al.* *(*2001)	27 (11M/16F)	Mean N/R Range (18-45)	Asymptomatic	Qualified sonographer; experience N/R	Standardised and stated	Finger Flexor	Intra rater	4 hours later or next day
Schmidt *et al.* (2004)	102 (48M/54F)	Mean 38.4 Range (20–60)	Asymptomatic	Experienced physician sonographer; experience N/R	Standardised and stated	Biceps Subscapularis Supraspinatus Index finger Extensor Carpi Ulnaris Patellar Tibialis Anterior Tibialis Posterior Peroneus Brevis Peroneus Longus	Inter and Intra rater	N/R
Sconfienza *et al.* (2011)	78 (37M/41F)	Young: Mean 26 Range (21–35) Elderly: Mean 73 Range (65–81)	Asymptomatic: Young (n=42) Asymptomatic Elderly (n=36)	Two Radiologists: 20 and five years' experience respectively	Standardised and stated	Rotator Cuff Tendon	Inter rater	N/A
Syha *et al.* (2014)	59 (35M/24F)	Median 44 Range (28-50)	Asymptomatic	Two examiners: (Experienced orthopaedic surgeon and resident); experience N/R	Standardised and stated	Achilles	Inter and Intra rater	N/R
Syha *et al.* (2007)	59 (sex	Asymptomatic	Asymptomatic	Two sonographers;	Standardised	Achilles	Inter and	N/R

	N/R)	Group: Mean 38.7 Range N/R Symptomatic Group: Mean 45.8 Range N/R	(n=35) Symptomatic (n=24)	experience N/R	and stated		Intra rater	
Skou and Aalkjaer (2013)	18 (9M/9F)	Mean 25.1 Range N/R	Asymptomatic	Two Examiners with six and two years' experience respectively	Standardised and stated	Patellar	Inter and Intra rater	45mins
Toprak *et al.* (2012)	120 (120F)	Volleyball Players: Mean 13.72 Range N/R Sedentary healthy females: Mean 13.71 Range N/R	Asymptomatic: volleyball players (n=60) Asymptomatic sedentary healthy females (n=60)	Radiologist: Five years' experience	Standardised and stated	Patellar	Intra rater	One day
Van Schie *et al.* (2009)	52 (28M/24F)	Symptomatic group: Mean 44.9 Asymptomatic group: mean 43.6 Range (18-70)	Symptomatic (n=26) Asymptomatic (n=26)	Two examiners: experience N/R	Standardised and stated	Achilles	Inter rater	N/R
Ying *et al.* (2002)	40 (32M/8F)	Mean N/R Range (19-25)	Asymptomatic: Frequent	Five examiners: experience N/R	Standardised and stated	Achilles	Inter rater	N/A

			exercise group (n=20) Infrequent exercise group (n=20)					

3. 4 Estimates of reliability

Table 3 presents the results and estimates of reliability. The ICC was the most commonly used measure of relative reliability with 13 of the 22 studies using this (Reaiche *et al.* 2001, Ying *et al.* 2003, Schmidt *et al.* 2004, Collinger *et al.* 2009, Dudley-Javoroski *et al.* 2010, van Schie *et al.* 2010, Lee *et al.* 2011, Kharate and Chance-Larsen 2012, Leong *et al.* 2012, Toprak *et al.* 2012, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013). Pearson's correlation coefficient was used in three studies (Reaiche *et al.* 2001, Klauser *et al.* 2004, Özçakar *et al.* 2011). The remaining studies did not provide any estimate of relative reliability but instead provided an estimate of absolute reliability. As regards estimates of absolute reliability, CV% was the most commonly used method utilised in five of the 22 studies (O'Connor *et al.* 2004, Brushoj *et al.* 2006, Fredberg *et al.* 2008b, Dudley-Javoroski *et al.* 2010, Leong *et al.* 2012). SEM% was calculated from four studies (Ying *et al.* 2003, Collinger *et al.* 2009, van Schie *et al.* 2010, Leong *et al.* 2012). LOA was reported in four of the included studies (Bjordal *et al.* 2003, Sconfienza *et al.* 2012, Krogh *et al.* 2013, Skou and Aalkjaer 2013). Root mean square difference (RMSD) values were reported in two studies (Ekizos *et al.* 2013, Syha *et al.* 2014). Other statistical methods of precision included coefficient of repeatability, percentage variability and percentage error. Measurements of both relative reliability and absolute reliability were available for 11 of the 22 studies, either by the original study authors providing both measures (Ying *et al.* 2003, Collinger *et al.* 2009, Dudley-Javoroski *et al.* 2010, van Schie *et al.* 2010, Lee *et al.* 2011, Özçakar *et al.* 2011, Kharate and Chance-Larsen 2012, Leong *et al.* 2012, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013) or by the review authors calculating SEM% from the available data (van Schie *et al.* 2010).

3.5 Estimates of Relative Reliability

Combined inter-rater and intra-rater ICC values for tendon thickness ranged from 0.45-0.99 indicating fair to excellent correlation, across all tendon sites. Combined inter-rater and intra-rater ICC values for tendon CSA ranged from 0.58-0.92, also indicating fair to excellent levels of relative reliability. Pearson's correlation coefficient ranged from 0.43-0.92 indicating moderate to strong correlations. The majority of the studies reporting ICC reliability statistics reported values >0.75 (Reaiche *et al.* 2001, Schmidt *et al.* 2004, Collinger *et al.* 2009, van Schie *et al.* 2010, Kharate and Chance-Larsen 2012, Leong *et al.* 2012, Toprak *et al.* 2012). The remaining six studies reported a range of ICC values above and below 0.75 (Ying *et al.* 2003, Dudley-Javoroski *et al.* 2010, Lee *et al.* 2011, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013). Comparing the reliability values of symptomatic and asymptomatic participants in the included studies it appears that ICC values for both populations were similar. Five of the included studies (Syha *et al.* 2007, van Schie *et al.* 2010, Lee *et al.* 2011, Leong *et al.* 2012, Krogh *et al.* 2013) reported ICC values in symptomatic population with values ranging from 0.43-0.98 across multiple tendons indicating fair to excellent reliability. The remaining studies utilising asymptomatic populations reported similar ICC values ranging from 0.55-0.99, which again indicates fair to excellent reliability.

3.6 Estimates of Relative Reliability: Inter-rater reliability

Nine of the included studies provided statistics for inter-rater reliability, with ICC values ranging from 0.45-0.99 across all tendon sites (Ying *et al.* 2003, Schmidt *et al.* 2004, Collinger *et al.* 2009, Dudley-Javoroski *et al.* 2010, van Schie *et al.* 2010, Lee *et al.* 2011, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013). In relation to the Achilles tendon, ICC values of 0.65-0.84 were reported (Ying *et al.* 2003, Dudley-Javoroski *et al.* 2010, van Schie *et al.* 2010) indicating fair to excellent levels of reliability. Inter-rater ICC values for patellar tendon sizes were similar, ranging from 0.69-0.78 (Dudley-Javoroski *et al.* 2010, Ekizos *et al.* 2013, Skou and Aalkjaer 2013). Finally, in relation to the inter-rater

reliability of supraspinatus tendon size ICC values of 0.92 were reported indicating excellent levels of reliability.

3.7 Estimates of Relative Reliability: Intra-rater

ICC values for intra-rater reliability were provided by ten of the included studies with values ranging from 0.59-0.99 (Reaiche *et al.* 2001, Schmidt *et al.* 2004, Collinger *et al.* 2009, Dudley-Javoroski *et al.* 2010, Kharate and Chance-Larsen, 2012, Leong *et al.* 2012, Toprak *et al.* 2012, Ekizos *et al.* 2013, Krogh *et al.* 2013, Skou and Aalkjaer 2013). Intra-rater reliability for the patellar tendon in four studies (Dudley-Javoroski *et al.* 2010, Toprak *et al.* 2012, Ekizos *et al.* 2013, Skou and Aalkjaer, 2013) was fair to excellent, with values ranging from 0.59-0.99. In relation to the Achilles tendon, reliability values of 0.65-0.94 were reported (Dudley-Javoroski *et al.* 2010, Kharate and Chance-Larsen 2012). Finally, ICC intra-rater values of 0.87-0.92 were reported for the supraspinatus tendon (Schmidt *et al.* 2004, Collinger *et al.* 2009, Leong *et al.* 2012).

3.8 Estimates of Absolute Reliability

CV% for tendon thickness and CSA ranged from 0-35% across all tendons. In relation to percentage variability for the most commonly affected tendons, CV% for the Achilles ranged from 0-15%, 0-12% for the patellar tendon, and 8-14% for the rotator cuff respectively. The remaining studies which reported CV% values of >15% involved various tendons of the upper and LL such as the triceps tendon, extensor pollicis longus as well as the tibialias anterior and posterior tendons. CV% for intra-rater reliability ranged from 5-32% (Brushoj *et al.* 2006, Fredberg *et al.* 2008a, Dudley-Javoroski *et al.* 2010, Leong *et al.* 2012). CV% for inter-rater was reported in one of the included studies only and ranged from 15-35% across multiple tendons (Brushoj *et al.* 2006).

SEM% figures for tendon thickness were only observed for the Achilles and rotator cuff tendons with combined inter-rater and intra-rater values generally low ranging from 3.33%-7.39%. Inter-rater SEM% values were reported in three of the included studies (Ying *et al.*

2003, Collinger *et al.* 2009, van Schie *et al.* 2010) with values ranging from 5-7%. Intra-rater SEM% values ranged from 3-6%, as reported in three of the included studies (Reaiche *et al.* 2001, Collinger *et al.* 2009, Leong *et al.* 2012). MDC values were calculated in six of the included studies (Reaiche *et al.* 2001, Collinger *et al.* 2009, Leong *et al.* 2012, Bjordal *et al.* 2003, Ying *et al.* 2003, Syha *et al.* 2007). MDC values for the Achilles tendon thickness ranged from 0.3-1.94mm, MDC values for the rotator cuff ranged from 0.611-0.748mm while MDC values 0.42-0.53mm were reported for the thickness of various finger tendons.
LOA were reported in in two of the included studies, Inter-rater LOA ranged from 0.13-0.17mm (Krogh *et al.* 2013) while LOA values for intra-rater reliability ranged from 0.06-0.35mm in two of the included studies (Bjordal *et al.* 2003, Krogh *et al.* 2013). RMSD values for Achilles tendon thickness ranged from 0.27-0.63mm^2, while RMSD values for patellar CSA ranged from 4.5-16.1 mm^2. Percentage error and percentage variability were reported infrequently in the remaining studies, generally indicating low-moderate variance.

Table 3: Reliability statistics and results of the included studies.

Author	Tendon Investigated	Tendon Size (Measurement Scale)	Absolute Reliability	Relative Reliability	Results
Bjordal *et al.* 2003	Supraspinatus Common wrist extensor origin Achilles Patellar	Thickness (mm)	95% LOA SEM	None Given	95% L.O.A. ± 0.35 mm. SEM 0.13 MDC: 0.36 mm
Brushoj *et al.* 2006	Achilles Tibialis Posterior Tibialis Anterior	Thickness (mm) CSA (mm^2)	CV%	None Given	Thickness Achilles CV 6% Intra-rater 13% Inter-rater 15% Tibialis anterior CV 8% Intra-rater 22% Inter-rater 22% Tibialis Posterior

					CV 9% Intra-rater 24% Inter-rater 24% <u>CSA</u> Achilles CV 7% Intra-rater 19% Inter-rater 19% Tibialis Anterior CV 9% Intra-rater 25% Inter-rater 25%. Tibialis Posterior CV% 13% Intra-rater 32% Inter-rater 35%.
Collinger *et al.* 2010	Biceps Supraspinatus	Thickness (mm)	SEM SEM%*	Generalisability Theory: ICC	<u>ICC</u> <u>Inter-rater</u> 0.75 (Both Tendons)

					<u>Intra-rater</u> Biceps 0.91 Supraspinatus 0.92 <u>SEM</u> Biceps Tendon 0.27 Supraspinatus 0.22 <u>SEM%</u> Biceps 6.73% Supraspinatus 4.55% MDC Biceps: 0.748 mm Supraspinatus: 0.611mm
Dudley-Javoroski *et al*. 2010	Patellar Achilles	Thickness (mm) CSA (cm^2)	CV%	ICC	<u>Intra-rater:</u> Novice Operator 1 Patellar: CV 9.12% ICC 0.82 Achilles: CV 9.46% ICC 0.76

					Novice Operator 2 Patellar: CV 12.08% ICC 0.58 Achilles: CV 9.10% ICC 0.77 Experienced Operator Patellar: CV 6.22% ICC 0.86 Achilles: CV 5.80% ICC 0.92 Inter-rater: (All operators) Patellar: ICC 0.69 Achilles: ICC 0.65
Ekizos *et al.* 2013	Patellar	CSA (mm^2)	RMSD	ICC	ICC Intra-rater 0.59 Inter-rater 0.79, 0.69 RMSD Proximal Tendon: 7.9-16.1 Mid Tendon: 5.7-9.9 Distal Tendon: 4.5-10.6
Fredberg *et al*. 2008	Achilles Patellar	Thickness (mm)	CV%	None Given	CV% Normal Achilles

					Intra-rater 5.4% Inter-rater 0% Normal Patellar Intra-rater 10.3% Inter-rater 0% Abnormal Achilles Intra-rater 4.9% Inter-rater 2.5% Abnormal Patellar Intra-rater 8.7% Inter-rater 0%
Kharate *et al.* 2012	Achilles	Thickness (mm)	95% CI	ICC	<u>ICC (95% CI)</u> Intra-rater 0.935 (0.89-0.96)
Klauser *et al.* 2004	Flexor tendon of 3rd finger	Thickness (mm)	no information provided	R^2	<u>R^2</u> Inter and Intra-rater Longitudinal R^2=0.43-0.81 Transverse dorsovolar R^2= 0.53-0.63

					Transverse radioulnar R^2 = 0.53-0.76
Krogh *et al.* 2013	Common extensor tendon of the elbow	Thickness (mm)	SDD 95% LOA	ICC	<u>ICC</u> Intra-rater 0.76-0.81 Inter-rater 0.45-0.65 <u>95% LOA</u> Intra-rater 0.06-0.13mm SDD: 0.39-0.57 Inter-rater 0.17-0.13mm SDD: 0.65-1.14
Lee *et al.* 2011	Common extensor tendon of the elbow	Thickness (mm) CSA (mm^2)	95%CI	ICC	<u>Thickness</u> <u>ICC (</u>95%CI) Symptomatic 0.75 (0.60-0.85) Control 0.86 (0.78-0.91) <u>CSA</u> <u>ICC (</u>95%CI)

					Symptomatic 0.63 (0.43-0.7) Asymptomatic 0.87 (0.80-0.92)
Leong *et al.* 2012	Rotator cuff	Thickness (mm)	CV 95%CI SEM SEM%*	ICC	Intra-rater ICC 95% CI 0.92 (0.90–0.98) CV% 12.06%–14.44% SEM 0.23 mm SEM%* 3.33% MDC 0.638 mm
O'Connor *et al.* 2004	Achilles Patellar Triceps Extensor pollicis longus (Pietrosimone *et al.*) Flexor carpi radialis (FCU)	Thickness (mm)	CV%	None Given	CV% FCR cross-section 16.54 Achilles SA 8.83 Patellar SA 9.78 Triceps SA 17.71 EPL SA 12.29 FCR SA 6.35

	Supraspinatus				Supraspinatus SA 8.01 Achilles LA 9.61 Patellar LA 7.92 Triceps LA 14.96 EPL LA 13.49 FCR LA 8.00
Ozcakar *et al*. 2011	Achilles	Thickness (mm)	%error Calculating: (Diff between 1st & 2nd /real test value x100)	Pearson's Correlation Coefficient: R^2	% Error Achilles LA.2% Achilles SA 7.5% Achilles CSA 6.5% R^2 Achilles LA 0.79
Reaiche *et al.* 2001	Flexor Digitorum Profundus (FDP) Flexor Digitorum Superficialis (FDS)	Thickness (cm)	as above	ICC R^2 SEM%	Intra-rater ICC FDS 0.83 FDP 0.82 FDP HMP 0.80

					$\underline{R^2}$ 0.60-0.92 SEM%* FDS 4.6% FDP 5.96% FDP HMP 5.69% MDC FDS: 0.53 mm FDP: 0.69 mm FDP HMP: 0.42 mm
Schmidt *et al*. 2004	Biceps Subscapularis Supraspinatus Infraspinatus Achilles Peroneus Longus Peroneus Brevis Tibialis Anterior Tibialis Posterior Patellar	Thickness (mm)	as above	ICC	ICC (95% CI) Inter-rater 0.96 (0.78–0.99) all tendon diameters Intra-rater 0.87 (0.74–0.99) for all tendon diameters

	Index finger flexor Extensor Carpi Ulnaris				
Sconfienza *et al.* 2011	Supraspinatus Infraspinatus	Thickness (mm)	Co efficient of repeatability 95% LOA	as above	<u>Coefficient of repeatability</u> Inter-rater 0.2 <u>95% LOA</u> Interobserver 1.3-1.8 (presented graphically)
Skou and Aalkjaer 2013	Patellar	Thickness (cm)	95% CI 95% LOA	ICC	<u>ICC</u> Intra-rater Examiner 1: 0.84, 0.94, 0.95 Examiner 2: 0.70, 0.89, 0.89 <u>95% CI</u> Examiner 1: (0.63-0.98) Examiner 2: (0.35-0.86) <u>95% LOA</u> Examiner 1: (17.6-21.6%)

					Examiner 2: (21.1-26.1%) Inter-rater <u>ICC</u> Examiner 1 & 2: 0.70, 0.78, 0.75 <u>95% CI</u> Examiner 1&2:(0.18-0.92) <u>%LOA</u> Examiner 1&2: (24.7-28.9%)
Syha *et al*. 2014	Achilles	Thickness (cm)	95% CI RMSD	as above	Intra-rater <u>95% CI</u> 0.11-0.19, 0.05-0.08 <u>RMSD</u> 0.06, 0.03 Inter-rater <u>95% CI</u> 0.20-0.12, 0.02-0.11

					RMSD 0.06, 0.04
Syha *et al.* 2007	Achilles	Thickness (mm)	% Variability	as above	% Variability Intra 17.8% Inter 20.7% % SEM* 3.4-3.6% MDC 1.66-1.94 mm
Toprak *et al.* 2012	Patellar	Thickness (mm) CSA (mm^2)	None Given	ICC	ICC Intra-rater (Active group) 0.87-0.99 (Non-Active Group) 0.86-0.99
Van Schie *et al.* 2009	Achilles	Thickness (mm)	SEM%*	ICC	ICC Inter-rater 0.84 SEM%

					Symptomatic 7.05% Asymptomatic 7.39%
Ying *et al.* 2002	Achilles	Thickness (mm) CSA (mm^2)	95% CI SEM%*	ICC	Inter-rater Thickness ICC (95%CI) 0.68 (0.55-0.78) CSA (95%CI) ICC 0.81(0.74-0.87) SEM%* Thickness 4.87% CSA 5.80% MDC Thickness: 0.704 mm CSA: 9.15 mm^2

95% LOA=95% Limits of Agreement; CV%=Percentage coefficient of variation; Mm=Millimeters; SEM=Standard error of the mean; SEM%=Percentage standard error of the mean; ICC=Intraclass correlation coefficient; $R^{2=}$Pearson's correlation coefficient; RMSD=Real mean square difference; 95% CI=95% confidence interval; R^2=Pearson's correlation coefficient; %error=Percentage error (to the test value); SDD=Smallest detectable difference; LOA=Limits of agreement; %LOA=Percentage limits of agreement;

SEM%* Calculated using the following formula from information provided in the studies: *SEM%=SD (√(1-ICC)) x100/1; LA=Long Axis; SA=Short Axis. MDC=Minimal Detectable Change.* Calculated using the following formula 1.96 x SEMx √*2.*

4.0 Discussion

The use of clinically reliable tools is necessary to ensure accurate visualisation of tendon structure; to formulate an effective treatment plan based on the obtained information and also for effective evaluation of the clinical outcomes acquired from the chosen intervention (Kharate and Chance-Larsen 2012). MRI and US are commonly used to visualise tendon size. In particular US has gained increasing popularity amongst musculoskeletal practitioners (Bjordal *et al.* 2003). However, in comparison to MRI US is perceived to have a higher risk of error or variance when evaluating tendon size due to factors such as operator inexperience, non-standardised imaging protocols and variations in transducer positioning (Gellhorn and Carlson 2013). This is the first review to systematically quantify the reliability of US measures of tendon size (CSA and thickness). The findings of this review suggest US measures of tendon size are reliable, both in terms of relative and absolute reliability.

The ICC was the most commonly used relative reliability statistic in this review. ICC values for Intra-rater reliability ranged from 0.59-0.99 across all tendon sites, while values of 0.45-0.99 were reported for Inter-rater reliability across all tendon sites. Although there is no generally agreed ICC "cut-off" point, the values proposed in the seminal paper by Shrout and Fleiss (1979) suggest that US has fair to excellent levels of reliability. As outlined, one of the frequent criticisms of US in comparison to MRI is the apparent user variability, which is thought to limit its reliability. Despite these concerns, similar ICC values were reported for both inter-rater and intra-rater reliability. Furthermore, Shrout and Fleiss (1979) also defined a clinically acceptable correlation being > 0.75, with the majority of studies in this review reporting values above this correlation value. However it is becoming clear that the use of only ICCs or similar relative reliability statistics for the analyses of reliability is not sufficient since ICC values do not out-rule the potential of a large measurement error (Vaz *et al.* 2013). Consequently relative reliability statistics should be accompanied by an estimate of precision or absolute reliability for judging the degree to which measurements vary for an individual which may allow interpretation of clinical significance of reported statistical values (Moloney *et al.* 2012).

Although statistical interpretation of US reliability in terms of change or group differences (e.g. statistical significance) and the magnitude of experimental effects (e.g. effect size or correlation) is important, so too is the degree of measurement error of a given outcome measurement tool. One method of interpreting this is through the use of minimum detectable change values. The "minimum

detectable change" (MDC), also referred to as the "smallest detectable difference," is an absolute measure of reliability (measurement error), which accounts for various sources of variability in defining a confidence interval in units of the measure. MDC differs from the "minimum clinically important difference," which is a change in performance judged to be relevant through comparison to some statistical or expert-based external criterion (Darter *et al.* 2013). Given the fact there is no gold standard tool (Imaging, MRI, Palpation, performance tests) for the diagnosis of tendinopathy minimum clinically important differences are not feasible given the lack of validity of other tests, consequently MDC would appear to be most appropriate method of interpreting the degree of measurement error. Differences between symptomatic and asymptomatic tendons of 1.23mm and 2.4mm have been reported for the Achilles tendon (Syha *et al.* 2007, van Schie *et al.* 2010) and 1.55mm for the supraspinatus tendon (Joensen *et al.* 2009). US is also used as an assessment tool to monitor the efficacy of interventions for tendon disorders. Previous research suggests favourable outcomes following loading interventions may be attributed to a reduction in tendon thickness visualised using US technology (Ohberg *et al.* 2004, Petersen *et al.* 2007). Ohberg *et al.* (2004) demonstrated a reduction in tendon thickness following a 12-week loading programme in participants with chronic Achilles tendon pain. Average tendon thickness of the participants was 9.00mm pre-intervention and 7.65mm post-intervention indicating a reduction of 1.35mm following the intervention. The reported values between symptomatic and asymptomatic populations and pre and post interventions appear to compare favourably to the MDC values reported for the Achilles tendon which ranged from 0.3mm-1.94mm respectively, while MDC values for the rotator cuff ranged from 0.611-0.748mm. Although the MDC value of 1.94mm is quiet high for the Achilles tendon, the higher measurement error values may be attributed to the variation in measurement protocol outlined in the study by Syha *et al* (2007), which differed considerably from the other Achilles tendon studies in the review. Consequently if one were to exclude the MDC values reported in this study, the MDC values for Achilles tendon thickness would range from 0.36-0.704mm which is well below the differences outlined previously.

Despite the low error values, it is important to remember the lack of correlation between structure and pain in tendinopathy (Cook *et al.* 2000, Gisslen *et al.* 2007, Giombini *et al.* 2013). Imaging techniques such as US may confirm the presence of abnormalities within a tendon, but this does not necessarily equate to symptoms. Numerous studies have demonstrated imaging findings which are considered "abnormal" in asymptomatic populations in tendinopathy; which is similar to research on the shoulder (Girish *et al.* 2011), hip (Lepage-Saucier *et al.* 2014), and lumbar spine (Brinjikji *et al.* 2015). This highlights the disconnect between pathology and pain in tendinopathy and reaffirms that

although reliability values for tendon size using US were high in the present study they must be considered in the overall context of clinical findings and patient presentation.

MRI and US imaging are the two of the most popular methods of visualising tendons. Despite this, studies directly comparing these imaging methods are scarce. The majority of studies investigating the reliability of MRI have focused on its reliability of identifying tendon tears as opposed to tendon size such as thickness and CSA. Brushoj *et al.* (2006) observed similar values for thickness and CSA when using US and MRI to assess the Achilles and tibialis (anterior and posterior) tendons. This is in line with a study by Richards *et al.* (2001) who investigated the reliability of Achilles tendon size using MRI and US. Their results indicated high intra-rater and inter-rater reliability (Kappa=0.7 and 0.8 respectively) for the assessment of Achilles tendon size using both MRI and US. Although studies comparing the reliability of tendon size between US and MRI are scarce, they have similar levels of reliability in detecting tendon tears (Westacott *et al.* 2010). Since both MRI and US seem to be reliable, advances in US transducer technology, improved sensitivity of doppler imaging, as well as reduced cost may make US more clinically applicable (Docking *et al.* 2015).

4.1 Limitations

One of the primary criticisms of US is its perceived higher risk of error or variance when evaluating tendon size due to operator experience. There was a large variation in operator experience in the current review, ranging from three months to 25 years. Unfortunately due to the large variation in tendon site, protocol used, and statistical methodology, it was not possible to directly compare levels of reliability between operators with different experience. A small proportion of the studies in this review (six of the 22 included studies) investigated reliability in symptomatic populations, with the remainder performed in an asymptomatic population. Given that US technology is aimed at clinical use in symptomatic participants, reliability studies should ideally reflect this by performing studies on appropriate symptomatic populations, as this affects the generalisability of the findings. One of the most often cited criticisms of US is examiner influence. One potential solution to address this issue is the use of tracking devices in the measurement of tendon size. One of the included studies utilising UTC (van Schie *et al.* 2010) reported using such a device to reduce examiner influence, however the majority of studies used grey-scale ultrasound and did not utilise such a device, which is a potential limitation of the included studies. Limited control of environmental factors was a further limitation. For example, the time scale between repeated testing varied from 30 minutes to 12 days with little or no reporting of whether external load, which could affect tendon size (McCreesh *et al.*

2014). Although the majority of studies standardised the participant position, defined the scanning point, and used appropriate image acquisition frequencies, there was a distinct variation in these variables across all of the studies, and even within tendons. For example the measurement of Achilles tendon thickness ranged from "maximum anterior posterior (AP) diameter at level of medial malleolus" to "thickness where tendon separates from the calcanei" to "the maximum AP diameter of the tendon". A final limitation is in relation to the variation in statistical measures used in the study. As detailed previously, appropriate statistical analysis in reliability studies should utilise a measure of relative reliability as well as a measure of absolute reliability. Only nine of the 22 included studies provided both a measure of relative and absolute reliability. Furthermore, even within relative and absolute reliability, there was a large variation in the statistical methods used limiting the ability to perform a meta-analysis. It is acknowledged that other intra-tendinous aspects, as opposed to tendon size, may also be relevant in tendinopathy (Comin *et al.* 2012, Hirschmüller *et al.* 2012) and this review did not examine the reliability of measuring neovascularity within tendons.

4.2 Perspectives

The findings of this review suggest US measures of tendon size are reliable, both in terms of relative and absolute reliability. The degree of error in this review is less than the difference reported between symptomatic and asymptomatic tendons in previous studies. This may have potentially important clinical implications regarding the identification, monitoring and management of tendinopathy. However, findings must be considered in light of the presence of tendon abnormalities in a large percentage of asymptomatic populations, thus highlighting the complex association between structural pathology and pain, with further research into understanding the pathophysiology of tendon pain required.

STUDY II: Can ultrasound imaging predict the development of Achilles and patellar tendinopathy? A systematic review and meta-analysis

ABSTRACT: US imaging is commonly used to visualise tendon structure. In many athletes with symptoms of tendinopathy, US imaging of the painful tendons will reveal structural abnormalities, typically localised tendon thickening with hypoechoic areas and altered vascularity. However, tendon "abnormalities" have been identified in a large percentage of asymptomatic sporting populations also. It is not clear whether the presence of structural abnormalities in asymptomatic tendons predicts the development of future tendon symptoms in the Achilles or patellar tendon. Consequently, clinicians face a dilemma on whether to modify an athletes training and/or intervene using preventative strategies if they observe structural abnormalities on US imaging. Therefore, the aim of this review was to investigate the ability of US imaging to predict future symptoms of Achilles and patellar tendinopathy.

Prospective studies that performed US imaging of Achilles or patellar tendon structure among asymptomatic subjects at baseline and a clinical measure of pain and/or function at follow-up were included. The final number of studies for inclusion was 17, with all but one of the 17 included studies investigating athletic populations.. Two independent reviewers assessed study quality using the critical appraisal skills programme tool and predictive ability of US was assessed using meta-analysis. The majority of participants in the review were from sporting populations.

Meta-analysis revealed tendon abnormalities on US are associated with future symptoms of both patellar and AT (Relative Risk (RR) =4.97, 95% C.I: 3.20-7.73). Subgroup analysis indicated tendon abnormalities at baseline were associated with an increased risk of both Achilles (RR = 7.33, 95% CI: 2.95-18.24) and patellar (RR = 4.35, 95% CI: 2.62-7.23) tendinopathy.

This systematic review and meta-analysis indicates that tendon abnormalities visualised using US in asymptomatic tendons are predictive of future tendinopathy and are associated with at least a four-fold increased risk. Identification of at risk athletes using screening tools such as US may allow preventative programmes to be implemented. However, it is clear other factors beyond tissue structure are involved in the development of LL tendinopathy.

1.0 Introduction

Tendinopathy is an umbrella term commonly used to describe the clinical presentation of localised tendon pain with loading, tenderness to palpation or impaired function (Cook and Purdam 2009). It is a highly prevalent musculoskeletal condition affecting both athletes and non-athletes commonly affecting the Achilles, patellar and rotator cuff tendons (McCreesh and Lewis 2013).

US and magnetic resonance imaging appear to be the most common methods for visualising tendon structure, and display similar levels of accuracy and sensitivity (De Jesus *et al.* 2009). In particular US has gained increasing popularity amongst musculoskeletal practitioners, by offering the advantages of being minimally invasive, as well as being quick and feasible to use in the community or even the sports field (Lian *et al.* 2005).

Imaging of tendons with US has been utilised in the clinical setting to assist in the diagnosis of tendinopathy, monitor the efficacy of treatments and assess the risk of developing symptoms (Kainberger *et al.* 1997, Rasmussen 2000, Scott *et al.* 2013). In many athletes with symptoms of tendinopathy, US imaging of the painful tendons will reveal structural abnormalities, typically localised tendon thickening with hypoechoic areas and altered vascularity (Cook *et al.* 2005, Comin *et al.* 2012). In addition, structural abnormalities have previously been suggested to increase the risk of developing future symptoms of tendinopathy in various prospective studies (Fredberg *et al.* 2008b, Giombini *et al.* 2013). Therefore it has been proposed that if one were to identify those tendon abnormalities at baseline which may predispose an athlete to the development of future symptoms, one may be able to screen or identify asymptomatic athletes who are at high risk and introduce modifications to their training regimen and/or prophylactic interventions (Comin *et al.* 2012). However, tendon "abnormalities" have been identified in a large percentage of asymptomatic sporting populations, with hypoechoic areas, increased thickness and neovascularisation present in as many 59% of asymptomatic individuals (Khan *et al.* 1997, Fredberg and Bolvig 2002, Brasseur *et al.* 2004, Leung and Griffith 2008, Hirschmüller *et al.* 2012, Giombini *et al.* 2013). Consequently, the correlation between pain and structure in tendinopathy is not linear. This replicates research in other musculoskeletal disorders e.g. shoulder, hip, knee, low back pain (LBP) where structural abnormalities are evident amongst asymptomatic participants in the shoulder, knee and hip (Miniaci *et al.* 2002, Reuter *et al.* 2008, Silvis *et al.* 2011, Schmitz *et al.* 2012, Soder *et al.* 2012, Papavasiliou *et al.* 2014).

The cross-sectional design of many studies investigating tendon structure means it is unclear whether structural abnormalities on imaging predict future symptoms or whether they are simply a normal physiological response to specific sporting demands, which does not indicate an increased risk of future symptoms. The lack of clarity in this area has led to considerable uncertainty in the management of sporting populations with a high prevalence of tendon related injuries. Medical professionals face a dilemma on whether to modify an athletes training and/or intervene using preventative strategies if they observe structural abnormalities on US imaging. Therefore, the aim of this review was to investigate the ability of US imaging to predict future symptoms of Achilles and patellar tendinopathy.

2.0 Methods

2.1 Search strategy and study selection

This review has been registered in the PROSPERO database (CRD42015020664). The PRISMA statement for systematic reviews was used to guide the format and reporting of this review (Moher *et al.* 2010). The following databases were searched in October 2015; Academic Search Complete, AMED, Biomedical Reference Collection, CINAHL, MEDLINE, SPORTDiscus, Web of Science and EMBASE. The strategy used a range of keywords in four categories which were combined: 1) tendinopathy 2) patellar and Achilles 3) US and, 4) cohort/prospective studies. The keywords for the search strategy are outlined in Table 4. Two independent reviewers (SMA and FC) assessed the potential studies retrieved from the databases, with any disagreements mediated by a third reviewer (KMC). Once duplicates were removed, titles and abstracts of the studies were screened for eligibility.

Table 4: Keywords and search strategy

Tendin* OR Tendon* (abstract)
And
knee* OR patella* OR 'jumpers knee' OR Achilles OR heel OR 'tendo calcane*' OR tendocalcane* OR tendoAchilles OR 'tendo Achilles' (abstract)
AND
ultrasound* OR ultrason* OR imag* OR sonograph* OR " tissue character*" OR UTC (abstract)
AND
risk* OR predict* OR associat* OR relat* OR correlat* OR develop* OR prognos* OR prospect* OR longit* OR cohort* OR future (abstract)

2.2 Inclusion Criteria

- Prospective studies investigating the predictive value of patellar or Achilles tendon structure viewed at baseline using US.
- US measurements must have been accompanied with a clinical measure (pain, disability, function, time off sport/activity) to assess the risk of developing future clinical symptoms of Achilles or patellar tendinopathy.
- Duration of follow-up must have been at least 24 hours.
- Tendon structure may have been analyzed qualitatively or quantitatively.
- Studies must have been in English, and published in the last 20 years.
- Studies could include participants of any age.
- Studies could include both insertional and mid portion tendinopathy as well as including participants with associated co-morbidities.

2.3 Exclusion Criteria

- Studies looking only at development of changes in tissue structure, without accompanying clinical measures (as listed above).
- Studies that investigated tendons other than the patellar or Achilles tendon.
- Studies investigating tendon structure in non-human populations.

2.4 Assessment of methodological quality

In the absence of an optimum methodological quality-rating tool for prospective studies of this nature, the CASP checklist for cohort studies was used (Critical Appraisal Skills Programme (2014)) (Appendix 2). This checklist contains 12 questions; the first two questions are screening questions, the remaining ten questions explore the results of the study and its validity and applicability to the local population (Checklists 2014). Questions two, seven, eight and nine explore similar areas and were consequently merged for the purpose of this review. Therefore, the included studies were appraised using seven guiding questions. As the CASP has many considerations for each question, consistency is key when reviewing studies. Therefore, a list of criteria for each question to be considered when appraising the quality of the included studies was drawn up and agreed between the

authors (Appendices). Two authors (SMA & FC) scored the studies independently using the criteria outlined, with any disagreements in scoring mediated by a third reviewer (KMC). As a result of the CASP checklist being originally designed to be used as an educational tool as part of a workshop setting, no overall quality score was awarded to the included studies. Instead the strengths and weaknesses of each study were noted based on these specific criteria.

2.5 Data extraction

Data from the included studies were extracted by two reviewers (SMA and FC), including patient demographics, population sample, measures of tendon structure and the number of tendons that became symptomatic amongst those with normal or abnormal imaging at baseline, and the definition of tendon abnormality provided in each study. Tendon abnormalities were described as any deviation in tendon structure; e.g. hypoechogenicity, increased thickness or increased vascularity as seen on power doppler US. Similarities in the outcome measures used, the tendons involved, the participants included and the prediction of future symptoms allowed for pooled analysis of the data. Where data were not available, or the methods required clarification, the corresponding authors for the original studies were contacted. If data on measures of tendon structure and the number of tendons that became symptomatic amongst those with normal or abnormal imaging at baseline were not available after contacting the study authors the results were not included in the meta-analysis and results were instead reported descriptively.

2.6 Data analysis

Data analysis was performed by a statistician (HP). Data were entered into the Review Manager (RevMan) meta-analysis software, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Fixed-effects models using the Mantel-Haenszel method were selected to compute pooled unadjusted RR values with confidence intervals where studies had low or moderate heterogeneity, with random-effects models selected otherwise. Heterogeneity between studies was assessed using the I^2 statistic, where an I^2 of 30% or less is considered to indicate low heterogeneity and the cut-offs of $I^2 > 30\%$ and $I^2 > 50\%$ are indicative of moderate and substantial heterogeneity, respectively. I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance and seeks to determine whether there are genuine differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity) (Higgins *et al.* 2003). Summary RR are presented using forest plots, stratified by tendon type. Differences between the tendon subgroups were tested for

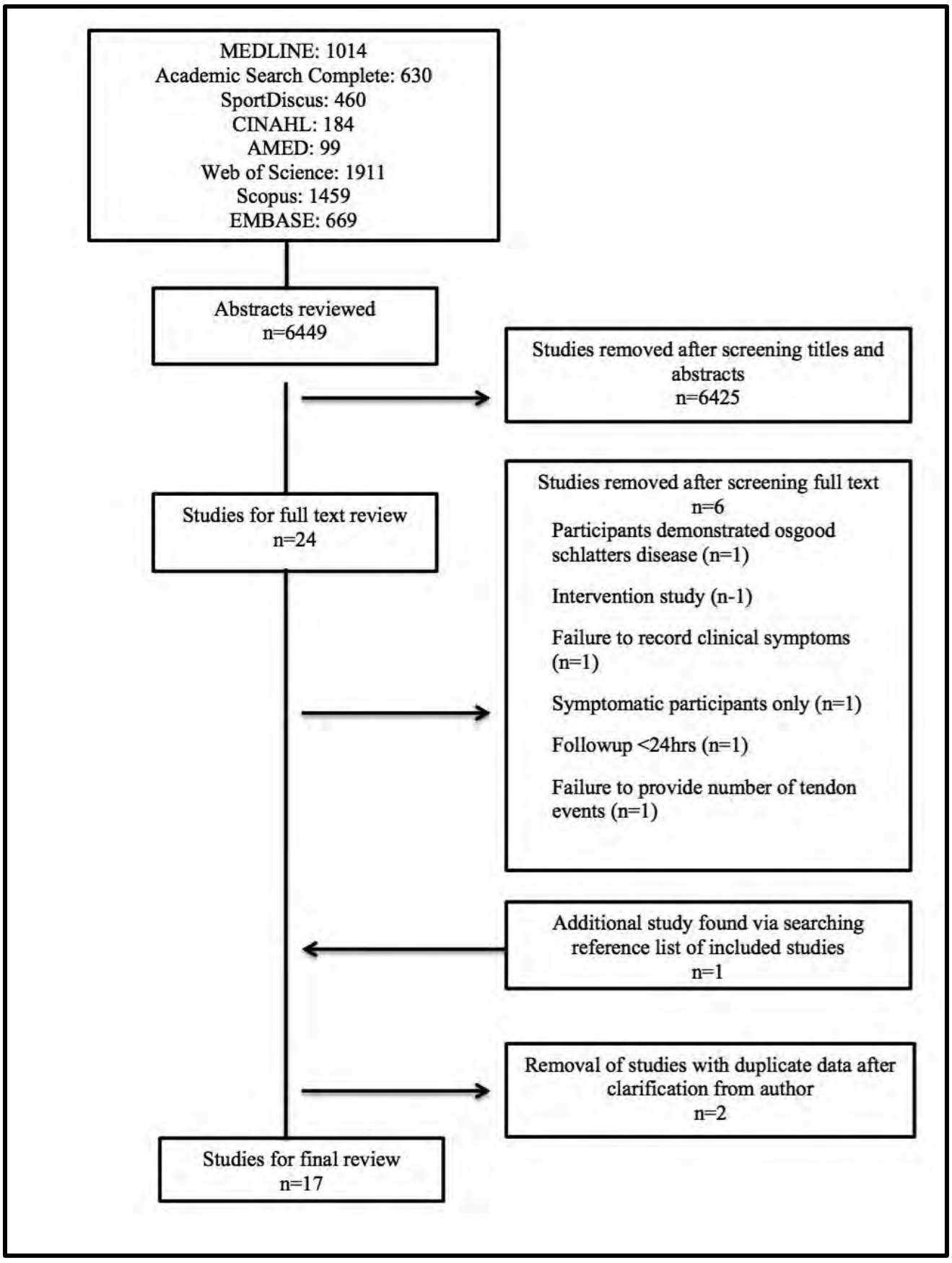
significance using the Chi-square test. Small study bias and publication bias were assessed with funnel plot analysis. The 5% level of significance was used throughout analyses.

3.0 Results

3.1 Identification of studies

The electronic search yielded a total of 6,449 potentially relevant studies. Twenty-four full-text studies were identified as potentially relevant after screening the title and abstract of each study. Six additional studies were removed after screening the full-texts of the identified studies (Paavola *et al.* 2000, Ducher *et al.* 2010, Koenig *et al.* 2010, Mahieu *et al.* 2010, Richards *et al.* 2010, Rosengarten *et al.* 2014). Searching the reference lists of these full-text studies led to one additional study, (Fredberg and Bolvig 2002) totaling 19 studies for final review. Following communication with one author of several eligible studies, two of the three shortlisted studies from his group were excluded as there was overlapping data between the studies (Malliaras and Cook 2006, Malliaras *et al.* 2006, Malliaras *et al.* 2010). Consequently, the final number of studies for inclusion was 17 (Khan *et al.* 1997, Cook *et al.* 2000, Cook *et al.* 2001, Fredberg and Bolvig 2002, Khan *et al.* 2003, Gisslén and Alfredson 2005, Malliaras *et al.* 2006, Gisslén *et al.* 2007, Fredberg *et al.* 2008a, Jhingan *et al.* 2011, Boesen *et al.* 2012, Comin *et al.* 2012, Hirschmüller *et al.* 2012, Giombini *et al.* 2013, Ooi *et al.* 2015, van Ark *et al.* 2015, Visnes *et al.* 2015). The identification procedure is presented in Figure 15.

Figure 15: Study III Flowchart



3.2 Characteristics of the included studies

A detailed description of the selected studies is outlined in Table 5. The mean ages of the participants were similar across the included studies with participants' ages ranging from 15-66 years. In relation to the participant characteristics, all but one of the 17 included studies was carried out within athletic populations. Specifically, five involved volleyball (Gisslén and Alfredson 2005, Malliaras *et al.* 2006, Gisslén *et al.* 2007, van Ark *et al.* 2015, Visnes *et al.* 2015), two involved basketball (Khan *et al.* 1997, Cook *et al.* 2000), three involved soccer players, (Fredberg and Bolvig 2002, Fredberg *et al.* 2008a, Jhingan *et al.* 2011) one involved fencing, (Giombini *et al.* 2013) one involved badminton (Boesen *et al.* 2012), one involved ballet dancers (Comin *et al.* 2012), two involved running (Hirschmüller *et al.* 2012, Ooi *et al.* 2015), and one involved various sporting populations (Cook *et al.* 2001). The remaining study (Khan *et al.* 1997) was performed on participants from the general population referred to a sports medicine center. Twelve of the included studies included both male and female participants, four used male participants only, (Cook *et al.* 2001, Fredberg and Bolvig 2002, Fredberg *et al.* 2008a, Jhingan *et al.* 2011) while the remaining study, (Khan *et al.* 1997) used female participants only. The length of the follow-up period ranged from five days to four years. The majority of studies used real-time US as the modality of choice to investigate tendon structure, with only one study using UTC (van Ark *et al.* 2015). In relation to the tendon structures investigated over the prospective period, nine studies investigated hypoechogenicity, thickness and vascularity (Khan *et al.* 2003, Gisslén and Alfredson 2005, Gisslén *et al.* 2007, Jhingan *et al.* 2011, Comin *et al.* 2012, Hirschmüller *et al.* 2012, Giombini *et al.* 2013, Ooi *et al.* 2015, Visnes *et al.* 2015), six investigated only hypoechogenicity and thickness (Khan *et al.* 1997, Cook *et al.* 2000, Cook *et al.* 2001, Fredberg and Bolvig 2002, Malliaras *et al.* 2006, Fredberg *et al.* 2008a), while the remaining two studies investigated only vascularity (Boesen *et al.* 2012), and hypoechogenicity (van Ark *et al.* 2015), respectively. There was a large variation in the clinical measures of pain and/or function used amongst the included studies ranging from subjective reporting of pain, measures of function (e.g. VISA scale), time absent from sport, performance measures such as single leg squatting and plyometric jumping movements, as well as clinical measures such as tenderness on palpation.

Table 5: Characteristics of included studies

Author	Participant Demographics	Population	Tendon	Parameter investigated	Tendon abnormality definition
Boesen *et al.* 2012	n=86 (56M/30F) Mean age 21.7	Semi Professional Badminton Players	Achilles and Patellar	Vascularity	**Abnormal:** Presence of increased vascularity (≥ grade 1) according to a defined six-point scale (grade 0-5).
Comin *et al.* 2012	n=79 (35M/44F) Mean age 27.4	Professional Ballet Dancers	Achilles and Patellar	Thickness Hypoechogenicity Vascularity Tendon clefts Intratendinous calcifications	**Abnormal:** Presence of (i) hypoechogenicity, or, (ii) increased thickness, or, (iii) vascularity, or, (iv) intratendinous calcifications. (all undefined)
Cook *et al.* 2000	n=26 (8M/18F) Age Range 14-18	Elite junior basketball players	Patellar	Thickness Hypoechogenicity	**Abnormal:** Presence of (i) thickness, or, (ii) hypoechogenicity (all undefined).
Cook *et al.* 2001	n=24 (24M) Mean age 27.5	Athletes from various sports: basketball, cricket, netball, and Australian rules football.	Patellar	Thickness Hypoechogenicity	**Abnormal:** Presence of (i) thickness, or, (ii) hypoechogenicity (all undefined).
Fredberg and Bolvig 2002	n=54 (54M) Age Range 18-35	Professional Soccer Players	Achilles and Patellar	Thickness Hypoechogenicity	**Abnormal:** Presence of (i) thickening >1mm, or, (ii) hypoechogenicity >1mm
Fredberg *et al.* 2008	n=207 (207M) Mean age 25	Professional Soccer Players	Achilles and Patellar	Thickness Hypoechogenicity	**Abnormal:** Presence of (i) thickness > 0.5mm in the Achilles and patellar tendon, or, (ii) hypoechogenicity >0.5mm in the Achilles tendon and >1mm in the patellar tendon.

Giombini *et al.* 2013	n=37 (15M/22F) Mean age 27.2	Elite Fencers	Achilles and Patellar	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased thickness (undefined), or, (ii) hypoechogenicity (undefined), or, (iii) increased vascularity (≥ stage 2) as defined by Gisslen et al. (2007).
Gisslén *et al.* 2007	n=22 (11M/11F) Mean age 16.25	Elite Junior Volleyball Players	Patellar	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased thickness (undefined), or, (ii) hypoechogenicity (undefined), or, (iii) vascularity (≥ stage 2) to a defined four-point scale (grade 0-3).
Gisslén *et al.* 2005	n=60 (29M/31F) Mean age 17.6	Junior Volleyball players	Patellar	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased thickness (undefined), or, (ii) hypoechogenicity (undefined), or, (iii) vascularity (≥ stage 2) according to a defined four point scale (grade 0-3).
Hirschmuller *et al*. 2010	n=634 (425M/209F) Mean Age 41.2	Long distance runners	Achilles	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased thickness (undefined), or, (ii) hypoechogenicity (undefined), or, (ii) presence of vascularity according to a defined five-point scale.
Jhingan *et al.* 2011	n=18 (18M) Mean age 23.5	Elite Soccer Players	Achilles	Thickness Hypoechogenicity Vascularity	**Abnormal:** presence of (i) increased thickness > 1mm, or, (ii) hypoechogenicity >1mm, or, (iii) paratenon blurring, or, (iv) vascularity (undefined).
Khan *et al.* 2003	n= 45 (27M/18F) Mean Age 42	Patients from a university sports medicine center	Achilles	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased thickness >6mm, or, (ii) hypoechogenicity (undefined) Presence of the above features were graded according to a defined 3-point scale.

Khan *et al.* 1997	n=30 (30F) Mean age 24.05	Basketball Players	Patellar	Thickness Hypoechogenicity	**Abnormal:** Presence of (i) increased thickness (undefined), or, (ii) hypoechogenicity (undefined)
Malliaras *et al.* 2010	n=58 (36M/22F) Mean age 26.1	Elite and Recreational Volleyball Players	Patellar	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased thickness (undefined), or, (ii) hypoechogenicity (undefined), or, (iii) vascularity of at least one vessel in the sagittal plane >1 mm in length.
Ooi *et al.* 2015	n=41 (25M/16F) Mean age 37.25	Marathon Runners	Achilles	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) increased tendon thickness (undefined), or, (ii) hypoechogenicity (≥ grade 2) according to a defined three point scale (grade 1-3), or, (iii) vascularity (≥ grade 2) according to a defined three point scale (grade 1-3).
Van Ark *et al*. 2015	n=41 (30M/11F) Mean Age 17.2	Elite Junior Volleyball players	Patellar	Hypoechogenicity	**Abnormal:** Presence of hypoechogenicity (undefined).
Visnes *et al*. 2015	n=158 (84M/74F) Mean age 17	Elite Junior Volleyball Players	Patellar	Thickness Hypoechogenicity Vascularity	**Abnormal:** Presence of (i) hypoechogenicity (undefined), or, (ii) increased vascularity (≥ stage 2) as defined by Gisslen et al. (2007).

n= sample size; M= Male; F= Female; UTC= Ultrasound tissue characterisation

3.3 Methodological Study Quality

The critical appraisal of included studies using the CASP checklist is shown in Table 6. Overall, most studies satisfied the criteria outlined. All of the included studies utilised a representative study population and recruited participants using predefined appropriate inclusion criteria. One of the main weaknesses of the included studies (Fredberg and Bolvig 2002, Jhingan *et al.* 2011, Comin *et al.* 2012) involved the controlling of confounding factors, such as the use of blinding and/or controlling of training load. In relation to appropriate follow-up of the included participants there was a variation in the methodological quality. Six of the included studies reported dropouts between baseline and follow-up (Gisslén *et al.* 2007, Jhingan *et al.* 2011, Boesen *et al.* 2012, Hirschmüller *et al.* 2012, Giombini *et al.* 2013, Visnes *et al.* 2015). However only one of these studies (Boesen *et al.* 2012) described the characteristics of the participants who dropped out. A final methodological concern is the aforementioned large variation in how pain and/or function were measured. Because some studies did not meet some of the criteria, the completeness, interpretation and generalisability of the results may each have been affected. However, in general all of the included studies all had clear aims, used sound methodological quality and used appropriate study designs.

Table 6: Critical appraisal of included studies using the CASP checklist

Study	Acceptable Recruitment	Acceptable controls	Exposure accurately measured	Confounding factors	Do you believe the results	Applied to local population	Fit with other evidence
Alfredson et al. 1998a	✓	✓	✓	✓	✓	✓	✓
Alfredson et al. 1998b	✓	✓	✓	✓	✓	✓	✓
Alfredson et al. 1996	✓	✓	✓	✓	✓	✓	✓
Alfredson et al. 1998c	✓	✓	✓	✓	✓	✓	✓
Arya et al	✓	✓	✓	X	✓	X	✓
Azevedo et al	✓	✓	X	X	✓	X	✓
Baur et al	X	X	X	X	✓	X	✓
Chang et al. 2015	✓	✓	✓	✓	✓	✓	✓

Child et al. 2010	✓	✓	✓	X	✓	X	✓
Chimenti et al	✓	✓	✓	X	✓	X	X
Debenham et al	✓	X	✓	X	✓	X	X
Firth et al. 2010	✓	X	✓	X	✓	X	✓
Grigg et al 2013	✓	✓	X	✓	✓	X	✓
Grigg et al 2012	✓	✓	✓	✓	✓	✓	✓
Haglund-Akerlind & Eriksson 1993	✓	✓	✓	✓	✓	✓	✓
Maquirriain 2012	✓	✓	✓	✓	✓	✓	✓
Masood et al 2014	✓	✓	X	X	✓	X	X
McCrory et al. 1999	✓	✓	✓	✓	✓	✓	✓
Ohberg et al. 2001	✓	✓	✓	✓	✓	✓	✓
Ooi et al	✓	✓	✓	✓	✓	✓	✓
Silbernagel et al. 2006	✓	✓	✓	✓	✓	✓	✓

Wang et al. 2012	✓	✓	✓	X	✓	X	✓
Wang et al 2011	✓	✓	✓	X	✓	X	✓

3.4 Meta-analysis

Twelve of the 17 studies were deemed eligible for meta-analysis due to similarities in study characteristics (Khan *et al.* 1997, Cook *et al.* 2000, Cook *et al.* 2001, Fredberg and Bolvig 2002, Khan *et al.* 2003, Gisslén and Alfredson 2005, Malliaras *et al.* 2006, Gisslén *et al.* 2007, Jhingan *et al.* 2011, Giombini *et al.* 2013, Ooi *et al.* 2015, van Ark *et al.* 2015). The remaining five studies could not be included in the meta-analysis due to insufficient data provided on the number of tendons that became symptomatic at follow-up.

3.4.1 Does ultrasound predict LL tendinopathy (Achilles and patellar combined)

Tendon abnormalities on US are predictive of the development of future symptoms of Achilles or patellar tendinopathy (RR =4.97, 95% C.I: 3.20-7.73). In relation to the combined overall number of tendons that developed Achilles or patellar tendinopathy, 21% (49/229) of asymptomatic abnormal tendons developed symptoms versus 3% (19/635) of asymptomatic structurally normal tendons. In addition, observed I values of 14% indicated low levels of heterogeneity (Green 2011). These figures are displayed in figure 16 with representation of the publication bias represented by the funnel plot in figure 17.

3.4.2 Does ultrasound predict patellar tendinopathy?

Thirteen studies investigated the predictive role of US imaging in the development of future patellar tendinopathy. Nine of these studies were included in the meta-analysis (Khan *et al.* 1997, Cook *et al.* 2000, Cook *et al.* 2001, Fredberg and Bolvig 2002, Gisslén and Alfredson 2005, Malliaras *et al.* 2006, Gisslén *et al.* 2007, Giombini *et al.* 2013, van Ark *et al.* 2015). Patellar tendon abnormalities at baseline were found to increase the risk of development of future patellar tendinopathy (RR = 4.35, 95% CI: 2.62-7.23). In addition observed I values of 1% indicated low levels of heterogeneity (Green, 2011). These figures are displayed in figure 16 with representation of the publication bias represented by the funnel plot in figure 17.

The remaining four studies investigating the patellar tendon included in this review could not be included in the meta-analysis, and instead are reported descriptively (Fredberg *et al.* 2008a, Boesen *et al.* 2012, Comin *et al.* 2012, Visnes *et al.* 2015). Fredberg *et al.* (2008a) reported the RR for

developing patellar tendinopathy was 2.2 in those with structural abnormalities at baseline, however this did not reach statistical significance (95% C.I: 0.90-5.7; p >0.05). Visnes *et al.* (2015) reported that a baseline finding of a hypoechoic area increased the risk (Odds Ratio (OR) 3.3, 95% C.I: 1.10-9.2, p<0.05) of developing patellar tendinopathy, while Comin *et al.* (2012) also concluded there was a weak association between the presence of hypoechogenicity at baseline, and an increased incidence of patellar tendinopathy (OR 6.3, 95% C.I: 1.30-30.8, p<0.05). The remaining study by Boesen *et al.* (2012) investigated the predictive value of vascularity in the development of future patellar tendinopathy, and found that vascularity did not predict symptomatic outcome during an 8-month-long badminton season.

In relation to the overall number of events, 21% (33/159) of abnormal asymptomatic patellar tendons became symptomatic versus 4% (16/431) of structurally normal asymptomatic patellar tendons.

3.4.3 Does Ultrasound predict Achilles tendinopathy?

Nine studies investigated the predictive role of US imaging in the development of future AT. Five of these studies were included in a meta-analysis (Fredberg and Bolvig 2002, Khan *et al.* 2003, Jhingan *et al.* 2011, Giombini *et al.* 2013, Ooi *et al.* 2015). Achilles tendon abnormalities at baseline were associated with an increased risk of development of future AT (RR = 7.33, 95% C.I: 2.95-18.24). In addition observed I values of 27% again indicated low levels of heterogeneity (Green, 2011).

Figure 16: Risk ratio for predictive value of ultrasound imaging

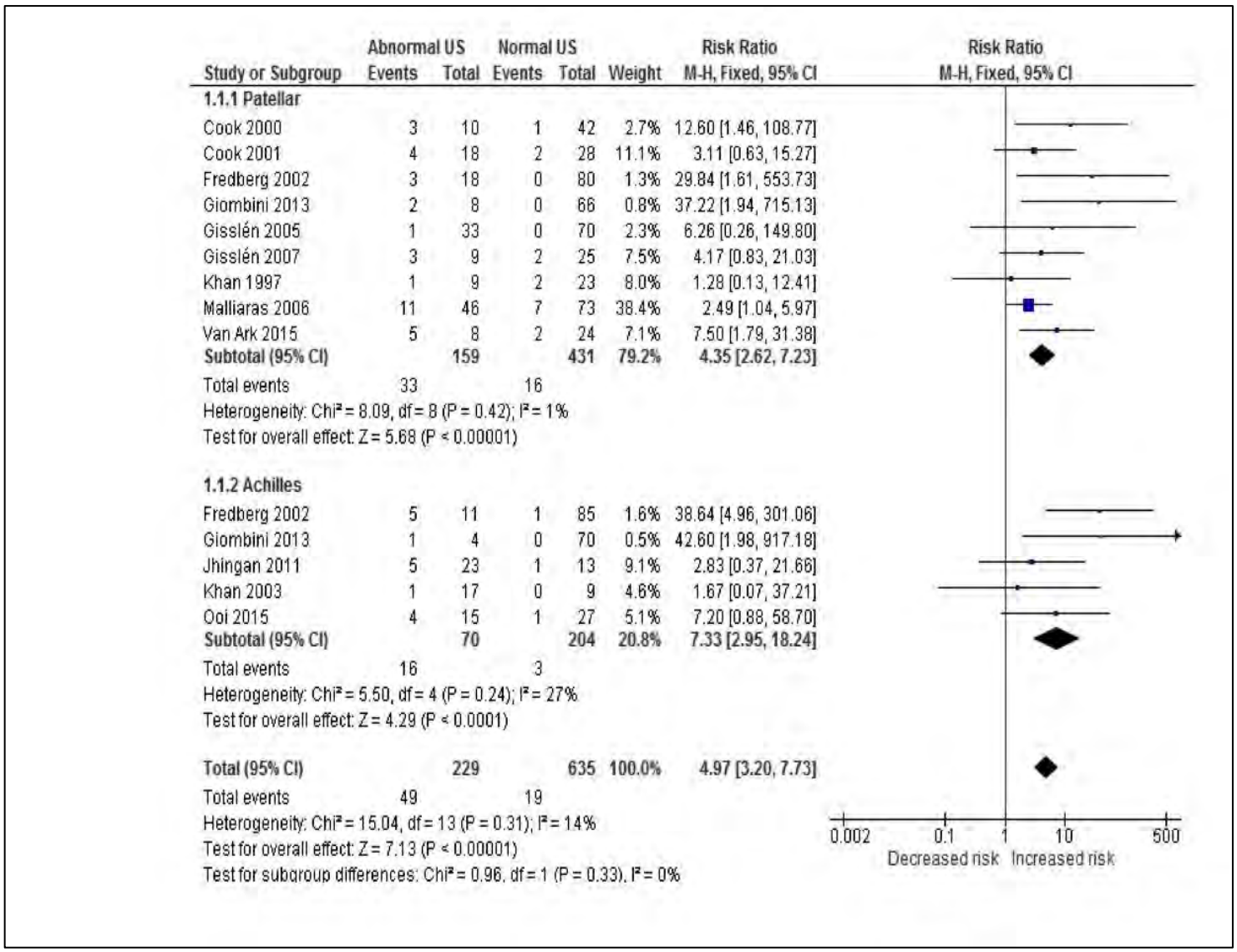
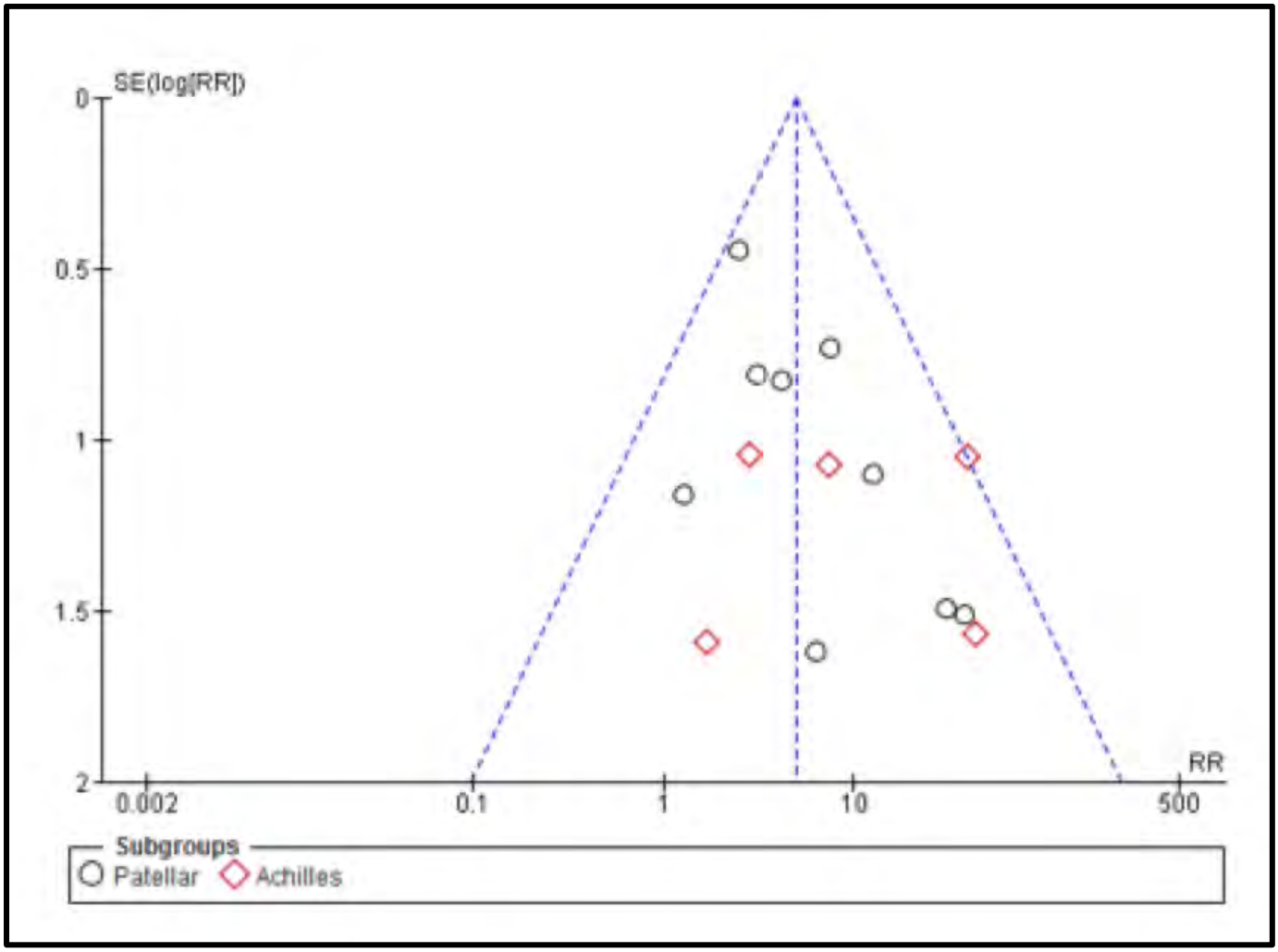


Figure 17: Study II Funnel plot analysis of study and publication bias



The remaining four Achilles tendon studies, (Fredberg *et al.* 2008a, Boesen *et al.* 2012, Comin *et al.* 2012, Hirschmüller *et al.* 2012) could not be included in the meta-analysis. Three of these four studies reported a similar relationship between Achilles tendon abnormalities at baseline and the development of future symptoms. A relationship between the presence of Achilles tendon abnormalities and the development of future Achilles tendinopathy was reported by both Comin *et al.* (2012) (OR =6.3, 95% C.I: 1.30-30.8, $p<0.05$) and Fredberg *et al.* (2008a) (RR of 2.8, 95% C.I: 1.60-4.9; $p <0.05$). Hirschmüller *et al.* (2012) found that the presence of neovascularisation was associated with a 7 fold (OR=6.9, 95% C.I: 2.60-18.8, $p <0.05$) increased risk of developing Achilles tendinopathy, while the predictive value of thickening was found to be just outside the values needed for statistical significance ($p >0.05$).

Finally, similar to the findings for the patellar tendinopathy, one study by Boesen *et al.* (2012) found that intratendinous flow did not predict the development of Achilles tendinopathy during an 8-month-long badminton season. In relation to the overall number of events, 23% (16/70) of abnormal asymptomatic tendons became symptomatic versus 2% (3/204) of structurally normal asymptomatic tendons.

Heterogeneity and publication bias:

The funnel plots provided in figure 17 indicates a symmetrical distribution of the intervention effect estimates from individual studies included in the review indicating no evidence of publication bias. In terms of heterogeneity of the included studies, statistical analysis revealed the percentage of total variation across studies was low with I^2 all below <30% (Higgins *et al.* 2003).

4.0 Discussion

4.1 Main findings

The results of this review demonstrated a consistent pattern across the included studies of an increased risk of developing Achilles and patellar tendinopathy if tendons displayed abnormalities on US at baseline. The meta-analysis pooled RR statistics estimated tendons with an abnormal US to have nearly a 5-fold increased risk of becoming symptomatic compared to tendons with a normal US.

4.2 The burden of tendinopathy

The prevalence of Achilles tendinopathy is as high as 30% in runners while patellar tendinopathy is common particularly in jumping sports (Ackermann and Renström 2012). Despite the relatively high prevalence of LL tendinopathy, particularly in sporting populations, rehabilitation continues to be lengthy, with mixed outcomes often reported (Sayana and Maffulli 2007, Jonsson *et al.* 2008a, Kongsgaard *et al.* 2009). Consequently this leads to frustration both from the athletes' and health practitioners' perspective. Furthermore, lengthy and sometimes unsuccessful rehabilitation in both amateur and professional sporting domains lead to an increased financial burden on individuals and sporting organisations.

4.3 The role of imaging in predicting tendinopathy: the case for

Given the substantial impact of Achilles and patellar tendinopathy, identification of "at risk" athletes is a priority to try and prevent the negative consequences of tendinopathy on sporting participation and quality of life. MRI and US technology are commonly used imaging modalities when visualising tendon dimensions (Brushoj *et al.* 2006). In particular US has gained increasing popularity amongst musculoskeletal practitioners, and recent technical advancements have made US more affordable and accessible, particularly in the area of sports medicine and tendon disorders (Bjordal *et al.* 2003). Results of this meta-analysis demonstrated a consistent pattern that structural abnormalities at baseline are associated with the development of future tendinopathy. Thus it is possible that structural changes in asymptomatic populations may represent markers of early pre-symptomatic pathology, which is later characterised by episodes of pain and/or reduced function. The strength and consistency of these findings have potentially important implications for the clinical management and prevention of patellar and Achilles tendon disorders. Visualising tendon abnormalities using US may identify potential at risk athletes and may allow appropriate intervention through the

implementation of preventative strategies, such as adapting training load (Hulin *et al.* 2015) or appropriate tendon loading programmes (Fredberg *et al.* 2008a). However evidence to support such strategies is lacking at this time with future studies warranted. Similar to results in this review, a meta-analysis by Steffens *et al.*(2014) demonstrated the presence of structural abnormalities, in particular the combined number of abnormalities, was moderately predictive of future symptoms of LBP using MRI. Furthermore, in other health conditions such as cardiovascular disease, structural pathology in the form of atherosclerosis has been shown to be a predictor in the aetiology of the disorder (Duncan *et al.* 2007).

4.4 The role of imaging in predicting tendinopathy: the case against

Intervening in all cases of structurally abnormal tendons identified using US imaging may not be warranted given the overall poor correlation between structure and pain in tendinopathy. Tendon structural abnormalities have been reported in a large percentage of asymptomatic individuals (Docking *et al.* 2015) with studies suggesting tendon abnormalities are present in many as 59% of asymptomatic populations, particularly increasing with age and sporting involvement. Structural abnormalities in asymptomatic populations are not limited to tendons, with a wide variety of studies demonstrating structural changes in asymptomatic sporting populations throughout the body. Papavasiliou *et al.* (2014) investigated structural changes of the hip in asymptomatic gymnasts using MRI, finding up to 63% of the sample group displayed signs of hip "impingement" on imaging. These findings are replicated through numerous regions of the body amongst sporting populations with structural abnormalities present in as many as 89% of asymptomatic athletes across the shoulder, knee, hip, and spine (Kong and Zelozny 2008, Reuter *et al.* 2008, Silvis *et al.* 2011, Soder *et al.* 2012).

The Cochrane guidelines for interpreting RR ratios advise that the clinical importance of a given RR ratio cannot be assessed without knowledge of the typical risk of events without treatment. This review indicates that the overall number of normal tendons that developed symptoms was small (19/635 = 3%), while the meta-analysis estimates the relative risk for an abnormal Achilles tendon is 7.33, 4.35 for abnormal patellar tendons, and 4.97 for both tendons combined. Consequently the actual risk of asymptomatic athletes with a structural abnormality in their tendon developing tendinopathy ranges from 13-22% (RR x percentage risk in a "normal" population) depending on the tendon in question.

The overall relative risk of 3% in "normal" tendons appears to be quiet low given the high

prevalence and incidence of tendinopathy outlined in the introduction chapter. However this discrepancy may be related to the population samples involved. The relative risk of 3% is based on a range of sports such as ballet, running, volleyball, fencing which may or may not have a high prevalence or incidence of tendinopathy when comparing to single cross sectional studies based on high risk populations e.g. AT prevalence in distance runners. Based on the studies included in the current review, tendon abnormalities may be present in 11-39% of patellar tendons and 5-61% of Achilles tendons depending on the study. Theoretically, a sample of 100 athletes may include as many as 61 Achilles abnormalities, while as many as 39 may have patellar abnormalities. Of these asymptomatic tendon abnormalities 13/61 of Achilles tendons may go on to develop symptoms (RR x percentage risk in a "normal" population equates to 21% risk), while 6/39 of patellar tendons may go on to develop symptoms (RR x percentage risk in a "normal" population equates to 15% risk). Consequently, although there is a clear statistical relationship between tendon abnormalities and development of future symptoms, the relationship is not a linear one given the high percentage of tendon abnormalities in asymptomatic athletes. One may therefore argue that routine imaging in athletic populations may be inappropriate, time consuming, and costly to perform in every athlete and tendon imaging may be combined with other risk factors.

There is also evidence to suggest that intervening with unnecessary imaging can actually result in adverse and harmful effects on patient's beliefs and behaviors (Deyo 2013). As one illustration, one study involving low risk patients with LBP demonstrated worse overall outcomes in relation to pain and overall health in those who underwent imaging compared to those who did not receive any imaging (Ash *et al.* 2008). Unfortunately there is no comparable research to date in relation to tendon disorders and making direct comparisons between LBP and tendon disorders should be done with caution. The growing popularity, and potential advantages, of modalities such as UTC or elastography offer the potential to better visualise tendon structure. However, with enhanced visualisation comes the need to weigh up potentially enhanced visualisation against the potential negative consequences of making an athlete feel their body is vulnerable based on what may be potentially normal physiological responses to the loading demands. Perhaps this indicates the fundamental role of clinicians' communication strategies when relaying imaging findings to athletic populations. This reflects the complex nature, and our limited understanding, of tendinopathy (Docking *et al.* 2015) .

4.5 Clinical implications: To image or not to image

While structural abnormalities are predictive of the development of future tendinopathy, how to interpret this relationship in the clinical setting is difficult given the high percentage of abnormalities in asymptomatic populations. Therefore, it may be the case that structural abnormalities should be considered as just one of several risk factors used to predict the development of tendinopathy as opposed to a sole predictor. Numerous other intrinsic and extrinsic risk factors have been identified for the development of tendinopathy. Training volume and frequency, (Janssen *et al.* 2014) higher impacts caused by faster training (Hein *et al.* 2014), as well as a change in surface density and shock absorption (Crossley *et al.* 2007) have all been proposed as extrinsic risk factors. In relation to intrinsic risk factors, altered foot function (Crossley *et al.* 2007), reduced ankle dorsiflexion (Malliaras *et al.* 2006), sex (Cook *et al.* 2000), diabetes (Ranger *et al.* 2015), adiposity (Gaida *et al.* 2009), muscle weakness (Mahieu *et al.* 2006), and genetic factors (September *et al.* 2007) have all been proposed. Unfortunately, the majority of studies investigating these factors have been cross-sectional, leading to an inability to clarify a direct cause and effect relationship. As a result, despite advancements in our understanding of LL tendinopathy, how these factors might combine to predict the development of tendinopathy remains unclear.

Given the high proportion of structural abnormalities in asymptomatic populations, one may argue that routine imaging may be costly and time consuming. However, given the financial burden and the potential career threatening impact of tendinopathy in athletic populations, (Reinking 2012) any modality which facilitates the identification of athletes at higher risk of injury may outweigh the financial or time consuming nature of routine imaging.

Increasing recognition of the limitations of the biomedical structure-pain model have led to calls to investigate sports injury and injury prevention from a biopsychosocial viewpoint where aspects other than local tissue damage, such as socio-demographic, psychological, lifestyle and social factors are considered (Santi and Pietrantoni 2013). Psychosocial issues such as sleep (Milewski *et al.* 2014), disturbed breaks, fatigue (Laux *et al.* 2015), and anxiety (Alizadeh *et al.* 2012), all have been demonstrated as risk factors for the development of injury in sporting populations. However, despite the importance of intrinsic psychosocial factors in the development of injury there has been a reluctance to combine these factors with other traditional biological risk factors such as biomechanics, strength, or training load in injury prediction studies. Prospective studies monitoring traditional risk factors such as tendon imaging in conjunction with some of the psychosocial factors

outlined above may provide some much needed clarity and knowledge in the difficult area of tendinopathy, or perhaps even sports injury prevention in general.

4.6 Limitations

One of the most frequently cited criticisms in relation to US imaging is in relation to its reliability. In comparison to MRI, US is perceived to have a higher risk of error or variance when evaluating tendon dimensions, due to factors such as operator inexperience, non-standardised imaging protocols and variations in transducer positioning (Gellhorn and Carlson 2013). Although there was a large variation in the operator experience in the included studies, a recent systematic review (Mc Auliffe *et al.* 2014) demonstrated that US displays good-excellent levels of inter- and intra-rater reliability in measuring tendon thickness and cross-sectional area. Furthermore Smith *et al.* (2011) concluded that US imaging was reliable in diagnosing partial and full thickness tears of the rotator cuff. Emerging imaging modalities such as UTC or sonoelastography are gaining popularity in the management of tendon disorders and may provide new insights into tendon structure by providing higher resolution and quantifying tendon structure more objectively compared to traditional US (Docking *et al.* 2015). Furthermore, while MRI is frequently used to visualise tendon structure, this review looked only at the role of US imaging. The variation in terms of the length of the follow up periods utilised in the respective studies is another potential limitation of the review. The length of the follow-up period ranged from five days to four years. A study included in the review by Van Ark et al (2015) prospectively followed volleyball players over the duration of a 5 day tournament. Although transient changes in structure may indeed be possible in such a time frame, a 5 day follow up period may be too short to capture the development of symptoms given tendon disorders are usually gradual in terms of onset and is therefore considered a limitation of the included study. Another potential limitation of this review centers on the variability of terminology used in defining what is accepted as a structurally 'abnormal' tendon when viewed using US. For example, Comin *et al.* (2012) used the presence (mild, moderate, severe) or absence of hypoechoicity to define abnormality. Three studies defined tendon thickening >1mm as abnormal (Fredberg and Bolvig 2002, Fredberg et al. 2008a, Jhingan et al. 2011). One study required thickening >3mm to classify a tendon as abnormal (Hirschmüller et al. 2012), while another study required thickening of >6mm to classify a tendon as abnormal (Khan et al. 2003). Thus the large variability on what constitutes an abnormal tendon across the included studies raises the possibility of over- or under-estimation of the relationship between structure and future symptoms. Another limitation is in relation to the population investigated in the included studies, the majority of the included studies investigated athletic

populations. Given the incidence of Achilles and patellar tendinopathy in non-athletic populations caution is advised when extrapolating findings to non-athletic populations.

A further potential issue is the lack of gold standard tests for diagnosing tendinopathy. There is a lack of consensus within the research and clinical field as regards the most appropriate clinical diagnostic test for tendinopathy. The large variation in diagnostic tests utilised in the studies in this review, and the lack of a widely accepted gold standard test, contributes to the difficulty in assessing the diagnostic value of US findings. Finally, a number of studies in the review investigated the predictive value of tendon vascularity using doppler US. Temperature is an important confounding factor when using doppler settings (Petrofsky 2012). However, none of the included studies utilising doppler US indicated controlling for this confounding factor. Nevertheless, only one study relied on vascularity as the only measure, such that this concern is unlikely to have affected the findings.

4.7 Conclusions

The results of this systematic review and meta-analysis found that tendon abnormalities are predictive of the development of future Achilles or patellar tendinopathy. This may have potentially important clinical implications in the prevention and management of tendon disorders. However, this association between tendon abnormalities and the development of future symptoms was only moderate. Furthermore, given the high percentage of tendon abnormalities in asymptomatic tendons, imaging findings should only be considered as one component of the clinical prediction of tendinopathy.

CHAPTER 3: Functional deficits in AT: are we addressing the observed deficits?

STUDY III: Altered strength profile in Achilles tendinopathy: A systematic review and meta-analysis.

ABSTRACT: Despite the relative strength of the Achilles musculotendinous unit, AT is one of the most common musculoskeletal complaints particularly in athletes involved in SSC activities such as running and jumping. It is postulated that persistent strength deficits secondary to the presence of AT may account for the inability to perform high intensity SSC tasks such as running and jumping and may also lead to continued recurrence of symptoms. To date there is little consensus on the presence of strength deficits in AT. Consequently uncertainty exists in relation to the appropriate methods of assessment, which may inform rehabilitation in clinical practice. To address this uncertainty, a systematic review and meta analysis was performed to evaluate and synthesise the literature on strength deficits observed in people with AT.

Two independent reviewers searched nine electronic databases. Studies compared strength measures (maximal strength, reactive strength, explosive strength and tendon mechanical properties) between participants with AT and healthy controls, or between injured and non-injured sides of a person with AT. Results were pooled using meta-analysis where possible. Twenty-three studies were deemed eligible.

Pooled meta-analysis for isokinetic dynamometry demonstrated significant reductions in maximal strength (Concentric Plantar Flexion (PF) Peak Torque (PT) slow (Hedges' g: 0.52), Concentric PF PT fast (Hedges' g: 0.61) and Eccentric PF PT slow (Hedges' g: 0.26). Similarly, pooled meta-analyses for tendon mechanical properties demonstrated increased strain (Hedges' g: -1.09) and reduced tendon stiffness (Hedges' g: 1.22). Furthermore, those studies not included in the meta-analysis revealed reduced maximal strength with effect sizes ranging from small to large (Hedges'g = 0.27- 1.88). Reactive strength, particularly hopping, was also reduced (Hedges' g: 0.32-2.61). Explosive strength, in terms of rate of force development, was reduced (Hedges' g: 0.31-1.73) while the findings for ground reaction force varied. Findings for leg stiffness were variable.

Deficits were identified across maximal, reactive and explosive strength as well as tendon mechanical properties, with similar effect sizes reported. These deficits may have a significant impact on an athlete's ability to perform SSC activities. The results of this study suggest that the assessment and rehabilitation of tendon function in AT should be tailored to individuals loading demands and capacity.

1.0 Introduction

The Achilles tendon is the largest and strongest tendon in the body (Bjur *et al.* 2005, O'Brien 2005). Despite the relative strength of the Achilles musculotendinous unit (Ash *et al.* 2008), AT is one of the most common musculoskeletal complaints particularly in athletes involved in SSC activities such as running and jumping, (Kvist 1994, Józsa and Kannus 1997, Alfredson and Lorentzon 2000) where the Achilles tendon is subjected to loads as high as 6–12 times body weight (Fukashiro *et al.* 1995, Komi 2000). The SSC is a natural type of muscle function in which the muscle is stretched immediately before being contracted (Komi 2008). SSC activities demand considerable strength of the PF muscle and MT unit.

It is postulated that persistent strength deficits secondary to the presence of AT may account for the inability to perform high intensity SSC tasks such as running and jumping and may also lead to continued recurrence of symptoms (Silbernagel *et al.* 2007c). The mechanism behind proposed strength deficits as a result of AT remains unclear, with various theories proposed. One theory suggests local changes in the MT unit such as local inflammatory changes, (Rio *et al.* 2014) altered tendon mechanical properties, (Child *et al.* 2010) disuse and atrophy (Edgerton *et al.* 2002), may lead to an inability to tolerate high loads or lead to strength deficits. Alternatively, changes in the central nervous system may lead to pain inhibition and altered motor output (Ngomo *et al.* 2015, Rio *et al.* 2015b).

Regardless of the mechanisms involved, strengthening interventions are among the most popular and effective methods of conservative treatment in AT (Malliaras *et al.* 2013). Despite their widespread implementation, individuals with AT continue to suffer from recurrence (Gajhede-Knudsen *et al.* 2013) or demonstrate ongoing strength deficits (Silbernagel *et al.* 2007c). One possible explanation may be the failure of traditional tendon rehabilitation to adequately address the entire strength spectrum (Haff and Nimphius 2012). Three main strength categories constitute the strength spectrum; maximal strength, explosive strength and reactive strength. Maximal strength targets maximal force development through high-load low-velocity movements, explosive strength involves the development of maximal power output and reactive strength targets MT stiffness and the SSC through plyometric exercises (Beattie *et al.* 2014). Rehabilitation to date has primarily favoured low-velocity maximal PF strengthening interventions, with little focus on explosive or reactive strength

rehabilitation. The bias towards these strengthening interventions may be influenced by the assessment techniques used to quantify muscle strength in AT. For example, maximal strength is often quantified using isokinetic dynamometry (Haglund-Åkerlind and Eriksson 1993, Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998b, Alfredson *et al.* 1998c, Alfredson *et al.* 1999a, McCrory *et al.* 1999, Ohberg *et al.* 2001). However, such measures may not provide sufficient assessment of strength capabilities during rapid SSC movements (Rio *et al.* 2015a). Moreover, single-joint isolated assessment bears little resemblance to running or jumping movements which require considerable amounts of explosive and reactive muscle strength (Mirkov 2013). In addition, despite the fundamental role of tendon mechanical properties and LL stiffness in the functioning of the SSC, little is known how they are affected in the presence of AT. To date there is little consensus on the presence of strength deficits in AT. Consequently uncertainty exists in relation to the appropriate methods of assessment, which may inform rehabilitation in clinical practice. Therefore, the aim of this review was to evaluate and summarise the evidence regarding the strength profile of people with AT.

2.0 Methods

2.1 Search strategy and study selection

The review was registered on the PROSPERO database (CRD42015025386) and has been reported in accordance with the PRISMA statement for systematic reviews (Moher *et al.* 2009). The following databases were searched; Academic Search Complete, AMED, Biomedical Reference Collection, MEDLINE, CINAHL, SPORTDiscus, Web Of Science, Embase and Scopus using an agreed set of keywords. Two reviewers (SMA & JH) conducted the database searches independently. The exact search strings utilised are shown in table 7.

Table 7: Study III Search Strategy

achill* OR calf* OR plantarflex* OR tendocalcan* OR heel* OR soleus OR gastroc* (Abstract) AND tendon* OR tendin* (Abstract) AND strength* OR weak* OR strong* OR power* OR force* OR isokinetic* OR muscle* OR concentric* OR eccentric* OR isometric* OR torque* OR jump* OR hop* OR muscular OR neuromuscular OR neuro-muscular OR function* OR land* OR drop* OR raise OR endurance OR fatigue* OR stiff* OR Hysteresis OR Rate of force development OR RFD OR Ground reaction force OR GRF OR stress OR Strain OR Kinetic* OR fluctuation* OR oscillation* OR vibration* (Abstract) AND non-injured OR noninjured OR asymptomatic OR contralat* OR opposite OR pain-free OR painfree OR control* OR healthy (Abstract)

2.2 Inclusion Criteria

- Studies comparing PF muscle strength between participants with AT and asymptomatic controls or between injured and non-injured sides within an AT population.
- Data could be cross-sectional, or baseline data from prospective or intervention studies.
- Studies must have been in English, and published in the last 20 years.
- Studies could include participants of any age.
- Studies could include both insertional and mid portion AT as well as including participants with associated co-morbidities.

2.3 Exclusion Criteria

- Studies that looked at kinematic variables only were excluded.
- Studies that investigated PF muscle strength in asymptomatic populations only were excluded.
- Studies those explicitly included participants with Achilles tendon rupture.
- Studies only reporting PF muscle strength post operatively or following a strengthening intervention.

2.4 Assessment of methodological quality

In the absence of an optimum methodological quality-rating tool for studies of this nature, the CASP checklist for case-control studies was used (Critical Appraisal Skills Programme (2014)) (Appendix 2). This checklist contains 12 questions; the first two questions are screening questions and were removed. The remaining ten questions explore the results of the study and its validity and applicability to the local population. Questions two, seven, eight and nine explore similar areas and were consequently merged for the purpose of this review. Therefore, the included studies were appraised using seven guiding questions. A list of criteria for each question was drawn up and agreed between the authors (Appendix 2). Two authors (SMA & MOK) scored the studies independently using the criteria outlined, with any disagreements in scoring mediated by a third reviewer (KOS). Providing an overall score for the CASP is not appropriate given the checklist was originally designed to be used as part of an educational tool as part of a workshop setting. Instead the strengths and weaknesses of each study were noted based on these specific criteria.

2.5 Data extraction

Data from the included studies were extracted by two reviewers (SMA and JH)including study design, patient demographics, strength variable investigated and study results. The term strength was used to describe any measure of (1) maximal strength that involves maximal force development through high-load, low-velocity movements (e.g. isokinetic/isometric/isoinertial); (2) reactive strength that involves MT SSC movements (e.g. hopping, jumps); (3) explosive strength (strength-speed and speed-strength) that focuses on producing force at high-velocity i.e. rate of force development (RFD) and ground reaction force (GRF); and (4) mechanical properties of the tendon that relate to strength (e.g. tendon stiffness, leg stiffness, tendon strain). Data on endurance or related concepts such as total work and average work were not extracted.

2.6 Statistical analysis

Studies were pooled for meta-analysis according to similarities in study characteristics and methodologies. Given the range of variables used in isokinetic dynamometry results were pooled according to the mode of contraction (Eccentric or Concentric) and speed of contraction (Fast >120 degrees/second or Slow ≤120 degrees/second). Effect sizes for the continuous strength variables

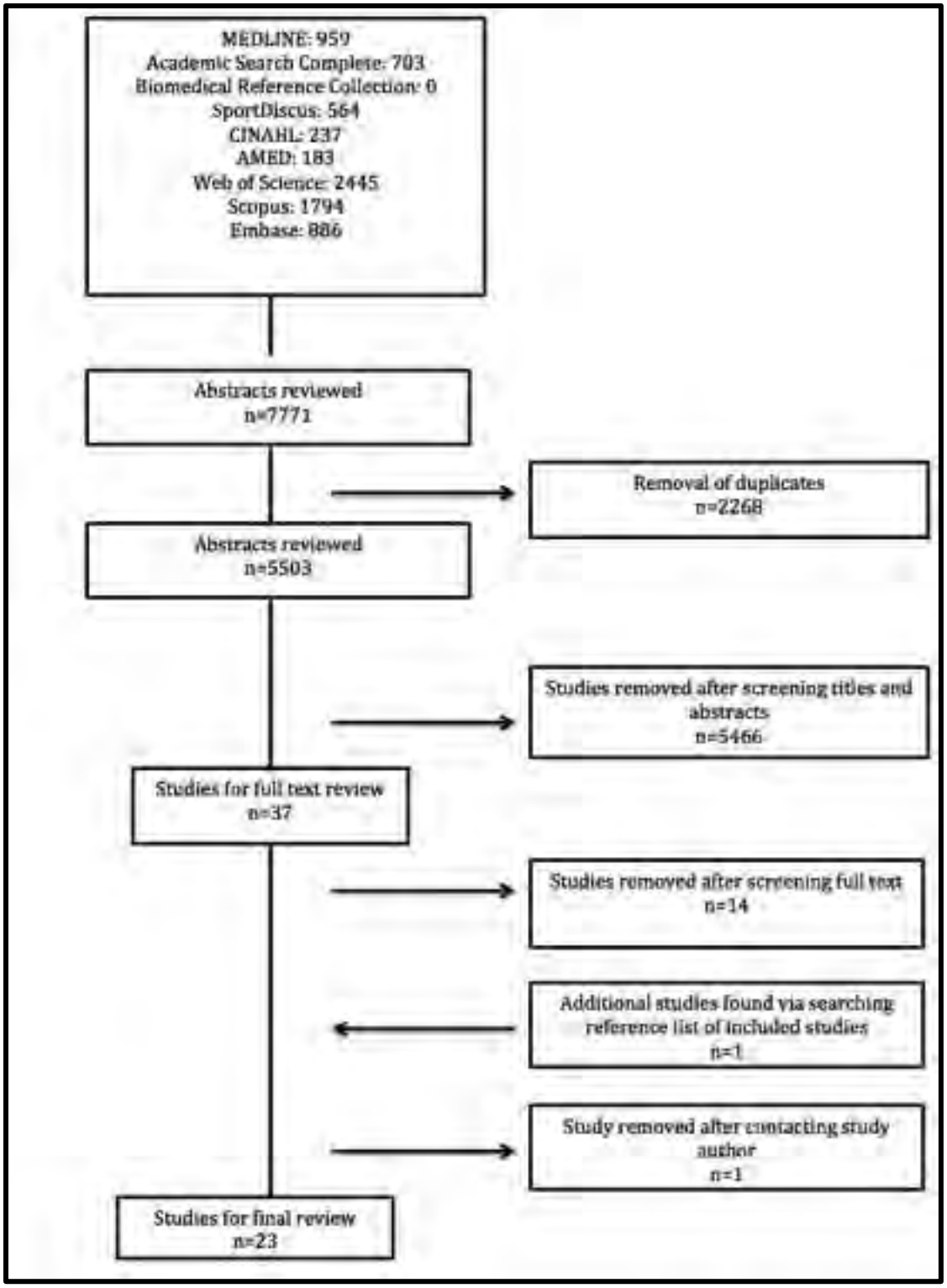
were calculated using Hedges'g with associated 95% confidence interval (Borenstein *et al.* 2009). In studies that compared participants' injured and non-injured sides, within-subject correlations were not reported and a conservative estimate of r=0.7 in the calculation of Hedges' g was used, as recommended by Rosenthal (1991). A positive effect size indicated the measure investigated was greater for the non-injured leg or asymptomatic group. The magnitude of Hedges' g effect size was interpreted using Cohen's convention as small (0.2), medium (0.5), and large (0.8) (Cohen 1988). Hedges' g statistics were also computed, where possible, for studies not included in the meta-analysis. Effect sizes were pooled using random-effects models. Random-effects models were selected a priori to account for expected differences in study characteristics. Heterogeneity between studies was assessed using the I^2 statistic, where an I^2 of 30% or less is considered to indicate low heterogeneity and the cut-offs of $I^2 > 30\%$ and $I^2 > 50\%$ are indicative of moderate and substantial heterogeneity respectively.(Higgins *et al.* 2003) I^2 describes the percentage of total variation across studies due to differences between studies rather than chance. Hedges' g effect sizes were computed manually using the formulae provided in Borenstein *et al.* (2009) and all meta-analysis were carried out using the Microsoft Excel spreadsheets of Neyeloff *et al.* (2012)

3.0 Results

3.1 Identification of studies

The electronic search yielded a total of 7771 potentially relevant studies. Thirty-seven full-text studies were identified as potentially relevant after screening the title and abstract of each study. Fourteen additional studies were removed after screening the full texts of the identified studies (Silbernagel *et al.* 2001, Paavola *et al.* 2002, Petersen *et al.* 2007, Donoghue *et al.* 2008, Baur 2011, Morrissey *et al.* 2011, Yu *et al.* 2013, Maquirriain and Kokalj 2014, Nawoczenski 2015, Ooi *et al.* 2015, Sobhani *et al.* 2015, Bah *et al.* 2016, Chimenti *et al.* 2016, Kuhman *et al.* 2016). Searching the reference lists of these full-text studies led to one additional study, (Haglund-Åkerlind and Eriksson 1993) while one further study was excluded following correspondence with the lead author due to both studies using the same data set (Silbernagel *et al.* 2007c). The final number of studies included for review was 23. The identification procedure is presented in Figure 18.

Figure 18: Study III Flowchart



3.2 Participants

A detailed description of the selected studies is outlined in table 8. The mean ages of the participants were similar between studies, ranging from 23 to 59 years. Twelve of the included studies included both male and female participants (Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998b, Alfredson *et al.* 1998c, Öhberg *et al.* 2001, Silbernagel *et al.* 2006, Azevedo *et al.* 2009, Firth *et al.* 2010, Wang *et al.* 2011, Maquirriain 2012, Chimenti *et al.* 2014, Debenham *et al.* 2014, Ooi *et al.* 2015), five studies included males only (Arya and Kulig 2010, Child *et al.* 2010, Grigg *et al.* 2012, Wang *et al.* 2012, Grigg *et al.* 2013), while six studies did not specify the participants' gender (Haglund-Åkerlind and Eriksson 1993, Baur *et al.* 2004, Masood *et al.* 2014, Chang and Kulig 2015). Twelve studies compared strength measures between symptomatic and asymptomatic participants (Haglund-Åkerlind and Eriksson 1993, McCrory *et al.* 1999, Azevedo *et al.* 2009, Arya and Kulig 2010, Child *et al.* 2010, Firth *et al.* 2010, Grigg *et al.* 2012, Grigg *et al.* 2013, Chimenti *et al.* 2014, Debenham *et al.* 2014, Masood *et al.* 2014, Ooi *et al.* 2015), eight studies compared strength values between injured and non-injured sides of the same participants (Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998b, Alfredson *et al.* 1998c, Öhberg *et al.* 2001, Wang *et al.* 2011, Maquirriain 2012, Wang *et al.* 2012), and two studies compared strength variables between both injured and non-injured sides of the same participant, as well as between the injured side and asymptomatic participants (Baur *et al.* 2004, Chang and Kulig 2015). The remaining study (Silbernagel *et al.* 2006) compared strength values between the most and least symptomatic sides. A detailed description of the included studies is outlined in table 8.

Table 8: Study III Characteristics and results of included studies

Study	Participant Characteristics	Groups Compared	Strength Variable Investigated	Test	Result	
					Injured	Non-injured/Asymp
Alfredson *et al.* 1998a	10 (5 male and 5 female) Mean ± SD Age 40.9 ± 10.9 years Height 172.7 ± 9.7 cm	Injured vs. non-injured side	**Maximal Strength:** Isokinetic dynamometry	Conc. PF peak torque (Doral *et al.*) - 90◦/sec - 225◦/sec Ecc. PF peak torque (Doral *et al.*) - 90◦/sec	 65.3 ± 17.5 32.3 ± 9.1 140.3 ± 44.2	 80.2 ± 21.6* 38.5 ± 12.0* 158.2 ± 40.4*
Alfredson *et al.* 1998b	30 (23 Male and 7 Female) <u>Calf muscle strengthening group</u> 15 (12 Male and 3 Female) Age 44.3 ± 7.0 Height 176.3 ±	Injured vs. non-injured side	**Maximal Strength:** Isokinetic dynamometry	Calf muscle strengthening group Conc. PF peak torque (Doral *et al.*) - 90◦/sec - 225◦/sec Ecc. PF peak torque (Doral *et al.*) -90◦/sec	 69.1 ± 24.6 30.9 ± 10.4	 78.6 ± 20.8* 37.7 ± 10.3*

	9.4 cm <u>Surgical group (pre-operatively)</u> 15 (11 Male and 4 Female) Surgical treatment Age 39.6 ± 7.9 Height 175.5 ± 9.4 cm			Surgical group (pre-operatively) Conc. PF peak torque (Doral *et al.*) - 90◦/sec - 225◦/sec Ecc. PF peak torque (Doral *et al.*) - 90◦/sec	152.0 ± 57.4 70.8 ± 24.4 34.4 ± 15.3 146.3 ± 56.3	171.1 ± 48.6* 87.1 ± 21.6* 45.1 ± 12.3* 169.4 ± 48.0*
Alfredson *et al.* 1998c	11 (7 Male and 4 Female) Age 40.9 ± 10.1 Height 172.5 ± 9.7 cm	Injured vs. non-injured side	**Maximal Strength:** Isokinetic dynamometry	Conc. PF peak torque (Doral *et al.*) - 90◦/sec - 225◦/sec Ecc. PF peak torque (Doral *et al.*) - 90◦/sec	64.7 ± 16.7 32.1 ± 8.7 135.8 ± 95.5	80.1 ± 20.5* 39.2 ± 11.6* 157.4 ± 38.4*

Alfredson *et al.*1996	13 (10 Male and 3 Female) Age 44.1 ± 8.5 Height 175.6 ± 8.8 cm	Injured vs. non-injured side	**Maximal Strength:** Isokinetic dynamometry	Conc. PF peak torque (Doral *et al.*) - 90◦/sec - 225◦/sec Ecc. PF peak torque (Doral *et al.*) - 90◦/sec	 76.3 ± 27.9 36.2 ± 17.4 155.9 ± 56.4	 86.1 ± 21.4 45.8 ± 14.0* 161.7 ± 53.0
Arya and Kulig. 2010	24 (24 Male) AT group (n=12) Age 47.33 ± 8.3 Height 173 ± 0.009 cm Asymptomatic group (n=12) Age 44.83 ± 7.2 Height 176 ± 0.009 cm	Injured side vs. asymptomatic controls	**Tendon mechanical properties:** Stiffness: dynamometry and ultrasound **Tendon mechanical properties:** Strain: dynamometry and ultrasound	Stiffness (N/mm): slope of the resultant tendon force and tendon elongation curve in the last 40% of the linear region Percentage strain: elongation during MVC/resting length of tendon.	300.37 +/- 37.60 5.14% +/- 0.57	375.25 +/- 61.88* 4.36% □+/- 0.31*

Azevedo *et al.* 2009	42 (32 Male and 10 Female) AT group (n=21) Age 41.8 ± 9.7 Height 177.8 ± 7.4 cm Asymptomatic group (n=21) Age 38.9 ± 10.1 Height 174.3 ± 8.0 cm	Injured side vs. asymptomatic controls	**Explosive strength:** Ground reaction Force **(**GRF): force plate	Vertical and horizontal forces normalized by body weight using a standardized force plate (960z).	Horizontal breaking force: HBF (BW) 0.20 ± 0.05 Horizontal Propulsive force: HPF (BW) 0.16 ± 0.04 Vertical impact force: VIF (BW) 1.45 ± 0.23 Vertical Loading Rate: VLR (BW/s) 44.79 ± 11.27 Vertical Propulsive Force: VPF (BW) Injured	HBF 0.21 ± 0.05 HPF 0.15 ± 0.02 VIF 1.34 ± 0.20 VLR 42.87 ± 9.31 VPF 2.19 ± 0.15

					2.18 ± 0.23	
Baur *et al.* 2004	22 (Male/Female: not specified) AT group (n=8) Asymptomatic group (n=14) Age 36 ± 9	Injured side vs. Non-injured side vs. asymptomatic controls	**Explosive strength:** GRF: ADAL -Ergometer	GRF: vertical impulse BW(%) and the passive and active peak in percent of body weight. In posterior-anterior direction, braking and pushing peak BW(%) and braking and pushing impulse BW(%) were calculated.	There was no difference in the quantities of ground reaction forces in vertical direction between Control and AT.	
Chang and Kulig. 2015	19 (Male/Female: not specified) AT (n=9) Age 46.8 ± 6.3	Injured side vs. Non-injured side vs. asymptomatic controls	**Tendon mechanical properties:** Stiffness: dynamometry and ultrasound	Stiffness: Tendon elongation during maximal voluntary. Plotting tendon elongation with tendon force. N/mm	Injured 164.82 ± 43.8	Non-injured 295.39 ± 60.37 Asymptomatic Right

	Asymptomatic group (n=10) Age 48.7 ± 4.4					358.24 ± 33.43 Asymptomatic Left 360.47 ± 31.24*
Child *et al.* 2010	29 (29 Male) AT group (n=14) Age 40 ± 8 Height 1.77 ± 0.06 m Asymptomatic group (n=15) Age 35 ± 9 Height 1.78 ± 0.05 m	Injured side vs. asymptomatic controls	**Maximal Strength:** Isometric: Customised calf raise apparatus with a calibrated load cell **Tendon mechanical properties:** Strain: maximal voluntary contraction using a seated calf raise apparatus.	Isometric Plantar flexion force (N) Percentage Strain = tendon elongation/tendon length (%)	826.5 ± 246.8 5.2% ± 2.6	755.6 ± 214.3 3.4% ± 1.8*
Chimenti *et al.* 2014	40 (18 Male and 22 Female)	Injured side vs. non-injured	**Tendon mechanical properties:** Strain:	Percentage Strain = tendon elongation/tendon length	Injured	Non-injured

	AT group (n=20) Age 58.6 ± 7.8 Asymptomatic group (n=20) Age 58.2 ± 8.5	side vs. asymptomatic controls	dynamometry and ultrasound **Tendon mechanical properties:** Stiffness: dynamometry and ultrasound **Maximal Strength:** Isokinetic dynamometry	(%) Stiffness: change in tendon force/change in tendon strain. (N/mm) Force: passive plantar flexion torque divided by the moment arm of the Achilles tendon (tendon force = passive torque of ankle/ moment arm of Achilles tendon). (N)	3.4% ± 1.5 Injured 33.5 ± 12.6 Injured 194.9 ± 56.8	2.8% ±1.0 Asymptomatic 2.2% ± 0.6* Non-inj 43.7 ± 19.1* Asymptomatic 46.4+/-20.0 Non-injured 206.6 ± 59.6 Asymptomatic 187.6 ± 48.3
Debenham *et al*. 2014	26 (14 Male and 12 Female) AT group (n=15)	Injured side vs. asymptomatic controls	**Tendon mechanical properties:** Leg Stiffness: custom built sledge-jump system	Leg Stiffness: calculated in (kNm) using a defined stiffness equation.	8.8 ± 1.3	4.5 ± 2.6 *

	Age 41.2 ± 12.7 Asymptomatic group (n=11) Age 23.2 ± 6.7					
Firth *et al.* 2010	55 (21 Male and 34 Female) AT group (n=29) Age 44.5 ± 10.7 Asymptomatic group (n=26) Age 27.6 ± 5.4	Injured side vs. asymptomatic controls	**Reactive strength:** Single leg hop test	Single leg hop: Hop distance (cm)	87 ± 29	130 ± 29*
Grigg *et al.* 2013	20 (20 Male) AT (n=11) Age 48.2 ± 8.5 Asymptomatic group (n=9)	Injured side vs. asymptomatic controls	**Explosive strength:** GRF: force plate technology.	GRF: recorded during an eccentric heel drop movement using force plate.	7Hz 0.032 8Hz 0.050 10Hz 0.024 11Hz 0.006	7Hz 0.022* 8Hz 0.035* 10Hz 0.067* 11Hz 0.024*

	Age 49.0 ± 10.3					
Grigg *et al.* 2012	20 (20 Male) AT group (n=11) Age 48.2 ± 8.5 Asymptomatic (n=9) Age 49.0 ± 10.3	Injured side vs. Non-injured side. Injured side vs. asymptomatic controls	**Tendon mechanical properties:** Strain: ultrasound imaging during a muscle contraction.	Percentage Strain: using an eccentric muscle contraction: Strain=(In(L/Lo)x100	Injured -8.3% ± (N/R)	Non-injured -13.0% ± (N/R) Asymptomatic 14.6%* ± (N/R)
Haglund-Akerlind *et al.* 1993	20 (Male/Female: not specified) AT group (n=10) Age 26.9 ± 5.7 Asymptomatic group (n=10) Age 24.0 ± 6.5	Injured side vs. asymptomatic controls	**Maximal Strength:** Isokinetic dynamometry	Conc. PF muscle torque (Doral *et al.*) at - 30◦/sec - 60◦/sec - 120◦/sec - 180◦/sec Ecc. PF muscle torque (Doral *et al.*) at - 30◦/sec - 60◦/sec - 120◦/sec - 180◦/sec	Conc. - 30◦/sec 92.2 ± 17.9 - 60◦/sec 78.0 ± 12.6 - 120◦/sec 58.1 ± 8.8 - 180◦/sec 43.5 ± 7.0 Eccentric - 30◦/sec 122.4 ± 20.1	 103.2 ± 8.5 84.2 ± 10.9 66.6 ± 12.8 50.2 ± 9.9 140.0 ± 15.2*

					- 60◦/sec 128.4 ± 22.7 - 120◦/sec 118.6 ± 19.1 - 180◦/sec 108.0 ± 16.9	149.4 ± 20.7* 138.2 ± 18.2* 127.7 ± 12.8*
Maquirriain 2012	51 (40 Male and 11 Female) AT group (n=51) Age 39.8 ± 11.8	Injured vs. non-injured side	**Reactive strength:** Single leg hop **Tendon mechanical properties:** Leg Stiffness: contact mat.	Single leg hop: Jump height (cm) Leg Stiffness: Modeling the vertical ground reaction force using a contact mat. (kN/m)	11.48 ± 6.34 14.07 (3.74)	13.60 ± 6.54 15.61 ± 4.01*
Masood *et al.* 2014	22 (Male/Female: not specified) AT group (n=11) Age 28 ± 4 years	Injured side vs. asymptomatic controls	**Maximal Strength:** Isometric: an in-house custom-built portable force transducer	MVC PF Force (N) 30%MVIC Isometric (N)	1101 ± 176 325 ± 46	1250 ± 192* 369 ± 52*

	Asymptomatic Group (n=11) Age 28 ± 4 years					
Mc Crory *et al.* 1999	89 (Male/Female: not specified) AT group (n= 31) Age 38.4 ± 1.8 years Asymptomatic Group (n=58) Age 34.5 ± 1.2 years	Injured side vs. asymptomatic controls	**Maximal Strength:** Isokinetic dynamometry **Explosive strength:** GRF: ATMI force platform and runway.	PF peak torque - 60◦/sec - 180◦/sec PF peak torque/BW (%) - 60◦/sec - 180◦/sec Flexion/extension work ratio (%) - 60◦/sec - 180◦/sec Vertical GRF	87.48 ± 4.59 29.47 ± 2.21 40.86 ± 1.64 13.83 ± 0.93 30.53 ± 1.17 42.26 ± 2.90 First NV Peak 1.81 ± 0.08	90.00 ± 3.28 33.84 ± 1.36* 43.11 ± 1.23* 16.37 ± 0.65 29.71 ± 0.91* 36.99 ± 1.36 First NV Peak 1.73 ± 0.04

				Anteroposterior GRF Mediolateral GRF	Max Propulsive Force -0.321 ± 0.011 Max Braking force (BW) 0.428± 0.021 Max Medial Force 0.109 ± 0.010 Max Lateral Force 0.129 ± 0.017	Max Propulsive Force -0.314 ± 0.006 Max Braking force (BW) 0.387 ± 0.009 Max Medial Force 0.110 ± 0.008 Max Lateral Force 0.093 ± 0.005
Ohberg *et al*. 2001	24 (17 Male and 7 Female) AT group (n= 24) Age 43.0 years	Injured vs. non-injured side	**Maximal Strength:** Isokinetic dynamometry	Conc. PF peak torque - 90◦/sec - 225◦/sec Ecc. PF peak torque - 90◦/sec	71.0 ± 25.7 32.5 ± 13.4 141.2 ± 57.2	83.8 ± 21.0* 41.9 ± 13.6* 155.9 ± 47.6*

Ooi *et al*. 2015	240 (Male/Female: not specified) AT group (n=120) (90 Male and 30 Female) Age 45.2 ± 13.1 Asymptomatic controls (n=120) Age 44.9 ± 13.6	Injured side vs. asymptomatic controls	**Tendon mechanical properties:** Strain: Axial strain Sonoelastography	Percentage strain: strain ratio (%)	1.70 ± 0.84	0.76 ± 0.30*
Silbernagel *et al.* 2006	42 (23 Male and 19 Female) AT group (n=42) Age 46 ± 8 Height 178 ± 8.5 cm Weight 80.7 ± 13.1 kg	Most symptomatic vs. least symptomatic sides	**Reactive strength:** Drop jump (CMJ) followed by a vertical jump on one leg. **Reactive strength:** Single leg Hop **Reactive strength:** Single leg Hop: LL symmetry index (LSI) the ratio of the	Jump height Single leg hop: height (cm) % Hopping Plyometric Quotient	11.3 +/- 4.8 2.8 ± 1.93 0.4 +/- .22	11.4 +/- 4.3 3.4 ± 1.43* 0.5* +/- .14

			involved limb score and the uninvolved limb score expressed in percent (involved/uninvolved · 100 = LSI). **Maximal Strength:** Isoinertial: concentric toe-raises, eccentric–concentric toe-raises.	Strength tests - Conc. power 23kg (W) - Conc. Power 33kg (W) - Eccentric-concentric power 23 kg (W) - Eccentric-concentric power 33 kg (W)	 213 ± 97 199 ± 122 284 ± 136 301 ± 147	 252 ± 137 275 ± 128* 348 ± 141* 384 ± 160*
Wang *et al*. 2012	17 (17 Male) AT group (n=17) Age 27.3 ± 2.0	Injured vs. non-injured side	**Reactive strength:** Single leg hop **Tendon mechanical**	Single leg hop: One-leg triple-jump hopping distance (cm) Stiffness: slope of the	285.8 ± 59.4	436.6 ± 46.1*

	Height 183.2 ± 7.1 cm Weight 75.9 ± 10.8 kg		**properties:** Stiffness: isokinetic dynamometry with ultrasound. **Explosive strength:** RFD: MVIC Using dynamometry	ascending phase of the muscle contraction between 50 and 100% of maximal force. (N/mm) RFD: Slope of the torque time curve normalised to peak torque of MVIC and determined at normalised force intervals.	105.9 ± 19.8 **Normalized 1/4 RFD (%MVIC/s)** Injured 1188.0 ± 523.8 **Normalized 1/2 RFD (%MVIC/s)** Injured 1511.3 ± 525.1	132.7 ± 26.3 Non-injured 1414.7 ± 509 Non-injured 1844.2 ± 479.2*

					Normalized 3/4 RFD (%MVIC/s) Injured 1127.3 ± 394.1 **Normalized 4/4 RFD (%MVIC/s)** Injured 404.2 ± 179.1	Non-injured 1330.8 ± 490.3* Non-injured 507.6 ± 253.0
Wang *et al*. 2011	14 (10 Male and 4 Female) AT group (n=14) Age 24.2 ± 1.7 Height 177.3 ± 8.4 cm Weight 69.2 ± 9.0	Injured vs. non-injured side	**Maximal Strength:** Isometric: customised force plate. **Explosive Strength:** RFD: customised force plate.	Maximal PF torque (Doral *et al.*) Normalised RFD: RFD relative to the maximal torque. (%MVC/s)	137.6 ± 16.2 **Normalized RFD** 0-30 ms 277.0 +/- 58.5	145.8 ± 17.1 **Normalized RFD** 0-30 ms 337.0 +/- 47.2*

				Absolute RFD: average slope of the torque-time curve over time spans relative to the onset of contraction. (Nm/s)	0-50 ms 294.7 +/- 65.1 0-100 ms 272.9 +/- 44.4 0-200 ms 190.9 +/- 61.2 0-30 ms 319.8 +/- 60.0 0-50 ms 338.8 +/- 78.7 0-100 ms 299.8 +/- 45.3 0-200 ms 215.7	0-50 ms 364.3 +/- 51.0* 0-100 ms 337.6 +/- 48.5* 0-200 ms 232.4 +/- 54.8 0-30 ms 361.5 +/- 0-50 ms 393.1 +/- 66.1 0-100 ms 357.9 +/- 38.5 0-200 ms 238.6

					+/- 37.7	+/- 26.4

*Non-Inj Asymp: Non-Injured or Asymptomatic; AT: Achilles Tendinopathy; *=(p>0.05); Conc: Concentric; Ecc: Eccentric; RFD: Rate of force development; GRF: Ground reaction force; MVIC: Maximal Voluntary Isometric Contraction; Nm/s: Newton meters per second; cm: centimeters; Nm: Newton meters; CMJ: Counter Movement Jump; PF: Plantar Flexor; B/W(%): Percentage Bodyweight; N: Newtons; N/R; Not reported: Hz: Hertz; ◦/sec: Degrees per second.*

3.3 Outcome Measures

Maximal strength values using isokinetic dynamometry were reported in eight of the included studies (Haglund-Åkerlind and Eriksson 1993, Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998b, Alfredson *et al.* 1998c, McCrory *et al.* 1999, Öhberg *et al.* 2001, Chimenti *et al.* 2014). There was a large variation in the speed and mode of contraction investigated. Seven studies investigated PF PT at slow speeds (≤120 degrees/second) (Haglund-Åkerlind and Eriksson 1993, Alfredson *et al.* 1998a, Alfredson *et al.* 1998b, Alfredson *et al.* 1998c, McCrory *et al.* 1999, Öhberg *et al.* 2001), while six studies investigated PF PT at fast speeds (>120 degrees/second) (Haglund-Åkerlind and Eriksson 1993, Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998b, Alfredson *et al.* 1998c, Öhberg *et al.* 2001). Maximal isometric strength measures were reported in three of the included studies using various force apparatus (Child *et al.* 2010, Wang *et al.* 2011, T. Masood *et al.* 2014), while one study (Silbernagel *et al.* 2006) investigated muscle strength using a range of isoinertial strength tests. Explosive strength variables were investigated in six studies, four investigated GRF (McCrory *et al.* 1999, Baur *et al.* 2004, Azevedo *et al.* 2009, Grigg *et al.* 2013), and two studies reported values for RFD (Wang *et al.* 2011, Wang *et al.* 2012), with a large variation across the studies in terms of the methodology utilised. In relation to reactive strength variables, four studies investigated various single leg hop or jumping variables (Silbernagel *et al.* 2006, Firth *et al.* 2010, Maquirriain 2012, Wang *et al.* 2012). In terms of tendon mechanical properties; four studies investigated tendon stiffness (Arya and Kulig 2010, Wang *et al.* 2012, Chimenti *et al.* 2014, Chang and Kulig 2015), and five studies investigated tendon strain (Arya and Kulig 2010, Child *et al.* 2010, Grigg *et al.* 2012, Chimenti *et al.* 2014, Ooi *et al.* 2015), while two of the included studies investigated leg stiffness (Maquirriain 2012, Debenham *et al.* 2014) (Table 8).

3.4 Methodological Study Quality

Results of the critical appraisal of included studies using the CASP checklist is shown in Table 9. One of the main weaknesses of the included studies involved the controlling of confounding factors. A common confounding factor was in relation to the measurement tools used. Studies investigating GRF or maximal PF force utilised varying methodological approaches and measurement protocols with little information in relation to the psychometric properties of these measurement tools. This finding limits the generalisibility of the findings. A further methodological issue related to the population characteristics potentially affecting the generalisabilty of results. Two of the included studies included male only participants (Arya and Kulig 2010, Wang *et al.* 2012), two of the included studies involved a control younger than the AT group (Firth *et al.* 2010, Debenham *et al.* 2014), while another study excluded participants older than 30 years. Finally one of the included studies involved insertional AT participants only in the population sample (Chimenti *et al.* 2014).

Table 9: Study III Quality assessment of included studies

Study	Acceptable Recruitment	Acceptable controls	Exposure accurately measured	Confounding factors	Do you believe the results	Applied to local population	Fit with other evidence
Alfredson *et al.* 1998a	✓	✓	✓	✓	✓	✓	✓
Alfredson *et al.* 1998b	✓	✓	✓	✓	✓	✓	✓
Alfredson *et al.* 1998c	✓	✓	✓	✓	✓	✓	✓
Alfredson *et al.*1996	✓	✓	✓	✓	✓	✓	✓
Arya and Kulig. 2010	✓	✓	✓	X	✓	X	✓
Azevedo *et al.* 2009	✓	✓	X	X	✓	X	✓
Baur et al. 2004	X	X	X	X	✓	X	✓
Chang and Kulig. 2015	✓	✓	✓	✓	✓	✓	✓
Child *et al*. 2010	✓	✓	✓	X	✓	X	✓
Chimenti *et al.* 2014	✓	✓	✓	X	✓	X	X
Debenham *et al.* 2014	✓	X	✓	X	✓	X	X
Firth et al. 2010	✓	X	✓	X	✓	X	✓
Grigg *et al.* 2013	✓	✓	X	✓	✓	X	✓

Grigg *et al.* 2012	✓	✓	✓	✓	✓	✓	✓
Haglund-Akerlind *et al.* 1993	✓	✓	✓	✓	✓	✓	✓
Maquirriain 2012	✓	✓	✓	✓	✓	✓	✓
Masood *et al.* 2014	✓	✓	X	X	✓	X	X
Mc Crory *et al.* 1999	✓	✓	✓	✓	✓	✓	✓
Ohberg *et al.* 2001	✓	✓	✓	✓	✓	✓	✓
Ooi *et al.* 2015	✓	✓	✓	✓	✓	✓	✓
Silbernagel *et al.* 2006	✓	✓	✓	✓	✓	✓	✓
Wang *et al.* 2012	✓	✓	✓	X	✓	X	✓
Wang *et al.* 2011	✓	✓	✓	X	✓	X	✓

3.5 Maximal strength profile

3.5.1 Isokinetic dynamometry

Meta-analysis: The meta-analysis revealed moderate effect sizes for concentric PF PT slow (Pooled Hedges' g: 0.52, 95% C.I: 0.34-0.69) (Figure 19) and concentric PF PT fast (Pooled Hedges' g: 0.61, 95% C.I: 0.43-0.80) (Figure 20), while small to moderate effect sizes were reported for Eccentric PF PT slow (Pooled Hedges' g: 0.26, 95% C.I: 0.10-0.414) (Figure 21). Mean differences for concentric PF PT slow ranged from 6-14.9N, Concentric PF PT fast ranged from 6.2-9.6 N, while the mean differences for eccentric PF PT slow ranged from 2.5-21.9 N. Data analysis revealed no evidence of systematic publication bias, which is highlighted in the respective funnel plots for each variable in figures 22-24.

Figure 19: Study III Effect size for concentric PF PT slow

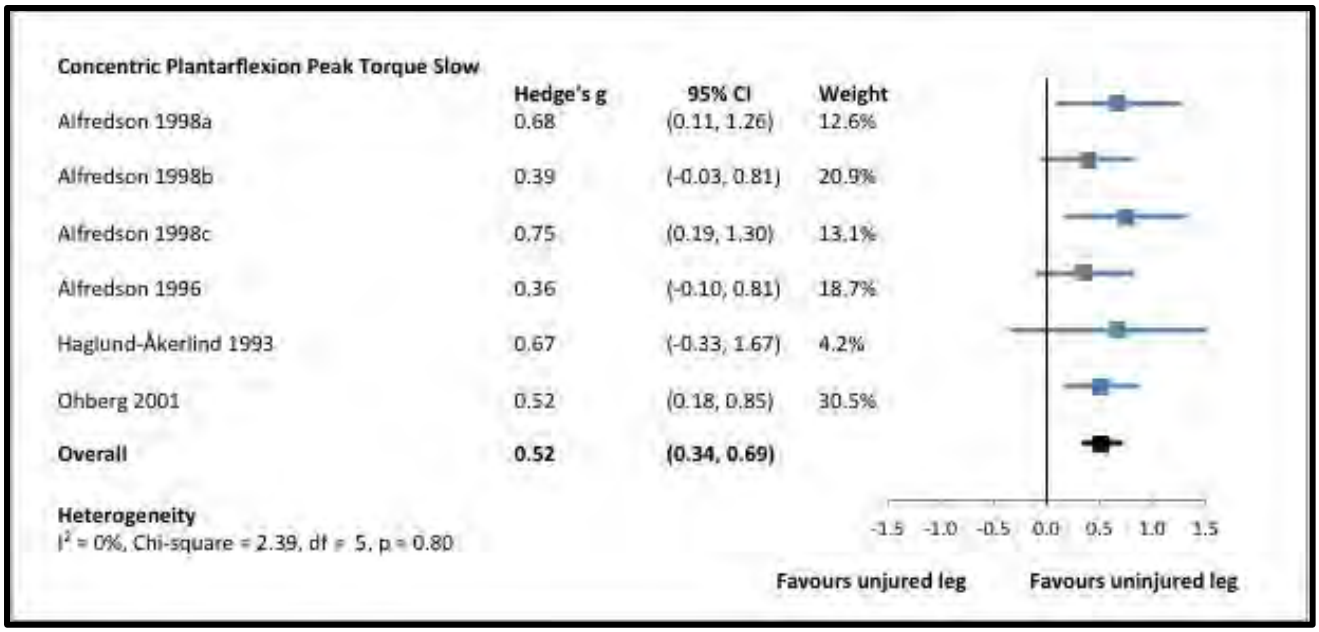


Figure 20: Study III Effect size for concentric PF PT fast

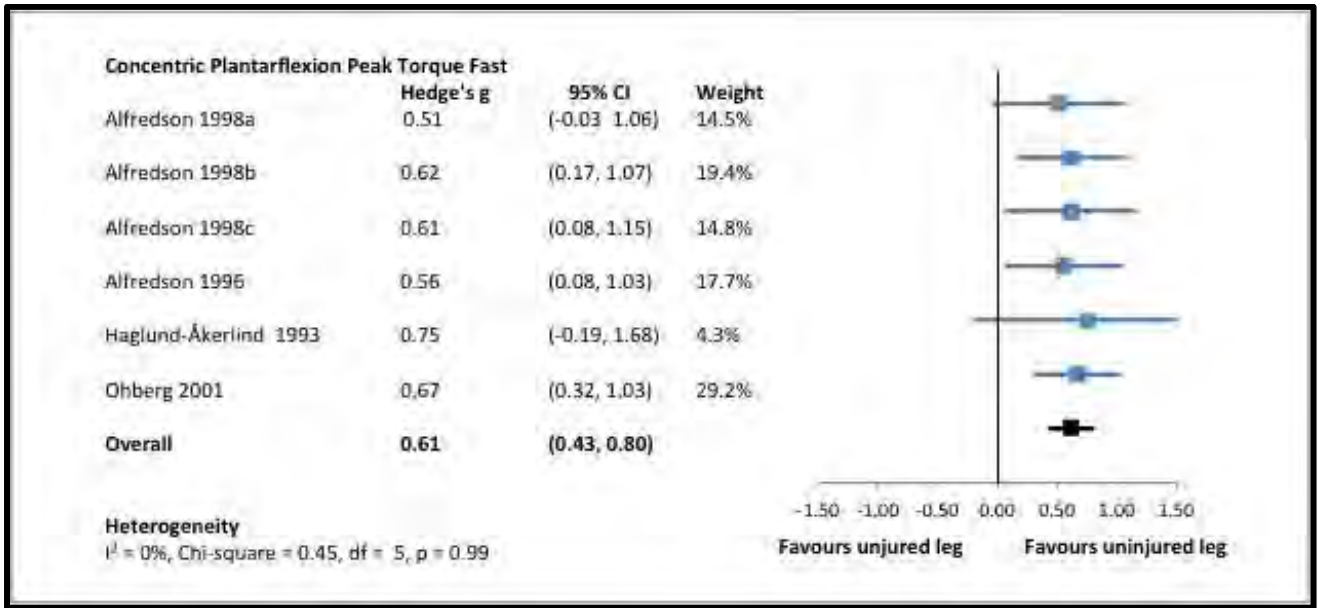


Figure 21: Study III Effect size for eccentric PF PT slow

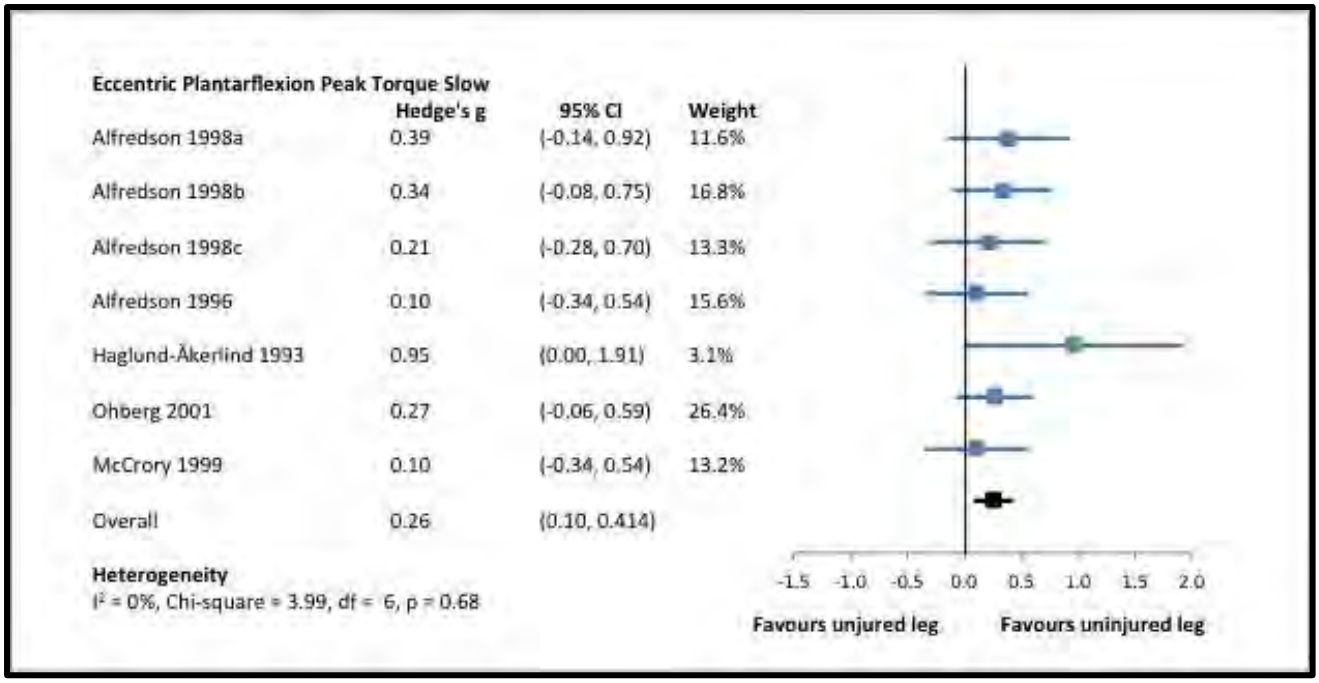


Figure 22: Study III Funnel Plot Concentric PF PT Slow

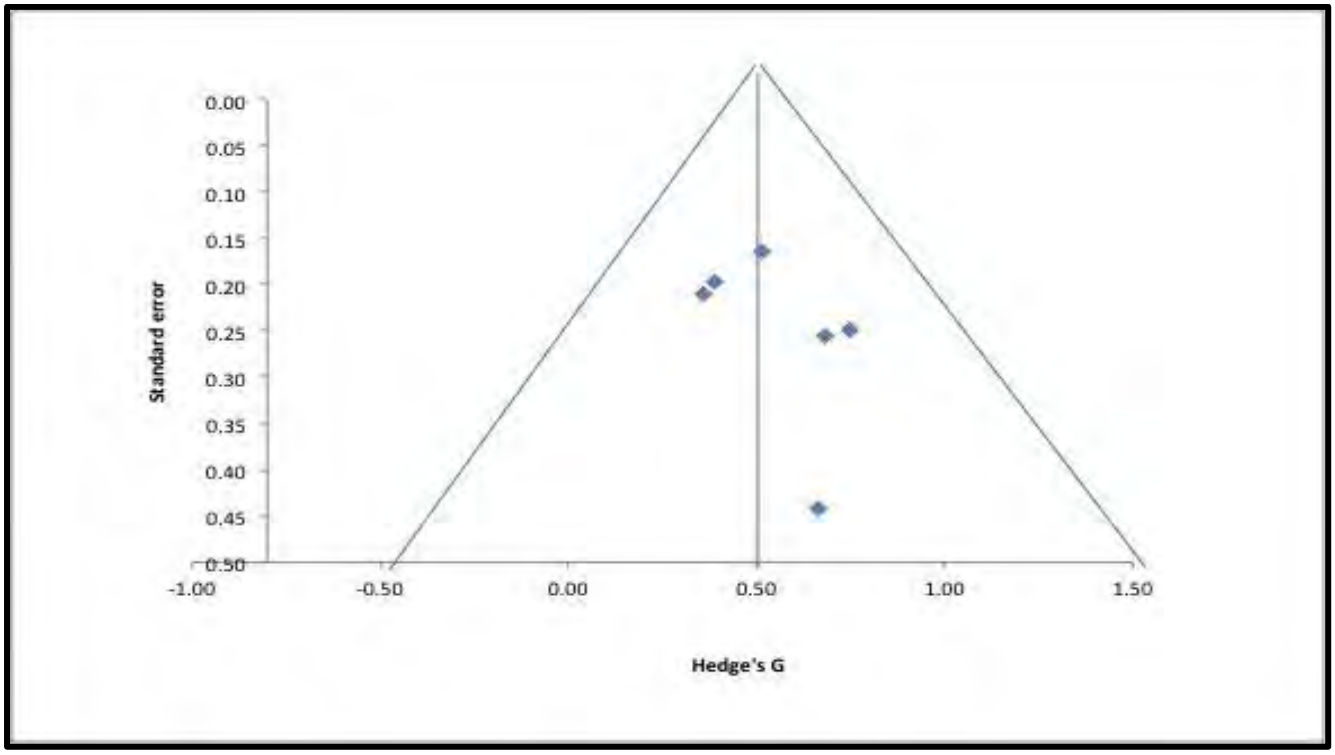


Figure 23: Study III Funnel Plot Concentric PF PT Fast

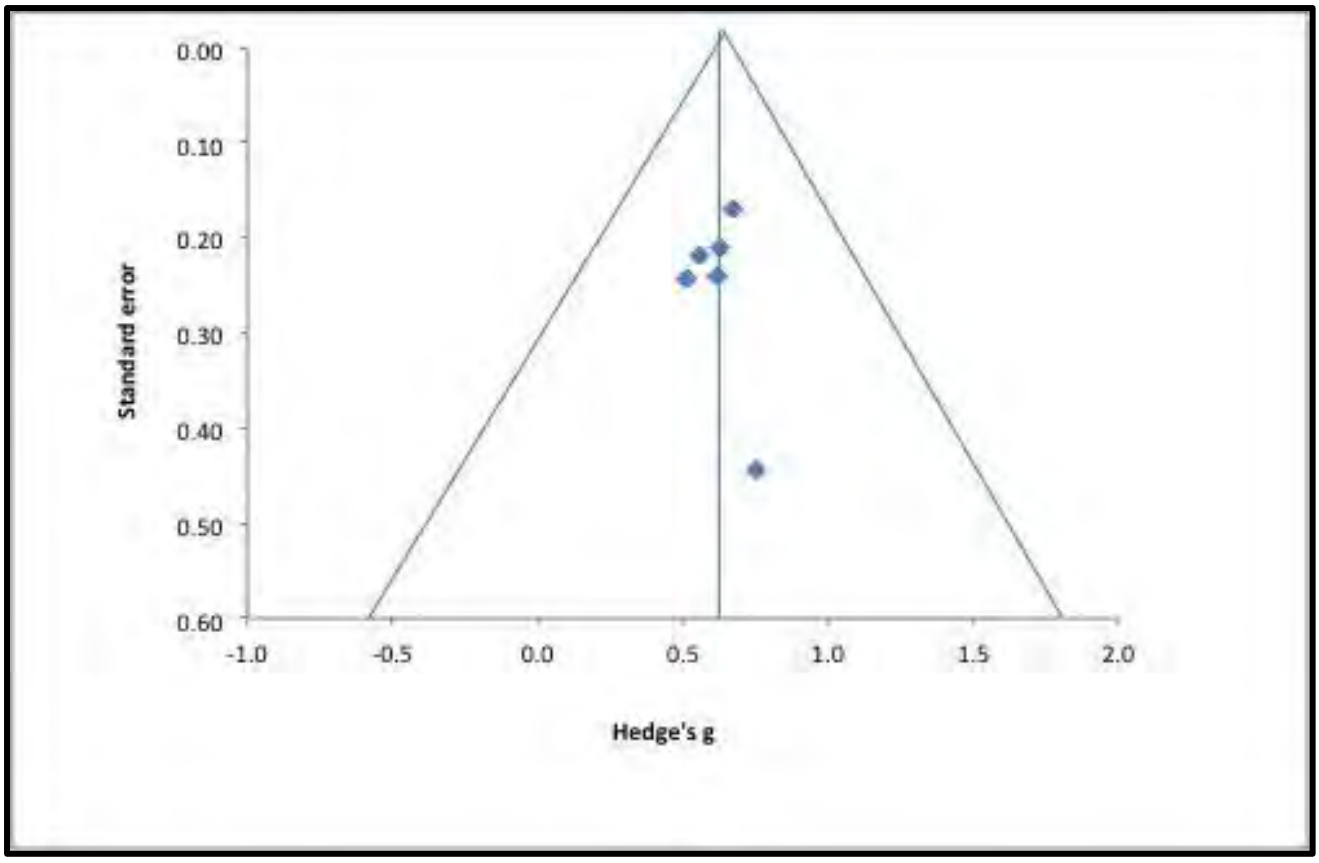
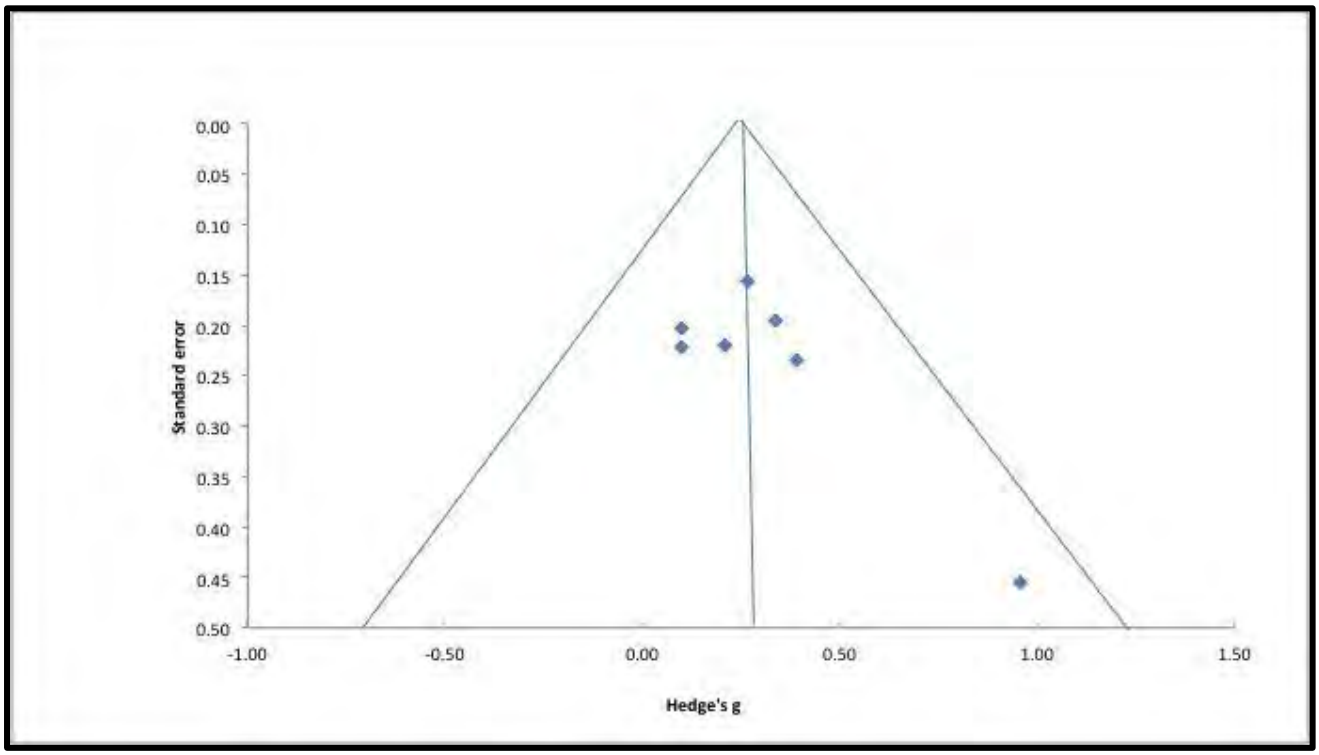


Figure 24: Study III Funnel Plot Eccentric PF PT Slow



Descriptive statistics: Large effect sizes were reported for eccentric PF PT fast (Hedges' g: 1.26, 95% C.I: 0.27-2.25), moderate effect sizes for eccentric PF PT as a percentage of bodyweight (B/W%) at 180 degrees/second (Hedges' g: 0.56, 95% C.I: 0.06-0.95), and small effect sizes for eccentric PF PT percentage bodyweight (B/W%) at 60 degrees/second (Hedges' g: 0.24, 95% C.I: 0.20-0.68) (Table 10).

3.5.2 Isometric strength

Descriptive statistics: Two studies reported small to moderate effect sizes indicating reduced isometric PF strength in those with AT (Hedges' g: 0.46-0.78) (Wang *et al.* 2011, Masood *et al.* 2014). In contrast Child *et al.* (2010) reported larger isometric strength in those with AT compared to controls (Hedges' g: -3.0, 95% C.I: -1.04 -0.54) (Table 10).

3.5.3 Isoinertial strength

Descriptive statistics: Silbernagel *et al.* (2006) investigated PF strength using weighted eccentric–concentric toe-raises and concentric toe-raise tests. Results of this study demonstrated significant reductions in PF strength in the most symptomatic side compared to the least symptomatic side (Hedges' g: 0.30-0.60) (Table 10).

3.6 Explosive strength profile

3.6.1 Ground reaction force (GRF)

Descriptive statistics: Studies reported inconsistent results of both increased and decreased GRF in those with AT (Hedges' g: -3.31-0.86) (Azevedo *et al.* 2009, McCrory *et al.* 1999) (Table 10).

3.6.2 Rate of force development (RFD)

Descriptive statistics: Results reported small-large effect sizes indicating reduced RFD in those with AT (Hedges' g: 0.31-1.73) (Wang *et al.* 2012, Wang *et al.* 2011) (Table 10).

3.7 Reactive strength profile

Due to the heterogeneity of tests used, it was not possible to pool any of these values for inclusion in a meta-analysis.

3.7.1 Hopping

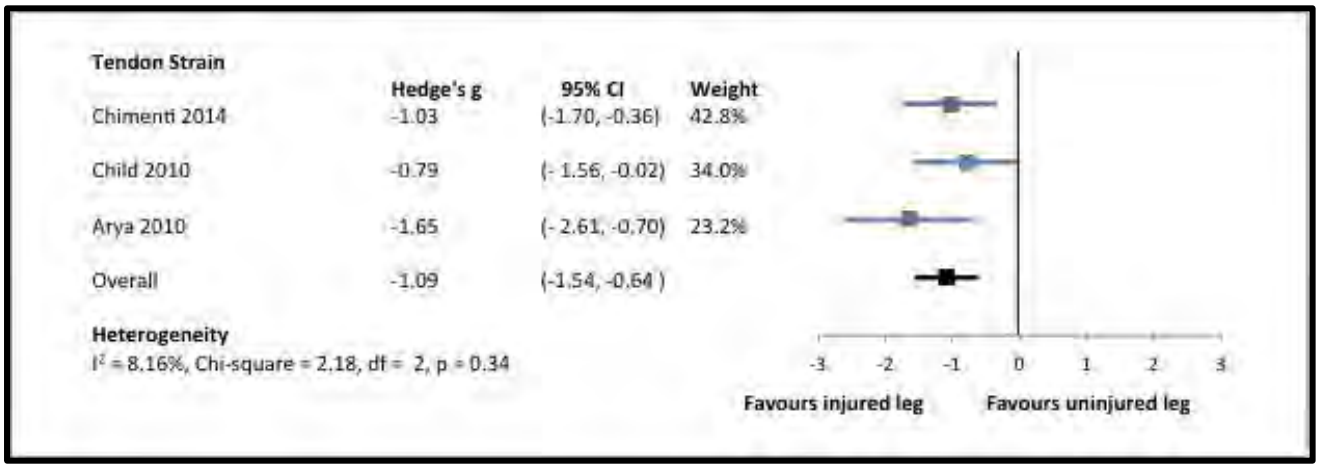
Descriptive statistics: Reactive strength was reported in four studies in the form of various hop tests (Silbernagel *et al.* 2006, Firth *et al.* 2010, Maquirriain 2012, Wang *et al.* 2012). Small to large effect sizes were reported for reduced hop performance in those with AT (Hedges' g: 0.32-2.61) (Table 10) (Silbernagel *et al.* 2006, Firth *et al.* 2010, Maquirriain 2012, Wang *et al.* 2012).

3.8 Tendon mechanical profile

3.8.1 Strain

Meta-analysis: The meta-analysis revealed large effect sizes, indicating increased tendon strain in those with AT compared to the non-injured side or asymptomatic controls (Pooled Hedges' g: -1.09, 95% C.I: 0.64-1.54) (Figure 25).

Figure 25: Study III Effect size for tendon strain

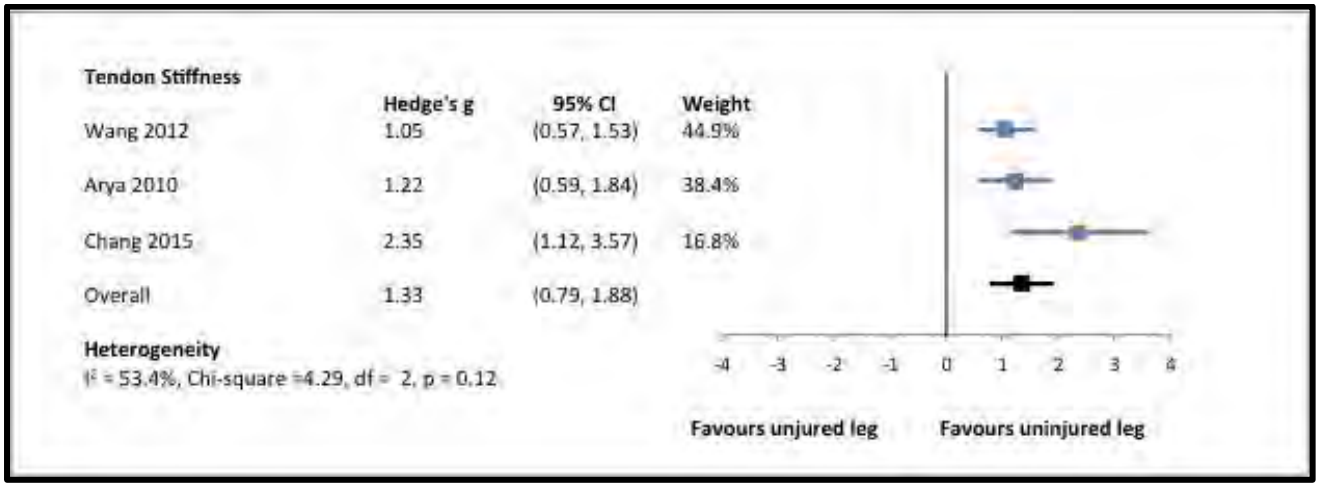


Descriptive statistics: Two additional studies investigated strain values but due to heterogeneity they could not be included in the meta-analysis. Similar to the results of the meta-analysis, Ooi *et al.* (2015) reported significantly higher strain in participants with AT compared to asymptomatic controls (-1.49, 95% C.I: -1.77-1.20). In contrast Grigg *et al.* (2012) reported lower strain in those participants with AT compared to asymptomatic controls and the asymptomatic side during an eccentric heel drop exercise (P<0.05) (Table 10).

3.8.2 Stiffness

Meta-analysis: The meta-analysis revealed large effect sizes indicating decreased tendon stiffness in those with AT compared to the non-injured side or asymptomatic controls (Pooled Hedges' g: 1.22, 95% C.I: 0.89-1.55) (Figure 26).

Figure 26: Study III Effect size for tendon stiffness



Descriptive statistics:

Tendon Stiffness: One additional study could not be pooled for meta-analysis (Chimenti *et al.* 2014) Similar reductions in tendon stiffness were reported in the symptomatic side compared to the non-injured side or asymptomatic participants (0.56, 95% C.I: 0.18-0.93) (Table 10).

Leg stiffness: (Debenham *et al.* 2014) reported higher levels of leg stiffness in those with AT (-2.14, 95% C.I: -3.14-1.13) compared to asymptomatic controls, while (Maquirriain 2012) reported reduced leg stiffness compared to non-injured side (0.39, 95% C.I: 0.17-0.61) (Table 10).

Table 10: Study III Effect sizes on studies not included in the meta-analysis

Study	Measure	Mean difference (MD)	Hedges' g (95% CI)
Maximal Strength Profile			
Isokinetic Dynamometry			
Haglund-Åkerlind and Eriksson (1993)	Eccentric PF peak torque - 180◦/sec	19.7	1.26 (0.27-2.25)
Mc Crory *et al.* (1999)	Eccentric PF peak torque/BW (%) - 180◦/sec	-2.54	0.50 (0.06-0.95)
Mc Crory *et al.* (1999)	Eccentric PF peak torque/BW (%) - 60◦/sec	-2.25	0.24 (-0.20-0.68)
Isometric Strength			
Masood *et al.* (2014)	PF Force (N)	149	0.78 (-0.11-1.67)
Wang *et al.* (2011)	PF Torque (N)	8.2	0.46 (0.02-0.91)
Child *et al.* (2010)	PF Force (N)	-70.9	-0.30 (-1.04-0.45)
Isoinertial strength			
Silbernagel *et al.* (2006)	Concentric Power at 23kg (W)	39	0.30 (0.06-0.55)
	Concentric Power at 33kg (W)	76	0.60 (0.34-0.85)

	Eccentric Power at 23kg (W)	64	0.45 (0.20-0.70)
	Eccentric Power at 33kg (W)	83	0.53 (0.27-0.78)
Reactive Strength Profile			
Hopping			
Firth *et al.* (2010)	Single leg hop distance (cm)	43	1.46 (0.86-2.06)
Wang *et al.* (2012)	Single leg triple hop distance (cm)	150.8	2.61 (1.79-3.44)
Silbernagel *et al.* (2006)	Hop height: repeated single leg hop (cm) using a contact mat Hopping quotient: flight time/contact time during a single leg hop using a contact mat	0.6 0.1	0.33 (0.09-0.57) 0.48 (0.23-0.73)
Maquirriain *et al.* (2012)	Maximal hop height during single leg hop (cm)	2.12	0.32 (0.10-0.54)
Explosive Strength Profile			
GRF			
Azevedo *et al.* (2009)	Horizontal Braking force	0.01	0.20 (-0.42-0.81)
	Horizontal Propulsive Force	-0.01	-0.31 (-0.93-0.31)
	Vertical Impact Force	-0.11	-0.50 (-1.12-0.12)
	Vertical Loading Rate	-1.92	-0.18 (-0.80-0.43)
	Vertical Propulsive Force	0.01	0.05 (-0.56-0.66)
McCrory *et al.* (1999)	First Normalised Vertical Peak	-0.08	-1.39 (-1.87- -0.91)

	Maximal Propulsive Force	0.007	0.86 (0.40-1.32)
	Maximal Braking Force	-0.041	-2.84 (-3.45- -2.23)
	Maximal Medial Force	0.001	0.11 (-0.33-0.55)
	Maximal Lateral Force	-0.036	-3.31 (-3.97--2.65)
Normalized RFD			
Wang *et al.* (2012)	Normalized 1/4	226.7	0.42 (0.02-0.82)
	Normalized 1/2	332.9	0.63 (0.21-1.05)
	Normalized 3/4	203.5	0.43 (0.03-0.82)
	Normalized 4/4	103.4	0.42 (0.02-0.82)
Wang *et al.* (2011)	0-30ms	100	1.73 (1.04-2.42)
	0-50ms	69.6	1.09 (0.54-1.63)
	0-100ms	64.7	1.31 (0.72-1.90)
	0-200ms	41.5	0.67 (0.20-1.14)
Absolute RFD			
Wang et al. (2011)	0-30ms	41.7	0.60 (0.14-1.06)
	0-50ms	54.3	0.69 (0.22-1.17)
	0-100ms	58.1	1.29 (0.70-0.70)
	0-200ms	22.9	0.62 (0.16-1.09)
Tendon Mechanical profile			
Strain			
Ooi *et al.* (2015)	% Strain using sonoelastography	0.94	-1.49 (-1.77—1.20)
Tendon Stiffness			

Chimenti *et al.* (2014)	Isokinetics and dynamometry (N/mm)	-10.2	0.56 (0.18-0.93)
Leg Stiffness			
Maquirriain *et al.* (2012)	Modelling Vertical GRF using a force plate: (kN/m)	-1.58	0.39 (0.17-0.61)
Debenham *et al.* (2014)	Custom built sledge system: (kN/m)	4.3	-2.14 (-3.14—1.13)

4.0 Discussion

The results of this review consistently demonstrated alterations in the strength profile of participants with AT compared to the non-injured side or asymptomatic controls. Deficits in **maximal strength** were consistently reported using a diverse range of maximal strength methods with isokinetic dynamometry being the most common method used to quantify deficits. The observed deficits in strength are consistent with deficits reported in other peripheral musculoskeletal disorders including hamstring (Maniar *et al.* 2016) and anterior cruciate ligament (ACL) injuries (Thomas *et al.* 2013).

Reactive and explosive strength variables (hopping and RFD) were generally reduced among those with AT, with similar reported deficits following ankle (Caffrey *et al.* 2009) and ACL injury (Augustsson *et al.* 2004, Angelozzi *et al.* 2012). However, GRF was not consistently reduced in AT.

In terms of **tendon mechanical properties,** this review also demonstrated alterations in those with AT with decreased tendon stiffness and a concurrent increase in tendon strain evident. The inverse relationship between these variables may be attributed to SSC mechanics. Tendon stiffness plays an important role in the functioning of the SSC by acting as an energy storage and release mechanism improving economy and performance (Butler *et al.* 2003). Consequently, reduced stiffness in the tendon may lead to reduced energy storage capacity and increased tendon strain (Muraoka *et al.* 2005). Finally, studies investigating **leg stiffness** in AT reported mixed results with reports of both increased and decreased leg stiffness in AT using varying methodologies.

4.1 Clinical implications for assessment

This review indicates that strength is reduced in people with AT and that isokinetic dynamometry and other custom-built force transducers demonstrate a sufficient ability to detect deficits. While isokinetic dynamometry was most commonly used, this type of assessment is not without its limitations, most notably in terms of costs, training requirements, familiarisation and functional specificity (Brown and Weir 2001, Mirkov 2013). In relation to assessment of isometric strength, one of the most commonly cited criticisms of this method is the dependence on the level of familiarisation, type of instruction

given and being specific to the point(s) in the range of motion at which the isometric contraction occurred (Mirkov 2013, Brown and Weir 2001). The size of the deficit in strength does not appear to vary dramatically according to the speed or mode of contraction. This may suggest that any affordable, reliable method of measuring maximal strength may be acceptable.

In terms of reactive strength, impaired hopping ability was consistently demonstrated in this review suggesting it may be a cheap, clinically useful tool in the assessment of reactive strength in AT (Swearingen *et al.* 2011). While only a small number of studies examined hopping, it is worth noting that the largest effect size among hopping tasks was yielded for a triple hop task (Wang *et al.* 2012). The triple hop is often cited as a reliable method of assessing muscular strength (Hamilton *et al.* 2008) which we hypothesise may provide a more useful assessment of SSC profile by reflecting a fast SSC movement. Schmidtbleicher, (1992) has suggested that the SSC can be classified as either slow or fast. The fast SSC is characterised by short contraction times and small angular displacements of the LL (e.g. depth jumps). On the other hand, slow SSC involve longer contraction times, larger angular displacements and is observed in maximal effort vertical jumps (e.g. box jumps). Unfortunately there is a scarcity of studies investigating either fast or slow SSC variables in people with AT despite their relative importance to the functioning of the SSC. One potential variable that may be used in future research in quantifying reactive strength profile in AT is the reactive strength index (RSI). The RSI has been described as an individual's ability to change quickly from an eccentric to concentric contraction and can be considered as a measure of ''explosiveness''(Young 1995). The future investigation of RSI among people with AT may offer more relevant neuromuscular insights into a participant's fast SSC function. Furthermore, the large contribution of the whole kinetic chain to hopping tasks makes it impossible to infer that deficits are related to one particular region of the LL such as the PF muscle group alone.

The confounding contribution of other parts of the LL may also explain why some explosive strength measures (GRF) demonstrated mixed results in people with AT. In addition, there is large variation in methodology in how GRF is quantified (e.g. measures of direction, sample speeds, mode of contraction) (Maffiuletti *et al.* 2016) perhaps limiting its clinical applicability. In summary, while RFD appears useful in identifying explosive strength

deficits, reactive strength measures such as hopping tests appear to be the most appropriate outcome measure in terms of clinical applicability and ease of use.

Tendon stiffness and strain also demonstrated large effect sizes in this review. Elastic or mechanical properties such as stiffness and strain play an important role in the storage and release of energy during SSC tasks (Muraoka *et al.* 2005). In addition, the literature suggests that these variables correlate closely with traditional maximal strength measures (Muraoka *et al.* 2005). Although large effect sizes were reported for this variable, quantifying tendon mechanical properties and the proposed relationship to traditional strength outcomes remains relatively underutilised in clinical practice. Furthermore, these measures may be clinically impractical given the specialised training and equipment required, highlighting the need for more research examining its use in the routine assessment of AT.

Ultimately in clinical practice the choice of the various outcome measures outlined in this review will depend on the loading demands and tendon capacity of each individual. For example, reactive strength assessments such as hopping and jumping are high load energy storage tasks and may not be appropriate for all AT patients.

Appropriate comparative group in assessing strength variables:

An area of debate in the assessment of strength outcomes in tendinopathy centers on the suitability of the use of what is termed the "uninjured" side in tendinopathy. It has been hypothesized that individuals with tendinopathy display alterations in sensory and motor differences, compared with pain-free controls, in the limb contralateral to the side of symptoms in patients with unilateral tendinopathy (Heales et al 2014). The systematic review investigated sensory and motor deficits of the non-injured side of patients with unilateral tendon pain. Results of this review indicated motor deficits in the contralateral limb in unilateral tendinopathy compared to asymptomatic controls. This finding suggests caution when interpreting and comparing injured and uninjured sides in unilateral tendon pain. However, statistical analysis and visual analysis of the forest plots included in this review indicated no differences in outcome in the studies that compared the symptomatic side to the asymptomatic side or asymptomatic controls. A potential explanation for the contrasting finding may relate to the characteristics of the included studies in each review. The majority of studies included in review by Heales et al (2014) investigated upper limb tendons, with a

paucity of literature investigating sensory and motor changes in lower limb tendinopathy. It is possible that differences in functional reorganisation in the primary somatosensory (and/or primary motor cortex (M1) cortices following upper limb versus lower limb injury may exist that limit the extrapolation of upper limb findings to the lower limb (Rio et al 2015). Furthermore in contrast there is evidence to suggest that the contralateral limb in unilateral tendon pain is actually stronger. Research reports that people with rotator cuff (RC) tendinopathy have been shown to be 15% stronger in measures of abduction on their asymptomatic side than controls (and comparable in strength to controls on their symptomatic side), and this has also been seen in lateral epicondylalgia and patellar tendinopathy (Chourasia et al 2012, Slater et al 2005, Coombes et al 2011). These findings suggest research investigating this phenomenon is required.

4.2 Clinical implications for rehabilitation: are we addressing observed deficits?

Strengthening interventions have become the cornerstone of conservative treatment in AT, mainly utilising slow heavy strength interventions. Initially these interventions were in the form of slow eccentric loading programmes as proposed by Alfredson *et al.* (1998b) The intervening years has seen the growth in popularity of other strengthening programmes, most notably progressive concentric/eccentric loading (Silbernagel *et al.* 2007b) and heavy slow resistance training (Kongsgaard *et al.* 2009, Beyer *et al.* 2015). Regardless of the mode of contraction it appears that strength interventions have been effective in improving pain, function, and return to work/sport in those with AT (Kingma *et al.* 2007, Magnussen *et al.* 2009, Rowe *et al.* 2012, Sussmilch-Leitch *et al.* 2012, Habets and van Cingel 2015). Unfortunately few strengthening interventions to date in AT have reported the change or the degree of improvement in strength variables following an intervention. Yu et al (2012) and Alfredson et al (1998) reported improvement in concentric PF PT ranging between 7-10 newtons following a strengthening intervention using isokinetic dynamometry using 90 degrees per second. In terms of improvements in eccentric PF PT following strength interventions, Alfredson et al (1998) reported improvements ranging from 27-33 newtons following the intervention period. The mean changes in strength reported for in these studies reporting concentric PF PT are below the observed mean differences reported in the current

review, while the improvements reported in the literature for eccentric PF PT are above the reported mean differences of 2-21.9 N reported in this review. Unfortunately there is distinct lack of research reporting the magnitude of change in other strength variables (Reactive, explosive strength) following exercise interventions in AT resulting in difficulty in comparing to the mean differences reported in this review. In addition, despite the positive outcomes following strength interventions, there is some evidence that strength deficits (particularly reactive strength) persist (Silbernagel *et al.* 2007c) and recurrence rates remain high (Paavola *et al.* 2000, Gajhede-Knudsen *et al.* 2013). It is possible that despite relatively positive outcomes from strength training, the persistence of strength deficits leaves the tendon unable to withstand the desired load, leading to recurrence.

By only training one aspect of strength (i.e. slow heavy load maximal strength), it is possible that athletes do not optimally improve their performance across the entire strength spectrum. For example, plyometric interventions in the LL consistently improve running performance (Spurrs *et al.* 2003), jump performance (Ramírez-Campillo *et al.* 2014) and tendon mechanical properties (tendon stiffness) (Foure *et al.* 2010) in asymptomatic populations. Despite this finding, there is a paucity of research investigating reactive strength interventions such as plyometrics in individuals with AT. However, it is noteworthy that reactive strength interventions like plyometrics place a high demand on a person's tendon capacity and therefore strength interventions should be tailored to the person's capacity and functional demands. It is possible that the use of heavy slow maximal strength training may be sufficient in those with AT who are not involved in high load SSC type activities whereas interventions targeting reactive or explosive strength may be more important in athletes that require higher functioning of their SSC (e.g. those who regularly engage in jumping or running activities), highlighting the need for targeted rehabilitation programmes.

4.3 Mechanisms underlying altered strength profile:

Alterations in strength profile are not isolated to AT. Reductions in muscle strength have been observed in a range of musculoskeletal disorders including ACL injury (Urbach *et al.* 1999, Urbach *et al.* 2001, Urbach and Awiszus 2002), ankle injuries, (Behm and St-Pierre 1997, Kangas *et al.* 2011) hip and knee osteoarthritis (OA) (Alnahdi *et al.* 2012, Loureiro *et al.* 2013) and groin pain (Thorborg *et al.* 2014), amongst others. Numerous theories have

been proposed to explain the mechanisms responsible for alterations in muscle strength in musculoskeletal disorders including AT. One theory relates to the altered integrity of the musculotendinous unit as a result of AT. This theory proposes that structural alterations in the tendon (e.g. disorganised collagen architecture, thinner collagen fibers, increased water content in the extracellular matrix) may alter a tendon's capacity to store kinetic energy thus affecting strength and functional performance (Wang 2006, Child *et al.* 2010). Another local structural change relates to disuse or muscle atrophy, namely the plantar flexors in the case of AT (Schweitzer and Karasick 2000). This is similar to other peripheral musculoskeletal disorders as seen in hip (Loureiro *et al.* 2013) and knee OA (Fink *et al.* 2007). Structural alterations such as atrophy may be compounded by a reluctance to load the pathological tendon. However, evidence to substantiate this theory appears contradictory with previous literature demonstrating that improvements in pain and function after exercise interventions in tendinopathy could not be attributed to accompanying alterations in the structural properties of the tendon (Drew *et al.* 2014). However, this does not discount the possibility of local changes in the muscle itself, with research in relation to AT lacking to date. Another theory proposes alterations in muscle strength manifest as a result of pain inhibition. Pain is known to have an inhibitory effect on motor output (Rio *et al.* 2014). It is proposed that continued and persistent peripheral nociceptive activity from the pathological tendon tissue may contribute to this inhibitory effect on motor output from higher centers (Rio *et al.* 2014). Potential sources of peripheral nocioception in tendinopathy include matrix changes, altered vascularity, changes to ion channel expression, cytokine and neurotransmitter expression, amongst (Rio *et al.* 2014). However, assuming that peripheral nociception is necessarily a primary driver of altered strength in AT is again questionable given the high prevalence of structural abnormalities and "pathology" in asymptomatic tendons and joints throughout the body (Cook *et al.* 1998, Brasseur *et al.* 2004, Silvis *et al.* 2011, Lepage-Saucier *et al.* 2014, Brinjikji *et al.* 2015). In light of these findings, an ever growing body of literature is emerging highlighting the increasing influences of central mechanisms on sensory and motor systems in AT. Individuals with tendinopathy display an altered sensory profile in terms of their pressure pain threshold, simple reaction time, speed of movement and thermal sensory testing compared to those without tendinopathy (Wilgen *et al.* 2013, Heales *et al.* 2014, Plinsinga *et al.* 2015, Tompra *et al.* 2015). This highlights the potential role of alterations in central pain processing in AT (Heales *et al.* 2014, Tompra *et al.* 2015). Furthermore there is

evidence demonstrating altered motor volitional strategies and increased cortical inhibition in people with LL tendinopathies (Edwards *et al.* 2010, Ngomo *et al.* 2015, Rio *et al.* 2015b), similar to previous studies on ACL injury (Héroux and Tremblay 2006) and knee pain (Torry *et al.* 2000). Additionally there is evidence of strength deficits in the contralateral limb of people with tendinopathy, despite no apparent pain or injury in this contralateral side (Slater *et al.* 2005, Coombes *et al.* 2011, Chourasia *et al.* 2012, Chimenti *et al.* 2014), further highlighting the role of the central motor cortex in the regulation of muscle strength. Consequently, the precise mechanisms underlying strength deficits in AT are still unclear and the concept of muscle strength as an output of higher centers is a shift from viewing tendinopathy as a purely local or peripheral issue towards an appreciation of the role of the central nervous system. In addition this raises the added potential of the role of non-physical factors such as fear avoidance beliefs or catastrophising on pain and motor outputs (Leeuw *et al.* 2007). Not only does pain have an inhibitory role on motor output, but pain anticipation or fear of pain has been shown to affect motor outputs in a similar manner (Dubé and Mercier 2011). One may postulate that ongoing fear, anxiety or catastrophising in relation to one's AT (fear of rupture, fear of damage, apprehension to load the tendon, or anxiety as a result of restricted activities) may lead to ongoing sensitisation of the central nervous system which may ultimately affect pain and/or motor output. Finally given the cross-sectional nature of the majority of the studies in this review, it is not clear whether strength deficits are in response to, or precede, the onset of AT making it difficult to infer causation. Despite the lack of prospective studies in this area, a study by Mahieu *et al.* (2006) reported that reduced PF strength predicted the onset of AT in a cohort of military recruits over a 6-month period, however similar prospective studies are lacking limiting generalisation of results.

4.4 Limitations

As outlined, it is difficult to assess whether strength deficits precede AT or are a consequence of AT. The bias towards cross-sectional studies in the absence of prospective studies is one of limitations of this review. There was considerable variability of methodologies used when calculating each strength variable. For example in terms of isokinetic dynamometry, there was a large variety of speeds and modes of contraction assessed throughout the studies when quantifying maximal strength values. This finding was also replicated for reactive and

explosive strength variables where a large variety of methodologies were used for assessing both GRF and hopping tests, thus limiting recommendations. There is evidence to suggest that strength deficits exist on the non-inured side in those with unilateral tendinopathy. Therefore direct comparison to the non-injured side as evident in a number of studies in this review may not be sufficient.

4.5 Conclusion

This review indicated that people with AT display an altered strength profile compared to the non-injured side or asymptomatic controls. Deficits were identified across maximal, reactive and explosive strength as well as tendon mechanical properties, with similar effect sizes reported. These deficits may have a significant impact on an athlete's ability to perform SSC activities. To date, assessment and rehabilitation of AT has focused on traditional maximal strength parameters with little focus on the assessment and management of reactive or explosive deficits which are fundamental to optimal SSC performance. The current review is novel in that it is the first of its kind to identify and quantify strength deficits across an individual's entire strength spectrum. The implications of these findings may have important impact in designing future strengthening interventions in AT. Additionally, future studies investigating the effects of strength interventions in AT should not only report the magnitude of change in pain and disability outcomes, but also report the magnitude of change following an intervention period in order to assess if the improvements in strength are greater than the observed mean differences quoted in this review. This highlights the need for future research investigating rehabilitation programmes based on the deficits identified in the review.

CHAPTER 4: Loading interventions in AT: More than just structural change?

STUDY IV: Clinical improvements following a loading intervention in Achilles tendinopathy are associated with a range of factors: an uncontrolled pilot intervention study.

ABSTRACT: Exercise interventions, predominantly in the form of eccentric or mixed contraction loading, have become the cornerstone of conservative treatment in AT. Despite the relative success of these interventions, little is known in relation to the factors associated with improved clinical outcomes following interventions. Identification of the factors associated with improved clinical outcomes following loading interventions may facilitate more targeted rehabilitation interventions. The aim of this study was to investigate the factors associated with clinical outcomes which following a progressive loading intervention in AT. An uncontrolled pilot intervention study was performed involving participants with AT persisting >3 months, recruited from the local community. The Consensus on Exercise Reporting Template (CERT) (Appendix 3) was used to guide the reporting of this study. A selection of structural, functional, psychosocial, somatosensory and general health outcome measures were completed pre- and post- a 12 week loading intervention.
Thirty-one participants (25 Male, 6 Female) underwent baseline assessment, with twenty-three participants completing post intervention assessment. Significant improvements were demonstrated for VISA-A scores (p=0.000, Mean Difference (SD) 21.61(18.27) and fear avoidance (p=0.000, Mean Difference (SD) 6.48 (6.01). The remaining subjective health variables did not demonstrate any significant change (p=0.200, Mean Difference 0.61 (2.21). There was no significant change in tendon thickness (p=0.650, Mean Difference (SD) 0.01 (0.10). Maximal strength variables improved post intervention, with only changes in isoinertial strength reaching statistical significance (p=0.000, Mean Difference (SD) 9.46 (9.77). Single leg hop demonstrated significant change post intervention (p=0.003, Mean Difference (SD) 15.82 (22.38), while drop countermovement jump did not for both contact time (p=0.384, Mean Difference (SD) 21.30 (115.12) and jump height (p=0.586, Mean Difference (SD) 0.30 (2.58). In general significant reductions in mechanical hyperalgesia were reported following the intervention ranging from (p=0.008-0.545, Mean Difference (SD) 0.31-0.78 (2.34-5.18).

Results of this study suggest improvements associated with loading interventions may be attributed to a range of psychosocial, somatosensory, functional health factors. The relative contribution of each factor may vary between individuals, suggesting that clinicians may need to adapt and tailor interventions according to multiple factors. The findings of this study may highlight important potential avenues for future research using multifactorial interventions.

1.0 Introduction

AT is a highly prevalent and disabling musculoskeletal complaint affecting both athletic and non-athletic populations (Kujala *et al.* 2005, de Jonge *et al.* 2011). Exercise interventions, predominantly in the form of eccentric loading interventions have become the cornerstone of conservative treatment in AT (Alfredson *et al.* 1998, Rompe *et al.* 2007, Kongsgaard *et al.* 2009). In recent years the emergence of mixed contraction programmes (Silbernagel *et al.* 2007b), isolated concentric programmes (Mafi *et al.* 2001), and heavy slow resistance training (HSR)(Beyer *et al.* 2015). In general, it appears that these interventions have reported similar benefits in pain and disability (Silbernagel *et al.* 2007b, Silbernagel *et al.* 2007c, Kongsgaard *et al.* 2009, Beyer *et al.* 2015). Traditionally the rationale behind loading interventions in AT was that a progressive loading regime would stimulate a process of re-conditioning and improve the capacity of a tendon to withstand greater load and stress by altering its physiological or structural properties (Reeves 2006, Couppe *et al.* 2008, Seynnes *et al.* 2009, Kjaer and Heinemeier 2014). However, this assumption that alterations in tissue structure are responsible for the improved clinical outcomes following loading interventions appears to be a tenuous one. A recent systematic review by Drew *et al.* (2014) concluded that structural change does not adequately explain the response to loading interventions in tendinopathy. Furthermore, evidence suggests that collagen in the tendon matrix is relatively stable with limited turnover after puberty (Heinemeier *et al.* 2013).

In light of the failure of structural paradigms to fully explain the outcomes following loading interventions it appears that the application of load has a potential effect on a number of systems in conjunction with potential structural changes. Potentially, the prescription of loaded exercise in AT within a framework that suggests hurt does not equal harm (Littlewood *et al.* 2013) may positively influence psychosocial (fear-avoidance beliefs, catastrophising) (Mannion *et al.* 2001), somatosensory (pain or thermal sensitivity), functional (maximal/reactive/explosive strength variables) and general health variables (sleep, mood or stress).

Although some of these factors have been investigated in AT to date these interventions have focused on investigating the effects of loading interventions from a unidimensional perspective. Hence, the mechanism or factors associated with the efficacy of the therapeutic

exercise remains unclear (Rees *et al.* 2008). Identification of such factors may shed light on a complex topic as well as ensuring that rehabilitation interventions are targeted to patient deficits and clinical outcomes can be maximized. Consequently the objective of the present study was to investigate the effects of a progressive heavy load rehabilitation program on a variety of subjective and objective test variables. A second objective of the current study sought to investigate the factors and correlates associated with clinical improvements following the rehabilitation program. To achieve this an uncontrolled pilot intervention study was chosen. Although the methodological quality and rigor of uncontrolled pilot studies is often criticized, these studies can play an important role in research as a first step in clinical investigation of a hypothesis (Nissen and Wynn 2014).

2.0 Methods

2.1 Ethical Approval

The study was approved by the Education and Health Sciences Research Ethics Committee at the University of Limerick, Ireland (Ethics Number: EHSREC2014-05-14). The Consensus on Exercise Reporting Template (CERT) was used to guide the format and reporting of this study (Slade *et al.* 2016) (Appendix 3). The CERT is a sixteen-item checklist designed specifically for the reporting of exercise programmes across all evaluative study designs for exercise research.

2.2. Participants

Participants were recruited from the local community by means of e-mail and through existing contacts in running clubs in the community. Following expressions of interest, participants were screened for inclusion by the primary investigator (SMA), who determined if participants met the required eligibility criteria to participate.

2.3 Inclusion and Exclusion criteria

Men and women, aged between 18 and 60 years with AT with duration of more than 3-

months were included. The clinical diagnosis of AT was determined by a combination of a subjective history of pain in the Achilles tendon region, along with tenderness and impaired physical performance (Heel raise test, single leg hop test) The exclusion criteria were: under the age of 18, non-English speakers, injury to the foot, knee, or hip on the same side of the AT, injury to the back and/or history of rheumatoid arthritis or any other injury or illness thought to interfere with participation. Participants were classified as either bilateral or unilateral and either mid portion AT or insertional AT depending on the location of symptoms (Mid tendon symptoms or insertional symptoms).

2.4 Procedure

Testing took place in a research laboratory at the local university. All participants received an information leaflet (Appendix 6) regarding the purpose of and procedure involved in the study as well as providing written informed consent (Appendix 5) prior to assessment. Following identification of relevant participants, participant characteristics were collected. These included age, height, body mass, symptom duration and the most symptomatic side.

2.5 Clinical Evaluation

2.5.1 Subjective outcomes

A selection of subjective outcome measures was used to examine several psychosocial, disability and wellness factors. These measures are outlined in Table 11, with a detailed description on each measure provided in the accompanying appendix 4. Following collection of baseline demographic data and subjective outcome measures, participants underwent a range of objective performance outcome measures performed by two of the study authors (SMA & AT). Subjective and objective outcome measures were repeated following the completion of a 12-week loading intervention.

Table 11: Study IV Subjective Wellness and psychosocial outcome measures

Test Domain	Subjective Measure Description
Severity of Achilles tendinopathy	**Victorian Institute of Sports Assessment Achilles Questionnaire (VISA-A):** The Victorian Institute of Sport (VISA-A) is a self-administered questionnaire is an index of the severity of AT which evaluates symptoms and their effect on physical activity in AT. Results range from 0 to 100 points with asymptomatic persons expected to score 100 points. Lower scores indicate higher levels of pain and disability (Viersen *et al.* 2012).
Fear Avoidance Beliefs	**Fear Avoidance Beliefs Questionnaire (FABQ):** The FABQ was developed by Waddell *et al.* (1993) to investigate fear-avoidance beliefs among LBP patients in the clinical setting. The physical activity subscale of the FABQ quantifies the level of fear about physical activity. The scale was modified and adapted to relate to the Achilles tendon. Items are scored from 0 to 6. Higher scores indicate greater levels of fear avoidance beliefs.
General Health	**Subjective Health Complaints Inventory (SCHI):** The SCHI is a thirteen-item scale that concerns subjective somatic and psychological complaints experienced during the previous 30 days. Higher scores indicate greater levels of subjective health complaints (Tschudi-Madsen et

	al. 2011).
Sleep	**Sleep quality and quantity:** Sleep quantity and quality were categorized into three categories according to the number of hours sleep per night or presence of sleep disturbances. The three categories were sufficient, intermediate or insufficient (Auvinen *et al.* 2010).
Mood	**Profile of Moods State (POMS):** The POMS assesses transient, fluctuating feelings, and enduring affect states. Three subscales of the POMS namely tension-anxiety, anger-hostility and confusion-bewilderment were completed. Higher scores indicated greater levels of anxiety, anger and confusion (Mc Nair *et al.*1971).
Stress	**Depression Anxiety Stress Scale (DASS):** The DASS is designed to measure depression, anxiety and stress. The seven-item stress subscale only was completed. A higher score indicates greater levels of stress (Lovibond and Lovibond 1995).
Disordered Eating	**Sick, Control, One stone, Fat, Food (SCOFF):** The SCOFF is a five-item questionnaire used to assess the possible presence of an eating disorder. A score of two or more indicates disordered eating (Morgan *et al.* 2002).

2.5.2 Objective outcomes

2.5.2.1 Maximal strength

2.5.2.1.1 Isokinetic strength

Isokinetic PF muscle strength was measured using a Biodex System 3 Pro Isokinetic Dynamometer (Biodex Medical Systems, Shirley, New York, USA. Concentric PF PT and peak torque/body weight (PT/BW) were measured at 90 degrees/second (Five repetitions) of angular velocity. Eccentric PF PT and PT/BW were measured at 90 degrees/second (Five repetitions) (Moller *et al.* 2005).

2.5.2.1.2 Isoinertial strength

Isoinertial strength was assessed using a single leg concentric eccentric heel-raise test (Silbernagel *et al*. 2006). The subject was asked to perform as many single leg heel-raises as possible. The test was terminated when the participant stopped, could not keep the frequency or did not perform a proper heel-raise.

2.5.2.2 Reactive strength

2.5.2.2.1 Single leg hop:

Participants were instructed to hop as far as possible on one leg and land on the same limb. No restrictions were placed on arm movement. For the attempt to be deemed successful, the single-footed landing position must have been maintained for at least two seconds (Reid *et al* 2007). Unsuccessful attempts were repeated. The average of three successful attempts on each leg was recorded to the nearest centimeter.

2.5.2.2.2 Drop countermovement jump (dCMJ)

Participants were instructed to “fall” down from a wooden box (15cm high) onto a contact mat system (Chronojump-BoscosystemTM) and immediately on landing, perform a maximal vertical one-legged jump (Silbernagel *et al* 2006). Participants performed three jumps per leg. The jump height (JH) and contact time (CT) of the highest jump from each leg were recorded for data analysis.

2.5.2.2.3 Tendon thickness

US examinations were undertaken on both ankles using a GE Logiq e ultrasound scanner (GE Medical, Wauwatosa, WI, USA) with a 7-12 MHz linear array transducer. Both transverse and longitudinal views were obtained, with participants lying in prone to ascertain tendon thickness. A detailed description of the measurement protocol is provided in appendix 4.

2.5.2.2.4 Quantitative sensory testing

2.5.2.2.4.1 Mechanical Hyperalgesia

Three testing locations were identified for measuring pressure pain threshold (PPT): tibialis anterior, common extensor tendon of the elbow, and the Achilles tendon. The rubber-tipped probe of the handheld algometer (Force Ten TM FDX Force gage, Wagner Instruments, Greenwich, CT, USA) was applied in random order to the sites listed above. Participants were requested to indicate immediately the point at which the sensation of pressure turned into a sensation of pain before randomly moving to the next test location. A single measurement was made at each site by recording the pressure threshold in newton's (N) (Skinner *et al.* 2014).

2.5.2.2.4.1 Thermal hyperalgesia

Thermal hyperalgesia was determined using a Somedic Roll Temp 2 device set to a pre-defined temperature of 40 degrees celcius (Hot) and 25 degrees celcius (Cold) respectively. Thermal hyperalgesia was assessed at the forearm (posterior aspect from the dorsal wrist joint line to the elbow joint line) and posterior aspect of LL (from the knee joint line to the calcaneus) respectively. Participants were requested to rate the (1) temperature and (2) pain experienced on a scale of 0-10 for both hot and cold modalities. Tests were performed three times at each location bilaterally and in a random order. An average of the three measurements was used as a total score at each site (Pathirana *et al.* 2011).

The sample sizes for data collection varied across the outcome measures used on account of unforeseen circumstances such as in-service recalibration of the biodex apparatus. Pre and post intervention sample sizes are provided for each outcome measured to illustrate this.

2.6 Treatment Intervention

After assessment of subjective and objective outcome measures, participants underwent a "washout" period for one month prior to commencing the intervention protocol. The washout period was undertaken to negate the influence of any engagement in calf specific strengthening or treatment, which potentially influenced the outcome of the intervention. During this washout period participants were advised not to engage in any specific active treatment for their AT or perform any calf or Achilles tendon or PF specific exercises. Subsequent to completing this one-month washout period, participants were provided with a 12-week intervention programme as well as engaging in a group educational session. Both components were delivered by the main author of the study (SMA) a qualified physiotherapist with four years experience in prescribing exercise interventions in AT.

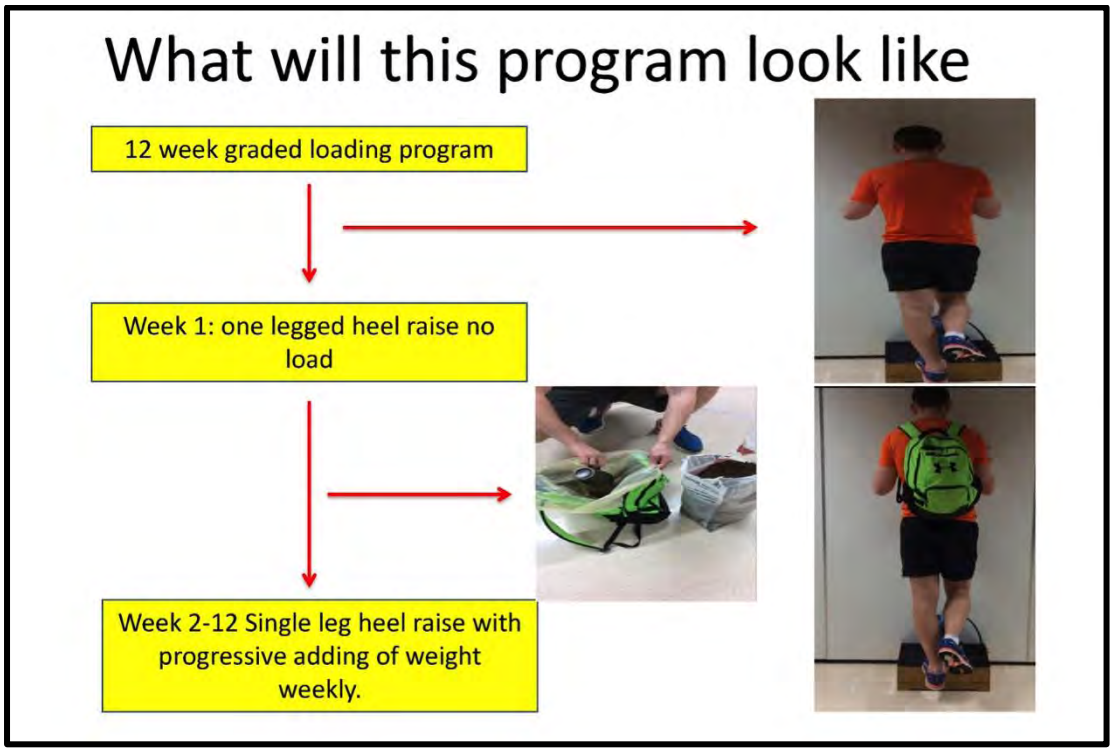
2.6.1 Educational component

The primary investigator (SMA) guided a 20-minute educational session as well as facilitating a group discussion, each consisting of 4-6 participants. The educational component followed concepts outlined previously in the Common Sense Model of self-regulation of health and illness (Hale *et al.* 2007, Littlewood *et al.* 2014) which has been shown to be effective in shoulder pain. Using this concept the patient was encouraged to communicate their understanding of the problem and the physiotherapist (SMA) encouraged the participants to consider their AT from the perspective that the muscles and tendons are de-conditioned and need a progressive programme of exercise to restore condition and function. Descriptions of tissue based pathology, *e.g.* Achilles tendon rupture, were avoided, or challenged using a pain neuroscience or cognitive approach (Blickenstaff and Pearson 2016). Participants were also provided with information and practical advice on dealing with potential flare-ups during the programme. Educational material utilised in the group discussion was made accessible to participants for any future reference (https://www.dropbox.com/s/3ayyic2ooy2my99/Participant%20Presentation%20Jan.pptx?dl=0).

2.6.2 Loading intervention

The loading intervention consisted of a progressive mixed concentric/eccentric heavy slow loading programme based on previous research in the area (Kongsgaard *et al.* 2009, Beyer *et al.* 2015). The loading exercise consisted of a one-legged concentric–eccentric toe-raise/heel drop (three second concentric raise, three seconds isometric hold at the top, and three seconds eccentric lowering phase) whilst standing on the edge of a step (Figure 27). Participants performed four sets of 10-12 repetitions. Participants were encouraged to allow a 2-3-minute rest between sets. Exercises were performed every second day and participants performed the same the number of repetitions each week for a 12-week period. After one week of bodyweight only heel raises, participants were encouraged to attempt to gradually increase the load at which the exercises were performed. To increase the load, participants were provided with sand material and instructed to progressively add load to a backpack each week so that they could perform no more than 10-12 repetitions of the exercises for the given load. Participants were instructed that some pain response post exercise was expected but if symptoms increased by more than 3-4 points on a pain numerical rating scale (NRS) during or in the 24hours post exercise they were instructed to decrease the load. All participants were provided with a physical demonstration of the exercise programme as well as access to online material providing instructions on how to perform the exercise programme (https://www.dropbox.com/s/57cis1wll0vnb0z/Video%203.MOV?dl=0). Participants were also allowed to engage in running activities if they desired throughout the intervention period, using a similar pain monitoring tool as outlined for the loading intervention (Silbernagel *et al.* 2007b, Kongsgaard *et al.* 2009, Beyer *et al.* 2015). Participants were provided with advice on how to manage potential flare-ups such as advice on altering training load, pain relieving modalities, and education stressing a flare does not mean damage. Participants were also advised to contact the study author if they required additional advice. Participants completed the intervention individually, unsupervised in a setting of their convenience. Although there were no follow up points in this 12-week period participants were encouraged to contact the primary investigator (SMA) if they wished to discuss the programme.

Figure 27: Study IV 12-Week loading intervention



2.6.2 Training Diaries

Participants were provided with and encouraged to keep a training diary for the duration of the intervention. Within this diary they documented their rehabilitation exercises, other physical activities, symptoms, or other comments.

2.7 Statistical analysis

Data was summarised using mean (SD), median (IQR) or percentage as appropriate. Continuous variables were assessed for skewness using the Shapiro-Wilk test of normality and through the visual inspection of histograms. Pre- and post- measures were compared using the paired t-test, where the differences were approximately normally distributed, and using the Wilcoxon Signed-Rank test where the data was ordinal or the differences were found to be skewed. Pearson correlation coefficients were used to assess bivariate to examine associations between change scores for chosen variables within each of the primary outcomes (strength, QST, Pain and disability, and psychosocial factors). The 5% level of significance

was used throughout. The 5% level of significance was used throughout. All analyses were conducted using SPSS Version 22 (Armonk, NY: IBM Corp).

3.0 Results

3.1 Subject Characteristics and Clinical Findings

Thirty-one participants underwent baseline assessment. Twenty-three participants were eligible and completed the post intervention assessment. Four participants failed to attend the intervention meeting day following the one-month washout period, one sustained a LL injury preventing continued participation, while three participants contacted the study author to report that they were unable to commit to the exercise programme. The baseline demographics of the included participants are outlined in Table 12.

Table 12: Study IV Demographics of included participants

Variable	Mean (SD)
Sex (Male: Female)	(25:6)
AT Classification (Mid Tendon: Insertional)	(25:6)
AT Classification (Unilateral: Bilateral)	(19:12)
Age (Years)	41.16 (7.32)
Height (Centimeters)	174.45 (11.11)
Mass (Kilograms)	77.16 (16.31)
Symptom Duration (Months)	30.79 (33.97)
Volume of running per week (Miles)	18.67 (11.81)
Volume of running per week (Minutes)	143.57 (96.47)
Alcohol per Week (Units)	3.8 (4.97)
Sleep per night (Hours)	6.88 (1.07)

3.2 Effect of intervention on severity of AT

VISA-A scores improved significantly post intervention (p=0.000, Mean Difference (SD) 21.61(18.27)) (Table 13).

3.3 Effect of intervention on strength profile

Maximal strength improved post intervention (range 6.2 to 9.8 Nm), however these improvements did not reach statistical significance (p=0.068-0.273, Mean Difference (SD) 0.66-14.66(19.68-48.69). Isoinertial strength improved significantly (p=0.000, Mean Difference (SD) 9.46(9.77). Statistical analysis revealed a significant improvement in reactive strength during single leg hopping (p=0.003, Mean Difference (SD) 15.82(22.38), while no significant change was found for both contact time (p=0.384, Mean Difference (SD) 21.30(115.12) and jump height (p=0.586, Mean Difference (SD) 0.30(2.58). (Table 13).

3.4 Effect of intervention on wellness and psychosocial profile

Significant improvements were seen in the physical activity subscale of the FABQ (p=0.000, Mean Difference (SD) 6.48(6.01). The remaining wellness and psychosocial variables did not demonstrate any significant change (p=0.200, Mean Difference 0.61(2.21)) (Table 13).

3.5 Effect of intervention on tendon structure

No significant effect was reported for change in tendon thickness (p=0.650, Mean Difference (SD) 0.01(0.10) (Table 13).

3.6 Effect of intervention on quantitative sensory profile

Significant improvements were demonstrated in mechanical hyperalgesia (PPT) following the intervention period in five of the six sites investigated ranging from (p=0.008-0.545, Mean Difference (SD) 0.31-0.78 (2.34-5.18)). Reductions in thermal hyperalgesia were also reported following the intervention, with three of the sixteen measures reaching statistical significance ($p<0.05$) (Table 13).

3.7 Correlations of change following the exercise intervention:

Pearson's correlation coefficent analysis indicated change in FABQ had a positive correlation with Change in VISA-A changes (r=0.494) (Table 13).

3.8 Results of exercise dose of included participants:

Participants were required to record weekly using an exercise diary the weight at which they were able to complete the exercise program for the 12-week intervention period. Data on the weight lifted at the completion of the exercise intervention period was analysed and calculated relative to participant body weight. The results of which are outlined in table. The mean change in VISA of the participants who lifted greater than 14% of BW was 29.4 compared to VISA mean change of 18.78 for those participants who lifted less than 14% BW.

Table 13: Study IV Mean and median pre and post intervention results

Variable	Pre Mean (SD) OR Median (IQR)	n	Post Mean (SD) OR Median (IQR)	n	Mean Difference	95% C.I.	P
AT SEVERITY							
VISA-A	62.87 (15.37)	31	85.57 (9.78)	23	21.61	29.51-13.71	0.000
STRENGTH PROFILE							
MAXIMAL STRENGTH							
Concentric PT	50.8 (11.7)	10	58.3 (13.3)	9	0.66 (19.68)	10.15-8.82	0.068
Concentric PT BW	71.5 (16.1)	10	81.3 (13.2)	9	1.77 (24.69)	13.68-10.13	0.068
Eccentric PT	116.7 (32.2)	10	122.9 (30.3)	9	4.15 (25.51)	-8.15-16.44	0.273
Eccentric PT BW	132.5 (35.5)	10	139.5 (38.8)	9	14.66 (48.69)	-38.13-8.80	0.273
ISOINERTIAL STRENGTH							
Isoinertial Calf Raise (Number of repetitions)	29.03 (9.58)	31	33.17 (12.16)	23	9.46 (9.77)	-13.68—5.23	0.000
REACTIVE STRENGTH							
Single Leg Hop	135.27 (42.55)	31	148.49 (31.65)	23	15.82	-25.50—6.15	0.003

(Distance cm)					(22.38)		
CMJ (Contact Time)	409.71 (95.13)	31	400.61 (114.99)	23	21.30 (115.12)	-28.48-71.09	0.384
CMJ (Jump Height-cm)	10.81 (4.37)	31	10.76 (3.72)	23	0.30 (2.58)	-1.41-0.82	0.586
WELLNESS AND PSYCHOSOCIAL FACTORS							
General health	3.58 (1.57)	31	3.96	23	0.61 (2.21)	-0.35-1.56	0.200
Number of painful body parts	1 (1,2)	31	2 (1,2)	23	NA	NA	0.284
Disordered eating	0 (0,0)	31	0 (0,1)	23	NA	NA	0.739
Sleep	2 (1,2)	31	2 (1,2)	23	NA	NA	0.527
Stress (DASS)	10 (4,12)	31	6 (4,10)	23	1.70 (7.26)	-1.44-4.83	0.178
Tension	2 (0,2)	31	1 (0,3)	23	NA	NA	0.645
Anger	2 (1,4)	31	2 (1,4)	23	NA	NA	0.580
Confusion	0 (0,1)	31	0 (0,1)	23	NA	NA	1.0
Fear (FABQ)	16 (2, 21)	31	10 (5,12)	23	6.48 (6.01)	3.88-9.08	0.000
TENDON STRUCTURE							
Tendon Thickness (cm)	0.61 (0.14)	30	0.62 (0.14)	23	0.01 (0.10)	-0.03-0.05	0.650

QUANTITATIVE SENSORY PROFILE QST							
THERMAL HYPERALGESIA							
Injured Leg Heat Sensitivity (NRS/10)	2.42 (1.57)	31	1.96 (1.15)	23	0.48 (1.08)	0.01-0.95	0.045
Injured Leg Heat Hyperalgesia (NRS/10)	0.32 (0.48)	31	0.13 (0.34)	23	0.22 (0.52)	0.01-0.44	0.057
Non-Injured Leg Heat Sensitivity (NRS/10)	2.37 (1.16)	19	1.73 (0.96)	15	0.73 (1.03)	0.16-1.31	0.016
Non-Injured Leg Heat Hyperalgesia (NRS/10)	0.13 (0.35) [a]	19	0.13 (0.35) [a]	15	NA	NA	N/A
Injured Leg Cold Sensitivity (NRS/10)	2.35 (1.54)	31	2.26 (1.36)	23	0.04 (1.66)	-0.68-0.76	0.901
Injured Leg Cold Hyperalgesia (NRS/10)	0.26 (0.51)	31	0.09 (0.29)	23	0.13 (0.34)	-0.02-0.28	0.083
Non-Injured Leg Cold Sensitivity (NRS/10)	2.32 (1.25)	19	2.00 (1.25)	15	0.33 (1.72)	-0.62-1.28	0.965

Non-Injured leg Cold Hyperalgesia (NRS/10)	0.11 (0.32)	19	0.07 (0.26)	15	0.07 (0.26)	-0.08-0.21	0.334
MECHANICAL HYPERALGESIA							
ECRB Right (lbs.)	40.52 (17.22)	29	40.61 (15.93)	22	0.31 (2.34)	-1.35-0.73	0.545
ECRB Left (lbs.)	39.19 (16.46)	29	41.77 (16.10)	21	1.26 (2.51)	-2.41—0.12	0.032
Tibialis Anterior Right (lbs.)	52.45 (23.13)	29	63.25 (23.49)	22	2.65 (5.18)	-4.95—0.36	0.026
Tibialis Anterior Left (lbs.)	57.38 (23.67)	29	66.77 (26.51)	22	2.76 (2.56)	-5.09—0.43	0.023
Injured Achilles (lbs.)	43.19 (21.22)	28	55.47 (21.66)	21	2.78 (4.30)	-4.73—0.82	0.008
Non-Injured Achilles (lbs.)	49.61 (21.97)	17	59.92 (17.93)	14	2.23 (3.71)	-4.37—0.09	0.043

Table 14: Correlations of change following the intervention period

		PPTInjuredATchange	SLH_change	ChangeFABQ	ChangeVISA-A
PPTInjuredATchange	Pearson Correlation	1	-.169	.208	.324
	Sig. (2-tailed)		.464	.365	.153
	N	21	21	21	21
SLH_change	Pearson Correlation	-.169	1	.223	.265
	Sig. (2-tailed)	.464		.318	.222
	N	21	23	22	23
ChangeFABQ	Pearson Correlation	.208	.223	1	.494*
	Sig. (2-tailed)	.365	.318		.020
	N	21	22	23	22
ChangeVISA-A	Pearson Correlation	.324	.265	.494*	1
	Sig. (2-tailed)	.153	.222	.020	
	N	21	23	22	23

PPT: Pressure pain threshold; SLH: Single leg hop

Table 15: Exercise dose of the included participants

Participant	Lifting Weight (kg)	Participant weight (kg)	Lifting weight as per %BW
1	5.9	56	11
2	N/R	79	N/R
3	12	64	18.75
4	N/R	79	N/R
5	7	71	10
6	9	50	18
7	12	65	19
8	7	71	10
9	NA	94	N/R
10	9.5	66	14
11	7.8	71	11
12	N/R	68.5	N/R
13	15	91	17
14	5	82	7
15	8	108	8
16	6	99	6
17	NA	88	N/R
18	4.5	97	5
19	N/R	85	N/R
20	N/R	83	N/R
21	N/R	69	N/R
22	9	59	15
23	16.1	106	15

N/R= Not reported

4.0 Discussion

The primary aim of this study was to investigate the change structural, functional, psychosocial, somatosensory and general health factors following a 12-week loading intervention in AT. To date interventions have focused post intervention analysis on unimodal factors such as pain, disability or structure.

4.1 Change in AT severity

The magnitude of change in the VISA-A score following this 12-week loading intervention ranged from 7-71 points, with a mean change of 23 points reported which is comparable to the improvements reported in similar loading interventions in AT (Rompe *et al.* 2007, Yelland *et al.* 2011, Beyer *et al.* 2015). Although there is no agreed minimal clinical important change (MCIC) in terms of VISA-A score, an increase of 20 points has been suggested as being considered clinically significant (Tumilty *et al.* 2008).

4.2 Change in tendon structure

It has been suggested that the loading forces applied to tendons will help stimulate the remodeling of the abnormal tendon structure through altering fluid and blood flow (Ohberg 2004, Maffulli *et al.* 2008, Khan and Scott 2009, Wearing *et al.* 2011). US is commonly used to image tendon dimensions with features such as thickness, hypoechogenicity and neovscularisation commonly used to monitor change following an exercise intervention (Ohberg 2004, Beyer *et al.* 2015). The mean tendon thickness pre intervention was 6.1mm, which appears to be slightly smaller than the thickness measurements reported in other intervention studies which reported pre intervention thickness ranging from 6.9-9.9mm (de Vos *et al.* 2010, Van der Plas *et al.* 2011, Beyer *et al.* 2015). The lack of reported change in tendon thickness following the intervention period is comparable with findings of a recent systematic review by Drew *et al.* (2014) who demonstrated that there is strong evidence to refute observable structural change as an explanation for the response to exercise interventions in LL tendinopathy. The mechanism behind the lack of change may be attributed to the fact that younger tendons appear to be able to adapt structurally (Kongsgaard *et al.* 2005) but have limited turnover after puberty (Heinemeier *et al.* 2013), with the mean age of the participants in this study reflecting this time point. Furthermore evidence suggests

that once a tendon becomes degenerative and the matrix is affected there is little possibility of that region resolving (Malliaras *et al.* 2010). However the authors acknowledge that US is only one method of visualizing tendon structure and the emergence of alternative imaging modalities such as UTC and sonoelastography may provide further insight into potential structural response following loading interventions.

4.3 Change in function

In terms of maximal strength although concentric and eccentric strength variables both improved following the intervention, these did not reach statistical significance. The absence of statistical significance may be attributed to the sample size. Due to unforeseen circumstances the biodex isokinetic system underwent a service and recalibration during the study period. Consequently maximal strength variables measured before the calibration were excluded which led to a reduction in the sample size, which may have limited findings. Nevertheless, it is worth noting that the mean change in maximal strength compared favourably to the degree of change reported following similar interventions (Haglund-Åkerlind and Eriksson 1993, Alfredson *et al.* 1998, Öhberg *et al.* 2001).

Alterations in the reactive strength profile were also evident following the intervention. Post-intervention analysis revealed significant improvements in single leg hop distances; however there was no significant improvement in dCMJ variables (JH and CT). One potential explanation for this finding may relate to the mechanisms controlling each movement. Reactive strength variables such as hopping and dCMJ are considered plyometric exercises that utilise the SSC (Flanagan 2007). Fast SSC movements (dCMJ) rely on elastic energy contribution based on a short transition period between eccentric and concentric phases, while slow SSC (single leg hop distance) activities are more reliant on neural potentiation of the contractile machinery during the eccentric phase and increased time to develop force (Bobbert *et al.* 1997, Walshe *et al.* 1998). As a result, the slow and fast SSC may represent different muscle action patterns, affecting performance in different ways. Slow SSC movements (single leg hop distance) may be more related to maximal strength compared to fast SSC movements (dCMJ) which are associated with elastic storage and the muscle spindle reflex (Flanagan 2007). Therefore by only training one aspect of strength (i.e. slow heavy load maximal strength) it is possible that athletes do not optimally improve their performance

across the entire strength spectrum, which may account for the findings in the current study. Unfortunately, there is a paucity of research investigating reactive strength interventions such as plyometrics in individuals with AT which highlights the need for future research.

4.4 Change in general health and psychosocial profile

Results of the study indicated a significant reduction in FABQ scores following the intervention period. Research in other musculoskeletal disorders to date has highlighted the negative influence of fear avoidance beliefs on recovery times in patients with a range of musculoskeletal disorders (Westman *et al.* 2011, Landers *et al.* 2008, George and Stryker 2011, Ross *et al.* 2002, Scopaz *et al.* 2009, Kromer *et al*. 2014). The concept of fear avoidance beliefs was first highlighted in the Fear Avoidance Model (FAM) by Leeuw *et al.* (2007). According to this model, some individuals consider a painful stimulus as negative and avoid or postpone an event or movement that is considered painful (Sindhu *et al.* 2012). This in turn may lead to deconditioning or atrophy of the musculoskeletal system (Littlewood *et al.* 2013). It may be postulated that reductions in FABQ following the intervention may be attributed to the prescription of strengthening exercises within a framework that suggests pain does not equal damage and in some circumstances suggests a tissue is de-conditioned and should be exercised. Such an approach may have resulted in patients reconceptualising their beliefs surrounding their tendon pain as well as altering the manner in which they approached movement, exercise and activity throughout the programme (Littlewood *et al.* 2013). The remaining psychosocial variables and wellness measures did not report any significant change following the intervention period. Non-significant changes in the remaining psychosocial variables may suggest a ceiling effect considering that baseline measures for these variables were relatively low before the intervention began suggesting that such variables may not suitable in this present cohort of AT participants.

4.5 Changes in somatosensory profile

Increased responsiveness to non-noxious stimulus is referred to as hyperalgesia (Latremoliere and Woolf 2009). Hyperalgesia is thought to a consequence of sensitisation as a result of altered processing in the peripheral or central system. Exercise has been shown to result in hypoalgesia or reduction in sensitisation in a process known as exercise-induced hypoalgesia (EIH) (Naugle *et al.* 2012). EIH has been used to evaluate sensitization, and it has been hypothesized that impaired EIH may be indicative of a dysfunction of the pain inhibitory systems (Vaegter *et al.* 2016). Evidence suggests that exercise of sufficient intensity and duration (both short and long term) results in the release of peripheral and central beta-endorphins which have been associated with changes in pain sensitivity (Naugle *et al.* 2012) and has been shown to increase pressure pain thresholds in the upper and lower extremities (Kosek *et al.* 1996, Koltyn *et al.* 2001, Ylinen *et al.* 2005, Burrows *et al.* 2014, Jones *et al.* 2014). Reductions in thermal and mechanical pain thresholds were found following the intervention period. These changes were found to have manifested locally especially in the injured side as well as in remote body parts. This finding lends to the theory that similar to other persistent or chronic MSK disorders tendinopathy results in sensitisation, manifesting as hyperalgesia to mechanical, thermal, or similar stimuli (Graven-Nielsen and Arendt-Nielsen 2002, Arendt-Nielsen *et al.* 2010). Alterations in somatosensory profile resulting in widespread sensitisation thought to represent central sensitization have been reported in a range of UL tendinopathies (Heales *et al.* 2014, Plinsinga *et al.* 2015). In contrast studies the manifestation of central sensitization in in LL tendinopathies is less clear (Wilgen *et al.* 2013, Skinner *et al.* 2014, Tompra *et al.* 2015), with some authors suggesting local alterations in hyperalgesia in the absence of widespread changes indicates local sensitization rather than central sensitization. Despite this, the implications of these findings suggest that improvements in pain and disability following loading interventions in AT may be related to alterations in pain sensitivity, implicating the potential role of central mechanisms in response to loading interventions.

4.6 Limitations

There are a number of methodological considerations that may adversely influence the generalizability of the research. The most obvious limitation of this study relates to the

absence of an appropriate contemporaneous comparison group. Although uncontrolled pilot studies can strengthen the suspicion of a causal relationship, cause-effect relationships require planned studies including control groups that to the extent possible control for chance, bias and confounders (Nissen and Wynn 2014). Another potential limitation relates to the various outcome measures used in the study. The psychometric properties of measures such as dCMJ using the chronojump system, FABQ, and somedic roll temp test are relatively unknown in AT with no reliability analysis undertaken prior to the study. This may have potentially accounted for the non-significant change or varying results seen for these respective variables. The current study did not involve a long-term follow up of participants following the study, such that it is unclear whether improvements in pain and function were maintained. Additionally, the current study did not categorize or group participants according to their presentation. Finally participants with bilateral and unilateral tendinopathy as well as mid-portion AT and insertional AT were all included in the study. It may be argued that these presentations represent distinct and contrasting mechanisms, which highlights the potential flaws with including unilateral and bilateral participants in one group.

4.7 Conclusions

To date research investigating the effects of loading interventions in AT have focused mostly on unimodal or structural based variables. Despite the popularity of these interventions, structural outcomes have failed to fully explain the mechanism or changes in clinical outcomes following a loading intervention, highlighting the possibility of a multifactorial response post loading. Results of this study suggest changes in clinical outcomes following a loading intervention may be attributed to a range of psychosocial, somatosensory, functional factors. The relative contribution of each factor may vary between individuals, suggesting that clinicians may need to adapt and tailor interventions using a multifactorial approach. The findings of this study may serve as an important first step by identifying potential avenues for future research.

STUDY V: Beyond the tendon: Patient experiences of Achilles tendinopathy, a qualitative study

ABSTRACT: AT is often associated with persistent and disabling pain, leading to a significant impact on physical and recreational activities. It is hypothesised the burden associated with AT may result in the manifestation of psychosocial factors which may impact on the overall treatment outcomes. Psychosocial factors are considered to be important mediators following exercise interventions in a range of MSK disorders. To date there is a lack of qualitative research investigating these factors in AT. To address this a qualitative study, exploring the perceptions and experiences of people with AT was performed in participants with AT. A qualitative, interpretive description design was performed using semi-structured telephone interviews. The questioning route covered participants' history of AT, perceived cause of AT, impact of AT pain, experience in managing AT, and perspective on prognosis of AT pain. Interviews were transcribed verbatim utilising an interpretive descriptive analysis. The study has been reported in accordance with the consolidated criteria for reporting qualitative research (COREQ) checklist.

Eight participants (Five male and three female) participated in the interview process. Four main themes were identified: (i) meaning and impact of AT; (ii) participants experience with the management process; (iii) identifying with and self managing AT, and, (iv) looking to the future. Participants expressed concerns and fears surrounding the potential of future tendon damage associated with AT. This was compounded by participants' belief that rest was required in order to allow the tendon necessary time to heal and perhaps due to participants' experience with treatment primarily consisting of unimodal passive interventions.

Findings of this qualitative study, the first of its kind suggest that AT is associated with significant psychosocial variables particularly in relation to fear surrounding future tendon damage and confusion expressed by participants surrounding diagnosis and management of the disorder. These findings may have important implications in the management of AT with findings highlighting the potential role of pain neuroscience education in the reconceptualisation of pain beliefs and exercise adherence. Future studies are needed to integrate to investigate psychosocial variables with traditional quantitative research in AT.

1.0 Introduction

Pain, a cardinal feature in AT, may be persistent or chronic and results in a significant impact on daily and recreational activities (Cook and Purdam 2013). Research indicates tendinopathies are associated with a substantial physical, economic and psychological burden (Hopkins *et al.* 2016).

The value of qualitative research to improve the understanding of patients' experiences and of the complex processes involved in treatment outcomes is well recognised and accepted in other MSK disorders (Beaton and Clark 2009). These elements has become increasingly relevant with the move towards a patient-centered paradigm of healthcare (Hush *et al.* 2011). Psychosocial variables such as fear avoidance, self-efficacy, anxiety and hypervigilance have highlighted the impact on baseline disability, ability to perform daily activities and sporting performance in other musculoskeletal disorders (Ross, 2010, Kromer *et al.* 2014). Furthermore psychosocial factors are considered to be important prognostic indicators following exercise interventions (Vlaeyen and Linton 2000, George and Stryker 2011). Consequently, awareness of psychosocial factors may help shape clinicians' management, which may optimise patient outcomes.

Despite a recognition of the value of qualitative research in understanding patients' experiences, and the role of psychosocial factors in treatment outcomes, (Beaton and Clark 2009), research to date in tendinopathy demonstrates a lack of qualitative research, and has instead focused on the physical or structural implications of the disorder utilizing quantitative methods. Consequently, this paper seeks to qualitatively explore the experiences and perceptions of pain in people with AT.

2.0 Methods

2.1 Study Design

A qualitative interpretive description design was chosen as an appropriate methodological approach (Thorne *et al.* 1997). Interpretive description is a non-categorical methodological approach created to allow healthcare practitioners explore clinically occurring phenomena within a conducive framework (Thorne *et al.* 2004). This methodological approach facilitates the exploration of complex experiential clinical phenomena and provides direction in the creation of an interpretative account using techniques of reflective and critical examination (Thorne *et al.* 1997, Hunt 2009). Due to the individual experiences of AT, semi-structured interviews were employed. Semi-structured interviews allow the researcher with a framework with topics or themes to cover, but with a fluid and flexible structure (Edwards et al. 2013). To ensure that the questions had a valid and meaningful theoretical scaffolding, the questioning route for this study was generated based on a literature review of relevant research articles (Hunt 2009). The route was then refined by discussion within the research team to ensure the questions, content and structure were suitably open-ended, neutral and sensitive (Gill *et al.* 2008). Ethical approval for the study was granted by the local Education and Health Sciences Research Ethics Committee in the University of Limerick (Ethics Number: EHSREC2014-05-14). This included obtaining written consent from participants for the publication of their anonymised data.

2.2 Participants

Participants were recruited from the local community including various running clubs by means of e-mail and through word of mouth. Participants were recruited as part of an existing 12-week intervention study.

2.3 Inclusion and Exclusion criteria

Men and women, aged between 18-60 years with AT symptoms for more than 3-months were included. A diagnosis of AT was determined by a combination of Achilles tendon pain, tenderness and impaired physical performance. The exclusion criteria were: under the age of 18, non-English speakers, injury to the foot, knee, or hip on the same side of the AT, injury to

the back and/or history of rheumatoid arthritis or any other injury or illness thought to interfere with the participation in the study.

2.4 Data collection

Semi-structured telephone interviews were carried out by a final year undergraduate physiotherapy student (HC), who was unknown to the participants and was guided by a flexible questioning route. The telephone interviews were recorded by HC at the University of Limerick, with participation in the telephone interviews occurring before commencement of an intervention study. The questioning route covered: participants: participants history of AT, perceived cause of AT, impact of AT pain, experience in managing AT, and perspective on future prognosis of their AT (Appendix 9). To ensure competency prior to conducting the interviews, the interviewer (HC) undertook a number of practice interviews with feedback provided by the primary investigator (SMA). Interviews lasted from approximately 30-60 minutes. Interviews were recorded using a digital voice recorder. During the interviews the researcher took notes, as needed, and statements of relevance and contextual field notes were written verbatim. This aided in the identification of the point of data saturation, as it was evident when no new material or concepts arose (DiCicco-Bloom and Crabtree 2006). Data saturation was achieved after the completion of eight interviews. At the conclusion of each interview, the researcher debriefed the participant on the main content of the interview and time was permitted for any additional commentary to facilitate the emergence of new unanticipated information (Gill *et al.* 2008).

2.5 Data analysis

Interviews were transcribed verbatim. Data generated from the interviews was analaysed using a thematic analysis approach as proposed by Braun and Clarke (2006). Thematic analysis is a qualitative analytic method for 'identifying, analysing and reporting patterns (themes) within data. Three transcripts were randomly selected and initial inductive codes were formed individually by two authors (SMA and AS). The two initial code lists were then amalgamated and a comprehensive code list was finalised in view of the codes most representative of the dataset informed by background reading related to the research question. The finalised code list was then applied to all transcripts by the study author (SMA). Coded

data was categorised and through a process of repetitive interpretation, synthesising and theorising – themes were identified (Thorne *et al.* 1997). Transcripts were then re-read several times and the selected themes were finalised based on consensus discussion between three study authors (SMA, AS and KOS). Four categories were identified to account for all identified themes. Throughout data collection and analysis, widely accepted strategies for ensuring quality in qualitative analysis were maintained, including auditability, fit and transferability (Lincoln and Guba 1985).The consolidated criteria for reporting qualitative research (COREQ) checklist provided guidance during the reporting of this study (Tong *et al.* 2007). To facilitate the rigor of methodology and the transparency of the research process an audit trail was created. Audit trails are a principal technique for establishing the dependability and confirmability of qualitative research findings or to help in assessing the degree of trustworthiness of a naturalistic inquiry (Lincoln and Guba 1985, Bowen 2009).

3.0 Results

3.1 Participants

Eight participants (Five male and three female) with AT were invited to participate in the telephone interviews. The sample size of eight participants reflects the time constraints associated with the intervention study, and the feasibility regarding recruitment. The use of an interview study design and a flexible questioning route ensures no restriction on learning about individual experiences. Table 1 details the characteristics of the included participant's. Elements of the audit trail are detailed in appendix 11.

3.2 Key themes

Four main themes were identified in the data: (i) the meaning and impact of Achilles tendon pain; (ii) participants experience with the management process; (iii) identifying with and self managing Achilles tendon pain, and (iv) looking to the future. Table 15 presents the categories constituting each theme. The frequency and relative weighting of the identified themes is highlighted in table 16 and figure 28.

Theme 1: Pain as a feature of everyday life

Pain and daily activities

Many participants stated that the pain associated with AT resulted in a substantial highlighted their experience of pain and the ability to perform daily activities. The physical disruption was varied and contingent on participant's' symptoms, however morning pain and its associated consequences was a commonly cited issue.

"But in the morning times in particular, very sore in the mornings. You're literally hobbling around the place until you get moving as such." Participant 8

"The morning pain oh its constant. I'd say I haven't had a morning since the start of the year where coming down the stairs i haven't been very tentative about it." Participant 5

While symptoms did not cause disruption at work for all participants, it did have significant consequences for some individuals, depending on the demands of the job. One participant reported not working due to their symptoms, while others reported the pain with their daily work routine.

"Aww, it's just when you have to go anywhere, walk around the office, walking to go get a coffee. You get up; you've forgotten about it sitting down … once you get up it's like ouch. Then you're almost limping everywhere. It's noticeable enough in that people would say are you all right, what are you limping for". Participant 5

Loss of self

AT could also affect personal activities, with participant's highlighting the implications of giving up recreational activities (e.g. running) on their social life and sense of personal achievement and sense of self.

"Frustration, needing …. Wanting to run. Seeing my peers going to races, winning races or getting PBs. Progressing ... and I'm stuck here. That has been horrendous I have to say. Now, I know there are worse things in life that can happen. But it's been horrible." Participant 6

"I get frustrated with myself, you know like feels there nothing at the end of the tunnel you know like. Like I'm not saying me life is around the running but Like I was an alcoholic and I haven't had in drink twelve and a half year ago. And i took up running and it's me life since, you know like." Participant 3

Theme 2: Participant's experience with management process

Frustration with treatment process

Participants frequently outlined their frustration with the treatment process as well as outlining their lack of confidence in the various health care practitioners they had encountered.

"For me there were a lot of grey areas. Everybody was giving me, like telling me different things. So like nobody knew 100% everything about Achilles and it was varying, you know people opinions were varying." Participant 2

Experience with treatment process

The participants expressed the belief that, in order for a treatment to be beneficial, a forceful hands-on treatment was required.

"He wore a kind of a knuckle duster and really rubbed them hard. And I think that's the only thing that got rid of the morning stiffness." Participant 6

Participants also highlighted the expected role of exercise interventions in the management of their AT.

"but i know there are some exercises you should be doing and things like but that. I probably haven't done as much strength work. I don't go to the gym. I don't do any strength work or anything like that." Participant 1

However, in contrast participants also discussed their disbelief and lack of confidence in relation to a proposed exercise intervention.

"There was a therapy that was recommended to me maybe at the start of the year, it was called heel drops or painful heel drops? They're on the edge of the steps and you basically flex, you basically flex down and flex up...Was it 10 minutes a night every night for 12 weeks but in my head that was crazy." *Participant 5*

Theme 3: Identifying with and self-managing AT

Beliefs surrounding causation

Participants outlined a range of factors which they felt were associated with the onset and development of AT.

"It might be just maybe the step up in miles like. Might be the miles. Might have gone too... gone from 40 miles up to 70 miles too fast kinda." Participant 3

"Obviously there's some weakness there i suppose. Or some, or is it down to running style or something. Footwear yeah". Participant 2

Despite the numerous factors proposed by participants there was also a considerable amounts of confusion in relation to the causation of AT.

"I don't know. It's a question people often ask. Definitely people would say to you it's an overuse. And well I'm not doing enough for it to be overuse. That's what wrecks me." Participant 4

Rest as a management approach

Rest was often cited as a self-management strategy in many of the interviews. Often participants expressed the belief that rest would be appropriate in allowing the pain to settle or ensure that time necessary for healing. The adoption of this management approach was as a result of participants own belief system or as a result of advice from health care practitioners or non health care practitioners.

"I possibly didn't rest it enough. That's the only assumption I can come up with that I didn't rest it enough Yeah. As in I've stopped running altogether in the hope that the rest will allow it to recover. The problem is its back to the whole thing of not knowing is that the problem." Participant 5

However the concept of rest as a successful management approach was also contradicted in some of the interviews where participant's outlined their lack of belief in rest as a management approach and expressed a desire to continue running despite this advice.

"I've gone to a lot of physios and they tell me it's an overuse injury but I don't think it is 'cause I've stopped. People say stop and don't do anything for 6 or 8 weeks but if I did stop and went back even for a jog a couple of miles after not doing anything for a period of time id still be in pain like it never stopped." Participant 4

Theme 4: Looking to the future

Fear of future prognosis

A common theme reported in the study was fear, concerns and uncertainty surrounding potential future damage to participant's Achilles tendon. Many participants felt that if they continued to exercise and or failed to address their AT it may lead to greater disability but more specifically the risk of rupturing their Achilles tendon in the future.

"Yeah it could like. It probably... I'd be thinking that like. By running on it as it is, i think it would. It might get to the stage where it will rupture... If I don't get it fixed like."
Participant 3

The desire to run

During the course of the interviews participants were asked to discuss what they would define as a cure in relation to their AT. Some participants spoke about reduction of pain.

"Being able to go to a class and not have pain like after a class. Being able to touch my heel without it being painful is a big thing. That would be it really, not to have pain really."
Participant 2

However, the majority of the participants outlined their desire return to previous running levels or even re-engaging in running to some capacity.

"I suppose being able to get back to running in some shape or form. In an ideal world obviously back to full health and going back to running marathons again. But at the other end of the scale being able to run in some shape or form, any distance just to get out and something." Participant 7.

Table 16: Frequency of statements and interviews for codes and categories

Categories/Codes	No of statements
Pain as a feature of everyday life	12
Pain and daily activities	8
Loss of self	4
Theme 2: Participant's experience with management process	11
Frustration with treatment process	5
Experience with treatment process	6
Identifying with and self-managing AT	13
Beliefs surrounding causation	7
Rest as a management approach	6
Looking to the future	14
Fear of future prognosis	7
The desire to run	7

Figure 28: Graphical illustration for codes and categories expressed in the interviews

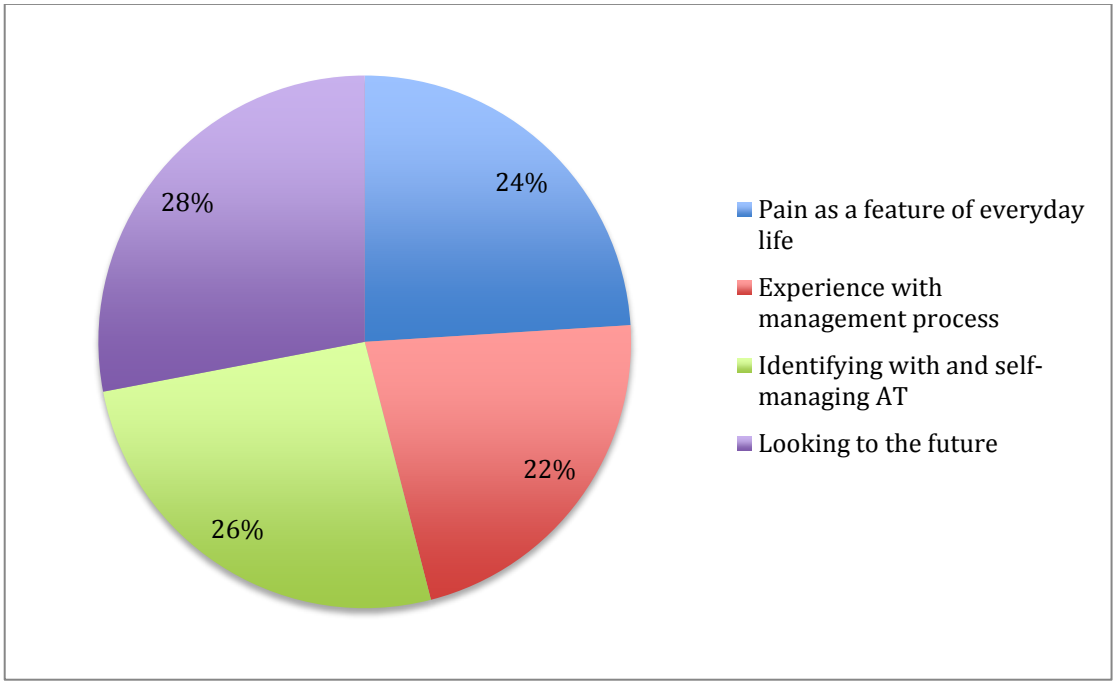


Table 17: Study V Characteristics of the study participants

Participant	Age (Years)	Height (Cm)	Mass (Bobbert *et al.*)	VISA	Unilateral/Bilateral	Mid Tendon/Insertional	Sex	Symptom Duration (Months)	Running per week (Minutes)
1	36	170.5	71	83	Bilateral	Mid Tendon	Male	5	210
2	39	158.4	79	38	Bilateral	Mid Tendon	Female	17	0
3	49	160.4	59	54	Unilateral	Mid Tendon	Male	5	0
4	37	170.3	71	78	Bilateral	Mid Tendon	Male	96	200
5	39	169.7	65	73	Bilateral	Mid Tendon	Male	7	215
6	51	160	50	74	Bilateral	Mid Tendon	Female	17	95
7	33	191.7	106	28	Unilateral	Mid Tendon	Male	8	0
8	36	174.1	73	81	Unilateral	Insertional	Male	9	360

Table 18: Study V Identified Themes

Impact of AT	Participants experience with management process	Identifying with and self-managing AT pain	Looking to the future
• Impact on daily activities • Loss of self	• Treatment expectations • Frustration with treatment process	• Beliefs surrounding Causation • Rest as a management approach	• Fear of the future prognosis • The desire to run

4.0 Discussion

The prime focus of research and scientific investigation to date in AT has utilised quantitative methodologies which has helped improve the management of the physical impairments associated with AT. Despite the relative success of such approaches, AT can often remain resistant to treatment, and dominance of peripheral tissue focused interventions are unlikely to address complex psychosocial adaptions associated with persistent pain (Rio *et al.* 2015, Mallows *et al.* 2016). This is the first study to utilise a qualitative methodological approach in AT to investigate participant's beliefs and experiences of AT. Four main themes emerged from the data: (i) pain as a feature of everyday life (ii) participant's experience with the management process; (iii) identifying with and self-managing AT and (iv) looking to the future.

The psychological burden of AT and the loss of self

One of the main findings of this study highlighted the physical, emotional and social disruption associated with persistent AT. Participants reported disruption and change in their ability to perform and engage in normal daily activities. This was particularly evident in the morning, with participants also describing an extension of physical symptoms into their daily work routine.

Perhaps of most interest was the effect of persistent AT on individual's social and emotional wellbeing. Pain and injury is often a traumatic event where emotional and psychological reactions are produced, often based on an individual's perception of loss (Green and Weinberg 2001). Although the concept of a perceived loss affects individuals differently, injury or pain can often prevent an individual from pursuing a self-defining activity. As a result, they are particularly vulnerable to a milieu of psychological reactions such as anxiety, depression, fear, and loss of self-esteem or identity . A common theme highlighted in the interviews was participant's experiences of giving up recreational activities (e.g. running) on participant's social life, and its effect on the participant's sense of sense of self. The disruption to social and recreational activities experienced by participants may be closely attributed to reductions in individual's self-esteem or loss of what is known as athletic identity. Individuals who are intensely involved with athletic activities (e.g. running) and receive encouragement for their

participation may focus their self-identity on the role of an athlete (Rotella 1993). If an individual then becomes injured, his or her identity might be threatened due to the inability to fully engage in athletic pursuits which may lead to emotional and psychological reactions, which are typically negative (Green and Weinberg 2001). Results of the current study suggest that in individuals with persistent AT, the inability to engage in recreational or athletic activities may result in loss of an individual's identity. Similar findings have been expressed in other qualitative MSK studies in adults with Osteoarthritis (OA) .

Cognitive appraisal and associated coping strategies in AT

Research exploring the psychological consequences of injury suggests that once an injury occurs, an individual begins a process of cognitive appraisal resulting in the generation of emotional and behavioural responses (Albinson and Petrie 2003). The cognitive appraisal may involve two processes; primary and secondary appraisal. For the primary appraisal, the individual asks, "Is this harmful to me?" Once this initial assessment is made, the secondary appraisal begins with the question "Will I be able to deal with this situation, and, if so, how?". The concept of primary appraisal was highlighted in the current study where participants consistently reported concerns and fears surrounding potential future damage and/or risk of rupturing their Achilles tendon. In order to deal with this situation, participants commonly outlined a view that rest was a necessary management strategy in order to allow the tendon necessary time to heal and prevent what they perceived as future potential damage. This avoidance as a result of a cognitive appraisal by decreasing physical activity levels was in spite of the associated negative effect on their recreational activities and identity as outlined previously. Such concerns or associated behaviours may be labeled fear-avoidance beliefs. The concept of fear avoidance beliefs was first proposed in the Fear Avoidance Model (FAM) of musculoskeletal pain (Vlaeyen and Linton 2000). According to this theory, some individuals consider a painful stimulus as negative, and avoid or postpone the event that is considered painful (Sindhu *et al.* 2012). Over a long period of time, hypervigilance and avoidance of physical activity may result in deconditioning or atrophy of the musculoskeletal system (Littlewood *et al.* 2013). Ongoing fear, anxiety or catastrophising regarding one's Achilles tendon (fear of damage, apprehension about loading the tendon, distress

due to restricted activities) may lead to ongoing sensitisation of the central nervous system. This may ultimately affect pain and/or motor output or reinforce avoidance of loading their Achilles tendon. Research in other persistent MSK conditions has highlighted the negative influence of fear-avoidance beliefs on recovery times (Landers *et al.* 2008, George and Stryker 2011, Westman *et al.* 2011, Kromer *et al.* 2014, Ross *et al.* 2002). However, the process and outcome of cognitive appraisal is highly variable between individuals. Despite a dominance of fear and restriction of activities within the study, some participants outlined their desired to continue to run despite the pain, which would appear to contradict the FAM and highlights the diversity of individual's response to pain. Additionally, cognitive appraisal and associated behavioural responses are influenced by societal factors and social support (Green and Weinberg 2001). Social support appears to facilitate the coping process by providing additional resources such as advice, information, and material services that could increase an individuals coping resources (Pearson 1986). Results of this study appear to indicate that participant's beliefs surrounding rest and its potential role in the development of fear avoidance beliefs may have been contributed to by advice from health care practitioners and non- health care practitioners.

Active interventions in AT: The need to combine exercise with pain reconceptualization

The variability in participants' perceptions in terms of coping strategies was further reiterated in participants' experience with the treatment process. The concept of rest expressed by many of the participants in the study appeared to be contradicted by some participants who highlighted the belief that forceful hands on treatment was beneficial for their AT. Despite this, many participants expressed their frustration at their experiences with the management process to date. Interestingly despite the evidence to support the use of strengthening interventions in AT (Alfredson *et al.* 1998, Malliaras *et al.* 2013, Beyer *et al.* 2015), few participants reported a history of, or a belief in, the use of strengthening interventions. This finding highlights the potential importance of aligning exercise prescription and instructions with the key messages of pain education in AT. The manifestation of avoidance behaviours as a result of cognitive appraisal resulting in avoidance of loading a painful tendon would seem a sensible approach given that pain is normally a necessary protective mechanism by your body. However, while

relative rest and avoidance of loading a painful tendon may be appropriate in the early stage of AT, research suggests that progressive strengthening interventions in AT may be important to improve pain and disability. Thus, prescribing exercise interventions to individuals without spending appropriate time rationalising their importance using pain neuroscience education may affect compliance with an exercise program. Pain neuroscience education is a cognitive approach which seeks to change beliefs and cognitions related to pain (Blickenstaff and Pearson 2016). It appears that when individuals understand more about pain neuroscience they will alter the manner in which they approach movement, exercise and activity (Blickenstaff and Pearson 2016). Pain with movement is no longer seen as an experience to endure, or as an experience from which to flee or avoid (Blickenstaff and Pearson 2016). Pain neuroscience education has been shown to be effective in changing pain beliefs and improving health status and reducing healthcare expenditure in chronic pain disorders (Moseley 2002, Moseley 2004, Meeus *et al.* 2010, Louw *et al.* 2011, Louw *et al.* 2014). Unfortunately the concept of aligning pain education with rehabilitation of MSK disorders is still relatively new, with research to date focused mainly on chronic spinal conditions (Moseley 2002, Louw *et al.* 2014).

Limitations

There are a number of methodological considerations that may influence the generalisability of the research. One potential limitation relates to the recruitment of the participants, which may have resulted in "volunteer bias". Participants included in this study were predominantly athletic or recreationally active, interviewed prior to engaging in an exercise intervention. The fact that these participants were willing to engage in an exercise intervention study may indicate that these participants displayed similar views and experiences relating to their AT pain, and were at least willing to consider an active intervention for their AT. This affects the generalisability of the results considering the prevalence of AT in non-athletic populations. A further limitation relates to the sample size of the study. As a result of time constraints it was not possible to perform additional interviews, which may have provided further insights. Another limitation of the current study relates to patient and public involvement (PPI). The interview route was designed through a process of consultation amongst the study authors, with interviews

undertaken by a final year undergraduate student. Although the interviewer did probe other issues that arose and encouraged people to discuss whatever they felt pertinent, participant's data was not used to inform future questioning and is a potential limitation of the study. Finally, the sample set of participants recruited for this study excluded individuals with acute AT which may have gone on to be resolved and their experiences may not be reflected in the current sample.

Conclusion:

Research in AT has mostly focused on the associated physical impairments utilising quantitative means. Despite the often-persistent nature of AT, no studies have look at the psychosocial aspects of AT using qualitative methods. This study suggests that persistent AT is associated with a significant psychosocial burden, particularly in terms of participation in daily life and valued activities. Considerable confusion and frustration regarding management of AT, and its course, were reported. Better understanding the personal experiences of AT may enhance management of this persistent disorder, and facilitate individuals with AT complying with evidence-based approaches including exercise and pain reconceptualization.

CHAPTER 5: DISCUSSION

The aim of Chapter 5 is to review the studies from each chapter in this doctoral thesis, and link the results of each study to the current scientific literature on AT. This chapter will discuss how the findings of this doctoral thesis contribute to the current knowledge, regarding the relationship between structure, function, and pain in AT. The findings of this thesis will also be discussed in light of its potential impact on the clinical management of AT. Finally, the limitations of this thesis, and its implications for future research, will be discussed.

KEY FINDINGS

- A systematic review indicated that US imaging of tendon size displays good to excellent inter and intra-rater reliability in a range of upper and LL tendons, with a small degree of measurement error.

- A systematic review and meta-analysis established that tendon abnormalities were associated with a 5 fold increased risk of developing Achilles or patellar tendinopathy in asymptomatic athletes.

- A systematic review and meta-analysis highlighted that people with AT display an altered strength profile, across the entire strength spectrum, using a range of outcome measures.

- Results from a pilot intervention study suggest that clinical improvements following a 12-week loading intervention are associated with a range of psychosocial, somatosensory, and functional factors.

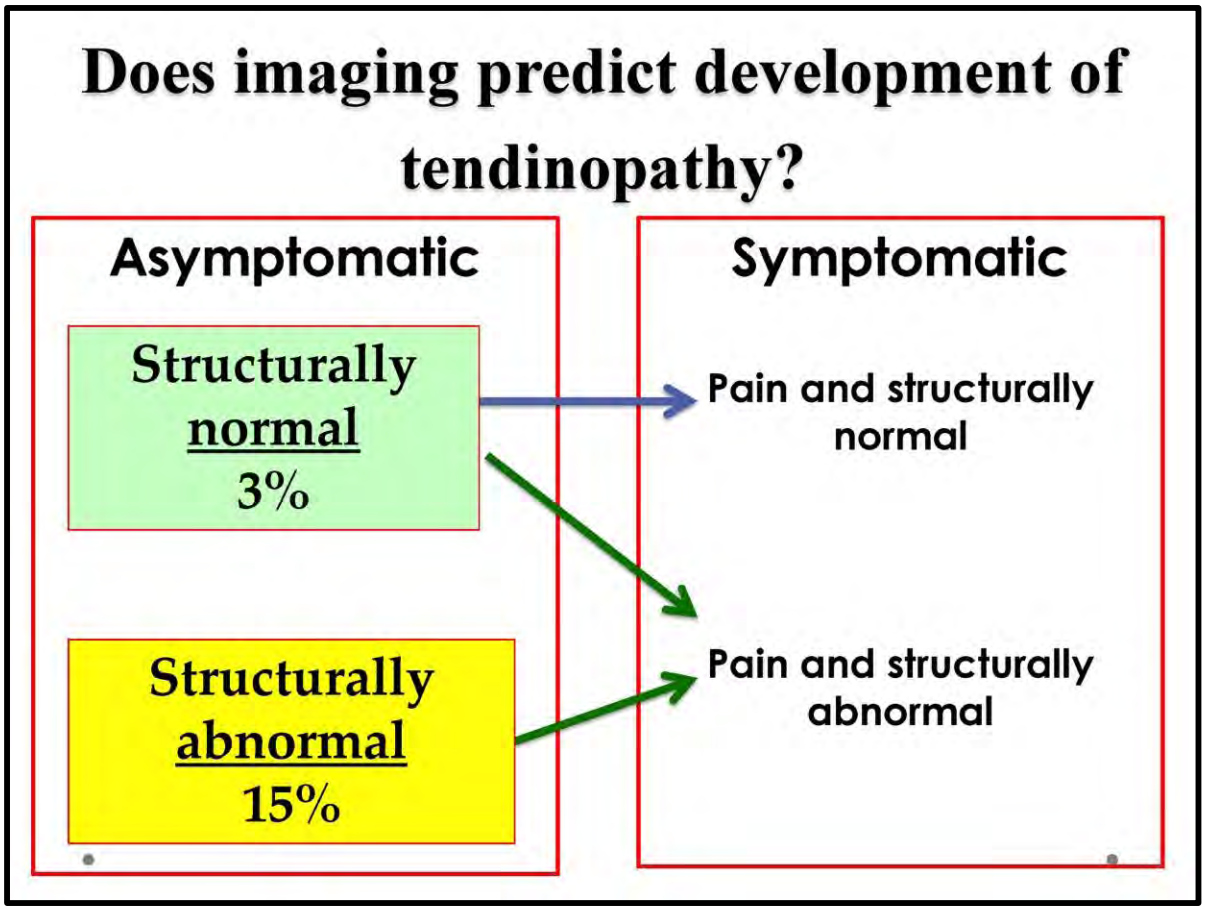
- Findings of a qualitative study, suggests that AT is associated with significant psychosocial variables, particularly participants' fear surrounding future tendon damage and confusion in relation to diagnosis, and management of the AT.

Change in tendon structure is associated with the development of pain

The results of Chapter 2 indicate that US imaging is a reliable and clinically important tool in the management of AT. Traditionally US imaging has been used to visualise alterations in tendon structure, referred to as tendon abnormalities. Tendon abnormalities include hypoechogenicity, increased thickness, or increased vascularity. Although US has gained increasing popularity in routine clinical practice over the past decade, in comparison to MRI, it is perceived to have a higher risk of error or variance when evaluating tendon size. The results obtained from the systematic review in Study I appear to refute this perception by demonstrating that US is reliable, both in terms of relative and absolute reliability, across a range of upper and LL tendons, and in athletic and non-athletic populations. The assumption that US is associated with user variability also appeared to be unwarranted, with results of study I reporting similar levels of inter and intra-rater reliability. Furthermore, study I also established that US imaging of tendon structure is associated with a low degree of measurement error when quantifying tendon size. Results of Study I may have important clinical implications for the management of tendon related disorders in clinical practice. Although speculation at this time, the recognition of US as a clinically reliable measurement tool may reduce unnecessary referral for time consuming and expensive procedures such as MRI in the management of tendon related disorders, which may result in reduced cost and burden for patients and healthcare providers alike (Sheehan *et al.* 2016).

Results of Study I also highlights potentially important implications in the context of the findings of Study II, in relation to the overall context of the relationship between structure and pain in AT. Results of a meta-analysis in Study II indicated that structural abnormalities visualised using US imaging, are associated with a 5 fold increased risk of the development of Achilles or patellar tendinopathy compared to structurally normal tendons (Figure 28). These findings suggest that US imaging may be a useful prediction tool in identifying athletes potentially at risk for the development of AT, which may allow the implementation of prophylactic programmes or alterations in training routine to prevent or offset the development of future symptoms.

Figure 29: Summary of predictive ability of ultrasound imaging



Is imaging a useful prediction tool in AT?

Study II indicates that structural changes in asymptomatic populations might represent markers of early pre-symptomatic pathology, which is then later characterised by episodes of pain and/or reduced function. Visualising tendon abnormalities using US may identify potential at-risk athletes and may allow appropriate intervention through the implementation of preventative strategies, such as adapting training load (Hulin *et al.* 2015) or appropriate tendon loading programmes (Fredberg *et al.* 2008a). While results of study II indicate that structural abnormalities increase the risk of developing symptoms, it is clear the outcome is far from dichotomous. How to clinically interpret the relationship between structural changes in the

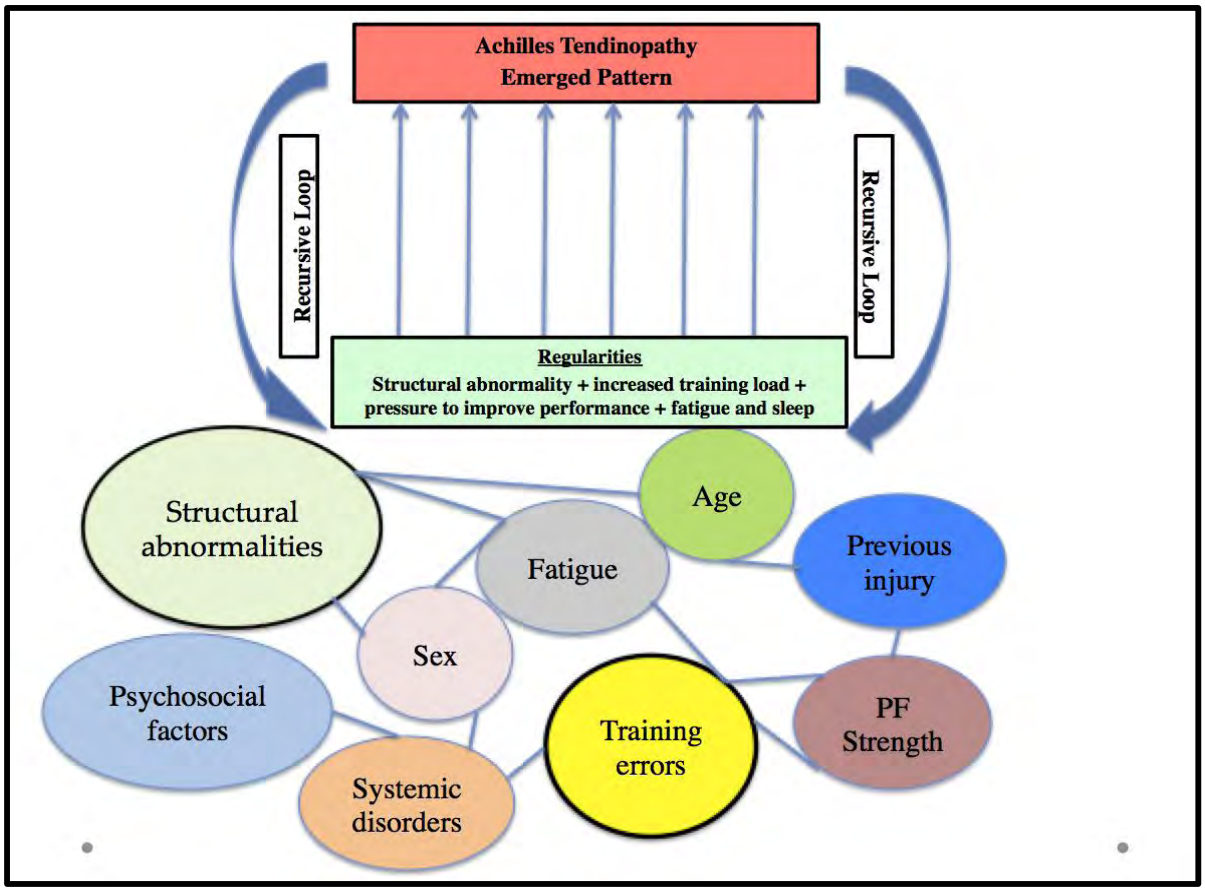
Achilles tendon and pain is difficult in the context of the high percentage of abnormalities in asymptomatic populations.

The Cochrane guidelines for interpreting RR ratios advise that the clinical importance of a given RR ratio cannot be assessed without knowledge of the typical risk of events without treatment. This review indicates that the overall number of normal tendons that developed symptoms was small (19/635 = 3%), while the meta-analysis estimates the relative risk for an abnormal Achilles tendon is 7.33, 4.35 for abnormal patellar tendons, and 4.97 for both tendons combined. Consequently the actual risk of asymptomatic athletes with a structural abnormality in their tendon developing tendinopathy ranges from 13-22% (RR x percentage risk in a "normal" population) depending on the tendon in question.

Findings of chapter II indicate risk of asymptomatic athletes with a structural abnormality in their tendon developing tendinopathy ranges from 13-22% (RR x percentage risk in a "normal" population) depending on the tendon in question. Theoretically, in a sample of 100 athletes as many as 61 of these may have Achilles abnormalities, while as many as 39 may have patellar abnormalities. Of these asymptomatic tendon abnormalities 13/61 of Achilles tendons may go on to develop symptoms (RR x percentage risk in a "normal" population equates to 21% risk), while 6/39 of patellar tendons may go on to develop symptoms (RR x percentage risk in a "normal" population equates to 21% risk). Consequently, although there is a clear statistical relationship between tendon abnormalities and development of future symptoms, this relationship is far from dichotomous. This highlights the issue of the over-simplification of complex problems such as AT into basic units focused on identifying isolated factors (structural abnormalities), that are frequently assumed as causes or predictors of pain (Philippe and Mansi 1998, Galea *et al.* 2010). The assumption of linearity between tendon structure and the development of pain is the classical science method of a reductionist paradigm (Philippe and Mansi 1998, Quatman *et al.* 2009, Mendiguchia *et al.* 2012). A reductionist paradigm may not be sufficient in predicting those who will develop future AT, given the fact that there are several factors at multiple levels that may interact with each other in order to arrive at the initial manifestation of AT (Exposure) (Figure 29).

To highlight this concept further, we may consider structural abnormalities (Giombini *et al.* 2013), and training load (van Gent *et al.* 2007), two frequently hypothesised risk factors for developing AT. In some cases, structural abnormalities may only be relevant in the presence of athletes with a high training load or involved in sporting tasks that demand use of the Achilles tendon. Training load will influence the former because high frequency jumping/running increases the total mechanical energy reaching the tissues. Additionally, the amount of training load could be modulated by the excessive demands of coaches' training philosophy, or patients desire to exercise due to a host of psychosocial factors such as body image, peer pressure, stress relief etc. The complex chain of possible interrelated events highlights the multifactorial nature of injury prediction, and establishes a complex web of injury determinants, which requires a complexity approach to be better understood (Philippe and Mansi 1998). Therefore, although Study II identified tendon abnormalities are associated with an increased risk of developing future tendinopathy, the findings should be interpreted in the context of the complex interaction between multiple factors. Consequently, Bittencourt *et al.* (2016) have proposed a systems approach for sports injury which highlights the complex interaction between multiple factors in what they term as a "web of determinants". The complex systems approach in relation to AT is highlighted in figure 29, and its theoretical basis will be used to further discuss the implications of the findings from chapter 2.

Figure 30: Complex systems theory of AT



As indicated previously structural abnormalities and training errors are two of the most commonly cited risk factors in the development of tendinopathy, and in theory would make up the main elements of the web of determinants. In turn, these factors may be influenced by a host of contributing factors including altered foot function (Crossley *et al.* 2007), reduced ankle dorsiflexion (Malliaras *et al.* 2006), sex (Owens *et al.* 2013), diabetes (Ranger *et al.* 2015), adiposity (Gaida *et al.* 2009), muscle weakness (Mahieu *et al.* 2006) and genetic factors (September *et al.* 2006). The manner and combination of how these factors interact to lead AT may vary between individuals.

In summary, US imaging is a reliable method of quantifying tendon structure, and although

results of study II indicated structural abnormalities are associated with an increased risk of developing AT, the results must be interpreted with caution. Future research investigating the interactions between multiple risk factors using prospective study designs may improve our understanding of AT.

Pain is associated with alterations in tendon function

An initial objective of the current thesis was to investigate the presence and scope of alterations in MT function in people with AT. Results of the systematic review and meta-analysis in Study III demonstrated alterations in the strength profile of participants with AT, compared to the non-injured side or asymptomatic controls across the entire strength spectrum. As highlighted previously, the assessment of MT function to date in AT has demonstrated a bias towards the use of assessment of maximal strength using a concentric/eccentric heel raise test (Silbernagel *et al.* 2001, Haber *et al.* 2004, Möller *et al.* 2005, Madeley *et al.* 2007), or maximal PF strength using isokinetic dynamometry (Alfredson *et al.* 1996, Alfredson *et al.* 1998a, Alfredson *et al.* 1998c, McCrory *et al.* 1999, Öhberg *et al.* 2001). Although Study III indicated maximal strength is reduced in people with AT, it appears that this aspect of strength is only one component of the strength spectrum, or force velocity curve. The maximal strength tests outlined in study III may not provide sufficient assessment of muscle power capabilities of the Achilles tendon during rapid SSC maneuverers (Rio *et al.* 2015a), where single-joint, isolated assessment bear little resemblance to running or jumping movements which require considerable amounts of MT function (Mirkov 2013). Consequently assessment of reactive and explosive strength variables, which replicate the SSC, may provide additional information in relation to the ability of the MT unit to perform SSC maneuvers, which may ultimately provide insight into rehabilitation strategies.

Assessing reactive and explosive strength in AT: future potential

Explosive strength is the ability to increase force or torque as quickly as possible during a rapid voluntary contraction, realised from a low or resting level (Maffiuletti *et al.* 2016). GRF and

RFD appear to be the most common methods of investigating explosive strength variables in AT. The rationale for the inclusion of explosive strength measures such as RFD suggests that, compared to maximal strength, RFD seems to be (1) better related to most performances of both sport-specific and functional daily tasks, (2) more sensitive to detect acute and chronic changes in neuromuscular function, and (3) potentially governed by different physiological mechanisms (Crameri *et al.* 2007, Abate *et al.* 2009, Maffiuletti *et al.* 2010, Angelozzi *et al.* 2012, Tillin *et al.* 2013, Jenkins *et al.* 2014, Peñailillo *et al.* 2015). Results of study III suggest that people with AT display alterations or reductions in the RFD, while results for GRF were somewhat unclear, suggesting further investigation is warranted. This suggests that quantification of explosive strength variables may be adopted into the clinical assessment of tendon function in AT. However, the use of such measures in routine assessment of AT appears limited at this time. The methodologies used to quantify RFD and GRF display large variability in methodologies between studies, and even within variables. In addition RFD and GRF are often captured during multi joint actions such as running, jumping, hopping which increases the variability of the results. Although the assessment of explosive strength variables appears promising, additional research is needed to address some of the concerns expressed above.

Assessment of reactive strength involves quantification of movements where force production is largely derived from MT stiffness and SSC function (Karp 2007). Performance of the SSC is often measured by pre-stretch augmentation, i.e., comparing the increase in performance in a countermovement jump (CMJ), drop re-bound jump or single leg hopping (Hamilton 2009). To date in AT, quantification of hopping ability appears to be the most popular method of assessing reactive strength. This is reiterated by alterations or reductions in single leg hop distance in Study III, as well as in the pilot intervention study. This finding suggests reactive strength variables in the form of hopping may provide a cheap, quick assessment tool in AT, depending on the individual patient profile (Swearingen *et al.* 2011). However, as discussed previously single leg hop distance is an example of a slow SSC movement, highlighting the need for concurrent measures quantifying fast SSC variables. The largest effect size highlighted in amongst the hopping tasks in Study III was reported during a triple hop task (Wang *et al.* 2012). The triple hop is often cited as a reliable method of assessing muscular strength, and may be

attributed to the fact that it reflects a fast, rather than slow, SSC movement (Hamilton *et al.* 2008). Unfortunately, as discussed in study III there is a scarcity of studies investigating the distinction between fast or slow SSC variables in people with AT despite their relative importance to the functioning of the SSC. It is noteworthy that the assessment of reactive strength variables is not without limitations. The large contribution of the whole kinetic chain during hopping tasks makes it difficult to definitively infer deficits are related to the Achilles MT unit alone.

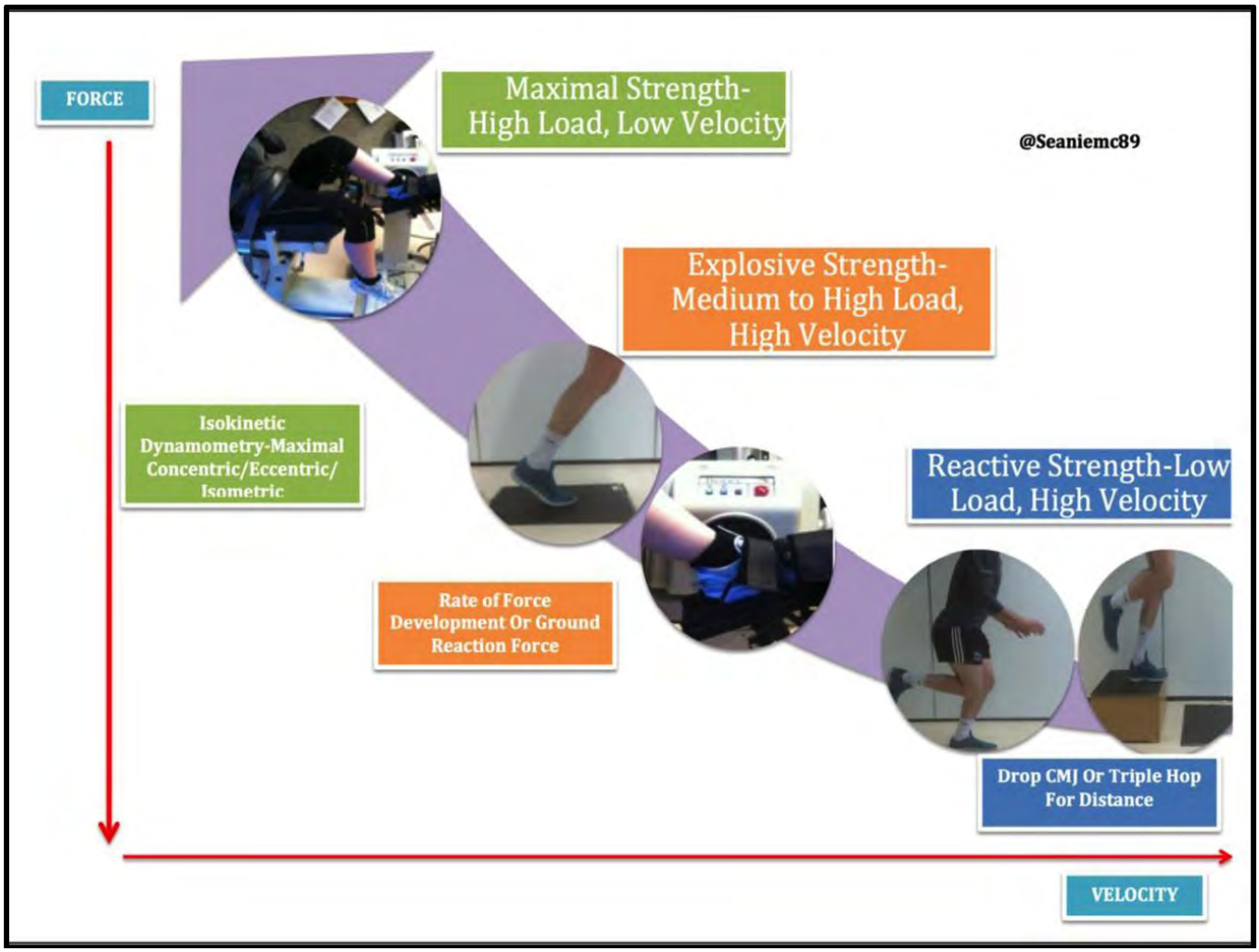
In summary, assessment of Achilles MT function to date has focused on maximal strength variables. Results of study III and IV highlight the potential need to adapt and utilise a range of assessments across the strength spectrum according to an individuals functional demands, and capacity. The clinical applicability and feasibility of many of these assessment techniques requires further clarification and investigation.

Tendon structure and function: future potential in "strength" assessment?

Tendons consist primarily of a collagenous matrix, with elastic properties enabling them to transmit force relative to the amount of the stretch they experience (Lichtwark and Wilson 2005). Stiffness is the ratio of force applied to the tendon and its elongation in response to the force (Arya and Kulig 2010). Athletes with increased MT unit stiffness have demonstrated superior SSC ability (Butler *et al.* 2003, Harrison *et al.* 2004), most likely due to increased energy storage in the MT unit and increased reflex activity during lengthening (Furlong 2014). Alterations in the mechanical or structural properties in AT were demonstrated in study III highlighting its potential in the assessment of AT. It may be postulated that decreased tendon stiffness as a result of AT may lead to increased hysteresis or strain on the Achilles tendon, which is hypothesised to result in ongoing recurrence of symptoms, due to an inability to dissipate forces during SSC loading activities (Muraoka *et al.* 2005, Arya and Kulig 2010, Child *et al.* 2010). Despite the potential importance of tendon mechanical properties to SSC functioning, assessment of tendon mechanical properties in AT, and their correlation with traditional strength variables is relatively unknown. This limits recommending such measures in routine clinical assessment of AT.

A schematic representation of the assessment outcome measures based on study III is outlined in figure 30.

Figure 31: Assessment techniques in AT



Matching rehabilitation to functional deficits and demands

Similar to the assessment techniques in AT, loading interventions in AT have mostly focused on slow maximal strength interventions. Although maximal strength interventions improve pain and disability, people with AT display persistent deficits in tendon function, particularly reactive strength variables, as well as suffering reoccurrence of symptoms (Paavola *et al.* 2000, Silbernagel *et al.* 2007c). Consequently, the one size fits all concept of assessment and rehabilitation of tendon function may fail to adequately address deficits in AT function throughout the entire strength spectrum or force velocity curve (Beattie *et al.* 2014).

Results of the pilot intervention study appear to reiterate this finding, where improvements in maximal strength variables were reported following the 12-week loading intervention. In contrast, there was no significant change in the reactive strength variable dCMJ, highlighting the potential importance of matching loading interventions to functional deficits across the entire strength spectrum. However, improvements in single leg hopping following the intervention period appear to contradict this finding that maximal strength interventions do not address other strength variables. One potential explanation for this finding may relate to the mechanisms controlling both dCMJ and single leg hopping. Reactive strength variables such as hopping and dCMJ are considered plyometric exercises that utilise the SSC (Flanagan 2007). SSC movements can be further categorized as either fast or slow (Schmidtbleicher 1992). The fast SSC is characterised by short contraction times (<0.25s), small angular displacements, and can be observed in depth jumping, while slow SSC movements involve longer contraction times, and larger angular displacements. Fast SSC movements (dCMJ) rely on elastic energy contribution based on a short transition period between eccentric and concentric phases, while slow SSC (single leg hop distance) activities are more reliant on neural potentiation of the contractile machinery during the eccentric phase and increased time to develop force (Bobbert *et al.* 1997, Walshe *et al.* 1998). As a result, slow and fast SSC may represent different muscle action patterns, affecting performance in different ways. Slow SSC movements such as hopping may be more related to maximal strength compared to fast SSC movements, which are associated with elastic storage and the muscle spindle reflex (Flanagan 2007). This highlights the varying

response of strength variables to loading interventions. Nevertheless, while there are distinctive components of the strength spectrum, which may respond to diverse interventions, there will be a degree of overlap or carryover in response to any specific loading intervention.

The findings of Study III and IV highlight the potential role of plyometric interventions in AT, in order to address reactive and explosive strength variables. Plyometric training is a category of explosive body weight resistance exercises which focus on exploiting the additional force output of the stretch reflex of a muscle, to increase speed and power (Booth and Orr 2016). Several studies have demonstrated improvements in running economy and running performance in athletic populations as a result of plyometric training (Spurrs *et al.* 2003, Booth and Orr 2016). Improvements in performance indicators as a result of plyometric training have been attributed to improvements in the functioning of the SSC and alterations in stiffness at the MT unit (Dalleau *et al.* 1998, Chelly and Denis 2001). Despite this finding, the majority of the studies have utilised asymptomatic populations, with a paucity of research investigating reactive/explosive strength interventions in AT, highlighting the potential need for future research in this area.

It is worth noting that plyometrics place a high demand on a person's MT capacity, and therefore loading interventions in AT may need to be tailored to a person's capacity and functional demands. For example, the use of heavy slow maximal strength training may be more appropriate in individuals not involved in high load SSC type activities (Hill walkers, Cyclists). In contrast, interventions targeting reactive or explosive strength may be more important in athletes that require higher functioning of their SSC (e.g. those who regularly engage in jumping or running activities), thus highlighting the potential importance of targeted rehabilitation programmes in AT. Interpreting the raw data values in the pilot intervention in study IV appear to illustrate this point further. It is evident from this data that those participants with lower VISA-A scores at baseline experienced the highest mean change in VISA-A scores following the intervention period, while those participants that displayed higher VISA-A scores >70, pre intervention. displayed less mean change following the loading intervention. Although participants with a higher baseline VISA score at baseline may already had a ceiling effect, it could also be plausible that the participants with the higher baseline VISA-A scores may have

benefited from a higher level loading intervention, such as plyometrics. This reiterates the potential importance of matching rehabilitation to patients' individual deficits and functional demands rather than the "one size fits all" policy to date. However, it is unknown whether VISA-A scores correlate with measures of function, or if explosive/reactive strength interventions improve function/pain outcomes in AT, highlighting the need for future research.

In summary, results of Study III and Study IV suggest that although maximal strength loading appears to be effective at improving pain and function in AT, they might not adequately address deficits in tendon function across the strength spectrum. Interventions targeting explosive and/or reactive strength variables using plyometric training may benefit individuals requiring high-level tendon function. A schematic representation of rehabilitation variables, based on the force velocity curve is outlined in figure 31.

How does pain alter tendon function?

Numerous theories have been proposed to explain the mechanisms associated with alterations in AT function as a result of pain. One theory suggests alterations in the structural properties of the MT unit as a result of AT. This theory proposes that structural alterations in the tendon (e.g. disorganised collagen architecture, thinner collagen fibers, increased water content in the extracellular matrix) may alter a tendon's capacity to store kinetic energy (stiffness and strain as outlined in study III), thus affecting strength and functional performance (Wang 2006, Child *et al.* 2010). Another hypothesis highlights the role of disuse atrophy, or muscular deconditioning as a result of pain as another potential mechanism associated with alterations in function. Ongoing fear, anxiety or catastrophising (fear of rupture, fear of damage, apprehension to load, or anxiety as a result of restricted activities) as outlined in the qualitative interviews in study V may lead to ongoing sensitisation of the central nervous system, which may ultimately lead to a reluctance to load what they perceive as a damaged tendon (Littlewood *et al.* 2013). A final theory proposes alterations in tendon function are as a result of altered motor output in the CNS, which manifest as a result of pain inhibition. Pain is known to have an inhibitory effect on motor

output (Rio *et al.* 2014). It is proposed that continued and persistent pain may have an inhibitory effect on motor output from higher centers (Rio *et al.* 2014). To highlight this theory, altered motor volitional strategies and increased cortical inhibition have been reported in tendinopathy (Edwards *et al.* 2010, Ngomo *et al.* 2015, Rio *et al.* 2015b), as well as in studies on ACL injury, (Héroux and Tremblay 2006) and knee pain (Torry *et al.* 2000).

A schematic representation of the possible mechanisms behind altered tendon function in AT are outlined in figure 32.

Figure 32: Rehabilitation variables in AT

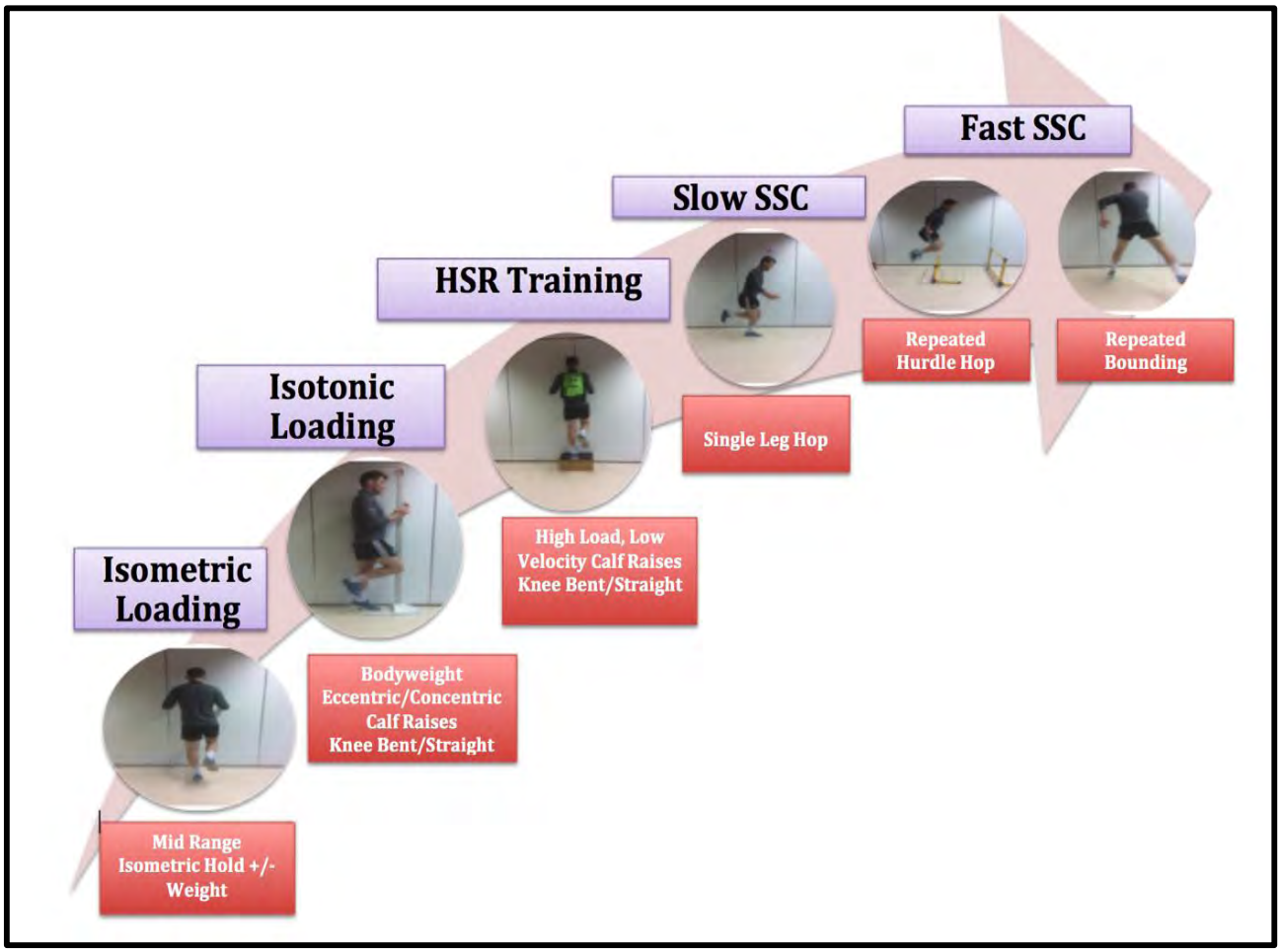
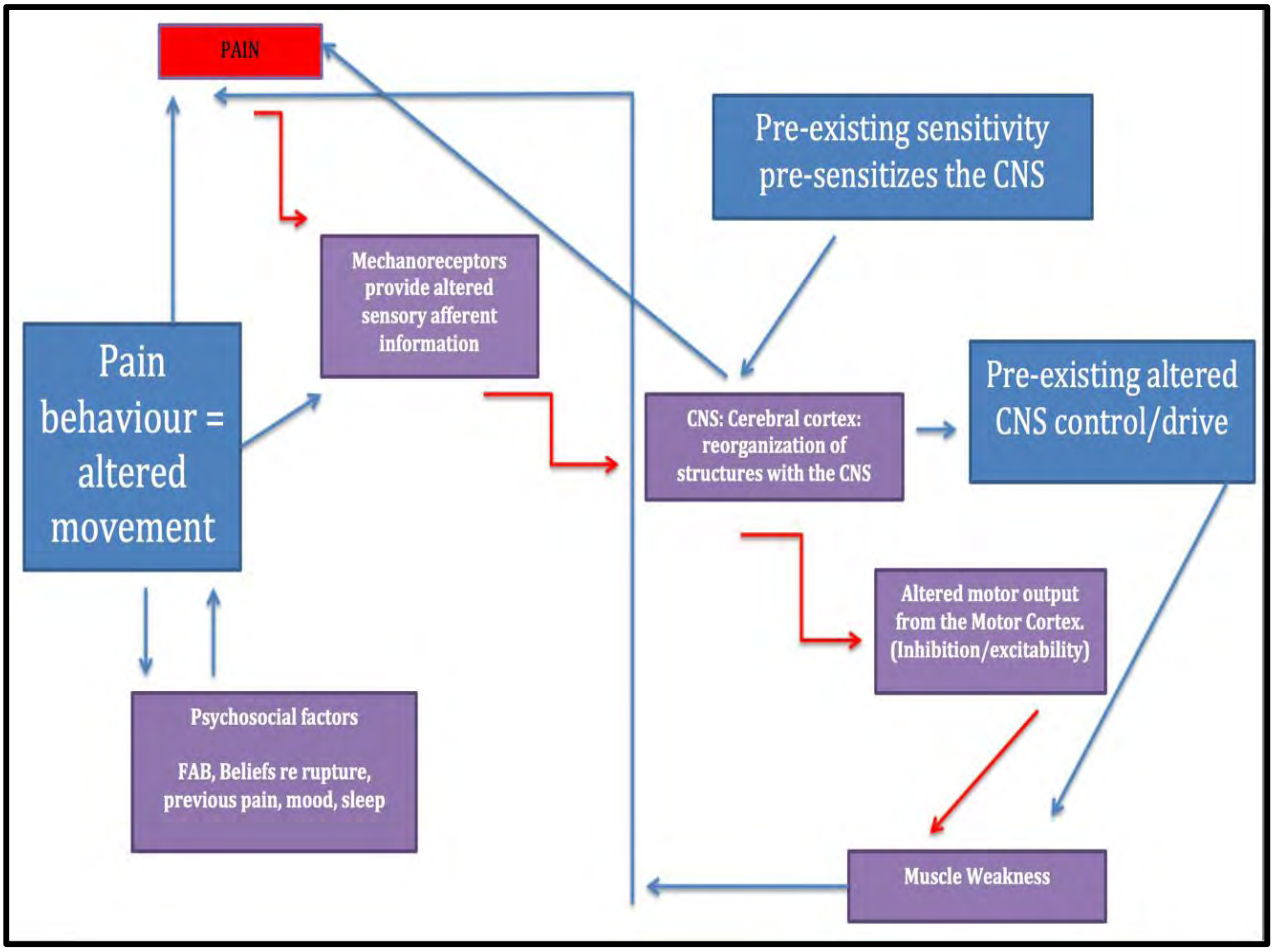
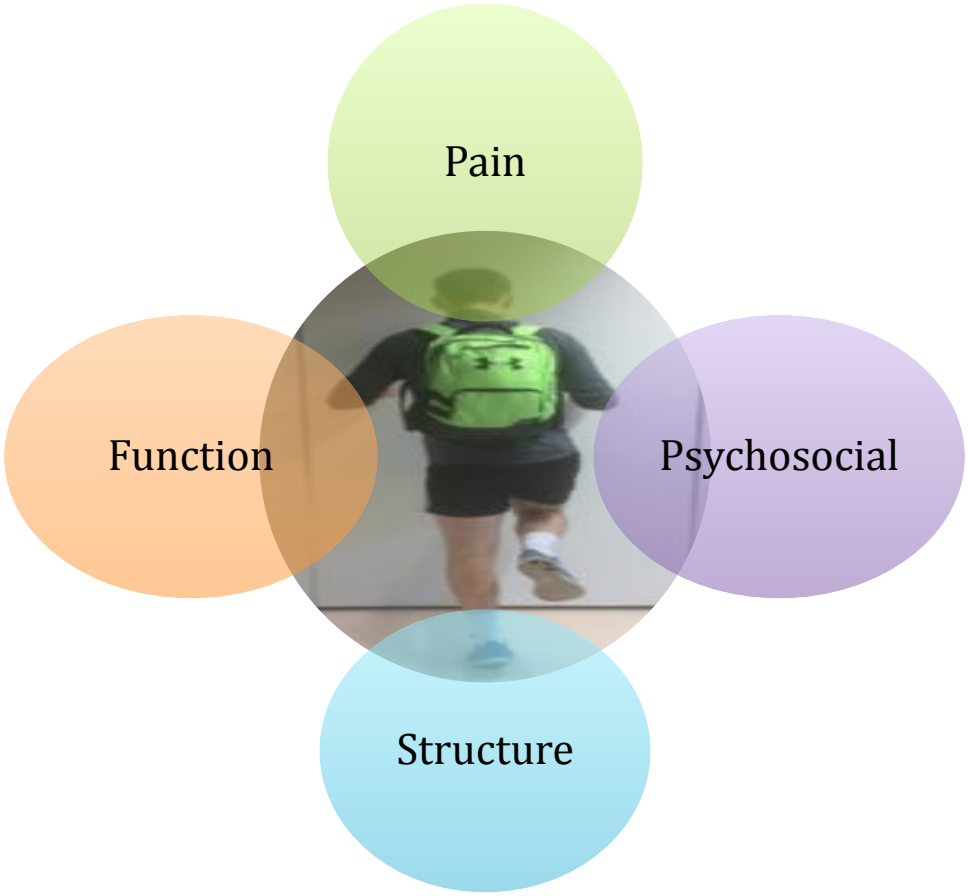


Figure 33: Potential mechanisms associated with altered strength profile



Clinical improvements following loading interventions in AT: A multifactorial response

Figure 34: Relationship between structure, function and pain in AT



Loading interventions play an important role in AT management, with an extensive body of literature highlighting improvements in pain outcomes as a result of loading (Alfredson *et al.* 1998, Rompe *et al.* 2007, Beyer *et al.* 2015). VISA-A measure has been used to highlight improvements in pain and disability following loading interventions, with mean changes of 17 - 28 points reported in the literature (Rompe *et al.* 2007, Silbernagel *et al.* 2007b, de Vos *et al.* 2010, Yelland *et al.* 2011, Beyer *et al.* 2015). Comparable improvements in VISA-A scores were found in study IV, with a mean change of 23 points reported following the 12-week loading intervention. Although there is no agreed MCIC in terms of VISA-A score, Tumilty *et al.* (2008) have suggested success as an increase of 20 points, which compares favorably to the VISA-A change reported following Study IV. Although the VISA-A has been shown to be sensitive to clinical changes, and is easily comprehensible to patients

and clinicians alike (Kingma *et al.* 2007, Iversen *et al.* 2012), subjective outcome measures provide us with little information in relation to the range of factors associated with improved clinical outcomes following loading interventions.

Structural change and loading in AT

Traditionally, the rationale behind loading interventions in AT was based on a tissue focused paradigm, which suggests a progressive loading regime would stimulate a process of re-conditioning, and improve the capacity of a tendon to withstand greater load and stress, by altering its physiological or structural properties hence improving pain outcomes (Reeves 2006, Couppe *et al.* 2008, Seynnes *et al.* 2009, Kjaer and Heinemeier 2014). Results of study IV in chapter 4 appear to contradict the assumption that structural change is necessary for improvements in pain and function by demonstrating no significant change in tendon structure (thickness) following the intervention period, despite improvements in pain and function. These findings corroborate the results of a recent systematic review by Drew *et al.* (2014), who concluded that there is strong evidence to refute observable structural change as an explanation for the response to exercise interventions in LL tendinopathy. Furthermore these findings appear consistent with the fact that collagen has little turnover after puberty (Heinemeier *et al.* 2013), with the mean age (41 years) of the participants in study IV appearing to reinforce this point. Despite this finding there is evidence to suggest potential alterations in tendon structure occur following loading interventions in tendinopathy, in particularly younger populations (<25 years) (Kongsgaard 2007, Seynnes 2009).

These findings have potentially important clinical implications in the management of AT. The results suggest that future research may need to shift attention from designing interventions based on the premise of fixing or healing what is regarded as an abnormal tendon, and instead focus on designing interventions based on pain and/or function.

Loading interventions are associated with changes in tissue sensitivity

Results of the pilot intervention in study IV reported statistically significant improvements in PPT scores locally at the Achilles tendon, and at some sites distant from the Achilles tendon. In addition these PPT scores were accompanied by improvements in thermal sensitivity scores, although only few of these reached statistical significance. The alterations in tissue sensitivity to mechanical or thermal stimuli may be attributed to exercise induced hypoalgesia (Naugle *et al.* 2012). Evidence suggests that exercise of sufficient intensity and duration (both short and long term) results in alterations in mechanical or thermal hyperalgesia, as a result of the release of peripheral and central beta-endorphins (Naugle *et al.* 2012). The findings reported in Study IV compare favourably with research into other MSK disorders highlighting alterations in PPT in the upper and lower extremities, in conjunction with reduction in pain, following exercise interventions (Kosek *et al.* 1996, Koltyn *et al.* 2001, Burrows *et al.* 2014, Jones *et al.* 2014). These findings suggest the potential contribution of central pain processing in the clinical improvements associated with loading interventions in AT.

The concept of altered pain processing and the role of sensitisation remains a contentious topic in tendinopathy. Two recent systematic reviews have reported the presence of widespread or central sensitization in individuals with tendinopathy (Heales *et al.* 2014, Plinsinga *et al.* 2015). Unfortunately the majority of these studies involved UL tendon pain, making it difficult to extrapolate the findings to the LL. However, Tompra *et al.* (2015) investigated conditioned pain modulation in 23 participants with AT, and reported reduced conditioned pain modulation effect in the symptomatic group compared to controls. Similarly Van Wilgen *et al.* (2013) reported reduced PPT locally at the Achilles tendon of the symptomatic group, while in contrast, Skinner *et al.* (2014) reported no reduction in widespread PPT in participants with AT in locations remote to the Achilles tendon.

The conflicting evidence has led to considerable debate in the field of tendinopathy research. The premise of the argument appears to relate to the presence or absence of central versus peripheral sensitization. Some argue that the absence of widespread pain or altered thresholds in locations remote to the AT highlights that central alterations in pain processing are not responsible for pain associated with AT, and that peripheral sensitization, is a result of some aspect of peripheral nociceptive input due to ongoing pathology (Cook *et al.* 2016). The dichotomous nature of viewing pain, and the role of the CNS ignores the complex and multifactorial nature of the pain experience. Perhaps the concept of sensitisation should be viewed as a continuum rather than a dichotomous outcome, which may vary

depending on the individual presentation. For example the absence of widespread pain or altered hyperalgesia in LL versus UL tendinopathy may be attributed to the fact that many of the studies investigating the concept in LL tendinopathy have focused on younger athletic populations, compared to the UL populations who are mainly non-athletic. Research suggests endurance athletes are predisposed to being less sensitive to mechanical pain (Geva and Defrin 2013), compared to controls. This raises the potential protective or buffering effect of exercise in the manifestation of widespread alterations in pain sensitivity, which perhaps with the persistence of symptoms and pain, may also lead to similar alterations in sensitisation to those reported in UL studies. Regardless, it should be recognised that tissue sensitivity is only one aspect of central processing in AT, and aspects such as motor control, tactile acuity, and psychosocial factors are all important aspects of any pain experience.

Reconciling the role of loading and education in AT

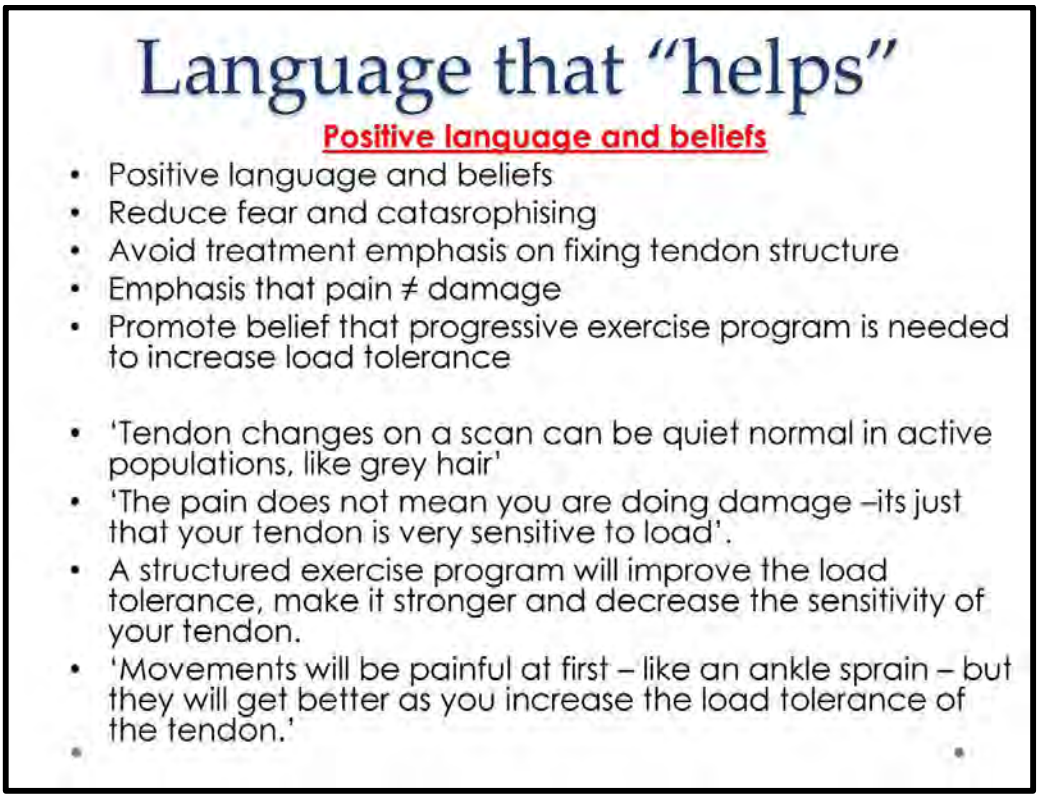
Psychosocial factors such as mood, personality and cognitive factors have been reported to influence a person's pain experience (Leeuw *et al.* 2007, Linton and Shaw 2011). Research in MSK disorders has highlighted the negative impact of fear-avoidance beliefs on recovery times in patients with neck pain (Landers *et al.* 2008, George and Stryker 2011), anterior cruciate ligament rehabilitation (Ross *et al.* 2002), knee OA (Scopaz *et al.* 2009), and patellofemoral pain (Piva et al. 2009, Kromer et al. 2014). However the presence of these factors in AT up to now has been relatively unknown, with studies focusing on the structural or quantitative aspects of AT. The qualitative interviews performed in study V highlight the psychosocial impact of AT, particularly beliefs and fears surrounding potential future damage and risk of rupture. This was compounded by participants' belief that rest was required in order to allow the tendon necessary time to heal. Such concerns or beliefs may be labeled as fear avoidance beliefs. The fear avoidance belief model proposed by Leeuw et al (Leeuw *et al.* 2007) is well known in the area of low back pain. According to this model, some individuals consider a painful stimulus as negative, and avoid or postpone an event that is considered painful (Sindhu *et al.* 2012). Over a long period of time, hypervigilance and avoidance of physical activity may lead to deconditioning or alterations in strength profile (Littlewood *et al.* 2013). It may be feasible that ongoing fear, anxiety or catastrophising in relation to ones Achilles tendon (fear of rupture, fear of damage, apprehension to load the tendon, or anxiety as a result of restricted activities) reported in the qualitative interviews, may have contributed to ongoing sensitization of the CNS which may ultimately

have contributed to the pain and altered tendon function highlighted in study IV. It is therefore feasible to suggest, the presence of psychosocial factors and manifestation of protective behaviours in AT may affect subsequent adherence to prescribed loading interventions.

Assuming every patient will understand and adhere to prescribed exercises, in relation to loading what they may perceive as a damaged tendon, fails to acknowledge the complex and important role of psychosocial factors in rehabilitation outcomes. Consequently, this highlights the possible importance of aligning exercise prescription and instructions with the key messages of pain education, or concepts of pain neuroscience to improve the management of AT (Ryan *et al.* 2010). Pain education has been shown to be effective in changing pain beliefs including catastrophising and hypervigilance, resulting in improved health outcomes in adult patients with various chronic pain disorders (Meeus *et al.* 2010, Louw *et al.* 2011, Blickenstaff *et al.* 2016). It appears that when individuals understand more about pain physiology they will alter the manner in which they approach movement, exercise and activity. Interestingly, results of study V also demonstrated statistically significant reductions in FABQ scores following the intervention period. Although quantifying a direct cause and effect relationship is not possible due to the lack of a comparative control group, it may be hypothesised that the educational session, in conjunction with the appropriate prescription of loaded therapeutic exercise within a concept of hurt doesn't equal harm, had an impact upon the fears and beliefs expressed in the interviews in study V. This highlights the potential contribution of language and education in potentially reinforcing or allaying beliefs and fears in people with AT (Figures 34 & 35). Further investigation is required to determine the impact and efficacy of psychosocial factors in AT, and the role of education in conjunction with loading interventions.

Figure 35: Language that harms in AT

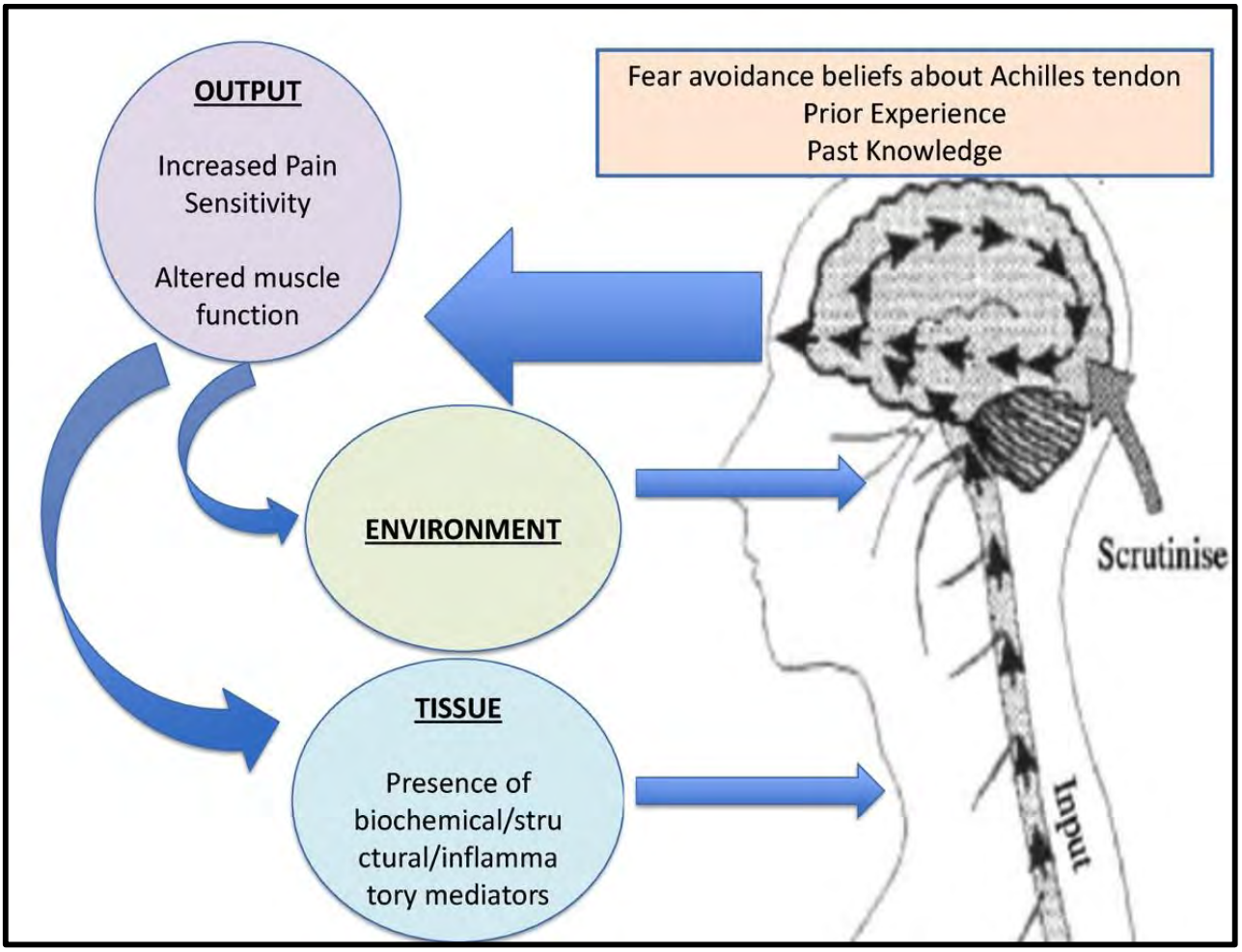
Figure 36: Language that helps in AT



Top down or bottom up: Integrating structure, function and pain in AT

To date, the pain experience in AT has predominantly been viewed from a unidimensional perspective, with models and paradigms focusing mainly on structural factors. However, as highlighted throughout this thesis, AT is a multifactorial MSK disorder involving a complex interaction between structure, function and pain. To facilitate integration and improve our understanding of AT, adopting and implementing the mature organism model (MOM) of pain previously described by Gifford (2013), may improve the understanding of these complex interactions (Figure 36). The MOM describes a cyclical process beginning with an input to the CNS (*"sampling"*), e.g. nocioception initiated by a structural/inflammatory or biochemical response to an interaction between risk factors (figure 29). In response CNS processing referred to as *"scrutiny"* occurs, which involves interpretation and evaluation of the provided input, before an output, for example an altered behaviour is generated (decrease in tendon function, avoidance of loading, increased tissue sensitivity). The output subsequently serves as a further input to the sampling loop. The MOM indicates that the CNS is continually sampling tissue health, the surrounding environment and itself, consciously and unconsciously, before scrutinising this input in the context of past experience, knowledge, beliefs, culture, and past successful behaviour observed in others (Gifford 1998b, Jones et al. 2002). The MOM may help improve our understanding of the complex interactions of the factors associated with AT by providing an integrated multifactorial approach.

Figure 37: Mature organism Model of AT



Strengths and Limitations

Strengths

The three systematic reviews have been published, or accepted for publication in reputable international ISI journals pending minor revisions. The three reviews have been presented or accepted for presentation at prestigious conferences such as International Tendon Symposium 2014, International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) 2016, and the International Olympic Committee (IOC) conference on prevention of injury and illness in sport 2017. The remaining qualitative and quantitative intervention studies are currently under review in reputable international journals. The study methodologies associated with these studies are strong. The reviews were prospectively registered using the PROSPERO database. The database searching and critical appraisal was completed by two independent reviewers for each review, and utilised appropriate quality appraisal of the included studies. Furthermore, the thesis contained a mix of quantitative and qualitative methods, which is strongly recommended in the design of complex interventions. Finally, the pilot intervention study is the first to consider and integrate central, local and systemic contributions in AT, highlighting the potential for future multifactorial interventions in AT.

Limitations

There was a large variability in study I in relation to the terminology used in defining a structurally 'abnormal' tendon, when viewed using US. The variability of what constitutes an abnormal tendon across the included studies, raises the possibility of over or underestimation of the relationship between structure and future symptoms. Another limitation of this doctoral thesis relates to the population sample of the participants in the included studies. The majority of the participants throughout the studies were athletic, and although AT is highly prevalent in athletic populations, there is a growing awareness of the prevalence of AT in non-athletic populations. Consequently this limits the generalisability of findings of this doctoral thesis. The methodologies in the studies reported in study III provides another potential limitation. There was large variability in isokinetic dynamometry methodologies, including different speeds and modes of contraction when quantifying maximal strength. Furthermore, the psychometric properties of variables such as RFD and GRF are still relatively unknown in AT, while the use of the non-injured side by the majority of studies in this review is another potential limitation. There is evidence to suggest that strength deficits exist on the

non-injured side in those with unilateral tendinopathy (Chourasia *et al.* 2012). Therefore direct comparison to the non-injured side as evident in a number of studies in this review may not be sufficient. The inclusion of bilateral and unilateral AT patients into the same group in the pilot intervention study IV may affect the findings of the results with evidence suggesting that individuals with unilateral and bilateral may have unique and differing aetiologies (Gaida *et al.* 2004). A further limitation relates to the sample size utilised to assess maximal strength variables in Study IV. Unfortunately due to unforeseen circumstances technical issues with the isokinetic dynamometry limited the sample size available for pre and post measurements of maximal strength variables, which may have accounted for the lack of statistical significance. Finally, although a pilot intervention study can strengthen the suspicion of a causal relationship, confirmation requires planned studies, including control groups to control for chance, bias and confounders, thus limiting definitive conclusions on cause and effect relationships. Given the complex and multifactorial nature of AT highlighted throughout this thesis, it is likely that the factors investigated in this thesis are only some of the many contributing factors in AT. It is possible that factors such as biomechanics, running style and training load may play a role in AT, and are worthy of future research within the framework presented in this thesis.

Implications for future research

- Results of study II indicated that alterations in tendon structure are associated with an increased risk of developing future Achilles or patellar tendinopathy. The high percentage of alterations in tendon structure in asymptomatic populations highlights the need for future research investigating the interactions between multiple risk factors including tendon structure using prospective study designs.
- Additionally, future research may investigate the impact and consequences of revealing findings of structural abnormalities using imaging on patient beliefs.
- AT is associated with alterations in tendon function across the entire strength spectrum. To date, assessment and rehabilitation of AT has focused on traditional maximal strength parameters, with little focus on the assessment and management of reactive or explosive deficits. This highlights the need for future research investigating the potential effects of targeted rehabilitation programmes including maximal, plyometric, and explosive programmes tailored to individual's functional demands.
- The uncertainties and lack of consensus in AT may be attributed to large heterogeneity of population samples used in tendinopathy to date. It may be plausible that differences exist in the pathoaetiology of athletic versus sedentary populations, unilateral versus bilateral tendinopathy, or UL versus LL tendinopathy. This highlights the potential need for future research to investigate whether differences exist, with insights potentially improving the management of this complex disorder.
- Results of this thesis suggests that clinical improvements following a 12-week loading intervention in AT may be attributed to a range of psychosocial, somatosensory and functional factors. The relative contribution of these factors may vary between individuals, and further research investigating these factors using sound methodological study design, may allow clinicians to adapt and tailor interventions to these individual factors which may result in improved treatment outcomes in AT.
- Results of this thesis suggest that similar to other MSK disorders, AT is associated with an increased psychosocial burden. Psychosocial factors such as fear avoidance beliefs or hypervigilance may impact the potential success of loading interventions in AT. Growing evidence supports the ability of pain neuroscience education in positively impacting a person's

pain ratings, disability, pain catastrophising, and movement limitations in MSK disorders. Future research is required to determine the potential role of pain neuroscience education in addressing psychosocial factors as part of the overall management process in AT.

CONCLUSION:

To date paradigms and interventions in AT have primarily focused on local tissue-based approaches, utilising unidimensional heavy slow loading programmes. The findings of this doctoral thesis indicate that AT is a multifactorial MSK disorder involving a complex interaction between structure, function and pain. Results of this thesis suggests that alterations in tendon structure may be associated with the development of pain as well as demonstrating alterations of tendon function in the presence of pain. The complex interaction is further highlighted by the findings that clinical improvements following a traditional loading intervention appear to be associated with changes in a range of physical, functional, psychosocial, and somatosensory factors, without the need for observable changes in tissue structure. Future research may need to target these various factors in accordance with the needs of individual patients.

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APPENDICES

APPENDIX 1: Summary of selected theoretical models in tendinopathy

Model	Key Events
Abate's Iceberg Theory	**Stage 1:** • Well-structured or long-term exercise stimulates collagen production, leading to enhanced capacity and resistance to future injury. However, if loading exceeds an individual's physiological capacity or threshold, micro-damage may occur. • Inadequate recovery time between repeated bouts of exposure may lead to increased weakening of the collagen crosslinking and tendon matrix. **Stage 2:** • Continued exposure of the tendon to strenuous exercise initiates the mechanisms for healing and repair. • Low metabolic rate of tendons and continued exposure to loading results in failed healing mechanisms leading to degradation of the tendon. • In this phase the individual is still asymptomatic, with transition to the symptomatic phase occurring following invasion of vessels, nerve proliferation and increase in glutamate levels which leads to pain when the production of alogenic substances reaches a critical threshold.
Cook and Purdam's Continuum Model	**Stage 1: Reactive tendinopathy:** • A non- inflammatory response within the cell and matrix following acute tensile or compressive overload. • Tendon will increase its surface area in response by thickening as a short term adaption, in order to reduce

	stress on the tendon, due to up-regulation of large proteoglycans and an increase in bound water, with minimal collagen damage or separation. • Imaging on ultrasound will reveal diffuse hypoechogenity between intact collagen structures in conjunction with spindle shaped thickening of the tendon. • Clinically, this stage is characterised by an acute change in load and is more common in the younger person but may be present in degerative tendons as "acute on chronic". • The tendon has the potential to revert to normal with appropriate control of the person's load. **Stage 2: Tendon Dysrepair:** • Stage is characterised by an attempt at tendon healing but is associated with a greater degree of matrix degredation. • Increased cell proliferation in the form of chondrocytic and myofibroblast cells resulting in enhanced production of proteoglycan and collagen, with possibility of increased vascular structures using doppler ultrasound. • Imaging at this stage will also reveal areas of fibrillar disruption and areas of hypoechogenicity. • Clinically hard to differentiate, but commonly associated with chronically overloaded tendons in the young. This stage demonstrates some potential for reversibility. **Stage 3: Degenerative tendinopathy** • Progressive or extensive matrix and cell changes, with even some areas of cell death. Considerable areas of the

	matrix are disordered, and may demonstrate presence of vascular structures, referred to as neovascularisation. • Large areas of hypoechogenicity or collagen disruption are evident on ultrasound imaging, while doppler US will reveal increased blood flow activity in areas of vascularisation. • Stage usually associated with the older athlete, however it is possible in younger populations with a history of chronic overload. • Little capacity for structural reversibility
Fu's Failed Healing Response	**Stage 1: Injury** • This model proposes initiation of tendinopathy may be attributed to repetitive tendinopathy, chemically induced tendinopathy, pathogen induced tendinopathy and previous traumatic injury. • Repetitive tendinopathy occurs as a result of tendon overuse, which may lead to the release of pro-inflammatory mediators. • Chemical induced tendinopathy occurs when chemicals such as fluoroquinolone can lead to cell death, oxidative changes and collagenolysis leading to the onset of tendinopathy. • Pathogen induced tendinopathy refers to exposure to a pathogen leading to tendon injury and inflammation. • Previous traumatic injury as the name suggests is tendinopathy due to a previous traumatic injury has also been attributed to the onset of tendinopathy in this model. • Tendon pain and mechanical weakness is not significant at this

	stage and it is possible for the tendon injury to heal spontaneously. **Stage 2: Failed Healing** • Characterized by activation of healing responses that fail to repair the collagenolytic injuries. • Exact mechanism behind this failed healing response is unknown. It is speculated that unfavourable hormonal background, genetic, environmental factors and pharmalogical exposures may interfere with the healing process. • Tendon pain becomes evident in this stage. **Stage 3: Clinical Presentation** • Characterized by symptomatic tendinopathy. • Alterations to the extracellular matrix, visible in MRI or US as a consequence of the failed healing stage are evident in this stage. • Shift in the pain mechanism towards a non-phlogistic mechanism such as irritation of peritendinous nerves by nocioceptive or inflammatory mediators. • In asymptomatic individuals, matrix disturbance following the failed healing stage may not activate a nocioceptive response, however alteration in structural properties may lead to ruptures.
Arnoczky's mechanobiological	• Model proposes mechanobiological under-stimulation of tendon cells, secondary to micro trauma and isolated collagen

aetiopathogenesis of tendinopathy	fibril damage, as a predisposing factor for the pathological changes reported in clinical cases of tendinopathy. • Suggest an absence of mechanical stimuli, secondary to micro trauma that is the mechanobiological stimulus for the degradative cascade that leads to tendinopathy. • If this micro trauma is not balanced by an active repair response from the tenocytes, it will result in cumulative damage and ultimately, degradation of the tendon. • This damage alters cell-matrix interactions (mechanobiologic signaling) in the area causing an up regulation in collagenase and a weakening of the collagen structure • This could make the tendon more susceptible to damage from additional loading at lower strains. • The loss of cells could further compromise the tendon's ability to repair itself or even maintain its local extracellular matrix.

APPENDIX 2: CASP Criteria

The following criteria for each question were considered when appraising the quality of the included studies.

Q1. Were the cases recruited in an acceptable way?

- Precisely defined cases
- Specific inclusion criteria to select patients with tendinopathy
- Representative of defined population

Q2.Was the exposure accurately measured to minimize bias?

- Exposure and measurement tools clearly defined:
    - Ultrasound protocol clearly defined.
    - Pain/Disability or time absent from sport/activity measurement outlined
    - Information on rater outlined
- Methods specified

Q3. Have the authors taken account of the potential confounding factors in the design and/or in their analysis?

- Use of same rater/tester for assessment
- Blinding of raters
- Controlling anything that may affect findings (e.g. training load)

Q4. Was the follow up of subjects complete and long enough.

- The good or bad effects should have had long enough to reveal themselves.
- The persons that are lost to follow-up may have different outcomes than those available for assessment

- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

Q5. Do you believe the results?

- Inclusion of:
    - Statistical values: fishers exact test values, relative risk or other similar predictive statistical values reported
    - Studies that provide only descriptive statistical results are not awarded a point
- Methods and design were appropriate

Q6. Can the results be applied to the local population?

- Population correlates with our population of interest
- The measurement tool they used is widely available

Q7. Do the results of this study fit with other available evidence?

- Are there available studies with similar measurements?

APPENDIX 3: CERT Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

APPENDIX 4: Description of outcome measures from pilot intervention study

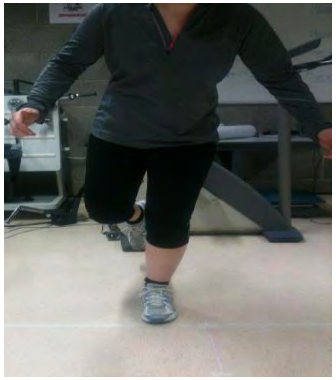
Test Domain	Outcome Measure Description
Index of severity of Achilles tendinopathy	**Victorian Institute of Sports Assessment Achilles Questionnaire (VISA-A):** The Victorian Institute of Sport tendon study group (Melbourne, Australia) first developed an index of severity for patellar tendinopathy and was later adapted for the Achilles tendon. As a standardised outcome measure, the VISA-A has proven to be a both reliable and valid instrument. It is a self-administered questionnaire which evaluates symptoms and their effect on physical activity in AT. VISA-A questionnaire contains eight questions that cover three domains of pain (questions 1–3), function (questions 4–6), and activity (questions 7 and 8.) The VISA-A is based on an inverted numeric rating scale (NRS) and results in a score range from 0 to 100 points with asymptomatic persons expected to score 100 points. Lower scores indicate higher levels of pain and disability (Iversen *et al.* 2012).
Fear Avoidance Beliefs	**Fear Avoidance Beliefs Questionnaire (FABQ):** The FABQ was developed by Waddell *et al.* (1993) to investigate fear-avoidance beliefs among LBP patients in the clinical setting. The FABQ consists of 2 subscales. The first subscale (items 1-5) is the Physical Activity subscale (FABQPA), and the second subscale (items 6-16) is the Work subscale (FABQW). The physical activity subscale of the FABQ was used in this study and quantifies the level of fear about physical activity. The work subscale of the FABQ was not used as a method of assessment in this study. The instrument consists of five items, with questions 2,3, 4 and 5 used for scoring.

	Items are scored from 0 to 6. Possible scores range from 0 to 24, with higher scores representing increased fear-avoidance beliefs. The scale was modified and adapted to relate to the Achilles tendon.
General Health	**Subjective Health Complaints Inventory (SCHI):** The SCHI concerns subjective somatic and psychological complaints experienced during the previous 30 days. Thirteen items including palpitations, chest pain, breathing difficulties, heartburn, stomach discomfort, diarrhoea, constipation, eczema, tiredness, dizziness, anxiety, depression/sadness and sleep problems. Each category is scored from 0-3. Higher scores indicate a greater level of subjective somatic and psychological health complaints (Tschudi-Madsen et al. 2011).
Sleep	**Sleep quality and quantity:** Sleep quantity and quality were categorised into sufficient, intermediate or insufficient, based on average hours spent sleeping, prevalence of nightmares, tiredness and sleeping problems. (1) Insufficient sleep quality or quantity was defined as sleeping 6 h or less per day, or often having nightmares, tiredness or general sleep problems; (2) intermediate sleep quantity and quality was defined as sleeping 7 or 10 h or more per day, or having nightmares, tiredness or general sleep problems to some extent or sometimes; and sufficient quality and quantity of sleep was defined as sleeping the recommended 8–9 h per day and having no nightmares, tiredness or general sleep problems (Auvinen *et al.* 2010).

Mood	**Profile of Moods State (POMS):** The POMS assesses transient, fluctuating feelings, and enduring affect states. Three subscales of the POMS namely tension-anxiety, anger-hostility and confusion-bewilderment were completed. Higher scores indicate greater levels of anxiety, anger and confusion (Mc Nair *et al.*1971).
Stress	**Stress subscale of the Depression Anxiety Stress Scale (DASS):** The DASS 21 is a 21 item self-report questionnaire designed to measure depression, anxiety and stress. The stress subscale of the DASS is a 7-item scale. In completing the DASS, the individual is required to indicate the presence of a symptom over the previous week. Each item is scored from 0 (did not apply to me at all over the last week) to 3 (applied to me very much or most of the time over the past week). A higher score indicates greater levels of stress (Lovibond and Lovibond 1995).
Disordered Eating	**Sick, Control, One stone, Fat, Food (SCOFF):** SCOFF is a five-item questionnaire used to assess the possible presence of an eating disorder. A score of two or more indicates disordered eating (Morgan *et al.* 2002).

Test Domain	Outcome Measure Description
Maximal strength:	***Isokinetic strength:*** Isokinetic calf muscle strength was measured using a Biodex isokinetic dynamometer. The test

	procedure described by Möller *et al.* (2005) was used for this study due to its acceptable test-retest reliability. The participants were seated in 110 degrees of hip flexion and 90 degrees of knee flexion as measured with a hand-held goniometer. Strength was measured between 10o of dorsiflexion and 30o of plantarflexion. Other studies set the ankle range of motion of 50 degrees [11] However, pilot testing revealed that 40o was the most comfortable range for testing. The warm-up procedure consisted of 5 submaximal concentric contractions and 7 submaximal eccentric contractions on each leg before the respective tests. Verbal encouragement were given to the subjects as previous studies have found that this increased muscle force production and helped to motivate patients in attaining maximum performance. Concentric plantarflexion peak torque (PT) and peak torque/body weight (PT/BW) were measured at 90°/second (5 repetitions) of angular velocity. Eccentric plantarflexion PT and PT/BW were measured at 90°/second (5 repetitions). Verbal encouragement were given to the participants as previous studies have found that this increased muscle force production and helped to motivate patients in attaining maximum performance
	***Isoinertial strength:*** Maximal concentric/eccentric bodyweight heel raise test. A heel-raise procedure has been described by Silbernagel *et al.* (2006) The subject's height was taken and the head plate was raised 5cm above this level and secured by tape. 5cm was the pre-set level that participants had to reach. The subject was asked to perform as many single leg heel-

	raises as possible. In order for a heel raise to be successful participants were required to touch the head plate for each heel-raise. The participant was allowed to have two fingertips per hand, placed at shoulder height, against the wall for balance. A metronome app was used to keep the frequency at 40 heel- raises per minute. The test was terminated when the participant stopped, could not keep the frequency or did not perform a proper heel-raise. At this point, the number of heel- raises that were performed was documented.
Reactive strength 	***Single Leg Hop distance:*** The single leg (SL) hop test was measured was based on the procedure outlined in the literature by Silbernagel *et al. (*2006), which has established validity and reliability. The participants started the test standing on one limb, with their foot behind a clearly marked starting line. They were instructed to hop as far as possible on one leg and land on the same limb. The subject's were allowed to maximise their hopping distance by performing a countermovement of quick knee bending. No restrictions were placed on arm movement and no instructions were given regarding where to look. For the attempt to be deemed successful, the single-footed landing position must have been maintained for at least two seconds. An unsuccessful attempt was classified by any of the following: touching down of the contralateral lower extremity or either upper extremity, loss of

balance or an additional hop on landing. Unsuccessful attempts were repeated. A rest period of less than 30 seconds between trials was allowed if needed. To reduce practice effects, subjects were first allowed to practice until they were happy with their method (Reid *et al.* 2007).

To calculate a score the average of three successful attempts was recorded to the nearest centimeter from the start position to the tip of their runners using a standard tape measure that was permanently affixed to the floor.

Drop Counter Movement Jump (dCMJ):

A drop countermovement jump (dCMJ) was measured using the Chronojump- Boscosystem measurement system. The Chronojump-Boscosystem is a data collection unit consisting of a microcontroller, which is connected to a contact platform and a personal computer with the free Chronojump software. The dCMJ test procedure outlined by Silbernagel *et al* (2006) was used to guide dCMJ in this study. Although the data collection unit used by Silbernagel *et al.* 2006 differed from the Chronojump-Boscosystem, it has been validated with satisfactory results. However, the reliability of the dCMJ on the Chronojump has not been explored.

To perform the dCMJ participants started the test by standing on one leg on a wooden box (15cm high). They were instructed to "fall" down onto the mat and immediately on landing, perform a maximal vertical one-legged jump. The participants had their hands on their hips throughout the whole test. After three practice trials, the participants started the test until three approved jumps per leg were performed. The jump height and contact time (CT) of the highest jump of each

	leg were recorded for data analysis.
Tendon Thickness 	Tendon thickness: Grey scale US imaging examinations were undertaken to quantify tendon thickness using a GE Logiq e US scanner equipped with a 7–12-MHz linear-array transducer (GE Healthcare, Wauwa- tosa, WI). Participants lay in prone with their heels overhanging the examination couch to enable movement of the feet. Tendon thickness was measured transversely with the transducer perpendicular to the Achilles tendon at the level between the medial and lateral malleoli as well as in a longitudinal plane by angling and positioning of the probe until maximal resolution and clarity was achieved with images of achilles tendon insertional and mid tendon area recorded. On longitudinal scans, measurements were carried out where the tendon was maximally enlarged. If there were no changes in tendon thickness, the Achilles tendon was assessed 10 mm proximally to the superior-posterior aspect of the calcaneus (Giombini *et al.* 2013).
Quantitative sensory testing	***Pressure Pain Threshold (PPT):*** Three testing loactions were identified for measuring PPT: tibialis anterior, common extensor tendon of the elbow, and the Achilles tendons (AT). PPT was defined as the minimum amount of pressure required to induce a sensation of pain, as opposed to pressure [19]. The rubber-tipped probe of the handheld algometer (Force Ten TM FDX Force gage, Wagner Instruments, Greenwich, CT, USA) was applied in random order to the sites listed above. Participants were told to state immediately when the sensation of pressure turned into a sensation of pain, at which point compression was stopped and the pressure was released. After a pause of 30 s before randomly moving to the next test location. A single measurement was made at each site

	(Skinner *et al.* 2014).
Quantitative sensory testing 	***Thermal sensitivity:*** Thermal thresholds were determined by using a Somedic Roll Temp 2 device. The somedic roll temp device consists of two metal rolling apparatus set to a pre defined maximum temperature of 40C and minimum temprature of 25C respectively. A demonstration on an area of skin to show difference between the hot and cold roller was performed to familiarise participants with the procedure. Participants were requested to you rate the temperature and pain experienced out of 10 for both hot and cold modalities. Tests were performed 3 times at each location bilaterally and in a random order. Testing location included the forearm (posterior aspect from the dorsal wrist joint line to the elbow joint line) and posterior aspect of LL (From the knee joint line to the calcaneous) respectively (Pathirana *et al.* 2011).

APPENDIX 5: Participant Consent Form

UNIVERSITY *of* LIMERICK
OLLSCOILLUIMNIGH

An uncontrolled pilot study investigating the effects of a 12-week graded exercise programme on pain and tendon structure in people with Achilles tendon pain.

PARTICIPANT CONSENT FORM

Please read the following questions and tick the appropriate Yes or No box. Please sign the bottom of the page if you consent to participate in this study.

	YES	NO
I have read and understood the information sheet.		
I know that my participation is voluntary and that I can withdraw from the project at any stage without giving any reason.		
I agree to permit access to my medical record by the study Investigator if required.		
I agreement to notify the Investigator of any side effects arising during the study.		
I agree to participate in this study.		

SIGNATURE **BLOCK CAPITALS** **DATE**

Subject: _____ _____ ___/___/___

Investigator: _____ _____ ___/___/___

Witness: _____ _____ ___/___/___

APPENDIX 6: Participant Information Sheet

UNIVERSITY of LIMERICK

OLLSCOIL LUIMNIGH

Title of study: A case series study investigating the effects of a 12 week graded exercise programme on pain and tendon structure in athletes with LL tendinopathy

Information Sheet

What is the study about?
This study is being done to establish the effects of a 12-week graded exercise programme on pain in individuals with LL tendinopathy.

Who can take part in the study?
Anyone over 18 years old who has Achilles tendinopathy for more than 2 months limiting physical activity participation in any degree, who has not started treatment for any back/LL injury six weeks prior to the commencement of the study and who has not sustained a back/LL injury within the six weeks prior to the start of the study.

What will I have to do?
If you wish to take part in the study, you will have to fill in the consent page attached to this document and return it to me.

There are two parts to the study:

During the first part of the study, you will also be asked to fill out a questionnaire about your injury background, a medical history and past interventions you have had for your tendinopathy. Testing will also occur in the first part of the study. A comprehensive assessment of your strength, flexibility, and tendon structure will all be assessed prior to the intervention. This will take about 60 minutes approximately.

The second part of the study involves giving you a tailored rehabilitation programme based on your initial testing which will compromise of advice on your pain and your injury and then providing you with a tailored exercise programme which will be progressed according to your response over a 12 week period. You will then come back after 12 weeks and you will then be re-assessed as outlined above in the first part of the study.

Benefits

- The exercise programme may lead to improvement of strength and functional performance, which are adversely affected in individuals with Achilles Tendinopathy.
- This study will help inform current athletes and those who will manage athletes with tendinopathy in the future about how to successfully manage people experiencing tendon injuries affecting participation. This may have positive impact on the potential for injury prevention.

Risks
Testing is non-invasive and therefore should have no serious risks. If you have any doubts about any possible risks, please don't hesitate to talk to the investigators about any concerns.

What if I do not want to take part?
Taking part in this study is completely voluntary. If you don't want to be in the study, you don't have to be. It won't affect you if you want to take part in other studies.

What happens to the information?
Your answers are anonymous so no one will know who you are. You will be given a code for identification. Information will be stored securely on laptops. Only the people running the study will look at this information. After 7 years paper data will be shredded and electronic data will be electronically deleted from the laptops.

Who else is taking part?
Other recreational athletes with Achilles tendon injury from local running clubs and the local community will be recruited to participate in the study.

What happens at the end of the study?
After all the information is collected, it will be analysed and a report of the main findings will be written up. It is hoped that this study is published in journals, which may hopefully inform physiotherapists and other medical professional how to better understand and treat tendon injuries. It is also intended to give talks on the results in relevant conferences and running clubs. All the data will be stored and destroyed as mentioned above.

What if I have more questions or do not understand something?
If you have any more questions, you can contact the project investigators at the details listed below at any time before, during or following the study. You can ask any questions you might have when you fill in the questionnaire, or during the physical screening.

Contact name and email details of project investigators
Sean McAuliffe: 0sean.mcauliffe@ul.ie 0872223564
Dr. Kieran O'Sullivan: kieran.osullivan@ul.ie 061234119

If you have any concerns about this study and wish to contact someone independent you may contact:
Chairman Education and Health Sciences Research Ethics Committee
EHS Faculty Office
University of Limerick
Tel (061) 234101

Email: ehsresearchethics@ul.ie

APPENDIX 7: Pilot Intervention Study Pre assessment

UNIVERSITY of LIMERICK

OLLSCOIL LUIMNIGH

Pre-Assessment

Name:_____ **Age:**_____
Mobile Number:_____ **Date:**_____
Subject Number:

Testing Checklist

- ☐ Patient Information Leaflet Given
- ☐ Consent Form Signed
- ☐ Subjective Questionnaires x3
  - VISA-A
  - FAB-Q
  - Sx Health/Training Load
- ☐ Anthropometric Data Taken
  - Height
  - Weight
  - Age
  - Waist Circumference
- ☐ Ultrasound
- ☐ Central Sensitisation
  - Hot/Cold
  - Pressure Pain Threshold
- ☐ Biomechanical Measurements

- Ankle ROM

- Biodex Measurements are you just doing eccentric strength? No concentric?
- Neuromuscular Performance
  - Single Leg Hop
  - CMJ Height/Contact (jump mat)
  - Single Leg Endurance

Subjective Assessment

TRAINING AND INJURY HISTORY

On average, how long do you run per week (to the nearest minute)? _____

On average how many **miles** a week do you run? _____

Do you **warm-up** before running. Please tick **one.**
Always ( ) Usually ( ) Often ( ) Sometimes ( ) Rarely ( ) Never ( )

Do you **cool-down** after running? Please tick **one.**
Always ( ) Usually ( ) Often ( ) Sometimes ( ) Rarely ( ) Never ( )

On a scale from 1 – 10, (1 – min exertion, 10 – max exertion) how **intense** is your running?
1 2 3 4 5 6 7 8 9 10

How do you deal **with warning signs of injury**? Tick as **many** as are applicable to you.
Take own preventative steps ( )
Seek professional treatment ( ) Soldier on ( )

How often do you run in pain? Please select one of the following
Never ( ) Rarely ( ) Sometimes ( ) Often ( ) Always ( )

What treatment, if any, did you seek to manage your Achilles injury?
_____
_____
_____

What do you think was the main cause(s) of your Achilles injury: List as many causes as you think apply
_____
_____
_____

Do you do any **other form of exercise** on a regular basis? YES / NO.

If yes, describe the type and duration of exercise per week (example, weight lifting, aerobics, Pilates, yoga, running, swimming, bicycling):

_____
_____
_____

Do you engage in lower body strength training YES/NO?
If **YES** do you do specific strength training for your calf muscles? Please specify?

_____
_____
_____

On a scale from 1 – 10, (1 – min exertion, 10 – max exertion) how intense is your other exercise?
1 2 3 4 5 6 7 8 9 10

At the onset of when your Achilles tendon pain occurred, can you recall any change in load (running speed, distance or terrain) around that time or in the weeks before?

_____
_____
_____

Do you currently/or have previously in the past year receive medical attention or treatment to address your Achilles tendon pain. YES/NO

If **yes** please specify what type of treatment?

_____
_____
_____

GENERAL HEALTH

Generally, how would you evaluate your own **physical and psychological health** during the past month?
Very good ( ) Good ( ) Neither good nor poor ( ) Poor ( ) Very poor ( )

During the past month, how much **energy** did you have?
Very much ( ) Quite a lot ( ) Some ( ) A little ( ) None ( )

The following are some common health problems and complaints. We want you to look at each and every one of them and report to what extent you have been affected during the last month.

	Not at all	A Little	Some	Severe
Palpitations/extra heartbeats	0	1	2	3
Chest pain	0	1	2	3
Breathing difficulties	0	1	2	3
Heartburn	0	1	2	3
Stomach discomfort	0	1	2	3
Diarrhoea	0	1	2	3
Constipation	0	1	2	3
Eczema	0	1	2	3
Tiredness	0	1	2	3
Dizziness	0	1	2	3
Anxiety	0	1	2	3
Sadness / depression	0	1	2	3
Sleep problems	0	1	2	3

Are you currently taking any medication? YES / NO.

If YES, please list:
_____
_____
_____

How many units of alcohol do you drink per week approximately? (A unit of alcohol is a pub measure of spirits, a small glass of wine, a half pint of normal beer or an alcopop) _____

Do you smoke?
Yes ( ) Previously, but not in the last month ( ) No ( )

If YES how many cigarettes on average per day? _____

PAIN & INJURY

Have you at any time during the **past 12 months** had trouble (ache, pain, discomfort, numbness, tingling etc.) in any other of the following body regions aside from your Achilles tendon, which affected your normal activity or changed your daily routine for more than one day? Please tick **all that apply**. If no trouble, tick none.

Head & Neck	( )	Lower back	( )	
Upper back	( )	One or both shoulders	( )	One or
both elbows/wrists/hands ( )		One or both hips/thighs ( )		
One or both knees	( )	One or both shins	( )	
One or both calves	( )	One or both ankles/feet	( )	
None	( )			

NUTRITION

Do you make yourself sick because you feel uncomfortably full? YES / NO
Do you worry you have lost control over how much you eat? YES / NO
Have you recently lost more than one stone (14 lb or 7.7 kg) in a 3 month period? YES / NO
Do you believe yourself to be fat when others say you are thin? YES / NO
Would you say that food dominates your life? YES / NO

SLEEP

On average, how many hours per night do you sleep? _____
How well does each of the following statements apply at present, or over the past 6 months?
(CIRCLE ONE)

I have nightmares :	Never	Sometimes	Often
I am too tired:	Never	Sometimes	Often
I have sleep problems:	Never	Sometimes	Often.

MOOD

Below is a list of words that describe feelings that people have. Please read each one carefully. Then circle the answer which best describes **HOW YOU FEEL OVER THE PAST WEEK**. Make sure you answer every question.

	Not at all	A Little	Moderately	Quite a bit	Extremely
Panicky	0	1	2	3	4
Confused	0	1	2	3	4
Annoyed	0	1	2	3	4
Mixed-up	0	1	2	3	4
Bitter	0	1	2	3	4
Anxious	0	1	2	3	4
Worried	0	1	2	3	4
Muddled	0	1	2	3	4

Nervous	0	1	2	3	4
Angry	0	1	2	3	4
Bad tempered	0	1	2	3	4
Muddled	0	1	2	3	4

STRESS

Please read each statement and tick a number 0, 1, 2 or 3 which indicates how much the statement applied to you ***over the past week*****.**

0 Did not apply to me at all.
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

Situation	0	1	2	3
I found it hard to wind down				
I tended to over-react to situations				
I felt that I was using a lot of nervous energy				
I found myself getting agitated				
I found it difficult to relax				
I was intolerant of anything that kept me from getting on with what I was doing				
I felt that I was rather touchy				

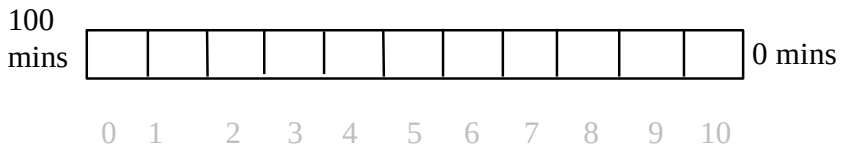
Here are some of the things other patients have told us about their pain. For each statement please circle the number from 0 to 6 to indicate how much physical activities such as walking, running, stairs or hopping affect or would affect your Achilles pain.

	Completely Disagree			Unsure			Completely agree
My pain was caused by physical activity	0	1	2	3	4	5	6
Physical activity makes my pain worse	0	1	2	3	4	5	6
Physical activity might harm my Achilles	0	1	2	3	4	5	6
I should not do physical activities which (might) make my pain worse	0	1	2	3	4	5	6
I cannot do physical activities which (might) make my pain worse	0	1	2	3	4	5	6

The VISA-A questionnaire: An index of the severity of Achilles tendinopathy

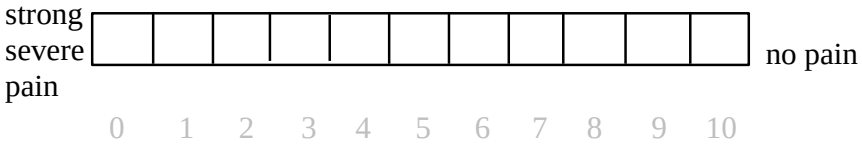
IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?



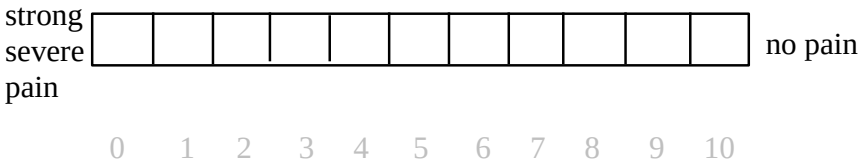
POINTS

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)



POINTS

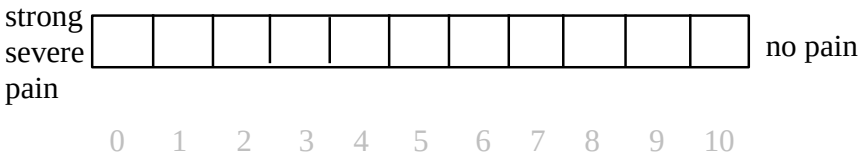
3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours? (If unable to walk on flat ground for 30 minutes because of pain, score 0 for this question).



POINTS

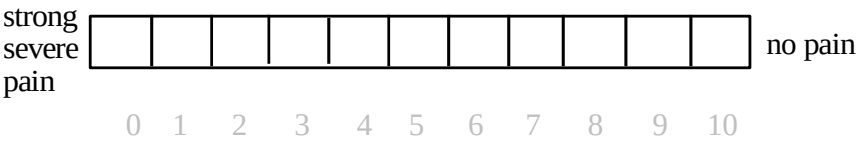
4. Do you have pain walking downstairs with a normal gait cycle?

POINTS



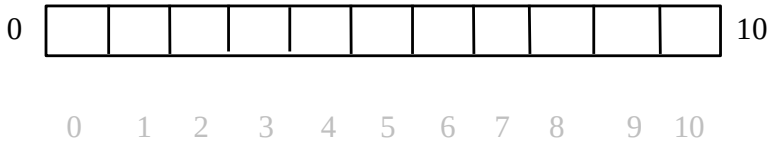
5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

POINTS



6. How many single leg hops can you do without pain?

POINTS



7. Are you currently undertaking sport or other physical activity?

		POINTS
0	Not at all	
4	Modified training ± modified competition	
7	Full training ± competition but not at same level as when symptoms began	
10	Competing at the same or higher level as when symptoms began	

8. Please complete EITHER A, B or C in this question.

- If you have no pain while undertaking Achilles tendon loading sports please complete Q8a only.
- If you have pain while undertaking Achilles tendon loading sports but it does not stop you from completing the activity, please complete Q8b only.
- If you have pain that stops you from completing Achilles tendon loading sports, please complete Q8c only.

A. If you have no pain while undertaking Achilles tendon loading sports, for how long can you train/practise?

	NIL	1-10 mins	11-20 mins	21-30mins	>30 mins
POINTS	0	7	14	21	30

OR

B. If you have some pain while undertaking Achilles tendon loading sport, but it does not stop you from completing your training/practice for how long can you train/practise?

	NIL	1-10 mins	11-20 mins	21-30mins	>30 mins
POINTS	0	4	10	14	20

OR

C. If you have pain that stops you from completing your training/practice in Achilles tendon loading sport, for how long can you train/practise?

NIL	1-10 mins	11-20 mins	21-30mins	>30 mins	
0	2	5	7	10	POINTS

Anthropometric Data

Patient Code: _____ Patient Name: _____
DOB: _____ Age: _____ Waist Circumference: _____
Patient Occupation: _____
Height: _____ Weight: _____

Ultrasound

Measure	Left	Right

Biomechanical Measurements

Measure	Left		Right	
	DF (◦)	PF (◦)	DF (◦)	PF (◦)
Ankle ROM				
Navicular Drop				

Central Sensitisation

Hot & Cold

		Left			Right		
	Reps	LL	UL	LL	LL	UL	LL
Pain Rating	1						
	2						
	3						
Hot & Cold Rating	1						
	2						
	3						

Pressure Pain Threshold

		Left			Right		
	Reps	PAT	CEO	AT	PAT	CEO	AT
Pain Threshold (Nm)	1						
	2						
	3						

Biodex

*Randomisation by tossing a coin – Heads = Right, Tails (Harp) = Left

Specific Mechanical Measurements

Starting Leg	**Biodex Chair**				**Outer Equipment**		
R/L	Tilt	Height	Forward seat	Whole chair	Height of knee stabiliser	Forward of knee stabiliser	Lever arm?

	Left	**Right**	**Deficit**
Peak Torque (Nm)			
Peak Torque/BW			
Avg. Torque			
Coeff Variation			
Time to peak torque			
Angle of peak torque			

Neuromuscular Performance

Single-Leg Hop

Left			**Right**		
Trial 1 (cm)	Trial 2 (cm)	Trial 3 (cm)	Trial 1 (cm)	Trial 2 (cm)	Trial 3 (cm)

CMJ

	Left				**Right**			
	1	2	3	Highest	1	2	3	Highest
Contact Time								
Jump Height								

Single Leg Endurance

	Left			**Right**		
	Trial 1	Trial 2	Average	Trial 1	Trial 2	Average
No. of heel raises						

Hot/Cold Testing

Hot

Left Arm	Right Arm
1	1

2	2
3	3

Left Leg	Right Leg
1	1
2	2
3	3

Cold

Left Arm	Right Arm
1	1
2	2
3	3

Left Leg	Right Leg
1	1
2	2
3	3

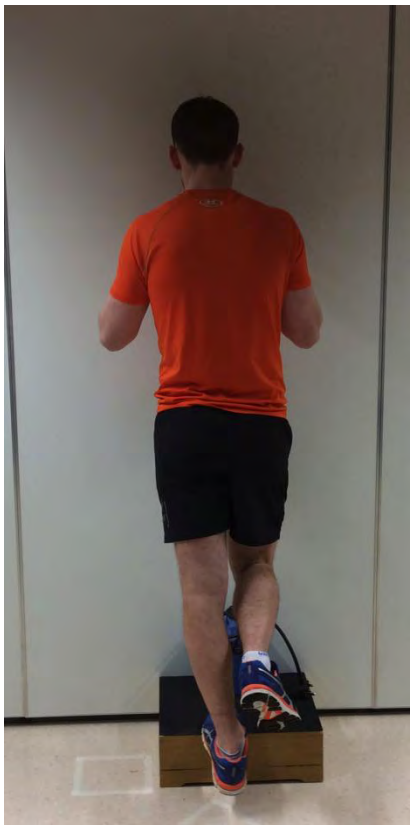
APPENDIX 8: Pilot Intervention Programme

Participant Programme Guidelines

Weeks 0-1

Perform exercises every 2nd day

- Place your foot over the edge of the step as shown in the picture. Hold onto support with your hand and keep the unaffected leg in the air as shown.
- Do exercises **SLOWLY**.
- Remember 3 seconds **UP**, 3 seconds hold at **TOP** and 3 seconds **DOWN**
- Repeat this process 12 times and rest for 2-3 minutes.
- Perform 4 sets
- If your pain is 2 points more on the pain scale during or the next morning after the exercises then you need to lessen the weight of the exercises.
- Using a scale of 0-10 where 10 is intense pain and 0 is none. (Example pain usually 2/10, exercises during or next day flared up to 6/10).



Note: If you cannot perform the required number of repetitions, start the exercises using both legs until you are strong enough to perform unilateral heel raises.

Weeks 1+

Perform exercises every 2nd day

In order to progress the exercise for the next few weeks we need to add some load. To do this place some sand into a backpack as demonstrated in the video and perform the exercises with the weighted backpack on. You can add/take away load accordingly but the load should be enough that you can perform 12 heel raises. Try to progress on a weekly basis depending on symptoms as discussed below.

So with the loaded backpack perform the exercises as below:

- Place your foot over the edge of the step as shown in the picture. Hold onto support with your hand and keep the unaffected leg in the air as shown.
- Do exercises **SLOWLY**.
- Remember 3 seconds **UP**, 3 seconds hold at **TOP** and 3 seconds **DOWN**
- Repeat this process 12 times and rest for 2-3 minutes.
- Perform 4 sets
- If your pain is 3 points more on the pain scale during or the next morning after the exercises then you need to lessen the weight of the exercises.
- Using a scale of 0-10 where 10 is intense pain and 0 is none. (Example pain usually 2/10, exercises during or next day flared up to 6/10).

Note: If you cannot perform the required number of repetitions, start the exercises using both legs until you are strong enough to perform unilateral heel raises.

Adding the load/progressing the exercises

What is the right load? How do I know?

There is no recipe to this, it is completely individual. If you can do 12 heel raises without great difficulty then **YOU NEED** to increase the weight by adding sand. The heavy load is really important in this programme so you need to progressively increase the weight, there is no point performing 12 reps comfortably, you must not be able to perform more than 12. Each week add more sand with the aim that you can do 12 repetitions and no more.

So load **MUST** be heavy!

Remember to record the weight of your backpack using a weighing scale as shown, this can be used to track improvements over the weeks.

Aim to increase the weight at the start of each week as a “new week”.

Can I still continue to run and am I damaging the tendon by running on it?

YES you can And NO you are not damaging your tendon (just aggravating a sensitive structure). But Provided your symptoms don't flare up as result. If your pain is 2 points more above your baseline on the pain scale during or the next morning after the running/engaging in physical activity then you need to lessen the weight of the exercises. On a scale of 0-10 where 10 is intense pain and 0 is none.

Training Diary

In order to capture your activity levels during the programme which may/may not affect outcome we want to keep a record of your physical activity levels using a simple weekly diary and RPE.

Week X				
Date	Activity	Distance	Time	RPE Score
12/1/15	Jogging	6km	31mins	4
14/1/15	Spinning Class	?	45mins	6

17/1/15	Walk	4km	50mins	3

Online weekly wellness questionnaire

Online wellness questionnaire via email

You will be emailed on a weekly basis with an invitation to filling an online wellness questionnaire, it is literally 30 secs to fill.

Flare Management

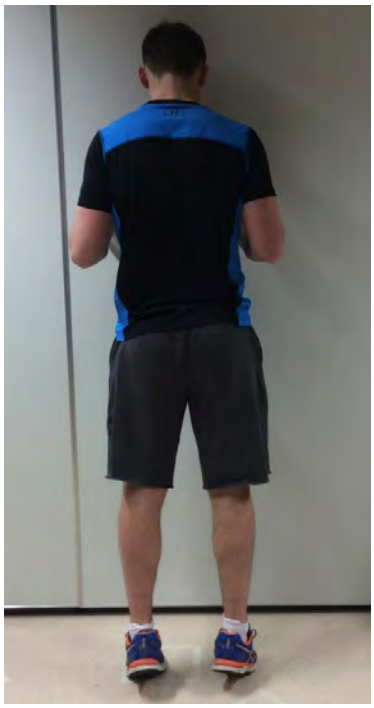
A flare up is a sudden increase in pain levels beyond the normal levels of pain experienced and often occurs if you suddenly overload the tendon. Ideally the aim of this programme is to prevent flare ups occurring by ensuring we trick the tendon in a very gradual way but a flare up may occur at some stage throughout the programme. This may occur if you progressed the weight of the heel raises too quickly or too heavy or progressed the running/physical activity too quickly.

So flare up usually occurs when one or both or these has been too high leading to flaring of that protective mechanism.

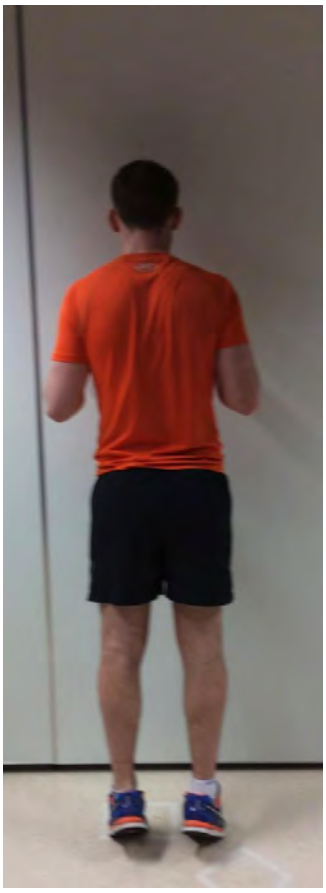
REMEMBER you have not damaged the tendon you have just over sensitised an already sensitive structure and initiated that protective pain response again.

If this occurs during the programme:

1. Contact me
2. Avoid running and excessive physical activity loading of the tendon.
3. Scale back your exercises and just perform double leg isometric heel raises as shown in the picture below. To perform isometric loading exercises rise up halfway on your tip toes as shown whilst holding onto support. Maintain this position for 45 seconds and repeat 4-5 times at various stages throughout the day. The aim of this is to reduce pain and maintain the tendons load ability.



4. Once your pain levels have settled back down to baseline values again you can begin to perform double leg heel raises. Position yourself as shown in the picture below. As per previous programme exercises, do exercises SLOWLY. Remember 3 seconds UP, 3 seconds hold at TOP and 3 seconds DOWN. Repeat this process 10 times and rest for 2-3 minutes. Perform 4 sets. If your pain is 2 points more on the pain scale during or the next morning after the exercises then you can return to week 1 of the programme again and gradually build the load if symptoms allow. Using a scale of 0-10 where 10 is intense pain and 0 is none. (Example pain usually 2/10, exercises during or next day flared up to 6/10).



5. Gradually return to previous physical activity levels symptoms allowing.

Contact details

If you have any questions/queries please use the dropbox discussion blog document or else you can contact me on

Mobile: 0872223564

Email: sean.mcauliffe@ul.ie

Rating of Perceived Exertion (RPE)

Category-Ratio Scale

0 Nothing at all

0.3

0.5 Extremely weak Just noticeable

0. 7

1 Very weak

1.5

2 Weak Light

2. 5

3 Moderate

4

5 Strong Heavy

6

7 Very strong

8

9

10 Extremely strong "Maximal"

11

• Absolute maximum Highest Possible

Rating of perceived exertion (RPE) is a widely used and reliable indicator to monitor and guide exercise intensity. The scale allows individuals to subjectively rate their level of exertion during exercise or exercise testing. This will be calculated against the amount of time you spend at a particular exercise and will be used to calculate your training load on a weekly basis throughout the programme.

Training Diary

On a weekly basis if possible please fill in your training diary under the columns provided below. I have filled out an example to show you what one may look like.

Week X				
Date	**Activity**	**Distance**	**Time**	**RPE Score**
12/1/15	**Jogging**	**6km**	**31mins**	**4**
14/1/15	**Spinning Class**	**?**	**45mins**	**6**
17/1/15	**Walk**	**4km**	**50mins**	**3**

APPENDIX 9: Qualitative Study Interview Guide

Interview guide

Introduction

In this interview, I will be asking you questions about your experience of achilles tendon pain and if it has affected factors like physical activity, sleep or daily activities. The information you provide may benefit healthcare professionals and may lead to better management of achilles tendon pain in the future. As a reminder, this interview will be recorded and the information will be kept confidential.

History of Achilles tendon pain

- Please tell me all about your achilles tendon pain? (follow up questions to find out when and and how the pain happened and obtain narrative history from participant).

Probes:

- Is it there all the time?
- What makes it better?
- What makes it worse?

Perceived Cause

- What do you think has caused your achilles tendon pain?
    - Anything else?

<u>Probes:</u>

Trauma (e.g. fall)

Specific movements or activity

Change in loading pattern

Ageing?

- How does it make you feel knowing (or not knowing) the cause of your achilles pain?
- What does your pain mean to you?
    - What do you think about when you are in pain? What do you think they mean?
- Most tendon pain heals and does not last for a long time, so why do you think your Achilles pain did not heal initially?
- Why do you think some people get better and others don't?

Impact of Achilles pain:

- Please tell me about how your Achilles pain affects you? (Follow up questions to explore impact upon activities of daily living, work, leisure & recreational activities, relationships, emotional impact, and to explore symptoms).

Management of pain:

- What do you do to manage your Achilles pain?
- Did your therapist give you ways to manage your Achilles pain?
    - If so, what were they? Did you think they were useful/effective?
    - If not, what ways do you think they could have helped you manage your pain better?
- Do you feel in control of your Achilles pain?

How do you feel about managing your Achilles pain from now on?

Future expectations:

- How do you see yourself in the future?
    - If better, why?

    - If worse/same, why? What will cause it to get worse/stay same?

- Do you believe your Achilles pain can be cured?
    - If so, what do you mean by cured?
    - If not, what do you think could be better?

Conclusions:

Is there anything else that we have not discussed that you would like to share?

Member Check Questions

1. Do you recognise this report as the content that was discussed by you during your interview?
2. Is there anything in the presented summary that you do not agree with?
3. Do you feel that there has been important information that was discussed during the interview excluded?
4. Are you satisfied that this is a true representation of all material discussed by you in response to questions asked during the interview?

APPENDIX 10: QAREL Checklist

1. Was the test evaluated in a sample of subjects who were representative of those to whom the authors intended the results to be applied?
2. Was the test performed by raters who were representative of those to whom the authors intended the results to be applied?
3. Were raters blinded to the findings of other raters during the study? (inter-rater studies only)
4. Were raters blinded to their own prior findings of the test under evaluation? (Intra-rater studies only)
5. Were raters blinded to the subjects' disease status or the results of the accepted reference standard for the target disorder (or variable) being evaluated?
6. Were raters blinded to clinical information that was not intended to form part of the study design or testing procedure?
7. Were raters blinded to additional cues that are not part of the test?
8. Was the order of examination varied?
9. Was the stability (or theoretical stability) of the variable being measured taken into account when determining the suitability of the time interval among repeated measures?
10. Was the test applied correctly and interpreted appropriately?
11. Were appropriate statistical measures of agreement used?

Appendix 11 Audit Trail for Study V: Qualitative Study

Institutional Ethics Board approval and Oversight: Ethical approval for the study was sought and granted by the local Education and Health Sciences Research Ethics Committee, in the University of Limerick (Ethics Number: EHSREC2014-05-14).

Literature review: A detailed literature review was undertaken as part of the research proposal. Given the distinct lack of qualitative research in the area of AT, the literature review was focused on other peripheral musculoskeletal disorders such as the knee, hip or shoulder. An extensive review of the literature allowed authors to draw parallels and identify potential gaps to inform the research proposal.

Conceptual/Theoretical framework: An inductive thematic analysis (Braun and Clarke 2006) was used to uncover participants experience of AT. Thematic analysis is a qualitative analytic method for identifying, analysing and reporting patterns (themes) within data. It minimally organises and describes the data set in (rich) detail while also providing flexibility in interpreting various aspects of the research topic.

Interview Protocol and instrument development: The questioning route and interview guide was drafted and agreed upon by the authors of the study. The questioning route covered: participants history of AT, perceived cause of AT, impact of AT pain, experience in managing AT, and perspective on future prognosis of their AT (For full interview guide see supplementary file 1).

Participant Selection: Men and women, 18-60 years of age with AT symptoms for more than 3 months were recruited from the local running clubs and members of the local community by means of e-mail and through word of mouth. Participants were recruited as part of an intervention study investigating the effects of a 12-week exercise intervention for individuals with persistent AT in the local community. A diagnosis of AT was

determined by a combination of Achilles tendon pain, tenderness and impaired physical performance undertaken by the main study author (SMA).

Data Collection and storage: Semi-structured telephone interviews (8 interviews) were carried out by a final year undergraduate physiotherapy student (HC), who was unknown to the participants and was guided by a flexible questioning route. Interviews lasted from approximately 30-60 minutes. Interviews were recorded using a digital voice recorder.

Raw Data: Audio files using a digital voice recorder, filed notes and site documents (participant information sheet, consent form, baseline screening) were all stored in a secured location.

Partially Processed Data: Coded interview transcripts and key informant responses; write ups of observational comments, and researchers field notes.

Coding Scheme: Interviews were transcribed verbatim. Data coding was performed using the six-step framework approach proposed by (Braun and Clarke 2006): (Generating initial codes, Searching for themes, Reviewing themes, Defining and naming themes, Producing the report, Producing the report) . Initial code lists were then amalgamated and a comprehensive code list was finalised in view of the codes most representative of the dataset informed by background reading related to the research question. The finalised code list was then applied to all transcripts by the study author (SMA). Coded data was categorised and through a process of repetitive interpretation, synthesising and theorising – themes were identified (Thorne *et al.* 1997). Transcripts were then re-read several times and the selected themes were finalised based on consensus discussion between three study authors (SMA, AS and KOS).

Trustworthiness techniques: In order to ensure trustworthiness of the data Guba's Four Criteria for Trustworthiness (credibility, transferability,

dependability, confirmability) were taken into consideration when undertaking the qualitative research. Some of the methods used to ensure trustworthiness of the research included:

- **Member checking:** Checks relating to the accuracy of the data were undertaken through member checking. Members were individually emailed their transcriptions and were provided with a set list of member check questions, which can be found in supplementary file 1.

- **Triangulation of data:** In order to improve the validity of the data and research project triangulation of data was undertaken to capture different dimensions of the same phenomenon. All participants included in the current study also engaged in a intervention study which involved baseline assessment of psychological, general health and functional impairments relating to their AT, thus ensuring a variety of data collection methods to improve trustworthiness.

- **Debriefing sessions:** HC, the undergraduate student involved in the data collection, engaged in regular debriefing sessions with a member of the research team (SMA) to ensure credibility of the data collected.

Case Studies and summaries

Research manuscript:

Following formation and generation of the interview themes using appropriate statistical methodologies a research manuscript was undertaken using a collaborative approach of the aforementioned study. Given the distinct lack of qualitative research in the area of AT the research reported compared findings to qualitative research in other peripheral musculoskeletal disorders and then discussed them in relation to AT to contextualise the findings. Limitations and recommendations for future research based on the study findings were also discussed in the research report.