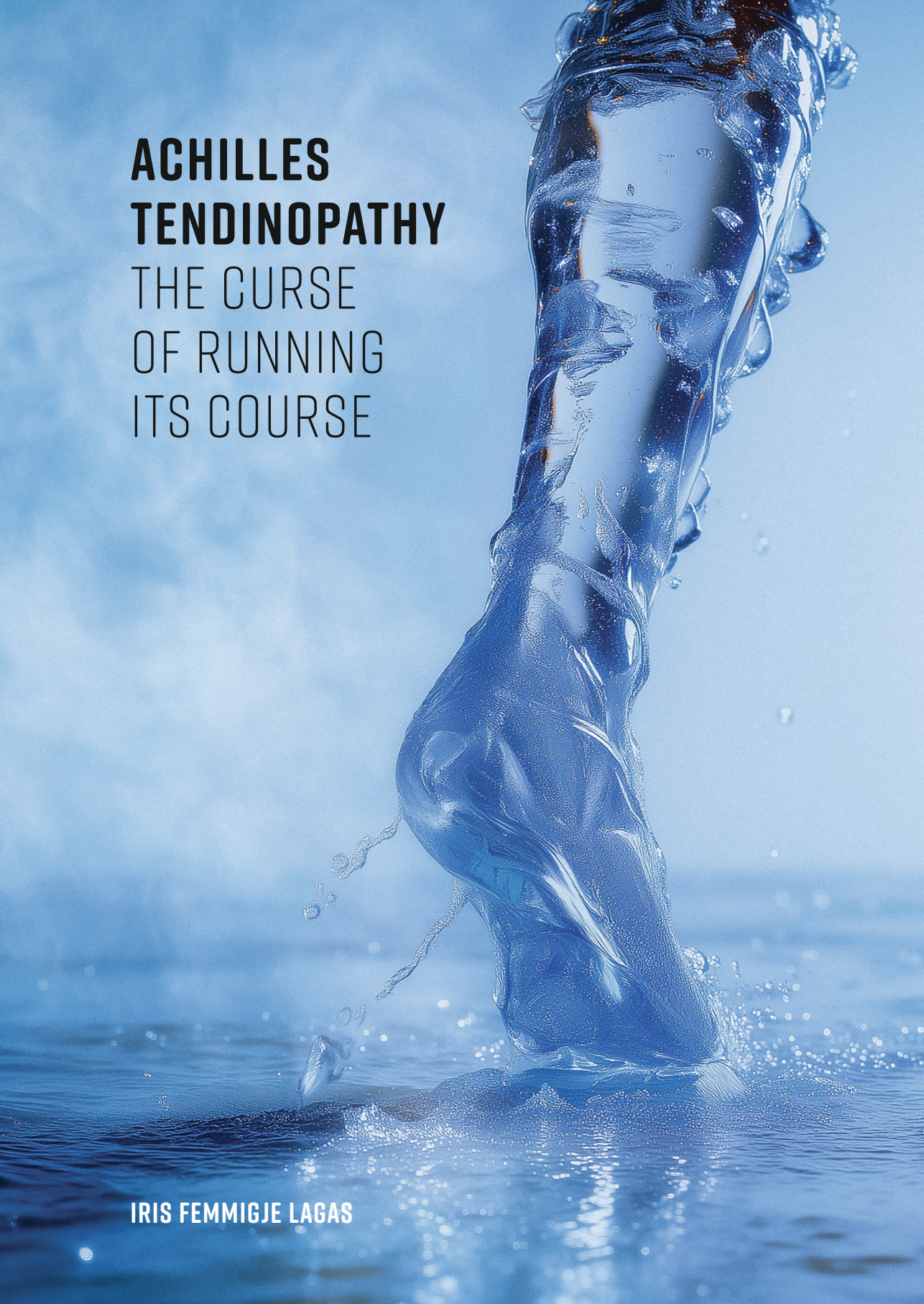

ACHILLES TENDINOPATHY
THE CURSE OF RUNNING ITS COURSE

IRIS FEMMIGJE LAGAS

ACHILLES TENDINOPATHY – THE CURSE OF RUNNING ITS COURSE

Achilles tendinopathie – De vloek van het beloop

Iris Femmigje Lagas

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Achilles tendinopathie – De vloek van het beloop

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TABLE OF CONTENTS

1

General introduction

Great power comes with great responsibility. Bearing the brunt of plantar flexion of the foot and taking the hits of walking, makes us highly dependent on a healthy Achilles tendon. The high loads also make the Achilles tendon prone to injury. Walking, running and jumping are all made possible by the Achilles tendon, as it conveys the contraction of the gastrocnemius and soleus muscles to plantar flection of the foot. It can bear up to 4,340 Newton,[1] which is equivalent to holding 400 litres of water.

Nomenclature

Historically, the Achilles tendon has had many names, such as *tendo magnus* ('great tendon') and *chorda Hippocrati* ('string of Hippocrates').[2] The first written record of the tendon referring to Achilles was by was by anatomist Phillipus Verheyen, who called it '*chorda Achillis*'.[3] This refers to Achilles, a hero of the Greek mythology, and central character of Homer's Iliad. Achilles' body was made invulnerable by a plunge in the river Styx. His mother held by the heel, leaving this area vulnerable. Achilles was ultimately killed by a poisoned arrow to the heel, which is the origin of the expression 'Achilles heel'.

Nowadays, we use *tendinopathy* to describe a persistent tendon pain and loss of function related to mechanical loading.[4] Before the term *tendinopathy* became widely accepted, the nomenclature changed frequently.[5] Surprisingly, the meaning of tendinopathy is not described in the Oxford English dictionary. Its older name, *tendinitis*, is described as an inflammation of a tendon.[6] This simple act of looking up the meaning of the pathology highlights the problem with terminology: it changed with trends and the whims of influential scientific researchers and health care professionals. Albert[7] was the first to describe pain in the region of the Achilles tendon in 1893, and named it *Achillodynia*. Later, it changed from the anatomy-based *tendinitis Achillea traumatica*,[8] to the histopathology-based *tendinitis, paratendinitis* and *peritendinitis*.[9,10] As the suffix *–itis* usually refers to a (bacterial) infection, this nomenclature is not fitting either.[11] Others proposed the term *tendinosis*, to reflect a 'degenerative' condition devoid of inflammation.[12,13] This term fell out of favour because it was considered to be a histopathological diagnosis, rather than a clinical one. Therefore, Maffulli et al.[10] suggested using *Achilles tendinopathy* in their publication in 1998 on terminology for Achilles tendon related disorders, helping to resolve the confusion. The suffix *–pathy* is derived from the Greek word παθος (pathos), which means 'suffering'. Maffulli et al.[10] defined Achilles tendinopathy as a clinical syndrome characterized by a combination of pain, swelling and impaired performance of the Achilles tendon. The most recent Dutch multidisciplinary guideline[14] defines Achilles tendinopathy as local pain in the Achilles tendon associated with tendon-loading activities.

Achilles tendinopathy can be subdivided based on location of symptoms, duration of symptoms and stage of tendinopathy. The most straightforward classification is based on the location; insertional Achilles tendinopathy and midportion Achilles tendinopathy. Insertional tendinopathy is defined as symptoms localized within the first 2 centimetre of the Achilles tendon's attachment to the calcaneus. This may involve tendinopathy of the Achilles tendon insertion, a Haglund's deformity (prominence of the superolateral tubercle of the calcaneus) and/or retrocalcaneal bursitis. Midportion Achilles tendinopathy is defined as symptoms occurring more than 2 centimetre above the distal insertion.[14]

Achilles tendinopathy can also be classified based on duration of symptoms. It has been suggested that symptoms lasting less than 2 weeks can be described as 'acute', while symptoms lasting for more than 6 weeks are considered 'chronic'.[15] There is no clear basis for this classification system, and it differs from the World Health Organization (WHO) definition of chronic pain, which is defined as lasting 3 months or more.[16] While the classification based on symptom duration appears to be clinically applicable, distinction based on duration is still based on fragmented information.

Others use the tendinopathy stage to define the progression of the disorder. The continuum model suggests that Achilles tendinopathy is fluent, which means that the Achilles tendon stage can move from its current stage to the next, and revert back to its previous stage.[17] The stages are new-onset tendinopathy, tendon disrepair and degenerative tendinopathy. New-onset tendinopathy is a non-inflammatory proliferative response which occurs with acute tensile or compressive overload. It is usually caused by an unaccustomed physical activity, which leads to metaplastic change where proteoglycans change the matrix due to an increase in bound water. Collagen integrity is mostly maintained. This reactive response causes thickening of the tendon, reduces stress and increases stiffness. The tendon could return to normal if overload is sufficiently reduced. Tendon disrepair is the stage where the body attempts to repair the tendon with an increase of protein production, especially proteoglycans. The proteoglycans separate the collagen and disorganizes the matrix. Vascularity and neuronal ingrowth may increase. The tendon disrepair stage might be reversible with load management and exercises to stimulate reformation of the matrix structure. Lastly, degenerative tendinopathy is characterized by matrix and cellular changes. Areas of the matrix can be disordered, containing matrix breakdown products and minimal collagen. The tendon consists of islands of disorganized matrix with breakdown products and little collagen within the normal tendon. Patients with degenerative tendinopathy often have a history of recurring tendon pain

and swelling. Recovery from degenerative tendinopathy takes a long time as it is challenging to find successful treatment options.[18] While the continuum model is mainly based on animal studies, its value in the clinical setting remains uncertain. It is likely that these tendon changes occur consecutively and that duration of symptoms interfere with these changes and thereby causing an overlap between the classification based on symptom duration and the continuum model.

In this dissertation, we use the definitions of insertional and midportion Achilles tendinopathy as stated above. When referring to the duration of symptoms, we define new-onset or acute Achilles tendinopathy as having a symptom duration up to 6 weeks, and chronic Achilles tendinopathy as symptoms persisting for 6 weeks or longer.

Having a closer look

The Achilles tendon transfers forces from the triceps surae; the gastrocnemius and soleus muscles, occasionally accompanied by the plantaris muscle. The musculotendinous junction typically starts 15 centimetre above the calcaneal insertion, and the Achilles tendon is fully incorporated at 7 to 10 centimetre above the calcaneal insertion.[19] Instead of a synovial sheath, the Achilles tendon is surrounded by the paratenon, a thin membrane-like structure. The paratenon ensures that the tendon glides smoothly among the surrounding structures.[19] Named after its location, the retrocalcaneal bursa lies between Achilles tendon and the tuberosity on the posterior surface of the calcaneus.[19] The Achilles tendon is supplied with blood by longitudinal arteries that run along the length of the tendon and at the calcaneal insertion. The vascularity is lowest approximately 2 to 7 cm above the calcaneal insertion. This midportion is mainly vascularized by the paratenon.[19] This area of low vascularity may prevent adequate tissue repair, and eventually lead to injury.

When looking at the structure of the Achilles tendon, a hierarchical composition of fascicles, fibres, and fibrils forms the Achilles tendon.[20] The dry tendon weight consists primarily of collagen, proteoglycans and elastin. Collagen comprises approximately 70% of the tendon dry weight and type I collagen is the most common type.[21,22] As collagen is a stiff protein, it provides tensile strength to tissues. Elastin composes 1-10% of the tendon dry weight. Elastin is a protein which can stretch to twice its original length and is highly resistant to fatigue and can store energy.[23] Proteoglycans bind the hierarchical composition of fascicles, fibres, and fibrils together and contribute to 1-5% of the tendon dry weight.[23] In maintaining the structural integrity of the tendon, glycosaminoglycans play a role in preventing excessive shearing between collagen components.[24] This brief summary of the tendon structure unravels

why the hierarchical tendon structure is able to withstand high tensile strength during efficient force transfer.

Incidence of Achilles tendinopathy

Midportion Achilles tendinopathy occurs in 1.85 per 1,000 patients, registered to a Dutch general practitioner clinic.[25] When we look at patients in the working population, aged 21-60 years, the incidence increases to 2.35 per 1,000 patients.[25] A sedentary lifestyle is reported by one-third of patients with Achilles tendinopathy,[26] which means that the largest group of patients participate in physical activities and sports. The incidence is highest in runners, varying from 3.5% to 8.3%.[27-31] A group of elite runners from Finland consisting of male athletes that competed at least once in international competitions, had a lifetime cumulative incidence of Achilles tendinopathy of 52%.[32] As the incidence of Achilles tendinopathy peaks in the working and sporting population, the total costs are high due to medical visits and absence of work.[33,34] It might be worthwhile to prevent Achilles tendinopathy by identifying risk factors and developing a suitable prevention strategy.

An ounce of prevention

While Benjamin Franklin once stated that *'An ounce of prevention is worth a pound of cure'*, we first need to research hów we can prevent Achilles tendinopathy. Given that elite runners have a cumulative risk of 52% for developing Achilles tendinopathy,[32] it may be worthwhile to analyse possible risk factors in runners. Step one of developing a prevention strategy (Figure 1) is establishing the extent of the problem.[35] Because most studies investigating Achilles tendinopathy in runners involve relatively small sample sizes and a high degree of variability within the running population,[28,29] the incidence of Achilles tendinopathy and its progression into chronic Achilles tendinopathy remains unclear.

The second step in developing a prevention strategy is to determine risk factors.[35] Risk factors can be categorized in intrinsic risk factors, such as obesity, or extrinsic risk factors, such as mechanical overload. An intrinsic pathway of developing Achilles tendinopathy might be inflammation. The hypothesis is that the chronic inflammatory state of metabolic diseases cause a disorganization of collagen fibres and increase in tendon stiffness, which might predispose patient to develop tendinopathy.[36] While there are anecdotal reports of metabolic diseases as a risk factor for tendinopathy, this has never been examined systematically.[37] Extrinsic factors, such as training load, are hypothesised to influence the risk of (Achilles) tendinopathy.[38] Due to heterogeneity of studies and small sample sizes, an association between Achilles tendinopathy and this risk factor cannot be established. As a result,

there is currently limited evidence linking risk factors to the onset of Achilles tendinopathy.[39]

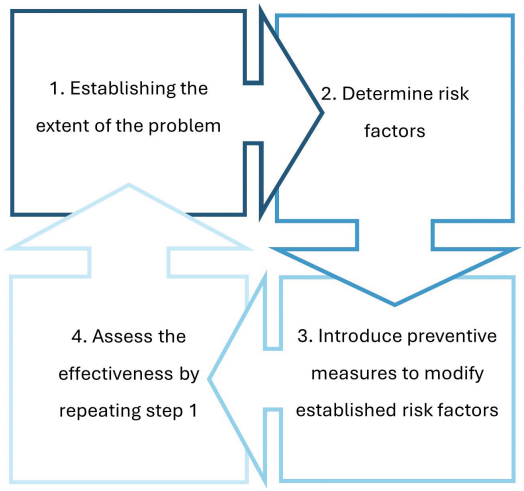

Figure 1. Injury prevention sequence

The third step in the injury prevention model is to introduce preventive measures to modify established risk factors.[40] One of the established risk factors is a decreased ankle dorsiflexion range, which is associated with a 2.5-3.6 times higher risk of developing Achilles tendinopathy.[41,42] Stretching and eccentric (lengthening) exercises are hypothesied to improve ankle dorsiflexion, and may therefore serve as a preventive measure to address decreased ankle dorsiflexion. Since the effect of stretching and eccentric (lengthening) exercises on ankle dorsiflexion has not yet been objectively measured, this should be examined first.

Quantifying symptom severity

As symptoms of Achilles tendinopathy are experienced in a wide range of severity, it is useful for studies to quantify symptom severity and its progress over time. A Delphi study determined that symptom evaluation in patients with Achilles tendinopathy should encompass nine core domains: patient overall rating, participation, pain on activity/loading, disability, function, physical function capacity, quality of life, psychology, and pain over a specified timeframe.[43] The Victorian Institute of Sport Assessment (VISA) – Achilles tendinopathy is a validated and disease-specific patient reported outcome measure for active patients with Achilles tendinopathy.[44] It quantifies the symptom severity of the core domain 'disability' with eight questions about pain, function and sports activity. The score ranges from 0 to 100, with 100

representing a healthy tendon. Since its introduction, it is widely used by clinicians and in studies as an outcome measure.

A quantitative outcome measure should be reliable (consistent scores in absence of change) and responsive (able to detect clinically important changes).[45] To interpret whether the change in VISA-A score over time is meaningful for the patient, the minimal clinically important difference (MCID) is used.[46] Previous literature reports an MCID ranging from 6.5 to 20 points in heterogenous study populations and determined with different statistical methods.[47-49] Furthermore, it is important to know which VISA-A score reflects a sufficient remission of symptoms. This is represented by the patient acceptable symptom state (PASS).[50] With an adequately determined MCID and PASS, the effect of a treatment can be interpreted with more accuracy in relation to a noticeable effect for the patient.

Numerous options

After being diagnosed with Achilles tendinopathy, frequently applied treatment options are wait-and-see, orthosis, exercise therapy, oral medication, injections, shockwave, and surgery.[51] For both midportion and insertional Achilles tendinopathy, patient education, load management advice and exercise therapy for at least 12 weeks after the start of symptoms is adviced.[51] The Dutch Guideline for Achilles tendinopathy comply with this advice, adding that shared decision making with the patient forms an important pillar of the treatment.[14] An important part of patient education is to inform patients about the expected course of symptoms. However, current knowledge about the long-term prognosis and factors influencing the course is limited.

General aim and outline of this dissertation

This dissertation aims to determine the incidence and risk factors for Achilles tendinopathy, investigate the course of symptoms in new-onset and chronic Achilles tendinopathy and assess whether targeted exercises increase ankle dorsiflexion.

While running is a popular sport associated with a high risk of injuries, the incidence of Achilles tendinopathy in a homogenous group of recreational runners remains unknown. In **Chapter 2** we conducted a large observational cohort study to determine the incidence of Achilles tendinopathy in recreational runners and identify risk factors for its development .

In **Chapter 3** we analysed whether lower extremity tendinopathies are associated with metabolic and chronic diseases. Since inflammation is suggested to be the key mechanism in both tendinopathies and metabolic and

chronic diseases, there might be an association. Awareness of this potential association could lead to early recognition and management of metabolic and chronic diseases.

A decreased ankle dorsiflexion angle is associated with an increased risk of Achilles tendinopathy. In **Chapter 4** we examined whether targeted stretching and eccentric exercises of the calf muscles increase ankle dorsiflexion in healthy soccer players with a decreased ankle dorsiflexion.

The Victorian Institute of Sports Assessment-Achilles (VISA-A) score is generally used to express the symptoms of Achilles tendinopathy on a numeric scale. As the minimal clinically important difference (MCID) and patient acceptable symptom state (PASS) are unknown, patient-centred interpretation of trial results is limited. In **Chapter 5** we therefore determined the MCID and PASS for the VISA-A score in patients with midportion Achilles tendinopathy.

The course of symptoms after developing Achilles tendinopathy remains unknown. In **Chapter 6** we describe the percentage of runners that develop persisting Achilles tendinopathy symptoms 1 year after developing acute Achilles tendinopathy. As a secondary aim, we sought to identify prognostic factors that are associated with developing persisting symptoms.

Symptoms of Achilles tendinopathy may persist even 5 to 10 years after diagnosis and treatment. Pain-coping might influence treatment response. Furthermore, different types of pain, specifically neuropathic pain may play a role in the chronicity of symptoms. In **Chapter 7** we analysed whether pain coping strategies and the presence of a neuropathic pain component influence the course of Achilles tendinopathy symptoms. In **Chapter 8** we investigated whether patients with chronic midportion Achilles tendinopathy continue to experience symptoms after 10 years.

We discuss the clinical implications and relevance of the findings and provide perspectives for future research in **Chapter 11**.

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Part I

Incidence, risk factors and prevention strategy for Achilles tendinopathy

2

Incidence of Achilles tendinopathy and associated risk factors in recreational runners: a large prospective cohort study

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Iris F. Lagas, Tryntsje Fokkema, Jan A.N. Verhaar, Sita M.A. Bierma-Zeinstra, Marienke van Middelkoop, Robert-Jan de Vos

ABSTRACT

Objectives
To determine the incidence of Achilles tendinopathy in a large group of recreational runners and to determine risk factors for developing AT.

Design
Observational cohort study.

Methods
Runners registering for running events (5–42 km) in the Netherlands were eligible for inclusion. Main inclusion criteria were: age ≥18 years, and registration ≥2 months before the running event. The digital baseline questionnaire obtained at registration consisted of demographics, training characteristics, previous participation in events, lifestyle and previous running-related injuries. All participants received 3 follow-up questionnaires up to 1 month after the running event with self-reported AT as primary outcome measure. To study the relationship between baseline variables and AT onset, multivariable logistic regression analyses were performed.

Results
In total, 2378 runners were included, of which 1929 completed ≥1 follow-up questionnaire, and 100 (5.2%, 95%CI [4.2;6.2]) developed AT. Runners registered for a marathon (7.4%) had the highest incidence of AT. Risk factors for developing AT were use of a training schedule (odds ratio (OR) = 1.8 (95%Confidence Interval(CI)[1.1;3.0])), use of sport compression socks ((OR = 1.7, 95%CI[1.0;2.8]) and AT in the previous 12 months (OR = 6.3, 95%CI[3.9;10.0]). None of the demographic, lifestyle or training-related factors were associated with the onset of AT.

Conclusion
One in twenty recreational runners develop AT. AT in the preceding 12 months is the strongest risk factor for having AT symptoms. Using a training schedule or sport compression socks increases the risk of developing AT and this should be discouraged in a comparable running population.

Trial registration number
The Netherlands Trial Register (ID number: NL5843).

INTRODUCTION

Achilles tendinopathy (AT) is a tendon disorder consisting of pain, swelling and impaired performance, and can cause prolonged absence from health-promoting activities.[1,2] An increase in physical activity level is often thought to be associated with the development of tendinopathy, which ranges from a reactive to a chronic state.[3] Reactive AT is considered to be caused by increased cell proliferation with an increase in water-attracting glycosaminoglycans. [3] Chronic AT is characterised by tissue degeneration with structural collagen changed and a long recovery time and the challenge of finding successful treatment options.[4] This emphasizes that developing a prevention strategy in an 'at risk' population is a priority.

The first step towards a prevention strategy is to establish the extent of the problem by reporting the injury incidence.[5] The incidence of tendinopathy is dependent on the population examined, as it is mainly described in the general, working and sporting population.[6] For example, in elite runners the cumulative incidence of AT is as high as 52%.[7] Running grows in popularity - it is estimated that around 50 million people in Europe (12% of inhabitants age 15-80 years) run on a regular basis.[8] Runners have a high risk to develop an injury, with 6.1 running-related injuries per 1000 running hours.[9] AT is one of the most frequent reported injuries in runners, with incidence rates varying from 3.5% to 8.3%.[10-14] Unfortunately, these studies mostly consist of relatively small sample sizes, with a high variability in running populations (for example; recreational versus elite runners, injuries with self-referral versus practitioner referred, or young versus old running athletes).[10-14]

The second step in developing a prevention strategy is to determine risk factors.[5] Risk factors can be categorised as modifiable (e.g. alcohol use, running distance) and non-modifiable (e.g. sex, age). Modifiable risk factors can be used for developing a prevention strategy. A recent systematic review showed limited evidence for 9 risk factors associated with AT onset in diverse populations .[15] Modifiable factors were moderate alcohol consumption, ofloxacin use and a reduced plantar flexor strength.[15] A limitation of this systematic review was the fact that these factors were assessed in many different populations, including runners ranging from novice to elite running experience.[15] This questions the generalizability of these associations for specific groups of athletes. Another limitation in current literature is the small numbers of injured participants (injury events) reported in the specific studies, as at least 20-50 injury cases are needed to detect strong to moderate associations.[16] Consequently, current evidence for risk factors associated with AT in runners is limited.

We conducted a large prospective study with the primary aim to determine the incidence of AT in recreational runners and with the secondary aim to determine risk factors for AT.

METHODS

This study is part of the INSPIRE trial (INntervention Study on Prevention of Injuries in Runners at Erasmus MC)[2] and was approved by the Medical Ethics Committee of the Erasmus MC University Medical Centre Rotterdam, The Netherlands (MEC-2016-292). The trial is registered in the Netherlands Trial Register (NTR number: NL5843).

Runners of 18 years or older signing up for one of three large running events (5-42.2 km) in the Netherlands were asked to participate in this study. Recruitment was from October 2016 until April 2017. Runners were excluded if they (1) did not have email access, (2) were not familiar with the Dutch language or (3) registered within two months before the running event.

All runners were asked to complete online questionnaires on four time points: at baseline (≤2 months before the running event), 2 weeks before the running event, 1 day after the running event and 1 month after the running event. The questions in the questionnaires were based on existing literature on risk factors for running related injuries.[2] The baseline questionnaire was divided in four different sections: (1) demographics, (2) training characteristics, (3) lifestyle and (4) running-related injuries in the previous 12 months (Supplementary file 1). The baseline questionnaire also inquired if the runner still had symptoms of a running-related injury. All runners received all follow-up questionnaires, regardless of injury status. Follow-up questionnaires consisted of questions about the status of previous reported running-related injuries. The next section of the questionnaire handled information about new running-related injuries. Runners were included in data-analysis if they completed one or more follow-up questionnaires.

The primary outcome measure was the incidence of self-reported AT during the follow-up period. Runners were asymptomatic at baseline and reported AT in the section about new running-related injuries in one of the follow-up questionnaires. AT was defined as an injury of the Achilles tendon caused by running, and when one or more of the following criteria were met: (1) the injury causes a reduction in running distance, frequency, speed or duration

for at least 1 week, or (2) the injury leads to an appointment with a doctor and/or physiotherapist or (3) medication is necessary to reduce symptoms (Supplementary file 1).

SPSS software (V.24.0.0.1; SPSS, Chicago, Illinois, USA) was used for statistical analysis. We used a Shapiro Wilk test for normality. We assumed normal distribution of the data if W>0.90. To evaluate differences between responders and non-responders, baseline characteristics of included runners and runners who did not complete any follow-up questionnaire were compared using an independent sample t-test (normally distribution) or Mann-Whitney U test (not normally distributed). Categorical variables were analysed using a chi square test. The incidence of AT (primary aim) was calculated by dividing the total number of included runners with the number of runners that reported AT. Incidence of AT per time frame was calculated by dividing the number of AT developed during that time frame by the mean days between two questionnaires. The incidence of AT per time frame is presented as number of patients developing AT per day.

Risk factors for developing AT (secondary aim) were identified using a multivariable logistic regression analysis [ENTER model]. We assessed the relationship between an event (onset of self-reported AT) and the following variables: sex, age, Body Mass Index (BMI), units of alcohol per week, running experience, running distance per week, use of a training schedule, use of sport compression socks, use of insoles, number of running shoes per year, landing type, running ≥80% on paved road and AT in the previous 12 months. Results were presented as odds ratio (OR) with 95% confidence interval(CI). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 2378 runners were included in the INSPIRE trial. Of these runners, 1929 (81.1%) completed one or more follow-up questionnaires with a mean follow-up (standard deviation, SD) of 20.5 (7.0) weeks, and were therefore included in the current study (Table 1). We found a number of statistical differences between the included runners and the runners who did not complete any follow-up questionnaire (Supplementary file 2).

Table 1. Baseline characteristics of included runners

	Included runners	
	N	%/Mean (SD)/ Median; IQR
N	1929	
Demographics		
Sex (male)		52.9%
Age (years)		41.9 (12.1)
BMI (kg/m^2)		23.6 (2.9)
Lifestyle		
Alcohol use (units per week)		3.0 ; 5.0
Running event		
5 or 7.5 km		5.8%
10 km		38.6%
21.1 km		31.1%
42.2 km		24.6%
Training		
Running experience (years)		4.0; 6.0
Running distance per week (km)		18.0; 20.0
Use of training schedule		62.3%
Use of sport compression socks		15.6%
Use of insoles		21.9%
Number of running shoes per year		2.0; 1.0
Landing type Hind- or midfoot Forefoot		60.5% 18.0%
Running ≥80% on paved road		77.3%
Injuries		
Injury in the previous 12 months		51.5%
Achilles tendinopathy in the previous 12 months		8.2%
Completed follow-up questionnaire		
Completed FU questionnaire 1		91.8%
Completed FU questionnaire 2		90.6%
Completed FU questionnaire 3		82.4%
Completed all FU questionnaires		74.0%
Mean number of FU questionnaires completed (1-3)		2.7 (0.6)

SD = Standard Deviation, IQR = inter quartile range, BMI = Body Mass Index, FU = follow-up

Of the 1929 included runners, 100 runners reported the onset of AT (5.2% (95%CI [4.2;6.2]). The included runners were mostly male (52.9%), were an average age of 41.9 (SD 12.1) years old and ran a median of 18.0 km (interquartile range (IQR) 20.0) per week. The incidence of AT increased with increasing event distance from 4.0% when running 10km to 7.4% when running a full marathon (Table 2). The incidence of AT was higher in runners who registered for a marathon compared to other distances (OR 1.7, p=0.014). The incidence of AT was low in the period from registration up to 2 weeks before the running event (0.5 AT per day), increased in the period from 2 weeks before until 1 day after the event (1.9 AT per day) and lowered in the period of 1 day after until 1 month after the event (1.0 AT per day) (Table 2).

Table 2. Incidence of Achilles tendinopathy per running distance

	Runners developing AT	Runners without AT	Incidence of AT % (95%CI)
N	100	1829	5.2% (4.2;6.2)
Event distance			
5 or 7.5 km	5	107	4.5% (0.6;8.4)
10 or 10.55 km (quarter marathon)	30	715	4.0% (2.6;5.4)
21.1 km (half marathon)	30	571	5.0% (3.2;6.7)
42.2 km (marathon)	35	440	7.4% (5.0;9.7)

*Statistically significant difference (p-value<0.05)
AT = Achilles tendinopathy, SD = Standard deviation, IQR = inter quartile range, CI = confidence interval

Risk factors for AT were presence of AT in the previous 12 months (OR 6.3, 95%CI[3.9;10.0]), use of a training schedule (OR 1.8, 95%CI[1.1;3.0]) and use of sports compression socks (OR 1.7, 95%CI[1.0;2.8]) (Table 3).

Table 3. Risk factors for AT in runners

	Runners developing AT		Runners without AT		Multivariable analysis
	N	%/Mean (SD)/ median; IQR	N	%/Mean (SD)/ median; IQR	OR (95%CI)
N	100		1829		
Demographics					
Sex (male)		67.0%		52.1%	1.39 (0.85;2.27)
Age (years)		45.0 (10.6)		41.7 (12.1)	1.02 (1.00;1.04)
BMI (kg/m^2)		23.8 (3.3)		23.6 (2.8)	1.00 (0.92;1.09)
Lifestyle					
Alcohol use (units per week)		2.0 ; 5.0		3.0 ; 5.0	0.99 (0.95;1.04)
Training					
Running experience (years)		4.6; 7.6		4.0; 6.0	1.00 (0.97;1.02)
Running distance per week (km)		20.0; 20.0		17.0; 21.0	1.00 (0.99;1.02)
Use of training schedule (yes)		77.0%		61.5%	1.82 (1.10;3.01)*
Use of sport compression socks (yes)		27.0%		14.9%	1.68 (1.03;2.75)*
Use of insoles (yes)		21.0%		21.9%	0.73 (0.43;1.23)
Number of running shoes per year		2.0;1.0		2.0;1.0	1.07 (0.86;1.33)
Landing type Hind- or midfoot (yes) Forefoot (yes)		63.0% 23.0%		60.4% 17.7%	1.14 (0.61;2.12) 1.29 (0.62;2.69)
Running ≥80% on paved road (yes)		81.0%		77.0%	1.32 (0.77;2.28)
Previous injuries					
AT in the previous 12 months (yes)		35.0%		6.7%	6.25 (3.90;10.00)*

*Statistically significant difference (p-value<0.05)
AT = Achilles tendinopathy, SD = standard deviation, IQR = inter quartile range, OR = odds ratio
CI = confidence interval, BMI = body mass index

DISCUSSION

This is the first large prospective cohort study in recreational runners reporting the incidence of AT and the risk factors for developing AT. We found an overall AT incidence in runners of 5.2% with the highest incidence in the subgroup of runners registered for a marathon (7.4%). In the two-week period before up to 1 day after the running event, onset of AT peaked to 1.9 developed AT per day. Presence of AT in the previous 12 months was the strongest risk factor for having (recurrent) AT symptoms. The use of a training schedule and sport compression socks also increased the risk of developing AT. Other demographics, lifestyle- or training-related factors at baseline were not identified as risk factors for AT.

These findings are relevant for sports medicine healthcare providers, as information about incidence rates of specific injuries in specific sports increases awareness of important problems within this field. Knowledge of risk factors aid in development of effective preventive intervention programs.

A study by Hirschmüller et al.[17] reported a 7.5% incidence of AT in long-distance runners after a follow-up of 1 year. Two major differences are that runners in the study by Hirschmüller et al.[17] ran twice as many kilometres per week (35.3 versus 19.9 km) and that they had twice as much running experience (12.7 versus 6.5 years) than runners included in our study. However, when comparing the incidence of AT in marathon runners in our study with the long-distance runners included by Hirschmüller, results are comparable (7.4% versus 7.5%, respectively). Another study by McKean et al.[10] divided runners in masters (age $\geq$40 years) and younger runners (age <40 years). Master runners had more AT than younger runners (6.2% versus 3.5%) . This is conflicting with our data, as we found no correlation with developing AT and age or running distance per week. One possible explanation could be that master runners report to run 2.5 times as many kilometres per week than our included runners,[10] which is a large difference. Lysholm et al.[11] reported a 8.3% incidence of AT in a mixed group of sprinters, middle-distance runners and marathon runners. While it is important to report incidence rates in specific groups of athletes, it can be even more valuable to subdivide the incidence rates of specific groups of running athletes as a previous systematic review showed a large variability in running-related injuries among runners.[18] Our study adds value by reporting incidence rates in recreational runners including all running event distances and divided by running event distance. Our results show that AT incidence is higher in marathon runners compared to smaller distances. Therefore, development of prevention strategies seems especially relevant for this target group.

The strongest risk factor for having (recurrent) AT symptoms was the presence of AT in the previous 12 months. Multiple other studies identified a previous injury as a risk factor for a new injury.[2,17,18] This suggests that certain individuals have a combination of unfavourable inherited or biomechanical characteristics which predispose them for developing recurrent AT. One unfavourable characteristic might be muscle strength, as persons with a lower plantar flexor strength have higher risk of developing an Achilles tendon injury.[19] Furthermore, insufficient healing of the AT, perhaps as a result of inadequate rehabilitation or inappropriate self-management, could also result in increased injury risk.[20] For instance, a premature return to sports after a previous AT might play a role in having (recurrent) AT symptoms. Objective training load measures of patients recovering from AT would be needed to test this hypothesis.

A training-related risk factor for AT in a previous study was training in cold weather.[15] Other training-related risk factors have not been reported in literature. We identified two training-related risk factors that were associated with developing AT: use of a training schedule and use of sport compression socks. Use of a training schedule was included in the analysis with the hypothesis that it might be a protective factor for developing AT. A training schedule could help prevent an imbalance of acute (level of fatigue) to chronic (level of fitness) training load by aiding the runner to progress training load gradually.[21] Since it has been demonstrated that a peak in training load per week, compared to the average training load of that month leads to an increased risk of injury,[21] we did not expect that use of a training schedule would be associated with a higher AT injury risk. This is the first time that this factor is explored in a running population with AT as outcome. One explanation for this finding could be that runners were more likely to use a training schedule when they are more prone to injury throughout their running career. Another explanation might be that runners are too focussed on pursuing their schedule, rather than paying attention to the onset of pain which may precede injuries that eventually can result in reduction or cessation of running activity .

Another unexpected risk factor for AT was the use of sport compression socks. Sport compression socks are thought to improve the venous return, which reduces venous stasis the lower leg.[22] This corresponds with an increased arterial perfusion and deeper tissue oxygenation,[23] which in turn may eventually lead to a decreased muscle soreness and lower likelihood of hypoxia-induced injuries.[24] Contrary to this hypothesis, we found the use of sport compression socks to be a risk factor for AT. The following theories might explain this finding. First, it could be that runners started

wearing sport compression socks because they were more prone to injuries throughout their running career. Second, one could hypothesise that the use of ankle-length compression socks causes increased pressure on the Achilles tendon. As compressive forces are thought to have an important role in insertional tendinopathies, this could be a potential mechanism of developing AT.[25] We did not ask which level of compression or height of the sport compression socks were used, and there is no research performed on the level of compression or height of sport compression socks in relation to injury incidence. This leads us to the third interesting theory, which is that sport compression socks cause restriction of total blood volume and oxygen uptake, and this repeated restriction can eventually lead to hypoxia and eventually result in AT. Studies showed a reduction in total blood volume and peak oxygen uptake when wearing sport compression socks.[26,27]. This could potentially lead to hypoxic degeneration, which is one of the mentioned histopathological features of AT.[28]

Moderate alcohol use is suggested as a risk factor for developing AT with limited evidence (OR1.33, 95%CI[1.00;1.76]) in military personnel.[15,29] It is hypothesised that alcohol consumption is associated with risky behaviour and that it affects metabolic factors predisposing for AT.[30] Contrary to Owens et al,[29] we did not find a relation between units of alcohol per week and AT onset. Our different results can be explained by the difference in runner sample and the classification of alcohol use. Owens et al.[29] defined moderate alcohol use as 7-13 drinks per week for men and 4-6 drinks per week for women, while we analyzed alcohol in units per week.[29] Using numerical data leads to no data reduction, compared to using categorical data.

A major strength of our study is the fact that we were able to include a very large cohort of recreational runners. We did not select specific runners based on age, experience or running distance in our analysis to be able to represent the general running population. This increases the generalizability of our results to the general running population. All included runners were asked whether they experienced an injury through online questionnaires. With this approach, we were able to reach a large part of the target population and not only the runners with AT who presented to a healthcare provider. Another advantage of this large cohort is the fact that we had a high likelihood to identify risk factors for AT. As our study reported 100 cases, we were able to detect even moderate associations.[16]

There are some limitations of our study. First, we used online questionnaires to inquire about potential injuries. With this approach of self-reported injuries, it remains uncertain whether the diagnosis of AT is correct. Recent studies

showed that pain can be located adequately by patients.[31,32] To increase the likelihood that the reported injury was indeed an AT, we used a very strict criteria as definition for injury.

Another limitation is the loss to follow-up rate in our study. Of the included runners, 74% completed all follow-up questionnaires. The included runners had some differences compared to runners who did not complete any questionnaire, which might indicate selection bias. However, there were no clinically relevant differences, as all differences were very small and probably statistically significant as a result of the large sample size. This increases the likelihood that the responders were comparable to the non-responders. Furthermore, the questionnaire in this study was not validated. This could have led to inaccurate answers. For example, we asked runners to describe their landing type. As we did not use video analysis to affirm their choice, it could be that runners had a different landing type than thought.[33,34] However, most questions are straightforward to answer and not susceptible for interpretation (e.g. sex, running experience, running shoes etc.).

A last limitation could be that we surpassed the one in ten rule, as we analysed thirteen variables in the multivariable logistic regression analysis. We included these variables as they were identified by previous studies as potential risk factors or hypothesised to be risk factors.[15] We used cross-validation to verify this outcome. As this analysis showed similar outcome to our statistical analysis, we ruled out potential bias by including more than ten variables.

The outcome of our study provides more insight in the incidence and risk factors for AT in recreational runners. Studies on prevention of AT in runners should be focussed on marathon runners, as the incidence is highest in this subgroup. We recommend to focus future research on modifiable risk factors as these are promising for designing new effective prevention programs. The finding that use of sport compression socks is a modifiable risk factor for AT warrants further investigation. We suggest non-invasive blood flow measurements in runners wearing sport compression socks to analyse why sport compression socks lead to development of AT. For use of a training schedule, further research should be conducted aimed at the correlation between the progression of actual training load and the development of AT.

CONCLUSION

The incidence of AT in the recreational running population is 5.2% and this incidence rate is especially high in the runners preparing for a marathon (7.4%). AT in the previous 12 months was the strongest risk factor for having (recurrent)

AT symptoms. Use of a training schedule and use of sport compression socks are two newly discovered risk factors for developing AT. Contrary to popular belief, often suggested demographics-related, lifestyle-related and training-related risk factors did not influence the risk of developing AT.

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SUPPLEMENTARY FILE(S)

Supplementary file 1. Four different sections of the baseline questionnaire with subdivided variables.

Demographics		Training characteristics		Lifestyle		Running-related injuries	
Question	Option(s)	Question	Option(s)	Question	Option(s)	Question	Option(s)
Age	In years	Running experience	In years	Alcohol use	Units of alcohol per week	Any running-related injury ≤12 months	Yes No
Sex	Male Female	Running distance per week in the past week	In km			Achilles tendinopathy ≤12 months	Yes No
Length	In cm	Running event distance	5 or 7.5 km 10 km 21.1 km (half marathon) 42 km (full marathon)				
Weight	In kg	Use of training schedule	Yes No				
		Use of sport compression socks	Yes No				
		Use of insoles	Yes No				
		Number of running shoes per year					
		Landing type	Hind- or midfoot Forefoot I don't know				
		Running on paved road	≥80% running on paved road <80% running on paved road				

Supplementary file 2. Baseline characteristics of the runners that competed one or more follow-up questionnaire versus runners that did not complete any follow-up questionnaire

	Completed one or more FU questionnaires		Completed no FU questionnaire		p-value
	N	%/Mean (SD)/ median;IQR	N	%/Mean (SD)/ median;IQR	
N	1929		449		
Demographics					
Sex (male)		52.9%		51.7%	0.645
Age (years)		41.9 (12.1)		38.3 (10.6)	<0.001*
BMI (kg/m^2)		23.6 (2.9)		23.9 (2.9)	0.053
Lifestyle					
Alcohol use (units per week)		3.0 ; 5.0		2.0 ; 5.0	0.123
Running event					
5 or 7.5 km		5.8%		6.0%	0.866
10 km		38.6%		35.9%	0.277
21.1 km		31.2%		24.5%	0.006*
42.2 km		24.6%		33.4%	<0.001*
Training					
Running experience (years)		4.0;6.0		3.5;4.8	<0.001*
Running distance per week (km)		18.0;20.0		15.0;18.0	0.008*
Use of training schedule		62.3%		58.8%	0.168
Use of sport compression socks		15.6%		18.0%	0.196
Use of insoles		21.9%		16.5%	0.011*
Number of running shoes per year		2.0;1.0		2.0;1.0	0.786
Landing type Hind- or midfoot Forefoot		60.5% 18.0%		55.2% 19.6%	0.105
Running ≥80% on paved road		77.3%		77.5%	0.923
Previous injuries					
Injury in the previous 12 months		51.5%		54.3%	0.282
Achilles tendinopathy in the previous 12 months		8.2%		9.4%	0.424

*Statistically significant difference (p-value<0.05)
FU = follow-up, SD = standard deviation, IQR = inter quartile range, BMI = body mass index

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3

Are lower extremity tendinopathies associated with metabolic and chronic diseases? A systematic review

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ABSTRACT

Background
Recent narrative reviews suggest an association between lower extremity tendinopathies and metabolic and chronic diseases. This association might lead to early recognition and change in clinical management, but it has – however – never been assessed systematically.

Objective
To analyse the association between lower extremity tendinopathies and metabolic and chronic diseases.

Design
Systematic review.

Data sources
Embase, Medline Ovid, Web of Science, Cochrane library and Google Scholar.

Eligibility criteria
Articles were eligible if the association between clinically diagnosed lower extremity tendinopathies and a metabolic or chronic disease in adult patients was reported.

Results
From 4287 eligible studies, we included 10 cohort studies and 10 case-control studies, involving 83,948 participants. Almost all (90%) included studies were assessed as having a high risk of bias. These studies had moderate evidence for an association between lower extremity tendinopathies and obesity, ankylosing spondylitis, psoriatic arthritis, and reactive arthritis. There was limited evidence for an association between lower extremity tendinopathies and heterozygous familial hypercholesterolaemia, and Systemic Lupus Erythematosus.

Conclusions
We found multiple associations between lower extremity tendinopathies and metabolic and chronic diseases. These results suggest that medical professionals should screen for these specific metabolic and chronic diseases in patients with lower extremity tendinopathies.

Trial registration number
Prospero (CRD42019140317).

INTRODUCTION

Tendinopathies of the lower extremity and metabolic and chronic diseases, such as diabetes, occur frequently in the general population[1-5]. Previous narrative reviews suggest a link between both conditions[6-8].

Lower extremity tendinopathies can be chronic, impact negatively on quality of life and have substantial socioeconomic consequences[9,10]. The aetiology is mainly unknown, but degeneration and inflammation are hypothesised to play an important part in the pathogenesis[8,11]. There may be subgroups of lower extremity tendinopathies with variable underlying causes, in which metabolic or chronic diseases may play a role[6,7].

Inflammation is suggested to be the key mechanism occurring both in tendinopathies as well as in metabolic and chronic diseases[6,12,13]. In tendons, tenocytes and immune cells produce pro-inflammatory cytokines in response to loading[13]. These pro-inflammatory cytokines affect several complex pathways and interactions, which may promote tendon healing and repair. On the other hand, persisting or recurring pro-inflammatory responses are thought to induce tendinopathy[7,14-16]. Metabolic and chronic diseases, such as obesity, diabetes and hypercholesterolaemia, also lead to increased production of local or systemic low-grade pro-inflammatory cytokines[17]. For instance in diabetes, the increased blood glucose levels raise the production of Advanced Glycation End-product (AGE's), which causes pro-inflammatory responses[18].

The above-mentioned hypotheses imply that there is an association between tendinopathies and metabolic or chronic diseases. Awareness of this association could lead to early recognition and management of metabolic and chronic diseases in patients with lower extremity tendinopathies. To date, the association between tendinopathy and metabolic or chronic diseases has never been systematically examined. Therefore, we conducted this systematic review with the primary aim to analyse whether there is an association between lower extremity tendinopathies and metabolic and chronic diseases.

MATERIALS AND METHODS

Protocol and registration

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement[19]. We prospectively registered the protocol in the international PROSPERO

database. Protocol details were submitted in June 2019 and registered in September 2019 (registration number: CRD42019140317).

Search strategy

We conducted a search strategy in multiple databases with the assistance of a medical librarian (WM Bramer). Embase, Medline Ovid, Web of Science, Cochrane library and Google Scholar were searched up to the 9th of October 2023. The search strategy is shown in Supplementary File 1.

Eligibility criteria

The following lower extremity tendinopathies were included: adductor tendinopathy, hamstring tendinopathy (proximal and distal), quadriceps tendinopathy, patellar tendinopathy, tibialis posterior tendinopathy, peroneal tendinopathy, Achilles tendinopathy (insertional and midportion) and plantar fasciopathy. The diagnosis of tendinopathy should be based on clinical findings. Imaging was not deemed necessary for establishing the diagnosis and studies describing tendinopathy defined by imaging findings only were excluded. We did not pre-define specific metabolic conditions or chronic diseases as we aimed to provide an extensive overview of all possible associations with common tendinopathies. Examples of included metabolic and chronic diseases were: obesity (body mass index (BMI) $\geq$30 kg/m^2), metabolic syndrome, diabetes, dyslipidaemia, cardiovascular disease, hypertension, thyroid dysfunction (hypo- and hyperthyroidism), rheumatic disease, renal failure, inflammatory bowel disease (such as Crohn's and Colitis Ulcerosa), sarcoidosis, infectious diseases, polycystic ovarian syndrome (PCOS) and fibromyalgia. We did not pre-define specific criteria for metabolic disorders or chronic disease, as we did not pre-define specific conditions. Studies were excluded if (1) the population was aged younger than 18 years, (2) there was no adequate control group (e.g., contralateral tendon), (3) it was conducted in animals or (4) in the laboratory (preclinical in-vitro studies), (5) the design was a case report or (6) the article was not available in English.

Study selection and data extraction

Titles and abstracts of all eligible articles were screened independently by two researchers (IL and BN). The same researchers read all included articles full-text. Disagreements were resolved by discussion, with the involvement of a third researcher (RV) if necessary. References of the included studies were screened for relevant studies that were not identified by the search strategy. In case of unpublished records, authors were contacted for availability of their data. We uploaded all selected studies to the Covidence platform (Melbourne, Australia). This not-for-profit management system facilitates an independent

data selection, data extraction, and risk of bias assessment when performing systematic reviews.

Two researchers (IL and BN) performed data extraction and recorded study design, number of participants, study population, type of tendinopathy, type of metabolic or chronic diseases, outcome measures, duration of follow-up and conclusion(s) using standardized data extraction forms.

We noted the diagnostic criteria used to establish tendinopathy, type of imaging used (if applicable), severity of pain (expressed by patient-reported outcome measure), duration of tendinopathy, participation in sports activities, and whether the pain was unilateral or bilateral.

For metabolic and chronic diseases, we noted the definition, the associated measurements (e.g., laboratory values, body mass index (BMI)), use of medication, and duration of the condition since the diagnosis.

Risk of bias assessment

Two reviewers (IL and BN) independently assessed risk of bias (ROB) of the included studies using a standardized form, the Newcastle-Ottawa quality assessment Scale (NOS) (Supplementary file 2). Studies could receive a total of 4 stars in the selection domain (selection of cases), 2 stars in the comparability domain (whether the study corrects for variables) and up to 3 stars in the outcome/exposure domain (objectivity of the main outcome). The pre-defined thresholds for converting the NOS to good, fair and poor were as follows[20]:

- Good quality: ≥3 stars in selection domain AND ≥1 star(s) in comparability domain AND ≥2 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND ≥1 star(s) in comparability domain AND ≥2 stars in outcome/exposure domain
- Poor quality: 0-1 star(s) in selection domain OR 0 stars in comparability domain OR 0-1 star(s) in outcome/exposure domain

Data synthesis

We considered pooling the data if studies were sufficiently homogeneous from both a statistical and clinical point of view. If data could not be pooled because of heterogeneity, we planned to perform a best evidence synthesis. If a best evidence synthesis was indicated, we dichotomized 'good quality' to 'high quality'. 'Fair quality' and 'poor quality' was deemed 'low quality' in the best evidence synthesis. The best evidence synthesis holds five levels of evidence[21]:

- Strong evidence: ≥2 studies of high quality and generally consistent findings in all studies (≥75% of the studies report consistent findings)
- Moderate evidence: 1 study of high quality and/or ≥2 studies of low quality and generally consistent findings in all studies (≥75% of the studies reporting consistent findings).
- Limited evidence: 1 study of low quality
- Conflicting evidence: inconsistent findings in multiple studies (<75% of the studies report consistent findings)
- No evidence: no studies could be found

Data analysis

Presented Odds Ratios (ORs) and their 95% confidence intervals (CIs) from cross-sectional and longitudinal case-control studies were used. In case the OR was not presented in the article, we chose to calculate the OR with the following formula: $\frac{exposed\ cases\ x\ not\ exposed\ controls}{exposed\ controls\ x\ not\ exposed\ cases}$. Results were considered statistically significant if the 95% confidence interval (CI) did not cross 1.

For the included single arm cohort studies, there was no control group with the presented outcome (tendinopathy or metabolic conditions and chronic diseases). In these cases, we decided to compare these data to existing data in the scientific literature about the prevalence of the outcome in the general population. Through this method, we were also able to estimate the OR in these single arm cohort studies. This study was identified by searching the MeSH term of the outcome in the missing study in combination with "/ epidemiology" on PubMed on the 1st of November 2019.

RESULTS

Study selection

After database searching, we identified 6469 records; 4287 studies remained after duplicates were removed (Figure 1). Of all articles, 4186were excluded after title and abstract screening. A total of 101 full-text articles were assessed for eligibility, of which 82 were excluded. One additional record was included through reference screening. The remaining 20 publications, involving 83,948 participants, were included for analysis[22-41].

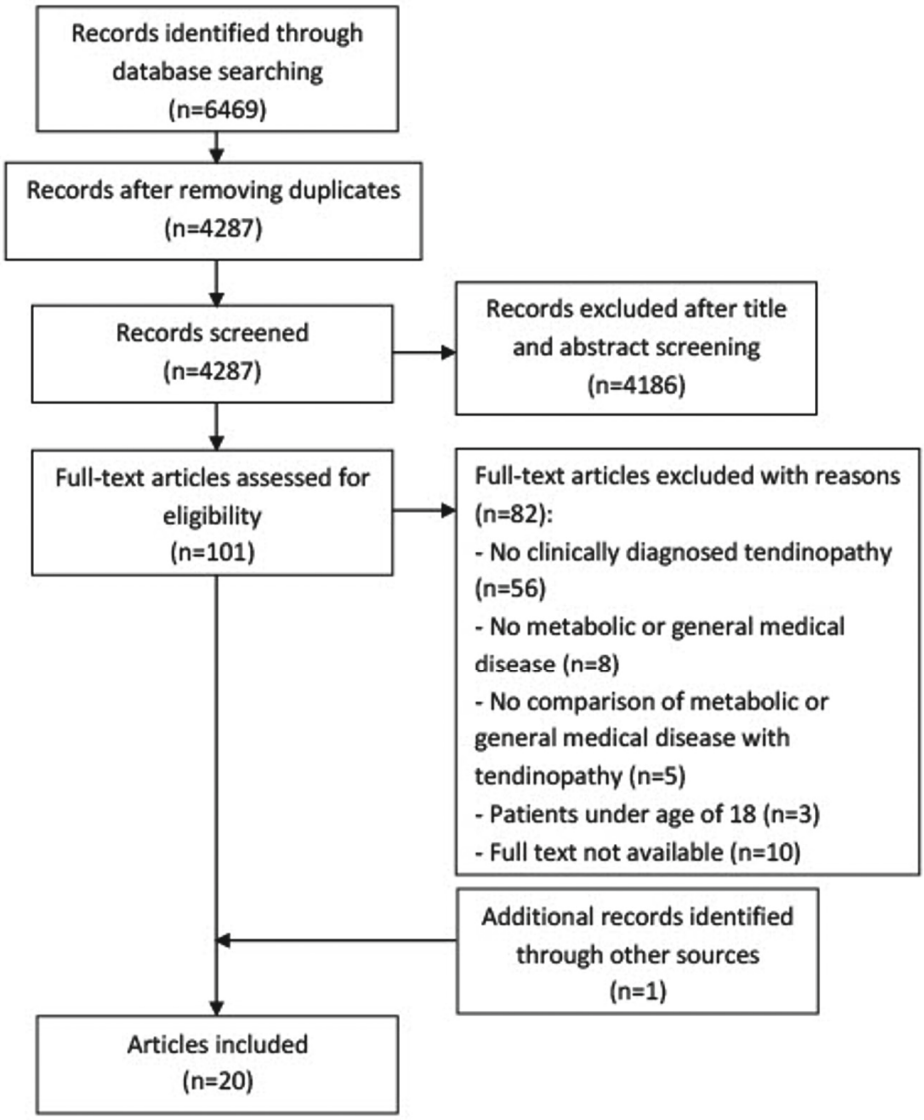

Figure 1. PRISMA flowchart of included articles

Description of included studies

We included 10 case-control and 10 cohort studies. The mean age of the participants in these studies ranged from 37 to 69 years, holding 0 to 84% males (Supplementary file 3). Reported tendinopathies were Achilles tendinopathy (n=16), plantar fasciopathy (n=8), patellar tendinopathy (n=1) and gluteal tendinopathy (n=1). Reported metabolic and chronic diseases were obesity (n=4)[22,32,34,36-38], diabetes (n=4)[22,23,32,35], hypertension (n=3)[23,32,35],

hypercholesterolaemia (n=2)[35,41], heterozygous familial hypercholesterolaemia (n=2)[26,39], ankylosing spondylitis (n=3)[24,25,30], psoriatic arthritis (n=3)[27-29], rheumatoid arthritis (n=3)[30,31], reactive arthritis (n=2)[30,40], and Systemic Lupus Erythematosus (n=1)[33]. In Supplementary file 3 we present the data extraction table with the following items: year of publication, study design, baseline participant characteristics, primary aim, inclusion criteria disease, outcome disease and duration of follow-up. In Supplementary file 4 we present the characteristics of lower extremity tendinopathies and metabolic and chronic diseases.

Table 1. Risk of bias (RoB) assessment of the included studies. Good quality: ≥3 stars in selection

	Selection	Comparability	Exposure	ROB
Abate et al., 2016[22]	***	*	*	Poor
Abate et al., 2018[23]	***		*	Poor
Aggarwal et al., 2009[24]	***		***	Poor
Alam et al., 2017[25]	***		*	Poor
Beeharry et al., 2006[26]	***		*	Poor
Cantini et al., 2001[27]	**		**	Poor
Çatal et al., 2021[41]	***	**	**	Good
Elkayam et al., 2000[28]	***		**	Poor
Galluzo et al., 2000[29]	***		*	Poor
Gerster et al., 1977[30]	***		*	Poor
Hernandez-Diaz et al., 2019[31]	***		*	Poor
Holmes et al., 2006[32]	**		*	Poor
Jarrot et al., 2015[33]	***		*	Poor
Klein et al., 2013[34]	***	*	*	Poor
Kraemer et al., 2012[35]	**	*	*	Poor
Owens et al., 2013[36]	*	*		Poor
Plinsinga et al., 2018[37]	*		*	Poor
Riddle et al., 2003[38]	***	*	*	Poor
Singh, 2015[39]	***	*	**	Fair
Smith et al., 1980[40]	*	*		Poor

Domain AND ≥1 star(s) in comparability domain AND ≥2 stars in outcome/exposure domain. Fair quality: 2 stars in selection domain AND ≥1 star(s) in comparability domain AND ≥2 stars in outcome/exposure domain. Poor quality: 0-1 star(s) in selection domain OR 0 stars in comparability domain OR 0-1 star(s) in outcome/exposure domain.

Risk of bias assessment and best evidence synthesis

Due to the clinical heterogeneity of the included participants, variability in reported associations and low methodological quality of the studies, it was not possible to perform statistical pooling of the data. We therefore carried out a best evidence synthesis. When dichotomizing the risk of bias assessment, all but two studies were of poor quality (Table 1; there was one study with good methodological quality and one study with fair quality). The poor risk of bias score was frequently related to lack of adjustment for confounders.

Associations between metabolic or chronic diseases and lower extremity tendinopathies

Eight case-control[22,23,32,34-36,38,41] and two cohort studies[37,39] investigated whether having lower extremity tendinopathies is associated with an increased risk of having a metabolic or chronic disease (Table 2). Two case-control[26,27] and 8 cohort studies[24,25,28-31,33,40] investigated whether having metabolic or chronic disease was associated with an increased risk of lower extremity tendinopathies (Table 2). Below, an overview is provided of the studies assessing metabolic or chronic disease in association with lower extremity tendinopathies. We chose to describe this association with the metabolic or chronic diseases as point of departure, thus informing healthcare providers in musculoskeletal medicine about the most relevant chronic diseases to assess in their patient population. Table 2 depicts whether the association was described for a population with metabolic or chronic diseases or for a population with lower extremity tendinopathies. The strengths of the associations are illustrated in Figure 2. The corresponding baseline participant characteristics and odds ratio are described in Supplementary File 5.

Table 2. The association between lower extremity tendinopathies and metabolic and chronic diseases

Studies with lower extremity tendinopathies as primary inclusion criteria, and metabolic and chronic diseases as outcome		
Metabolic or chronic disease	**Study (first author and reference number)**	**Best evidence synthesis**
Obesity	Abate et al. (a) =[22], Holmes et al. ↑[32], Klein et al. ↑[34], Owens et al ↑[36], Plinsinga et al. ↑[37], Riddle et al. ↑[38]	Moderate evidence for a positive association
Diabetes	Abate et al (b) =[23], Holmes et al. =[32], Kraemer et al. =[35] Abate et al. (a) ↑[22]	Moderate evidence for no association
Hypertension	Abate et al (b) =[23], Kraemer et al =[35], Holmes et al. ↑[32]	Conflicting evidence

Table 2. The association between lower extremity tendinopathies and metabolic and chronic diseases (continued)

Studies with lower extremity tendinopathies as primary inclusion criteria, and metabolic and chronic diseases as outcome		
Metabolic or chronic disease	**Study (first author and reference number)**	**Best evidence synthesis**
Hypercholesterolaemia	Çatal et al. ↑[41], Kraemer et al. =[35]	Conflicting evidence
Heterozygous familial hypercholesterolaemia	Singh et al. =[39]	Limited evidence for no association
Metabolic or chronic disease	**Study (first author and reference number)**	**Best evidence synthesis**
Heterozygous familial hypercholesterolaemia	Beeharry et al. ↑[26]	Limited evidence for a positive association
Ankylosing spondylitis	Aggarwal et al. ↑[24], Alam et al. ↑[25], Gerster et al. ↑[30]	Moderate evidence for a positive association
Psoriatic arthritis	Cantini et al. ↑[27], Elkayam et al. ↑[28], Galluzzo et al. ↑[29]	Moderate evidence for a positive association
Rheumatoid arthritis	Gerster et al. =[30], Hernandez-Diaz et al. =[31]	Moderate evidence for no association
Reactive arthritis	Gerster et al. ↑[30], Smith et al. ↑[40]	Moderate evidence for a positive association
Systemic Lupus Erythematosus	Jarrot et al. ↑[33]	Limited evidence for a positive association

Studies with a metabolic and chronic disease as primary inclusion criteria and lower extremity tendinopathies as outcome

Obesity

There is moderate evidence that patients with lower extremity tendinopathies have an increased risk of being obese (Figure 2A, Supplementary File 5). One case-control study in elderly patients (included when age >65 years) reported no association[22]. Four case-control studies and one cohort study showed that having lower extremity tendinopathies is associated with an increased risk of being obese[32,34,36-38]. Obesity was defined by the all studies as having a BMI of ≥30 kg/m^2. The prevalence of obesity in patients with lower extremity tendinopathies ranged from 11-62%[23,32,34,36-38], while the prevalence in the general population is 12%[42].

No studies were conducted that had obesity as primary inclusion criterion and lower extremity tendinopathies as outcome.

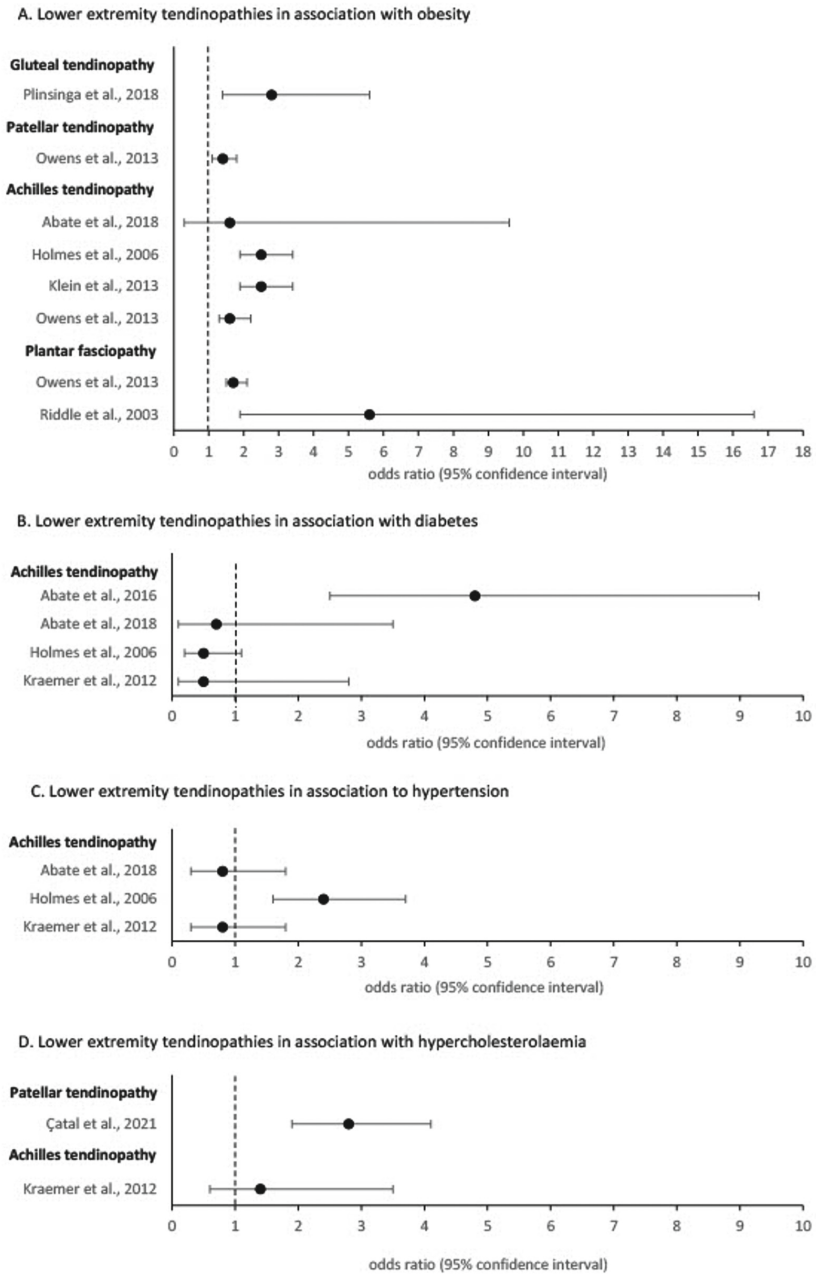

Figure 2. Forest plots of the association between lower extremity tendinopathies and metabolic and chronic diseases

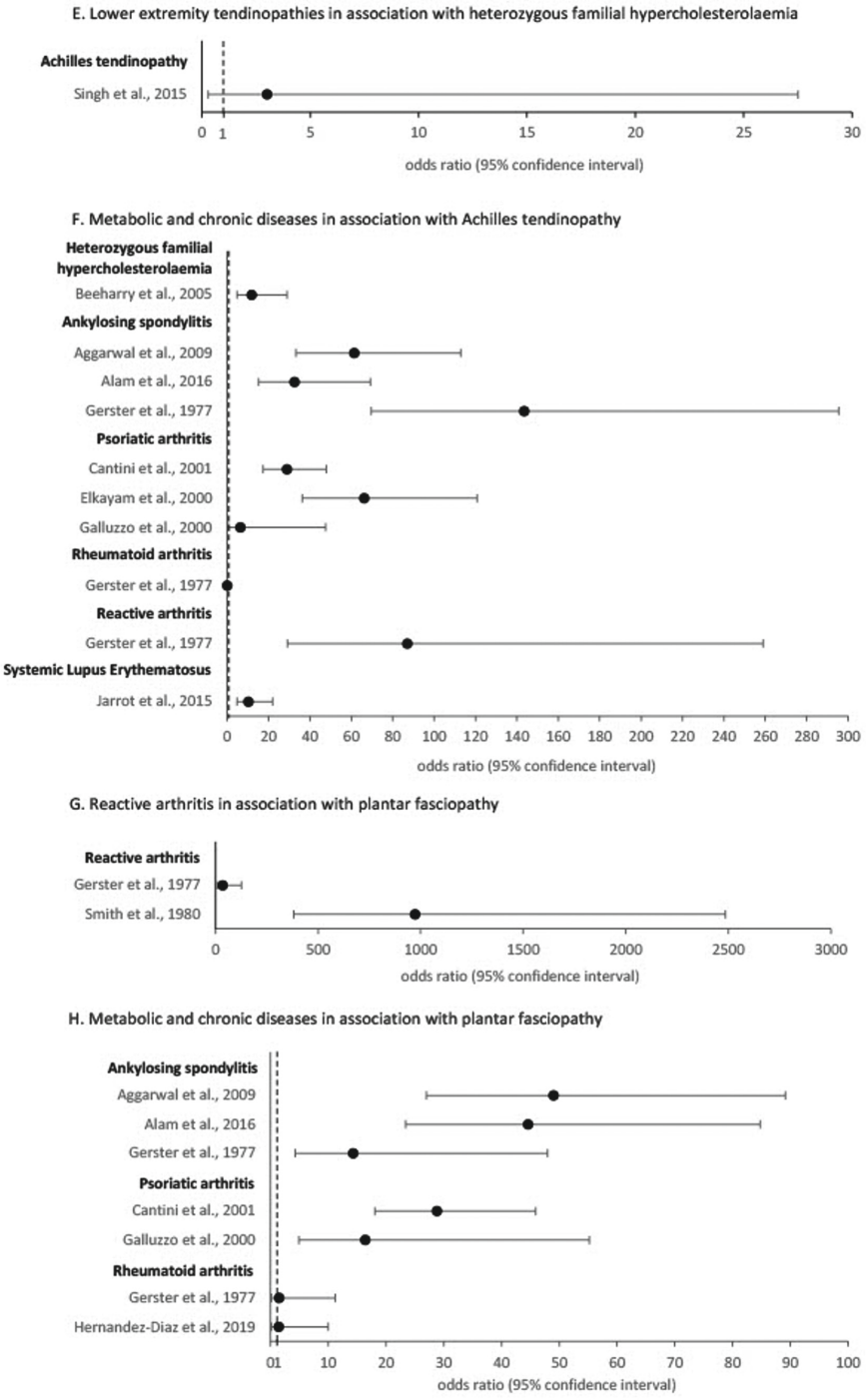

Figure 2. Forest plots of the association between lower extremity tendinopathies and metabolic and chronic diseases (continued)

Diabetes

There is moderate evidence that lower extremity tendinopathies are not associated with an increased risk of having diabetes (Figure 2B, Supplementary File 5). One case-control study showed that patients with lower extremity tendinopathies had an increased risk of having diabetes[22], while three case-control studies found no association[23,32,35]. Diabetes was defined by the studies as self-reported (n=1), confirmed diagnosis by an endocrinologist (n=1), or receiving treatment for diabetes (n=2). The reported prevalence of diabetes in patients with lower extremity tendinopathies was 1-42%[22,23,32,35], versus 14% in the general population[43].

No studies were conducted that had diabetes as primary inclusion criterion and lower extremity tendinopathies as outcome.

Hypertension

There is conflicting evidence on patients with lower extremity tendinopathies and the risk for hypertension (Figure 2C, Supplementary File 5). Two case-control studies with active patients found no association[23,35], while one case-control study demonstrated that patients with lower extremity tendinopathies had an increased risk of having hypertension[32]. Hypertension was defined by the studies as self-reported (n=1), or a systolic blood pressure of >140 mmHg and/or a diastolic blood pressure of >90 mmHg (n=2). The prevalence of hypertension in patients with lower extremity tendinopathies was 10-52%[23,32,35], and 32% in the general population[44].

No studies were conducted that had hypertension as primary inclusion criterion and lower extremity tendinopathies as outcome.

Hypercholesterolaemia

There is limited evidence that having lower extremity tendinopathies is not associated with an increased risk of having hypercholesterolaemia (Figure 2D, Supplementary File 5). One case-control study found that patients with lower extremity tendinopathies had an increased risk of developing hypercholesterolaemia[41], while one other study found no association[35]. Hypercholesterolaemia was defined by the studies as a cholesterol of ≥240mg/dL or as self-reported.[35,41] The prevalence of hypercholesterolaemia in patients with lower extremity tendinopathies ranged from 11% to 55%, and from 8% to 33% in the healthy control group.[35,41]

There were no studies conducted where hypercholesterolaemia was the primary inclusion criterion and lower extremity tendinopathies the outcome.

Heterozygous familial hypercholesterolaemia

There is limited evidence that having lower extremity tendinopathies is not associated with an increased risk of having heterozygous familial hypercholesterolaemia (Figure 2E, Supplementary File 5), as reported in one cohort study.[39] Heterozygous familial hypercholesterolaemia was diagnosed in a lipid clinic, but the further criteria were not reported in this study. The prevalence of heterozygous familial hypercholesterolaemia in patients with lower extremity tendinopathies was 1%,[39] versus 0.4% in the general population.[45]

There is limited evidence that heterozygous familial hypercholesterolaemia is associated with an increased risk of developing lower extremity tendinopathies (Figure 2F, Supplementary File 5), as reported in one case-control study.[26] The diagnosis was based on the following criteria: a total cholesterol >7.5 mmol/L or LDL-cholesterol >4.9 mmol/L, AND either (a) xanthomas in the patients or a first-degree relative or (b) evidence of LDL-receptor or APO-B gene mutation. The prevalence of lower extremity tendinopathies in patients with heterozygous familial hypercholesterolaemia was 47%, while healthy controls had a prevalence of 7%.[26]

Ankylosing spondylitis

No studies were conducted that had lower extremity tendinopathies as primary inclusion criterion and ankylosing spondylitis as outcome.

There is moderate evidence that having ankylosing spondylitis is associated with an increased risk of developing lower extremity tendinopathies (Figure 2F, Figure 2H, Supplementary File 5), as reported by 3 cohort studies. [24,25,30] Ankylosing spondylitis was defined by different criteria,[24,25,30] The prevalence of lower extremity tendinopathies ranged from 9-43% in patients with ankylosing spondylitis,[24,25,30] versus 0.02% in the general population.[2]

Psoriatic arthritis

No studies were conducted that researched the risk of developing psoriatic arthritis while having lower extremity tendinopathies.

There is moderate evidence that having psoriatic arthritis is associated with an increased risk of developing lower extremity tendinopathies (Figure 2F, Figure 2H, Supplementary File 5), as reported by one case-control study[27] and two cohort studies[28,29]. Psoriatic arthritis was based on multiple criteria (seronegative for rheumatoid factors, and who presented with psoriasis and arthritis affecting the axial and/or peripheral joints)[27], defined as inflammatory arthritis, usually rheumatoid negative,[28] or was based on the criteria of Vasey

and Espinoza[29]. The prevalence of lower extremity tendinopathies ranged from 3-26% in patients with psoriatic arthritis[27-29], and 0.02% in the general population[2].

Rheumatoid arthritis

There were no studies conducted that researched the risk of developing rheumatoid arthritis while having lower extremity tendinopathies.

There is moderate evidence that having rheumatoid arthritis is not associated with an increased risk of developing lower extremity tendinopathies (Figure 2F, Figure 2H, Supplementary File 5), as reported by two cohort studies[30,31]. Rheumatoid arthritis was defined as fulfilling the criteria of the American Rheumatism Association[30], or fulfilling the 2010 American College of Rheumatology criteria[31]. The prevalence of lower extremity tendinopathies was 1% in both cohorts of patients with rheumatoid arthritis[30,31], and 0.02% in the general population[2].

Reactive arthritis

There were no studies conducted that researched the risk of developing reactive arthritis while having lower extremity tendinopathies.

There is moderate evidence that having reactive arthritis is associated with an increased risk of developing lower extremity tendinopathies (Figure 2F, Figure 2G, Supplementary File 5), as reported by two cohort studies[30,40]. Reactive arthritis was defined as seronegative arthritis most compatible with Reiter's disease (polyarthritis, urethritis and conjunctivitis)[40], or as non-gonococcal urethritis, arthritis and conjunctivitis[30]. The prevalence of lower extremity tendinopathies ranged from 19-52% in patients with reactive arthritis[30,40], versus 0.02% in the general population[2].

Systemic Lupus Erythematosus

There were no studies conducted that researched the risk of developing systemic lupus erythematosus while having lower extremity tendinopathies.

There is limited evidence that having systemic lupus erythematosus is associated with an increased risk of developing lower extremity tendinopathies (Figure 2F, Supplementary File 5), as reported by one cohort study[33]. Systemic lupus erythematosus was defined as fulfilling the American College of Rheumatology criteria[33]. The prevalence of lower extremity tendinopathies was 5% in patients with systemic lupus erythematosus[33], versus 0.02% in the general population[2].

DISCUSSION

This is the first prospectively registered, large and structurally designed systematic review assessing the association between lower extremity tendinopathies and metabolic and chronic diseases. We included 10 case-control and 10 cohort studies, involving 83,948 participants. Almost all (90%) included studies were assessed as having a high risk of bias. There is moderate evidence for an association between lower extremity tendinopathies and obesity, ankylosing spondylitis, psoriatic arthritis, and reactive arthritis. There is limited evidence for an association between lower extremity tendinopathies and heterozygous familial hypercholesterolaemia, and Systemic Lupus Erythematosus. There was conflicting evidence for an association between lower extremity tendinopathies and hypertension, and lower extremity tendinopathies and hypercholesterolaemia.

We did not identify strong associations between lower extremity tendinopathies and metabolic and chronic diseases. This is partly due to the limited number of eligible studies and the high risk of bias of the included studies. Also, the way of measuring the outcome might have influenced the results of this systematic review (e.g. identifying hypercholesterolaemia with a blood test versus a patient-reported questionnaire). Another reason might be that tendinopathy is considered a multifactorial disease. When we evaluate the association in a population of patients with tendinopathy, it is understandable that a strong association could not be detected. This is because other factors (e.g., suddenly increased tendon load) are more important for developing tendinopathies. We did observe a trend that studies including younger active patients did not detect an association or only a small association with metabolic and chronic diseases compared to older populations. These older individuals might be a subgroup where metabolic and chronic diseases are more strongly associated because overload is less likely to be a strong risk factor in this subgroup. When we evaluated the association in the group with metabolic and chronic diseases, we identified a tendency of stronger associations. This might have been caused by the fact that this was most frequently observed in the single-arm cohort studies, where we had to calculate the odds ratios based on prevalence data. This method is less robust than a case-control study design. Another reason could be that these are more homogeneous groups with respect to the metabolic factor. This enables researchers to find a more direct association between the metabolic disease and tendinopathy.

Obesity

Tendinopathy in load bearing tendons occurs more frequently in patients with obesity. This may be caused by two mechanisms; (1) tendon stress is increased

due to the high body weight and (2) fat tissue releases low-grade detrimental systemic pro-inflammatory cytokines[17]. A higher body weight leads to a higher local tendon stress; for example, during walking the load on the Achilles tendon reaches 2-5 times the body weight, which can increase to up to 12 times the body weight when sprinting[46]. Furthermore, adipose tissue leads to a systemic state of low-grade inflammation by releasing adipokines[12]. These specific proteins cause an increase in production of proteoglycans and pro-inflammatory molecules[12], causing disorganisation of the collagen fibers and an increase in tendon stiffness, which leads to a decrease in maximum tendon load bearing capacity[47]. The combination of a decreased maximum tendon load, an elevated tendon load caused by a high body weight and impaired tendon healing may eventually predispose obese patients for developing lower extremity tendinopathies[32,34,36-38].

This study is not the first systematic review that evaluates the association between lower extremity tendinopathies and obesity. Franchesci et al.[48] included all clinical studies that researched the association between obesity and tendinopathy. The authors decided to also include upper extremity tendinopathies. They concluded that obesity is a risk factor for tendinopathy, also for upper extremity tendinopathies, but that the association was stronger for Achilles tendinopathy and plantar fasciopathy[48]. Since its publication in 2014[48], more recent studies demonstrated an association between obesity and tendinopathy of the gluteal and patellar tendons[36,37]. With this additional information, we are able to draw more robust conclusions concerning the relation between obesity and lower extremity tendinopathies.

Diabetes

We found that lower extremity tendinopathies were not associated with an increased risk of having diabetes. A systematic review by De Oliveira et al.[49] included studies that analysed the association between tendon disorders on imaging and diabetes. Although the included studies suggested an association, De Oliveira et al.[49] could not definitely draw this conclusion due to methodological limitations of the included studies. The difference between their tendency towards an association and our result of no association might be the way tendinopathy was diagnosed. The gold standard for diagnosing tendinopathy is currently based on diagnostic clinical criteria[50]. As abnormal imaging results are also observed frequently in asymptomatic individuals, we chose to exclude studies that used imaging as only diagnostic tool[50].

Hypertension

We found conflicting evidence for the association between lower extremity tendinopathies and hypertension[23,32,35]. This might be caused by the difference

in study population between the three studies. Abate et al.[23] and Kraemer et al.[35] found no association between Achilles tendinopathy and hypertension in a population of athletes, while Holmes et al.[32] detected an association in a general population not only consisting of athletes. This difference might be explained by the lower prevalence of hypertension in a population of athletes[51]. Hypertension damages the tunica intima of the artery, which eventually leads to restricted blood flow and hypoxia. Persisting hypoxia may lead to degenerative tendinopathy[52]. More case-control studies in separate active and sedentary populations are needed to analyse hypertension as a risk factor for developing lower extremity tendinopathies.

Hypercholesterolaemia and HeFH

We found conflicting evidence for the association between lower extremity tendinopathies and hypercholesterolaemia[35,41]. This might be due to the criteria set to define hypercholesterolemia: Çatal et al.[41] defined hypercholesterolaemia with a blood test (total cholesterol levels ≥240ml/dL), while hypercholesterolaemia was self-reported in the study by Kraemer et al.[35].

We found limited evidence that patients with lower extremity tendinopathies did not have an increased risk of having HeFH[35,39]. Due to the methodological limitations of these studies and the limited evidence, definite conclusions of these risk factors should be drawn with caution.

Interestingly, we found that patients with HeFH have an increased risk of developing lower extremity tendinopathies[26]. The hypothesis behind the association between these diseases is that the elevated blood lipid levels can lead to lipid accumulation in the tendon, so-called tendon xanthomas[53]. These xanthomas may increase tendon stiffness and increase the synthesis of pro-inflammatory proteins, which may increase the risk of tendinopathy[17]. We suggest that medical professionals offer a pharmacological intervention to decrease cholesterol, which may not only benefit the state of the tendon, but may also be life-saving[54].

Rheumatic diseases

There was limited to moderate evidence for an association between multiple rheumatic diseases and lower extremity tendinopathies[24,25,27-31,33,40]. We did not find any studies that included patients with tendinopathy and researched whether the patients had an increased risk of having a rheumatic disease. It would be interesting for future studies to research whether an association is present in this patient population. In the meanwhile, we suggest that clinicians bear in mind that patients with tendinopathy might have an underlying rheumatic disease.

Clinical implications

Medical professionals should be aware of the associations of metabolic or chronic diseases with lower extremity tendinopathies. Screening for metabolic diseases during history taking and physical examination in patients with tendinopathy might identify factors that are part of the cause of tendinopathy. Treating metabolic diseases might not only improve the health of patients as a whole, but also their tendon health specifically. Future research should be performed to investigate whether influencing the metabolic diseases indeed results in improved outcomes for the lower extremity tendinopathy. Additionally, when medical professionals prescribe exercise to improve the patient's metabolic profile or chronic disease, they should recommend seeking guidance to prevent development of lower extremity tendinopathies. This preventive intervention could be a very slow transition from non-weight bearing sports to weight bearing activities, although evidence for effectiveness of this intervention is currently lacking.

Strengths and limitations

A major strength of this systematic review is the use of the structured analysis according to the PRISMA guidelines[55]. Based on this robust approach, we included 10 cohort and 10 case-control studies that analysed the association between a clinically diagnosed lower extremity tendinopathies and a metabolic or chronic disease. By including clinically diagnosed lower extremity tendinopathies, we ensured that the data was not contaminated by asymptomatic patients with tendon imaging abnormalities, which are frequent in specific populations[56-59]. By presenting the overview of the currently available research on the association between lower extremity tendinopathies and metabolic and chronic diseases, we were able to recommend implications for clinical care.

Despite its strengths, this systematic review also has limitations. First, due to heterogeneity of the articles, we were not able to pool the data. This hindered us from performing a meta-analysis, which is why we evaluated the associations with a best evidence synthesis. Second, many of the included articles were single-arm cohort studies. The OR's of these studies could not be calculated with their chosen study population, but were calculated with the prevalence of the lower extremity tendinopathies in the general population. The obtained OR's are therefore only an indication of the true OR and should be interpreted with caution. Third, tendinopathy has many synonyms and closely related pathologies which complicated the article selection. We strictly included articles that described clinical diagnosis of lower extremity tendinopathies. Fourth, it is debatable whether tendinopathy is the correct term for all included outcomes in this study. Terminology such as 'enthesitis' and 'xanthoma' are

considered as other entities because they have a different pathogenesis. This is also supported by the findings of this systematic review. Last, many of the included studies did not correct for confounders. Subsequently, the effect of the reported metabolic or chronic diseases in association with lower extremity tendinopathies might be influenced by other factors. For example, studies investigating multiple metabolic or chronic diseases (e.g., obesity, diabetes and hypercholesterolaemia) did not assess whether these were independent factors.

Future research

To increase the evidence and to analyse further associations between lower extremity tendinopathies and metabolic or chronic diseases a large case-control study is needed. Patients should be diagnosed with metabolic or chronic diseases by valid criteria, such as blood tests. Healthy controls should have these criteria as exclusion criteria. In a follow-up study, all cases and controls should be screened for lower extremity tendinopathies. This study design should provide best evidence for the association between lower extremity tendinopathies and metabolic or chronic diseases.

We have included many metabolic or chronic diseases in this systematic review. There are probably more metabolic or chronic diseases possibly associated with lower extremity tendinopathies, such as hormonal disorders or thyroid disease.[60,61] To our knowledge, no clinical studies have been published that describe the association between tendinopathy and these conditions.

CONCLUSION

We found multiple associations between lower extremity tendinopathies and metabolic and chronic diseases. Lower extremity tendinopathies are moderately associated with obesity. There is also moderate evidence that patients with ankylosing spondylitis, psoriatic arthritis and reactive arthritis have an increased risk of developing lower extremity tendinopathies. There is limited evidence for an association between lower extremity tendinopathies and heterozygous familial hypercholesterolaemia, and Systemic Lupus Erythematosus. Medical professionals should recognize these diseases in an early stage, which might improve personalized management.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We would like to thank WM Bramer, Biomedical Information Specialist at Erasmus MC University Medical Center Rotterdam, for designing a sensitive search strategy. We furthermore thank JH Waarsing, researcher at Erasmus MC University Medical Center Rotterdam, for their help with interpreting the data.

SUPPLEMENTARY FILE(S)

Supplementary file 1. Search strategy
09-10-2023

Database searched	via	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 - Present	3192	3166
Medline ALL	Ovid	1946 - Present	1498	424
Web of Science Core Collection*	Web of Knowledge	1975 - Present	1524	552
Cochrane Central Register of Controlled Trials**	Wiley	1992 - Present	55	23
Other sources: Google Scholar (200 top-ranked)***			200	122
Total			**6469**	**4287**

*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2015-present)
** Manually deleted abstracts from trial registries
***Google Scholar was searched via "Publish or Perish" to download the results in EndNote.
No other database limits were used than those specified in the search strategies [62]

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('tendinitis'/exp OR (tendinitis OR tendinitid* OR tendinosis OR tendinoses OR tendonosis OR tendonoses OR tendonitis OR tendonitid* OR tendinopath* OR tendonopath* OR tenosynovit* OR (tendon* NEAR/6 (inflammat* OR irritat*))):ab,ti,kw) AND ('lower limb'/exp OR 'leg muscle'/exp OR 'achilles tendinitis'/de OR 'achilles tendon'/de OR 'hamstring tendon'/de OR 'quadriceps tendon'/de OR 'leg disease'/exp OR ((low* NEXT/1 (limb OR limbs OR extremit*)) OR hip OR leg OR foot OR heel OR heels OR hips OR legs OR feet OR thigh OR thighs OR ankle OR knee OR knees OR patella* OR Achilles OR plantar* OR peroneus* OR (tibialis NEAR/3 posterior*) OR (triceps NEAR/3 surae) OR gastrocnemius OR soleus OR adductor OR hamstring OR quadriceps OR (quadratus NEAR/3 femoris)):ab,ti,kw) AND ('cardiovascular disease'/exp OR Obesity/exp OR 'body mass'/de OR 'metabolic disorder'/exp OR 'glucose blood level'/exp OR 'thyroid disease'/exp OR 'rheumatic disease'/exp OR 'arthritis'/de OR 'chronic arthritis'/exp OR 'gout'/exp OR 'infectious

arthritis'/exp OR 'monarthritis'/exp OR 'polyarthritis'/exp OR 'pseudogout'/exp OR 'psoriatic arthritis'/exp OR 'reactive arthritis'/exp OR 'rheumatoid arthritis'/exp OR 'uric acid blood level'/exp OR rheumatology/de OR 'sarcoidosis'/exp OR 'infection'/exp OR inflammation/de OR 'inflammatory disease'/de OR 'endocarditis'/exp OR 'carditis'/de OR 'pericarditis'/exp OR 'kidney disease'/exp OR 'dialysis'/exp OR 'hypercalcemia'/exp OR 'hyperparathyroidism'/exp OR 'inflammatory bowel disease'/exp OR 'ovary polycystic disease'/exp OR 'fibromyalgia'/exp OR (((cardiovascular* OR heart OR cerebrovascul* OR vascul* OR cardiac OR metabol* OR thyroid* OR inflammat*) NEAR/3 (disease* OR syndrome* OR disorder*)) OR stroke OR cva OR hypertensi* OR (blood NEAR/3 pressure*) OR Obes* OR overweight OR body-mass* OR bmi OR adiposit* OR diabet* OR (insulin NEAR/3 resistan*) OR hyperinsulin* OR ((glucose OR lipid* OR cholesterol* OR uric-acid OR urate) NEAR/3 (blood OR level* OR plasma OR concentrate* OR serum)) OR dyslip* OR hypolip* OR hyperlip* OR dyscholesterol* OR hypocholesterol* OR hypercholesterol* OR dystriglycerid* OR hypotriglycerid* OR hypertriglycerid* OR dysthyroid* OR hypothyroid* OR hyperthyroid* OR dysuric* OR hypouric* OR hyperuric* OR thrombosis* OR thromboembol* OR embolism* OR rheuma* OR arthritis OR gout OR sarcoid* OR Lofgren* OR mening* OR infecti* OR carditis* OR endocarditis* OR pericarditis* OR renal OR kidney* OR dialys* OR hemodialys* OR haemodialys* OR hypercalc* OR hyperparathyroid* OR (electrolyte* NEAR/3 (disturb* OR imbalan*)) OR (inflamma* NEAR/3 bowel*) OR crohn* OR (ulcer* NEAR/3 colitis*) OR tuberculo* OR (ovar* NEAR/3 polycyst*) OR PCOS OR fibromyalg*):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim) AND [english]/lim

Medline Ovid

(Tendinopathy/ OR Tenosynovitis/ OR (tendinitis OR tendinitid* OR tendinosis OR tendinoses OR tendonosis OR tendonoses OR tendonitis OR tendonitid* OR tendinopath* OR tendonopath* OR tenosynovit* OR (tendon* ADJ6 (inflammat* OR irritat*))).ab,ti,kf.) AND (exp Lower Extremity/ OR Hamstring Muscles/ OR Fasciitis, Plantar/ OR Quadriceps Muscle/ OR Patellar Ligament/ OR Posterior Tibial Tendon Dysfunction/ OR Achilles Tendon/ OR Hamstring Tendons/ OR ((low* ADJ (limb OR limbs OR extremit*)) OR hip OR leg OR foot OR heel OR heels OR hips OR legs OR feet OR thigh OR thighs OR ankle OR knee OR knees OR patella* OR Achilles OR plantar* OR peroneus* OR (tibialis ADJ3 posterior*) OR (triceps ADJ3 surae) OR gastrocnemius OR soleus OR adductor OR hamstring OR quadriceps OR (quadratus ADJ3 femoris)).ab,ti,kf.) AND (exp Cardiovascular Diseases/ OR exp Overweight/ OR Body Mass Index/ OR exp Metabolic Diseases/ OR glucose/bl OR exp Thyroid Diseases/ OR exp Rheumatic Diseases/ OR Arthritis/ OR Gout/ OR Arthritis, Infectious/ OR Chondrocalcinosis/ OR Arthritis, Psoriatic/ OR Arthritis, Reactive/ OR Arthritis,

Rheumatoid/ OR uric acid/bl OR Rheumatology/ OR Sarcoidosis/ OR exp Infection/ OR Inflammation/ OR Endocarditis/ OR Myocarditis/ OR Pericarditis/ OR exp Kidney Diseases/ OR Renal Dialysis/ OR Dialysis/ OR Hypercalcemia/ OR Hyperparathyroidism/ OR exp Inflammatory Bowel Diseases/ OR Polycystic Ovary Syndrome/ OR Fibromyalgia/ OR (((cardiovascular* OR heart OR cerebrovascul* OR vascul* OR cardiac OR metabol* OR thyroid* OR inflammat*) ADJ3 (disease* OR syndrome* OR disorder*)) OR stroke OR cva OR hypertensi* OR (blood ADJ3 pressure*) OR Obes* OR overweight OR body-mass* OR bmi OR adiposit* OR diabet* OR (insulin ADJ3 resistan*) OR hyperinsulin* OR ((glucose OR lipid* OR cholesterol* OR uric-acid OR urate) ADJ3 (blood OR level* OR plasma OR concentrate* OR serum)) OR dyslip* OR hypolip* OR hyperlip* OR dyscholesterol* OR hypocholesterol* OR hypercholesterol* OR dystriglycerid* OR hypotriglycerid* OR hypertriglycerid* OR dysthyroid* OR hypothyroid* OR hyperthyroid* OR dysuric* OR hypouric* OR hyperuric* OR thrombosis* OR thromboembol* OR embolism* OR rheuma* OR arthritis OR gout OR sarcoid* OR Lofgren* OR mening* OR infecti* OR carditis* OR endocarditis* OR pericarditis* OR renal OR kidney* OR dialys* OR hemodialys* OR haemodialys* OR hypercalc* OR hyperparathyroid* OR (electrolyte* ADJ3 (disturb* OR imbalan*)) OR (inflamma* ADJ3 bowel*) OR crohn* OR (ulcer* ADJ3 colitis*) OR tuberculo* OR (ovar* ADJ3 polycyst*) OR PCOS OR fibromyalg*).ab,ti,kf.) NOT (exp animals/ NOT humans/) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.la.

Web of science

TS=(((tendinitis OR tendinitid* OR tendinosis OR tendinoses OR tendonosis OR tendonoses OR tendonitis OR tendonitid* OR tendinopath* OR tendonopath* OR tenosynovit* OR (tendon* NEAR/5 (inflammat* OR irritat*)))) AND (((low* NEAR/1 (limb OR limbs OR extremit*)) OR hip OR leg OR foot OR heel OR heels OR hips OR legs OR feet OR thigh OR thighs OR ankle OR knee OR knees OR patella* OR Achilles OR plantar* OR peroneus* OR (tibialis NEAR/2 posterior*) OR (triceps NEAR/2 surae) OR gastrocnemius OR soleus OR adductor OR hamstring OR quadriceps OR (quadratus NEAR/2 femoris))) AND ((((cardiovascular* OR heart OR cerebrovascul* OR vascul* OR cardiac OR metabol* OR thyroid* OR inflammat*) NEAR/2 (disease* OR syndrome* OR disorder*)) OR stroke OR cva OR hypertensi* OR (blood NEAR/2 pressure*) OR Obes* OR overweight OR body-mass* OR bmi OR adiposit* OR diabet* OR (insulin NEAR/2 resistan*) OR hyperinsulin* OR ((glucose OR lipid* OR cholesterol* OR uric-acid OR urate) NEAR/2 (blood OR level* OR plasma OR concentrate* OR serum)) OR dyslip* OR hypolip* OR hyperlip* OR dyscholesterol* OR hypocholesterol* OR hypercholesterol* OR dystriglycerid* OR hypotriglycerid* OR hypertriglycerid* OR dysthyroid* OR hypothyroid*

OR hyperthyroid* OR dysuric* OR hypouric* OR hyperuric* OR thrombosis* OR thromboembol* OR embolism* OR rheuma* OR arthritis OR gout OR sarcoid* OR Lofgren* OR mening* OR infecti* OR carditis* OR endocarditis* OR pericarditis* OR renal OR kidney* OR dialys* OR hemodialys* OR haemodialys* OR hypercalc* OR hyperparathyroid* OR (electrolyte* NEAR/2 (disturb* OR imbalan*)) OR (inflamma* NEAR/2 bowel*) OR crohn* OR (ulcer* NEAR/2 colitis*) OR tuberculo* OR (ovar* NEAR/2 polycyst*) OR PCOS OR fibromyalg*))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(english)

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((tendinitis OR tendinitid* OR tendinosis OR tendinoses OR tendonosis OR tendonoses OR tendonitis OR tendonitid* OR tendinopath* OR tendonopath* OR tenosynovit* OR (tendon* NEAR/6 (inflammat* OR irritat*))):ab,ti) AND (((low* NEXT/1 (limb OR limbs OR extremit*)) OR hip OR leg OR foot OR heel OR heels OR hips OR legs OR feet OR thigh OR thighs OR ankle OR knee OR knees OR patella* OR Achilles OR plantar* OR peroneus* OR (tibialis NEAR/3 posterior*) OR (triceps NEAR/3 surae) OR gastrocnemius OR soleus OR adductor OR hamstring OR quadriceps OR (quadratus NEAR/3 femoris)):ab,ti) AND ((((cardiovascular* OR heart OR cerebrovascul* OR vascul* OR cardiac OR metabol* OR thyroid* OR inflammat*) NEAR/3 (disease* OR syndrome* OR disorder*)) OR stroke OR cva OR hypertensi* OR (blood NEAR/3 pressure*) OR Obes* OR overweight OR body next mass* OR bmi OR adiposit* OR diabet* OR (insulin NEAR/3 resistan*) OR hyperinsulin* OR ((glucose OR lipid* OR cholesterol* OR uric next acid OR urate) NEAR/3 (blood OR level* OR plasma OR concentrate* OR serum)) OR dyslip* OR hypolip* OR hyperlip* OR dyscholesterol* OR hypocholesterol* OR hypercholesterol* OR dystriglycerid* OR hypotriglycerid* OR hypertriglycerid* OR dysthyroid* OR hypothyroid* OR hyperthyroid* OR dysuric* OR hypouric* OR hyperuric* OR thrombosis* OR thromboembol* OR embolism* OR rheuma* OR arthritis OR gout OR sarcoid* OR Lofgren* OR mening* OR infecti* OR carditis* OR endocarditis* OR pericarditis* OR renal OR kidney* OR dialys* OR hemodialys* OR haemodialys* OR hypercalc* OR hyperparathyroid* OR (electrolyte* NEAR/3 (disturb* OR imbalan*)) OR (inflamma* NEAR/3 bowel*) OR crohn* OR (ulcer* NEAR/3 colitis*) OR tuberculo* OR (ovar* NEAR/3 polycyst*) OR PCOS OR fibromyalg*):ab,ti) NOT "conference abstract":pt

Google scholar

tendinitis|tendinopathy "lower limb|extremity"|Achilles|plantar|peroneus "cardiovascular|heart|cerebrovascular|metabolis|thyroid|infection|infectious disease|syndrome"|hypertension|Obesity|overweight|"body-mass"|bmi|diabetes|hyperinsulinism|hypocholesterolism|thrombosis

tendinitis|tendinopathy 'lower limb|extremity'|Achilles|plantar|peroneus 'cardiovascular|heart|cerebrovascular|metabolis|thyroid|infection|infectious disease|syndrome'|hypertension|Obesity|overweight|'body-mass'|bmi|diabetes|hyperinsulinism|hypocholesterolism|thrombosis

Supplementary file 2. The Newcastle-Ottawa quality assessment Scale (NOS)

CASE-CONTROL STUDIES

Selection

1. Is the case definition adequate?

A. Yes, the case definition required independent validation (e.g. diagnosis was made by a medical professional based on clinical findings, laboratory measurements, imaging or surgery). 1 star
B. Yes, but the diagnosis was based on records (e.g. ICD codes in database) or self-reported with no reference to primary record.
C. No description

2. Representativeness of cases

A. All eligible cases with outcome of interest over a pre-defined period of time, catchment area, hospital, clinic, or health maintenance organization, or an appropriate sample of those cases (e.g. random sample) were included. 1 star
B. The cases do not meet the requirements in part A., or it is not described.

3. Selection of controls
   This item assesses whether the controls used in the study are derived from the same population of the cases and essentially would be cases if the outcome had been present.

A. Healthy control group (i.e. control group is derived from the same population as cases and would be cases if the outcome had been present). 1 star
B. Hospital control group, within same community as cases. The patients do not have the disease of interest, but they might have a disease that could influence the outcome.
C. No description

4. Definition of controls

A. Controls have the same inclusion criteria as the cases. If the cases have a first occurrence of the outcome, then it must explicitly be stated that controls have no history of this outcome. If cases have a new (not necessarily first) occurrence of the outcome, then controls with previous occurrence of the outcome of interest should not be excluded. 1 star
B. No mention of history of outcome.

Comparability

Either cases and controls must be matched in the design and/or the analysis must be adjusted for confounders. Statements that no differences between groups was found are not sufficient. A maximum of 2 starts can be given for this category.

5. Comparability of cases and controls on the basis of the design or analysis
A. The study corrects for age and sex. 1 star
B. The study corrects for any other variable, like duration of the primary outcome. 1 star
C. The study does not correct for any variable.

Exposure

6. Ascertainment of exposure
A. A medical professional diagnosed the patient based on clinical findings, laboratory measurements, imaging or surgery. If the outcome is based on medical reports, inclusion criteria should be clearly stated and should mention the diagnosis by a medical professional and/or the diagnosis should be supported by clinical findings, laboratory measurements, imaging or surgery. 1 star
B. A structured interview where the interviewer was blinded for case/control status. 1 star
C. The interviewer was not blinded for case/control status.
D. Self-reported or medical records only, which do not comply to 6A.
E. No description.

7. Same method of ascertainment for cases and controls
A. Yes, cases and controls were screened on same inclusion criteria and had the same outcome criteria. 1 star
B. No.

8. Non-response rate
A. Same rate of non-responders in both groups (in case of retrospective studies: similar percentage of missing data). 1 star
B. Non-responders are only described.
C. There is a difference in non-responders, or this is not described.

COHORT STUDY

Selection

1. Representativeness of the exposed cohort

A. The cohort is a true representative of the average person with metabolic or general medical diseases or the average person with tendinopathy of the lower extremities. 1 star
B. The cohort is somewhat representative of the average person metabolic or general medical diseases or the average person with tendinopathy of the lower extremities. Think of patients with severe diabetes or only active patients. 1 star
C. The cohort is a select group, like nurses or volunteers.
D. There is no clear description of the derivation of the cohort.

2. Selection of the non-exposed cohort

A. The group of patients without outcome are drawn from the same cohort as the group of patients with outcome. 1 star
B. The group of patients without outcome is drawn from a different source.
C. There is no description of the derivation of the non-exposed cohort.

3. Ascertainment of exposure

A. A medical professional diagnosed the patient based on clinical findings, laboratory measurements, imaging or surgery. If the outcome is based on medical reports, inclusion criteria should be clearly stated and should mention the diagnosis by a medical professional and/or the diagnosis should be supported by clinical findings, laboratory measurements, imaging or surgery. 1 star
B. A structured interview where the interviewer was blinded for case/control status. 1 star
C. Self-reported or medical records only, which do not comply to 6A.
D. No description.

4. Demonstration that outcome of interest was not present at the start of the study

o Yes, it is described that the outcome of interest was not present at the start of the study. 1 star
o No.

Comparability

Either cases and controls must be matched in the design and/or the analysis must be adjusted for confounders. Statements that no differences between groups was found are not sufficient. A maximum of 2 starts can be given for this category.

5. Comparability of cohorts on the basis of the design or analysis
A. The study corrects for age and sex. 1 star
B. The study corrects for any other additional variable, like duration of the primary outcome. 1 star
C. The study does not correct for any variable.

Outcome

6. Assessment of outcome
A. A medical professional diagnosed the patient based on clinical findings, laboratory measurements, imaging or surgery. If the outcome is based on medical reports, inclusion criteria should be clearly stated and should mention the diagnosis by a medical professional and/or the diagnosis should be supported by clinical findings, laboratory measurements, imaging or surgery. 1 star
B. A structured interview where the interviewer was blinded for case/control status. 1 star
C. The interviewer was not blinded for case/control status.
D. Self-reported or medical records only, which do not comply to 6A.
E. No description.

7. Was follow-up long enough for outcomes to occur?
A. Yes. The diagnosis of metabolic or general medical disease or lower limb tendinopathy was made by a medical professional based on clinical findings, or based on laboratory measurements, imaging or surgery OR follow-up was longer than 1 year in case of self-reported outcome. 1 star
B. Not described or does not comply with 7A.

8. Adequacy of follow-up of cohorts
A. Complete follow-up. 1 star
B. Less than 15% lost to follow-up. 1 star
C. Follow-up rate is less than 85% or it is not described.

Supplementary file 3. Baseline characteristics

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Abate, Italy, 2016	Case-control	76 (38) subjects aged > 65 years with Achilles tendinopathy (case) or upper extremity musculoskeletal disorder (matched case)	69.30 (3.05)	84.21%	To assess the relationship between symptomatic Achilles tendinopathy and type II diabetes in elderly subjects	Achilles tendinopathy	Diabetes type II	Not reported
Abate, Italy, 2018	Case-control	64 (36) regular runners who started running because of overweight/obesity/ abnormal metabolic parameters	39.21 (12.33)	62.50%	To evaluate whether overuse or metabolic pathologies were more responsible for midportion Achilles tendinopathy	Achilles tendinopathy	Obesity (BMI ≥30), hypertension, diabetes, dyslipidemia	Not reported
Aggarwal, India, 2009	Prospective cohort	70 patients with ankylosing spondylitis	Not reported	84.3%	To analyses the full spectrum of primary ankylosing spondylitis in Indian patients	Ankylosing spondylitis	Achilles tendinopathy, plantar fasciopathy	Not reported

Supplementary file 3. Baseline characteristics (continued)

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Alam, Qatar, 2016	Retrospective cohort	62 patients with ankylosing spondylitis	Not reported	83.9%	To explore the characteristics of ankylosing spondylitis of patients living in Qatar	Ankylosing spondylitis	Achilles tendinopathy, plantar fasciopathy	Not reported
Beeharry, United Kingdom, 2005	Case-control	220 (133) patients and their partners attending a lipid clinic	56.21 (range 42-64)	48.64%	To determine the prevalence of Achilles tendinopathy before diagnosis of heterozygous familial hypercholesterolaemia	Heterozygous familial hypercholesterolaemia	Achilles tendinopathy	Not reported
Cantini, Italy, 2001	Case-control	549 (183) patients with psoriatic arthritis or a different rheumatologic disease	51.27 (9.6)	49.18%	To evaluate the frequency of distal extremity swelling with pitting edema in patients with psoriatric arthritis	Psoriatic arthritis	Achilles tendinopathy	3 months

Supplementary file 3. Baseline characteristics (continued)

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Çatal, Turkey, 2021	Case-control	478 (238) patients with plantar fasciopathy	Not reported	23.4%	To investigate the relationship between hypercholesterolaemia and plantar fasciopathy	Plantar fasciopathy	Hypercholesterolaemia	Not reported
Elkayam, Israel, 2000	Prospective cohort	70 patients with psoriatic arthritis	Not reported	55.71%	To investigate the relationship between clinical characteristics of the skin and joint manifestations in a patients with psoriatic arthritis	Psoriatic arthritis	Achilles tendinopathy, plantar fasciopathy	Not reported
Galluzo,Italy, 2000	Prospective cohort	31 patients with psoriatic arthritis	48.1 (range 30-74)	58.06%	To evaluate ankle involvement in patients with psoriatic arthritis	Psoriatic arthritis	Achilles tendinopathy, plantar fasciopathy	Not reported

Supplementary file 3. Baseline characteristics (continued)

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Gerster, Switzerland, 1977	Prospective cohort	100 patients with rheumatoid arthritis, 35 with ankylosing spondylitis, 16 with Reiter's syndrome and 70 with osteoarthritis	59.58 (range 19-98)	42.99%	To determine the frequency of heel tenderness (talalgia) in rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome and generalized osteoarthritis	Rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome	Talalgia (Achilles tendinopathy or plantar fasciopathy)	Not reported
Hernandez-Diaz, Italy, 2019	Prospective cohort	112 patients with rheumatoid arthritis	51 (range 22-85)	10.71%	To describe the prevalence and distribution of clinical and ultrasound pathological findings at ankle level in patients with rheumatoid arthritis	Rheumatoid arthritis	Plantar fasciopathy	Not reported

Supplementary file 3. Baseline characteristics (continued)

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Holmes, USA, 2006	Case-control	282 (82) patients with Achilles tendinopathy or without any diseases	Not reported	Not reported	To determine the association between Achilles tendinopathy and obesity, diabetes mellitus and hypertension	Achilles tendinopathy	Obesity, diabetes mellitus, hypertension	Not reported
Jarrot, France, 2015	Retrospective cohort	158 patients with systemic lupus erythematosus	Not reported	9.49%	To describe the occurrence of Achilles tendinopathy in patients with systemic lupus erythematosus	Systemic lupus erythematosus	Achilles tendinopathy	Not reported
Klein, USA, 2013	Case-control	944 (472) patients with Achilles tendinopathy or other foot pathology	51.60 (13.90)	51.91%	To elucidate the role of BMI in the development and treatment of Achilles tendinopathy	Achilles tendinopathy	Obesity	Not reported

Supplementary file 3. Baseline characteristics (continued)

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Kraemer, Germany, 2012	Case-control	310 (161) sportsmen between 18-65 years old with Achilles tendinopathy or without any diseases	40.0 (11.0)	66.77%	To stratify risk factors for Achilles tendinopathy	Achilles tendinopathy	Diabetes mellitus, hypercholesterolaemia, arterial hypertension, cardiac diseases	Not reported
Owens, USA, 2013	Case-control	80106 (2262) military service members with patellar tendinopathy, Achilles tendinopathy, plantar fasciopathy or without any diseases	Not reported	Not reported	To identify risk factors for developing lower extremity tendinopathy and plantar fasciopathy in military personnel	Patellar tendinopathy, Achilles tendinopathy, plantar fasciopathy	Obesity	Not reported
Plinsinga, Australia, 2018	Prospective cohort	204 patients with gluteal tendinopathy	55 (9)	18.14%	To examine the differences in physical and physiological factors in patients with gluteal tendinopathy	Gluteal tendinopathy	Obesity	Not reported

Supplementary file 3. Baseline characteristics (continued)

First author (country, year of publication)	Type of study	Baseline participant characteristics			Primary aim	Inclusion disease / disease cases	Outcome disease	Duration of follow-up (weeks)
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)				
Riddle, USA, 2003	Case-Control	150 (50) patients with Plantar fasciopathy or without any diseases	Not reported	51%	To identify risk factors for developing plantar fasciopathy	Plantar fasciopathy	Obesity	Not reported
Singh, United Kingdom, 2015	Prospective cohort	83 patients with midportion Achilles tendinopathy	Median 46 (range 25-79)	68.67%	To analyze the usefulness of serum cholesterol measurements in patients with midportion Achilles tendinopathy	Achilles tendinopathy	Dyslipidemia, heterozygous familial hypercholesterolaemia	Not reported
Smith, USA, 1980	Retrospective cohort	29 female patients with Reiter's disease	36.7 (13.5)	0%	To report women with Reiter's disease	Reiter's disease	Achilles tendinopathy, plantar fasciopathy	Not reported

Abbreviations:, USA: United States of America, SD: Standard Deviation, BMI: Body Mass Index

Supplementary file 4. Additional study information

First author (country, year of publication)	Type of study	Type of tendinopathy	Unilateral or bilateral	Type of imaging used for confirming clinical diagnosis	Severity of pain	Duration of tendinopathy	Active/ sedentary
Abate, Italy, 2016	Case-control	Achilles tendinopathy	Not reported	Ultrasound	Not reported	Not reported	Not reported
Abate, Italy, 2018	Case-control	Achilles tendinopathy	Not reported	Ultrasound, color Doppler	VISA-A of 46.5 (9.0) in males and 45.1 (7.2) in females	Not reported	36 of 36 patients were active
Aggarwal, India, 2009	Prospective cohort	Achilles tendinopathy, plantar fasciopathy	Not reported	None	Not reported	Not reported	Not reported
Alam, Qatar, 2016	Retrospective cohort	Achilles tendinopathy, plantar fasciopathy	Not reported	None	Not reported	Not reported	Not reported
Beeharry, United Kingdom, 2005	Case-control	Achilles tendinopathy	Not reported	None	Severe in 24/62 (37.7%) of patients with HeFH, and none of the controls exceeded moderate severity.	Described as a few days to several weeks with a median of 4 days	Not reported
Cantini, Italy, 2001	Case-control	Achilles tendinopathy	Not reported	Not reported	Not reported	Not reported	Not reported

Supplementary file 4. Additional study information (continued)

First author (country, year of publication)	Type of study	Type of tendinopathy	Unilateral or bilateral	Type of imaging used for confirming clinical diagnosis	Severity of pain	Duration of tendinopathy	Active/ sedentary
Çatal, Turkey, 2021	Case-control	Plantar fasciopathy	Not reported	None	Not reported	154 patients with symptoms <1 year, 84 patients with symptoms >1 year	Not reported
Elkayam, Israel, 2000	Prospective cohort	Achilles tendinopathy, plantar fasciopathy	Not reported	Not reported	Not reported	Not reported	Not reported
Galluzo,Italy, 2000	Prospective cohort	Achilles tendinopathy, plantar fasciopathy	Unilateral	Radiography, ultrasound	Not reported	Not reported	Not reported
Gerster, Switzerland, 1977	Prospective cohort	Talalgia (Achilles tendinopathy or plantar fasciopathy)	Not reported	Radiography	Rheumatoid arthritis: 2% severe, 27% mild pain. Osteoarthritis: 1.4% severe, 15.7% mild pain. Reiter's syndrome: 31% severe, 19% mild pain.	Not reported	Not reported

Supplementary file 4. Additional study information (continued)

First author (country, year of publication)	Type of study	Type of tendinopathy	Unilateral or bilateral	Type of imaging used for confirming clinical diagnosis	Severity of pain	Duration of tendinopathy	Active/ sedentary
Hernandez-Diaz, Italy, 2019	Prospective cohort	Plantar fasciopathy	Not reported	Ultrasound	Not reported	Not reported	Not reported
Holmes, USA, 2006	Case-control	Achilles tendinopathy	Not reported	Radiography and MRI	Not reported	Not reported	Not reported
Jarrot, France, 2015	Retrospective cohort	Achilles tendinopathy	9 unilateral, 1 bilateral	Not reported	Not reported	Not reported	Not reported
Klein, USA, 2013	Case-control	Achilles tendinopathy	Not reported	Not reported	Not reported	Not reported	Not reported
Kraemer, Germany, 2012	Case-control	Achilles tendinopathy	Not reported	None	15% no pain in the morning, 44% mild pain, 31% moderate pain and 11% severe pain. 11% no pain during the day, 50% mild pain, 28% moderate pain and 11% severe pain.	22% 0-3 months, 15% 3-6 months, 13% 6-12 months, 25% 12-36 months, 25% >36 months	Active

Supplementary file 4. Additional study information (continued)

First author (country, year of publication)	Type of study	Type of tendinopathy	Unilateral or bilateral	Type of imaging used for confirming clinical diagnosis	Severity of pain	Duration of tendinopathy	Active/ sedentary
Owens, USA, 2013	Case-control	Patellar tendinopathy, Achilles tendinopathy, plantar fasciopathy	Not reported	Not reported	Not reported	Not reported	Not reported
Plinsinga, Australia, 2018	Prospective cohort	Gluteal tendinopathy	Not reported	MRI	VISA-G 59.5 (13.2)	Median 24 months (IQR 8-48, range 3-192)	Not reported
Riddle, USA, 2003	Case-control	Plantar fasciopathy	Unilateral	Not reported	Not reported	287 ± 550 days (median 123 days, range 14-3650 days)	Not reported
Singh, United Kingdom, 2015	Prospective cohort	Achilles tendinopathy	66 unilateral, 17 bilateral	Not reported	Not reported	Not reported	Not reported

Supplementary file 4. Additional study information (continued)

First author (country, year of publication)	Type of study	Type of tendinopathy	Unilateral or bilateral	Type of imaging used for confirming clinical diagnosis	Severity of pain	Duration of tendinopathy	Active/ sedentary
Smith, USA, 1980	Retrospective cohort	Achilles tendinopathy, plantar fasciopathy	Not reported	Not reported	Not reported	Not reported	Not reported

Abbreviations: USA: United States of America, VISA-A: Victorian Institute of Sports Assessment – Achilles tendinopathy, HeFH: Hereditary Familial Hypercholesterolaemia, MRI: Magnetic Resonance Imaging, VISA-G: Victorian Institute of Sports Assessment – Gluteal tendinopathy, IQR: interquartile range

First author (country, year of publication)	Type of study	Type of metabolic or chronic disease	Definition	Associated measurements	Use of medication	Duration of condition since diagnosis
Abate, Italy, 2016	Case-control	Diabetes	The diagnosis of diabetes based of history and current therapies	HbA1c	Not reported	Not reported
Abate, Italy, 2018	Case-control	Obesity, hypertension, diabetes	Obesity (BMI >30), hypertension (blood pressure 3 times at 4 minutes interval, systolic >140 mmHg and diastolic >90 mmHg), HbA1c >5.7	Obesity (BMI >30), hypertension (blood pressure 3 times at 4 minutes interval, systolic >140 mmHg and diastolic >90 mmHg), HbA1c >5.7	Antidiabetic agents (4 in study group, 2 in control group), antihypertensive drugs (2 in study group, 1 in control group)	Not reported
Aggarwal, India, 2009	Prospective cohort	Ankylosing spondylitis	Modified New York criteria	HLA-B27	Not reported	9.3 (6.5) years
Alam, Qatar, 2016	Retrospective cohort	Ankylosing spondylitis	Assessment of SpondyloArthritis International Society (ASAS)	HLA-B27	Yes (NSAID monotherapy, NSAID + anti-TNFα, anti-TNFα monotheraphy, NSAID + DMARD	Yes
Beeharry, United Kingdom, 2005	Case-control	Hypercholestero-laemia	Criteria of the Simon Broome Register	Serum cholesterol	Not reported	Not reported

Cantini, Italy, 2001	Case-control	Psoriatic arthritis	Seronegative for rheumatoid factors and who presented psoriasis and arthritis affecting the axial and/or peripheral joints	Rose-Waaler titer ≤1:40 or nephelometric determination ≤20 lu/ml on 2 or more occasions	Not reported	77.3 (70.5) months
Elkayam, Israel, 2000	Prospective cohort	Psoriatic arthritis	Anti-inflammatory arthritis, usually rheumatoid factor negative, associated with psoriasis	Not reported	Not reported	Not reported
Galluzo,Italy, 2000	Prospective cohort	Psoriatic arthritis	Criteria of Vasey and Espinoza	HLA-B27	Yes (NSAID's)	5.3 years (range 6 months – 16 years)
Gerster, Switzerland, 1977	Prospective cohort	Rheumatoid arthritis	American Rheumatism Association (1959)	Rheumatoid factor positive	Not reported	>6 months
Hernandez-Diaz, Italy, 2019	Prospective cohort	Rheumatoid arthritis	2010 American College of Rheumatology (ACR) criteria	Not reported	Not reported	72 months (range 2-456)

Holmes, USA, 2006	Case-control	Obesity, hypertension, diabetes mellitus	Obesity (BMI >30 kg/m^2), hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90mmHg or antihypertensive treatment), diabetes mellitus (treatment for diabetes or endocrinologist confirmed diagnosis)	Not reported	Yes (type not specified)	Not reported
Jarrot, France, 2015	Retrospective cohort	Systemic Lupus Erythematosus	American College of Rheumatology (ACR) criteria	ANA, dsDNA, complement fraction levels, antiphospholipid antibodies, rheumatoid factor, anti-CCP, HLA-B27 and serum uric-acid	Not reported	10.5 years (range 0-21 years)
Klein, USA, 2013	Case-control	Obesity	Obese (class I: 30.0-34.9 kg/m^2, class II: 35.0-39.9 kg/m^2), morbidly obese (>40 kg/m^2)	Not reported	Not reported	Not reported
Kraemer, Germany, 2012	Case-control	Diabetes mellitus, hypercholesterolaemia, hypertension	Self-reported medical history	None	Diabetes (metformin, sulfonylureas, insulin), hypercholesterolaemia (fibrates, HMG-CoA inhibitors), hypertension (beta-adrenoreceptor blockers, ACE inhibitors)	Not reported

Owens, USA, 2013	Case-control	Obesity	BMI >30 kg/m^2	Not reported	Not reported	Not reported
Plinsinga, Australia, 2018	Prospective cohort	Obesity	BMI >30 kg/m^2	Not reported	Not reported	Not reported
Riddle, USA, 2003	Case-control	Dyslipidemia	Not specified	Serum cholesterol	Not reported	Not reported
Singh, United Kingdom, 2015	Prospective cohort	Dyslipidemia	Not specified	Serum cholesterol	Not reported	Not reported
Smith, USA, 1980	Retrospective cohort	Reiter's disease	Not specified	Rheumatoid factor, ANA, HLA-B27	Yes (NSAID, phenylbutazone, 6-mercaptopurine, intramuscular gold therapy, corticosteroids	Not reported

Abbreviations: BMI: Body Mass Index, HbA1c: Hemoglobin A1c, HLA-B27: Human Leukocyte Antigen B27, Anti-TNFα: anti-Tumor Necrosis Factor alpha, NSAID: Non-Steroidal Anti-Inflammatory Drugs, DMARD: Disease-Modifying AntiRheumatic Drugs, ANA: AntiNuclear Antibodies, dsDNA: double-stranded DeoxyriboNucleic Acid, Anti-CCP: anti-Cyclic Citrullinated Peptide, HMG-CoA: HydroxyMethylGlutaryl-Coenzyme A reductase inhibitor, ACE inhibitor: Angiotensin-Converting Enzyme, USA: United States of America

Supplementary file 5. Baseline characteristics, and odds ratio of the association between metabolic or chronic disease and lower extremity tendinopathies.

Obesity													
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Gluteal tendinopathy**		**Patellar tendinopathy**		**Achilles tendinopathy**		**Plantar fasciopathy**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Abate, Italy, 2018	Case-control	64 (36) regular runners who started running because of overweight/ obesity/ abnormal metabolic parameters	39.21 (12.33)	62.50%	-	-	-	-	4 (11%)	1.6 (0.3;9.6)	-	-
Holmes, USA, 2006	Case-control	282 (82) patients with Achilles tendinopathy or without any diseases	Not reported	Not reported	-	-	-	-	49 (62%)	10.9 (5.2;23.0)[42]	-	-
Klein, USA, 2013	Case-control	944 (472) patients with Achilles tendinopathy or other foot pathology	51.60 (13.90)	51.91%					189 (40%)	2.5 (1.9;3.4)		
Owens, USA, 2013	Case-control	78486 (584) military service members with patellar tendinopathy or without any diseases	Not reported	Not reported	-	-	67 (12%)	1.4 (1.1;1.8)	61 (14%)	1.6 (1.3;2.2)	175 (14%)	1.7 (1.5;2.1)

Supplementary file 5. Baseline characteristics, and odds ratio of the association between metabolic or chronic disease and lower extremity tendinopathies. (continued)

Obesity													
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Gluteal tendinopathy**		**Patellar tendinopathy**		**Achilles tendinopathy**		**Plantar fasciopathy**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Plinsinga, Australia, 2018	Prospective cohort	204 patients with gluteal tendinopathy	55 (9)	18.14%	57 (28%)	2.8 (1.4;5.6)[42]	-	-	-	-	-	-
Riddle, USA, 2003	Case-control	150 (50) patients with Plantar fasciopathy or without any diseases	49 (11)	34%							29 (58%)	5.6 (1.9;16.6)
Diabetes												
Abate, Italy, 2016	Case-control	76 (38) subjects aged > 65 years with Achilles tendinopathy (case) or upper extremity musculoskeletal disorder (matched case)	69.30 (3.05)	84.21%					16 (42%)	4.8 (2.5;9.3)		

Supplementary file 5. Baseline characteristics, and odds ratio of the association between metabolic or chronic disease and lower extremity tendinopathies. (continued)

Obesity													
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Gluteal tendinopathy**		**Patellar tendinopathy**		**Achilles tendinopathy**		**Plantar fasciopathy**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Abate, Italy, 2018	Case-control	64 (36) regular runners who started running because of overweight/ obesity/ abnormal metabolic parameters	39.21 (12.33)	62.50%					4 (15%)	0.7 (0.1;3.5)		
Holmes, USA, 2006	Case-control	282 (82) patients with Achilles tendinopathy or without any diseases	Not reported	Not reported					6 (7%)	0.5 (0.2;1.1)[43]		
Kraemer, Germany, 2012	Case-control	310 (161) sportsmen between 18-65 years old with Achilles tendinopathy or without any diseases	40.0 (11.0)	66.77%					2 (1%)	0.5 (0.1;2.8)		
Hypertension												

Supplementary file 5. Baseline characteristics, and odds ratio of the association between metabolic or chronic disease and lower extremity tendinopathies. (continued)

Obesity													
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Gluteal tendinopathy**		**Patellar tendinopathy**		**Achilles tendinopathy**		**Plantar fasciopathy**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Abate, Italy, 2018	Case-control	64 (36) regular runners who started running because of overweight/ obesity/ abnormal metabolic parameters	39.21 (12.33)	62.50%					7 (27%)	0.5 (0.1;1.9)		
Holmes, USA, 2006	Case-control	282 (82) patients with Achilles tendinopathy or without any diseases	Not reported	Not reported					43 (52%)	2.4 (1.6;3.7)[44]		
Kraemer, Germany, 2012	Case-control	310 (161) sportsmen between 18-65 years old with Achilles tendinopathy or without any diseases	40.0 (11.0)	66.77%					16 (10%)	0.8 (0.3;1.8)		
Hypercholesterolaemia												

Supplementary file 5. Baseline characteristics, and odds ratio of the association between metabolic or chronic disease and lower extremity tendinopathies. (continued)

Obesity													
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Gluteal tendinopathy**		**Patellar tendinopathy**		**Achilles tendinopathy**		**Plantar fasciopathy**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Çatal, Turkey, 2021	Case-control	478 (238) patients with plantar fasciopathy or without any diseases	Not reported	23.43%			54 (23%)	2.8 (1.9;4.1)				
Kraemer, Germany, 2012	Case-control	310 (161) sportsmen between 18-65 years old with Achilles tendinopathy or without any diseases	40.0 (11.0)	66.77%					17 (11%)	1.4 (0.6;3.5)		
Heterozygous familial hypercholesterolaemia												
Singh, United Kingdom, 2015	Prospective cohort	83 patients with midportion Achilles tendinopathy	Median 46 (range 25-79)	68.67%					1 (1%)	3.0 (0.3;27.5)[45]		

Achilles tendinopathy

(continued)

Achilles tendinopathy

First author (country, year of publication)	Type of study	Baseline participant characteristics			Heterozygous familial hypercholesterolaemia		Ankylosing spondylitis		Psoriatic arthritis		Rheumatoid arthritis		Reactive arthritis		Systemic Lupus Erythematosus	
		Total group (cases) and population description	Age, mean (SD), years	Sex (% male)	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Heterozygous familial hypercholesterolaemia**		**Ankylosing spondylitis**		**Psoriatic arthritis**		**Rheumatoid arthritis**		**Reactive arthritis**		**Systemic Lupus Erythematosus**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Aggarwal, India, 2009	Prospective cohort	70 patients with ankylosing spondylitis	Not reported	84.3%			17 (24%)	61.4 (33.3; 113.0)[2]								
Alam, Qatar, 2016	Retrospective cohort	62 patients with ankylosing spondylitis	Not reported	83.9%			9 (15%)	32.5 (15.2; 69.3)[2]								

(continued)

Achilles tendinopathy

First author (country, year of publication)	Type of study	Baseline participant characteristics			Heterozygous familial hypercholesterolaemia		Ankylosing spondylitis		Psoriatic arthritis		Rheumatoid arthritis		Reactive arthritis		Systemic Lupus Erythematosus	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Beeharry, United Kingdom, 2005	Case-control	220 (133) patients and their partners attending a lipid clinic	56.21 (range 42-64)	48.64%	62 (47%)	11.8 (4.8; 28.9)										
Cantini, Italy, 2001	Case-control	549 (183) patients with psoriatic arthritis or a different rheumatologic disease	51.27 (9.6)	49.18%					24 (13%)	28.9 (17.4 48.0)[2]						
Elkayam, Israel, 2000	Prospective cohort	70 patients with psoriatic arthritis	Not reported	55.71%					18 (26%)	66.2 (36.3; 120.8)[2]						

(continued)

Achilles tendinopathy																	
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Heterozygous familial hyper-cholesterolae-mia**		**Ankylosing spondylitis**		**Psoriatic arthritis**		**Rheumatoid arthritis**		**Reactive arthritis**		**Systemic Lupus Erythematosus**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Galluzzo, Italy, 2000	Prospective cohort	31 patients with psoriatic arthritis	48.1 (range 30-74)	58.06%					1 (3%)	6.4 (0.9; 47.6)[2]						
Gerster, Switzerland, 1977	Prospective cohort	35 patients with ankylosing spondylitis	59.58 (range 19-98)	42.99%			15 (43%)	143.5 (69.6; 295.6)[2]			0 (0%)	0	5 (31%)	87.0 (29.2; 259.1)[2]		
Jarrot, France, 2015	Retrospective cohort	158 patients with systemic lupus erythematosus	Not reported	9.49%											8 (5%)	10.2 (4.8; 21.9)[2]
Plantar fasciopathy																
Aggarwal, India, 2009	Prospective cohort	70 patients with ankylosing spondylitis	Not reported	84.3%			14 (20%)	49.0 (27.0; 89.2)[2]								
Alam, Qatar, 2016	Retrospective cohort	62 patients with ankylosing spondylitis	Not reported	83.9%			14 (23%)	44.6 (23.4; 84.8)[2]								

(continued)

Achilles tendinopathy

First author (country, year of publication)	Type of study	Baseline participant characteristics			Heterozygous familial hyper-cholesterolae-mia		Ankylosing spondylitis		Psoriatic arthritis		Rheumatoid arthritis		Reactive arthritis		Systemic Lupus Erythematosus	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Cantini, Italy, 2001	Case-control	549 (183) patients with psoriatic arthritis or a different rheumatologic disease	51.27 (9.6)	49.18%					29 (16%)	28.8 (18.1 ;45.9)[2]						
Galluzzo, Italy, 2000	Prospective cohort	31 patients with psoriatic arthritis	48.1 (range 30-74)	58.06%					3 (10%)	16.4 (4.9; 55.2)[2]						
Gerster, Switzerland, 1977	Prospective cohort	35 patients with ankylosing spondylitis	59.58 (range 19-98)	42.99%			3 (9%)	14.3 (4.3; 48.0)[2]			1 (1%)	1.5 (0.2; 11.2)[2]	3 (19%)	35.3 (9.8; 126.7)[2]		
Hernandez-Diaz, Italy, 2019	Prospective cohort	112 patients with rheumatoid arthritis	51 (range 22-85)	10.71%							1 (1%)	1.4 (0.2; 10.0)[2]				

(continued)

Achilles tendinopathy																	
First author (country, year of publication)	**Type of study**	**Baseline participant characteristics**			**Heterozygous familial hyper-cholesterolae-mia**		**Ankylosing spondylitis**		**Psoriatic arthritis**		**Rheumatoid arthritis**		**Reactive arthritis**		**Systemic Lupus Erythematosus**	
		Total group (cases) and population description	**Age, mean (SD), years**	**Sex (% male)**	Number (%)	OR(95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)	Number (%)	OR (95% CI)
Smith, USA, 1980	Retrospective cohort	29 female patients with Reiter's disease	36.7 (13.5)	0%									15 (52%)	973.0 (380.8; 2486.1)[2]		

Abbreviations: SD: Standard Deviation, OR: Odds Ratio, USA: United States of America, BMI: Body Mass Index

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4

Effects of eccentric exercises on improving ankle dorsiflexion in soccer players

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ABSTRACT

Purpose
The purpose of this study was to determine the effect of targeted eccentric calf muscle exercises compared to regular training on ankle dorsiflexion in healthy adolescent soccer players with a decreased ankle dorsiflexion.

Methods
Male adolescent players (aged 14-21 years) from two professional soccer clubs were evaluated with the Weight Bearing Dorsiflexion Lunge Test (WBDLT) at baseline and after 12 weeks of this prospective controlled study. One club served as the control group and the other as the intervention group. Players with decreased ankle dorsiflexion (WBDLT) <10 cm) performed stretching and eccentric calf muscle exercises three times per week next to regular training in the intervention group, and performed only regular training in the control group. Primary outcome was the between-group difference in change in WBDLT between baseline and 12 weeks.

Results
Of 107 eligible players, 47(44%) had a decreased ankle dorsiflexion. The WBDLT (± standard deviation) increased in the intervention group from 7.1 (±1.8) to 7.4 (±2.4) cm (95% Confidence Interval (CI)[-0.493 to 1.108], p = 0.381) and in the control group from 6.1 (±2.4) to 8.2 (±2.9) cm (95% CI [1.313 to 2.659], p<0.001). The difference in change of WBDLT between both groups was statistically significant (95% CI [-2.742 to -0.510], p=0.005).

Conclusions
Targeted eccentric calf muscle exercises do not increase ankle dorsiflexion in healthy adolescent soccer players. Compared to regular training, eccentric exercises even resulted in a decreased calf muscle flexibility.

Trial registration
This trial was registered retrospectively on the 7th of September 2016 in The Netherlands Trial Register (ID number: 6044).

BACKGROUND

Although Achilles tendinopathy is a persevering injury with low treatment response, research for prevention strategies are limited[1]. Achilles tendon injuries account for 2.4% of all injuries in professional soccer players, and are associated with a prolonged absence in sports, work and other activities[2]. Besides the decrease in the athlete's wellbeing and performance, the lack of a highly effective treatment for Achilles tendinopathy makes prevention essential[3].

Decreased ankle dorsiflexion increases strain on the soleus and gastrocnemius tendons. Gait analysis shows that soleus and gastrocnemius muscles absorb peak mechanical power just before toe-off in a walking and running gait cycle[4]. When ankle dorsiflexion is limited, the force absorbed by both soleus and gastrocnemius increases. Theoretically, this continuously increased strain can lead to Achilles tendinopathy. Two prospective studies reported that a decreased ankle dorsiflexion was associated with a 2.5-3.6 times higher risk of Achilles tendinopathy[5,6].Consequently, ankle dorsiflexion angle is measured by many different medical professionals, such as physiotherapists, sports physicians and orthopaedic surgeons.

To reduce the risk of Achilles tendinopathy, stretching and eccentric (lengthening) exercises are postulated to improve ankle dorsiflexion. An eccentric exercise lengthens an active muscle while it is under load. By loading the Achilles tendon with eccentric (lengthening) exercises, lengthening of the musculotendinous junction may occur, leading to less strain on the tendon during movement[7]. Decreased plantar flexor muscle strength is also associated with a decreased ankle dorsiflexion[8]. Consequently, eccentric calf muscle exercises can also increase ankle dorsiflexion through an increase in calf muscle strength.

For the above mentioned reasons, a combination of stretching exercises and eccentric (lengthening) exercises are suggested as preventive intervention to increase ankle dorsiflexion. Our primary aim was to examine whether targeted stretching exercises and eccentric exercises of the calf muscles increase ankle dorsiflexion in healthy adolescent soccer players with a decreased ankle dorsiflexion. Our secondary aim was to determine the intra- and inter-observer reliability and minimal detectable change of the testing procedure.

METHODS

Design

This prospective controlled trial was approved by the Medical Ethics Committee of the Erasmus MC Rotterdam, The Netherlands (MEC-2016-237). The trial is registered in the Netherlands Trial Register (NTR number: 6044). This study adheres to STROBE guidelines.

Participants

Soccer players of Under-16, Under-17 and Under-19 squads of two Dutch professional premier division soccer clubs were asked to participate in this study. Before inclusion, informed consent was acquired from all players and parents (in case of players with age below 18 years). Players were eligible for inclusion if the following criteria were met: (1) age 14-21 years, (2) male sex, and (3) free of musculoskeletal injuries at baseline during physical testing. The soccer player was excluded if (1) he was not available in the week of baseline physical testing during the trial period.

Only players with a decreased ankle dorsiflexion were selected for further analysis. A decreased ankle dorsiflexion was defined as ≤10 cm toe-to-wall distance, or soleus muscle flexibility ≤34°, or gastrocnemius muscle flexibility ≤34°, measured with the WeightBearing Dorsiflexion Lunge Test (WBDLT).[6,9]. Soccer players with a decreased ankle dorsiflexion from one club were assigned to the intervention group, and soccer players with a decreased ankle dorsiflexion from the other club were assigned to the control group. Both groups followed regular training, and the intervention group performed additional stretching and eccentric exercises for 12 weeks.

Testing procedure and outcome measures

Age, body mass, height, and previous injuries were inquired with a baseline questionnaire. Testing procedures for calf muscle flexibility consisted of the WBDLT, the degree of soleus muscle flexibility and the degree of gastrocnemius muscle flexibility. The procedures for calf muscle flexibility were performed one week after the first training after the start of the soccer season for both teams. To ensure all players were fit, the tests were planned after a resting day. Before performing the WBDLT, a ruler was fixed on the floor (Figure 1A). A line was drawn on the shin 8 cm from the most prominent part of the distal fibula for placement of the lower part of the plurimeter (Dr. Rippstein, Zurich, Switzerland) The player stood barefooted with his heel and digit I of one foot aligned on the fixed ruler, facing the wall.[6] His knee was flexed with his patella against the wall above digit III. He was instructed to keep his trunk straight with his hands on his waist, and to dorsiflex his

ankle as far as possible. We made sure the heel and digit I of the player were aligned with the fixed ruler. When the player could not further increase the ankle dorsiflexion, we noted down the distance between digit I and the wall. To measure soleus muscle length, a plurimeter was placed on the marked anterior tibial cortex, while the player stood in position A (Figure 1B). The number of degrees between the tibial cortex and the floor was noted. To measure gastrocnemius muscle length, we instructed the player to stand in lunge position, while keeping his hind leg stretched (Figure 1C). The player bent his front leg to put strain on his fully extended knee joint. A plurimeter was placed on the marked anterior tibial cortex, while the player stood in position C. When the player could not further increase the ankle dorsiflexion of the hind leg, we noted the angle between the tibial cortex and the floor.

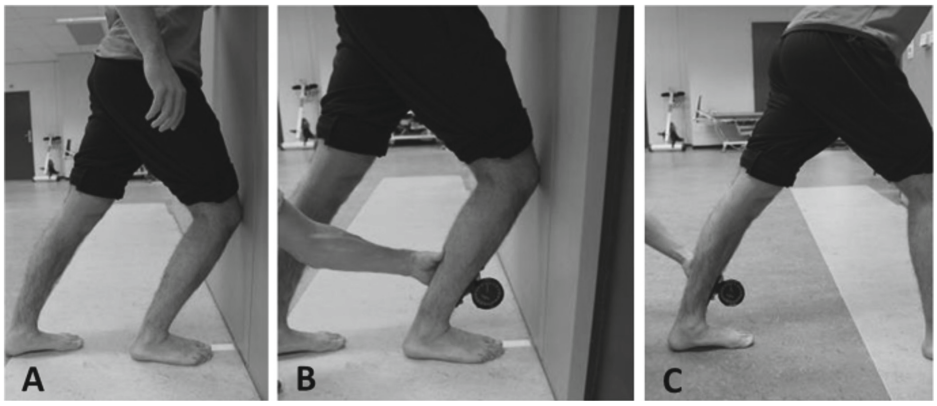

Figure 1. Outcome measures of ankle dorsiflexion. **a** Position of the weightbearing dorsiflexion lunge test. **b** Position for measuring the soleus muscle flexibility in degrees. **c** Position for measuring the gastrocnemius muscle flexibility in degrees

After every test, we asked the player if the limitation during dorsiflexion was felt on the anterior or dorsal side of the ankle (anterior blockage or dorsal tightness). The intervention group received their test results within one week after testing, with the aim to improve adherence to the intervention. The control group did not receive a report of their test results to prevent influencing their training habits as a consequence of their test results.

Intervention

Both groups performed regular soccer training four times per week, with an approximate duration of 2 hours per training. The intervention group was advised to perform targeted exercises after the soccer training. We instructed all players of the intervention group to perform the exercises three times a week for 12 weeks[10]. To ensure good performance of the exercises, they received detailed exercise instructions in groups by the principal investigator

(IL) during the first week. Individual advice was given during the 12 weeks of exercising to ensure consistently good performance of the exercises.

Exercises aimed to lengthen the soleus and gastrocnemius muscles were selected (Figure 2)[11]. For stretching of the soleus muscle, the player stood in a lunge position (Figure 2A1). He then lowered his knee until he felt a stretch in the calf. For stretching of the gastrocnemius muscle, the player stood in a lunge position and flexed the knee of his front leg, while keeping both heels on the ground and the knee of his hind leg stretched (Figure 2A2). Both stretching exercises (A1 and A2) were repeated three times for 30 seconds for the at-risk leg. The starting position of the eccentric exercises is showed in Figure 2B1, where the balls of the players' feet were on an elevation, with his heels above the ground. While keeping his posture straight, he slowly raised his heels until he was in a tiptoe position with both feet. For performing eccentric exercises of the soleus muscle, the player lifted up one leg from starting position so he stands on his to-be-trained leg (Figure 2B2). He flexed his knee slightly and slowly lowered his heel until he feels a slight stretch. The other foot was placed on the elevation again and the exercise was repeated. For performing eccentric exercises of the gastrocnemius muscles, the player lowered his heel until he felt a slight stretch, while keeping his knee extended. The other foot was placed on the elevation again and the exercise was repeated.

The number of sets and repetitions was gradually increased by approximately 20% every week to prevent overloading, starting at two times four repetitions (Figure 2). If the ankle dorsiflexion was only decreased at one side, the players only performed the exercises for that index leg. If only the soleus muscle flexibility was limited, they only performed soleus lengthening exercises. One minute of rest between sets was advised. Primary outcome measure was the change in WBDLT after twelve weeks of training[12].

The sets for eccentric calf muscle exercises were repeated twice in the first four weeks, with four repetitions in the first week, increasing with two repetitions per week. In week five to eleven, sets were repeated three times, starting with seven repetitions, and increasing with one repetition per week. Three sets of 15 repeats were accomplished in week twelve.

One researcher (IL) visited the physiotherapists of both clubs weekly for registration of Achilles tendon injuries. An Achilles tendinopathy was defined as a focal physical complaint of the Achilles tendon with pain on palpation leading to the athlete being unable to take part in training and/or competition[13].

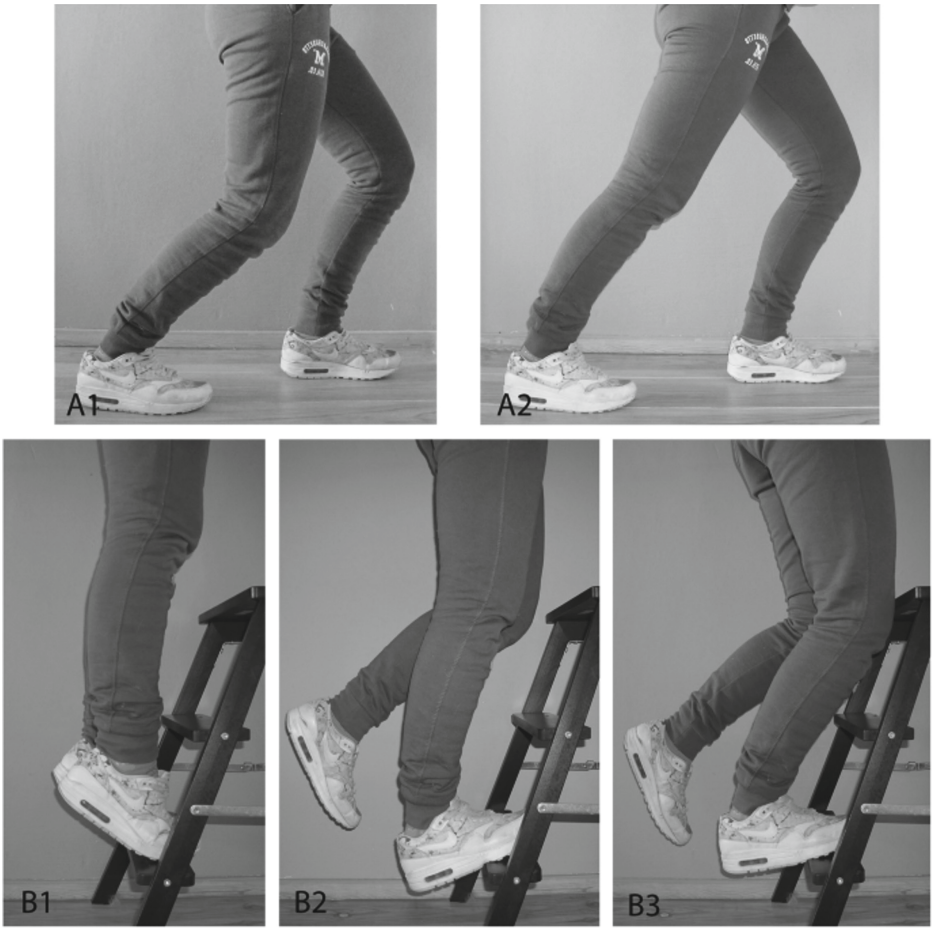

Figure 2. Stretching and eccentric (lengthening) exercises. A1) Stretching of the soleus muscle. A2 Stretching of the gastrocnemius muscle. B1) Starting position of eccentric exercises. B2) Eccentric exercise of the soleus muscle. B3) Eccentric exercise of the gastrocnemius muscles

Statistical analysis

SPSS software (V.21.0; SPSS, Chicago, Illinois, USA) was used for statistical analysis. In case of missing data at the 12 weeks' time point, the data was described as 'missing' in the analysis. The within-group changes in WBDLT, soleus and gastrocnemius muscle flexibility were analysed with a paired sample T-test and described as mean ± standard deviation. The change in centimetres on the WBDLT and degrees on the soleus and gastrocnemius muscle flexibility tests were analysed with a linear regression analysis. In an univariate model, we analysed if there was an association between baseline characteristics and the change in ankle dorsiflexion. If one of these variables

had an association with a p-value <0.10, this variable was included in a multivariate stepwise regression. To calculate the correlation between the change in centimetres on the WBDLT outcome and degrees on the soleus and gastrocnemius muscle flexibility tests and compliance to the targeted training programme, a Pearson correlation test was used. A p-value <0.05 was considered as statistically significant in the final analyses.

To ensure the reliability of the testing procedures for calf muscle flexibility, intra-class correlation coefficient (ICC) for the intra- and inter- observer reliability and minimal detectable change (MDC) were examined. The WBDLT was performed by ten healthy male participants. The test was independently instructed and measured by two researchers (RJdV, FG). One of these researchers (FG) performed the same test one day later. ICC values for intra- and inter-observer reliability were interpreted according to Fleiss as poor (<0.40), fair (0.40-0.59), good (0.60-0.75) and excellent (>0.75)[14]. MDC was calculated with the formula $MDC = SEM * 1.96 * \sqrt{2}$, where the standard error of the mean (SEM) was $SD * \sqrt{1 - ICC}$. The standard deviation (SD) was the SD of all scores from the participants[15].

RESULTS

Baseline player characteristics

In total, 107 players were assessed for eligibility in July and August 2016, and could be included in this study (Figure 3). There was no exclusion of players. Two weeks after baseline testing, the intervention group started the training programme. Baseline characteristics of players with a decreased ankle dorsiflexion (WBDLT of ≤10cm, soleus muscle flexibility ≤34°, or gastrocnemius muscle flexibility ≤34°) are presented in Table 1. No Achilles tendon injuries occurred in both groups during the exercise period and there was no loss to follow-up.

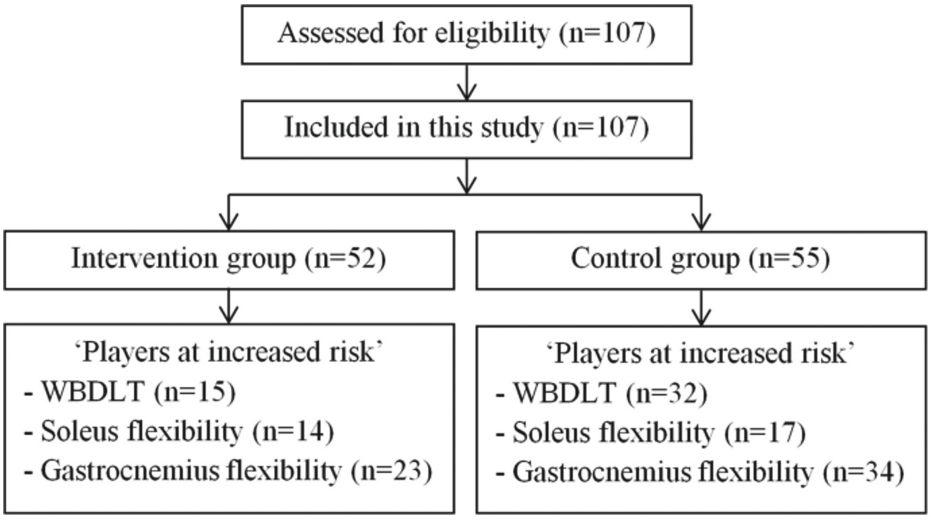

Figure 3. Flowchart of patients through the study

The mean WBDLT in the intervention group improved from 7.1 (±1.8) to 7.4 (±2.4) cm (p=0.381). In the control group mean WBDLT improved from 6.1 (±2.1) to 8.2 (±2.9) cm (p<0.001). The difference in change of WBDLT between both groups was statistically significant (95% CI [-2.7 to-0.5], p=0.005). Neither baseline characteristics, presence of anterior blockage or dorsal tightness or baseline influenced the magnitude of change in WBDLT. There was no significant association between the intervention and change in WBDLT (Table 2).

Table 1. Baseline statistics of players at increased risk of Achilles tendinopathy.

	Intervention group	Control group	p-value
Age, years	16.3 ± 1.2	16.3 ± 1.2	0.997
Height, meters	1.76 ± 0.07	1.76 ± 0.09	0.992
Weight, kg	65.6 ± 8.1	68.0 ± 10.5	0.344
BMI, kg/m^2	21.1 ± 1.8	21.7 ± 2.2	0.207
Weekly training, hours	9.4 ± 2.4	9.0 ± 2.2	0.490

Data is presented as mean±SD
* Statistically significant difference (p-value < 0.05). SD: Standard deviation. BMI = Body Mass IndexWeightbearing dorsiflexion lunge test

Table 2. Multivariate linear regression analysis of change in WBDLT after 12 weeks.

Test	Variables	Unstandardized Beta [95%CI]	p-value
WBDLT[a]	Intervention	1.626 [0.510;2.742]	0.005*
Soleus muscle flexibility[b]	Intervention	3.598 [0.992;6.205]	0.009*
	Age (years)	-0.987 [-2.156;0.183]	0.095
	BMI (kg/m^2)	-0.150 [-0.748;0.447]	0.609
	Anterior limitation	0.000 [0.000;0.001]	0.158
Gastrocnemius muscle flexibility[c]	Intervention	1.578[-0.997;4.132]	0.221
	Anterior blockage	0.852[-2.389;4.094]	0.600

[a] r^2=0.171., [b] r^2=0.338., [c] r^2=0.029., *Statistically significant difference (p-value<0.05), CI= Confidence Interval.

Soleus and gastrocnemius muscle flexibility

In the intervention group, mean soleus muscle flexibility improved from 31.0 (±1.7) to 32.5 (±3.3) degrees (p=0.075). The mean soleus muscle flexibility of the control group had a statistically significant improvement from 28.3 (±3.4) to 33.6 (±4.7) degrees (p<0.001). The baseline value differed between both groups (95% CI [0.7 to 4.7], p=0.011).

Age and BMI were univariably associated with a positive influence on change in soleus muscle flexibility. Older players and players with a higher BMI had a larger improvement in soleus muscle flexibility (Table 2). However, neither age (p=0.095) and BMI (0.609) were predictors of change in soleus muscle flexibility in a multivariable analysis. Other baseline characteristics, presence of anterior blockage or dorsal tightness did not influence the magnitude of change in soleus muscle flexibility. The intervention was significantly associated with a decrease in soleus muscle flexibility (p=0.009) (Table 2).

Mean gastrocnemius muscle flexibility of the intervention group improved from 29.8 (±3.0) to 31.0 (±3.5) degrees (p=0.188).The mean gastrocnemius muscle flexibility of the control group improved significantly from 28.3 (±4.4) to 31.2 (±5.6) degrees (p=0.004). There was no significant relation between the intervention and the change in gastrocnemius muscle flexibility (Table 2). Neither baseline characteristics, presence of anterior blockage or dorsal tightness influenced the magnitude of change in gastrocnemius muscle flexibility.

Compliance to exercises

The mean compliance to the exercise program was 69 (±14) % for WBDLT, 67.4 (±14.6) % for soleus muscle flexibility, and 63.9 (±16.4) % for gastrocnemius muscle flexibility. This means that on average, all players performed the exercises twice per week. The compliance of individual players did not significantly correlate with their corresponding change in WBDLT result (r=-0.313, p=0.275) and soleus muscle flexibility(r=-0.411, p=0.163). Compliance of individual players to stretching and eccentric exercises were correlated with their corresponding change in gastrocnemius muscle flexibility (r=0.474, p=0.022).

Reliability of testing procedure

The intra-observer reliability of the WBDLT was 0.98 (95% CI [0.94 to 0.99]), 0.95 (95% CI [0.76 to 0.96]) for soleus muscle flexibility and 0.94 (95% CI [0.86 to 0.98]) for gastrocnemius muscle flexibility. The inter-observer reliability was determined to be 0.99 (95% CI [0.999 to 0.999]) for the WBDLT, 0.98 (95% CI [0.94 to 0.99]) for soleus muscle flexibility and 0.98 (95% CI [0.94 to 0.99]) for gastrocnemius muscle flexibility. All can be defined as excellent agreement. The MDC for WBDLT was 1.5 cm, 4.7 degrees for soleus muscle flexibility and 4.9 degrees for gastrocnemius muscle flexibility.

DISCUSSION

Our study is the first to compare the effect of stretching and eccentric (lengthening) exercises with regular training on ankle dorsiflexion in a population of adolescent soccer players a decreased ankle dorsiflexion. Contrary to popular belief, ankle dorsiflexion did not improve after targeted stretching and eccentric exercises of the calf muscles.

Only one preventive intervention study has been performed in this field. A large Danish study showed that eccentric exercises as prevention had no influence on ultrasonographic abnormalities of the Achilles tendon[16]. In addition, stretching and eccentric exercises did not reduce the risk of developing symptoms of Achilles tendinopathy[16]. Our study provides a possible explanation for these results; stretching and eccentric exercises do not increase the limited ankle dorsiflexion and thereby do not influence a potential risk factor.

As a decreased ankle dorsiflexion is associated with a higher risk of Achilles tendinopathy[6], we used exercises that were thought to increase ankle dorsiflexion. As no prevention strategy is yet developed for Achilles tendon injuries, we looked at possible ways to increase the ankle dorsiflexion. Tendon length is often associated with the concept of tendon stiffness.[17]

It is hypothesized that it is desirable to make a muscle tendon unite more flexible (resulting in a larger ankle dorsiflexion angle). However, results vary in literature. In one study, patients with Achilles tendinopathy were included and randomized to either a 12-week eccentric calf muscle program or a control group.[18] There was no significant increase in dorsiflexion range of motion in the eccentric loading group. In another study by Mahieu et al., the ankle dorsiflexion angle increased after a 6-week eccentric training regime in healthy subjects when compared to the control group.[19] The differences between these studies might be explained by differences in included population; one included patients and the other healthy subjects.[18,19]As we also included healthy subjects, it is striking that our study results were opposite to the study results of Mahieu et al.[19] A reason for this might be the duration of the intervention. A recent systematic review showed that stretching exercising protocols shorter than 8 weeks do not change either muscle or tendon properties.[20]It is hypothesized that eccentric exercises result in changes at a sensory level in the short term and that tissue properties change on the long term.

From a mechanistic perspective, we hypothesized that hypothesized stretching and eccentric exercises would increase calf muscle flexibility through (1) induction of sarcomerogenenesis[21], (2)lengthening of the myotendinous unit[7,22] and (3) strengthening of the plantar flexors[8]. However, we did not find a correlation between compliance to exercises and change in ankle dorsiflexion. It is, based on our study results, unknown whether this is caused by decreased muscle flexibility, increased Achilles tendon stiffness or a combination of both. A recent study shows that an 8-week eccentric exercise program stimulates increased cross-sectional area of the tendon (hypertrophy) and simultaneous increased stiffness in healthy subjects.[23] The increased stiffness might be explained by a loss of collagen crimp or increased crosslinking of the tendon fibrils.[24,25] These mechanistic effects might explain our study findings.

We also investigated whether the effect of the intervention could be explained by baseline parameters. If a player is limited in ankle dorsiflexion due to blockage at the anterior side of the ankle, it is less likely that stretching and eccentric calf muscle exercises can influence the ankle dorsiflexion. However, both WBDLT and soleus muscle flexibility were not influenced by anterior blockage of ankle dorsiflexion. Feeling of calf muscle tightness during testing of the gastrocnemius muscle flexibility was associated with improvement of gastrocnemius muscle flexibility in the univariate regression analysis, but showed no statistically significant association in the multivariate regression analysis. Other baseline variables were also not associated with an improved ankle dorsiflexion. We did not find confounders that might have altered the effectiveness of the exercises.

The strengths of our study are the implementation of an adequate methodology and the fact that we adhered to the predefined study protocol. Before the testing moments, a clear consensus was made between all researchers. This ensured that during the testing moments, the same instructions were given to all soccer players with the aim to improve reliability of the testing procedure. This was reflected by the excellent intra-observer and inter-observer reliability of the performed tests. MDC values were low, which means that we were able to demonstrate clinically relevant changes outside the measurement error. This was true for the WBDLT, as the difference in change between both groups was outside the measurement error. However, the difference in change for soleus and gastrocnemius muscle flexibility was within the MDC and therefore the clinical relevance of the findings related to the soleus and gastrocnemius muscle flexibility is limited.

There are some limitations to our study. First, we determined clusters by the club at which a player was training, to avoid contamination of the intervention. However, because we used different clubs, it could be possible that the two clusters had different training regimes with a different total exercise time, although training frequency was equal. Both clubs followed our regulations to not alter their regular training, and not to perform extra prevention exercises. Our results showed that the player characteristics were not significantly different between both clusters, meaning that they were comparable. The baseline WBDLT and gastrocnemius muscle flexibility was similar in both groups, but the soleus muscle flexibility showed a significant difference at baseline; the control group had smaller soleus muscle flexibility than the intervention group. However, this difference was within the measurement error. We chose to use cluster randomisation for practical reasons. Nevertheless, there are systematic biases associated with cluster randomisation. The presence of selection bias can occur with cluster designs, such as age imbalance between clusters. While we cannot exclude occurrence of bias in our study, the between-group differences in baseline characteristics were similar.

Another limitation could be the cut-off of all tests. Although we based our cut-offs on previous studies[6,9], we are aware that the cut-offs are not determined by a large prospective trial. Unfortunately, both studies did not publish sensibility and sensitivity of the cut-offs, which adds to the limitation. A cut-off value for WBDLT and soleus muscle flexibility was needed to determine which group had a decreased dorsiflexion. We chose this approach, because we expected a better effect of the eccentric exercises in this subgroup.

Last limitation could be the moderate compliance to the exercises. In order for a prevention strategy to be effective, exercises should be performed at

least twice a week[11]. We made our intervention group perform the exercises three times a week, thus making sure they performed enough exercises in order for the intervention to be effective. The average compliance to exercises is approximately 66% of prescribed exercises (thus three times a week). This equals to an average performance of two times a week per player. We should be aware that the moderate compliance is at least a reflection of daily clinical practice.

Practical Applications

Stretching and eccentric (lengthening) exercises are generally advised as they are thought to improve the ankle dorsiflexion, a risk factor for developing Achilles tendon injuries.[6] However, the findings of this study demonstrate that stretching and eccentric (lengthening) exercises do not increase ankle dorsiflexion in adolescent high level soccer players with a decreased ankle dorsiflexion compared to regular training. The outcome of this study questions whether stretching and eccentric (lengthening) exercises should be used as prevention exercises. Future studies should be aimed at novel methods to improve ankle dorsiflexion.

CONCLUSION

Stretching and eccentric exercises do not increase ankle dorsiflexion in adolescent high level soccer players. Compared to regular training, eccentric exercises even resulted in a decreased calf muscle flexibility. This might explain why targeted eccentric calf muscle exercises are not effective as primary preventive intervention for Achilles tendon injuries.

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Conflicts of interest

There are no conflicts of interest to disclose.

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Part II

Course of symptoms and prognostic factors in new-onset and chronic Achilles tendinopathy

5

Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire: Minimal clinically important difference for active people with mid-portion Achilles tendinopathy – a prospective cohort study

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ABSTRACT

Objective
To determine the minimal clinically important difference (MCID) of the Victorian Institute of Sport Assessment-Achilles (VISA-A) score in patients with midportion Achilles tendinopathy (AT).

Design
Prospective cohort study.

Methods
We included physically active patients with midportion AT who received exercises and an injection. We measured the VISA-A score (0-100 points, where 100 points represent a healthy tendon) at baseline, and at 12 and 24 weeks after treatment, and the 7-point Global Assessment Scale (GAS; ranging from 'worse than ever' to 'completely recovered') at 12 and 24 weeks after baseline. We dichotomized GAS to not improved ('worse than ever' to 'unchanged') or improved (moderately improved to completely recovered). The area under the curve (AUC) and Youden's Index closest to 1 were determined for both MCID with corresponding sensitivity and specificity.

Results
Sixty-four patients were included and 61 patients (95%) completed the 24-week follow-up. The MCID was 14 points (95% confidence interval (CI) 3 to 19) over a 12-week period, corresponding to 57% sensitivity and 88% specificity. The MCID was 7 points (95% CI -10 to 28) over a 24-week period with 85% sensitivity and 62% specificity.

Conclusions
A change in VISA-A score of at least 14 points after 12 weeks or at least 7 points after 24 weeks of exercise therapy and an injection reflects a meaningful change for physically active patients with midportion AT.

Trial registration number
Clinical Trials (Identifier: NCT02996409).

INTRODUCTION

Symptom evaluation in AT patients should encompass 9 core domains recently outlined by health care providers and patients.[1] The domains are: patient overall rating, participation, pain on activity/loading, disability, function, physical function capacity, quality of life, psychology, and pain over a specified timeframe.[1] The impact of symptoms on an individual can be measured using patient-reported outcome measures (PROMs) within one of these 9 established core domains for tendinopathy.[2]

The Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire is a validated and disease-specific PROM within the core domain 'disability'.[1,3] The VISA-A was developed as a standardized outcome measure to evaluate treatment effects in physically active patients with AT.[3] It evaluates physical disability via questions about pain, functional status and sports activity, and ranges from 0-100 points with higher scores indicating less severe symptoms during activities.[3] Since its introduction in 2001, the VISA-A questionnaire has been validated and translated to nine other languages, and is widely used.[4,5]

Responsiveness is an important characteristic of a PROM, indicating the ability of an instrument to measure clinically significant changes. The minimal clinically important difference (MCID) reflects the smallest change in a score that is meaningful for patients.[6] Previous literature suggests the MCID for the VISA-A questionnaire ranges from 6.5 to 20 points.[7-9] However, the studies are heterogeneous: including people with insertional AT and midportion AT, a variable number of participants (15 to 54 patients) and applying different statistical methods [7-9].

The most accepted method for determining a MCID is an anchor-based method where a numerical outcome, such as the VISA-A score, is 'anchored' to a categorical assessment, such as a Likert scale.[10] While the MCID reflects improvement (feeling better), the patient acceptable symptom state (PASS) reflects wellbeing or sufficient remission of symptoms (feeling good).[11] While a certain increase in VISA-A score could reflect a clinically relevant improvement, it is not self-evident that AT symptoms are acceptable. Calculation of the PASS is performed by using an anchor to identify cut-points in numerical PROMs. The PASS could refine the interpretation of a treatment effect by identifying patients who consider their symptoms acceptable.

While the VISA-A score has been used in most of the intervention studies for midportion AT patients, there is absence of an anchor-based MCID value and PASS threshold, which limits patient-centred interpretation of trial results. We

aimed to determine the anchor-based MCID and PASS of the VISA-A score in patients with midportion AT.

METHODS

Our prospective cohort study is part of the High-volume image-guided injections in midportion Achilles Tendinopathy (HAT) trial.[12] In the trial, patients were randomized to either a high-volume injection (50 mL) or a low-volume injection (2 mL) and all patients performed calf strengthening exercises. The injections consisted of a 0.9% NaCl solution with 1% lidocaine. We considered the patients of the HAT trial as a cohort because there was no between-group difference in VISA-A score.[12] For more details about the interventions used in the HAT trial, see the main article [12] The HAT trial was approved by the Medical Research Ethics Committee of Southwest Holland, the Netherlands (MEC-14-100). Materials and methods were reported in the pre-registered protocol at clinicaltrails.gov (identifier: NCT02996409).

Patients

Patients were recruited at a large district general hospital (The Hague Medical Center, Leidschendam, The Netherlands) between December 2016 and January 2019. A sports medicine physician evaluated patient suitability for inclusion. Inclusion criteria were (1) the presence of clinically established midportion AT for more than 2 months, (2) having completed an exercise training program for at least six weeks with unsatisfactory outcome, (3) age between 18-70 years, and (4) presence of Doppler flow on Power Doppler Ultrasonography (PDU). Midportion AT was defined as a painful swelling of the Achilles tendon, 2-7 cm proximal to the calcaneal insertion.

Main exclusion criteria were (1) presence of other musculoskeletal disorders (such as insertional tendinopathy, tendon rupture, inflammatory internal disorders, or drug-induced tendinopathy), (2) pregnancy, and (3) the inability to perform an exercise program. Informed consent was obtained from all patients before inclusion and the rights of the patients were protected. As the VISA-A score is validated for active patients only, we also chose to exclude patients with an ankle activity score <4.[13] Other eligibility criteria are reported in the study protocol.

Outcome measures

The VISA-A questionnaire is a disease-specific questionnaire and has been validated in Dutch language.[14] We administered the questionnaire digitally at baseline and after 12 and 24 weeks follow-up. The 7-point Global Assessment Scale (GAS) was completed at 12 and 24 weeks. Participants rated their

symptoms of the prior week compared to the week before baseline, with answers ranging from 'worse than ever' to 'completely recovered'. To calculate MCID, we dichotomized the 7-point global assessment scale to 'not improved' ('worse than ever' to 'unchanged') and 'improved' ('moderately improved' to 'completely recovered') (Table 1).[7] According to existing literature, the cut-off was set at 'moderately improved', as the MCID reflects the minimal positive effect that is meaningful for the patient, with the emphasis on 'minimal'.[6] PASS was calculated by using the perception of symptoms, which was inquired via one single question: 'If you had to live with your current symptoms for the rest of your life, would this be acceptable or unacceptable? Answer options were 'acceptable' or 'unacceptable'.

Table 1. Statements with corresponding points of the 7-point Global Assessment Scale.

Number	Statement
1	Worse than ever
2	Much deteriorated
3	Moderately deteriorated
4	Not changed
5	Moderately improved
6	Much improved
7	Completely recovered

Statistical analysis

We used SPSS software (V.24.0.0.1; SPSS, Chicago, Illinois, USA) for statistical analysis. As the sensitivity analysis reported less than 5% missing data in the primary study,[15] imputation was not needed.[12] We used a Shapiro-Wilk test for normality, where we assumed normal distribution if $p>0.05$.

To calculate MCID, a Receiver Operating Characteristics (ROC) curve was created using the dichotomized GAS and the change in VISA-A score between baseline, 12, and 24 weeks. To determine the PASS, we created a ROC curve using the VISA-A score at 12 and 24 weeks and the perception of symptoms (acceptable/unacceptable). The Area Under the Curve (AUC) represented improvement and was interpreted as fail (0.50-0.59), poor (0.60-0.69), fair (0.70-0.79), good (0.80-0.89) and excellent (0.90-1.0).[16] Youden's Index was calculated to maximize sensitivity and specificity with the following formula: $\textit{Youden's index}: (\textit{sensitivity} + \textit{specificity}) - 1$. The MCID and PASS values were determined with a Youden's Index nearest to 1. The 95% confidence interval

of MCID and PASS values were calculated using pROC in R for Windows (i386 4.0.3). The positive predictive value (PPV) was calculated using the following formula: $\frac{sensitivity\ x\ prevalence}{sensitivity\ x\ prevalence + (1 - specificity)\ x\ (1 - prevalence)}$.

RESULTS

Sixty-four participants were included, of which 61 completed follow-up after 24 weeks (95%) (Table 2). Endpoint data for three participants were missing, of which 1 was unreachable and 2 did not complete all questions. The mean (standard deviation, SD) VISA-A score increased from 40 (15) points at baseline to 52 (20) points after 12 weeks and 60 (22) points after 24 weeks. The median ankle activity score (interquartile range, IQR) was 5 (5;6). Median score (interquartile range, IQR) of the 7-point GAS was 5 (4;6) after 12 weeks and 6 (5;6) after 24 weeks. The perception of symptoms was acceptable for 36% of participants after 12 weeks, which increased to 51% after 24 weeks.

Table 2. Baseline characteristics of patients

	Included patients		
	n (%)	Mean (SD)	Median (IQR)
N	64		
Sex (male)	30 (47%)		
Age (years)		47.5 (9.2)	50.0 (44.3;54.0)
BMI (kg/m^2)		27.5 (5.8)	25.4 (24.0;31.4)
Duration of symptoms (weeks)		118 (150)	77 (40;134)
VISA-A score		40 (15)	39 (28;54)
Ankle activity score		6 (1)	5 (5;6)
Level of activity			
Recreational	42 (66%)		
Competitive	17 (27%)		
Professional	3 (5%)		
Not disclosed	2 (3%)		

SD = standard deviation; IQR = interquartile range; BMI = body mass index; VISA-A = Victorian Institute of Sports Assessment-Achilles questionnaire

Minimal clinically important difference of the VISA-A score

After 12 weeks, 58% of participants reported improvement of their symptoms (Table 3). The mean improvement (SD) of this subgroup on the VISA-A scale

was 17 (16) points. The Area Under the Curve (AUC) of the ROC curve was 0.762, 95% confidence interval (CI) [0.640;0.884] (Figure 1A). The Youden's Index closest to 1 was 0.451, which corresponded to an improvement of 14 points (95% confidence interval (CI) 3;19) and a 57% sensitivity and 88% specificity. The PPV was 97%.

After 24 weeks, 79% of the participants reported that their symptoms had improved (Table 3). The mean improvement (SD) of this subgroup on the VISA-A scale was 25 (17) points. The AUC was 0.806, [95% CI of 0.669;0.943] (Figure 1B). The Youden's Index closest to 1 was 0.469, corresponding to 7 points (95% CI -10;28) improvement after 24 weeks. The sensitivity was 85.4% and specificity was 61.5%. The PPV was 89.3%.

Table 3. Global assessment score, perception of symptoms and VISA-A score at 12 and 24 weeks after baseline

	Week 12				Week 24			
	N	n(%)	Mean (SD)	Median (IQR)	N	n(%)	Mean (SD)	Median (IQR)
GAS	60		5 (1)	5 (4;6)	61		5 (1)	6 (5;6)
Dichotomized GAS (improved)	60	35 (58%)			61	48 (79%)		
Perception of symptoms (acceptable)	59	21 (36%)			61	31 (51%)		
VISA-A score	61		52 (20)	52 (37;64)	63		60 (22)	58 (41;79)

SD = standard deviation; IQR = interquartile range; GAS = Global Assessment Scale; VISA-A = Victorian Institute of Sports Assessment-Achilles questionnaire

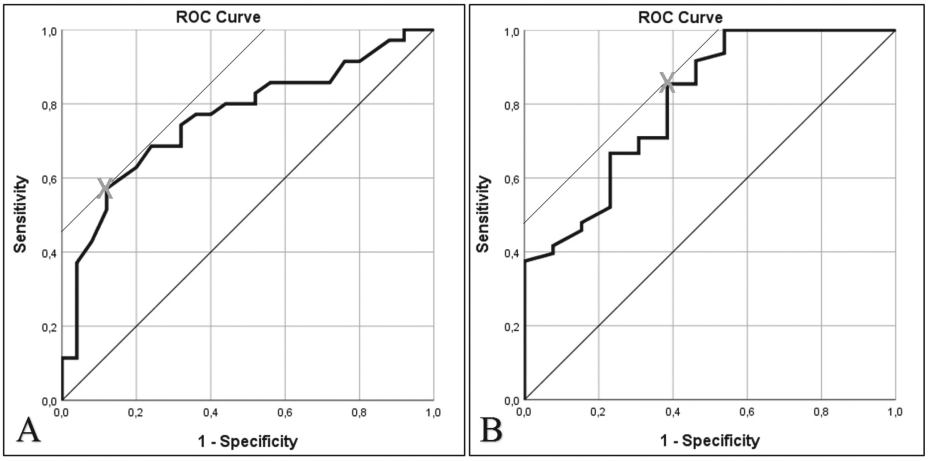

Figure 1. A. Receiver Operating Characteristic (ROC) curve for the Minimal Clinically Important Difference (MCID) per change in VISA-A score after 12 weeks. The ROC curve visualizes the probability distribution that a certain change in Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A score) is deemed as 'improved' by the patient. The point closest to the upper left corner has the most optimal balance between sensitivity and specificity, and is calculated with the Youden's index. B. ROC curve for MCID per change in VISA-A score after 24 weeks.

Patient acceptable symptom state of the VISA-A score

After 12 weeks, 36% of patients deemed their symptoms acceptable (Table 3). The AUC of the ROC curve was 0.852, [95% CI of 0.753;0.950] (Figure 2A). The Youden's Index closest to 1 was 0.589 and corresponded to a VISA-A score of 50 points (95% CI 47;70). The sensitivity was 91% and specificity was 68%. The PPV was 62%.

After 24 weeks, 51% of patients reported that their symptoms were acceptable (Table 3). The AUC was 0.766, [95% CI of 0.648;0.883] (Figure 2B). A Youden's Index of 0.444 was closest to 1 and corresponded to a VISA-A score of 60 points (95% CI 38;80). The sensitivity was 68% and specificity was 77%. The PPV was 75%.

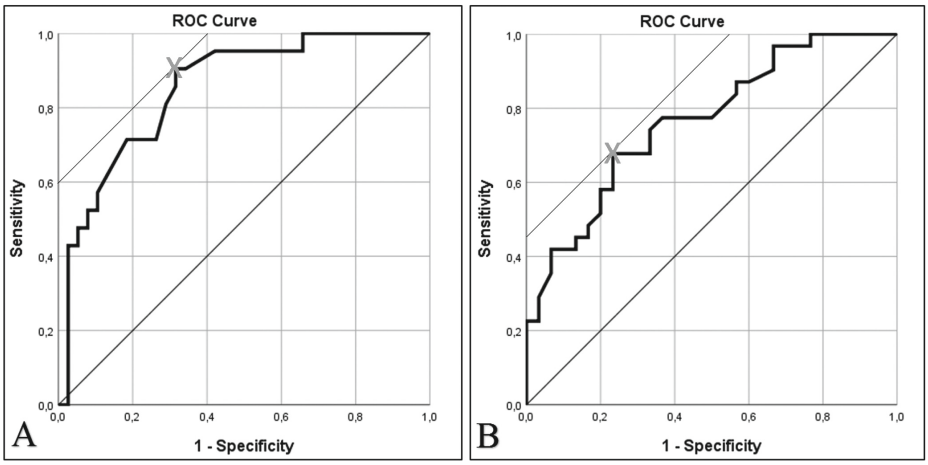

Figure 2. A. Receiver Operating Characteristic (ROC) curve for Patient Acceptable Symptom State (PASS) per Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A score) after 12 weeks. B. ROC curve for PASS per VISA-A score after 24 weeks.

DISCUSSION

The meaningful change of the VISA-A was 14 points over a 12-week period and 7 points over a 24-week period for physically active patients with midportion AT treated with exercise therapy and an injection. Symptoms of AT were perceived as acceptable (PASS) if the VISA-A score was ≥50 points after 12 weeks or ≥60 points after 24 weeks. Active people with Achilles tendinopathy are more likely to experience a meaningful change in their symptoms or perceive their symptoms acceptable if they meet these thresholds. The thresholds can be used by researchers and clinicians as a guide to estimate whether patients with midportion AT will notice improvement after exercise therapy and an injection or perceive their symptoms acceptable after a certain period of time.

While the VISA-A questionnaire is widely used to analyse treatment outcome and progression, anchor-based MCID and PASS had never been determined for VISA-A score for people with midportion AT. This enables comparative effectiveness research with a patient-centred approach. Our findings will guide researchers and clinicians in detecting clinically meaningful changes in AT symptoms qualified using the VISA-A score, rather than focussing on statistically significant differences. However, as both MCID and PASS are influenced by the study population, applied treatment and follow-up time, the outcomes should be interpreted cautiously.

Minimal clinically important difference in VISA-A score

Previous studies suggested that the MCID for the VISA-A score ranges from 6.5 to 20 points.[7-9] McCormack et al.[7] calculated the MCID of the VISA-A score in a small population of 15 patients with insertional AT after 12 weeks. They used a similar anchor-based method as our study, and defined a MCID of 6.5 points[7]. De Vos et al.[8] suggested a MCID of 12 points after 24 weeks in 54 active and sedentary patients with chronic midportion AT who underwent an injection. The MCID was calculated assuming a change of 10-15% on the scale is in general clinically meaningful. Tumilty et al.[9] suggested a MCID of 20 points after 12 weeks in 20 patients with AT, who received low level laser therapy with eccentric exercises. The MCID was calculated using a distribution based method, where MCID was based on 75% of patients achieving this change in VISA-A score or better. Our study included a larger population than McCormack et al. The methods used by De Vos et al. and Tumilty et al. lacks connection with the clinical relevance for the patient.[10] Therefore, our MCID probably best represents clinically meaningful improvement for patients with midportion AT.

There is a large difference in MCID over a 12-week period (14 points) compared to the 24-week period (7 points). As ours is the first study to analyse the MCID over different time periods in the same study population, we cannot compare our findings with the existing literature. One explanation for the large difference in MCID could be recall bias; patients could be remembering their symptoms worse than they were, and subsequently reporting improvement. The confidence interval for both MCID and PASS suggests that there is large variability, possibly caused by heterogeneity in patient characteristics within this sample size. The variability could also be caused by the different sensitivity and specificity of both cut-off points. The effect of difference in sensitivity and specificity on the variability is explained further below. Although we established the MCID based on data from a relatively large, homogenous cohort of patients with clinically diagnosed chronic midportion AT, interpretation should be done with caution.

Patient acceptable symptom state thresholds for VISA-A score

The thresholds for PASS of the VISA-A score were 50 points after a 12-week period and 60 points after a 24-week period. The threshold for acceptable symptoms increases when analysing a longer time period. An explanation could be that patients interpret the question as if the symptoms are 'acceptable at this moment' and not 'acceptable for life', despite our efforts to emphasize the 'for life' part of the question. Both thresholds are relatively low: in order to reach a VISA-A score of 50 or 60 points, the patient is limited in multiple domains (pain in activities of daily living, function and sports activity). It is

possible that patients accept living with negligible pain and a decreased sports activity level. It is important to determine the goals of the patients in order to set the correct targets in research and in a clinical setting.

Sensitivity and specificity

There is currently no gold standard to calculate the MCID and the PASS; the anchor-based method is currently the most accepted method.[10] Sensitivity for MCID represents the ability to correctly detect whether patients with midportion AT who noticed improvement of their symptoms are actually improved. Specificity represents the ability to correctly state that patients did not notice improvement of symptoms. To apply the MCID after 12 weeks of 14 points with a 57% sensitivity and 88% specificity to sports medicine practice: if the VISA-A score increases by 14 points, the clinician or researcher can be 57% sure that patients who notice improvement are truly improved, and 88% sure that they correctly state that patients did not improve their symptoms. Youden's Index balances sensitivity and specificity. However, in some situations it might be more important to identify patients who noticed improvement than to identify patients who did not notice improvement. In a randomized controlled trial that evaluates the efficacy of exercise therapy for AT, patients would probably benefit more from a high sensitivity – low specificity combination, which would correspond to a different MCID and PASS. The anchor-based method in combination with Youden's Index is currently most accepted to calculate MCID and PASS.[10] However, researchers and clinicians must consider that balancing sensitivity and specificity might not be ideal for answering their research or clinical questions.

Strengths and limitations

The most important strength of this study is the relatively large number of included patients, in comparison to other studies.[7-9] Second, we used a Global Assessment Scale with 7 points, which balances adequate discriminative ability, patient preference and reliability.[17] The advantage of using an anchor-based method is the connection between the subjective assessment of the patient and a numerical score.[10] However, anchor-based methods are limited by the choice of the anchor, as it might be susceptible to recall bias.[10] To improve interpretability and reliability, we explicitly mentioned the specific condition (AT) and time point, and used a 7-point scale with written descriptors.[17] By combining prospectively collected data with the anchor-based method, our reported MCID probably most accurately represents the true value of clinically relevant improvement on the VISA-A scale in patients with midportion AT.

We chose to classify the groups using the Global Assessment scale as 'not improved' ('worse than ever' to 'unchanged') and 'improved' ('moderately

improved' to 'completely recovered').[7] When changing the cut-off, we would probably find a different MCID. However, as the MCID represents the *minimal* clinically important difference, we think our dichotomization is accurate and should not be changed to 'stable' ('worse than ever' to 'moderately improved') and 'much improved' ('much improved' to 'completely recovered').

The MCID of both 12 weeks and 24 weeks lies within the standard deviation of the VISA-A score. A change within the standard deviation of a score makes interpretation difficult as the change could be either meaningful or due (lack of) precision of the score. This possible limitation applies to the individual patient, not to sample size calculations on the group level nor does it alter the interpretation of change in VISA-A score between different groups. The cohort participated in a trial where the effect of an injection in addition to exercise therapy was studied. The improvement of 20 points in VISA-A score is comparable to other studies that studied the effect of exercise therapy in patients with midportion AT.[18,19]

Recommendations for future research

Our results can guide sample size calculations when designing trials. The MCID and PASS for the VISA-A score can aid in interpreting study results. However, due to the limitations, specifically the difference in specificity and sensitivity of the cut-offs, calculations and interpretation of the outcome should be done with caution.

CONCLUSION

The MCID for the VISA-A score (0-100) in active patients with midportion AT after exercise therapy plus an injection is a change of at least 14 points over a 12-week period, and at least 7 points over a 24-week period. Patients consider their AT symptoms are acceptable if the VISA-A score is ≥50 points at 12 weeks post-treatment and ≥60 points after 24 weeks.

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6

How many runners with new-onset Achilles tendinopathy develop persisting symptoms? A large prospective cohort study

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ABSTRACT

Background
Achilles tendinopathy (AT) occurs in half of the elite runners. AT is a difficult-to-treat tendon disease, which may progress from new-onset to a chronic state. It is unknown how many runners with new-onset AT develop persisting symptoms and which prognostic factors are associated with this course.

Objective
To describe how many runners develop persisting symptoms 1 year after onset of reactive AT.

Study design
Prospective cohort study.

Methods
Runners registering for a Dutch running event (5-42.2 km) were eligible for inclusion. Runners reporting new-onset AT between registration for the running event and 1 month after received a 1-year follow-up questionnaire. The 1-year follow-up questionnaire inquired about persisting symptoms (yes/no), running activity, and metabolic disorders. We calculated the percentage of runners with persisting symptoms and performed a multivariable logistic regression analysis to study the association between potential prognostic factors and persisting symptoms.

Results
Of 1929 participants, 100 runners (5%) reported new-onset AT. A total of 62 runners (62%) filled in the 1-year follow-up questionnaire. Persisting symptoms were reported by 20 runners (32%). A higher running distance per week before new-onset AT was associated with a lower risk of developing persisting symptoms (odds ratio (OR): 0.9, 95% confidence interval (CI): [0.9;1.0]). There was a positive trend toward an association between metabolic disorders and persisting symptoms (OR: 5.7, 95% CI: [0.9;36.2]).

Conclusion
One third of runners develop persisting symptoms 1 year after new-onset AT. Interestingly, a higher running distance per week before new-onset AT potentially lowers the risk of developing persisting symptoms.

INTRODUCTION

Running grows in popularity due to its health benefits and low costs, and the incidence of running-related injuries is growing simultaneously.[1] While acute sports injuries already rank third place in total healthcare costs,[2] the subgroup of athletes with chronic injuries account for even higher costs due to more medical visits and absence of work.[3,4] One of the most common running injuries is Achilles tendinopathy (AT), with approximately half of elite runners developing AT during their running career.[5] It is therefore important to accurately identify the number of runners that develop persisting symptoms and additionally, to identify prognostic factors for developing persisting symptoms.

The phases of AT are currently considered to be a spectrum ranging from new-onset tendinopathy to degenerative chronic tendinopathy.[6] In new-onset AT, collagen integrity is considered to be normal, with presence of increased cell proliferation.[6] Chronic AT may develop when symptoms persist or recur and is characterized by a loss of well-organized tendon tissue structure.[6] We know that high activity levels and general health are important factors for the development of a chronic tendon disease.[6] In case of general health, metabolic disorders are frequently associated with AT and AT is more prevalent in runners with a worse metabolic profile.[7-9] It is however unknown which percentage of runners with new-onset AT develop persisting symptoms, and which prognostic factors are associated with an increased risk of developing persisting symptoms.

The primary aim of this study was to describe the percentage of runners that develop persisting AT symptoms 1 year after new-onset AT. Our secondary aims were to describe symptom severity in runners 1 year after development of new-onset AT, the course of symptoms, healthcare consumption and running activity, and to identify prognostic factors that are associated with developing persisting symptoms.

METHODS

Design

This prospective cohort study is a 1-year follow-up of runners who were included in the INSPIRE trial (INtervention Study on Prevention of Injuries in Runners at Erasmus MC) and reported new-onset AT. The INSPIRE trial study was approved by the Medical Ethics Committee of the Erasmus MC Rotterdam, the Netherlands (MEC-2016-292) and registered at the Netherlands Trial Registry (NTR number: NL5843). The INSPIRE trial is a randomized controlled

trial that investigated the effect of an online injury prevention program on the number or running-related injuries in runners preparing for a running event.[10] The online prevention program did not decrease the number of running-related injuries, which is why we can consider the included patients as a cohort.[10]

Extensive description of the methods is published by Fokkema et al.[11] Recruitment was from October 2016 until April 2017. Informed consent was obtained from all participants and their rights to privacy were protected. Runners received one baseline questionnaire ≤2 months before and three follow-up questionnaires 2 weeks before, 1 day after and 1 month after a Dutch running event (5-42.2 km). The baseline questionnaire inquired information about age, sex, body mass index (BMI), running experience in years, running distance in the week before baseline questionnaire, runs per week, average hours ran per week in the previous 3 months, average kilometers ran per week in the previous 3 months, and average pace in minute per kilometer in the previous 3 months, amongst others. The follow-up questionnaires inquired whether the runner had developed a running-related injury and on which location.

Prospective follow-up study

For the current study, runners who developed a self-reported new-onset AT between event registration and 1 month after the running event were included. AT was defined as an injury localized in the Achilles tendon caused by running, and one or more of the following criteria had to be met: (1) the injury caused a reduction in running distance, frequency, speed or duration for at least 1 week, (2) the injury led to an appointment with a doctor and/or physiotherapist and (3) medication was used to reduce symptoms.[10] There was no question to distinguish between insertional and midportion AT, as there is yet no validated questionnaire-based approach to make this distinction. An follow-up questionnaire was sent 1 year after the running event to runners who reported new-onset AT. This questionnaire was divided into six sections: (1) current symptoms of AT, (2) symptom severity, (3) healthcare consumption, (4) course of AT symptoms, (5) running activity and (6) presence of metabolic disorders (Figure 1).

Outcome measures

The primary outcome measure was the percentage of runners who reported developing persisting symptoms localized in the Achilles tendon 1 year after development of new-onset AT. Persisting symptoms were expressed in a single question 'Do you still experience symptoms of your Achilles tendinopathy?' (Figure 1).

Current symptoms
Question: Do you still experience symptoms of your Achilles tendinopathy?
1. Yes
2. No

Questionnaire: VISA-A score (Dutch language)

Course of Achilles tendinopathy symptoms
Question: Which image best describes the type of pain of your Achilles tendinopathy symptoms?
1. Gradually decreasing pain
2. Gradually increasing pain
3. Persisting pain with slight fluctuations
4. Persisting pain with pain attacks
5. Pain attacks with pain in between
6. Pain attacks without pain in between

Healthcare consumption
Question: Have you visited a medical professional for treatment of your Achilles tendinopathy in the period of your registry for the running event and now? Multiple answers allowed.
1. No
2. Yes, physiotherapist
3. Yes, general practitioner
4. Yes, medical specialist
5. Yes, other: …

Question: How many times have you visited a medical professional?
In numbers.

Question: Did you undergo one of the following examinations for your Achilles tendinopathy? Multiple answers allowed.
1. Ultrasound
2. X-ray
3. MRI
4. I have not had any imaging performed.

Question: Which treatments were applied to stimulate recovery of your Achilles tendinopathy? Multiple answers allowed.
1. I have not received or performed any treatments.
2. Rest (rest or temporary adjustments in running activities)
3. Exercise (stretching, strengthening exercises)
4. Orthotics (use of adjusted shoes, brace, bandage, insoles)
5. Medication (use of paracetamol, anti-inflammatories like diclofenac, topical agents)
6. Injections (e.g. corticosteroid injections)
7. Passive (sport compression socks, tape, dry needling, massage, ultrasound, shockwave)
8. Surgery (as a treatment for Achilles tendinopathy)

Running activity
Question: Have you adjusted your current running activities?
1. No
2. Yes, due to the Achilles tendinopathy
3. Yes, due to other injuries
4. Yes, due to other reasons.

Question: Which adjustments in running activity have you made because of the Achilles tendinopathy? Multiple answers allowed.
1. Frequency (frequency of training)
2. Duration of running activities
3. Speed during running
4. I have not made any adjustments
5. Other: …

Question: How many hours did you run per week on average in the previous 3 months?
In hours.

Question: How many kilometers did you run per week on average in the previous 3 months?
In kilometers.

Question: What was your average pace in minute per kilometer in the previous 3 months?
In minute per kilometer.

Metabolic disorders
Question: Are you or have you been diagnosed with one of the following disorders? Multiple answers allowed.
Options:
1. High blood pressure (systolic blood pressure of 140 mmHg or higher, and/or diastolic blood pressure of 90 mmHg or higher, and/or use of antihypertensive drugs)
2. Elevated cholesterol (total cholesterol of 6.5 mmol/l or higher, or use of cholesterol lowering medication)
3. Diabetes (fasting blood glucose of 7mmol/l or higher and/or use of blood glucose improving medication)
4. I have not been diagnosed with one or more of the abovementioned diseases.

Figure 1. Six different sections of the follow-up questionnaire with subdivided variables.

Secondary outcome measures were the symptom severity in runners 1 year after development of new-onset AT, expressed in the Victorian Institute of Sports Assessment-Achilles tendinopathy (VISA-A) score, course of AT symptoms, healthcare consumption, running activity, and potential prognostic factors for developing persisting symptoms. Potential prognostic factors were sex, age, body mass index (BMI), running experience in years, running distance per week and previous AT (all reported in the baseline questionnaire before onset of AT), and adjustments in running activity and having a metabolic disorder (both reported in the 1-year follow-up questionnaire, based on the answers on the questions in Figure 1) .

Statistical analysis

To assess possible differences in baseline characteristics of runners with new-onset AT who completed and who did not complete the 1-year follow-up questionnaire, we used an independent sample t-test (normal distribution), Mann-Whitney U test (no normal distribution) or chi-square test (categorical variables). A similar analysis was performed to assess possible differences in baseline characteristics and running activity between runners who reported persisting symptoms and runners who reported recovery. The percentage of runners reporting persisting symptoms was calculated by dividing the number of symptomatic runners by the number of recovered runners. Symptom severity was analyzed using descriptive statistics and expressed as mean VISA-A (standard deviation (SD)). Descriptive statistics were used to report the course of AT symptoms, healthcare consumption, and running activity (as recorded with the questions in Figure 1). Potential prognostic factors for developing persisting symptoms were analyzed using a multivariable binary logistic regression model (ENTER method). Results were presented as odds ratio (OR) with 95% confidence interval (CI).

In all statistical analysis, a p-value<0.05 was deemed significant. SPSS software (V.24.0.0.1; SPSS, Chicago, Illinois, USA) was used for statistical analysis.

RESULTS

A total of 1929 runners were included in the INSPIRE trial and completed at least one of the follow-up questionnaires, and 100 reported new-onset AT (5%). Of these runners with new-onset AT, 62 runners (62%) filled in the 1-year follow-up questionnaire. One runner (1%) did not fully complete the VISA-A questionnaire. Runners who filled in the 1-year follow-up questionnaire were on average 5.2 years older than runners who did not fill in the 1-year follow-up questionnaire. Additionally, runners who completed the 1-year follow-up questionnaire registered more often for a full marathon and less

for half a marathon (Supplementary file 1). Other baseline characteristics were comparable.

Persisting symptoms

In 32% of cases, runners reported having persisting symptoms. Table 1 describes differences in baseline characteristics between runners with persisting AT symptoms and runners that did not have persisting symptoms (recovery group).

Table 1. Baseline characteristics of the runners who reported persisting symptoms or recovery 1 year after new-onset of AT.

	Persisting symptoms		Recovered		p-value
	N	% / mean (SD) / median ; IQR	N	% / mean (SD) / median ; IQR	
N	20		42		
Demographics					
Sex (female)		35%		29%	0.608
Age (years)		49.0 (8.1)		46.2 (10.7)	0.318
Length (cm)		179.5 (9.7)		179.5 (10.3)	0.993
Weight (kg)		77.1 (12.3)		74.5 (12.0)	0.440
BMI (kg/m^2)		23.8 (2.3)		23.0 (2.4)	0.231
Training					
Running experience (years)		4.8 ; 9.5		4.3 ; 7.0	0.928
Running distance per week (km)		13.5 ; 15.0		25.0 ; 25.0	0.033*
Runs per week		2.0 ; 2.0		3.0 ; 1.0	0.052
Event distance					
5 km		-		7%	-
7.5 km		-		-	-
10 km		30%		24%	0.629
21.1 km		25%		17%	0.753
42.2 km		45%		52%	0.831

*Statistically significant difference (p-value<0.05)
SD = Standard deviation; IQR = Interquartile range; BMI = Body mass index

Symptom severity

After 1 year, runners who completed the VISA-A score (61%) had a symptom severity of 85.1 (17.9), expressed in mean VISA-A score (SD). When dichotomizing the VISA-A score with a cut-off of ≥97 points on the VISA-A scale (normal range for healthy runners),[12] 64% of the runners scored <97 points, while 36% of the runners scored ≥97 points. None of the runners who reported persisting symptoms had a VISA-A score of ≥97. Of runners who reported recovery, 52% had a VISA-A score of ≥97.

Course of symptoms

The pain as a consequence of AT was most frequently described as 'gradually decreasing pain'(60%) (Table 2). This description was used by 70% of runners who reported recovery. There was a large variation within the group of runners with persisting symptoms: 30% described their course as 'gradually decreasing pain', followed by 'persisting pain with slight fluctuations'(25%), 'pain attacks without pain in between'(15%), 'pain attacks with pain in between'(15%), 'gradually increasing pain'(10%) and 'persisting pain with pain attacks'(5%).

Healthcare consumption

Over the course of 1 year follow-up, more than half of all runners (56%) visited a medical professional for their AT (Table 2). Runners who visited a medical professional and reported persisting symptoms, had a median (interquartile range, IQR) of 5.0 (9.0) visits, and runners who reported recovery had a median (IQR) of 4.5 (4.0) visits. Most runners visited a physiotherapist (48%, Table 2). Ultrasound was the most frequently reported imaging tool (16%). Almost all runners used some form of treatment, of which relative rest (82%) and exercises (77%) were most popular. Descriptive statistics of applied treatments between runners with persisting symptoms and runners who reported recovery are displayed in Supplementary File 2.

Running activities

After development of new-onset AT, 66% of runners adjusted their running activities during the course of 1 year because of AT symptoms: 53% in frequency, 47% in speed and 45% in duration (Table 2). One year after development of new-onset AT, 23% of runners still had adjusted their running activities because of AT symptoms.

Runners with persisting symptoms decreased the distance ran per week from median (IQR) 20.0km (20.0) at 3 months before baseline to 15.0km (20.0) 3 months before 1-year follow-up (p=0.041). There was no significant change in median (IQR) running hours per week from 3.0hours (2.0) to 2.0hours (2.5) (p=0.100) and there was no significant change in median (IQR) pace

(5.0min/km (1.0) versus 5.5min/km (1.5), p=0.329). Runners who reported recovery decreased their median (IQR) pace significantly from 5.0min/km (1.0) to 6.0min/km (1.3), p=0.030, while hours per week (2.8hours (2.6) versus 3.0hours (2.0), p=0.196) and kilometers per week (20.0km (23.5) versus 20.0km (26.3), p=0.912) did not change significantly. There were no between-group differences in median running hours, kilometers covered or running pace.

Table 2. Course of AT symptoms, healthcare consumption, running activity and presence of metabolic disorders of included runners

	N	Included runners % / mean (SD)
N	62	
Course of AT symptoms		
Gradually decreasing pain	37	60%
Gradually increasing pain	3	5%
Persisting pain with slight fluctuations	9	15%
Persisting pain with pain attacks	1	2%
Pain attacks without pain in between	5	8%
Pain attacks with pain in between	7	11%
Healthcare consumption		
Visit of medical professional (yes)	35	56%
Physiotherapist	30	48%
General practitioner	7	11%
Medical specialist	4	6%
Other[§]	5	8%
Number of visits		5.0 (5.0)
Use of imaging (yes)	10	16%
Ultrasound	10	16%
X-ray	1	2%
MRI	0	-
Treatment applied (yes)	60	97%
Relative rest	51	82%
Exercises	48	77%
Orthotics	18	29%
Medication	18	29%
Passive modalities	30	48%
Injections	0	-

Table 2. Course of AT symptoms, healthcare consumption, running activity and presence of metabolic disorders of included runners (continued)

	N	Included runners % / mean (SD)
Surgery	0	-
Running activity		
Adjustments after onset of AT	41	66%
Frequency	33	53%
Speed	29	47%
Duration	28	45%
Adjustments at 1-year follow-up	14	23%
Metabolic disorder (yes)	11	18%
Hypertension	9	15%
Hypercholesterolemia	6	10%
Diabetes	1	2%

§: osteopath, podiatrist
SD = Standard deviation; AT = Achilles tendinopathy; MRI = Magnetic resonance imaging

Prognostic factors for developing persisting symptoms

A higher running distance per week before onset of AT was associated with a lower risk for developing persisting symptoms (OR 0.9, 95%CI [0.9;1.0]). There was a tendency that having one of the metabolic disorders (OR 5.7, 95%CI [0.9;36.2]) was associated with an increased risk for developing persisting symptoms. There were no significant associations between developing persisting symptoms and other included factors (Table 3).

Table 3. Potential prognostic factors for developing persisting symptoms, analyzed with a multivariable binary logistic regression analysis.

	Persisting symptoms		Recovered		Multivariable analysis
	N	% / mean (SD) / median; IQR	N	% / mean (SD) / median; IQR	OR (95%CI)
	20		42		
Sex (female)		35%		29%	2.8 (0.7;11.5)
Age (years)		49.0 (8.1)		46.2 (10.7)	1.0 (0.9;1.1)
BMI (kg/m²)		23.8 (2.3)		23.0 (2.4)	1.2 (0.9;1.7)
Running experience (years)		4.8 ; 9.5		4.3 ; 7.0	1.0 (1.0;1.1)
Running distance per week (km)		13.5 ; 15.0		25.0 ; 25.0	0.9 (0.9;1.0)*
Previous AT (yes)		40%		24%	2.6 (0.6;11.2)
Adjusted running activity (yes) §		70%		64%	0.8 (0.2;3.1)
Any metabolic disorder (yes) ¶		30%		12%	5.7 (0.9;36.2)

*Statistical significant difference (p-value<0.05)
§: adjusted running activity after development of new-onset AT.
¶: included metabolic disorders are hypertension, hypercholesterolemia and diabetes.
SD = Standard deviation; IQR = Interquartile range; OR = Odds ratio; BMI: Body mass index; AT: Achilles tendinopathy; CI: Confidence interval

DISCUSSION

This is the first study to report how many runners develop persisting symptoms at 1 year after new-onset AT. One third of runners reported persisting symptoms 1 year after new-onset AT. One quarter still adjusted their running activities one year after developing new-onset AT because of persisting AT symptoms. In runners that developed AT, a higher running distance per week before onset of AT was associated with a lower risk of developing persisting symptoms. Furthermore, we found a positive trend towards an association between having a metabolic disorder and developing persisting symptoms.

Persisting symptoms

Johannsen et al.[13] reported that 37% of patients with chronic AT experience some degree of pain and reduced function after 10 years follow-up, which is a similar to the 32% of self-reported persisting symptoms in our study.

Noticable is the small difference in persisting symptoms between our 1-year follow-up study and this 10-year follow-up study.[13] Other studies reported approximately 35-60% of patients with chronic AT having persisting symptoms after a follow-up of 5 years or longer.[4,14,15] The difference can be explained by the heterogeneity of the studies, as there were differences in the definition of recovery (self-reported recovery[13-15] versus pain free[4]), type of AT (insertional, mid-portion[4,15] or a mix[13,14]), duration of AT (chronic AT versus[4,14] a mix of new-onset and chronic AT[13,15]), and researched population (active patients[4,14] versus a mix of active and sedentary patients[13,15]). Nevertheless, all studies, including ours, reported a relatively large subgroup of patients with persisting symptoms. There is a need to better identify the characteristics of this specific subgroup with persisting symptoms at an early stage.

The percentage of self-reported persisting symptoms (32%) was lower than the percentage with persisting symptoms according to the dichotomized VISA-A score (64%). This difference might be explained by the acceptance of limitations by the patient: the patient experiences no AT symptoms due to, for example, decreased sports activity. Therefore, patients might not report persisting symptoms due to acceptance of limitations, while the patient has not fully recovered to the pre-injury sports activity. For adequate expectation management, it is important to inform runners with new-onset AT that their symptoms might cause long-lasting adjustments in sports activity.

Symptom severity

Symptom severity can be expressed with the validated VISA-A score (0-100 points, with 100 points representing full recovery). Patients reported a mean and SD of 85.1 (17.9) at 1 year after sustaining new-onset AT. We are the first to report symptom severity 1 year after development of new-onset AT. The patient acceptable symptom state (PASS), a value that represents the level of acceptable symptoms for the patient, is not yet determined for the VISA-A score.[16] It is currently unknown how to interpret the symptom severity in relation to the patients' experience of the symptoms. Determining the PASS for the VISA-A score will help future studies to interpret whether the symptom severity will be deemed acceptable by the patient. The high variability of this outcome in this homogenous population also suggests that a subgroup of patients with persisting severe symptoms is present.

Course of symptoms

The course of AT symptoms was by both runners with persisting symptoms and runners who reported recovery most frequently described as 'gradually decreasing pain'. However, the course of AT symptoms in runners with

persisting symptoms was more heterogeneous, and runners chose more frequently descriptions that included the word 'fluctuations' or 'pain attacks'.

In a clinical setting, runners can be informed that the course of symptoms after onset of AT is gradually decreasing in most cases. However, in case of recurring fluctuations or pain attacks, it could be helpful to seek medical advice.

Healthcare consumption

The majority of patients consulted a healthcare professional with a mean of almost 4 visits per patient. Almost all patients decided to apply some form of treatment. Use of treatment could influence the risk of developing persisting symptoms 1 year after new-onset AT. We think it is important to point out that we chose not include this variable in the multivariable analysis, as almost all runners used any form of treatment. This would severely influence the outcome of the analysis. Furthermore, a randomized study design is necessary for analyzing treatment effect on developing persisting symptoms.

Running activities

One in four runners adjusted their running activities at 1 year after development of new-onset AT because of AT symptoms. Runners with persisting symptoms decreased the distance ran per week by 5 km, while runners who reported recovery slowed down their pace by 1 min/km. The slower pace in runners who reported recovery fits the previously mentioned hypothesis why the percentage of self-reported recovery is higher than recovery according to the dichotomized VISA-A score. Runners presumably deem themselves recovered, while they have not returned to their pre-injury level of sports. Although AT occurs frequently in active persons, there are no other studies describing adjustments in (running) activity because of AT symptoms.

Prognostic factors for developing persisting symptoms

We analyzed a number of potential prognostic factors for development of persisting symptoms 1 year after new-onset of AT. Surprisingly, a higher running distance per week, reported before onset of AT, was associated with a lower risk of developing persisting symptoms. Although this result is difficult to explain, we propose two plausible hypotheses. First, runners with high training loads might have had a more constant training loads than the runners with low training load. This high variability in training load leads to 'spikes' in training load and theoretically this can be a prognostic factor for persisting symptoms.[17] We did, however, not record changes in training load. A second hypothesis is that we only found an association due to the relatively low number of runners with AT. It is interesting to study whether there is a

subgroup with a different training behavior over time that is more susceptible to develop persisting symptoms.

There was a tendency towards an association between having a metabolic disorder and developing persisting symptoms. We selected metabolic disorders (hypertension, hypercholesterolemia and diabetes) that were associated with AT in previous literature.[7,9,18] We noticed a similar tendency for BMI, which is part of the metabolic syndrome, although the clinical relevance of BMI was less striking (mean difference of 0.8 kg/m^2). Metabolic disorders influence the tendon via different mechanisms, which can lead to matrix destruction due to systemic inflammation and hypoxia.[19,20] As inflammation is part of many metabolic disorders,[7] it could maintain the chronic state of the tendinopathy and prevents proper healing. Tendinopathy could prevent patients from exercising and worsen the metabolic state.[21] This could eventually form a vicious circle: patient starts exercising to improve their metabolic state, the metabolic disorder leads to AT, which hampers mobility and the metabolic state is not improved or even worsens.[7]

Strengths and limitations

A major strength of our study is the number of included cases, which increases the likelihood to identify prognostic factors for the course of AT. As we report more than 50 cases, we were able to detect moderate to strong associations.[22] A limitation of this study is using online questionnaires to inquire about injuries. A strict injury definition, reported in the original publication by Fokkema et al.[10] was used to prevent contamination of the data by injuries that were not actually injuries. As distinguishing between insertional and midportion AT trough an online questionnaire has not been validated, we chose not to collect and present this information. We therefore do not know the difference in prognosis between these two entities. Another limitation was the response rate of 62%. The responding group consisted of slightly older runners and registered more often for a full marathon, which makes the results of this study more appropriate for slightly older marathon runners. Another possible limitation is recall bias, especially for presence of metabolic disorder. As metabolic disorders develop over a longer period of time, we assume that they were already present at baseline. However, we did not perform physical examination or blood tests. It could be that runners have had an underlying metabolic disorder, but were not diagnosed. This potential bias is possibly existent in both the recovered and non-recovered group.

Recommendation for future research

Our study shows an interesting association between running distance per week and persisting symptoms. It is currently unclear how the runners

exactly adjusted their running activities. Global Positioning System (GPS)-data is often used by runners to evaluate personal progress and it offers a valid alternative to subjective reporting.[23] It would be interesting to analyses association between running distance per week, analyzed with GPS-data, and development of persisting symptoms in runners 1 year after new-onset AT, in order to identify optimal training load adjustments for this patient group.

A tendency towards an interesting association between metabolic disorders and persisting symptoms was also identified. As runners could have undiagnosed metabolic disorders, we propose to perform a large prospective follow-up study with use of objective outcome measures representing metabolic disorder.

CONCLUSION

One third of runners develop persisting symptoms 1 year after new-onset AT. One year after developing new-onset AT, one quarter of runners still had adjusted their running activities because of AT symptoms. A higher running distance per week, reported before new-onset AT, was associated with a lower risk of developing persisting symptoms. There was a positive trend towards an association between metabolic disorders and developing persisting symptoms. Future research is needed for in-depth analysis of the association between external and internal prognostic factors and the development of persisting symptoms.

Perspective

One third of runners develop persisting symptoms 1 year after new-onset Achilles tendinopathy and one quarter of runners still had to adjust their running activities due to symptoms. We identified that a higher running distance per week before developing new-onset AT is associated with a lower risk of developing persisting symptoms. By describing the course of symptoms and the effect on running activities, this study supports the clinician in providing evidence-based information to the patient and forming adequate expectations.

Acknowledgements

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SUPPLEMENTARY FILE(S)

Supplementary file 1. Baseline characteristics of the runners who filled in and who did not fill in the 1-year follow-up questionnaire.

	Did not fill in follow-up questionnaire		Filled in follow-up questionnaire		p-value
	N	%/ mean (SD) / median ; IQR	N	%/ mean (SD) / median ; IQR	
N	38	38%	62	62%	
Demographics					
Sex (female)		39%		31%	0.366
Age (years)		41.9 (10.5)		47.1 (10.0)	0.014*
Length (cm)		178.9 (7.5)		179.5 (10.0)	0.755
Weight (kg)		78.6 (15.5)		75.3 (12.0)	0.239
BMI (kg/m²)		24.5 (4.4)		23.3 (2.4)	0.117
Training					
Running experience (years)		4.8 ; 6.9		4.5 ; 7.1	0.449
Running distance per week (km)		20.5 ; 23.3		20.0 ; 20.0	0.548
Runs per week		2.5 ; 1.0		2.0 ; 2.0	0.287
Event distance					
5 km		5%		5%	0.925
7.5 km		-		-	-
10 km		37%		26%	0.242
21.1 km		47%		19%	0.003*
42.2 km		11%		50%	<0.001*

*Statistically significant difference (p-value<0.05)
SD = standard deviation
IQR = interquartile range
BMI = body mass index

Supplementary file 2. Use of different treatment modalities by runners who reported persisting symptoms and who reported recovery.

	Persisting symptoms		Recovered	
	N	%	N	%
N	20		42	
Relative rest		75%		86%
Exercise therapy		90%		71%
Orthotics		25%		31%
Medication		30%		29%
Passive modalities		65%		40%
Injections [§]		-		-
Surgery [§]		-		-

[§]: both injections and surgery were not reported as a treatment by the included runners.

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7

Are pain coping strategies and neuropathic pain associated with a worse outcome after conservative treatment for Achilles tendinopathy? A prospective cohort study

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ABSTRACT

Objectives
To analyse whether 1) passive or active pain coping strategies and 2) presence of neuropathic pain component influences the change of Achilles tendinopathy (AT) symptoms over a course of 24 weeks in conservatively-treated patients.

Design
Prospective cohort study.

Methods
Patients with clinically-diagnosed chronic midportion AT were conservatively treated. At baseline, the Pain Coping Inventory (PCI) was used to determine scores of coping, which consisted of two domains, active and passive (score ranging from 0-1; the higher, the more active or passive). Presence of neuropathic pain (PainDETECT questionnaire, -1 to 38 points) was categorized as (a)unlikely (≤12 points), (b)unclear (13-18 points) and (c)likely (≥19 points). The symptom severity was determined with the validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire (0-100) at baseline, 6, 12 and 24 weeks. We analysed the correlation between 1)PCI and 2)PainDETECT baseline scores with change in VISA-A score using an adjusted Generalized Estimating Equations model.

Results
Of 80 included patients, 76 (95%) completed the 24-weeks follow-up. The mean VISA-A score (standard deviation) increased from 43 (16) points at baseline to 63 (23) points at 24 weeks. Patients had a mean (standard deviation) active coping score of 0.53 (0.13) and a passive score of 0.43 (0.10). Twelve patients (15%) had a likely neuropathic pain component. Active and passive coping mechanisms and presence of neuropathic pain did not influence the change in AT symptoms ($p=0.459$, $p=0.478$ and $p=0.420$, respectively).

Conclusions
Contrary to widespread belief, coping strategy and presence of neuropathic pain are not associated with a worse clinical outcome in this homogeneous group of patients with clinically diagnosed AT.

Trial registration number
Clinical Trials (Identifier: NCT02996409).

INTRODUCTION

Pain is a pesky and often persistent symptom of Achilles tendinopathy (AT), with swelling and impaired performance completing the triad of AT symptoms.[1] Despite best available management consisting of exercise therapy, 23-60% of patients remain symptomatic 5-10 years after diagnosis and treatment of AT.[2-4] Coping strategies and a neuropathic pain component might influence the course of AT symptoms. Therefore, coping strategies and assessing the type of pain might be relevant features in treating patients with longstanding AT.

Pain coping is defined as cognitive and behavioural attempts to manage or tolerate pain and its effects.[5] It can be classified into an active and a passive coping strategy. Active coping consists of the patient's attempt to control the pain or to function in spite of the pain, for example 'I distract myself by undertaking a physical activity'. Active coping could influence AT symptoms as patients could overload their tendon due to distraction from the pain; however, this has not been researched yet. Passive coping consists of helplessness and strategies that externalize pain control to other resources, for example 'I do not exert myself physically'.[6] Systematic reviews of musculoskeletal conditions associated with chronic pain, such as osteoarthritis, fibromyalgia and rheumatoid arthritis, demonstrate that a passive coping mechanism may be associated with increased pain and disability.[7, 8] As AT is also associated with chronic pain, its course could be influenced by the type of coping strategy.

Neuropathic pain might also play a role in the chronicity of AT symptoms.[9-12] Neuropathic pain can consist of both peripheral and central sensitization. Peripheral sensitization is an increased responsiveness and reduced threshold to afferent nerve stimuli.[9, 13] After an injury or cell damage to the area, an unrealistic flare response is created after release of many neuropeptides by nociceptors.[14, 15] Central sensitization is similar, with an increased responsiveness in the central nervous system, which is associated with a low pain threshold.[13] Sensitivity of pain transmission neurons is increased for various peripheral stimuli, including mechanical pressure.[12, 16] There appears to be an association between neuropathic pain and chronic tendinopathies,[10, 12] however, this has not been researched in AT.

Evaluating and recognizing specific pain coping strategies and specific subtypes of pain may have important clinical implications for treatment of patients with AT. Identification of patient subgroups with altered pain coping strategy or neuropathic pain components that do not respond to regular treatments would impact on clinical decision-making. However, until now it

is unknown whether these subgroups are present in an AT population and whether these subgroups have altered outcomes after conservative treatment.

We conducted this study with the primary aim to analyse whether the level of active coping strategy influences change of AT symptoms over a course of 24 weeks. We also analysed the level of passive coping strategy and its influence on AT symptoms over a course of 24 weeks. We hypothesized that a more active coping strategy would have a positive influence on the change of AT symptoms over the course of 24 weeks, as the treatment of AT stimulates the use of the active domains distraction and transformation. Our secondary aims were to analyse the influence of (1) the difference between an active and passive coping strategy on the course of AT symptoms; (2) the presence of a neuropathic pain component on the severity of AT symptoms at baseline, 6, 12 and 24 weeks; and (3) the influence of a neuropathic pain component on the course of AT symptoms over 24 weeks. We hypothesized that a larger discrepancy between an active and passive coping strategy had a positive influence on the course on AT symptoms. We also hypothesized that the presence of a neuropathic pain component increased the severity of AT symptoms and that it flattened the course of AT symptoms over 24 weeks.

METHODS

This study is part of a randomized clinical trial, the High-volume image-guided injections in chronic midportion Achilles Tendinopathy (HAT).[17] The RCT was approved by the Medical Research Ethics Committee Southwest Holland, Leiden, the Netherlands (MEC-14-100). Extensive description of the materials and methods are registered at clinicaltrials.gov (identifier: NCT02996409).

The HAT study evaluated the effect of high-volume image guided injection compared to a placebo injection in addition to eccentric exercises in patients with chronic midportion AT.[17] Written informed consent was acquired from all patients before inclusion. Patients were recruited in a large district hospital (Haaglanden Medical Center, The Hague, the Netherlands) between December 2016 and January 2019. Patients were examined by a sports physician, and had to comply to the following inclusion criteria: (1) 18-70 years old, (2) painful swelling of the Achilles tendon, 2-7 cm proximal of the calcaneal insertion, (3) symptoms for more than 2 months, (4) non-responsive to a minimum of 6-weeks of exercise therapy and (5) neovascularisations on Power Doppler Ultrasonography. Main exclusion criteria were clinical suspicion of Achilles tendon rupture, clinical suspicion of insertional tendinopathy and inability to participate in an active exercise program.

For the randomized clinical trial, patients were randomized into either intervention group (high-volume injection) or placebo group (low-volume image-guided injection). An independent secretary of the trial performed the randomization, which consisted of using a computer-generated randomization list using blocks, varying from 4-10 patients. A sports medicine physician administered the intervention, which consisted of a 50cc (40cc 0.9% sodium chloride and 10cc 1% lidocaine solution) injection in the peritendinous area were most Doppler flow was seen. The placebo group was injected using the same procedure with a 2cc solution (1.6cc 0.9% sodium chloride and 0.4 cc 1% lidocaine solution). Patients were blinded for the allocated treatment. After injection, both groups performed a progressive exercise training program for 6 to 24 weeks instructed by a blinded outcome assessor, depending on their personal goals and progress. As there were no between-group differences in patient-reported outcomes and patients were not able to predict whether they received the intervention or placebo treatment, we considered the included patients as a cohort. Length of follow-up was similar in both groups.

Patients filled in a baseline questionnaire, inquiring age, sex, duration of symptoms, sports participation and ankle activity score. The ankle activity score is a scoring system which ranks the patients activity level and ankle loading by their level and type of (sports) activity.[18] An ankle activity score of 4 or higher ranges from physical work and power lifting to competitive basketball.[18]

The outcome measures in this study were the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, the Pain Coping Inventory (PCI) and painDETECT questionnaire. The VISA-A questionnaire was completed at baseline, 6, 12, and 24 weeks, and the PCI and painDETECT were completed only at baseline. We used the VISA-A score as primary outcome measure, which is a reliable questionnaire to determine the severity of AT symptoms (both pain and activity level) and it has been validated in Dutch language.[19, 20] The patients completed the patients completed the Pain Coping Inventory (PCI) and painDETECT questionnaire were secondary outcome measures.[5, 21] The PCI is a validated questionnaire to determine the level of active and passive coping.[5] Patients were asked to rate 33 items on a 4-point Likert scale ranging from 1 (hardly ever) to 4 (very often). These items were used to calculate the score of their corresponding domains. The domains transformation, distraction and reducing demands formed the score for active coping; the passive coping score was formed by retreating, worrying and resting. The sum of the domains were added up and divided by the maximum score. Both active and passive coping have a score ranging from 0 to 1, where a score closest to 1 represents a high level of active or passive coping. The

painDETECT questionnaire is a validated tool to detect neuropathic pain components and has a maximum possible score of 38 points.[21, 22] The scores were divided in three categories: 1. ≤12 points, neuropathic pain component is unlikely (<15%), 2. 13-18 points, unclear result, and 3. ≥19 points, neuropathic pain component is likely (>90%).[21]

We used the Shapiro Wilk test to determine normality of the data, where we assumed a normal distribution when p>0.05. Normally distributed data were expressed as mean (standard deviation), and non-normally distributed data as median (interquartile range, IQR). To determine the association between active coping and the course of AT symptoms, expressed by the VISA-A score and measured at baseline, 6, 12 and 24 weeks, a Generalized Estimating Equation (GEE) model was used. To determine whether the course of AT symptoms was associated to the level of active coping, we added the interaction term active coping*time point. We adjusted for the predefined variables age, sex, body mass index (BMI), duration of symptoms at baseline in weeks and level of sports activity, measured with the ankle activity score.[18] This GEE model was also used to determine the association between the following variables and the course of AT symptoms: passive coping, neuropathic pain component and the difference between active and passive coping score. The difference between an active and passive coping score was calculated by the active score minus the passive score. Associations were considered significant if p<0.05. As reported in the study protocol, imputation was needed if the sensitivity analysis reported ≥ 5% missing data of the primary outcome.[17] We used SPSS software (V.24.0.0.1; SPSS, Chicago, Illinois, USA) for statistical analysis.

RESULTS

A total of 185 patients were screened for eligibility, of which 80 were included (Supplementary file 1). Included patients had a median age of 50 (interquartile range (IQR): 44;54) years, with equal sex distribution (51% female), had a median body mass index of 25.7 (IQR 24.0;30.1) kg/m^2, and 80% were physically active (ankle activity score of 4 or higher). The baseline characteristics are presented in Table 1. Only 1 patient (1%) was lost to follow-up at 24 weeks. The mean (standard deviation – SD) VISA-A score gradually increased from 43 (16) points at baseline to 63 (23) points at 24 weeks, with no difference between intervention groups.[17] The mean (SD) score for active coping was 0.53 (0.13) and 0.43 (0.10) for passive coping. A neuropathic pain component was likely in 12 patients (15%).

Table 1. Baseline characteristics.

	Included patients *N* (%)/mean (SD)/median (IQR)
N	80
Age (years)a	50.0 (44;54)
Sex (% male)	39 (49%)
BMI (kg/m^2)a	25.7 (24.0;30.1)
Duration of symptoms (weeks)[a]	63 (40;128)
Ankle activity score (0–10)[a]	5 (5;6)
Participation in sports activity	64 (80%)
Active coping score (0–1)	0.53 (0.13)
Transformation	2.1 (0.7)
Distraction	1.9 (0.6)
Reducing demands	2.3 (0.7)
Passive coping score (0–1)	0.43 (0.10)
Retreating	1.3 (0.4)
Worrying	1.8 (0.5)
Resting	2.0 (0.6)
PainDETECT (0–35):	
1. Neuropathic pain component unlikely (≤12)	34 (43%)
Unclear result (13–18)	34 (43%)
Neuropathic pain component likely (≥19)	12 (15%)
VISA-A (0–100) at baseline	43 (16)

SD: standard deviation. IQR: interquartile range. BMI: body mass index. VISA-A: Victorian Institute of Sports Assessment-Achilles questionnaire.
a: Non-normal distributed data, expressed in median (IQR

The interaction term active coping*time point was not statistically significantly (p=0.459), with a beta (95% wald confidence interval) at baseline of 19 (-12;50), 6 weeks of 20 (-7;47), and 12 weeks of 12 (-10;34). Similarly, the interaction term passive coping * time point was not statically significant (p=0.478, with a beta (95% wald confidence interval) at baseline of -18 (-58;21), at 6 weeks of 16 (-17;49), and at 12 weeks of 1 (-26;28). This means that both active and passive coping were not associated with the course of AT symptoms over

24 weeks, as change in VISA-A score over time does not depend on level of coping (Figure 1).

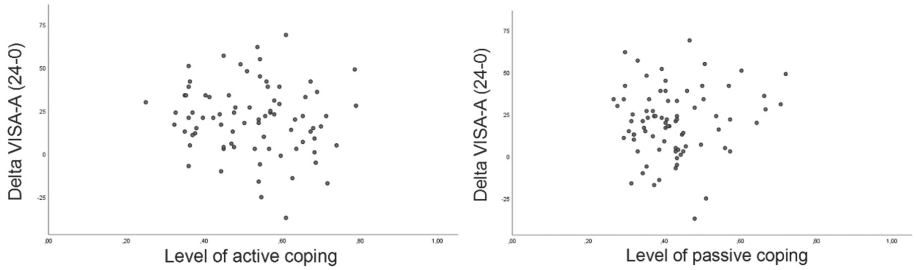

Figure 1. A) The influence of the level of active coping strategy on the change in VISA-A score at 24 weeks. B) The influence of the level of passive coping strategy on the change in VISA-A score at 24 weeks

When analyzing the difference between active and passive coping score, the interaction terms active-passive coping*time point was not statistically significant (p=0.158). This means that we found no association between the course of AT symptoms over 24 weeks and the difference in level of active and passive coping.

There was a difference in severity of AT symptoms, measured with the VISA-A score, between the 3 categories of the painDETECT score at baseline (p<0.001), 6 (p=0.002), 12 (p<0.001) and 24 weeks (p=0.011)(Figure 2). While the difference in severity of AT symptoms can be explained by the presence of a neuropathic pain component, it is also influenced by two other variables: a longer duration of symptoms negatively influenced the severity of AT symptoms (p=0.032), while a higher ankle activity score had a positive influence on the severity of AT symptoms (p=0.001). The interaction term neuropathic pain category*time point was not statistically significant (p=0.420), indicating that there was no association between likeliness of a neuropathic pain component and the course of AT symptoms over 24 weeks (Figure 2).

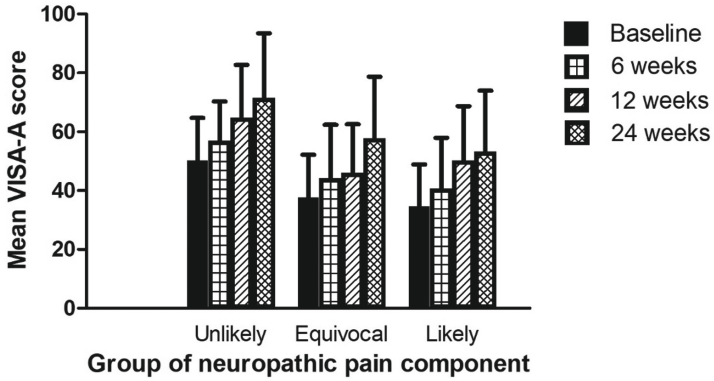

Figure 2. The mean VISA-A score per time point divided by the three subcategories of the painDETECT score. Error bars denote standard deviations.

DISCUSSION

This is the first study to analyse the association between pain coping strategy, presence of a neuropathic pain component and the course of AT symptoms. Contrary to widespread belief, we found no association between level of active or passive coping and the course of AT symptoms. Although patients with a neuropathic pain component had more severe AT symptoms at every time point, the course of AT symptoms was similar between patients with an unlikely, unclear and likely neuropathic pain component.

Degenerative joint diseases (e.g. osteoarthritis) and tendinopathy have multiple similarities: the main feature in both pathologies is extracellular matrix degeneration, they both respond well to mechanotherapy and they have similar risk factors.[23] Osteoarthritis and tendinopathy are both associated with a chronic pain component.[23] In osteoarthritis, a higher level of passive coping leads to more chronic pain.[7, 8, 24] Due to the similarities between osteoarthritis and tendinopathy, we wondered if passive coping is also associated with more severe symptoms in AT. Patients with AT had a similar score in all subscales of the passive coping score (AT versus osteoarthritis patients: retreating 2.1 versus 1.7, worrying 1.8 versus 2.0 and resting 2.0 versus 2.5).[24] We found no association between severity of AT symptoms and level of passive coping strategy. Rest of the Achilles tendon will result in an immediate decrease of pain, but it will also decrease the load tolerance.[25] Furthermore, a previous study proved no difference in outcome between patients who were treated with relative rest and patients who continued tendon-loading activities.[26] This might explain why a passive coping strategy is not beneficial, but also not detrimental, for patients with AT.

The level of active coping was also not associated with the course of AT symptoms. Although an active coping strategy was hypothesized to be beneficial,[5] results of multiple studies in osteoarthritis patients showed no conclusive results.[7, 24] Patients with AT had similar scores in subscales of active coping score as patients with osteoarthritis: transformation 2.1 versus 1.9, distraction 1.9 versus 1.9 and reducing demands 2.3 versus 2.6.[24] In patients with AT, there is a delicate balance between underloading and overloading of a recovering tendon.[27] There might be two subgroups of patients within the group with a high level of active coping: a group of patients that uses the coping strategies transformation and distraction to function in daily life and to rehabilitate, and a group of patients who use these coping strategies to continue their activities on their previous level, which may lead to overloading of the tendon and therefore might hamper recovery. This is supported by Smith et al.[28], who researched coping in patients with rheumatoid arthritis and found that active coping strategies are more context sensitive: they suggest that active coping might be harmful as patients ignore pain signals.[28] An active coping strategy might be beneficial when it facilitates adequate rehabilitation, but disadvantageous when patients continue to overuse their tendon. These delicate differences within the active coping strategy are unfortunately not detected by the PCI questionnaire.

The general hypothesis is that patients with a neuropathic pain component have abnormal pain processing, which causes an abnormal response to regular stimuli.[10-12, 29] We confirmed that patients with a neuropathic pain component started and ended a conservative treatment program with more severe AT symptoms than patients without a neuropathic pain component. One other study evaluated the prevalence of a neuropathic pain component with the painDETECT questionnaire in patients with tendinopathies, amongst which insertional (n=36) and midportion AT (n=31).[29] They found a prevalence of neuropathic pain in 28% of patients with insertional AT and 26% of patients with midportion AT, but neuropathic pain was not associated with a worse outcome.[29] Interestingly, we also found that all three groups (unlikely, unclear and likely neuropathic component) had a similar improvement in symptom severity at every time point. One explanation might be that patients with a neuropathic pain component respond similar to conservative treatment of AT as patients without a neuropathic pain component. However, as the neuropathic pain component is still present and untreated, they experience more severe symptoms.[30] As the treatment of neuropathic pain is centred around pharmacological intervention and non-pharmacological treatments like cognitive behavioural therapy,[30] addition of these therapies might be beneficial to patients with a high likeliness of having a neuropathic pain component.

This study has several strengths, which ensures the integrity of this data. First, this study is based on the robust study protocol of a pre-registered randomized clinical trial.[17] Second, our data was prospectively collected and corrected for baseline characteristics, which limits the influence of bias. Third, this study had a very low lost to follow-up rate, which ensures that the data was not biased by non-responders. Last, we used valid outcome measures which increases the reliability of our data and the validity of our conclusions.

A limitation of this study is the interpretation of active and passive pain coping strategy. There are no known thresholds to indicate that a patient has a 'high' active pain coping strategy. The ability to dichotomize the data would make it easier to analyse whether absence or presence of an active pain coping strategy influences the severity of AT symptoms. Another possible limitation could be that the pain coping questionnaire has not yet been validated for patients with (Achilles) tendinopathy. Although it has been validated for other musculoskeletal conditions with a chronic pain component, it can be possible that the pain coping questionnaire does not cover the complexity (e.g. coping strategy in patients with warm-up phenomenon versus increasing pain during sports activities) of Achilles tendinopathy. Furthermore, the fact that neuropathic pain is a clinical diagnosis and we did not physically examine patients on presence of neuropathic pain could also be a limitation.[30] While the painDETECT score is proven to be a valid and reliable tool to screen for neuropathic pain, it has not been validated in patients with AT and it is not a substitute for its diagnosis.[21] As the use of a questionnaire as screening tool for sports medicine healthcare providers is more feasible, we think that this choice has better practical implications. Another limitation might be that patients might adopt a different coping strategy when being treated with an intervention. Last limitation is that all patients received a painful injection at baseline, after completing the baseline questionnaires. This intervention might have had influence on the pain perception and consequently it could affect these study results. Last, it might be possible that we failed to detect an association while there might be a true association (type I error) due to an insufficient sample size. Selection bias might be another reason why we failed to find an association. One of the diagnostic criteria for AT is localized pain with pain on local palpation, which is opposing to the criteria for neuropathic pain (which includes widespread pain).

A subgroup of AT patients has a higher likelihood of having a neuropathic pain component. As these patients ended with more severe AT symptoms after conservative treatment, it might be interesting to treat this subgroup of patients for their neuropathic pain component in a future trial.[30] A randomized clinical trial is needed to analyse whether standard neuropathic pain treatment

in addition to AT treatment has a more beneficial effect on symptoms in this specific subgroup. Furthermore, it would be interesting to analyse whether coping strategy changes over time. This could be analysed by calculating the Pain Coping Inventory at baseline and after delivery of patient education.

CONCLUSION

The course of AT symptoms after conservative treatment is not altered by the employment of a more active or more passive coping strategy in patients who received exercise therapy and an injection. We were able to identify a subgroup of patients with a neuropathic pain component having more severe AT symptoms before and after conservative treatment. However, the presence of a neuropathic pain component does not influence the course of AT symptoms in patients with the clinical diagnosis, which includes having localized pain.. Future intervention trials might focus on this subgroup with the aim to further improve patient-reported outcomes.

Acknowledgements
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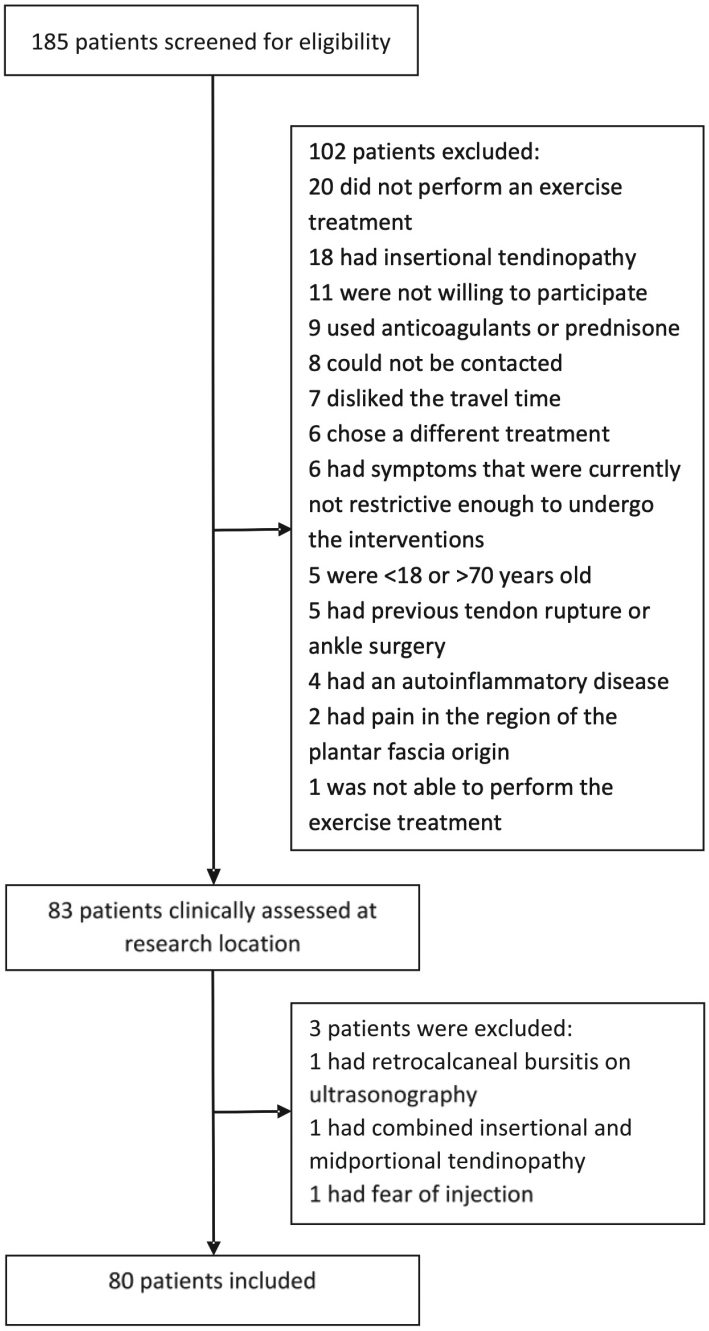
SUPPLEMENTARY FILE(S)



Supplementary file 1. Flow chart of patients.

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8

One fifth of patients with Achilles tendinopathy have persisting symptoms after 10 years: a prospective cohort study

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ABSTRACT

Patients with midportion Achilles tendinopathy (AT) are thought to experience a gradual symptomatic improvement over time. The aim of this study was to prospectively investigate if patients with chronic midportion AT have symptoms at 10-year follow-up. Patients with chronic midportion AT were invited to complete an online questionnaire 10 years after inclusion in an intervention trial. The primary outcome was the presence of AT symptoms. Secondary outcomes were: symptom severity, expressed with the Victorian Institute of Sports Assessment-Achilles tendinopathy (VISA-A, 0-100) score and sports activity level. Of the 54 patients included, 43 (80%) completed the questionnaire at an average follow-up of 10.4 years. Persisting symptoms were reported by 19%. The symptom severity expressed as mean (standard deviation-SD) VISA-A score improved from 52(17) at baseline to 80(17) at 10-years follow-up with a mean change of 28 (24, 95%confidence interval: 21;35, $p<0.001$). Of the 38 active patients, 16 (42%) returned to their pre-injury level sports, of whom 14 (37%) performed these at their pre-injury level without pain. One fifth of patients with conservatively treated chronic midportion AT still have symptoms after 10 years. One third of patients were able to perform sports pain-free at their pre-injury level. Patients should be adequately counselled to give realistic expectations.

Trial registration number

Clinicaltrials.gov (identifier: NCT00761423).

INTRODUCTION

We often refer to long-standing Achilles tendinopathy (AT) as being chronic, yet we know little about the actual chronicity of symptoms on the long term. Symptoms normally improve quickly during the first year of treatment, but recovery is usually only partial.[1-3] After 1 year there seems to be a relative stagnation in improvement.[4-6] It seems that a subgroup of patients experience persisting symptoms.

Other follow-up studies of AT have heterogeneous study designs, populations, types of AT, follow-up durations and treatments.[1-8] This results in large variation of recovery rates with subjective excellent or asymptomatic recovery rates varying from 40 to 77% between 2 and 10 years follow-up.[4-7,9-11] Participation in sports activity is scarcely described in the long-term follow-up studies, while this is important information from a patient perspective.[7]

Additional items that are very interesting from a clinician and healthcare perspective are the course of symptoms, and prognostic factors. The course of symptoms at a very long term follow-up have not been described sufficiently for this patient group and needs further investigation. Prognostic factors can help to identify important subgroups that develop longstanding symptoms. The subsequent development of specific interventions for this subgroup could have a large impact. Four studies have analyzed possible prognostic factors associated with persisting symptoms, but found no significant associations.[4,5,7,10] There is a scarcity of accurate prospectively collected long-term follow-up data in this specific patient population with chronic midportion AT.

The primary aim of our study was to analyze which proportion of patients with chronic midportion AT have persisting symptoms at 10-year follow-up. Our secondary aims were to evaluate (1) symptom severity, (2) sports activity level, (3) course of symptoms, and (4) prognostic factors associated with persisting symptoms.

METHODS

Original study design

This prospective cohort study is the 10-year follow-up of a previously published, double-blind, randomized placebo-controlled trial which compared the effects of an intratendinous platelet-rich plasma (PRP) injection for chronic midportion AT with a saline placebo injection.[12] Inclusion criteria were (1) a painful and thickened tendon in relation to activity and on palpation,

(2) location of tendon pain was 2 to 7 cm proximal to the insertion of the calcaneus and (3) symptoms had to be present for at least 2 months. Patients were recruited at a large district general hospital (The Hague Medical Center, Leidschendam, the Netherlands) between August 2008 and January 2009. A total of 54 patients were included in the original study. After injection, patients in the intervention and placebo group followed a rehabilitation program consisting of 1 week stretching and 12 weeks heavy-load eccentric calf muscle exercises.[13] Patients were advised not to undergo additional treatments before completing the 24-week follow-up. Detailed methods have been described in the trial register (clinicaltrials.gov, identifier: NCT00761423) and the original publication.[12] A PRP injection did not lead to a larger improvement in symptoms compared to the placebo injection at 24 or 52 weeks follow up.[2,12] For this reason, we can regard this patient group as one large cohort.

Prognostic factor analysis was performed with data collected at baseline or a change in parameters from baseline to 1-year follow-up. We pre-defined a number of potentially relevant prognostic factors for long-term follow-up outcome. These were demographic variables at baseline (sex, age and body mass index (BMI)), symptom duration at baseline, difference in VISA-A score from baseline to 1-year follow-up and ultrasonographic parameters.

Ultrasonographic parameters were tendon diameter and degree of neovascularization, as described by de Vos et al.[14] The degree of neovascularization was measured in longitudinal and transverse planes with color Doppler ultrasonography (MyLab30, Esaote Piemedical, Maastricht, the Netherlands) and assessed using the modified Öhberg score (0-4+).[15]

10-year follow-up

Our 10-year follow-up of the trial was approved by Medical Research Ethics Committee Southwest Holland, Voorburg, the Netherlands (MEC-18-114). We invited all patients who participated in the RCT (n=54) by email to complete an online questionnaire between March and September 2019. Non-responding patients received two e-mail reminders within 4 weeks and were contacted by phone. Consent was acquired from all patients who participated in this 10-year follow-up study.

The online questionnaire was divided into five sections: (1) current AT symptoms, (2) Victorian Institute of Sports assessment-Achilles tendinopathy (VISA-A) questionnaire, (3) current sports activity, (4) course of AT symptoms and (5) health care consumption (Figure 1). The VISA-A score represents symptom severity of AT, where 100 points represents no pain during functional tasks and full pain free sports participation.[16] This validated and disease-

specific questionnaire has been translated and validated in Dutch language.[17] Patients who did not do and did not wish to do any sports activities could score a maximum 60 points on the VISA-A scale.[17] Patients could fill in 'not applicable' if they could not safely perform single leg hops, lowering their maximum VISA-A score by 10 points. As the maximum achievable VISA-A score is lower for patients who did not participate in sports activity and for patients who could not safely perform leg hops, we calculated the percentage of maximal achievable VISA-A score per patient per time point. The maximum achievable VISA-A score was calculated by dividing the VISA-A score at one time point with the maximum achievable VISA-A score at that time point. Formula: $\frac{VISA-A\ at\ one\ time\ point}{Maximum\ achievable\ VISA-A} \times 100\%$ = percentage of maximum achievable VISA-A score.

Outcome measures

The primary outcome measure was the patient reported AT symptoms at 10 years follow-up. Secondary outcome measures were (1) the symptom severity using the VISA-A questionnaire (analyzed using the validated VISA-A score ranging from 0-100 or using the maximum achievable VISA-A score ranging from 0-60 for sedentary patients as previously explained), (2) sports activity, (3) course of symptoms, and (4) (5) identification of potential prognostic factors for having persisting symptoms at 10-years follow-up. We pre-defined the following potential risk factors prior to the initiation this follow-up study: sex, age at baseline, body mass index at baseline, duration of symptoms at baseline, difference in mean VISA-A score between baseline and 52 weeks, ultrasonographically measured tendon diameter at baseline and degree of Doppler flow at baseline.

Current symptoms of AT
Question: Do you still experience symptoms of your Achilles tendinopathy?
1. Yes
2. No

Questionnaire: **VISA-A score** (Dutch language)

Sports activity
Question: How would you describe your current sports activity compared to the situation before you developed Achilles tendinopathy?
1. No return to sport
2. Returned to sport, but not sport of preference
3. Returned to sport of preference, but not at pre-injury level
4. Returned to sport of preference and at pre-injury level

Question: Do you participate in sports activities? If yes, in how many different sports activities?
1. I do not participate in any sports activities
2. 1 Sports activity
3. 2 Sports activities
4. 3 Sports activities
5. 4 Sports activities
6. More than 5 sports activities

Question: How well can you participate in (sports) activities compared to before the onset of your Achilles tendinopathy? The level of activity before the onset of your Achilles tendinopathy is 100%.
1. 0-24% (I cannot or can barely participate in (sports) activities)
2. 25-49% (I can barely to moderately participate in (sports) activities)
3. 50-74% (I can moderately to reasonably participate in (sports) activities)
4. 75-100% (I can reasonably to fully participate in (sports) activities)

Question: Did you adjust your current sports activities?
1. No
2. Yes, due to the Achilles tendinopathy
3. Yes, due to other injuries
4. Yes, due to other reasons

Question: Which adjustments in sports activity did you make because of the Achilles tendinopathy? Multiple answers allowed.
1. Type of sports
2. Frequency of sports activities
3. Duration of sports activities
4. Intensity of sports activities
5. I have not made any adjustments

Question: how long did you adjust your sports activities?
In months

Course of Achilles tendinopathy symptoms
Question: Which of the following options describes the course of your Achilles tendinopathy symptoms best?
1. Gradually decreasing pain
2. Gradually increasing pain
3. Pain flares with milder pain in between
4. Pain flares without pain in between
5. Persisting pain with slight fluctuations
6. Persisting pain with pain flares

Health care consumption
Question: This question applies to the period between 1 year after your participation in the study and now. Which treatments were applied for your Achilles tendinopathy? Multiple answers allowed.
1. I have not received or performed any treatments.
2. Rest (rest or temporary adjustments in sports activities)
3. Exercise (stretching, strengthening exercises)
4. Orthotics (use of adjusted shoes, brace, bandage, insoles)
5. Medication (use of paracetamol, anti-inflammatories, topical agents)
6. Injections (e.g. corticosteroid injections)
7. Passive (sport compression socks, tape, dry needling, massage, ultrasound, shockwave)
8. Surgery of the Achilles tendon or peritendinous structures

Question: Did you receive treatment from a medical professional for your Achilles tendinopathy in the past year? If yes, please describe (1) type of medical professional(s), (2) type of imaging, (3) type of treatment(s) and (4) number of visits to the medical professional(s)

Question: did you continue the exercise program of the PRICT study after follow-up was completed?
1. No
2. Yes, but I have now stopped
3. Yes, and I still perform the exercises

Figure 1. Five sections of the follow-up questionnaire with subdivided questions

Statistical analysis

Data were checked for normal distribution using the Shapiro Wilk test. Normally distributed data are presented as mean with standard deviation (SD) and in case of non-normal distribution as median with interquartile range (IQR). Baseline characteristics of patients who completed and who did not complete the 10-year follow-up questionnaire were compared using an independent t-test (normal distribution), Mann-Whitney U test (non-normal distribution) or chi square test (categorical variables). With this method we were able to check for differences between responders and non-responders to the 10-year follow-up questionnaire. Patients were excluded from further analysis if they did not respond to the 10-year follow-up questionnaire.

The proportion of symptomatic patients was calculated by dividing symptomatic patients by the total of patients who filled in the 10-year follow-up questionnaire. The symptom severity of patients who filled in the 10-year follow-up questionnaire was reported using the mean VISA-A score. The change in mean VISA-A score was calculated with an independent samples t-test. Both mean and percentage of maximum achievable VISA-A score at 10-year follow-up were compared to the VISA-A scores at baseline, 6 weeks, 12 weeks, 24 weeks and 52 weeks.

We used descriptive statistics to report sports activity participation, and course of symptoms. Potential prognostic factors for the presence of persisting symptoms at 10-years follow-up were identified using a univariable binary logistic regression analysis. If more than 1 significant association was found with the univariable analysis, we performed a multivariable binary logistic regression analysis [ENTER model] with those specific variables. SPSS software (V.24.0.0.1; SPSS, Chicago, Illinois, USA) was used for statistical analysis.

RESULTS

Patient population

Of the 54 patients who were included in the original RCT, 43 (80%) agreed to participate in the 10-year follow-up study and filled in the follow-up questionnaire. The flow of patients in the study is shown in Figure 2. The average follow-up time was 10.4 years.

Table 1. Baseline characteristics at the start of the study of patients who completed the 10-year follow-up questionnaire

	Completed follow-up N (%) / mean (SD) / median; IQR
N	43
Baseline characteristics	
Age (years)	49.9 (9.5)
Sex (male)	23 (53%)
BMI (kg/m^2)	25.9 (3.2)
VISA-A score (t=0)	52 (17)
Symptoms at baseline	
Duration of symptoms (weeks)	32 (60)
Sports characteristics	
Level of sports	
No sports	5 (12%)
Recreational	30 (70%)
Competitive	8 (19%)
Professional	0 (0%)
Sports intensity	
No sports activity	5 (12%)
1-2 times per week	18 (42%)
3-4 times per week	16 (37%)
≥ 5 times per week	5 (12%)
Absence of sports (weeks)	1 (12)
Adjustments in sports	
No sports	5 (12%)
Stopped	17 (40%)
Reduced	11 (29%)
No adjustments	10 (23%)
Ultrasound examination	
Tendon thickness (mm)	10.0 (2.6)
Doppler flow	
0 (no vessels)	8 (19%)
1+ (peritendinous vessels)	4 (9%)
2+ (1 or 2 vessels)	12 (28%)
3+ (3 vessels)	12 (28%)
4+ (4 or more vessels)	7 (16%)

*Statistically significant difference (p-value<0.05)
BMI = body mass index; SD = standard deviation; IQR = interquartile range

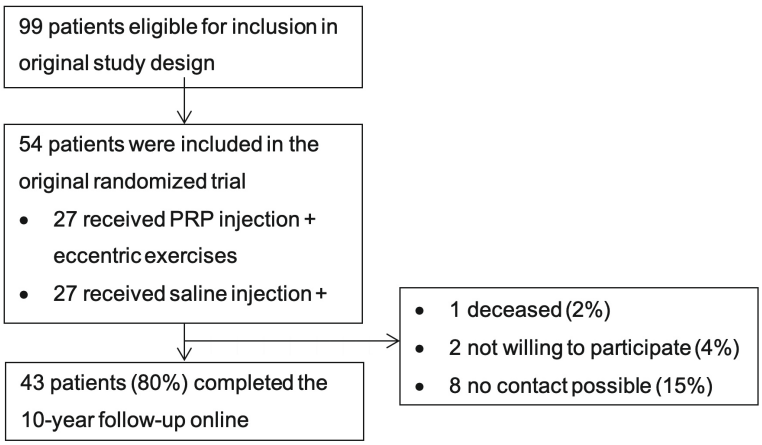

Figure 2. Flowchart of patients

Besides a statistically significant lower body mass index (BMI) in the group of patients who completed the 10-year follow-up (25.9 versus 28.6 kg/m^2, p = 0.029), there were no differences between the groups of patients who did and did not participate in the 10-year follow-up study (Table 1). Of all patients who completed the 10-year follow-up, 12 patients (28%) underwent no other treatment for AT symptoms between the 1 and 10-year follow-up. Treatments undergone between the 1 and 10-year follow-up were: rest or temporary adjustments in sports activities (44%), stretching and/or strengthening exercises (58%), orthotics such as adjusted shoes, brace, bandage and/or insoles (42%), medication (26%) and passive treatment such as compression socks, tape, ultrasound and/or shockwave (28%). No patients had injections or underwent surgery.

Primary outcome

Persisting AT symptoms

Persisting symptoms on the same side as baseline were reported by 8 patients (19%) at a 10-year follow-up. Of these 8 patients, 1 patient who had symptoms on the right Achilles tendon at baseline had bilateral symptoms at 10-year follow-up. Two other patients had symptoms on their left Achilles tendon at baseline and reported right sided symptoms after 10 years.

Secondary outcomes

Symptom severity

Symptom severity improved significantly from baseline to 1-year follow-up with the VISA-A score (SD) changing from 52 (17) to 79 (21) points with a mean

improvement of 27 (SD 21, 95%CI: 21;34, p<0.001) points (Figure 3A).[2,12] The symptom severity did not improve significantly from 1 year to 10-years follow-up with the VISA-A remaining 80 (17) points and a mean change of 1 (SD 27, 95%CI: -7;9, p=0.820) points.

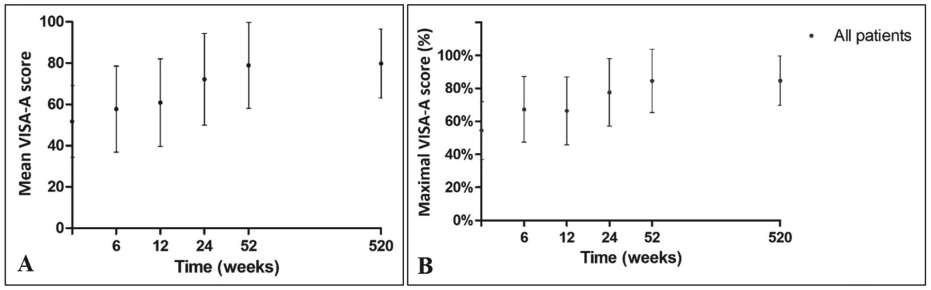

Figure 3. Symptom severity over time, expressed in VISA-A score, of patients who completed the 10-year follow-up. Error bars denote standard deviations. A) Mean VISA-A score per time point. B) Percentage of maximal achievable VISA-A score per time point.

When analyzing the VISA-A score expressed as a percentage of the maximum achievable VISA-A score, patients improved significantly from 55% (SD 18) at baseline to 85% (19) at 1-year follow-up with a mean change of 30% (SD 22, 95%CI: 23;37, p<0.001) (Figure 3B). The maximal achievable VISA-A score did not improve further between 1-year and 10-years follow-up with a mean change of 0% (SD 25, 95%CI: -7;8, p=0.980).

Table 2. Sports activity and adjustments at 10-year follow-up

	N	Included patients % / median ; IQR
Active at baseline	38	
Sedentary patients who became active	1	
Sports activity		
Return to sports		
No return to sports		
Return to sports, but not sports of preference	3	8%
Return to sports, but not old level	9	24%
Return to sports of preference and on previous level	10 16	26% 42%
Sporting activities (yes)	35	92%
1-2 sporting activities	22	63%
3-4 sporting activities	12	34%
>5 sporting activities	1	3%
Degree of sports participation	35	
0-24% (almost no participation)	1	3%
25-49% (moderate participation)	0	0%
50-74% (good participation)	7	20%
75-100% (full participation)	27	77%
Adjustments in sports activity		
Adjusted sports activity (yes)	21	55%
Because of the AT	11	52%
Because of different injury	0	0%
Other reasons	10	48%
Type of adjustments		
Type of sports activity		18%
Frequency of sports activity	7	11%
Intensity of sports activity	4	16%
Duration of sports activity	6	8%
Duration of adjustments (months)	3	24 ; 114

IQR = interquartile range; AT = Achilles tendinopathy

Sports activity

Sixteen of 38 patients (42%) returned to the preferred sports activity on their pre-injury level (Table 2), with 14 patients (33%) being pain free during sports activities of their preference at their pre-injury level. Three patients (8%) who participated in sports before their injury did not return to sports at 10-year follow-up. One patient who was sedentary at baseline took up sports during the follow-up period. In 52% of the cases, patients adjusted

their sports activities because of their AT (Table 2). The mean duration that patients adjusted their sports was 24 (IQR; 114) months and most frequently they switched to another type of sports (18%).

Course of symptoms

The patients described the course of their AT symptoms most frequently as a gradually decreasing pain (74% of the whole group, 82% of patients who recovered and 50% of patients reporting persisting symptoms) (Table 3). Within the group of patients, different patterns were described. Patients who subjectively recovered used pain flares without pain in between as second most frequent description (15% of patients who subjectively recovered compared to 10% of patients with persisting symptoms). Persisting pain with slight fluctuations were reported by 40% of patients with persisting symptoms, compared to none of the patients who recovered.

Table 3. Course of AT symptoms of the included patients

	Included patients N (%) / mean (SD)
N	43
Course of AT symptoms	
Gradually decreasing pain	32 (74%)
Gradually increasing pain	1 (2%)
Pain flares with milder pain in between	0 (0%)
Pain flares without pain in between	6 (14%)
Persisting pain with slight fluctuations	4 (9%)
Persisting pain with pain attacks	0 (0%)

SD = standard deviation; AT = Achilles tendinopathy

Prognostic factors

All pre-defined potential prognostic factors (demographics at baseline, symptom duration at baseline, change in VISA-A score within 1 year and ultrasonographic parameters) were not associated with an increased risk of having persisting symptoms at 10-years follow-up (Supplementary file 1).

DISCUSSION

Our prospective 10-year follow-up study shows that one fifth of patients have Achilles tendon symptoms. Symptom improvement tails off after 1 year. Only one third have returned to sports at their previous level without pain. More than 50% had adjusted their sports activities, and half of this subgroup made these adjustments because of AT symptoms. We did not identify prognostic factors for an increased risk of having symptoms at 10 years follow-up.

Symptoms at 10 year follow up

In our current study, 19% of patients had symptoms after 10 years. One other prospective study with a follow-up duration of 10 years in 77 patients with insertional or midportion AT reported that 37% experienced some form of physical limitation in the past 10 years.[7] Unfortunately, this global assessment of function only addresses physical limitation, and it is not specified whether patients experienced AT symptoms at 10-years follow-up. One prospective study with a follow-up duration of 5 years reported that 35% of 34 patients with midportion AT were symptomatic.[4] Another prospective study with a follow-up duration of 5 years reported that 61% of 58 patients with chronic midportion AT experienced some degree of pain.[5] The results of these long-term follow-up trials suggest that 23-61% of patients remain symptomatic between 5 to 10 year follow-up. The wide range in percentage of persisting symptoms can be explained by the heterogeneity of the studies: we suggest describing outcomes separately per specific type of pathology (e.g. insertional versus midportion AT). Another explanation might be the fact that this is not a validated outcome measure and therefore not assessed in a similar way across studies and cultures. We feel this simple dichotomous outcome is relevant, as it is easy to interpret in the clinical setting and aids in counselling patients to create realistic expectations.

Symptom severity

After 10 years, symptom severity in our study as measured with the VISA-A score was around 80 points. This is similar to the 10-year follow-up study of Johannsen et al.[7] who reported a VISA-A score of 84, with their primary study researching the effect of exercises in combination with glucocorticosteroid injections when necessary.[18] Although there is currently no gradation in symptom severity based on the VISA-A score, Iversen et al.[19] suggested that a VISA-A score of 96 or higher represents a healthy tendon. Only 9 out of 43 patients (21%) in our study had a VISA-A score of ≥96 points. An average VISA-A score of ≥96 was not achieved by patients in our study or the study of Johannsen et al.[7]. This might be due to limitations of the VISA-A score. The VISA-A score is based on pain, function and sporting activity.[16] If patients are

sedentary, their maximum VISA-A score is reduced by 40 points. In long-term follow-up studies, there can be other reasons why patients become less active resulting in a lower VISA-A score, while the tendon would actually be able to cope with higher loads. Furthermore, if patients cannot perform single legs hops due to poor balance or other reasons, their maximum VISA-A score is lowered by another 10 points. Give the above mentioned reasons, we also calculated the symptom severity as a percentage of maximal achievable VISA-A score. Even then, patients achieved around 85% of their maximal achievable score. These results suggest most patient with do not usually recover fully.

Sports activity

Only a third of patients were able to perform their preferred level of sports activity without pain. In total, 8% did not return to sports and 51% did not return to the sports of their preference or at their previous level. One 5-year follow-up study reported that 9% of the included active patients did not return to sports.[5] They did not report if patients returned to their preferred sport and whether this was at pre-injury levels. Additionally, they did not report whether patients adjusted their sports activity because of AT symptoms. In long-term follow-up studies, there might be other reasons for decreasing or stopping sports activities. Asking whether patients did not return to sports because of AT symptoms is relevant. In our study, half of the patients adjusted their sports activity because of symptoms and half due to other reasons. This implies that AT is an important reason for adjustments in sports activity and this impacts general health and quality of life.[20]

Course of symptoms

The course of symptoms in the subgroup of patients with symptoms at 10 years shows a characteristic profile of fluctuating pain over time in most. In practice it could be helpful to inform patients about this typical course. This expectation management can help patients with persisting symptoms to understand that there will be periods with less or no symptoms and periods with increased pain levels.

Potential prognostic factors

Establishing prognostic factors for chronicity of disease is important for developing targeted intervention strategies and providing individualized prognosis. We were not able to identify prognostic factors that were associated with an increased risk of having symptoms at 10-years follow-up. Our findings are in accordance with previous literature, where sex, BMI, duration of symptoms at baseline, Doppler flow and tendon thickness also did not influence the severity of AT symptoms after 5 years of follow-up.[4,5] Prognostic

factors associated with an increased risk of developing persisting symptoms remain unknown; based on currently available evidence, it is unknown which factors facilitate recovery or trigger the development of persisting symptoms. Van der Vlist et al. published a systematic review that identified nine clinical risk factors which increase the risk of developing Achilles tendinopathy.[21] Future studies should include at least one of the risk factors in the study and analyze the risk of having persisting AT symptoms.

Strengths and limitations

A strength of our study is the adequate prospective methodology, based on the robust study protocol of a randomized controlled trial. We were able to contact a high percentage of patients for long-term follow-up. We found no clinically relevant differences between responders and non-responders, making it more likely that the group of responders were representative for this patient group. A potential limitation of this study is the low power when trying to identify potential prognostic factors. With the relatively small number of cases, we were only able to detect strong associations.[22] For our main research question and other secondary research questions, our number of included patients are similar to other studies that researched long-term follow-up of chronic midportion AT. It is also possible that treatments undergone in the past 9 years might have influenced prognosis. We did not adjust for this, as recall bias could be present, as we asked our patients about treatments and course of symptoms in the past 9 years. A solution for this in future long-term follow-up studies would be to administer questionnaires more frequently. A potential limitation could be the lack of clinical examination by a physician at follow-up. However, all patients had the clinical diagnosis which was ultrasonographically confirmed at baseline. It is unlikely that the diagnosis changed, as the patients recognized their injury pain. Lastly, a possible limitation is that the VISA-A score is developed and validated for athletes, but not for sedentary individuals. During the validation process of the Dutch VISA-A questionnaire it was suggested to complete part of the questionnaire (pain and function questions, maximum score 60 points) by sedentary patients.[17] The VISA-A score is also limited by the use of single leg hops: as we included older patients, many could not safely perform these which reduced their VISA-A score by 10 points. We handled these data by calculating the percentage of maximum obtainable VISA-A score per time point per patient, thereby overcoming this potential limitation. For these mentioned limitations of VISA-A assessment at long-term follow-up, we decided to use this outcome measure as secondary outcome and presence of current symptoms as dichotomous and easy-interpretable outcome measure for daily practice.

Recommendations for future research

We were not able to detect prognostic factors. This emphasizes the need for better identification and treatment of patients experiencing persisting symptoms. Large cohort studies with long-term follow-up or data pooling from existing studies are needed to identify the subgroup of patients with persisting symptoms. Innovative research with measuring prognostic factors will enhance our understanding of the chronicity of symptoms and this will enable the development of prevention strategies and better treatments for this subgroup.

CONCLUSION

One fifth of patients with chronic AT report symptoms at 10 years of follow-up. There was no improvement in symptom severity after 1 year. Only one third of all patients returned to their preferred sports activities at their pre-injury level without pain. Half of the patients were forced to adjust their sports activities. No prognostic factors were identified that were associated with the persistence of symptoms. Patients should be adequately counselled about the longstanding nature of AT, to create realistic expectations.

Conflicts of interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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SUPPLEMENTARY FILE(S)

Supplementary file 1. Univariable binary logistic regression analysis on potential prognostic factors for the presence of persisting symptoms at 10-years follow-up

	Persisting symptoms		Recovered	Univariable analysis	
	N	N (%) / mean (SD / median; IQR	N	N (%) / mean (SD / median; IQR	OR (95% CI)
	8		35		
Sex (male)		4 (50%)		19 (54.3%)	0.8 (0.2;3.9)
Age (years)		48.3 (8.8)		50.2 (9.7)	1.0 (0.9;1.1)
BMI (kg/m^2)		23.2 ; 4.4		26.3 ; 4.0	0.8 (0.6;1.1)
Symptom duration (weeks)		84 (96)		55 (88)	1.0 (1.0;1.0)
Difference in VISA-A score[a]		27 (14)		27 (23)	1.0 (1.0;1.0)
US tendon diameter (mm)		8.3 (1.1)		10.3 (2.8)	0.6 (0.4;1.0)
Doppler flow 1+ (peritendinous vessels) 2+ (1 or 2 vessels) 3+ (3 vessels) 4+ (4 or more vessels)		0 3 (37.5%) 1 (12.5%) 1 (12.5%)		4 (11.4%) 9 (25.7%) 1 (2.9%) 1 (2.9%)	3.6 (0.3;46.4) 0.0 (0.0) 2.0 (0.2;24.1) 0.5 (0.0;10.4)

[a]Difference in mean VISA-A score between 52 weeks and baseline
SD = standard deviation, IQR = interquartile range, OR = odds ratio, CI = confidence interval, BMI = body mass index, VISA-A = Victorian Institute of Sports Assessment-Achilles, US = ultrasonographical

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Part III

Summary and general discussion

9

Summary

SUMMARY

The general aim of this dissertation was to determine the incidence, risk factors, prevention strategy, symptom course and prognostic factors for Achilles tendinopathy.

Part I - Incidence, risk factors and prevention strategy for Achilles tendinopathy

In **Chapter 2** our primary aim was to determine the incidence of self-reported Achilles tendinopathy in recreational runners. As a secondary aim, we sought to identify risk factors for Achilles tendinopathy as a secondary aim. In this observational cohort study, 2378 runners who registered for a 5- to 42-kilometer run were included. Participants registered at least 2 months before the running event and were asymptomatic for Achilles tendinopathy at the time of registration. Follow-up questionnaires were completed 2 weeks before the running event, 1 day after the running event and 1 month after the running event. Of all included runners, 1929 completed at least one follow-up questionnaire, of which 100 (5.2%) developed Achilles tendinopathy. The strongest risk factor for developing Achilles tendinopathy was having had Achilles tendinopathy in the previous 12 months. Other risk factors were using a training schedule and use of compression socks.

Inflammation is suggested to play a role in the pathophysiology of tendinopathies. For this reason, metabolic and chronic diseases are thought to be risk factors for tendinopathy. In **Chapter 3**, we analysed the association between lower extremity tendinopathies and metabolic and chronic diseases. In a systematic review we included 10 cohort studies and 10 case-control studies, comprising a total of 83,948 participants. The majority (90%) of the included studies had a high risk of bias. We found moderate evidence for an association between lower extremity tendinopathies and obesity, ankylosing spondylitis, psoriatic arthritis and reactive arthritis. There was limited evidence for an association between lower extremity tendinopathies and heterozygous familial hypercholesterolaemia and systemic lupus erythematosus (SLE). Based on these findings, we suggest that medical professionals screen for metabolic and chronic diseases during history-taking and physical examination in patients with tendinopathy. Early recognition of metabolic and chronic diseases might not only improve overall patient health, but also benefit tendon health.

A decreased ankle dorsiflexion is likely to increase strain on the Achilles tendon, which may theoretically lead to the development of Achilles tendinopathy.[1] Stretching and eccentric (lengthening) exercises are hypothesised to improve

ankle dorsiflexion. In **Chapter 4,** we examined whether stretching and eccentric (lengthening) exercises of the calf muscles increase ankle dorsiflexion in healthy adolescent soccer players with a decreased ankle dorsiflexion. The ankle dorsiflexion in both bent and extended knee positions were assessed in healthy adolescent soccer players. Soccer players with a decreased ankle dorsiflexion were divided into an intervention group (n=52) and a control group (n=55). Both groups performed regular training, and the intervention group performed additional targeted exercises for twelve weeks. We found no improvement of ankle dorsiflexion after targeted stretching and eccentric ('lengthening') exercises of the calf muscles.

Part II - Course of symptoms and prognostic factors in new-onset and chronic Achilles tendinopathy

The Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire was developed as a patient-reported outcome measure to evaluate treatment effects in physically active patients with Achilles tendinopathy. The VISA-A score quantifies physical disability through questions on pain, functional status and sports activity, using a numerical scale of 0 to 100, where a higher score indicates less severe symptoms. Although the VISA-A score is widely used to assess treatment effects, the minimal clinically important difference (MCID) and patient acceptable symptom state (PASS) were previously unknown. In **Chapter 5** we determined the MCID and PASS for the VISA-A score in 80 patients with conservatively treated midportion Achilles tendinopathy over a 24-week period. A change of 14 points in the VISA-A score after 12 weeks and a change of 7 points after 24 weeks reflects a meaningful change. Achilles tendinopathy symptoms were considered acceptable if the VISA-A score was equal to or above 50 points after 12 weeks of treatment, and equal to or above 60 points after 24 weeks of treatment.

In **Chapter 6**, we describe how many runners develop persisting symptoms 1 year after the onset of new-onset Achilles tendinopathy and which prognostic factors are associated with this course. Of the 1929 included runners, 100 (5%) reported acute Achilles tendinopathy. A total of 62 runners (62%) filled out the 1-year follow-up questionnaire. One third of runners with acute Achilles tendinopathy reported persisting symptoms after 1 year. Interestingly, we found that a higher weekly running distance before developing Achilles tendinopathy potentially reduces the risk of developing persisting symptoms.

Despite treatment of Achilles tendinopathy, symptoms may persist. In **Chapter 7,** we analysed whether passive or active coping strategies and a neuropathic pain component influence the course of Achilles tendinopathy symptoms. In a prospective study including conservatively treated patients with chronic

midportion Achilles tendinopathy, the Pain Coping Inventory (PCI) was determined. The PCI consists of an active and a passive domain and ranges from 0 to 1; a higher score reflects a more active or passive coping strategy. Furthermore, the presence of a neuropathic pain component was determined with the PainDETECT questionnaire (-1 to 38 points), where the outcome was categorized as an unlikely, unclear, or likely presence of neuropathic pain component. Symptom severity was expressed with the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire. Of the 76 included patients, the mean active coping score was 0.53 and mean passive coping score was 0.43. Twelve patients (15%) had a likely neuropathic component. We found no association between coping strategy or presence of neuropathic pain component and the course of Achilles tendinopathy symptoms as expressed with the VISA-A score.

In **Chapter 8** we investigated how many patients with chronic midportion Achilles tendinopathy continue to experience symptoms after 10 years. Patients (n=54) who had previously participated in an intervention trial were invited to complete an online questionnaire, with the presence of Achilles tendinopathy symptoms as the primary outcome. Secondary outcomes were symptom severity expressed by VISA-A score (0-100 points) and sports activity level were secondary outcomes. One fifth of patients with conservatively treated midportion Achilles tendinopathy reported symptoms of Achilles tendinopathy after 10 years. Symptom severity was around 80 points, expressed by VISA-A. Performing sports pain-free on pre-injury level was possible for one third of the patients.

10

Samenvatting

SAMENVATTING

Het doel van dit proefschrift was om de incidentie, de risicofactoren, een preventie strategie, het beloop en prognostische factoren voor achilles tendinopathie te beschrijven.

Deel I – Incidentie, risicofactoren en preventie strategie voor achilles tendinopathie

Het doel van **Hoofdstuk 2** was om de incidentie van zelf-gerapporteerde achilles tendinopathie bij recreatieve hardlopers te bepalen. Het nevendoel was om risicofactoren voor het ontwikkelen van achilles tendinopathie te identificeren. In een observationele cohort studie werden 2378 hardlopers geïncludeerd die zich hadden ingeschreven voor een hardloopevenement met loopafstanden van 5 tot 42 kilometer. De geïncludeerde hardlopers hadden zich ten minste 2 maanden voor het hardloopevenement ingeschreven en waren zonder klachten van achilles tendinopathie op het moment van inclusie (baseline). Digitale vragenlijsten werden op baseline, 2 weken voor het hardloopevenement, 1 dag na het hardloopevenement en 1 maand na het hardloopevenement verstuurd. Van de 2378 geïncludeerde hardlopers voltooiden 1929 ten minste 1 opvolgende vragenlijst. 100 (5.2%) hardlopers rapporteerden het ontstaan van achilles tendinopathie. De sterkste risicofactor voor het ontwikkelen van achilles tendinopathie was het hebben gehad van achilles tendinopathie in de voorgaande 12 maanden. Andere risicofactoren waren het gebruik maken van een trainingsschema en het dragen van compressiesokken.

Inflammatie speelt mogelijk een rol bij de pathogenese van tendinopathie. Ontsteking is ook in verhoogde mate aanwezig bij veel metabole en chronische aandoeningen. Om die reden hebben we in **Hoofdstuk 3** geanalyseerd of er een associatie is tussen tendinopathie van de onderste extremiteit en de aanwezigheid van metabole en chronische aandoeningen. We includeerden 10 cohort studies en 10 case-control studies met in totaal 83.948 participanten in een systematische review. Een groot deel van de geïncludeerde onderzoeken (90%) had een hoog risico op bias. We vonden gemiddelde bewijskracht voor een associatie tussen tendinopathie van de onderste extremiteit en obesitas, ankyloserende spondylarthritis, artritis psoriatica, en reactieve artritis. We vonden beperkte bewijskracht voor een associatie tussen tendinopathie van de onderste extremiteit en de aanwezigheid van heterozygote familiaire hypercholesterolemie en Systemische Lupus Erythematosus. Op basis van deze bevindingen adviseren we medische professionals om te screenen voor metabole en chronische aandoeningen bij de klinische beoordeling van patiënten met een tendinopathie van de onderste extremiteit. Vroege

herkenning van metabole en chronische aandoeningen kunnen niet alleen de algemene gezondheid van de patiënt verbeteren, maar ook de gezondheid van diens pees.

Een verminderde dorsaalflexie van de enkel kan zorgen voor verhoogde belasting de achillespees, wat theoretisch gezien kan leiden tot achilles tendinopathie. Rekkende en excentrische (verlengende) oefeningen worden gedacht de dorsaalflexie van de enkel te verbeteren. In **Hoofdstuk 4** onderzochten we of rekkende en excentrische (verlengende) oefeningen van de kuitmusculatuur de dorsaalflexie van de enkel verbeterden in gezonde, adolescente voetbalspelers met een verminderde dorsaalflexie van de enkel. De dorsaalflexie van de enkel in zowel gebogen- als gestrekte knie positie werd bepaald in gezonde, adolescente voetbalspelers. Voetbalspelers met een verminderde dorsaalflexie van de enkel werden verdeeld in een interventiegroep en een controle groep. Beide groepen volgden hun reguliere trainingsschema, waarnaast de interventiegroep gerichte oefeningen uitvoerde voor twaalf weken. Wij vonden geen verbetering in dorsaalflexie van de enkel na gerichte rekkende en excentrische ('verlengende') oefeningen van de kuitmusculatuur.

Deel II – Het klachtenbeloop en prognostische factoren voor nieuw ontstane en chronische achilles tendinopathie

Om het effect van een behandeling in fysiek actieve patiënten met achilles tendinopathie te evalueren werd de Victorian Institute of Sports Assessment-Achilles (VISA-A) vragenlijst ontwikkeld. In deze patiënt-gerapporteerde VISA-A vragenlijst wordt de ernst van achilles tendinopathie symptomen bepaald door het stellen van vragen over pijn, functionele status en sportactiviteit. Dit leidt tot een numerieke score van 0 tot 100, waarbij een hogere score mildere symptomen weerspiegelt. Hoewel de VISA-A score frequent wordt gebruikt om het effect van behandelingen te kwantificeren, zijn het minimaal klinisch relevante verschil (Eng: *minimal clinically important difference*, MCID) en de voor de patiënt aanvaardbare status van symptomen (Eng: *patient acceptable symptom state*, PASS) onbekend. In **Hoofdstuk 5** hebben we de MCID en PASS bepaald voor de VISA-A score in 80 patiënten met conservatief behandelde midportion achilles tendinopathie. Een verandering in VISA-A score van 14 punten na 12 weken, en 7 punten na 24 weken reflecteerde een betekenisvolle verandering voor de patiënt. Symptomen van Achilles tendinopathie werden acceptabel geacht als de VISA-A score 50 punten of hoger was na 12 weken behandeling, en gelijk was of boven de 60 punten kwam na 24 weken behandeling.

In **Hoofdstuk 6** beschreven we hoeveel hardlopers nog klachten hadden 1 jaar na het ontstaan van achilles tendinopathie, en welke prognostische factoren

er geassocieerd waren met dit beloop. Van de 1929 geïncludeerde hardlopers rapporteerden er 100 (5%) een nieuw ontstane achilles tendinopathie. In totaal vulden 62 hardlopers van deze groep (62%) de follow-upvragenlijst na 1 jaar in. Een derde van hardlopers met achilles tendinopathie rapporteerde persisterende symptomen na 1 jaar. Een opvallende bevinding was dat de kans op het ontwikkelen van persisterende symptomen mogelijk wordt verlaagd door het lopen van een langere afstand per week vóórdat achilles tendinopathie ontstaat.

Symptomen van achilles tendinopathie kunnen persisteren, ondanks behandeling. In **Hoofdstuk 7** analyseerden we of een passieve of actieve coping strategie en een neuropathische pijncomponent het klachtenbeloop van achilles tendinopathie beïnvloedden. In een prospectieve studie werden patiënten met chronische midportion achilles tendinopathie conservatief behandeld. De Pain Coping Inventory (PCI) en PainDETECT vragenlijsten werden op baseline afgenomen voorafgaande aan de start van de behandeling. De PCI bestaat uit een actief en een passief domein, waarbij de score wordt uitgedrukt in een getal tussen 0 en 1. Hoe hoger de score, hoe meer actief of passief de coping strategie. De aanwezigheid van een neuropathische pijncomponent werd onderzocht middels de PainDETECT vragenlijst (-1 tot 38 punten), waarbij de uitkomst werd gecategoriseerd in een onwaarschijnlijke, onduidelijke of waarschijnlijke aanwezigheid van een neuropathische pijncomponent. De ernst van de achilles tendinopathie symptomen werd uitgedrukt met de VISA-A score. In de 76 geïncludeerde patiënten was de gemiddelde actieve coping 0.53 en de gemiddelde passieve coping 0.43. Bij twaalf patiënten (15%) bestonden aanwijzingen voor een neuropathische pijncomponent. We vonden geen associatie tussen coping strategie en de aanwezigheid van een neuropathische pijncomponent en het beloop van achilles tendinopathie symptomen.

In **Hoofdstuk 8** onderzochten we hoeveel patiënten met chronische midportion achilles tendinopathie persisterende klachten hadden na 10 jaar. Patiënten (n=54) die eerder deelnamen aan een interventiestudie werden gevraagd een online vragenlijst in te vullen, waarbij de aanwezigheid van symptomen van achilles tendinopathie de primaire uitkomstmaat was. Secundaire uitkomstmaten waren de ernst van de symptomen (uitgedrukt in de VISA-A score, 0-100 punten) en het activiteiten niveau in sport. Een vijfde van de patiënten met conservatief behandelde midportion achilles tendinopathie rapporteerde symptomen van achilles tendinopathie na 10 jaar. De ernst van de symptomen was ongeveer 80 punten, uitgedrukt met de VISA-A score. Een derde van de patiënten kon pijnvrij sporten op het niveau van vóór de blessure.

11

General discussion

GENERAL DISCUSSION

Achilles tendinopathy is a prevalent and often persistent condition, which affects a significant portion of the population somewhere at some point during their lifetime, especially the physically active population. Despite its high incidence, effective prevention and treatment strategies remain elusive. This dissertation aimed to determine the incidence and risk factors of Achilles tendinopathy, investigate the course of symptoms in both new-onset and chronic Achilles tendinopathy, and identify prognostic factors and potential mechanisms of treatment success. By exploring these areas, we aimed to identify targets for future prevention and treatment for patients with Achilles tendinopathy.

Incidence, risk factors and prevention strategies for Achilles tendinopathy

Running is well-known to be associated with the onset of injuries. Our study found that one in twenty recreational runners developed Achilles tendinopathy during their preparation and participation in a running event.[2] We identified the presence of Achilles tendinopathy in the previous 12 months as the strongest risk factor, while use of a training schedule and sport compression socks were also associated with an increased the risk of developing AT.

Metabolic and chronic diseases were risk factors of interest in our systematic review. In the general population, we found moderate evidence for an association between lower extremity tendinopathies and obesity, ankylosing spondylitis, psoriatic arthritis, and reactive arthritis. There was limited evidence for an association between lower extremity tendinopathies and heterozygous familial hypercholesterolaemia, and systemic lupus erythematosus. We found conflicting evidence for an association between lower extremity tendinopathies and hypertension, as well as between lower extremity tendinopathies and hypercholesterolemia.

In the search for an effective prevention strategy for Achilles tendon injuries, we investigated the effect of stretching and eccentric exercises on ankle dorsiflexion in adolescent high-level soccer players. We found that the ankle dorsiflexion angle did not improve after a targeted 12-week training program.

Contrasts and parallels with previous work

A study by Hirschmüller et al.[3] reported an incidence of 7.5% of Achilles tendinopathy in long-distance runners, which is 1.5 times as high as the incidence reported in our study. This difference could be due to variations in

weekly running distance per week and running experience, as the runners in the study by Hirschmüller et al.[3] were twice as experienced and ran twice as far as the runners included in our study. From that perspective, our findings align with previous studies, as marathon runners in our study were more likely to develop Achilles tendinopathy (7.4%).[2] Another study by McKean et al.[4] reported a 6.2% incidence in master runners (age ≥40 years) and an incidence of 3.5% in younger runners (age <40 years). Lysholm et al.[5] reported a 8.3% incidence of Achilles tendinopathy in a mixed group of sprinters, middle-distance runners and marathon runners. A more recent study with a similar running population as ours reported an incidence of 4.2% of new-onset Achilles tendinopathy (141 of 3379 runners).[6] Of the runners with Achilles tendinopathy, 39 (27.7%) had insertional Achilles tendinopathy, 90 (63.8%) had midportion Achilles tendinopathy and 12 (8.5%) had combined Achilles tendinopathy. Marathon runners enveloped the largest group of runners with Achilles tendinopathy (84 runners, 57%). Studies reporting the incidence of Achilles tendinopathy in runners reveal a striking difference in type of Achilles tendinopathy and running distance. Therefore, future studies should differentiate between the type of Achilles tendinopathy (midportion versus insertional), as well as type of running discipline (long versus short distance).

In our analysis of risk factors, we found that a history of Achilles tendinopathy in the previous 12 months was the strongest risk factor for having Achilles tendinopathy symptoms with an odds ratio of 6.25 (95% confidence interval of 3.90;10.00). Chen et al. reported that a history of Achilles tendinopathy in the past 12 months was a risk factor for new-onset Achilles tendinopathy (odds ratio: 6.47 (95% confidence interval of 4.27–9.81)).[6] No other studies included a previous Achilles tendinopathy in the search of risk factors for Achilles tendinopathy, but multiple other studies identified a previous injury as a risk factor for a new one.[3,7-9] This may suggest an incomplete recovery from a previous episode of the condition, which causes the injury to relapse again. Another possibility is that there are unmodifiable characteristics that increase the risk of developing Achilles tendinopathy. However, multiple studies have not identified any strong non-modifiable risk factors. The finding that a previous Achilles tendinopathy predisposes for a new or recurrent Achilles tendinopathy underscores the importance of researching modifiable risk factors. Modifiable risk factors increase the potential of an effective prevention strategy.

In our cohort of recreational runners, we found two modifiable risk factors; the use of sport compression socks (odds ratio 1.68 (95% confidence interval of 1.03;2.75)), and the use of a training schedule (odds ratio 1.82 (95% confidence interval of 1.10;3.01)). For compression socks, we hypothesised

that runners might use them because of minor symptoms from previous injuries, or that compression socks could influence the microvascular supply.[10] No other studies researched compression socks as a risk factor for Achilles tendinopathy. One study by Chen et al. investigated the risk for new-onset midportion Achilles tendinopathy when using a training schedule.[6] The use of a training schedule was only a risk factor in the univariate analysis, not in the multivariate analysis. A study by Naderi et al. studied the incidence and risk factors of running related injuries in 143 recreational runners, of which 37% (53 runners) developed an injury.[11] They found that the use of a training schedule protected against running related injuries, with an odds ratio of 0.24 (95% confidence interval of 0.09-0.66). As (running related) injuries each have their own pathophysiology, the finding of Naderi et al. might not be applicable on Achilles tendinopathy. We hypothesise that runners may become so focussed on following their training schedule, that they ignore the pain signals that precede injuries. Another hypothesis is that runners more frequently follow a training schedule after a previous injury. A third possibility is that the association between Achilles tendinopathy and the use of a training schedule or the use of sport compression socks may not be significant or even might be negligible in a larger study population. In our study, the association was moderate in strength, with substantial variation in its magnitude.[12] It would be interesting to include these two modifiable potential risk factors in future studies, to test our findings.

Through a systematic review, we found multiple associations between lower extremity tendinopathies and metabolic and chronic diseases. One key mechanism linking these conditions is chronic low-grade inflammation. For example, pro-inflammatory cytokines play a prominent role in patients with obesity. The mRNA expression of COX-2 and IL-6 was increased in patients with obesity and in patients with painful and ruptured Achilles tendons.[13] This may trigger cell proliferation, angiogenesis, overexpression of MMPs and pain mediators, which could result in extracellular matrix degeneration, tissue metaplasia and eventually tendon pain.[14] Furthermore, Kager's fat pad shares a blood supply with the Achilles tendon, allowing cytokines that influence Kager's fat pad to migrate and directly influence the tendon. The mRNA of cytokines is not only elevated in the tendon in patients with chronic Achilles tendinopathy, but also in Kager's fat pad.[15] In patients with hereditary hypercholesterolaemia, it is hypothesised that the lipid accumulation in the tendon, known as xanthomas, may increase stiffness and enhance the synthesis of pro-inflammatory proteins.[16,17] Another possible reason for the association between obesity and tendinopathy is a higher local tendon strain due to increased body weight.[18] However, upper limb tendinopathies have also been associated with obesity which challenges this hypothesis.[19] As suggested

by these multiple hypotheses, it is likely that metabolic and chronic diseases exert systemic effects on tendons, altering their structure and function, and ultimately increasing their susceptibility to tendinopathy.

In our search for a prevention strategy, we chose a known modifiable risk factor and aimed to develop a preventive intervention. A decreased ankle dorsiflexion is associated with a 2.5 to 3.6 times increased risk of developing Achilles tendinopathy,[20,21] For this reason, we chose to develop an exercise therapy program aimed to improve ankle dorsiflexion angle. After screening healthy adolescent soccer players for decreased ankle dorsiflexion, we assigned one 'at-risk' group to a 12-week program of stretching and eccentric exercises, while the other group performed no additional exercises. The ankle dorsiflexion did not improve significantly compared to the control group.[22] While we hypothesised that the stretching and eccentric exercises would increase calf muscle flexibility through induction of sarcomerogenesis,[23] lengthening of the myotendinous junction,[24,25] and strengthening of the plantar flexors,[26] it seems that this effect is not observable in clinical practice. A study published after our research found that an eight-week eccentric exercise program led to Achilles tendon hypertrophy and increased stiffness in healthy, active males aged 18-35.[27] Tendon hypertrophy was assessed using ultrasound, while relative stiffness was measured through the force-elongation curve during maximal voluntary isometric contraction. The authors suggested that the increased stiffness might result from collagen crimp loss or enhanced fibril crosslinking.[28,29] These new insights might explain our study findings, as the addition of eccentric exercises might have counteracted the passive stretching exercises. Whether stretching exercises alone would have a more favourable effect is currently unknown.

Course of symptoms in new-onset and chronic Achilles tendinopathy

The recurrent and relapsing aspect of Achilles tendinopathy makes it a burdensome injury to have. The Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire is most commonly used to express the severity of Achilles tendinopathy symptoms.[30] In the International Scientific Tendinopathy Symposium Consensus of 2019, 'disability' was deemed one of the core health-related domains for tendinopathy.[31] In a recent international follow-up project, the VISA-A questionnaire was selected as part of the core outcome set by patients and health professionals.[32] The VISA-A questionnaire was developed to express in a numeric scale of 0 to 100 how physically disabling Achilles tendinopathy is. Our study showed that patients with Achilles tendinopathy consider symptoms acceptable if the VISA-A score was equal to or above 50 points after 12 weeks of treatment, and equal to or

above 60 points after 24 weeks of treatment. Furthermore, we determined that the minimal clinically important difference (MCID) for the VISA-A score was 14 points after 12 weeks, and 7 points after 24 weeks. This means that an improvement in symptoms was noticeable for a patient if their VISA-A score improved by 7 points in 24 weeks. Knowing the MCID of the VISA-A score is useful for the power analysis in future research and for interpreting whether study outcomes are relevant for patients, particularly when evaluating the effect of a new treatment.

In our study, one third of patients reported persisting symptoms one year after developing Achilles tendinopathy.[33] When looking at the VISA-A score, two-thirds of patients did not reach the VISA-A score of a person with a healthy tendon. We think this difference might be explained by the acceptance of the limitations due to Achilles tendinopathy; patients adjusted, for example, their sports activities, which resulted in experiencing less or no symptoms. This is not completely reflected by the study, as a quarter of patients adjusted their running activities. Interestingly, a higher running distance per week before the onset of Achilles tendinopathy was associated with a lower risk of developing persisting symptoms. We found a positive trend towards an association between having a metabolic disorder and developing persisting symptoms.

As some express that 'pain is an emotion', one could also imagine that coping with pain may play a role in developing persisting symptoms. In our study,[34] we defined active coping as a mechanism where the patient attempts to control the pain or increase function despite pain, and passive coping as a mechanism that consists of helplessness and externalization of the pain control to other resources. We found no association between the course of Achilles tendinopathy symptoms and the level of active coping, or the level of passive coping. Furthermore, we wondered if patients with persisting Achilles tendinopathy were affected by abnormal pain processing due to a neuropathic pain component. A neuropathic pain component is associated with a low pain threshold. We found that patients with a likely neuropathic pain component experienced more severe Achilles tendinopathy symptoms at every time point, but the course of symptoms was similar to patients with an unlikely or unclear neuropathic pain component. This shows that patients with a likely neuropathic pain component respond similar to regular treatment, but they do experience more severe symptoms than patients with an unlikely or unclear neuropathic pain component.

To complete our insight in the course of Achilles tendinopathy, we performed a 10-year follow-up study in 54 patients with chronic midportion Achilles tendinopathy.[35] One fifth of the patients reported having Achilles tendinopathy

symptoms at this long-term follow timepoint. More than half of patients had to adjust their sports activity, with half of those making these adjustments because of Achilles tendinopathy symptoms. Only one third of patients returned to sports at their previous level without pain. In this study, we did not identify prognostic factors for an increased risk of having symptoms after 10 years follow-up.

Comparison to literature

Persisting symptoms of Achilles tendinopathy, measured with the VISA-A score (0-100 points), is a preferred and validated outcome of most Achilles tendinopathy studies.[30] To understand what patients consider 'persisting symptoms' on this numeric scale, we investigated the patient acceptable symptom state threshold (PASS). The patient acceptable symptom state thresholds for the VISA-A score at 12 and 24 weeks after developing Achilles tendinopathy is relatively low.[36] To interpret the meaning of the VISA-A scores of 50 points at 12 weeks follow-up and of 60 points at 24 weeks follow-up, insight of the limitations of the VISA-A score is essential. The VISA-A score is based on pain, function and sporting activity.[37] Sports activity takes up 40 points of the 100 point-scale. If a patient is satisfied with their sports adjustment, they would never return to the full 100 points. In our study, where we sent an online questionnaire to runners 1 year after developing Achilles tendinopathy, a VISA-A score with a mean of 85 was reported.[33] One in four runners adjusted their running activities, thus did not return to their previous sports level. When we look at the 1-year and 10-year follow-up of patients with chronic midportion Achilles tendinopathy,[35] the reported VISA-A score was 79 at 1-year follow-up and 80 at 10-year follow-up. More than half of patients had to adjust their sports activity. Patients may gradually accept the restrictions caused by the Achilles tendinopathy over time, and live with negligible pain and a reduced level of sports activity level. As patient-reported study outcome, the VISA-A is useful for quantifying disability on a numeric scale. However, as it is heavily influenced by sports activity, it should be interpreted with caution. Patients may also accept a reduced level of sports activity level, which can significantly influence the VISA-A score and therefore the patient acceptable symptom state (PASS). Determining the patients' end goal is crucial to set appropriate targets in research and in clinical practice.

Another useful measure for interpreting change in VISA-A score is the minimal clinically important difference (MCID). The MCID reflects the smallest change in a score between groups that is that is meaningful for a patient. We determined the MCID to be 14 points at 12 weeks and 7 points at 24 weeks. In our discussion, we explained that this large discrepancy in MCID may result from recall bias or the differences in sensitivity and specificity at each

cut-off point. It is worth noting that some participants reported subjective improvement despite experiencing negative changes in their VISA-A scores, suggesting that self-perceived recovery may not always align with objective measures; the MCID at 24 weeks was 7 points (95% CI -10;28), where the lower part of the confidence interval indicates that a patient reported improvement, but their change in VISA-A score was a negative 10 points. This variation in MCID suggests that the MCID may decrease over time, potentially due to factors such as the natural progression of healing, adaptation to treatment, or changes in patient perception of improvement. A recent study by Paantjens et al.[38] analysed soldiers with midportion Achilles tendinopathy and determined the MCID at 26 weeks and 1 year. They used the same anchor-based method as we did in our study, and also determined the MCID by selecting the Youden's index closest to 1. This study found an MCID of 7 at both 26 weeks and after 1 year. This study confirmed that an MCID of at least 7 points represents a noticeable change in symptoms for patients after 6 months.

One third of runners reported persisting symptoms of Achilles tendinopathy after 1 year,[33] which drops to one fifth in a group of patients with chronic midportion Achilles tendinopathy.[35] Current literature reports a wide range in reported persisting symptoms of Achilles tendinopathy, ranging from 23% to 61% over a follow-up from 2 to 10 years.[39-45] Despite considerable heterogeneity between these studies in terms of recovery, type of Achilles tendinopathy, duration of symptoms at baseline and study population, the general trend is that fewer patients report persisting symptoms as time progresses. Nevertheless, the group of patients with persisting symptoms remains high, underlining the importance of developing an intervention strategy for this challenging disorder. An effective treatment can be developed when modifiable prognostic factors are known. These could be taken into account in a personalised treatment approach. However, we could not identify prognostic factors and information on this is currently limited.[46] This suggests that Achilles tendinopathy behaves like fluent stage – remitting and relapsing.

Persisting Achilles tendinopathy is associated with a chronic pain component. To cope with the chronic pain component, patients employ cognitive and behavioural strategies to manage and tolerate their pain.[47] Coping mechanisms can be classified in various ways, such as active or passive coping, as explained previously. Contrary to our hypothesis, we found no evidence that passive coping influenced the course of Achilles tendinopathy symptoms.[34] As both relative rest (passive coping mechanism) and tendon-loading activities (active coping mechanism) are part of the treatment of Achilles tendinopathy, this may explain why passive coping has no effect.[48] We also found no association between active coping scores and the course of Achilles tendinopathy

symptoms. We hypothesise that this lack of associations may be due to two subgroups of patients within the group with a high level of active coping: one subgroup that uses transformation and distraction for rehabilitation and function in daily life, and another group using active coping strategies to continue their activities on their pre-injury level, which might lead to continued overloading of the tendon. A study by Smith et al.[49] supports this hypothesis, finding that active coping may be harmful in patients who use it to ignore pain signals. Another reason for not finding an association between active or passive coping strategy and the course of Achilles tendinopathy symptoms may be the categorization of coping; there are over 100 classification systems for coping.[50] Based on these hypotheses, we suggest that different coping mechanisms may be suitable for different stages of Achilles tendinopathy (new-onset or chronic), and the most effective approach varies per patient. We hypothesise that for new-onset Achilles tendinopathy a passive coping strategy might be more suitable, which contains relative rest, and for chronic Achilles tendinopathy an active coping strategy might be more suitable, as a patient should perform eccentric exercise therapy. A valuable aim for future studies could be to investigate whether patients with new-onset or chronic Achilles tendinopathy experience different outcomes based on their coping strategy, whether this is active or passive.

Last, the presence of neuropathic pain did not affect the improvement of Achilles tendinopathy symptoms over time, compared to the improvement of patients with an unlikely or unclear neuropathic pain component.[36] A study by Wheeler et al.[51] supports this finding, as they also found no association between a neuropathic pain component and poorer outcomes of Achilles tendinopathy. A surprising finding of our study was that patients who had a likely neuropathic pain component experienced more severe symptoms at baseline and during follow-up.[36] We hypothesise that while these patients respond similarly to treatment of Achilles tendinopathy, they may also need their neuropathic pain component addressed. Since the standard treatment of neuropathic pain is pharmacological,[52] it would be valuable to study whether patients with a likely neuropathic pain component and Achilles tendinopathy might benefit from pharmacological treatment.

Caveats and contingencies

Injury incidence is best studied in a large cohort, with clinical assessments of injuries and potential risk factors conducted by a physician. However, as this was challenging to organize for a cohort as large as ours, we opted for online questionnaires. Since Achilles tendinopathy was self-reported, the accuracy of the diagnosis remains uncertain. To improve diagnostic accuracy, we applied strict criteria for its definition.[2] Furthermore, studies confirmed that patients

can accurately locate their pain,[53,54] and recent research confirm that self-reported pain location is correlated with the physician diagnosis.[55] Although a physician did not always confirm the diagnosis in our study, these measures helped minimize the risk of inaccurate diagnoses affecting our data.

The study type and size appear to limit the identification of risk factors for Achilles tendinopathy. As many studies are single-arm cohort studies, we had to estimate the odds ratio in their population by using other studies which report the prevalence of lower extremity tendinopathies (or metabolic and chronic diseases, whichever was missing). The obtained odds ratio's should therefore be regarded as estimates. To better determine risk factors of a given population for lower extremity tendinopathies, we recommend using case-control studies with a large study population.

The use of validated questionnaires is widely accepted and encouraged to convert the experience of symptoms into a numeric scale. However, all questionnaires have their limitations. Understanding these limitations enhances the correct interpretation of outcomes. Not only we, but also others highlight several limitations of the VISA-A questionnaire.[56] This questionnaire may not fully capture the multidimensional nature of tendinopathy, as it primarily focuses on pain and function but overlook other important aspects such as psychosocial factors. There are also concerns about the questionnaire's responsiveness to change over time, suggesting that the VISA-A score might not accurately reflect clinical improvements or deteriorations during rehabilitation. These developments indicate the need for an update of the VISA-A questionnaire that better addresses the complexities of Achilles tendinopathy. A new and promising scoring system called TENDINS-A still includes activity, but not sports as a scoring outcome.[57]

Future Perspectives

As this dissertation consists of two main parts, I would like to suggest two different studies.

To identify risk factors for developing Achilles tendinopathy, a large cohort study would be most suitable. For identifying modifiable risk factors, we would need at least 200 patients, which means that we would need 4000 participants. The cohort should consist of an active population, for example runners, with no Achilles tendinopathy. The participants are screened for potential risk factors such as hypercholesterolaemia with a blood test, and interviewed for other potential risk factors, such as use of a training schedule. The participants would share their GPS data to determine their training load, and whether this is a risk factor for developing Achilles tendinopathy. Patients

would be followed for at least one year, to allow the injury to develop. A well-executed study this size may identify modifiable risk factors that can be used to develop a primary prevention strategy.

To analyse the influence of coping style in the course of Achilles tendinopathy, again a large cohort would be most suitable. This cohort should consist of approximately 200 active patients with new-onset Achilles tendinopathy. The patients would receive digital surveys at baseline and monthly for 1 year, asking about their coping style, severity of symptoms and relapses of injury. The severity of symptoms would be expressed in VISA-A and/or TENDINS score. The set-up of this study defers from our study as it would analyse coping style in patients with new-onset Achilles tendinopathy. It would also be able to detect changes in behaviour over time. The suggested study may identify whether coping style influences the symptom severity and course of Achilles tendinopathy in active patients with new-onset Achilles tendinopathy.

Key points

- Achilles tendinopathy affects a significant portion of runners, with an incidence rate of one in twenty.
- One-third of runners with Achilles tendinopathy develop persisting symptoms after one year and one-fifth of patients with midportion Achilles tendinopathy experience persisting symptoms after 10 years.
- Several risk factors were identified and require clinicians' awareness;
  - Achilles tendinopathy in the previous 12 months
  - Use of a training schedule
  - Use of compression socks
  - Obesity
  - Ankylosing spondylitis
  - Psoriatric arthritis
  - Reactive arthritis
  - Heterozygous familial hypercholesterolemia
  - Systemic lupus erythematosus
- Targeted eccentric calf muscle exercises do not increase ankle dorsiflexion in healthy adolescent soccer players.
- Patients considered their Achilles tendinopathy acceptable if the VISA-A score was ≥50 points after 12 weeks or ≥60 points after 24 weeks. They regarded a change in VISA-A score of 14 points over a 12-week period and 7 points over a 24-week period "as a noticeable change". These scores are essential for interpreting the study as clinically relevant.
- Coping style, whether active or passive, does not influence Achilles tendinopathy symptoms nor does it affect recovery.
- Patients with a neuropathic pain component experience more severe Achilles tendinopathy symptoms both before and after treatment. However, they show a similar improvement in symptoms after treatment compared to patients without a neuropathic pain component.

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Part IV

Appendices

DANKWOORD

We zijn toegekomen aan het dankwoord, of zeg gerust lofzang, aan iedereen die direct of indirect heeft bijgedragen aan dit proefschrift op het gebied van onderzoek, schrijven, doorzetten, planning, gezelligheid en ontspanning. Allereerst wil ik alle studiedeelnemers bedanken voor hun bijdrage aan de verschillende studies, en daarmee aan de wetenschap. Daarnaast wil ik meerdere mensen specifiek bedanken voor hun bijdrage en hulp.

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Beste **dr. Van Middelkoop**, beste Marienke, als bewegingswetenschapper gaf jij mij een andere invalshoek om de onderzoeksresultaten te bekijken en te interpreteren, wat de wetenschap ten goede kwam. Ik heb veel van je geleerd over statistiek, en wat je vooral niet moet doen. Van de discussies over de data en jouw kritische blik heb ik veel geleerd. Dank hiervoor!

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ABOUT THE AUTHOR

Iris Femmigje Lagas was born on January the 1st, 1993 in Haarlem, the Netherlands. She grew up in Zandvoort with her parents Menno Lagas and Jenny Alberta Lagas-Van der Vinne, and her brother Ivar Anton Lagas. Iris graduated high school in 2011 (gymnasium, Kennemer Lyceum, Overveen), after which she started Medicine at the Erasmus University Rotterdam, Rotterdam. Besides her studies, she worked as a radiology assistant at Orthopedium. During her master's degree in 2016, she started her master thesis under supervision of dr. Robert-Jan de Vos, with sports injuries of adolescent soccer players as a subject. This master thesis was conducted at Stichting Betaald Voetbal Excesior and the Feyenoord Academy. The master thesis was the spark that lead to this dissertation.

Since 2016, Iris collaborated with Tryntsje Fokkema (main researcher of the INSPIRE trial, Intervention Study on Prevention of Injuries in Runners at Erasmus MC) and Arco van der Vlist (main researcher of the HAT study, High-volume image-guided injections in midportion Achilles Tendinopathy). After obtaining her master in Medicine in 2019, Iris started her PhD trajectory with supervision of dr. Robert-Jan de Vos, dr. Marienke van Middelkoop and professor Jan AN Verhaar. This PhD trajectory bundled the many different research questions, all aimed at the incidence, course and risk factors of Achilles tendinopathy. After a brief writing period, she started as a resident-not-in-training at the Orthopaedic department of the University Medical Centre Groningen from 2019 to 2020. In 2021, she started her orthopaedic surgery residency at the Franciscus Gasthuis & Vlietland, followed by an academic hospital residency at the Erasmus University Medical Centre and a general hospital residency at Elisabeth-TweeSteden Ziekenhuis.

Iris started dating Dennis Hamminga in 2012, with whom she bought their first house in 2016 in Rotterdam. They moved to Zwolle for one year in the period 2019-2020 for Iris' residency at the University medical Center Groningen. After being accepted as an orthopedic resident by the Regionale OpleidingsGroep Orthopedie (ROGO) Rotterdam, they moved to Heusden in 2020. Iris and Dennis registered their partnership in 2021, and celebrated their wedding on the 23th of October in 2025.. They were blessed with their daughter Emily Jaina Hamminga on the 29th of November 2022.

PHD PORTFOLIO

Courses	Year	ECTS*
Pubmed Workshop *Medical Library, Erasmus MC*	2016	1.0
Endnote Workshop *Medical Library, Erasmus MC*	2016	0.2
Limesurvey Workshop *Medical Library, Erasmus MC*	2018	1.0
Gemstracker Workshop *Medical Library, Erasmus MC*	2018	1.0
Consultation center for Pationt Oriented Research (CPO) course *Congress bureau, Erasmus MC*	2019	0.3
Scientific Integrity *Graduate school, Erasmus MC*	2018	0.3
Basiscursus Regelgeving en Organisatie van Klinische Trials (BROK) *e-BROK academy*	2019	1.5
Biostatistical Methods I: Basic Principes CCO2 *Graduate school, Erasmus MC*	2019	5.7

Teaching activities	Year	ECTS*
Evaluation Minor Orthopedic Sporttraumatology	2019	0.8
Teaching 'Imaging of the tendon' for minor students	2020	0.5

Conferences and (oral) presentations)	Year	ECTS*
Do male youth-elite football (soccer) players with an abnormal physical test outcome have the ability to improve this during a three-month targeted neuromuscular training program? A prospective cohort study *Feyenoord academy, Stichting Betaald Voetbal Excelsior*	2016	2.0

Verbeteren excentrische oefeningen en rekoefeningen van de kuitspier de flexibiliteit? Een gecontroleerde studie bij adolescente voetballers *Vereniging voor Sportgeneeskunde*	2017	1.0
Which runners transit from reactive to chronich Achilles tendinopathy? *International Scientific Tendinopathy Symposium (ISTS)*	2018	1.0
Risk factors for Achilles tendinopathy in runners: a large prospective cohort study *International Scientific Tendinopathy Symposium (ISTS)*	2018	1.0
Risicofactoren voor het ontstaan van Achilles tendinopathie bij hardlopers – een grote prospectieve cohort studie *Vereniging voor Sportgeneeskunde*	2018	1.0
Welke factoren beïnvloeden de transitie van een reactieve naar chronische achilles tendinopathie bij hardlopers? Een prospectieve cohort studie *Vereniging voor Sportgeneeskunde*	2018	1.0
Effects of targeted training on calf muscle flexibility in adolescent soccer players *Erasmus MC Science day*	2019	1.0
The course and risk factors of Achilles tendinopathy *Erasmus MC Department meeting*	2019	1.0
Incidence of Achilles tendinopathy and associated risk factors in recreational runners – a large prospective cohort study *Academic Center for Bone & Joint meeting*	2019	1.0
Are pain coping strategies and neuropathic pain associated with a worse outcome after conservative treatment for Achilles tendinopathy? A prospective cohort study *Scandinavian Sports Medicine Congress*	2020	1.0
A quarter of patients with midportion Achilles tendinopathy has persisting symptoms after 10 years: a prospective cohort study *Scandinavian Sports Medicine Congress*	2020	1.0

Other scientific activities		
Reviewer for Erasmus Journal of Medicine	2016-2019	4.0
Evidence based Espresso *Erasmus MC weekly Journal Club*	2019, 2023	2.0
Total ECTS		**30.3**

LIST OF PUBLICATIONS

Dit proefschrift

Incidence of Achilles tendinopathy and associated risk factors in recreational runners: A large prospective cohort study
Iris F Lagas, Tryntsje Fokkema, Jan AN Verhaar, Sita MA Bierma-Zeinstra, Marienke van Middelkoop, Robert-Jan de Vos
Journal of Science and Medicine in Sport, 2020 May; 23(5): 448-452

Are lower extremity tendinopathies associated with metabolic and chronic diseases? A systematic review
Iris F Lagas, Branco KJF Nijst, Fred Hartgens, Rob A de Bie, Marijn Vis, Jan AN Verhaar, Robert-Jan de Vos
Muscles, Ligaments and Tendons Journal, 2024 Jan; 14 (1):102-130

Effects of eccentric exercises on improving ankle dorsiflexion in soccer players
Iris F Lagas, Duncan Meuffels, Edwin Visser, Floor P Groot, Max Reijman, Jan AN Verhaar, Robert-Jan de Vos
BMC Musculoskeletal Disorders, 2021 May; 22(1): 485

Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire - Minimal Clinically Important Difference for active people with midportion Achilles tendinopathy: a prospective cohort study
Iris F Lagas, Arco C van der Vlist, Robert F van Oosterom, Peter LJ van Veldhoven, Max Reijman, Jan AN Verhaar, Robert-Jan de Vos
Journal of Orthopaedic & Sports Physical Therapy, 2021 Oct; 51(10): 510-516

How many runners with new-onset Achilles tendinopathy develop persisting symptoms? A large prospective cohort study
Iris F Lagas, Tryntsje Fokkema, Sita MA Bierma-Zeinstra, Jan AN Verhaar, Marienke van Middelkoop, Robert-Jan de Vos
Scandinavian Journal of Medicine & Science in Sports, 2020 Oct; 30(10): 1939-1948

Are pain coping strategies and neuropathic pain associated with a worse outcome after conservative treatment for Achilles tendinopathy? A prospective cohort study
Iris F Lagas, Arco C van der Vlist, Robert F van Oosterom, Peter LJ van Veldhoven, Erwin H Waarsing, Sita MA Bierma-Zeinstra, Jan AN Verhaar, Robert-Jan de Vos
Journal of Science and Medicine in Sport, 2021 Sept; 24(9): 871-875

One fifth of patients with Achilles tendinopathy have symptoms after 10 years: a prospective cohort study
Iris F Lagas, Johannes L Tol, Adam Weir, Suzanne de Jonge, Peter LJ van Veldhoven, Sita MA Bierma-Zeinstra, Jan AN Verhaar, Robert-Jan de Vos
Journal of Sports Sciences, 2022 Nov; 40(22): 2475-2483

Overige publicaties

Een man met opvallende claviculae
Iris F Lagas, Joost W Colaris
Nederlands Tijdschrift voor Geneeskunde, 2016 Jun; 160: D176

High knee loading in male adolescent pre-professional football players: effects of a targeted training programme
Iris F Lagas, Duncan E Meuffels, Floor P Groot, Max Reijman, Jan AN Verhaar, Robert-Jan de Vos
Journal of Science and Medicine in Sport, 2019 Feb; 22(2):164-168