REVIEW

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Lower Extremity Tendinopathies are Associated with Metabolic and Chronic Diseases: A Systematic Review

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SUMMARY

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 analyze the association between lower extremity tendinopathies and metabolic and chronic diseases in a systematic review. We searched studies in Embase, Medline Ovid, Web of Science, Cochrane library and Google Scholar. 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 4,287 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 hypercholesterolemia, 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.

Study registration. The review has been prospectively registered in the international PROSPERO database. Protocol details were submitted in June 2019 and registered in September 2019 (registration number: CRD42019140317).

KEY WORDS
Epidemiology; infection; inflammation; risk factors; tendon.

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 etiology is mainly unknown, but degeneration and inflammation are hypothesized 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 hypercholesterolemia, 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 analyze whether there is an association between lower extremity tendinopathies and metabolic and chronic diseases.

MATERIALS AND METHODS

Protocol

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement (19).

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 October 9, 2023. The search strategy is shown in **appendix 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) ≥ 30 kg/m^2), metabolic syndrome, diabetes, dyslipidemia, 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 (I.L. and B.N.). 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 (I.L. and B.N.) 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 tendinopa-

thy, 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 (I.L. and B.N.) independently assessed risk of bias (ROB) of the included studies using a standardized form, the Newcastle-Ottawa quality assessment Scale (NOS) (**appendix 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):

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

1. Strong evidence: ≥ 2 studies of high quality and generally consistent findings in all studies (≥ 75% of the studies report consistent findings).
2. 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).
3. Limited evidence: 1 study of low quality.
4. Conflicting evidence: inconsistent findings in multiple studies (< 75% of the studies report consistent findings).
5. 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: *exposed cases* × *not exposed controls* / *exposed controls* × *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 November 1, 2019.

RESULTS

Study selection

After database searching, we identified 6,469 records; 4,287 studies remained after duplicates were removed (**figure 1**). Of all articles, 4,186 were 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

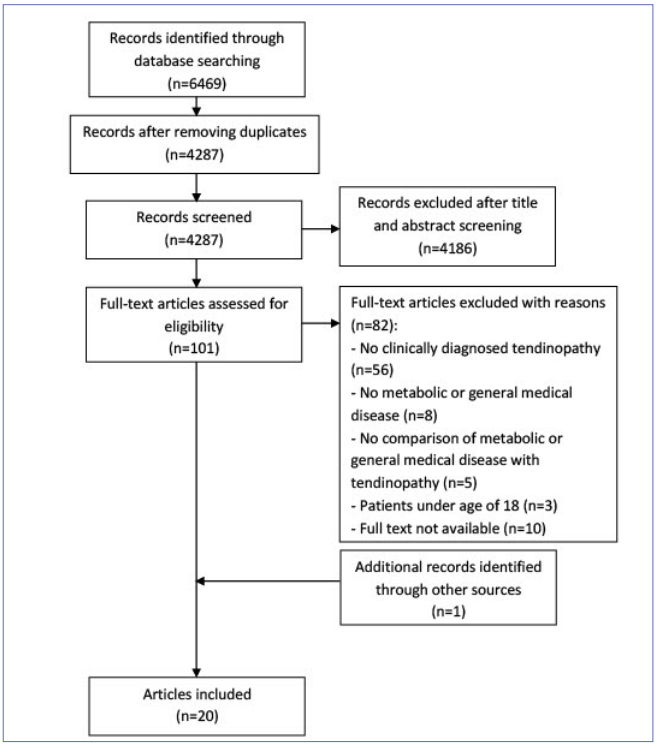

Figure 1. PRISMA flowchart of included articles..

reference screening. The remaining 20 publications, involving 83,948 participants, were included for analysis (22-41).

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 (**appendix 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), hypercholesterolemia (n = 2) (35, 41), heterozygous familial hypercholesterolemia (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 **appendix 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 **appendix 4** we present the characteristics of lower extremity tendinopathies and metabolic and chronic diseases.

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 I**; 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

Table I. Risk of bias (RoB) assessment of the included studies.

	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

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.

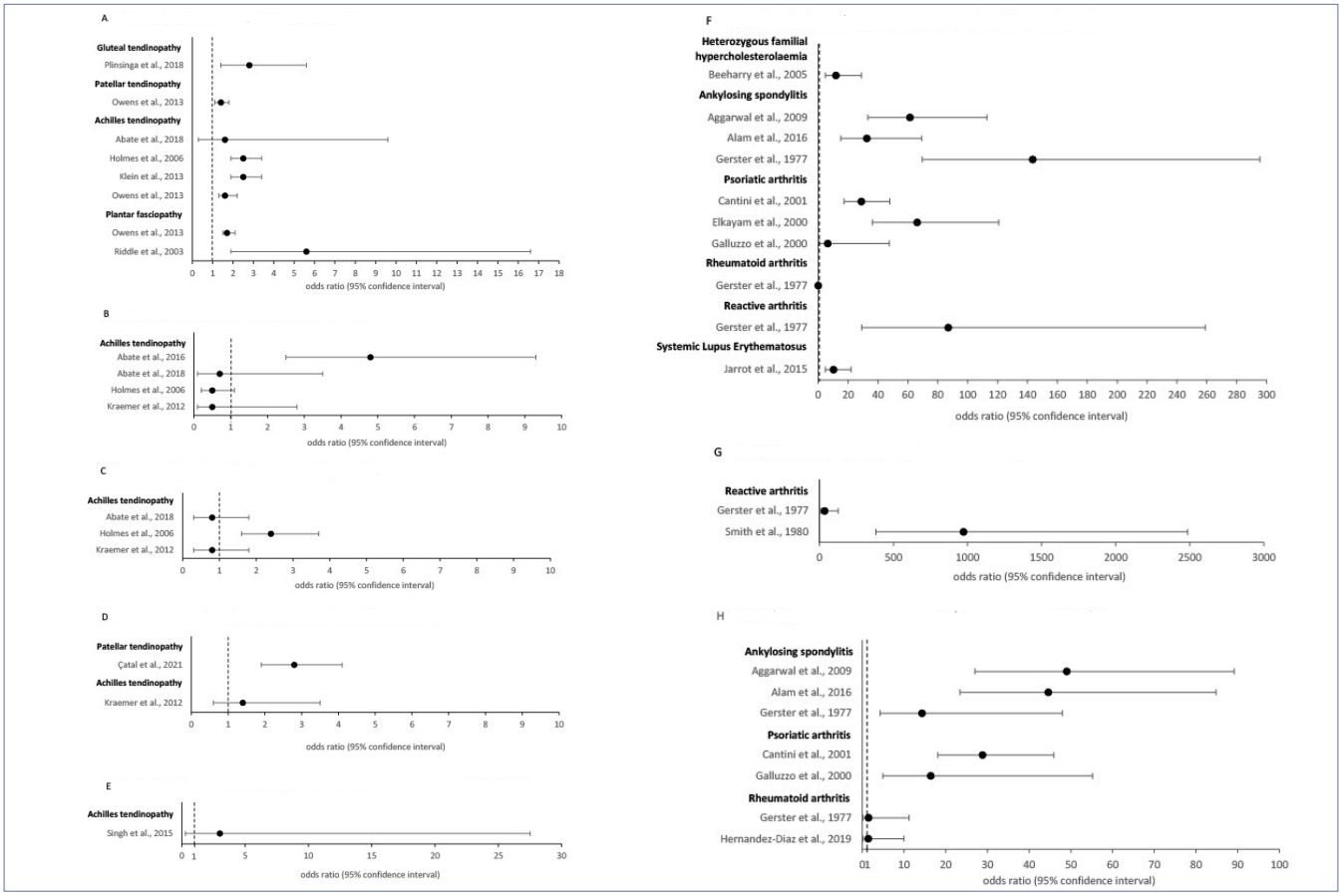

Figure 2. Forest plots of the association between lower extremity tendinopathies and metabolic and chronic diseases.

Lower extremity tendinopathies in association with: **(A)** obesity; **(B)** diabetes; **(C)** hypertension; **(D)** hypercholesterolemia; **(E)** heterozygous familial hypercholesterolemia. **(F)** Metabolic and chronic diseases in association with Achilles tendinopathy heterozygous familial; **(G)** Reactive arthritis in association with plantar fasciopathy; **(H)** Metabolic and chronic diseases in association with plantar fasciopathy.

a metabolic or chronic disease (**table II**). 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 II**). 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 II** 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 **appendix 5**.

Obesity

There is moderate evidence that patients with lower extremity tendinopathies have an increased risk of being obese (**figure 2A**, **appendix 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 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.

Table II. 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
Hypercholesterolaemia	Çatal *et al.* ↑(41), Kraemer *et al.* = (35)	Conflicting evidence
Heterozygous familial hypercholesterolaemia	Singh *et al.* = (39)	Limited evidence for no association
Studies with a metabolic and chronic disease as primary inclusion criteria and lower extremity tendinopathies as outcome		
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

Diabetes

There is moderate evidence that lower extremity tendinopathies are not associated with an increased risk of having diabetes (**figure 2B**, **appendix 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**, **appendix 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.

Hypercholesterolemia

There is limited evidence that having lower extremity tendinopathies is not associated with an increased risk of having hypercholesterolemia (**figure 2D**, **appendix 5**). One case-control study found that patients with lower extremity tendinopathies had an increased risk of developing hypercholesterolemia (41), while one other study found no association (35). Hypercholesterolemia was defined by the studies as a cholesterol of ≥ 240 mg/dL or as self-reported (35, 41). The prevalence of hypercholesterolemia 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 hypercholesterolemia was the primary inclusion criterion and lower extremity tendinopathies the outcome.

Heterozygous familial hypercholesterolemia

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

There is limited evidence that heterozygous familial hypercholesterolemia is associated with an increased risk of developing lower extremity tendinopathies (**figure 2F**, **appendix 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 hypercholesterolemia 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,H**, **appendix 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,H**, **appendix 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,H**, **appendix 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 **figure 2F,G**, **appendix 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**, **appendix 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 hypercholesterolemia, and Systemic Lupus Erythematosus. There was conflicting evidence for an association between lower extremity tendinopathies and hypertension, and lower extremity tendinopathies and hypercholesterolemia.

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 hypercholesterolemia 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 disorganization 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 analyzed 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 analyze hypertension as a risk factor for developing lower extremity tendinopathies.

Hypercholesterolemia and HeFH

We found conflicting evidence for the association between lower extremity tendinopathies and hypercholesterolemia (35, 41). This might be due to the criteria set to define hypercholesterolemia: Çatal *et al*. (41) defined hypercholesterolemia with a blood test (total cholesterol levels ≥ 240ml/dL), while hypercholesterolemia 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 analyzed 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" is 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 hypercholesterolemia) did not assess whether these were independent factors.

Future research

To increase the evidence and to analyze 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.

CONCLUSIONS

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 hypercholesterolemia, and Systemic Lupus Erythematosus. Medical professionals should recognize these diseases in an early stage, which might improve personalized management.

FUNDINGS

None.

DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

IL, BN, FH, RB, MV, JV, RV: conceptualization, data performance, writing – original draft. IL, BN: data collection. IL, BN: data analysis.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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ONLINE SUPPLEMENTS

Appendix 1. Search strategy.
09-10-2023

Database searched	Via	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 - Present	3192	3,166
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**	**4,287**

*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.

1. Barbero-Aznarez P, Perez-Tanoira R, Aguirre-Mollehuanca D, Trascasa-Caño A, Fortes-Alen J, Manzarbeitia-Arrambari F, et al. Isolated central nervous system Whipple disease. Surg Neurol Intl. 2022;13.

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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

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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)

Cochrane CENTRAL

((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

Appendix 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
   A. 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.
   B. 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
   C. 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.
   D. 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
A. Yes, it is described that the outcome of interest was not present at the start of the study. 1 star
B. 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.

Appendix 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
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
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 patients with psoriatric 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 psoriatric arthritis	Psoriatic arthritis	Achilles tendinopathy, plantar fasciopathy	Not reported
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

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)				
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
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
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
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

USA: United States of America; SD: Standard Deviation; BMI: Body Mass Index.

Appendix 4. Additional study information.

(A)

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
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

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
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
Smith, USA, 1980	Retrospective cohort	Achilles tendinopathy, plantar fasciopathy	Not reported	Not reported	Not reported	Not reported	Not reported

(B)

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	Hypercholesterolaemia	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)

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
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

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
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

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

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

(A)

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)(1)	-	-
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)
Plinsinga, Australia, 2018	Prospective cohort	204 patients with gluteal tendinopathy	55 (9)	18.14%	57 (28%)	2.8 (1.4;5.6) (1)	-	-	-	-	-	-
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)

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)
Obesity												
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)		
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) (2)		
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												
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) (3)		
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)		

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)
Hypercholesterolemia												
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 hypercholesterolemia												
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) (4)		

(B)

Achilles tendinopathy																
First author (country, year of publication)	Type of study	Baseline participant characteristics			Heterozygous familial hypercholesterolemia		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) (5)								
Alam, Qatar, 2016	Retrospective cohort	62 patients with ankylosing spondylitis	Not reported	83.9%			9 (15%)	32.5 (15.2;69.3) (5)								
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) (5)						
Elkayam, Israel, 2000	Prospective cohort	70 patients with psoriatic arthritis	Not reported	55.71%					18 (26%)	66.2 (36.3;120.8) (5)						
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) (5)						
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) (5)			0 (0%)	0	5 (31%)	87.0 (29.2;259.1) (5)		
Jarrot, France, 201	Retrospective cohort	158 patients with systemic lupus erythematosus	Not reported	9.49%											8 (5%)	10.2 (4.8;21.9) (5)

Achilles tendinopathy																	
First author (country, year of publication)	Type of study	Baseline participant characteristics			Heterozygous familial hypercholesterolemia		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)
Plantar fasciopathy																
Aggarwal, India, 2009	Prospective cohort	70 patients with ankylosing spondylitis	Not reported	84.3%			14 (20%)	49.0 (27.0;89.2) (5)								
Alam, Qatar, 2016	Retrospective cohort	62 patients with ankylosing spondylitis	Not reported	83.9%			14 (23%)	44.6 (23.4;84.8) (5)								
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) (5)						
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) (5)						
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) (5)			1 (1%)	1.5 (0.2;11.2) (5)	3 (19%)	35.3 (9.8;126.7) (5)		
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) (5)				
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) (5)		

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

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