Supplementary file Module 1

Scoping question
Which individuals are at increased risk of developing Achilles tendinopathy and how can this be prevented?

Literature search and selection
Sub-question 1 (risk factors)
In order to answer sub-question 1, a systematic literature search was carried out using the following question:
Which modifiable and non-modifiable factors in individuals without complaints are associated with the onset of Achilles tendinopathy?

The following PICO (population/patient, intervention, outcome and comparison) was drawn up to answer this question:

P: Individuals without complaints of Achilles tendinopathy;
I: Presence of modifiable and non-modifiable factors;
C: Absence of modifiable and non-modifiable factors;
O: Development of Achilles tendinopathy.

Relevant outcome measures
The primary outcome for this sub-question is the onset of symptomatic Achilles tendinopathy. This means that there must be local symptoms in the Achilles tendon in association with tendon-loading activities. This means that the Achilles tendon is less able to tolerate loading or that the complaints affect performance (during sport and/or work). This clinical outcome measure may have been diagnosed by a healthcare provider or be self-reported. The working group stressed that the presence of an abnormal Achilles tendon on imaging without the presence of complaints is not a relevant outcome measure for this sub-question.

The working group considered an odds ratio of 2.0 or higher to be a clinically important difference for the onset of Achilles tendinopathy. However, since there is no scientific literature on which this threshold can be based, the individual determinants that influence the risk will be discussed in the considerations on the degree of clinical importance.

Literature search and selection
For sub-question 1, a systematic review of biomedical risk factors for Achilles tendinopathy was completed at the start of the guideline development.[1] A search strategy had already been drawn up on 12th February 2018 with the help of an information specialist (Table 1.1). This search strategy was repeated on 10th January 2019 for the development of this module.

The working group considered that results from imaging techniques are also relevant for investigating risk factors. For this reason, an exploratory search was carried out for systematic reviews and guidelines regarding abnormalities on imaging as a risk factor for the onset of Achilles tendinopathy. In addition, on 10th January 2019, a second search strategy was added, which focused on retrospective examinations and parameters based on X-ray examinations and MRI examinations as risk factors for Achilles tendinopathy (Table 1.2). In total, 2 different searches were carried out to answer sub-question 1.

The studies were selected for both biomedical risk factors and also imaging parameters as risk factors based on the selection criteria below:
Inclusion criteria:

- The study examined a potential risk factor in relation to Achilles tendinopathy with statistical analysis of the data.

- It was a clinical risk factor. This means that the risk factor can be measured in a clinical setting (e.g. a clinical practice or at a sports club) and that it is not invasive (such as a biopsy). Imaging techniques that are available in daily practice were also included.
- The diagnosis of Achilles tendinopathy is based on clinical findings (local pain and reduced load bearing capacity).
- The study was retrospective or prospective cohort study design.

Exclusion criteria:

- The study did not use an adequate control group (e.g. the contralateral Achilles tendon).
- Preclinical studies

In addition, the presence of existing guidelines was sought for the answer to sub-question 1. The Previous Dutch multidisciplinary chronic Achilles tendinopathy guideline (2007) was consulted. In addition, the (inter)national guideline databases of the Dutch General Practitioners Association (NHG), National Institute for Health and Care Excellence (NICE), National Guidelines Clearinghouse (NGC) and Guidelines International Network (G-I-N) were searched.

Results

The systematic search for biomedical risk factors for sub-question 1 (risk factors) yielded a total of 3544 references after removal of duplications. All references found were reviewed based on title and abstract. After this preselection, the full text of 113 articles was reviewed. A total of 104 of these articles were excluded. A flowchart (Figure 1.1) is attached, containing the reasons for exclusion. In the end, 9 studies met the criteria and were included in the literature analysis for biomedical risk factors.

A recent systematic review was found for the answer to sub-question 1, focusing on parameters on imaging as a risk factor.[2] In this systematic review, the authors included prospective studies that described the predictive value of ultrasound parameters of the Achilles tendon (both insertional and midportion). This systematic review does not include retrospective cohort studies and not all conventional imaging techniques were included (X-ray examinations and MRI examinations are not included).

Eight of the 17 included studies from the systematic review[2] were selected by the working group based on the criteria for this guideline. Through the additional search strategy, 657 references were found, and these were assessed by title and abstract. After this preselection, the full text of 12 articles was reviewed. Potentially relevant reviews were screened for references. A total of 4 additional articles were included from the additional search strategy. Thus, 12 articles (8 from the recent systematic review and 4 from the additional search strategy) are included in the final analysis (Figure 1.1) for answering the question of whether parameters on imaging are risk factors for Achilles tendinopathy.

In the previous multidisciplinary guideline on chronic Achilles tendinopathy (VSG, 2007) no systematic search was carried out to answer the sub-question on risk factors for Achilles tendinopathy. A number of recommendations were made based upon 13 studies with limited methodological quality. Of these studies, 8 were found to be unsuitable to use for answering this question because of the research design (2 cross-sectional studies and 6 case-series or case-reports). The other 5 studies concerned (systematic) reviews, with the reference list being screened for relevant publications. No additional articles are included to answer this question. The Guideline of the Orthopaedic Section of the American Physical Therapy Association described risk factors.[3] NHG, NICE, NGC and G-I-N databases did not identify existing guidelines on Achilles tendinopathy risk factors.

Sub-question 2 (primary prevention)

For the answer to sub-question 2, a systematic literature analysis was carried out with the following question:

Which primary prevention strategy is effective for preventing Achilles tendinopathy in individuals without complaints?

The following PICO was drawn up to answer this question:

P: Individuals without complaints of Achilles tendinopathy;
I: Implementation of a primary preventive intervention programme;
C: Not performing a primary preventive intervention programme;
O: Development of Achilles tendinopathy.

Relevant outcome measures
The primary outcome for this sub-question is the onset of Achilles tendinopathy. The outcome measure may have been self-reported or diagnosed by a healthcare provider. Abnormalities on imaging are not a relevant outcome measure for this sub-question.

The working group considers a 'number needed to prevent' (NNP) of 25 or less to be a clinically relevant preventive effect for the onset of Achilles tendinopathy. This would mean, for example, that the implementation of a preventive intervention in a group of athletes (e.g. a football team with n=25) should prevent at least 1 case of Achilles tendinopathy. This number has also been found to be clinically important in research into an exercise based preventive intervention for hamstring injuries.[4] However, since there is no scientific literature on which this can be based for Achilles tendinopathy and there are multiple factors that determine the NNP, the extent of the effect of the individual interventions will be discussed in the considerations on the degree of clinical importance.

Literature search and selection
In preparation for the development of the sub-question 2, a recently published systematic review of sufficient methodological quality was found.[5] With the support of an information specialist, a search strategy was developed on 10th January 2019 to identify recently published articles on primary prevention effectiveness (Table 1.3) that appeared after the last review of the systematic review (February 2015). Of the articles found, the title and the abstract were screened based upon the criteria below.

Inclusion criteria:
- The study examines a primary prevention strategy for Achilles tendinopathy.
- The diagnosis of Achilles tendinopathy is based on clinical findings (local pain and reduced load bearing capacity).
- The study had a randomised study design.

Exclusion criteria:
- The study did not use an adequate control group (e.g. the contralateral Achilles tendon).
- The design was a cohort study or comparison in which no randomisation has been applied.
- The design was a preclinical study.

In response to sub-question 2, the presence of existing national and international guidelines was also checked: the previous Dutch multidisciplinary chronic Achilles tendinopathy guideline (2007), Guideline Databases of the NHG, NICE, NGC and G-I-N. Existing systematic reviews were also been sought for.

Results
A recent systematic review described and analysed the primary prevention of Achilles tendinopathy and patellar tendinopathy.[5] From this systematic review, 5 articles could be included for answering sub-question 2.

A total of 218 references were found in the systematic search strategy for articles published after the publication of this recent systematic review, and the titles and abstracts were screened. After this preselection, the full text of 12 articles was reviewed. Eventually, 2 additional articles could be added. A flowchart of the selection process is shown in Figure 1.2. A total of 7 studies were included for the answer to sub-question 2, focusing on primary prevention.

The previous Dutch multidisciplinary chronic Achilles tendinopathy guideline (2007) did not describe the subject of primary prevention. The Guideline of the Orthopaedic Section of the American Physical Therapy Association described preventive interventions.[3] The databases of the NHG, NICE, NGC and G-I-N did not contain existing guidelines in the field of primary prevention for Achilles tendinopathy.

Literature Summary

Sub-question 1 (risk factors)

Description of the studies

A total of 21 studies were included for the answer to this sub-question (19 prospective cohort studies and 2 retrospective cohort studies). The characteristics and main results of these studies can be found in Table 1.4. The majority of studies (15/21 studies) did not specify the location of the complaints (midportion or insertional).

The population size varied between 18 and 80,106 participants (median 86) with the number of patients developing Achilles tendinopathy (number of events) ranging between 0 and 450 events (median 10). The mean age was between 18 and 59 years (median 24). The relatively young age of the patients can be explained by the populations studied (military personnel in 5 studies, students in 1 study and professional athletes in 10 studies). The percentage of male participants was higher in 15 studies, compared to 6 studies in which the percentage of female participants was higher (median percentage of male participants 78%). The data for the above mentioned characteristics were not presented in 3 studies. The follow-up period for prospective cohort studies ranged between 1.5 and 156 weeks (median 46 weeks). A total of 45 determinants were studied as possible risk factor for developing Achilles tendinopathy.

The risk of bias (ROB) assessment was done with a standardised tool consisting of 10 items described in the recent systematic review.[1] As a result, some of the studies had already been assessed for quality and these studies were all at high risk of bias. The additional articles focusing on risk factors for imaging were similarly assessed and these studies were also found to have a high risk of bias. For the detailed results of the ROB assessment, see Table 1.5. In order to determine the quality of the evidence, GRADE assessment was carried out.

Results

The results are shown for the onset of Achilles tendinopathy as the only and primary outcome measure for sub-question 1. A division was made into non-modifiable and modifiable risk factors. The risk factors are divided into patient characteristics (including lifestyle), biomechanical factors, pre-existent diseases, medication use, training-related factors and imaging parameters. Table 1.6 presents an overview of the risk factors, the direction of the associations with the primary outcome measure and the level of evidence of the included studies. Due to the heterogeneity of the data, it was not possible to pool the different outcomes, so it was chosen to perform a 'best-evidence synthesis'.[6] Based on the GRADE-assessment and the best-evidence synthesis of the individual studies, a level of evidence for each potential risk factor was determined.

Non-modifiable factors

Patient characteristics

Age

There is no association between age and the onset of Achilles tendinopathy (very low quality evidence). In the largest cohort with 80,106 participants in which 450 events (0.6% of the total

population) occurred, participants with a year of birth of 1980 or later (age approximately ≤ 30 years) had an odds ratio of 0.62 (95% CI: 0.38 to 1.00) for developing Achilles tendinopathy compared to a birth year before 1960 (age approximately ≥ 50 years).[7] This study also shows a not-significantly lower risk of a birth year between 1960 and 1969 and 1970 and 1979, with a dose-response relationship. Three smaller cohort studies found no link between age and developing Achilles tendinopathy.[8-10] Hirschmuller et al.[9] investigated this in 634 long distance runners (29 events; 4.6%) with a mean of 41 years and Van Ginckel et al.[10] investigated129 novice runners (10 events; 7.8%) with a mean age of 39 years. Barge-Caballero et al.[8] investigated this outcome measure in a population that had undergone a heart transplant and was prescribed fluoroquinolones (14 events in 149 participants; 9.4%). As a result, this study examined a relatively older (59 years on average) and very specific population.

Sex

There is no association between sex and the onset of Achilles tendinopathy (very low quality evidence). A study conducted by Wezenbeek et al.[11] in a relatively young population of 18 years old reported that the hazard ratio for women for developing Achilles tendinopathy was 2.82 (95% CI: 1.16 to 6.87). In this study, there were 27 events in 300 participants (9.0%). Three other studies showed no association between sex and the development of Achilles tendinopathy.[7-9] Hirschmuller et al.[9] and Owens et al.[7] demonstrated this with data from large cohort studies (634 and 80,106 participants respectively; 29 and 450 events; 4.6% and 0.6%). Barge-Caballero et al.[8] only investigated this factor in a population that had undergone a heart transplant and was prescribed fluoroquinolones.

Ethnicity

There is no association between ethnicity and the onset of Achilles tendinopathy (very low quality evidence). Owens et al.[7] found no difference in incidence of Achilles tendinopathy between non-Hispanic participants (Americans without European backgrounds) with a white skin colour, non-Hispanic participants with dark skin colour and other ethnicities.

Height

There is no association between body length and the onset of Achilles tendinopathy (very low quality evidence). A study conducted by Wezenbeek et al.[11] in a relatively young population of 18 years old found that patients who developed Achilles tendinopathy were on average 3 cm taller than those who had not developed symptoms. With a standard deviation of 8 cm reported in this study, it is unlikely that this is a clinically important risk factor for the onset of Achilles tendinopathy. In addition, in 4 other studies there was no association between height and the development of Achilles tendinopathy.[9 10 12 13]

Leg dominance

Achilles tendinopathy does not occur more often in the dominant leg than on the non-dominant leg (very low quality evidence). Wezenbeek et al.[11] assessed adolescent students to see whether symptoms developed more often on the dominant leg than on the non-dominant leg. This was found to be not the case in this cohort.

Past history of lower limb tendinopathy

A previous tendinopathy of the lower limb is associated with Achilles tendinopathy (low quality evidence). All 3 studies that examined this outcome measure show an increased risk of developing Achilles tendinopathy symptoms in presence of previous lower limb tendinopathy.[7 9 14] Owens et al.[7] showed an odds ratio (adjusted for baseline characteristics) in a military population of 3.87 (95% CI: 3.16 to 4.75) for those with previous lower limb tendinopathy compared to those without. A similar odds ratio was found in the study by Hirschmuller et al.[9] among long-distance runners. This study found an odds ratio of 3.8 (95% CI: 1.7 to 8.5). The most recent study on this topic by Docking et al.[14] also showed a similar increased risk in professional Australian football players with a relative risk of 3.0 (95% CI: 1.8 to 4.8) (Docking, 2019). In this study, 163 tendons were assessed, with 30 events occurring (18.4%). The increased

risk of Achilles tendinopathy was independent of the side (index or contralateral) of the previous tendinopathy in all studies.

Biomechanical factors

Characteristics of the knee measured with physical examination tests
There is no association between the intercondylar distance of tibia and the onset of Achilles tendinopathy (very low quality evidence). Milgrom et al.[13] described that this parameter, measured with physical examination, did not provide an increased or reduced risk of Achilles tendinopathy in a population of 1405 soldiers in training. During the study, 95 events occurred (6.8%). It is unclear how this test was exactly performed in this study.

Pre-existent diseases

Kidney function disorders
Kidney function disorders (creatinine clearance < 60 ml/min) are associated with the onset of Achilles tendinopathy (very low quality evidence). Barge-Caballero et al.[8] investigated this in a population that had undergone a heart transplantation and had been prescribed fluoroquinolones. A creatinine clearance of < 60 ml/min in this study gave an odds ratio of 6.14 (95%CI: 1.23 to 30.64) compared to a creatinine clearance of ≥ 60 ml/min. Importantly, this was a very specific population in which there are likely to be many co-morbidities and treatments that may play a role in the onset of Achilles tendinopathy. Therefore, these results cannot be extrapolated to the general population.

Modifiable factors

Patient characteristics

Body Mass Index (BMI) and weight
There is no association between BMI or weight and the onset of Achilles tendinopathy (very low quality evidence). The largest cohort study that evaluated BMI as a risk factor for the onset of Achilles tendinopathy, described that in the case of overweight (BMI ≥ 25) there was an odds ratio of 1.29 (95% CI:1.04 to 1.59) and in obesity (BMI ≥ 30) an odds ratio of 1.59 (95% CI:1.16 to 2.17).[7] Six smaller studies showed no link between BMI and the onset of Achilles tendinopathy.[9-13 15] Importantly, only in the studies of Hirschmuller et al.[9] and Van Ginckel et al.[10], adult populations with a mean age of 39 and 41 years old respectively were studied. In the other studies, adolescent populations were studied with a mean age ranging from 18 to 20 years, in which the number of events was lower. For body weight as a risk factor for Achilles tendinopathy, no significant associations were found in 5 studies.[9-13] Once again, adolescent populations were studied for the investigation of this risk factor. One study reported that lower body weight (64.4 versus 61.0 kg, p=0.015) was a risk factor for developing Achilles tendinopathy.[11] However, this did not represent a clinically important difference.

Alcohol consumption
Average alcohol consumption is associated with the onset of Achilles tendinopathy (very low quality evidence). Owens et al.[7] reported in a population of military personnel that 7 to 13 units per week for men and 4 to 6 units per week for women was associated with Achilles tendinopathy with an odds rate of 1.33 (95% CI: 1.00 to 1.76) when compared to non-drinkers. There was no dose-response relationship in this study, because the risk did not increase further at >13 units for men and at >6 units for women.

Smoking
There is no association between smoking and the onset of Achilles tendinopathy (very low quality evidence). Owens et al.[7] found no difference among military personnel between non-smokers, previous smoking or current smokers and the risk of developing Achilles tendinopathy.

Biomechanical factors

Footwear
There is no association between the type of footwear and the onset of Achilles tendinopathy (very low quality evidence). Milgrom et al.[13] investigated in military training whether onset of Achilles tendinopathy is more common when performed on basketball shoes or on lightweight military boots. This was found to be not the case in this young population with mean age of 19 years.

Foot characteristics assessed using physical examination tests
There is no association between static hindfoot inversion or eversion, static position of the medial arch, a pronated foot and the height of the medial arch during dynamic analysis and the onset of Achilles tendinopathy (very low quality evidence). Kaufman et al.[16] concluded that static hindfoot inversion or eversion, the static position of the medial arch, the dynamic height of the medial arch were not associated with the onset of Achilles tendinopathy in 449 soldiers in training. This study involved 30 events (6.7%). Milgrom et al.[13] investigated the relationship between static examination of the medial arch and the development of Achilles tendinopathy in military training; no relationship was demonstrated. A third study assessed the relationship between a static pronated foot position and the development of Achilles tendinopathy in students, and no relationship was shown.[11] These determinants have only been studied in an adolescent population.

Ankle characteristics assessed using physical examination tests
There is conflicting evidence that a reduced 'non-weight-bearing' ankle dorsiflexion angle both with the knee extended and flexed is associated with the development of Achilles tendinopathy (very low quality evidence). Kaufman et al.[16] found that during military training limited ankle dorsiflexion with an extended knee (<11.5°) gave a relative risk of developing Achilles tendinopathy of 3.57 (95% CI: 1.01 to 12.68) compared to normal dorsiflexion angles (11.5 to 15.0°). Mahieu et al.[12] also included soldiers in training (10 events in 69 participants; 14.5%), but did not find an association between the ankle dorsiflexion angle and the onset of Achilles tendinopathy. Rabin et al.[15] studied 70 soldiers in training (5 events; 7.1%) with measurement of the 'non-weight-bearing' dorsiflexion test of the ankle with the knee flexed. Per degree increase in dorsiflexion, the odds ratio changed by 0.77 (95% CI: 0.59 to 0.94) for the onset of Achilles tendinopathy. This means that a larger ankle dorsiflexion angle lowers the risk of the onset of Achilles tendinopathy. Conversely, it can therefore be argued that a limited dorsiflexion therefore increases the risk for developing Achilles tendinopathy. Both the studies of Kaufman et al.[16] and Mahieu et al.[12] show no association between the ankle dorsiflexion angle with the knee flexed and the onset of Achilles tendinopathy.

Calf muscle strength
A higher isokinetic strength of the calf muscles is associated with a lower risk of Achilles tendinopathy (very low quality evidence). Mahieu et al.[12] described that adolescent soldiers in training with a lower isokinetic calf strength had a higher risk of developing Achilles tendinopathy during follow-up (68 vs 86 Nm, $p<0.05$). Using a Receiver Operating Characteristic (ROC) analysis, the authors determined that a cut off value for isokinetic calf strength of 50 Nm gave 85% sensitivity and 4.5% specificity. They therefore consider a value below 50 Nm as a risk factor for Achilles tendinopathy. In this study no association was found between the explosive muscle strength of the m. gastrocnemius and m. soleus (measured by the 'standing broad jump' test) and the onset of Achilles tendinopathy.

Hip characteristics assessed using physical examination tests
There is no association between the external rotation of the hip and the onset of Achilles tendinopathy (very low quality evidence). Milgrom et al.[13] reported that this value, measured on physical examination, did not result in an increased or reduced risk of Achilles tendinopathy in a population of soldiers in training. It is unclear how this test was exactly performed in this study.

Gait analysis
An abnormal gait pattern with a (1) decreased forward progression of the centre of mass during the propulsion phase or an (2) increased lateral foot roll-over during the full contact phase is associated with the onset of Achilles tendinopathy (very low quality evidence). In the study of van Ginckel et al.[10], novice adult runners were analysed using a gait analysis during running on a treadmill before starting a training programme. This showed that a greater displacement of the centre of mass during the propulsion phase has a protective effect on the onset of Achilles tendinopathy (OR 0.92 per mm, 95% CI: 0.86 to 0.98). In addition, the ratio was calculated to assess the roll-over of the foot by the following formula: (force under metatarsal I-force under metatarsal V)/sum of forces under all metatarsals. A negative value means a more lateral roll-over of the foot and a positive value a more medial roll-over. The participants who developed Achilles tendinopathy were found to have a more lateral roll-over of the foot during the full contact phase (-0.27 versus -0.17, p=0.009) (Van Ginckel, 2009). It is unknown whether these values fall within the measurement error. In addition, the number of events is low, especially if this is related to the number of factors analysed in this study.

Medication

Fluoroquinolones
The use of ofloxacin (fluoroquinolone antibiotic) is associated with the onset of Achilles tendinopathy (very low quality evidence). This was investigated in one study by van der Linden et al.[17], where patients taking different types of fluoroquinolones were compared to a group who had been prescribed antibiotics from another class (amoxicillin, trimethoprim, cotrimoxazole or nitrofurantoin). A total of 10,800 patients participated, with only 8 events occurring (0.07%). When using ofloxacin, an odds ratio of 10.1 (95% CI: 2.2 to 46.0) was found. This association was not demonstrated in the use of ciprofloxacin, norfloxacin and fluoroquinolones as a group. Barge-Caballero's et al.[8] evaluated the use of levofloxacin as a risk factor for the onset of Achilles tendinopathy in patients wo had undergone a heart transplantation. No association was shown in this particular group. In addition, there is a very low level evidence that an increased time between heart transplantation and starting fluoroquinolones is associated with the onset of Achilles tendinopathy. The risk of Achilles tendinopathy in this particular population increased each year that fluoroquinolones treatment was started later with an odds ratio of 1.39 (95% CI: 1.11 to 1.74). So the later the fluoroquinolone treatment was initiated after the heart transplantation, the higher the risk of developing Achilles tendinopathy. These outcomes cannot be extrapolated to the general population.

Corticosteroids
There is no association between the daily dose of prednisone and the onset of Achilles tendinopathy (very low quality evidence). Barge-Caballero et al.[8] investigated this in a population that had undergone a heart transplantation and had been prescribed long-term prednisone for the prevention of graft rejection. The total duration of the prednisone was not described. No association was found between the daily prescribed amount of prednisone and the onset of Achilles tendinopathy in this particular population (9.0 versus 10.0 mg per day).

Training-related factors

Number of training hours
There is no association between the number of training hours and the onset of Achilles tendinopathy (very low quality evidence). Wezenbeek et al.[11] showed this in a population of students with a mean age of 18 years. Hirschmuller et al.[9] investigated this association in a population of long-distance runners (mean age 41 years). This study also found no association between the number of training hours and the onset of Achilles tendinopathy. It should be stressed that this risk factor has been measured at one point in time, so it does not reflect a change in training hours.

Level of physical activity and performance

There is no association between the level of physical activity and performance and the onset of Achilles tendinopathy (very low quality evidence). This is based on 3 studies that found no association between activity level and the onset of Achilles tendinopathy.[10 12 13] Mahieu et al.[12] included an adolescent population of military personnel in training and found that the activity index (intensity multiplied by duration of the training) did not differ between participants who developed Achilles tendinopathy and those who did not. The same method was used by Van Ginckel et al.[10] in a population of runners (mean age 39 years) and where no association was found between activity level and the onset of Achilles tendinopathy. Milgrom et al.[13] included an adolescent population of soldiers in training and showed that the results of a 2-km running test and the maximum number of pull-ups and sit-ups were not a risk factor for the onset of Achilles tendinopathy. These studies investigated the level of activity at one point in time and no studies have been carried out on changes in activity level as a risk factor.

Training season

Physical training in the winter season is associated with the onset of Achilles tendinopathy (very low quality evidence). Milgrom et al.[13] investigated this by comparing soldiers in training who followed their 14-week basic training in winter or summer. The incidence of Achilles tendinopathy was 9.5% in the winter period versus 3.6% in the summer period (p=0.001). It is not clear which seasonal factor may influence this. Hypothetically, this difference can be caused by, for example, a lower temperature or by harder ground during the training sessions. These factors are not mentioned in the particular study.

Imaging

Ultrasound thickness of the Achilles tendon

There is conflicting evidence that Achilles tendon thickness on ultrasound is associated with the development of Achilles tendinopathy. Five studies showed that a greater antero-posterior tendon diameter inferred a higher risk of developing Achilles tendinopathy, compared to 6 studies that showed no association. Most studies did not distinguish between midportion and insertional Achilles tendinopathy, except the study of Wezenbeek et al.[11] which clearly described that it was on midportion Achilles tendinopathy. Fredberg et al.[18] included 54 professional male footballers between the age of 18 and 35 years. They measured the presence of fusiform thickening on ultrasound before the start of the season (6 events in 96 screened tendons; 6.3%). The risk of developing symptoms of the Achilles tendon during the season (total 46 weeks) was higher with baseline ultrasound abnormalities; 45% of players with fusiform thickening developed symptoms during the season, while only 1.2% of players without fusiform thickening developed symptoms (p<0.05). In a similar study by Fredberg et al.[19], 122 professional male footballers with a mean age of 25 years were included. The presence of a fusiform thickening on ultrasound before the start of the season resulted in a relative risk of 2.8 for developing symptoms localised to the Achilles tendon during the following season (95% CI: 1.6 to 4.9). In this study, 39 events occurred in 244 screened tendons (16.0%). Jhingan et al.[20] studied male footballers (mean age 23 years). There were 6 events in 36 screened tendons. This study showed that tendons that became symptomatic during the 12 months follow-up were significantly thicker on baseline as measured with ultrasound (median 0.53 cm versus 0.48 cm, p=0.041). Ooi et al.[21] examined 42 male rugby players (mean age 22.5 years; 6 events; 14.3%). This study showed that tendons that became symptomatic during the season (duration 39 weeks) were significantly thicker on baseline ultrasound examination compared to players who did not develop symptoms (0.57±0.05 cm vs 0.50±0.03 cm, p<0.001). The last study in which a positive association was found was conducted in an adult population (mean age 41 years) of 634 long-distance runners.[9] This study showed that tendons that became symptomatic during the following year were significantly more likely to show fusiform thickening on ultrasound examination (48% vs 14%, p<0 .001).

Of the studies that showed no association, two were conducted in 18 and 163 professional male footballers aged on average 24 years (3 and 30 events, respectively; 16.7% and 18.4%). The other studies were carried out on 22 cross country runners aged 19 years (0 events; 0%), 37

professional fencers aged 27 years (1 event; 2.7%), 79 ballet dancers and dancers aged 27 years (7 events; 8.9%) and 300 students aged 18 years (27 events; 9.0%). The follow-up duration for these studies ranged between 22 and 156 weeks (in two studies the follow-up duration was not reported).[11 14 22-25]

Ultrasound Doppler flow

There is no association between intratendinous and peritendinous ultrasound Doppler flow and the onset of Achilles tendinopathy (very low quality evidence). Only 1 study showed a positive association, compared to 7 that showed no association. The only study that showed a positive association was conducted by Hirschmuller et al.[9] in 634 long distance runners (mean age 41 years) (29 events in 634 participants; 4.5%). In this study, the presence of Doppler flow at baseline resulted in an odds ratio of 6.9 (95% CI: 2.6 to 18.8) for the development of Achilles tendinopathy in the following year. Of the studies that showed no association, 2 were conducted in 22 and 21 runners respectively, aged 19 and 37 years on average (0 events in 22 participants, and 4 events in 21 participants; 19.1%, respectively), 1 in 18 professional male footballers (mean age 23 years, 6 events in 36 screened tendons; 16.7%), 1 in 42 professional male rugby players aged 23 years (6 events in 42 participants), 1 in 37 professional fencers (mean age 27 years, 1 event in 74 screened tendons; 1.4%), 1 in 86 semi-professional badminton players aged 22 years (20 events in 172 screened tendons; 11.6%) and 1 in 79 professional ballet dancers and dancers averaging 27 years old (7 events in 158 screened tendons; 4.4%). The follow-up duration for these studies ranged between 1.5 and 166 weeks (in 1 study the follow-up duration was not reported).[20-22 24-27] In 4 studies, only intratendinous Doppler flow was assessed, in 1 study both intratendinous and peritendinous Doppler flow was assessed and in 3 studies the location of the Doppler flow was not specified. Seven studies used a semi-quantitative scale to assess the Doppler flow, and 1 study did not specify how the Doppler flow was graded. The location and grading of Doppler flow was no different in the study of Hirschmuller et al.[9] compared to the 3 studies that found no association between intratendinous Doppler flow and the onset of Achilles tendinopathy. The 4 other studies that did not show an association did not specify where the Doppler flow was located (3 studies) or also assessed peritendinous Doppler flow (one study). Even if these studies are not included in the best-evidence synthesis, there would still be a very low quality evidence that there is no association between Doppler flow and the onset of Achilles tendinopathy.

Presence of hypoechoic regions on ultrasound

There is conflicting evidence whether hypoechoic areas on ultrasound are associated with the onset of Achilles tendinopathy. Two studies showed a positive association, compared to 5 studies that showed no association. Comin et al.[22] included 79 professional ballet dancers and dancers (mean age 27 years). This study showed that the presence of moderate to severe hypoechoic regions on ultrasound at baseline was present in 42.8% of Achilles tendons of the participants who developed symptoms over the following 2 years (n=7) versus 10.6% (n=16) of the tendons of the participants who did not develop symptoms (p=0.038). The other study that showed a positive association was conducted by Hirschmuller et al.[9] in 634 long distance runners with a mean age of 41 years. It found that baseline hypoechoic areas were more common in participants who developed symptoms of midportion Achilles tendinopathy the following year (38% in symptoms of midportion Achilles tendinopathy compared to 12% in asymptomatic runners, p<0.001). Of the studies that showed no association, 2 were conducted in 22 and 21 runners (mean age 19 and 37 years), 1 in 18 professional male footballers (mean age 23 years), 1 in 42 professional male rugby players (mean age 23 years) and 1 in 37 professional fencers (mean age 27 years) (Giombini, 2013; Hagan, 2018; Jhingan, 2011; Ewe, 2015; Ewe, 2016).[20 21 24 25 27]

Achilles tendon cross-sectional surface area on ultrasound

There is a very low quality evidence that a larger ultrasound cross-sectional surface area is associated with the onset of Achilles tendinopathy. Ooi et al.[21] examined this potential risk factor in 42 male rugby players (mean age 22.5 years). This study demonstrated that tendons that became symptomatic during the season (duration 39 weeks) had a significantly larger Achilles

tendon cross-sectional area on ultrasound examination at baseline compared to players without complaints (0.67±0.07 cm² versus 0.57±0.06 cm², p<0.001).

Partial ruptures of the Achilles tendon on ultrasound
There is conflicting evidence whether ultrasound-detected partial ruptures are associated with the onset of Achilles tendinopathy. Ooi et al.[21] examined a population of 42 male rugby players (mean age 23 years) for the presence of partial ruptures of the Achilles tendon (defined as intratendinous delaminations observed during ultrasound). Partial ruptures were present in 50% of the Achilles tendons of the participants who developed symptoms over the following 2 years (n=6), compared to 11% of the tendons of the participants who did not develop symptoms (n=36). A significant association was reported (p=0.048). Comin et al.[22] found no association among 79 professional ballet dancers and dancers (mean age 27 years). This study found that partial ruptures were not observed in the participants who developed symptoms over the following 2 years (n=7), but in 7.3% (n=11) of the participants who did not develop symptoms (n=151).

Ultrasound tendon structure
There is no association between the ultrasound tendon structure and the onset of Achilles tendinopathy (very low quality evidence). Hagan et al.[25] investigated this in 22 cross country runners (mean age 19 years), measuring the tendon structure at baseline using a qualitative assessment of the organisation of the tendon structure. At baseline, there was a normal ultrasound tendon structure in all runners. None of the runners developed Achilles tendinopathy during follow up, which meant that no association could be described (exact follow-up duration not mentioned).

Intratendinous calcifications on ultrasound
There is no association between the presence of intratendineous calcifications on ultrasound examination and the onset of Achilles tendinopathy (very low quality evidence). Comin et al.[22] found among 79 professional ballet dancers and dancers (mean age 27 years) that calcifications did not occur in any of the participants who developed symptoms in the following 2 years (n=7), but in 2% of the tendons (n=3) of the participants who did not develop symptoms (n=151).

Ultrasound abnormalities of the peritendineum
There is no association between ultrasound blurring of the peritendineum and the onset of Achilles tendinopathy (very low quality evidence). Jhingan et al.[20] investigated this in 18 professional male footballers with a mean age of 23 years, where no association was found. The incidence of blurring of the peritendineum at baseline among football players who developed Achilles tendinopathy complaints the following year was not reported.

The quality of the evidence
The quality of the evidence is reported for each individual factor and is based in all cases on results from cohort studies. Therefore, the quality starts at low level for the GRADE assessment. The quality per factor is shown in Table 1.7. The level was not increased during the GRADE process for any of the determinants, instead this level was further reduced for the majority of the determinants. This has been done for a number of reasons. In most studies, a small number of participants developed Achilles tendinopathy (for 26 determinants, the total number of events was < 20). Only very strong associations can be demonstrated with this low power and medium to weak associations cannot be detected.[28] A number of determinants were studied primarily in a young adolescent population (7 determinants). A number of determinants were only studied in a very specific patient population (patients undergoing heart transplant; 2 factors).

Sub-question 2 (primary prevention)
Description of studies
A total of 7 randomised trials (RCTs) were included to answer this sub-question. The characteristics and main results of these studies can be found in Table 1.8. Most of the studies (6) did not specify the location of the symptoms (midportion or insertional). Only 1 study explicitly

described that cases involved midportion tendinopathy.[29] The population size varied from 146 to 1093 participants (median 390) with the number of patients developing Achilles tendinopathy (number of events) during follow-up ranging between 1 and 41 (median 8). The mean age ranged from 22 to 39 years (median 25), noting that only 3 out of 7 studies reported the mean age. The percentage of male participants ranged from 79% to 100% (median percentage male 100%). The populations studied were soldiers in training in 4 studies, recreational runners in 2 studies and professional football players in 1 study. The follow-up time ranged from 11 weeks to 52 weeks (median 14). In total, 5 different preventive interventions for Achilles tendinopathy were investigated.

Some of the studies had already been assessed for quality in the recent systematic review.[5] In order to assess all studies consistently in accordance with the current guidelines for RCTs, the working group chose to re-evaluate all included studies with the Cochrane Risk of Bias assessment Tool 1.0. For the detailed results of the assessment of the quality of these studies, we refer to Table 1.9.

Results

The results are shown for the onset of Achilles tendinopathy as the primary outcome measure for this sub-question 2. A subdivision has been made into 5 different preventive interventions for Achilles tendinopathy: shock-absorbing sports shoes, inlays, warming-up and stretching exercises, strengthening exercises for the calf muscles and a specific running training programme. The effectiveness of these interventions was compared to the incidence of Achilles tendinopathy in a control group.

Shock-absorbing sports shoes

Shock-absorbing sports shoes are not effective for the prevention of Achilles tendinopathy (low quality evidence). One RCT was carried out on the effectiveness of shock-absorbing sports shoes compared to conventional army boots in 390 soldiers in training.[30] There was no difference in incidence of Achilles tendinopathy between the two groups after 14 weeks of follow-up (12% in the intervention group, 9% in the control group). The relative risk or the 95% confidence intervals were not presented.

Inlays

It is unclear whether prefabricated inlays are effective for the prevention of Achilles tendinopathy (very low quality evidence). In one RCT the effect of a semi-rigid inlay was compared with no intervention in 77 soldiers in training.[31] After 12 weeks of follow-up, there was no difference in incidence of Achilles tendinopathy between the two groups (13% in the intervention group, 9% in the control group). The relative risk or the 95% confidence intervals were not presented for the Achilles tendinopathy subgroup. In a more recent RCT, the effect of a prefabricated medial support inlay was evaluated compared to a flat sole (placebo) in 306 trainee soldiers.[29] Due to the low incidence of Achilles tendinopathy (2% in the intervention group, 0% in the control group) after 11 weeks of follow-up, it was not possible to apply an adequate statistical analysis in this study. The relative risk or the 95% confidence intervals were not presented.

Warming-up and stretching exercises

A warming-up and stretching exercises are not effective in the prevention of Achilles tendinopathy (low quality evidence). One study of 421 recreational runners assessed the effect of a general warming-up with running exercises and stretching exercises for muscles of the lower extremities.[32] Due to the low incidence of Achilles tendinopathy (1.0% in the intervention group, 0.9% in the control group), it was not possible to apply an adequate statistical analysis in this study. The relative risk or the 95% confidence interval were not presented. In another RCT, the effect of static stretching exercises of the calf muscles (both gastrocnemius and soleus) was investigated compared to stretching exercises of the upper extremities in 1093 soldiers in training.[33] After 12 weeks of follow-up, only 1 individual developed Achilles tendinopathy (0.1%). Therefore, no statistical analysis could be performed in this study due to the low incidence. The relative risk or the 95% confidence interval were not presented.

Strengthening exercises for the calf muscles
Strengthening exercises of the calf muscles are not effective for the prevention of Achilles tendinopathy (low quality evidence). In an RCT of 244 professional football players, cluster randomisation was applied and teams were instructed to do stretching exercises and eccentric strength exercises of the deep and superficial calf muscles 3 times a week during the football season.[19] No additional weights were used when performing the exercises. In the control group regular football training was advised. After 1 year follow-up, there was no difference in incidence of Achilles tendinopathy between the teams performing the exercises and the control teams (15% intervention group (95% CI 8 to 24%), 17% control group (95% CI 11 to 24%)). In the intervention group an average of 2.25 sessions per week were done compared to the 3 sessions prescribed.

Specific running training programme
A running training programme with volume progression is not more effective compared to a schedule with progression of intensity for the prevention of Achilles tendinopathy (low quality evidence). In an RCT with 839 runners, runners were advised to maintain a fixed running schedule for 8 weeks.[34] After these 8 weeks, 1 group was advised to increase the volume of running training for 16 weeks and in the other group the intensity was increased. Due to the low incidence of Achilles tendinopathy (0.8% in the intervention group, 1.2% in the control group), it was not possible to apply an adequate statistical analysis in this study. The relative risk or the 95% confidence interval were not presented.

The quality of the evidence
The quality for preventive interventions is based on results from RCTs and therefore starts as high in the GRADE-assessment. The quality per preventive intervention is shown in Table 1.10. For the majority of preventive interventions, there is a very low to low quality of the evidence. The value for the primary outcome measure; onset of Achilles tendinopathy, was reduced by one level in all studies due to methodological limitations. In addition, 4 out of 5 preventive interventions also involved imprecision due to a very low number of patients developing Achilles tendinopathy and/or not presenting the confidence intervals.

Conclusions
Sub-question 1. Which modifiable and non-modifiable factors infer an increased risk of Achilles tendinopathy?

Modifiable risk factors

Midportion and insertional Achilles tendinopathy

Very low GRADE	It is uncertain whether consuming more than 7 units of alcohol per week for men and more than 4 units for women increases the risk of developing Achilles tendinopathy, compared to less alcohol consumption. *Source: Owens et al.*[7]

Very low GRADE	Ofloxacin (fluoroquinolone antibiotic) appears to give a 10-times increased risk of developing Achilles tendinopathy, compared to antibiotics not belonging to the fluoroquinolone group. *Source: van der Linden et al.*[17]

Very low GRADE	A higher isokinetic force of the planter flexors of the ankle may protect against the onset of Achilles tendinopathy. *Source: Mahieu et al.*[12]

Very low GRADE	A more lateral foot roll-over and decreased forward motion during the propulsion phase on gait analysis may increase the risk of developing Achilles tendinopathy. *Source: Van Ginckel et al.*[10]

Very low GRADE	Training in the winter seems to give a 2 to 3 times higher risk of Achilles tendinopathy compared to training in the summer. *Source: Milgrom et al.*[13]

Very low GRADE	An increased cross-sectional surface of the Achilles tendon, measured by ultrasound, may increase the risk of Achilles tendinopathy. *Source: Ooi et al.*[21]

Non-modifiable risk factors

Midportion and insertional Achilles tendinopathy

Low GRADE	A previous lower limb tendinopathy seems to infer a 3 to 4 times higher risk of Achilles tendinopathy, compared to those with no previous tendinopathies *Source: Docking et al.*[14]*; Hirschmuller et al.* [9] *and Owens et al.* [7]

Very low GRADE	In patients who have undergone a heart transplantation, impaired kidney function (creatinine clearance < 60 mL/min) and an increased time between transplantation and starting fluoroquinolone antibiotics may increase the risk of Achilles tendinopathy. *Source: Barge-Caballero et al.*[8]

Sub-question 2. Which primary prevention strategy is most effective for Achilles tendinopathy?

Midportion and insertional Achilles tendinopathy

Low GRADE	The following interventions do not seem to be effective for preventing Achilles tendinopathy: shock-absorbing sports shoes, warming-up and stretching exercises and calf muscle strengthening exercises. *Source: Fredberg et al.*[19]*; Milgrom et al.* [30]*; Pope et al.* [33] *and van Mechelen et al.*[32]

Very low GRADE	It is unclear whether prefabricated inlays are effective for the prevention of Achilles tendinopathy. *Source: Bonanno et al.* [29] *and Larsen et al.*[31]

Low GRADE	A running program with gradual increase in volume does not appear to be more effective for the prevention of Achilles tendinopathy than a program aimed at increasing intensity. *Source: Ramskov et al.*[34]

Considerations

Sub-question 1 (Risk factors)

Advantages and disadvantages of the intervention and the quality of the evidence
The primary purpose of answering sub-question 1 (risk factors) was to obtain information on modifiable risk factors and to identify those at higher risk of developing Achilles tendinopathy. This has the main advantage of providing additional information for preventive interventions. The main outcome in all studies was a new onset Achilles tendinopathy. In many studies, no distinction was made in the location of tendinopathy (midportion or insertional), so we discuss Achilles tendinopathy in general. The quality of the studies for answering this sub-question was generally very low. It should also be considered that these type of studies are challenging due to multiple variables that could influence risk and need to be taken into account (e.g. training load). In addition, for almost all potential risk factors, the magnitude of risk was not definitely clinically important (an odds ratio of 2.0 or higher). For this reason, the working group considered that correcting these risk factors should only be considered in a few cases. The considerations are discussed in detail below.

Previous lower limb tendinopathy
There is a higher risk in those with previous lower limb tendinopathy and if people start with a new form of physical activity or want to increase the current load. This is in line with the guideline of the Orthopaedic Section of the American Physical Therapy Association.[3] In 3 studies, previous lower limb tendinopathy was as a significant risk factor.[7 9 14] In these studies, the association achieved or almost achieved the level of predefined clinical importance. Increase or change of (sports) load has not been explicitly investigated as a risk factor. However, in almost all studies involved populations where some form of increase in exercise and sports was initiated. For this reason, the working group made a recommendation on the modification of training loads as a preventive intervention. Recent studies in team sports [35] and endurance sports[36] show that the overall risk of injury is increased when there is a high acute load (e.g. the distance run in km in the past week) compared to the loadbearing capacity (the average distance covered in the previous four weeks). Although this has not been specifically investigated as a risk factor or preventive intervention for Achilles tendinopathy, the working group felt it important to take this into consideration.

Alcohol consumption
It is uncertain whether alcohol consumption is a risk factor for Achilles tendinopathy. One study showed no dose-response relationship; individuals who had higher alcohol consumption (more than 13 alcoholic units per week for men and more than 6 alcoholic units per week for women), had no increased risk of Achilles tendinopathy.[7] The strength of the association was probably not clinically relevant. In addition, a very recent study of runners found that alcohol was not a risk factor for the development of self-reported Achilles tendon pain.[37] This study was not included in the search strategy due to the recent publication date. For these reasons, the working group considered that the role of alcohol consumption as a risk factor for Achilles tendinopathy is limited. As such, specific advice related to alcohol consumption should not be given with the aim of preventing Achilles tendinopathy.

Fluoroquinolones
Ofloxacin appears to be the only antibiotic within the group of fluoroquinolones associated with the onset of Achilles tendinopathy. It is likely that the strength of the association is clinically relevant. In both the previous Dutch multidisciplinary chronic Achilles tendinopathy guideline (2007) and the Guideline of the Orthopaedic Section of the American Physical Therapy Association[3], this association was confirmed. This association was not demonstrated for the entire group of fluoroquinolones. This may have been caused by the low number of cases in this study (n=8).[38] A systematic review (including 5 studies with high risk of bias) has shown that there is an association between fluoroquinolones use as a group and the onset of an Achilles tendon rupture.[39] It is therefore plausible that fluoroquinolones have a direct negative effect on

Achilles tendon tissue. However, the risk of developing Achilles tendinopathy seems very low due to the low number of events and it is not possible to determine whether this is more likely in a certain high-risk population. Only if an equally effective alternative antibiotic is available and the clinical picture allows, then avoiding fluoroquinolones for this reason can be considered. This view is also supported by the European Medicines Agency (EMA).

Heart transplantation

Patients who have undergone a heart transplantation and are given fluoroquinolone antibiotics may have an increased risk of Achilles tendinopathy in combination with the following factors: impaired kidney function (creatinine clearance < 60 mL/min) and an increased time between transplantation and starting fluoroquinolone antibiotics.[8] Because the levels of fluoroquinolone antibiotics in the blood were not included as variables in the multivariable model, it is possible that the fluoroquinolone antibiotics were the cause of tendinopathy and of impaired kidney function. This makes it even more uncertain that impaired kidney function is a risk factor for Achilles tendinopathy. As this concerns a very specific population and these results cannot be extrapolated to mainstream clinical practice, the working group chose not to include these potential risk factors in the recommendations.

Calf muscle strength

Reduced calf muscle strength may be a risk factor for Achilles tendinopathy. The strength of the association was not described in an odds ratio or relative risk, which makes it hard to estimate the clinical relevance of this finding. Although this is a modifiable factor, improving it with preventive exercise therapy is not considered as an effective preventive intervention (sub-question 2, considerations).[19] A disadvantage of the study in question in was that calf muscle strength was measured with isokinetic equipment that is not widely available and is expensive.[12] The single leg explosive jump height was also evaluated (as an easily applicable parameter) in this study, but this was not a risk factor for Achilles tendinopathy. Another drawback of this research is that only the m. Gastrocnemius was tested (in extended knee position) and not the m. Soleus. Low strength in this deep calf muscle was associated with the onset of Achilles tendinopathy in recent research.[40]

Gait analysis

Some parameters measured during gait analysis (a more lateral foot roll-over and a decreased forward progression during the propulsion phase) appear to indicate an increased risk of Achilles tendinopathy. The strength of the association for the decreased forward progression during the propulsion phase did not appear to be clinically important. For the more lateral foot roll-over the association may be clinically important. However, the number of events in this study was low (n=10), while the number of parameters examined for a potential association is relatively high (n=6).[10] Eventually, 2 parameters were tested in a multivariable model. According to the 'rule of thumb', 1 factor can be tested for every 10 events. Therefore, the working group considers this to be an ambitious statistical analysis and recommendations for carrying out a running analysis for this indication should be made with caution. This is in line with the recommendations of the previous Dutch multidisciplinary chronic Achilles tendinopathy guideline (2007).

Winter training

Training during the winter season seems to be associated with the onset of Achilles tendinopathy, compared to training in the summer season. The strength of the association was not clearly reported, so the clinical relevance of this finding is unclear. From this study it is unclear what the difference in temperature was and the role of other possible associated factors (e.g. the hardness of the ground at this time of year resulting in a greater ground reaction force).[13] A large-scale study of a cohort of professional footballers also found that footballers in northern Europe were more likely to develop Achilles tendinopathy than players in southern European countries (rate ratio 1.8, 95% confidence interval 1.1 to 2.7).[41] Although the climate between these countries is demonstrably different, there are also many other factors that can explain this small difference (e.g. difference in training load, intensity of play, tactics etc.). The working group considers that

the interpretation of this risk factor is complex and therefore only cautious recommendations can be made based on the current information on this topic.

Cross-sectional surface area on ultrasound
An increased cross-sectional surface area on ultrasound may be a risk factor for developing Achilles tendinopathy. The strength of the association was not shown in an odds ratio or relative risk, making the clinical importance of this finding unclear. For the other ultrasound parameters, no association was found or there was conflicting evidence for an association. In a recent meta-analysis, all abnormal ultrasound parameters were assessed simultaneously in a model for the prognostic value for the onset of Achilles tendinopathy.[2] In this study, a 7 times increased risk for the onset of Achilles tendinopathy in the presence of an ultrasound abnormality (relative risk 7.3, 95% confidence interval 3.0 to 18.2). Although this suggests that structural ultrasound abnormalities are a risk factor for Achilles tendinopathy, the working group considers that this should not affect clinical practice. There are two main reasons for this. First of all, the absolute number of individuals who will develop Achilles tendinopathy with an ultrasound abnormality is relatively low. Thus, while the statistical relationship is strong, the clinical implication is moderate.[2] In addition, it should also be taken into account what the message of "abnormal" images does to the views and behaviour of individuals. Studies in the field of low back pain have shown that abnormal imaging has a negative effect on experienced pain and quality of life.[42] Given that we are not yet able to predict whether we really can improve or modify "abnormal" structure in individuals with Achilles tendinopathy, the working group is cautious with providing recommendations on this topic.

Sub-question 2 (Primary prevention)

When answering sub-question 2, a low quality evidence was found for the ineffectiveness of the various preventive interventions. No study described the 'number needed to prevent' (NNP), which makes it more difficult to estimate the strength of the preventive effect and therefore the clinical importance of these findings.

Interventions not to be recommended
There does not appear to be a preventive effect of shock-absorbing shoes, warming-up and stretching exercises for the calf muscles. In addition, the manner of increasing running load (increase in volume versus intensity) does not seem to have any effect on the onset of Achilles tendinopathy. The working group considers that these preventive interventions should not be recommended. There is also very low quality evidence that inlays have no preventive effect on the onset of Achilles tendinopathy: it is therefore unclear whether there is an effect of inlays. The Guideline of the Orthopaedic Section of the American Physical Therapy Association states that shock-absorbing inlays may have a preventive effect.[3] This is based on a study that, due to the retrospective design, has not been included in our guideline.[43]

Interventions to be considered
Eccentric strengthening exercises of the calf muscles using the body weight during the football season are unlikely to have a preventive effect on the onset of Achilles tendinopathy in professional footballers. Although reduced strength of the calf muscles is a risk factor for developing Achilles tendinopathy, eccentric strength exercises of the calf muscles were not an effective preventive intervention. This finding is in contrast to the clinical expertise of several international research groups and experts in this field.[44 45] There are a number of possible explanations as to why the preventive effect of the exercises was not been demonstrated in this study. It is possible that the adherence (2.25 sessions per week) was too low and the intended effect of increasing the loadbearing capacity of the calf was never achieved. Furthermore, additional weights were not used, while this is recommended as a treatment for lower limb tendon injuries.[46] It seems reasonable to add weights to the strengthening exercises as preventive intervention. Preventive exercises during the season were advised and not during preparation for the season. The working group considers that preventive exercises can be of added value, especially in preparation for a sports season or planned increase in the (work)load. During the

season these exercises may results in too much load on the Achilles tendon for some individuals, with a possible negative effect. This may also explain the ineffectiveness of the intervention. However, also when preventive exercises are advised during preparation for a season, then there is a risk of developing Achilles tendinopathy as a result of the exercises. Too much or too little load can increase the risk of Achilles tendinopathy. The working group is aware of this, but it is also possible that these individuals would also have developed symptoms during a season without performing preventive exercises. Guidance for finding this balance together with a (sports) physiotherapist or sports medicine physician is a consideration. In inactive individuals, the isotonic exercises (combination of concentric and eccentric exercises) of the calf muscles may be sufficiently effective, and in athletes one can consider adding external weights and/or using plyometric forms, to achieve improved calf muscle strength as a potential protective factor. The working group considers that the exercises should then be started in the weeks or months before the start of the new sports season and give an appropriate load to the Achilles tendon in order to maximise the chance of a preventive effect.

Values and preferences of individuals at increased risk of Achilles tendinopathy

Barriers and facilitators for performing preventive interventions by individuals at increased risk of Achilles tendinopathy are currently unknown. Data from a recent running study shows that a previous running injury is the main reason for using preventive measures.[47] Those with previous injuries may be more open to using preventive interventions. In addition, it already appears that 82% of the runners use some form of preventive intervention. However, the type of intervention used is highly variable and there is no specific preference for a particular type.

Cost

There are little to no costs involved in the recommended lifestyle interventions, avoiding specific medications, using strengthening exercises, adjusting the clothing to the season and optimizing the training schedule.

However, performing a gait analysis and possible intervention as a result of the gait analysis (adjusting running technique, the running shoe or using inlays) leads to additional costs. The same applies to undergoing ultrasound examinations.

Acceptability for other stakeholders

The trainer or coach is an important stakeholder in the acceptability of potential interventions for athletes. Implementation of a preventive intervention via a trainer (36%) was chosen by runners as the preferred way of offering the intervention.[47] Trainers or coaches are not always aware of the effectiveness of preventive interventions. Only a small proportion of football coaches (14%) at professional clubs had knowledge of an effective warm-up program to prevent injuries in among youth players.[48] This number increased considerably after an implementation program in which knowledge about this programme was disseminated among football trainers using a website, an instruction DVD, information posters, a workshop and an accompanying (sports)physiotherapist. It is important that information on effective prevention strategies is communicated to the right people. The contextual factors of the individual, the injury and the preventive intervention must therefore always be taken into account and the expectation is that this will be given increasing attention in the future.[49]

Feasibility and implementation

Recent research among runners has shown that a history of a previous running injury is the main reason for starting to use prevention.[47] This shows that runners without previous injury are less open to prevention; this makes applying primary prevention more complex. Almost half (45%) of the runners report that they do not know what kind of preventive intervention they should use. Preference for type of delivery of a preventive intervention is through a website or application (45 to 49%) or through the trainer (36%). Digital media allows widespread accessibility. However, it is questionable whether this large group of people is willing to proceed with the implementation of an intervention, given that previous running injury is the main motivator. The advantage of offering an intervention through a trainer or coach is that the athletes are more

willing to actually implement this intervention. Good cooperation with professional bodies of coaches and trainers with implementation of available knowledge is probably of importance.

Balance between the arguments for and against the intervention

Given the low quality of evidence of the conclusions, no firm recommendations can be made for prevention. The working group considers that it is only possible to consider applying certain interventions in high-risk individuals (a previous history of lower limb tendinopathy and those starting to become active or plan to increase their (sports) load). Given the favourable balance of low costs and potential benefits, the following interventions can be considered: avoiding specific medication (fluoroquinolones), using calf muscle strengthening exercises, adjusting clothing during the winter season and optimising the training programme (gradual progression of training load over time).

If the individual is not concerned about costs of an intervention and understands that there is a very low quality evidence for its effectiveness, then a gait analysis that may result in an intervention (adjusting the running technique, the running shoe or applying inlays) can be considered. If ultrasound is used to determine the risk of Achilles tendinopathy, the trade-off between the cost and the very low quality of evidence must be discussed with the individual. The working group considers that the added value of these analyses (performing a gait analysis or ultrasound) and the potentially resulting preventive interventions is negligible. In addition, the potential negative effect of abnormal findings on specific analyses (gait analysis and/or imaging) on pain and quality of life should be considered.

Figures and Tables in supplementary file Module 1

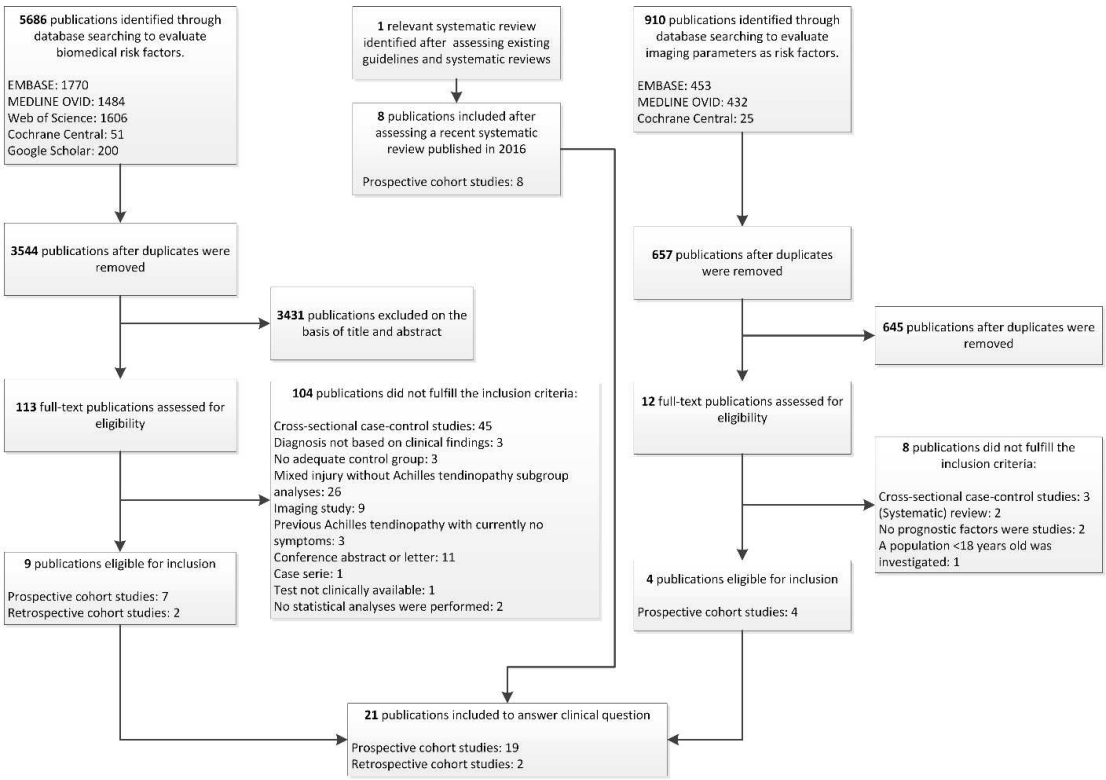

Figure 1.1 – PRISMA flowchart of the selection process for sub-question 1.1: Which modifiable and non-modifiable risk factors are associated with the onset of Achilles tendinopathy?

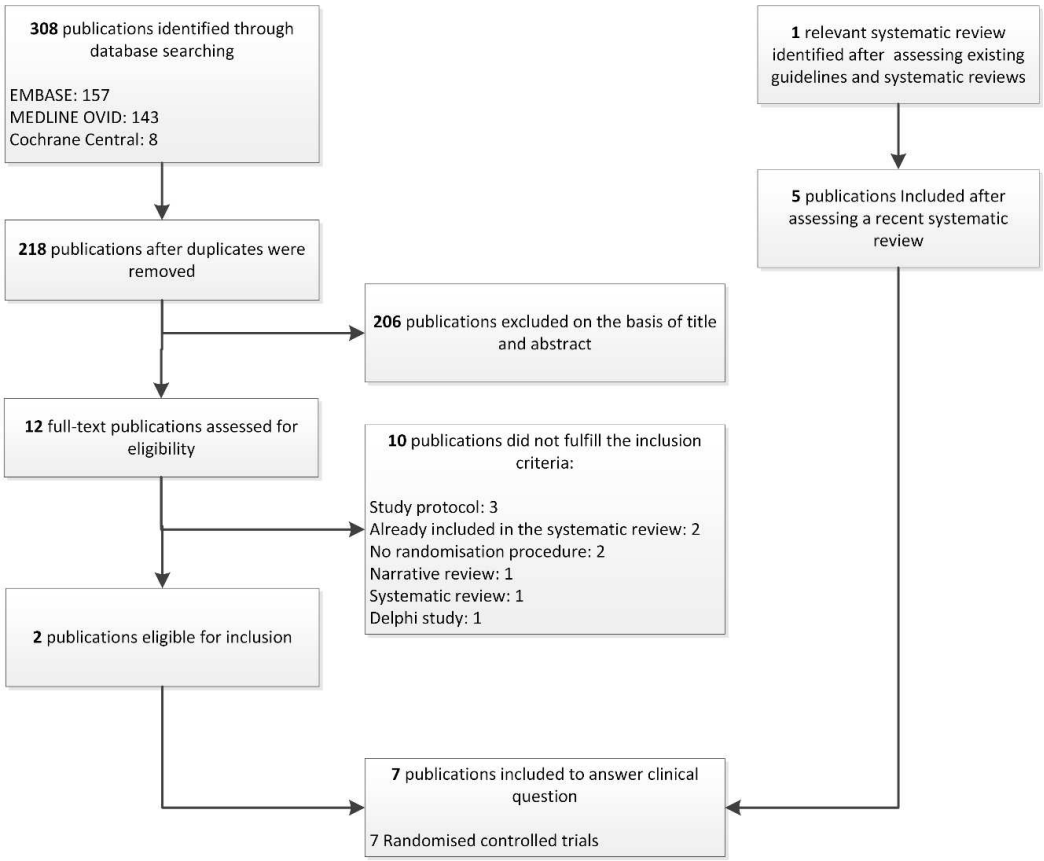

Figure 1.2 – PRISMA flowchart of the selection process for sub-question 1.2: Which primary prevention strategy is effective for the primary prevention of Achilles tendinopathy?

	Initial search	After deduplication
Embase.com	1770	1733
Medline Ovid	1484	560
Web of Science	1606	844
Cochrane	51	1
Google Scholar	200	87
Total	**5111**	**3225**

Database	Search terms
Embase.com	('Achilles tendinitis'/exp OR ((tendinitis/de OR pathology/de) AND 'Achilles tendon'/de) OR (((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))):ab,ti) AND ('risk factor'/exp OR risk/de OR 'disease predisposition'/de OR 'genetic predisposition'/exp OR 'heredity'/de OR 'genetic association'/de OR 'genetic background'/de OR heritability/de OR 'genetic variability'/de OR 'gait'/de OR 'joint mobility'/de OR 'body posture'/de OR 'hyperlipidemia'/de OR 'hypercholesterolemia'/exp OR 'cholesterol blood level'/de OR 'drug induced disease'/de OR 'adverse drug reaction'/de OR 'rheumatoid arthritis'/de OR 'sarcoidosis'/de OR 'gout'/de OR 'spondyloarthropathy'/de OR 'sport injury'/de OR 'biophysics'/de OR biomechanics/de OR 'etiology'/exp OR 'Achilles tendinitis'/exp/dm_et OR interleukin/exp OR 'disease association'/de OR obesity/de OR 'body weight'/de OR 'weight change'/de OR 'weight change'/de OR 'body mass'/de OR mechanics/de OR Pliability/de OR (risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot NEAR/6 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) NEAR/6 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) NEAR/6 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) NEAR/6 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* NEAR/3 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) NEAR/6 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* NEAR/3 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR change* OR gain) NEAR/3 weight) OR 'body mass' OR bmi OR pliabil* OR (foot NEAR/3 position*)):ab,ti)
Medline ovid	(((Tendinopathy/ OR Pathology/) AND "Achilles tendon"/) OR "Achilles tendon"/pa OR (((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))).ab,ti.) AND ("risk factors"/ OR risk/ OR exp "Disease Susceptibility"/ OR "Genetics"/ OR "genetic background"/ OR Heredity/ OR "gait"/ OR "Pliability"/ OR "Posture"/ OR "Hyperlipidemias"/ OR exp "hypercholesterolemia"/ OR "cholesterol"/bl OR "Drug-Related Side Effects and Adverse Reactions"/ OR "Arthritis, Rheumatoid"/ OR "sarcoidosis"/ OR exp "gout"/ OR "Spondylarthropathies"/ OR "Athletic Injuries"/ OR "biophysics"/ OR "Causality"/ OR "Tendinopathy"/et OR exp interleukins/ OR exp obesity/

	OR exp "body weight"/ OR exp "Body Weight Changes"/ OR "Body Mass Index"/ OR mechanics/ OR (risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot ADJ6 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) ADJ6 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) ADJ6 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) ADJ6 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* ADJ3 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) ADJ6 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* ADJ3 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR change* OR gain) ADJ3 weight) OR "body mass" OR bmi OR pliabil* OR (foot ADJ3 position*)).ab,ti.)
Web of Science	TS=(((((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))))) AND ((risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot NEAR/5 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) NEAR/5 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) NEAR/5 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) NEAR/5 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* NEAR/2 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) NEAR/5 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* NEAR/2 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR change* OR gain) NEAR/2 weight) OR "body mass" OR bmi OR pliabil* OR (foot NEAR/2 position*))))
Cochrane	((((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))):ab,ti) AND ((risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot NEAR/6 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) NEAR/6 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) NEAR/6 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) NEAR/6 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* NEAR/3 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) NEAR/6 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* NEAR/3 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR

	change* OR gain) NEAR/3 weight) OR 'body mass' OR bmi OR pliabil* OR (foot NEAR/3 position*)):ab,ti)
Google Scholar	"Achilles | calcaneal tendinitis | tendinopathy | tendinosis" "risk factor | factors" | predisposition | predisposing | susceptibility | "disease association" | etiology | aetiology | etiologic | aetiologic

Table 1.1 – Search strategy for clinical risk factors (sub-question 1)

	Initial search	**After deduplication**
Embase.com	453	446
Medline ovid	432	200
Cochrane CENTRAL	25	11
Total	**910**	**657**

Database	**Search terms**
Embase.com	('Achilles tendinitis'/exp OR ((tendinitis/de OR pathology/de) AND 'Achilles tendon'/de) OR (((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))):ab,ti) NOT ((Conference Abstract)/lim) AND (English)/lim NOT ((animals)/lim NOT (humans)/lim) AND ('risk factor'/exp OR risk/de OR 'disease predisposition'/de OR 'genetic predisposition'/exp OR 'heredity'/de OR 'genetic association'/de OR 'genetic background'/de OR heritability/de OR 'genetic variability'/de OR 'gait'/de OR 'joint mobility'/de OR 'body posture'/de OR 'hyperlipidemia'/de OR 'hypercholesterolemia'/exp OR 'cholesterol blood level'/de OR 'drug induced disease'/de OR 'adverse drug reaction'/de OR 'rheumatoid arthritis'/de OR 'sarcoidosis'/de OR 'gout'/de OR 'spondyloarthropathy'/de OR 'sport injury'/de OR 'biophysics'/de OR biomechanics/de OR 'etiology'/exp OR 'Achilles tendinitis'/exp/dm_et OR interleukin/exp OR 'disease association'/de OR obesity/de OR 'body weight'/de OR 'weight change'/de OR 'weight change'/de OR 'body mass'/de OR mechanics/de OR Pliability/de OR (risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot NEAR/6 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) NEAR/6 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) NEAR/6 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) NEAR/6 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* NEAR/3 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) NEAR/6 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* NEAR/3 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR change* OR gain) NEAR/3 weight) OR 'body mass' OR bmi OR pliabil* OR (foot NEAR/3 position*)):ab,ti) AND ('diagnostic imaging'/exp OR 'echography'/exp OR 'nuclear magnetic resonance imaging'/exp OR (imaging OR echogra* OR ultraso* OR sonogram* OR (tissue NEAR/3 characteristic*) OR utc OR mri):ab,ti)

Medline ovid	(((Tendinopathy/ OR Pathology/) AND "Achilles tendon"/) OR "Achilles tendon"/pa OR (((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))).ab,ti.) AND English.lg NOT (exp animals/ NOT humans/) AND ("risk factors"/ OR risk/ OR exp "Disease Susceptibility"/ OR "Genetics"/ OR "genetic background"/ OR Heredity/ OR "gait"/ OR "Pliability"/ OR "Posture"/ OR "Hyperlipidemias"/ OR exp "hypercholesterolemia"/ OR "cholesterol"/bl OR "Drug-Related Side Effects and Adverse Reactions"/ OR "Arthritis, Rheumatoid"/ OR "sarcoidosis"/ OR exp "gout"/ OR "Spondylarthropathies"/ OR "Athletic Injuries"/ OR "biophysics"/ OR "Causality"/ OR "Tendinopathy"/et OR exp interleukins/ OR exp obesity/ OR exp "body weight"/ OR exp "Body Weight Changes"/ OR "Body Mass Index"/ OR mechanics/ OR (risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot ADJ6 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) ADJ6 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) ADJ6 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) ADJ6 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* ADJ3 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) ADJ6 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* ADJ3 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR change* OR gain) ADJ3 weight) OR "body mass" OR bmi OR pliabil* OR (foot ADJ3 position*)).ab,ti.) AND (exp Diagnostic Imaging/ OR exp Ultrasonography/ OR Magnetic Resonance Imaging/ OR (imaging OR echogra* OR ultraso* OR sonogram* OR (tissue ADJ3 characteristic*) OR utc OR mri).ab,ti.)
Cochrane CENTRAL	((((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))):ab,ti) AND ((risk OR predisposit* OR susceptib* OR genetic* OR heritabil* OR inherit* OR gait OR (foot NEAR/6 (posture* OR dynamic* OR static*)) OR mobil* OR flexib* OR hypercholesterol* OR hyperlipid* OR ((cholesterol* OR lipid*) NEAR/6 (blood OR level*)) OR ((drug OR medicat* OR pharmac*) NEAR/6 (induc* OR adverse* OR reaction*)) OR ((induced OR associat*) NEAR/6 (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*)) OR (rheumat* NEAR/3 arthrit*) OR sarcoidos* OR gout* OR spondyloarthropath* OR spondylarthropath* OR ((sport OR athlet*) NEAR/6 (injur* OR induc*)) OR overus* OR biomechanic* OR biophysics* OR etiolog* OR aetiolog* OR pathogenes* OR (tendon* NEAR/3 (characteristic* OR shape OR composition*)) OR mechanic* OR strain* OR stiff* OR interleukin* OR obes* OR overweight* OR ((body OR change* OR gain) NEAR/3 weight) OR 'body mass' OR bmi OR pliabil* OR (foot NEAR/3 position*)):ab,ti) AND ((imaging OR echogra* OR ultraso* OR sonogram* OR (tissue NEAR/3 characteristic*) OR utc OR mri):ab,ti)

Table 1.2 – Additional search strategy for imaging parameters as risk factors (sub-question 1)

	Initial search	After deduplication
Embase.com	157	156
Medline ovid	143	58
Cochrane CENTRAL	8	4
Total	**308**	**218**

Database	Search terms
Embase.com	('Achilles tendinitis'/exp OR ((tendinitis/de OR pathology/de) AND 'Achilles tendon'/de) OR (((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))):ab,ti) NOT ((Conference Abstract)/lim) AND (English)/lim NOT ((animals)/lim NOT (humans)/lim) AND ('prevention'/de OR 'primary prevention'/de OR 'secondary prevention'/de OR 'tertiary prevention'/de OR prevent*:lnk OR (prevent*):ab,ti)
Medline ovid	(((Tendinopathy/ OR Pathology/) AND "Achilles tendon"/) OR "Achilles tendon"/pa OR (((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))).ab,ti.) AND English.lg NOT (exp animals/ NOT humans/) AND (Primary Prevention/ OR secondary prevention/ OR tertiary prevention/ OR prevent*.fs. OR (prevent*).ab,ti.)
Cochrane CENTRAL	((((Achilles OR calcaneal) AND (tendinitis* OR tendinopath* OR tendinosis* OR tendonitis* OR tendon-patholog*))):ab,ti) AND ((prevent*):ab,ti)

Table 1.3 – Search strategy for primary prevention (sub-question 2)

Study	**Study type**	**Duration of follow-up (weeks)**	**Participants/tendons (cases of AT)**	**Sex (% male)**	**Age, mean ± SD (years)**	**Location injury**	**Risk factors** (Risk ratio, odd's ratio, hazard ratio)	**Quality score** (points)
Barge-Caballero (2008)	RC	NR	149 (14); Heart transplant patients who were prescribed fluoroquinolones	80%	58.8 ± 10.6	Achilles tendinopathy (not specified midportion or insertional)	• A creatinine clearance <60 ml/min was associated with AT compared to a creatinine clearance ≥ 60 ml/min (OR 6.14; 95% CI 1.23-30.64; p=0.03) • Increased time (in years) between heart transplantation and initiation of fluoroquinolone treatment for infectious disease was associated with AT (OR 1.39; 95% CI 1.11-1.74; p=0.005) • No associations were found for age, sex, levofloxacin use and daily prednisone dose (mg)	5
Boesen (2012)	PC	32	86 / 172 tendons (20 tendons); Semi-professional badminton players	65%	21.7 ± 5.0	Achilles tendinopathy (not specified midportion or insertional)	• Intratendinous Doppler flow (grade 1-5) on ultrasound did not predict the development of AT (statistical analysis NR)	6
Comin (2013)	PC	104	79 / 158 tendons (7 tendons); Professional ballet dancers	44%	27.4 (SD NR)	Achilles tendinopathy (not specified midportion or insertional)	• Presence of moderate-to-severe hypoechoic areas on ultrasound were associated with an increased incidence of AT (p=0.038) • No association was found for presence of ultrasonographic tendon thickness, tendon tears, grade of Doppler flow (not specified intratendinous or peritendinous) and intratendinous calcifications	6

Docking (2016)	PC	22	18 / 18 tendons (3 tendons); elite football players in pre-season training	100%	23.8 ± 3.6	Achilles tendinopathy (not specified midportion or insertional)	• Antero-posterior thickness at 3.0 cm proximal of the disappearance of the calcaneus on ultrasound was not associated with the development of AT	6
Docking (2019)	PC	NR	163 / 163 tendons (30 tendons); elite football players	100%	23.9 ± 3.7	Achilles tendinopathy (not specified midportion or insertional)	• A previous history of AT symptoms was associated with the development of AT (RR 3.0, range 1.8-4.8). It was not specified whether this was only true for the side that was previously symptomatic or also for the previously asymptomatic side. • The greatest antero-posterior thickness on ultrasound was not associated with development of AT	4
Fredberg (2002)	PC	46	54 / 96 tendons (6 tendons); Professional football players	100%	NR (inclusion age range 18-35)	Achilles tendinopathy (not specified midportion or insertional)	• Presence of spindle-shaped thickening of the Achilles tendon on ultrasound increased the risk for developing AT (Risk of developing AT 45% if present versus. 1.2% if not present), $p<0.05$)	7
Fredberg (2008)	PC	46	122 / 244 tendons (39 tendons); Professional football players	100%	25.0 (SD NR)	Achilles tendinopathy (not specified midportion or insertional)	• Presence of spindle-shaped thickening of the Achilles tendon on ultrasound at baseline was associated with AT (RR 2.8, 95% CI, 1.6-4.9; P=0.002)	6
Giombini (2013)	PC	156	37 / 74 tendons (1 tendon); Elite fencers	41%	27.1 ± SD NR	Achilles tendinopathy (not	• Presence of increased tendon thickness, hypoechogenicity and increase in the grade of	5

						specified midportion or insertional)	intratendinous and/or peritendinous Doppler flow on ultrasound were not associated with an increased incidence of AT	
Hagan (2018)	PC	NR	22 / 44 (0 tendons); collegiate cross-country runners	41%	19 ± 1.5	Achilles tendinopathy (not specified midportion or insertional)	• Grade of Doppler flow (not specified intratendinous or peritendinous), collagen organisation, hypoechogenicity and tendon thickness on ultrasound were not associated with the development of AT	4
Hirschmuller (2012)	PC	52	634 / 1268 tendons (29 subjects); Long-distance runners	69%	41.2 ± 11.2	Midportion Achilles tendinopathy	• A history of healed Achilles tendons complaints and presence of increased intratendinous Doppler flow on ultrasound were associated with development of symptoms (OR 3.8, p<0.01 and OR 6.9, p<0.001). It was not specified whether the first risk factor was only true for the side that was previously symptomatic or also for the previously asymptomatic side. • The prevalence of ultrasonographically detected spindle-shaped thickening and hypoechogenicity was significantly higher in subjects who developed AT (p<0.001) • The maximum tendon thickness was significantly greater in those subjects who developed AT (p<0.001) • No association between age, height, weight, BMI, sex, running experience, training hours, training volume, weekly mileage and development of AT	6

Jhingan (2012)	PC	52	18 / 36 tendons (6 tendons); Elite football players	100%	23.2 (SD NR)	Achilles tendinopathy (not specified midportion or insertional)	• Mid-tendon thickness on ultrasound was increased at baseline in tendons that became symptomatic during follow-up (p=0.041) • There was no association between hypoechogenicity, paratenon blurring and increased Doppler flow (not specified intratendinous or peritendinous) on ultrasound and the development of AT symptoms	6
Kaufman (1999)	PC	104	449 (30); Navy Sea, Air and Land (SEAL) candidates	100%	22.5 ± 2.5	Achilles tendinopathy (not specified midportion or insertional)	• A tight ankle dorsiflexion with knee extended (<11.5°) was associated with AT compared to a normal dorsiflexion (11.5-15.0°) (RR 3.57; 95% CI 1.01-12.68; p<0.05) • No associations were found for hindfoot inversion, hindfoot eversion, static arch index of the foot, dynamic arch index of the foot, dorsiflexion of the ankle with the knee bent	5
Mahieu (2006)	PC	6	69 (10); Officer cadets	100%	18.4 ± 1.3	Midportion Achilles tendinopathy	• Isokinetic plantar flexion strength at 30 degrees/s was decreased in patients who developed AT for both the right and the left leg and at 120 degrees/s for the right leg (p=0.042, p=0.036 and p=0.029 respectively). Plantar flexion strength was measured using the Cybex Norm dynamometer, which measures strength at constant velocity. • No associations were found for weight, BMI, length, physical activity level, Achilles tendon stiffness, isokinetic plantar flexion strength at 120 degrees/s for the left leg, explosive gastrocnemius-soleus muscle strength	4

							(standing broad jump test) and passive and active ankle joint range of motion outcomes.	
Milgrom (2003)	PC	14	1405 (95); Infantry recruits	100%	18.7 ± 7	Midportion Achilles tendinopathy	• An increase in AT was seen when training in the winter season compared to summer training (p=0.001) • No differences were found in height, weight, BMI, external rotation of the hip, tibial intercondylar distance, arch type, physical fitness performance (2-km run and maximum number of chin-ups and sit-ups done) and shoe type	4
Ooi (2015)	PC	1.5	21 / 42 tendons (4 subjects); Marathon runners	62%	37.1 ± 11.3	Midportion Achilles tendinopathy	• Intratendinous hypoechogenicities and the grade of intratendinous Doppler flow on ultrasound were not associated with development of AT at follow-up after a marathon race	9
Ooi (2016)	PC	39	42 (6); Elite Australian Rules football players	100%	22.5 ± 3.7	Achilles tendinopathy (not specified midportion or insertional)	• The presence of baseline delaminations on ultrasound were associated with development of AT (p=0.048) • Baseline midportion tendon thickness and cross-sectional surface area on ultrasound were significantly greater in players who developed AT compared to those who did not (p<0.001, p<0.001). • Hypoechogenicity and grade of intratendinous Doppler flow on ultrasound were not associated with the development of AT.	6
Owens (2013)	PC	52	80 106 (450); Military service members	70%	NR	Achilles tendinopathy (not specified	• Being overweight and obesity were associated with AT compared to underweight or normal weight (AOR 1.29, 95% CI 1.04-1.59 and AOR 1.59, 95% CI 1.16-2.17 respectively)	6

						midportion or insertional)	• A prior lower limb tendinopathy or fracture was associated with AT (AOR 3.87, 95% CI 3.16-4.75). It was not specified whether this was only true for the side that was previously symptomatic or also for the previously asymptomatic side. • Moderate alcohol use (7-13 units per week for men, 4-6 units per week for women) was associated with AT compared to no alcohol use (AOR 1.33, 95% CI 1.00-1.76) • A birth year of 1980 and later was associated with a decreased risk for AT compared to a birth year before 1960 (AOR 0.62, 95% CI 0.38-1.00) • No associations were found for sex, ethnicity, smoking status and heavy alcohol use (14+ units per week for men, 7+ units per week for women)	
Rabin (2014)	PC	26	70 (5); Military recruits	100%	19.6 ± 1.0	Midportion Achilles tendinopathy	• Every one-degree increase in ankle dorsiflexion with the knee bent was associated with a decreased risk for AT (OR 0.77; 95% CI 0.59-0.94) • No associations were found for BMI and lower extremity quality of movement	7
Van der Linden (1999)	RC	NR	10 800 (8); Patients using fluoroquinolones (index group) or amoxicillin, trimethoprim, cotrimoxazole or nitrofurantoin (reference group)	30%	46.3 (SD NR)	Achilles tendinopathy (not specified midportion or insertional)	• The use of ofloxacin was associated with AT compared to the reference group (AOR 10.1; 95% CI 2.20-46.04) • No associations were found for fluoroquinolones as a group, ciprofloxacin use and norfloxacin use compared to the reference group	3

Van Ginckel (2008)	PC	10	129 (10); Novice runners	15%	39 ± 10	Midportion Achilles tendinopathy	• An increased total anterior displacement of the Y-component of the Center of Force was associated with a decreased risk for AT (OR 0.919; 95% CI 0.859-0.984; p=0.015) • A more medial directed force distribution underneath the forefoot at forefoot flat was associated with a decreased risk for AT (OR 0.000; 95% CI 0.000-0.158; p=0.016) • No associations were found for age, height, weight, BMI or physical activity score	6
Wezenbeek (2018)	PC	104	300 (27); First-year students	47%	18.0 ± 0.8	Midportion Achilles tendinopathy	• Female sex was associated with AT (HR 2.82, 95% CI 1.16-6.87) • Height and body weight were increased in patients with AT (p=0.028 and p=0.015) • No association was found for a pronated foot posture and Achilles tendon thickness 2 or 5 cm proximal to the calcaneal border on ultrasound • No differences were found for BMI, rating of perceived exertion, hours of sports participation and leg dominance	7

Table 1.4 – Data extraction of the prospective and retrospective cohort studies examining risk factors for the onset of Achilles tendinopathy.
AOR, adjusted odds ratio; AT, Achilles tendinopathy; BMI, body mass index; CI, confidence interval; CON; unaffected controls; HR, hazard ratio; km, kilometre; NA, not applicable; NR, not reported; OR, odds ratio; PC, prospective cohort study; RC, retrospective cohort study; RR, risk ratio; SD, standard deviation.

Study	Criteria										Total score	Risk of bias
	1	2	3	4	5	6	7	8	9	10		
Barge-Caballero (2008)	1	1	1	0	0	0	0	1	0	1	5	High
Boesen (2012)	1	1	1	0	1	0	1	0	1	0	6	High
Comin (2013)	1	1	0	1	1	0	1	1	0	0	6	High
Docking (2016)	1	1	1	0	1	0	1	1	0	0	6	High
Docking (2019)	1	0	0	0	1	0	1	1	0	0	4	High
Fredberg (2002)	1	1	1	1	1	0	0	1	1	0	7	High
Fredberg (2008)	1	1	1	1	1	0	0	1	0	0	6	High
Giombini (2013)	1	0	1	1	1	0	0	1	0	0	5	High
Hagan (2018)	0	0	1	1	1	0	0	1	0	0	4	High
Hirschmuller (2012)	1	0	1	1	1	0	0	1	0	1	6	High
Jhingan (2012)	1	0	1	1	1	0	1	1	0	0	6	High
Kaufman (1999)	1	1	0	1	1	1	1	0	0	0	5	High
Mahieu (2006)	0	1	0	1	1	1	1	0	0	1	6	High
Milgrom (2003)	0	0	0	1	1	1	0	0	0	0	3	High
Ooi (2015)	1	1	1	1	1	1	1	1	1	0	9	High
Ooi (2016)	1	1	1	0	1	0	1	1	0	0	6	High
Owens (2013)	1	1	0	1	1	0	1	1	0	0	6	High
Rabin (2014)	1	1	1	1	1	1	1	0	1	1	9	High
Van der Linden (1999)	1	1	1	0	1	0	1	1	0	0	6	High
Van Ginckel (2008)	1	0	1	1	1	1	1	0	0	1	7	High
Wezenbeek (2018)	1	1	1	0	1	1	0	1	0	1	7	High

Table 1.5 – Risk of bias assessment of the cohort of studies examining risk factors for Achilles tendinopathy.
Outcomes of the risk of bias (ROB) assessment tool as presented in the ROB table. Publications were considered to be of low risk of bias if (1) a total score of at least six points was given and (2) one point was given to questions 6, 7, 8 and 10 (marked with the grey columns). The following items were assessed: (1) aim reported; (2) inclusion consecutive subjects; (3) description eligibility criteria; (4) inclusion/exclusion reported; (5) prospective collection of data; (6) use of valid outcome measure; (7) unbiased assessment of outcome measure and risk factor; (8) accuracy of risk factor measurement; (9) loss to follow-up rate and (10) adequacy of statistical analyses.

Potential risk factors	Study (first author and direction of association)	Best evidence synthesis
Patient characteristics (non-modifiable)		
Age	Barge-Caballero =, Hirschmuller =, Owens birth year >1980 ↓, Van Ginckel =	Limited evidence for no association
Sex	Barge-Caballero =,Hirschmuller =, Owens =, Wezenbeek female ↑	Limited evidence for no association
Ethnicity	Owens =	Limited evidence for no association
Height	Hirschmuller =, Mahieu =, Milgrom =, Van Ginckel =, Wezenbeek ↑	Limited evidence for no association
Prior symptoms of lower extremity tendinopathy	Owens ↑, Docking 2019 ↑, Hirschmuller ↑	Limited evidence for positive association
Patient characteristics (modifiable)		
Body Mass Index	Hirschmuller =, Mahieu =, Milgrom =, Owens BMI >25.0 ↑, Rabin =, Van Ginckel =, Wezenbeek =	Limited evidence for no association
Body weight	Hirschmuller =, Mahieu =, Milgrom =, Van Ginckel =, Wezenbeek ↓	Limited evidence for no association
Alcohol use	Owens 7-13 units per week for men, 4-6 units per week for women↑ , Owens 14+ units per week for men, 7+ units per week for women =	Limited evidence for positive association (moderate alcohol use)
Smoking	Owens =	Limited evidence for no association
Biomechanical factors		
Shoe type	Milgrom =	Limited evidence for no association
Leg dominance	Wezenbeek =	Limited evidence for no association
Limited non-weight-bearing ankle dorsiflexion with knee extended	Kaufman <11.5° ↑, Mahieu =	Conflicting evidence
Increased non-weight-bearing ankle dorsiflexion with the knee bent	Kaufman =, Mahieu =, Rabin ↓	Conflicting evidence
Hindfoot inversion	Kaufman =	Limited evidence for no association
Hindfoot eversion	Kaufman =	Limited evidence for no association
Static arch index of the foot	Kaufman =, Milgrom =	Limited evidence for no association
Dynamic arch index of the foot	Kaufman =	Limited evidence for no association
Pronated foot posture	Wezenbeek =	Limited evidence for no association
Increase in isokinetic plantar flexor strength at 30 degrees/s (low velocity)	Mahieu ↓	Limited evidence for protective association

Explosive gastrocnemius-soleus muscle strength	Mahieu =	Limited evidence for no association
External rotation of the hip	Milgrom =	Limited evidence for no association
Tibial intercondylar distance	Milgrom =	Limited evidence for no association
lower extremity quality of movement test	Rabin =	Limited evidence for no association
Increased total displacement of the Y-component of the Center of Force	Van Ginckel ↓	Limited evidence for protective association
Increased medial directed force distribution	Van Ginckel ↓	Limited evidence for protective association
Pre-existing diseases		
Renal dysfunction (Creatinine clearance <60 ml/min)	Barge-Caballero ↑	Limited evidence for positive association
Medication		
Fluoroquinolones as group	Van der Linden =	Limited evidence for no association
Levofloxacin	Barge-Caballero =	Limited evidence for no association
Ofloxacin	Van der Linden ↑	Limited evidence for positive association
Ciprofloxacin	Van der Linden =	Limited evidence for no association
Norfloxacin	Van der Linden =	Limited evidence for no association
Increased time between heart transplantation and initiation of fluoroquinolone treatment for infectious disease	Barge-Caballero ↑	Limited evidence for positive association
Daily prednisone dose	Barge-Caballero =	Limited evidence for no association
Training factors		
Training amount	Hirschmuller =, Wezenbeek =	Limited evidence for no association
Physical activity level and performance	Mahieu physical activity level =, Milgrom physical activity performance (2-km run and maximum number of chin-ups and sit-ups) =, Van Ginckel physical activity level=	Limited evidence for no association
Training in the winter season	Milgrom ↑	Limited evidence for positive association
Imaging parameters		
Tendon thickness (AP) measured on ultrasound	Comin =, Docking 2016 =, Docking 2019 =, Fredberg 2002 ↑, Fredberg 2008 ↑, Giombini =, Hagan =, Hirschmuller ↑, Jhingan ↑ , Ooi 2016 ↑, Weezenbeek =	Conflicting evidence

Intratendinous and/or peritendinous Doppler flow on ultrasound	Boesen =, Comin =, Giombini =, Hagan =, Hirschmuller ↑, Jhingan = , Ooi 2015 =, Ooi 2016 =	Limited evidence for no association
Hypoechogenicity on ultrasound	Comin moderate to severe hypoechoic areas ↑, Giombini =, Hagan =, Hirschmuller ↑, Jhingan = , Ooi 2015 =, Ooi 2016 =	Conflicting evidence
Cross-sectional surface area of the tendon measured on ultrasound	Ooi 2016 ↑	Limited evidence for positive association
Partial tendon ruptures on ultrasound	Comin =, Ooi 2016 ↑	Conflicting evidence
Collagen organisation on ultrasound	Hagan =	Limited evidence for no association
Intratendinous calcifications on ultrasound	Comin =	Limited evidence for no association
Paratenon blurring on ultrasound	Jhingan =	Limited evidence for no association

Table 1.6 – Overview of potential risk factors for Achilles tendinopathy examined in the cohort studies included. The presence of associations is marked by a grey-coloured bar. = no association; ↑ positive association; ↓protective association.

Potential risk factors	Number of studies	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Effect size	Dose-response relationship	Effect of confounders	Quality
Patient characteristics (non-modifiable)										
Age	4	High risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Sex	4	High risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Ethnicity	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Height	6	High risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Prior symptoms of lower extremity tendinopathy	3	High risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Large	No	No effect	Low
Patient characteristics (modifiable)										
Body Mass Index	7	High risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Body weight	5	High risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Alcohol use	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	Small	No	No effect	Very low
Smoking	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Biomechanical factors										
Shoe type	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Leg dominance	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Limited non-weight-bearing ankle dorsiflexion with knee extended	2	High risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low

Increased non-weight-bearing ankle dorsiflexion with the knee bent	3	High risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Hindfoot inversion	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Hindfoot eversion	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Static arch index of the foot	2	High risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Dynamic arch index of the foot	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Pronated foot posture	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Increase in isokinetic plantar flexor strength at 30 degrees/s (low velocity)	1	High risk of bias	-	Serious indirectness[1]	Serious imprecision[3]	None	Not reported	Not reported	No effect	Very low
Explosive gastrocnemius-soleus muscle strength	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
External rotation of the hip	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Tibial intercondylar distance	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	-	-	-	Very low
lower extremity quality of movement test	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Increased total displacement of the Y-component of the Center of Force	1	High risk of bias	-	No serious indirectness	Serious imprecision[4]	None	Small	Yes	No effect	Very low
Increased medial directed force distribution	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	Small	Yes	No effect	Very low
Pre-existing diseases								**-**	**-**	

Renal dysfunction (Creatinine clearance <60 ml/min)	1	High risk of bias	-	Serious indirectness[2]	Serious imprecision[3]	None	Large	No	No effect	Very low
Medication										
Fluoroquinolones as group	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Levofloxacin	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Ofloxacin	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	Large	No	No effect	Very low
Ciprofloxacin	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Norfloxacin	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Increased time between heart transplantation and initiation of fluoroquinolone treatment for infectious disease	1	High risk of bias	-	Serious indirectness[2]	Serious imprecision[3]	None	Small	No	No effect	Very low
Daily prednisone dose	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Training factors										
Training amount	2	High risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Physical activity level and performance	3	High risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	Very low
Training in the winter season	1	High risk of bias	-	No serious indirectness	No serious imprecision	None	Not reported	No	No effect	Very low
Imaging parameters										
Tendon thickness (AP) measured on ultrasound	11	High risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	Very low

Intratendinous and/or peritendinous Doppler flow on ultrasound	8	High risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Hypoechogenicity on ultrasound	6	High risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Cross-sectional surface area of the tendon measured on ultrasound	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	Not reported	No	No effect	Very low
Partial tendon ruptures on ultrasound	2	High risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Collagen organisation on ultrasound	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Intratendinous calcifications on ultrasound	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low
Paratenon blurring on ultrasound	1	High risk of bias	-	No serious indirectness	Serious imprecision[3]	None	-	-	-	Very low

Table 1.7 – GRADE assessment for potential risk factors for Achilles tendinopathy. The presence of associations is marked by a grey-coloured bar.
= no association; ↑ positive association; ↓protective association.
[1] Study investigated a young population (mean age 18.4 years) in which Achilles tendinopathy is less common, therefore these findings should be interpreted with caution.
[2] Both outcomes have only been investigated in patients who had underwent a heart transplantation and therefore these findings cannot be translated to the general population.
[3] The majority of the studies had very low number of Achilles tendinopathy events (20 cases or less) and these studies could influence the best evidence synthesis.

Study	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and results	Comments
Bonanno (2018)	Type of study: RCT Setting: The Royal Australian Navy Recruit School, Cerberus, Australia Source of Funding: Non-commercial funding[2]	Inclusion criteria: - naval recruits from the Australian Defence Force undertaking 11 weeks of initial defence training Exclusion criteria: - already using foot orthoses - a lower limb injury (worst pain at least 30 mm on a 100 mm VAS-scale) • Number of participants (intervention/control): 306 (153/153) • Mean age: 22.2 years • Male subjects: 79% • Important prognostic factors: NR	Prefabricated contoured full-length foot orthoses made from single-density, closed-cell polyethylene foam	Prefabricated 3mm flat full-length insoles made from single-density, closed-cell polyethylene foam	Length of follow-up: 11 weeks Loss to follow-up: Intervention: N= 31 (20%) Reasons: discharge before completion of 11-week training program (n=4) and unavailable for exit interview (n=27) Control: N= 33 (22%) Reasons: discharge before completion of 11-week training program (n=6) and unavailable for exit interview (n=27)	Outcome measure: Midportion AT using standardised clinical assessment with a severity of pain that scored at least 30 mm on a 100 mm VAS when at its worst. Results: Intervention: N = 2 (1%) Control: N = 0 (0%). No statistical analysis performed.	The prefabricated orthosis group reported a greater number of adverse events (20% versus 12%). The majority of adverse events were reported by the participants as mild (47%) or moderate (39%) in severity and mostly occurred in the first 2 weeks of the trial (77%).
Fredberg (2008)	Type of study: RCT	Inclusion criteria: - Being Football player in the Danish Super League	The team physiotherapists were requested to	The team physiotherapists were instructed not	Length of follow-up: 52 weeks	Outcome measure: AT sustained by a player that results	The players performed

	Setting: Stadium Clinic, Atletion, Aarhus, Denmark Source of Funding: Non-commercial funding[2]	Exclusion criteria: - Symptoms of the Achilles tendon at baseline • Number of participants (intervention/control): 244 (98/146) • Mean age: 25 years • Male subjects: 100% • Important prognostic factors: results were reported separately for players with and without ultrasound abnormalities of the Achilles tendon at baseline	instruct a short training program (less than 10 minutes) throughout the whole season, including eccentric training and stretching of the Achilles tendons. The exercises were done after training with a frequency of three times weekly. All subjects participated in their normal training and match schedule.	to perform eccentric training (usually they did not use eccentric training prophylactically) as a part of the normal training routine. However, they were allowed to continue the different kinds of flexibility training that they all used. All subjects participated in their normal training and match schedule.	Loss to follow-up: Intervention: none Control: none Because one team randomised to the training group had not yet started the training program as of March 1 due to internal problems in the club, the club was moved to the control group.	from a football match or football training, irrespective of the need for medical attention or time loss from football activities Results: Intervention: N = 15 (15%) Control: N = 25 (17%). No significant between-group difference (risk difference 2%, CI -8% – 10%, p-value 0.86)	The exercises with a mean of 2.25 times per week (advice was three training sessions per week) The exercises were not performed with additional weights.
Larsen (2002)	Type of study: RCT Setting: Jutland Dragoon Regiment, Holstebro, Denmark Source of Funding: NR	Inclusion criteria: - recruits aged 18-24 years - Start at the Jutland Dragoon Regiment Exclusion criteria: - serious back or lower extremity problems - current use of a shoe orthosis	Use of custom-made semi-rigid biomechanic shoe orthoses. All subjects participated in a basic military training during 3 months.	No intervention. All subjects participated in a basic military training during 3 months.	Length of follow-up: 12 weeks Loss to follow-up: Intervention: N= 10 (13%) Reasons: NR	Outcome measure: A self-reported AT with at least one day off-duty because of the injury. Results: Intervention: N = 3 (4%)	There was no difference in outcome between the intention to treat analysis and per protocol analysis for AT.

		• Number of participants (intervention/control): 146 (77/69) • Mean age: NR • Male subjects: 99% • Important prognostic factors: NR			Control: N= 6 (9%) Reasons: NR	Control: N = 9 (13%). No significant between-group difference (p-value 0.28)	
Milgrom (1992)	Type of study: RCT Setting: Department of Orthopaedics, Hadassah University Hospital, Ein Kerem, Jerusalem, Israel Source of Funding: NR	Inclusion criteria: - Israeli male infantry recruits Exclusion criteria: - NR • Number of participants (intervention/control): 390 (187/203) • Mean age: NR • Male subjects: 100% • Important prognostic factors: NR	Wearing modified basketball shoes (850 g) with improved shock attenuation properties All infantry recruits participated in a standard training program	Wearing standard lightweight (1250 g) infantry boots All infantry recruits participated in a standard training program	Length of follow-up: 14 weeks Loss to follow-up: Intervention: none Control: none	Outcome measure: Reported AT, which was verified by orthopaedic examination of a military doctor. Results: Intervention: N = 22 (12%) Control: N = 19 (9%). No significant between-group difference (p-value NR)	There was full adherence to the intervention.
Pope (1998)	Type of study: RCT (a blocked, quasi-random allocation procedure was used)	Inclusion criteria: - male Australian Army recruits aged 17-35 years - recruit training between September 1992 and May 1993	Stretching exercises designed to lengthen the gastrocnemius and soleus muscles (two 20s static stretches for each	No stretching exercises of the gastrocnemius and soleus muscles. Instead, the participants received	Length of follow-up: 12 weeks Loss to follow-up:	Outcome measure: Reported AT, which was verified by examination of the medical officer or physiotherapists.	

	Setting: The Australian Army's 1st Recruit Training Battalion, situated at Kapooka, in rural New South Wales, Australia Source of Funding: NR	Exclusion criteria: - an injury at baseline - an injury between the recruiting medical examination and the start of the intervention • Number of participants (intervention/control): 1093 (549/544) • Mean age: NR • Male subjects: 100% • Important prognostic factors: NR	muscle group) before undertaking any strenuous physical exercise. All subjects participated in a 11-week period (47 hours) of intense physical exercise.	stretches for their wrist flexor and triceps muscles (two 20s static stretches for each muscle group) before they undertook any strenuous physical exercise. All subjects participated in a 11-week period (47 hours) of intense physical exercise.	Intervention: N= 98 (18%) Reasons: discharged or backsquadded before the end of the training program Control: N= 112 (21%) Reasons: subjects were discharged or backsquadded before the end of the training program. 48 subjects in this group withdrew from the study.	The AT had to meet the following criteria: prominent thickening (compared with the contralateral side), palpable crepitus, palpable nodules or lesions, or blistering over the tendon. Results: Intervention: N = 1 (0.2%) Control: N = 0 (0%). No statistical analysis performed.	
Ramskov (2018)	Type of study: RCT Setting: Section for Sports Science, Department of Public Health, Aarhus, Denmark	Inclusion criteria: - healthy recreational runners between 18-65 years of age - the runner owned an iOS- or Android smartphone - running 1 to 3 times per week for at least 6 consecutive months	Intervention 1(S-I preconditioning): Running schedule consisting of running 3 times per week followed by a 4-week periodisation cycle that was repeated for a total of six times. The initial 8 weeks	Intervention 2 (S-V preconditioning): Running schedule consisting of running 3 times per week followed by a 4-week periodisation cycle that was repeated for a total of six times. The initial 8 weeks	Length of follow-up: 24 weeks Loss to follow-up: Intervention: N= 279 (67%) Reasons: Lost to follow-up without specific	Outcome measure: AT sustained during or after running and attributed to running. The injury must have caused a training reduction for at least 7 days. The diagnosis was	Despite the interventional focus of S-I being a progression of a hard relative running intensity, only 8% of running

	Source of Funding: Non-commercial funding[2]	Exclusion criteria: - an injury within the past 6 months - being pregnant - contra-indication for vigorous physical activity • Number of participants (intervention/control): 839 (419/420) • Mean age: 39.1 years • Male subjects: 38% • Important prognostic factors: NR	(preconditioning) of both groups followed a similar running schedule. During the subsequent 16 weeks, S-I progressed the proportion of weekly running at a hard intensity (88% maximal oxygen consumption).	(preconditioning) of both groups followed a similar running schedule. During the subsequent 16 weeks, S-V progressed the proportion of weekly running with a percentage change in total weekly kilometres.	reason, pregnancy, Injury during other activities or illness. Control: N= 288 (69%) Reasons: Lost to follow-up without specific reason, pregnancy, Injury during other activities, illness, discontinuation due to surgery or an accident.	established by a physical therapist. Results: Intervention 1: N = 3 (0.8%) Intervention 2: N = 5 (1.2%). No statistical analysis performed.	sessions averaged an absolute intensity of 12 km/h or faster.
Van Mechelen (1993)	Type of study: RCT Setting: Department of Health Science, Faculty of Human Movement Sciences, Vrije Universiteit, Amsterdam, The Netherlands	Inclusion criteria: - civil servant of Amsterdam - healthy/no current injury - no sick leave - running at least 10 km/week all year-round - not performing sports as part of their profession Exclusion criteria: - NR	A warmup of 6 minutes of running exercises, 3 minutes of loosening exercises, and 10 minutes of stretching to be performed before each running session. A cooldown after each running session consisted of the inverse of the warmup. Stretching	NR. All subjects were asked to continue running in the same way as they had done before.	Length of follow-up: 16 weeks Loss to follow-up: Intervention: N= 159 (24%). Reasons: NR Control: N= 168 (20%). Reasons: NR	Outcome measure: Reported AT, which was verified by examination of physician. The AT had to meet the following criteria: 1) the subject had to stop running, 2) the subject could not run on the next occasion, 3) the	The implementation of the intervention was successful, given the significant improvement of the specific knowledge scores of warmup and cooldown in the subjects of the intervention group (mean

	Source of Funding: Commercial and non-commercial funding[1]	• Number of participants (intervention/control): 421 (210/211) • Mean age: NR • Male subjects: 100% • Important prognostic factors: Participants were matched for age and estimated weekly running distance before randomisation.	exercises (three bouts of 10 seconds each of static stretching of the iliopsoas, quadriceps muscles, hamstrings, soleus and gastrocnemius muscles) were performed as outlined above twice a day regardless of running performance. All subjects were asked to continue running in the same way as they had done before.			subject could not go to work the next day, 4) the subject needed medical attention, or 5) the subject suffered from pain or stiffness during 10 subsequent days while running. Results: Intervention: N = 2 (1%) Control: N = 2 (0.9%). No significant between-group difference (p-value NR)	60%) compared with the control group (mean 11%).

Table 1.8 – Data extraction of the randomised trials investigating the effectiveness of primary prevention measures.
AT, Achilles tendinopathy; NR, not reported.
[1]The Dutch Ministry of Health Welfare and Cultural Affairs as the Dutch contribution to a coordinated research project of the Council of Europe: "Sports for All: Sports Injuries and Their Prevention."; This study was also financially supported by the Municipal Health Authority of the city of Amsterdam and by Sportcom, publisher of Runners monthly magazine.
[2] Financial support from the Initiative Foundation of the Danish Soccer Association.
[3] La Trobe University Sport, Exercise and Rehabilitation Research Focus Area.
[4] The Graduate School of Health at Aarhus University and the Danish Rheumatism Association.

Study	Domains						
	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of patients and staff	Blinding of outcome assessment	Completeness of outcome data	Selective reporting	
Milgrom 1992	?	?	-	-	+	+	? [1]
Van Mechelen 1993	?	?	-	-	-	+	? [1]
Pope 1998	-	?	-	-	-	+	- [1,2]
Larsen 2002	?	?	-	+	-	+	- [1,2,3]
Fredberg 2008	?	?	-	-	+	+	- [4]
Bonanno 2018	+	+	+	+	-	+	- [2]
Ramskov 2018	+	+	-	+	-	?	- [2]

Table 1.9 – Risk of bias assessment of randomised studies investigating the effectiveness of primary prevention measures.
+ low risk of bias, ? unclear risk of bias, - high risk of bias.
[1] No baseline characteristics reported.
[2] Low number of events.
[3] Diagnosis of AT not assessed clinically, but self-reported by patient.
[4] Cross-over of a football team after randomisation.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shock absorb shoes	Control	Relative (95% CI)	Absolute		
Incidence of AT (follow-up 6-24 weeks; measured as: self-reported AT or AT established as clinical diagnosis; Better indicated by lower values)												
1	RCT	Very serious	NA	No serious indirectness	Serious [1]	None	22/187	19/203	-	AT risk intervention 12% versus 9% in control group[2]	++00 Low	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Insoles	Control	Relative (95% CI)	Absolute		
Incidence of AT (follow-up 6-24 weeks; measured as: self-reported AT or AT established as clinical diagnosis; Better indicated by lower values)												
2	RCTs	Serious	No serious inconsistency	No serious indirectness	Serious [3,4]	None	5/230	9/222	-	AT risk intervention 2.2% versus 4.0% in control group [1]	+000 Low	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Warm up and stretch exercise	Control	Relative (95% CI)	Absolute		
Incidence of AT (follow-up 6-24 weeks; measured as: self-reported AT or AT established as clinical diagnosis; Better indicated by lower values)												
2	RCTs	Very serious	No serious inconsistency	No serious indirectness	Serious [3]	None	3/759	2/755	-	AT risk intervention 0.4% versus 0.3% in control group [2]	++00 Low	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calf muscle strength training	Control	Relative (95% CI)	Absolute		
Incidence of AT (follow-up 6-24 weeks; measured as: self-reported AT or AT established as clinical diagnosis; Better indicated by lower values)												
1	RCT	Serious	NA	No serious indirectness	Serious [3]	None	15/98	25/146	–8% to 10%	AT risk intervention 15% versus 17% in control group	++00 Low	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Build up volume of running	Build up intensity of running	Relative (95% CI)	Absolute		
Incidence of AT (follow-up 6-24 weeks; measured as: self-reported AT or AT established as clinical diagnosis; Better indicated by lower values)												
1	RCT	Serious	NA	No serious indirectness	Serious [3]	None	5/420	3/419	-	AT risk progression in volume 4% versus 2% with progression in intensity [2]	++00 Low	CRITICAL

Table 1.10 – GRADE assessment per preventive intervention.

[1] No data available of confidence intervals

[2] Statistical comparisons have not been made

[3] No data available of confidence intervals. Very low number of events.

[4] A clinically relevant difference could be present when the number of events would be adequate. Therefore, imprecision is rated down by two levels.

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