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Which treatment classes and combinations are more effective for the management of common tendinopathies? A systematic review and network meta-analysis.

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Abstract

Objective To quantify the comparative effectiveness of treatment classes used for the management of the most common tendinopathies.

Design Network meta-analyses comparing combinations of exercise, non-exercise, and non-active treatments across a range of tendinopathy locations and outcome domains.

Eligibility criteria Randomised and quasi-randomised controlled trials including an exercise arm and persons with a tendinopathy diagnosis at any location and of any severity or duration.

Outcome measures Outcomes assessing disability, function, pain, shoulder range of motion, physical function capacity, or quality of life.

Methods Network meta-analyses of broad (exercise/non-exercise/combined/non-active) and more specific (exercise/biomechanics/injection/electrotherapy/manual-therapy/non-active/surgery) treatment class models were fitted with hierarchical Bayesian models. Results were interpreted using pooled standardised mean difference effect sizes and ranking through Surface Under the Cumulative Ranking curves (SUCRA). Treatment hierarchies were assessed using the GRADE minimally contextualised framework.

Results Two-hundred studies comprising 458 treatments arms were identified. Many comparisons were within the same class reducing data available to assess comparative effectiveness. Data from 85 studies generating 140 pairwise comparisons consistently identified the superiority of combining exercise and non-exercise treatment classes (SUCRA: 0.70 to 0.88). Central estimates indicated that combining exercise and non-exercise treatments increased effect sizes by ~0.1 to 0.3 compared with exercise alone. Analysis of more specific treatment classes identified with low/very low certainty the superiority of combining exercise with either biomechanical (e.g. taping, bracing or splinting; SUCRA: 0.73) or injection therapies (SUCRA: 0.72).

Summary/Conclusion Clinicians should consider as a starting point for tendinopathy management combining exercise and non-exercise therapies. The most effective treatment combinations include exercise with the use of biomechanical or injection therapies.

Keywords: Tendinopathy, Exercise therapy; Physiotherapy; Effect size

Introduction

The clinical management of symptomatic tendinopathy requires complex clinical reasoning with reference to the pathoanatomical diagnosis. Management strategies often vary depending on the stage and location of the tendinopathy, contributing issues within the kinetic chain, and patient factors including activity level, psychosocial factors and comorbidities.[1] Current research supports the role of appropriate load management and progressive rehabilitation that includes strength training as the primary treatment for tendinopathy.[2] Different loading types, including eccentric, combined, heavy-slow-resistance, and isometric, have each been recommended with similar goals including initiation of structural tendon adaptation, reduction of pain and restoration of function.[3] In order to optimise outcomes, which are at best partial and typically slow, management may combine exercise with other treatment categories (classes) including manual-therapy,[4] electrotherapy,[5] biomechanical interventions,[6] injection therapy of various types,[7] and surgery typically reserved for the most recalcitrant.[8]

Currently, the best choice of treatment class, or combination of classes for the management of tendinopathy remains uncertain. Previous systematic reviews have generally focused on single tendinopathies and resorted to narrative syntheses due to concerns of both statistical and clinical heterogeneity.[9,10] Where meta-analyses have been conducted, these typically pool data from small numbers of homogenous studies employing conventional pairwise approaches that limit inference regarding comparative effectiveness across a range of treatment classes and subsequent development of treatment hierarchies. A range of contemporary approaches including the use of network meta-analyses (NMA) that can account for multiple outcomes reported in the same study have been developed to better synthesise complex data.[11] Recent NMAs investigating the management of tendinopathy, however, have focused on localised site-specific tendinopathies with pain relief and function as the primary outcomes.[12-16] Four NMAs have investigated comparative effectiveness of treatments in the upper extremity, three of which studied injection treatments in the shoulder [13] and elbow, [14,15] while another focused on a range of non-surgical treatments for chronic calcific tendinitis of the shoulder.[12] In an NMA investigating non-surgical treatments for patellar tendinopathy comprising eleven trials, Chen et al. [16] concluded that platelet-rich plasma therapy results in the greatest improvements in pain and function compared with other treatments. The review, however, excluded studies that compared different types of exercise treatments from their analysis.

Two recent NMAs investigating the management of Achilles tendinopathy reported somewhat conflicting findings. In an analysis comprising twenty-nine trials, van der Vlist et al. [17] concluded there was strong evidence that all active treatments were superior to wait-and-see, but no one active treatment could be recommended over another. In contrast, Rhim et al. [18] reported that improvements were highest when

eccentric exercise was combined with high-volume injection and corticosteroid, or combined with extracorporeal shockwave therapy. Confidence in these findings were low, however, as the results from the highest ranked therapies were derived from only two studies. Such comparisons across relatively fine-grained treatment classes from small numbers of homogenous studies are unable to address questions regarding general trends that can be derived from comparisons across many studies and popular treatment classes using data from different tendinopathy locations and outcome domains. Therefore, the purpose of the present systematic review and NMA was to quantify comparative effectiveness of broad treatment classes across the tendinopathy management literature, assessing whether combining exercise and non-exercise treatments were more effective than either in isolation. Following this general overview, the review sought to quantify comparative effectiveness of more specific combinations of treatment classes to inform clinical practice, service redesign, and future research.

Methods

This review was part of a project funded by the National Institute for Health Research (Health Technology Assessment: 129388 Exercise therapy for the treatment of tendinopathies) which examined the exercise therapy evidence base for multiple tendinopathies to make research and practice recommendations. The methods reported here were influenced by the overall project aims, the results of an initial scoping review mapping the exercise and tendinopathy literature,[19] as well as stakeholder workshops. The review was conducted according to the PRISMA extension statement for reporting of systematic reviews incorporating NMAs of health care interventions (Supplementary file 1)[20] and the recent Grading of Recommendations Assessment Development and Evaluation (GRADE) approach to drawing conclusions from NMA using a minimally contextualised framework.[21] An a priori protocol was created and followed for this review. [22]

Inclusion criteria

This review included randomized and non-randomized controlled trials comprising at least two trial arms featuring different treatment classes. As exercise therapy was the focus of the overall project, all studies included at least one trial arm that featured exercise components. This review included people of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. Based on the results of our initial reviews [19,23] and stakeholder workshops we included outcomes that assessed six domains: 1) disability; 2) function; 3) pain (e.g. pain on loading, pain over a specified time, pain without further specification); 4) range of motion for the shoulder joint; 5) physical function capacity (PFC, e.g., objective assessment of hops/stair-climbing/squats); and 6) quality of life (QoL). Definitions of each domain and example tools are presented in supplementary file 2. We also included studies with trial arms whose treatment class comprised: 1) exercise; 2) non-active (e.g. placebo, sham, wait-and-see); 3) injection; 4) electrotherapy; 5) biomechanics; 6) manual-therapy; or 7) surgery. Definitions of each treatment class are presented in supplementary file 3. Inclusion was restricted to studies conducted in primary care, secondary care or community locations in any developed nation (defined as the top 62 countries in the Human Development Index at the time of protocol development).

Search strategy

The search strategy used for this study was part of a larger search conducted to scope the entire exercise therapy for tendinopathy management research base. The search comprised three steps; firstly, a limited search of MEDLINE and CINAHL using initial keywords (MH tendinopathy OR TX tendin* OR TX tendon*) AND (MH exercise OR TX exercis*) was conducted with analysis of the text words in the titles/abstracts and those used to describe articles to develop a full search strategy. Secondly, the full search strategy was adapted to each database and applied systematically to: MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, Cochrane library (Controlled trials, Systematic reviews), JBI Evidence Synthesis, PEDRo, and Epistemonikos. The following trial registries were also searched: ClinicalTrials.gov, ISRCTN

Registry, The Research Registry, EU-CTR (European Union Clinical trials Registry), ANZCTR (Australia and New Zealand Clinical trials Registry). Finally, the third step involved conducting a search of cited and citing articles using Scopus and hand-searching a total of 130 systematic reviews that were identified to include information relevant to exercise therapy and tendinopathy. No limit was placed on language, with research studies published in languages other than English translated via Google Translate or via international collaborations of the review team members. Searches were initiated from 1998 as (i) the heavy load eccentric calf-training protocol for Achilles tendinosis by Alfredson et al [24] was published in 1998 and may be considered seminal work in the field of tendinopathy, and (ii) there has been a proliferation of research on exercise interventions for tendinopathies post 1998. Search terms and results for MEDLINE are presented in Supplementary file 4 according to the last date of the search which was 21/01/21.

Study selection and Data extraction

Two independent reviewers screened titles and abstracts followed by full-text copies. Conflicts were resolved by a third reviewer with all screening conducted within the Covidence (Melbourne, Australia) platform. Data were extracted independently by eight members of the review team (PS/KC/LA/RM/LG/EP/JS/AP) into pre-piloted excel sheets and coded as described in the codebook presented in the Supplementary file 5. Each entry was then independently checked.

Risk of bias assessment

We used Cochrane's Risk of Bias (RoB) tool [25] to assess six domains: 1) selection bias (random sequence generation & allocation concealment); 2) performance bias (blinding of participants); 3) detection bias (blinding of outcome assessors); 4) attrition bias (incomplete outcome data); 5) reporting bias (selective reporting); and 6) other biases. RoB was recorded for each outcome and time point within each study. The Cochrane's RoB tool [25] was selected as a recent review of popular tools in tendinopathy management highlighted none were superior [26] and Cochrane's RoB tool [25] could be semi-automated with RobotReviewer,[27] a machine learning system software. RobotReviewer was used to make initial assessments on selection bias and performance bias domains, with manual validation made on the relevant free texts extracted to support the final selection of low, high, or unclear RoB. This semi-automated process was more efficient and provided an additional element of consistency in the review process.

Statistical analysis

We fitted treatment class (broad and specific) Bayesian NMA models, first categorising broad treatments as exercise only, non-exercise only, non-active, or combined exercise and non-exercise. Second, more specific treatments classes and their combination (e.g. exercise + electrotherapy, or exercise + manual-therapy + injection) were categorised. All outcome measures included in meta-analysis models were continuous with comparative pairwise effect sizes calculated using standardised mean differences

(SMD_{pre}), where the mean difference from one trial arm was subtracted from another and standardised by dividing by the pooled baseline standard deviation. A small sample size correction was made,[28] and where required SMD_{pre} values were reflected by multiplying by –1 to ensure that positive values represented an improved clinical effect.

Hierarchical class-level models were used to account for the inclusion of multiple outcomes from the same study. Models were fitted in a Bayesian framework using Markov chain Monte Carlo simulations. Analyses were conducted initially with data pooled across all tendinopathy locations and outcome domains, with subset analyses conducted across the individual levels where sufficient data was available. We planned to conduct moderator analyses investigating the effects of assessment duration after separating outcomes according to short (≤12 weeks), medium (13-52 weeks) and long (>52) time frames. However, data were predominantly collected across short time frames and analyses resulted in estimates that did not converge. Following the initial set of analyses, attempts were made to quantify comparative effectiveness across all unique treatment combinations. Stepwise pruning of the network was conducted by removing the node comprising the lowest number of trial arms until all network parameter estimates converged producing plausible values. Ranking of effectiveness across treatment classes was summarised through calculation of Surface Under the Cumulative Ranking curves (SUCRA) which ranges from zero to one.[29] The higher the SUCRA value, the higher the probability that a therapy is in the top ranks of thos treatments considered. Analyses were performed using WinBUGS [30] and the R package R2WinBUGS.[31]

Following the GRADE approach for presentation and interpretation of results, the most connected node in the network was selected as the reference.[25] Using the minimally contextualised framework, a no effect threshold was adopted and any treatment class where the 95% credible interval did not span the threshold was moved above or below the reference accordingly. Second classifications were then made based on comparisons of treatment classes moved relative to the reference. In each of the classifications, treatment classes were separated into moderate to high certainty, and low to very low certainty based on: 1) overall risk of bias ranked as high, low or unclear risk (as identified by the mode rating across all data in the specific analysis); 2) inconsistency assessed comparing the NMA and direct reference pairwise effect sizes; 3) imprecision judged by the number of available data points (studies, trial arms, outcome measures) and width of effect size credible intervals; 4) indirectness identified as low risk for all outcomes based on inclusion criteria from our previous scoping review and stakeholder recommendation; and 5) small-study effects assessed by visual inspection of effect size distribution and sampling variance. Categorisations of overall certainty in evidence began with high certainty in cumulative evidence and were downgraded a level for each domain not judged as low risk.

Results

A flow diagram illustrating study selection with reasons for exclusions is presented in figure 1. A total of 200 studies (Supplementary file 6) were identified comprising 458 trial arms, 326 direct pairwise comparisons, and 11,873 participants. A breakdown of the tendinopathies investigated, the outcome domains measured, and the treatment class combinations are presented in table 1. The most frequently investigated tendinopathy locations included rotator cuff (43.0% of trial arms), elbow (22.5% of trial arms) and Achilles (20.3%). Pain (74.9% of trial arms) and disability (80.1% of trial arms) were the most frequently measured outcome domains across a range of treatment combinations comprising primarily exercise, electrotherapy, and manual-therapy (table 1). Summary risk of bias from each of the 200 included studies are presented in Supplementary file 7.

Figure 1: PRISMA chart illustrating study selection.

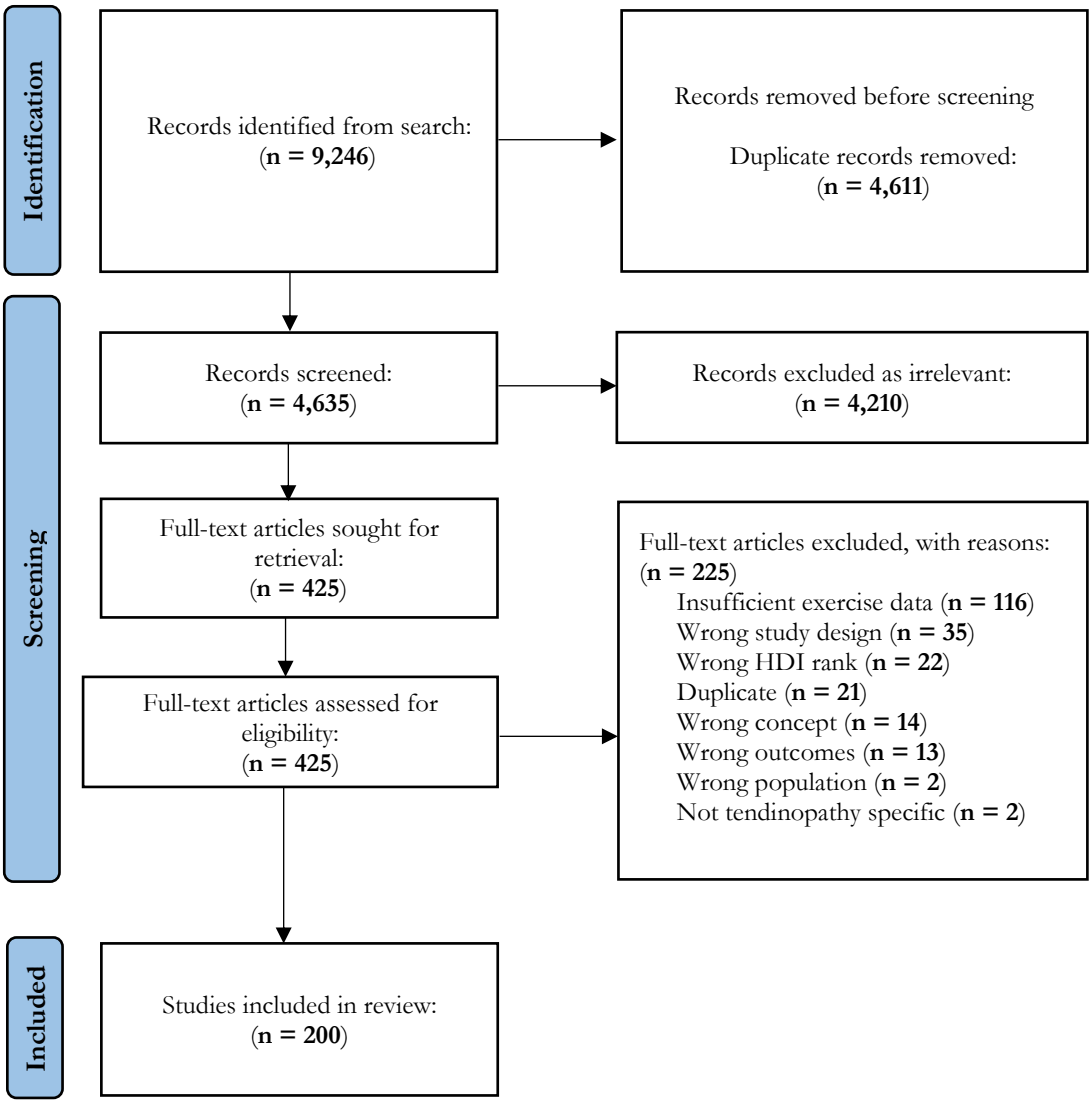


Table 1: Tendinopathies and outcome domains investigated across 200 studies and 458 trial arms.

Tendinopathies	Number of trial arms (%)	Outcome Domain	Number of outcomes (%) / Number of trial arms (%)
Rotator cuff	197 (43.0)	Pain	961 (32.2) / 343 (74.9)
Elbow	103 (22.5)	Disability	856 (28.6) / 367 (80.1)
Achilles	93 (20.3)	Physical function capacity	531 (17.8) / 176 (38.4)
Patellar	43 (9.4)	Range of motion	300 (10.0) / 82 (17.9)
Gluteal	9 (2.0)	Function	203 (6.8) / 102 (22.3)
Tibialis posterior	9 (2.0)	Quality of Life	137 (4.6) / 46 (10.0)
Hamstring	2 (0.4)		
Biceps	2 (0.4)		

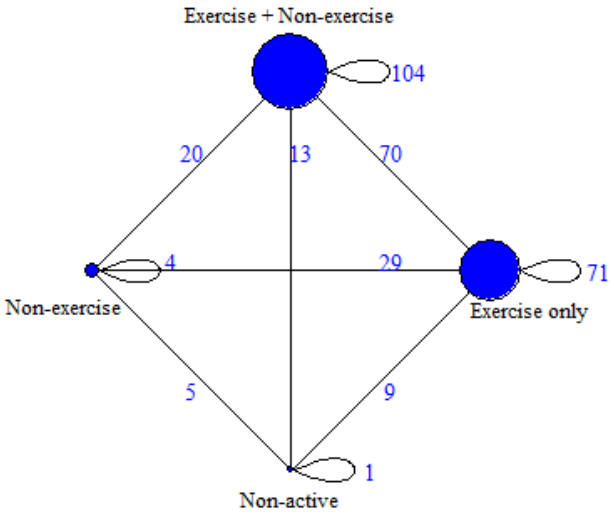
Treatment Combinations	Number of trial arms (%)	Treatment Combinations	Number of trial arms (%)
Exercise only	180 (39.3)	Exercise + Electrotherapy	63 (13.8)
Non-exercise only	36 (7.9)	Exercise + Biomechanics	30 (6.6)
Exercise + Non-active	30 (6.6)	Exercise + Manual-therapy	27 (5.9)
Exercise + Injection	23 (5.0)	Exercise + Electrotherapy + Manual-therapy	22 (4.8)
Non-active	18 (3.9)	Exercise + Surgery	8 (1.7)
Exercise + Electrotherapy + Biomechanics + Manual-therapy	4 (0.9)	Exercise + Manual-therapy + Non-active	4 (0.9)
Exercise + Electrotherapy + Non-active	3 (0.7)	Exercise + Injection + Manual-therapy	3 (0.7)
Exercise + Injection + Biomechanics	2 (0.4)	Exercise + Biomechanics + Manual-therapy	2 (0.4)
Exercise + Electrotherapy + Injection + Manual-therapy	1 (0.2)	Exercise + Electrotherapy + Biomechanics	1 (0.2)
Injection + Non-active	1 (0.2)		

Non-active treatments comprised placebo, sham or wait-and-see.

The relative frequencies of the broad treatment classes across the 458 trial arms were: combined exercise and non-exercise (48.9% of trial arms); exercise only (39.3% of trial arms); non-exercise only (7.9% of trial arms); and non-active (3.9% of trial arms). The network diagram illustrating the 326 direct pairwise comparisons across the broad treatment classes is presented in figure 2, with most comparisons occurring within the combined exercise and non-exercise class, and a substantive number occurring within the exercise only class. In total, 85 studies provided data comparing different broad treatment classes to generate 140 pairwise comparisons to be included in the primary NMA combining all tendinopathy locations and outcome domains. Results from the primary NMA and subset NMAs across individual tendinopathy locations are presented in Table 2. Combined exercise and non-exercise treatments were ranked most effective (SUCRA: 0.70 to 0.88), and non-active treatments ranked least effective (SUCRA: 0.22 to 0.39) across all analyses. When pooling data across all tendinopathy locations, non-active and exercise-only treatments were identified as inferior with high and low certainty, respectively. Although central estimates indicated that non-exercise only treatments were also inferior, credible intervals were

wide such that it was deemed with low certainty these treatments may be among the most effective (along with combined exercise and non-exercise). When restricting analyses to studies comparing outcomes for rotator cuff tendinopathy, all mean differences and credible intervals indicated combining exercise and non-exercise treatments was superior. Where certainty of evidence was low, this was due to likely bias associated with inconsistency and small-study effects generating large numbers of very large effect sizes. Collectively, central estimates indicated that combining exercise and non-exercise treatments produced on average a ~0.1 to 0.3 increase in standardised mean difference effect size (Table 2). Analyses combining results across all tendinopathy locations but separated according to outcome domains are presented in Figure 3. Across all outcome domains SUCRA values were highest for combined exercise and non-exercise treatments (SUCRA: 0.71 to 0.88) and lowest for non-active treatments (SUCRA: 0.07 to 0.30). Frequently, exercise only treatments ranked second (SUCRA: 0.45 to 0.71), followed by non-exercise only treatments (SUCRA: 0.37 to 0.69).

Figure 2: Network diagram illustrating distribution of pairwise comparisons between broad treatment classes. The size of each node is scaled to the number of pairwise comparisons.



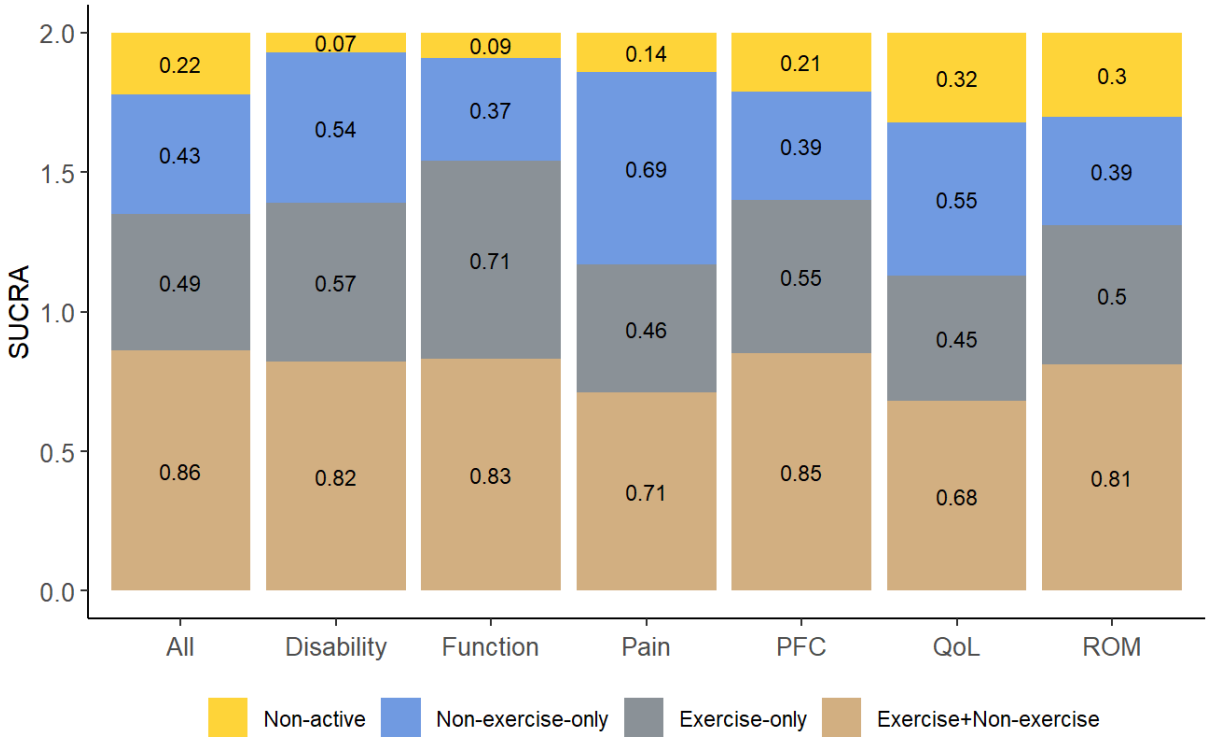
The size of each node is scaled to the number of pairwise comparisons. Values on each edge quantifies the number of direct pairwise comparisons between nodes.

Table 2: Application of minimally contextualised GRADE framework to rank effectiveness of broad treatment classes for tendinopathy management. Analyses presented for network meta-analyses conducted with pooled data across all tendinopathy locations, and individual tendinopathies where sufficient data were available.

Analysis	Number of treatment comparisons/ Number of outcomes	Broad treatment class	Comparison with Exercise + Non-Exercise median difference (95% CrI)	Surface under the cumulative ranking
All tendinopathies				
High certainty (moderate to high certainty evidence)				
Category 2: Among the most effective	100/1041	Exercise + Non-exercise	NA	0.86
Category 1: Inferior to the most effective	28/317	Non-active	-0.22 [-0.43 to -0.03]	0.22
Low certainty (low to very low certainty evidence)				
Category 2: Might be among the most effective	50/454	Non-exercise only	-0.12 [-0.46 to 0.22]	0.44
Category 1: Might be inferior to the most effective	103/916	Exercise only	-0.10 [-0.21 to -0.01]	0.49
Rotator cuff				
High certainty (moderate to high certainty evidence)				
Category 2: Among the most effective	50/595	Exercise + Non-exercise	NA	0.88
Category 1: Inferior to the most effective	8/100	Non-active	-0.21 [-0.41 to -0.01]	0.39
Low certainty (low to very low certainty evidence)				
Category 1: Might be inferior to the most effective	14/146	Non-exercise only	-0.38 [-0.55 to -0.21]	0.31
	50/517	Exercise only	-0.19 [-0.36 to -0.03]	0.41
Achilles				
High certainty (moderate to high certainty evidence)				
Category 2: Among the most effective	17/109	Exercise + Non-exercise	NA	0.71
Low certainty (low to very low certainty evidence)				
Category 2: Might be among the most effective	15/111	Non-exercise only	-0.16 [-0.71 to 0.38]	0.45
	21/133	Exercise only	-0.10 [-0.55 to 0.35]	0.55
	5/7	Non-active	-0.30 [-0.93 to 0.33]	0.29
Elbow				
High certainty (moderate to high certainty evidence)				
Category 2: Among the most effective	27/283	Exercise + Non-exercise	NA	0.70
Low certainty (low to very low certainty evidence)				
Category 2: Might be among the most effective	14/153	Non-exercise only	-0.09 [-0.65 to 0.50]	0.45
	21/164	Exercise only	-0.08 [-0.41 to 0.26]	0.46
	12/170	Non-active	-0.11 [-0.42 to 0.22]	0.38

Negative effect sizes favour exercise combined with non-exercise Number of treatment comparisons quantifies the total number of all pairwise comparisons that include the specific treatment class. CrI: Credible interval.

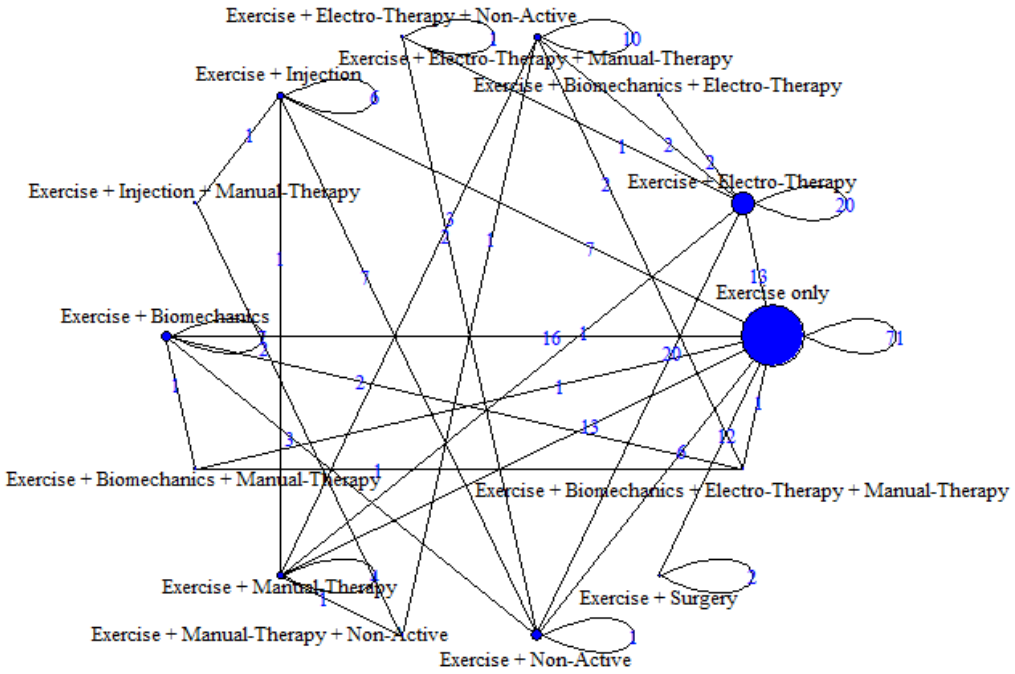
Figure 3: Surface under the cumulative ranking (SUCRA) values for broad treatment classes pooled across all tendinopathy locations for different outcome domains.



PFC: Physical function capacity; QoL: Quality of life; ROM: Range of motion.

The network-diagram illustrating the pairwise comparisons between exercise and exercise combined with different non-exercise treatments is presented in Figure 4. Most comparisons were within the same class, or comparisons with either exercise-only or exercise plus non-active treatments. As a result, there were limited direct comparisons between combined exercise and active non-exercise treatments (e.g. exercise + electrotherapy; exercise + biomechanics; and exercise + injection). Due to the low number of direct comparisons, initial NMAs failed to converge producing plausible values for pairwise estimates. Pruning of the network was conducted and estimates converged for a NMA pooling data across all tendinopathy locations and outcome domains, which comprised six combined treatment classes (exercise + biomechanics; exercise + injection; exercise + electrotherapy; exercise + manual-therapy; exercise + electrotherapy + manual-therapy; exercise + non-active) and exercise only therapy as a reference (Table 3). Exercise combined with biomechanics interventions (SUCRA:0.73) or injection therapy (SUCRA: 0.72) were identified with low certainty as the most effective treatments, with all other treatments identified with low certainty as inferior (SUCRA: 0.27 to 0.50).

Figure 4: Network diagram illustrating distribution of pairwise comparisons between treatment classes. The size of each node is scaled to the number of pairwise comparisons.



The size of each node is scaled to the number of pairwise comparisons. Values on each edge quantifies the number of direct pairwise comparisons between nodes.

Table 3: Application of minimally contextualised GRADE framework to rank effectiveness of treatment classes for tendinopathy management. Analyses presented for network meta-analysis conducted with pooled data across all tendinopathy locations.

Analysis	Number of treatment comparisons/ Number of outcomes	Exercise and combined treatment classes	Comparison with Exercise only median difference (95% CrI)	Surface under the cumulative ranking
All tendinopathies				
Low certainty (low to very low certainty evidence)				
Category 2: Might be among the most effective	19/182	Exercise + Biomechanics	0.24 [0.03 to 0.41]	0.73
	15/126	Exercise + Injection	0.24 [0.01 to 0.45]	0.72
	5/41	Exercise + Electrotherapy + Manual-therapy	0.08 [-0.29 to 0.46]	0.50
	35/301	Exercise + Electrotherapy	0.07 [-0.32 to 0.48]	0.50
Category 1: Might be inferior to the most effective	35/307	Exercise + Non-active	0.03 [-0.19 to 0.25]	0.40
	53/439	Exercise only	NA	0.37
	18/162	Exercise + Manual-therapy	-0.15 [-0.50 to 0.25]	0.27

Negative effect sizes favour exercise only. Number of treatment comparisons quantifies the total number of all pairwise comparisons that include the specific treatment class. CrI: Credible interval.

Discussion

This systematic review and NMA represents one of the most comprehensive attempts at quantitative evidence synthesis of the effectiveness of relatively broad treatment classes for the management of common tendinopathies. Consistent findings were obtained across different tendinopathy locations and outcome domains that combining exercise and non-exercise treatment classes were superior to either exercise in isolation or to non-active treatments such as placebo, sham or wait-and-see. Central estimates from NMAs indicated that combining exercise and non-exercise treatments may produce on average ~0.1 to 0.3 increases in standardised mean difference effect sizes compared with exercise alone. An overview of all treatment comparisons identified that trials tended to make comparisons within treatment classes rather than between. As a result, the ability to compare across classes and identify clear treatment hierarchies was limited. The results obtained here, however, indicate with low certainty, that exercise combined with biomechanical interventions or injection treatments may be the most effective. Whilst group and individual responses to treatment are likely to be influenced by a wide range of factors, the findings obtained in the present review provide insight into general and consistent patterns that can inform clinical practice, service redesign and future research.

The present review is one of the few evidence synthesis studies to combine information across different tendinopathy locations and found that exercise is best combined with other treatments, with there being a particular need for further assessment of this finding at medium- and long-term follow-up. The relative frequencies of treatment classes identified in the present review are likely influenced by its focus and the associated inclusion criteria that all studies required at least one trial arm to comprise exercise therapy. The focus does, however, reflect the move towards therapeutic exercise as a mainstay of rehabilitation supported by a large volume of evidence in the form of trials and systematic reviews.[32-35] The finding that combining exercise and non-exercise treatments may result in additional small to moderate clinical benefit is in line with previous evidence syntheses. In a recent umbrella review evaluating twenty-five systematic reviews of high quality, Irby et al.[36] concluded that exercise therapy is the best treatment option for tendinopathy when combined with the use of other therapeutic modalities. Additionally, previous NMAs conducted by van der Vlist et al.[17] and Rhim et al.[18] both ranked exercise combined with shockwave or injection therapies more favourably than exercise alone for Achilles tendinopathy. Rhim et al.[18] further identified the largest sustained improvements at twelve months with treatments combining exercise and shockwave. It seems likely that the consistent recommendation to combined interventions reflets different mechanisms of therapeutic effect alongside the partial efficacy observed for even the best interventions. Further, the additional benefit from combining interventions is consistent with clinical reasoning. In the present review we planned to assess whether comparative effectiveness was influenced by assessment duration. Most outcomes measurements, however, were conducted across short time

frames such that any comparison was unlikely to be stable, indicating that further research with longer follow-up times is required.

Following evidence of superior effectiveness when combining exercise and non-exercise treatments, the review sought to identify potential differences across different treatment combinations. With low certainty and limitations in fitting a suitable NMA model, we identified that combining exercise with either biomechanical interventions or injection treatments may be superior to other combinations such as exercise and electrotherapy and/or manual-therapy. Analysis of the network structure demonstrated that most comparisons were conducted within treatment classes. This may reflect researchers' and clinicians' interest in more specific manipulations to popular treatments including dosing parameters. In addition, where comparisons were made outside of the same treatment class, this was most often with exercise only or exercise combined with non-active treatments acting as control conditions. The lack of comparison across different treatment classes limits the ability to establish general treatment hierarchies as the relatively small number of direct comparisons meant only a single NMA with a restricted range of comparisons could be conducted. The need for more trials comparing combinations of treatments across treatment classes is notable and would ideally follow guidelines on intervention development to ensure the optimal likelihoods of successful comparisons of meaningful interventions. [37]

In addition to uncertainty due to a lack of direct comparisons, uncertainty of the most effective combination of treatments stems from the fact that the pathophysiology of tendinopathy and the working mechanisms of existing treatments are not completely understood.[38,39] Some evidence suggests a failed healing response due to degeneration caused by repetitive overloading rather than an inflammatory process,[38-40] while more recent thinking suggest a stronger role for low-grade inflammation.[41]. Additionally, the disconnect between observed structural change and reported symptomatic state, and the absence of effective biomarkers of tendinopathy severity limit clinical innovation. The proposed mechanisms for biomechanics interventions depend upon the specific implementation. Taping is purported to act by limiting joint movement (rigid tape), influencing circulatory and neurological systems (kinesiotape), and altering the loading of musculotendinous structures (biomechanical tape).[42] Counterforce bracing for lateral elbow tendinopathy is reported to have mechanical and neurological effects on elbow proprioception, essentially creating a new tendon origin, allowing for tissue healing.[43] There is limited evidence that they may provide short-term pain relief,[44] especially in younger patients.[43] Night splints have been used mainly in Achilles tendinopathy, and are thought to optimize tendon microcirculation.[45] In contrast, corticosteroid injections reduce pain caused by inflammatory agents but are known to decrease collagen production and therefore, slow the healing process. Given the potential weakening of the tendon matrix structure, there are concerns for the long-term use of corticosteroid injections especially for Achilles tendinopathy.[46] More recently, the use of regenerative injections has

emerged as a potential treatment to facilitate tissue healing and regeneration in tendinopathy with long-term improvements.[47] Whilst there was less evidence for an additional benefit of combining electrotherapy with exercise, the electrotherapy class comprises a range of different technologies that are widely applied in clinical settings, with shockwave the most commonly used.[48] Studies have postulated that shockwave therapy may influence nociceptive transmission in the central nervous system, which provoke peripheral, sensory nerve fibres resulting in pain relief.[49] It is also plausible that shockwave has an indirect influence on neovascularisation which leads to better tissue regeneration in tendinopathies through a better blood supply.[50] Collectively, improved biomarkers of tendon pathology and clarity of therapeutic mechanisms would enable more targeted treatment, particularly when the innovations afforded by precision medicine are applied to tendinopathy.

The findings of the present review have implications for the design and commissioning of services for the management of tendinopathies. The potential for additional improvements combining biomechanical interventions with exercise compared to exercise alone is important at a time when access to such services is increasingly restricted. In addition, if injections are shown to lead to the same long-term superior results as identified in the short-term when combined with exercise, this will have implications on the need for relevant training and service provision. The inclusion of any of the active treatments investigated in the present analysis require face to face patient assessments while exercise therapy on its own may have comparable effectiveness when delivered remotely – at least in part.

It was outside the remit of this review to compare the cost-effectiveness of different treatment classes but there is a need for such cost-effectiveness analyses in the future to further inform service redesign. In considering the findings and suggested implications of the present review, several limitations are relevant. The focus of the review was on exercise therapy and therefore not all relevant trials comparing non-exercise therapies were included. The present review sought to identify more general trends in the management of tendinopathy, synthesising evidence across a range of outcome domains, tendinopathy locations and broad treatment classes. Whilst this provided the benefit of increasing the available data to synthesise, there is likely to be large variation in expected trial results of any specific treatment class or combination based on interactions of factors such as the specifics of the treatment (e.g. type of electrotherapy and dose), the tendinopathy location, the outcome and the population. Further research is required to identify the extent and pattern with which these factors may influence the comparative effectiveness of different treatments. Treatment heterogeneity effects should also be expected at the individual level, where patient characteristics interact with treatments to determine which are most effective. Therefore, the findings obtained here and the associated low certainty in the evidence, provide a starting point for clinicians in the treatment prescribed to each individual, and that in general combining exercise with other classes such as biomechanics interventions or injection therapy may be most effective.

This systematic review and NMA also highlights novel insight into the necessary changes in future trial designs on tendinopathy.

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Conflicts of interest

The authors declare no conflict of interest.

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Supplementary file 1: PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	3-4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	SF4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	SF5
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	6-7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	7
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	10,13
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	11

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	SF7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	NI
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	11,14
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	11,14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	11,14
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	19

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary File 2: Outcome domains and example outcomes included in review.

Domain	ICON Definition	Example Tools
Disability	Composite scores of a mix of patient-rated pain & disability due to the pain, usually relating to tendon-specific activities/tasks	VISA scales; DASH; quick DASH; SPADI; Patient-rated tennis-elbow evaluation questionnaire; Constant Murley Score; WORC (Western Ontario Rotator Cuff Index); AOFAS (American Orthopaedic Foot & Ankle Society); Roles and Maudsley score; ASES (American Shoulder & Elbow Surgeons Index; Tegner activity score; Lysholm knee scale; Pain free function questionnaire; Ankle activity score; Subjective elbow Value (SEV); Placzek score; Shoulder disability questionnaire; International Knee Documentation Committee form (IKDC); Penn Shoulder score (university of Pennsylvania shoulder score) (PSS); Brief pain inventory (BPI); UCLA Shoulder Rating Scale; FILLA - functional index of leg and lower limb; Neer Shoulder Score; Nirschl phase rating scale; American Shoulder and Elbow Surgeon's (MASES) questionnaire; Mayo Elbow Performance Score (MEPS); Shoulder rating questionnaire (SRQ)
Function	Patient-rated level of function (and not referring to the intensity of their pain).	Patient-specific functional scale
Pain	Pain on loading/activity: Patient reported intensity of pain performing a task that loads the tendon.	VAS; NRS; Pain experience scale
	Pain over a specified time: Patient-reported pain intensity over period of time e.g. morning/night/24-hours/1-week.	VAS; NRS Painful days in 3 months
	Pain without further specification: Patient asked about pain levels without reference to activity or timeframe.	VAS; NRS; Borg CR10 Scale; Pain status
Physical function capacity	Quantitative measures of physical tasks (e.g. hops, times walk, single leg squat) includes muscle strength	Counter movement jump; One-leg triple hop; Single-leg decline squat; Muscle strength measured by dynamometry (hand-held, isokinetic); Repetition maximum; Manual muscle testing.
Quality of Life	General wellbeing	EQ5D; EQ3D; SF-36 or SF-12; Assessment of Quality of Life (AQoL); Nottingham Health Profile; Gothenburg QoL Instrument
Range of Motion (Shoulder only)	Active or passive range of motion in specified plane, measured in degrees.	Hand-held goniometer; inclinometer

Supplementary File 3: Definitions used to define broad and more specific treatment classes.

Broad treatment class	Definition	More specific treatment class	Definition
Exercise only	Exercise therapy is defined as a regimen or program of physical activities specifically designed and prescribed to correct impairments, restore musculoskeletal function, and/or maintain a state of wellbeing.	Same as broad treatment class	Same as broad treatment class
Non-active (placebo, sham, wait and see)	Includes any appropriate inactive treatment such as waiting list control, sham shockwave, sham laser, sham taping or true placebo.	Same as broad treatment class	Same as broad treatment class
Non-exercise only	Active treatments used to treat tendinopathy that do not meet the criteria to be considered exercise.	Electrotherapy	Modality that delivers therapeutic levels of physical energy into a biologic system e.g. soft tissue. Includes shockwave, laser and other systems.
		Biomechanics	Treatment using external devices that immobilises (e.g. splinting) or alters the kinematics/kinetics of the limb (e.g. taping, bracing and orthotics).
		Manual-therapy	Manual therapy is the skilled application of "hands-on" techniques to treat soft tissues and joint structures for the purpose of improving pain, increasing range of motion, stimulating tissue repair response, and/or improving function.
		Injection therapy	Injection therapy for tendinopathy typically involves direct administration of a pharmacologically active drug, or combination of drugs using a syringe and needle or equivalent. It may or may not be image-guided. Includes Autologous, drug, and volumetric types.
		Surgery	Any relevant surgical intervention for tendinopathy including minimally invasive peritendinous and open intra-tendinous.

Exercise and non-exercise	Treatment comprising multiple components which collectively meet both exercise and non-exercise criteria	Same as broad treatment class	Same as broad treatment class

Supplementary file 4: Search terms and results for MEDLINE search

MEDLINE (EBSCoHost)
Search conducted on 21/01/21.

Search	Query	Records retrieved
#1	MH exercise OR AB exercis* OR MH "isometric contraction" OR MH rehabilitation OR TX eccentric OR TX concentric OR TX "heavy slow resistance" OR TX isokinetic	362,722
#2	MH tendinopathy OR MH "shoulder injuries" OR MH tendons OR MH "tendon injuries" OR TX tendin* OR TX tendon* OR MH bursitis OR AB bursitis OR MH "posterior tibial tendon dysfunction" OR MH "shoulder impingement syndrome" OR AB "greater trochanteric pain syndrome"	96,490
#3	#1 AND #2	4,363

Limited to 1998 to present

Supplementary file 5: Extraction codebook

Column		Heading	Description
Study Details	A	Initials Reviewer	Identification of individual extracting information
	B	Covidence Identifier	Reference number for Covidence
	C	Author	First author surname *et al.,*
	D	Year	Year of publication
	E	Title	Study title
	F	Country	Country where study was conducted
	G	Journal	Journal name
	H	Aims/Purpose	Study aims/purpose
	I	Tendinopathy type	1=Achilles; 2= Elbow; 3 = Patellar; 4 = Rotator cuff; 5 = Gluteal; 6 = Tibialis posterior; 7 = Hamstring; 8 = Biceps
	J	Study Design	RCT = 1; Quasi-experimental = 2
	K	Age Mean	Mean age of study sample as a whole
	L	Age SD	Standard deviation age of study sample as a whole
	M	Baseline Total N	Total sample across all interventions measured at baseline
	N	Training Status Description	Brief description of training status of study sample as a whole
	O	Training Status Code	1 = Performance; 2 = Sporting; 3 = Other
	P	Sex	Percentage female of study sample as a whole
	Q	BMI Mean	Mean BMI of study sample as a whole
	R	BMI SD	Standard deviation of BMI of study sample as a whole
	S	Symptom Severity Mean	Mean severity measure at baseline of study sample as a whole
	T	Symptom Severity SD	Standard deviation of severity measure at baseline of study sample as a whole
	U	Symptom Duration Mean (Months)	Mean symptom duration reported in months
	V	Symptom Duration SD (Months)	Standard deviation symptom duration reported in months
	W	Population Comments	Any additional information relevant to the participants investigated including diagnostic criteria
Outcomes	X	Outcome Category	1 = Disability; 2 = Pain on loading/activity; 3 = Pain over a specified time; 4 = Pain without further specification; 5 = Function; 6 = Physical function capacity; 7 = Quality of life; 8 = Range of motion
	Y	Outcome Tool	Description of outcome tool
	Z	Reflection	1 = Increase in outcome indicates positive treatment; -1 = Decrease in outcome indicates positive treatment
	AA	Measurement Time (Weeks)	Time of measurement in weeks
Intervention	AB	Dominant Broad Treatment Class	**Only one dominant theme to be selected** 1 = Exercise; 2 = Non-active; 3 = Non-exercise;
	AC	Total Broad Treatment class	**Multiple themes to be selected as required** 1 = Exercise; 2 = Non-active; 3 = Non-exercise;
	AD	Dominant Specific Treatment Class	**Only one dominant theme to be selected** 1 = Exercise; 2 = Non-active; 3 = Electrotherapy; 4 = Biomechanics; 5 = Manual-therapy; 6 = Injection Therapy; 7 = Surgery
	AE	Total Specific Treatment Class	**Multiple themes to be selected as required** 1 = Exercise; 2 = Non-active; 3 = Electrotherapy; 4 = Biomechanics; 5 = Manual Therapy; 6 = Injection Therapy; 7 = Surgery
	AF	Intervention N	Intervention sample size at specified time
	AG	Intervention Total Duration	Total duration of exercise intervention in weeks
	AH	Intervention Adherence %	Reporting of adherence to exercise (reported as a percentage) if applicable
	AI	Intervention Location	Location exercise was performed 1 = Home; 2 = Clinic; 3 = Fitness facility; 4 = NR; 5 = NA
	AJ	Intervention Volume	Numerical value describing volume
	AK	Intervention Volume Category	1 = Duration of session (mins); 2 = sets * repetitions; 3 = number of repetitions; 4 = number of sets

	AL	Intervention Volume Comments	Any additional information relevant.
	AM	Intervention Intensity	Numerical value describing intensity
	AN	Intervention Intensity Category	1 = Absolute; 2 = Relative
	AO	Intervention Frequency	Number of sessions per week. Where there is progression, average value is to be entered.
	AP	Intervention Frequency Comments	Any additional information relevant.
	AQ	Intervention Progression	**Multiple themes to be selected as required** 1 = No progression; 2 = NR; 3 = Progression volume; 4 = Progression intensity; 5 = Progression frequency; 6 = Progression specificity; 7 = Progression capacity; 8 = Other
	AR	Intervention Progression Comments	Any additional information relevant.
Data	AS	Intervention Baseline Mean	Baseline mean for exercise therapy
	AT	Intervention Baseline SD	Baseline standard deviation for exercise therapy
	AU	Intervention Measurement Mean	Mean of outcome for exercise therapy at stated time point
	AV	Intervention Measurement SD	Standard deviation of outcome for exercise therapy at stated time point
	AW	Control Baseline Mean	Baseline mean for control
	AX	Control Baseline SD	Baseline standard deviation for control
	AY	Control Measurement Mean	Mean of outcome for control at stated time point
	AZ	Control Measurement SD	Standard deviation of outcome for control at stated time point
	BA	Measurement Comments	State if a different value has been entered for means (e.g. median), a different value for standard deviations (e.g. standard error, IQR, percentiles, distance from mean to upper bound). Provide the relevant statistic (width of CI's, width of percentiles). Also state if data has extracted by digitization

Supplementary file 6: Reference list of included studies

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Supplementary file 7: Summary risk of bias of included studies

Risk of bias assessments were made for each outcome and time point in a study. The results presented here represent a summary, with the mode value selected.

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Abat et al 2016 [1]	Not applicable (quasi)	Not applicable (quasi)	Unclear	Unclear	Low risk	Unclear	High risk
Aceituno-Gómez et al 2019 [2]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
Akkaya et al 2016 [3]	Low risk	Unclear	High risk	High risk	Low risk	Unclear	Low risk
Aktas et al 2007 [4]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Akyol et al 2012 [5]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
Alfredson et al 1998 [6]	High risk	Unclear	High risk	Unclear	Low risk	Unclear	High risk
Alfredson et al 1999 [7]	Not applicable (quasi)	Not applicable (quasi)	High risk	High risk	Low risk	Unclear	High risk
Arias-Buría et al 2015 [8]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Arias--Buría et al 2017 [9]	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk	High risk
Bae et al 2011 [10]	Not applicable (quasi)	Not applicable (quasi)	Unclear	Unclear	Unclear	Unclear	High risk
Bagcier et al 2019 [11]	Not applicable (quasi)	Not applicable (quasi)	Unclear	Low risk	Unclear	Unclear	High risk
Bahr et al 2006 [12]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Balius et al 2016 [13]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Bang et al 2000 [14]	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Başkurt et al 2011 [15]	Low risk	Unclear	High risk	Unclear	Low risk	Unclear	Low risk
Beaudreuil et al 2012 [16]	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Bek et al 2012 [17]	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Bell et al 2013 [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bennell et al 2010 [19]	Bennell *et al.*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Beyer et al 2015 [20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Blume et al 2015 [21]	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Boesen et al 2017 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Boesen et al 2019 [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Boudreau et al 2019 [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Breda et al 2020 [25]	Low risk	Low risk	High risk	Low risk	Low risk	High risk	High risk
Brox et al 1999 [26]	High risk	High risk	High risk	High risk	No Data	No Data	No Data
Buyuksireci et al 2020 [27]	Low risk	Unclear	High risk	Unclear	Low risk	Unclear	High risk
Cacchio et al 2011 [28]	Low risk	Low risk	High risk	Low risk	Unclear	Unclear	Low risk
Calis et al 2011 [29]	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Celik et al 2009 [30]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Celik et al 2009 [31]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	High risk
Celik et al 2019 [32]	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Cha et al 2014 [33]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Chaconas et al 2017 [34]	Low risk	Unclear	Unclear	Low risk	High risk	Unclear	High risk
Chary-Valckenaere et al 2018 [35]	Low risk	Low risk	Unclear	Low risk	High risk	Low risk	Low risk
Chen et al 2017 [36]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Cheng et al 2007 [37]	High risk	High risk	Unclear	Unclear	Unclear	Unclear	High risk
Cho et al 2017 [38]	High risk	High risk	Unclear	Unclear	Low risk	Low risk	Unclear
Chung et al 2004 [39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Clarke et al 2010 [40]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Conroy et al 1998 [41]	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Coombes et al 2013 [42]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Croisier et al 2007 [43]	Not applicable (quasi)	Not applicable (quasi)	Unclear	Low risk	Unclear	Unclear	High risk
de Jonge et al 2008 [44]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
de Miguel Valtierra et al 2018 [45]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
De Oliveira et al 2020 [46]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk
de Vos et al 2007 [47]	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk	High risk
de Vos et al 2010 [48]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dejaco et al 2017 [49]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Devereaux et al 2016 [50]	Low risk	High risk	High risk	High risk	High risk	Unclear	Low risk
Dimitrios et al 2012 [51]	Not applicable (quasi)	Not applicable (quasi)	Low risk	Low risk	Low risk	Unclear	High risk
Dimitrios et al 2013 [52]	Not applicable (quasi)	Not applicable (quasi)	Low risk	Low risk	Low risk	Unclear	High risk
Dogan et al 2010 [53]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Dupuis et al [54]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
EkenGedik et al 2016 [55]	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	High risk
Ellegaard et al 2016 [56]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Engebretsen et al 2009 [57]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Engebretsen et al 2011 [58]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Eraslan et al 2018 [56]	Eraslan *et al.*	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear
Faria et al 2006 [59]	High risk	High risk	Unclear	Unclear	Unclear	Unclear	Unclear
Fournier Belley et al 2018 [60]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ganderton et al 2018 [61]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
García et al 2016 [62]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
Gatz et al 2020 [63]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	High risk
Genc et al 2020 [64]	Low risk	Low risk	High risk	High risk	Unclear	Unclear	High risk
Giray et al 2019 [65]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
Granviken et al 2015 [66]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gürsel et al 2004 [67]	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Hallgren 2017 [68]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Hallgren et al 2014 [69]	High risk	Low risk	High risk	Low risk	Unclear	Low risk	Low risk
Heron et al 2017 [70]	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Holmgren et al 2012 [71]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	High risk
Hotta et al 2020 [72]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
Houck et al 2015 [73]	Low risk	Unclear	Unclear	High risk	Low risk	Low risk	Low risk
Ilhanli et al. 2015 [74]	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk
Ingwersen et al 2017 [75]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Jasnauskaitė-Gedrimė et al 2018 [76]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	High risk
Jeong et al 2008 [77]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Johansson et al 2005 [78]	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	High risk
Jonsson et al 2005 [79]	Unclear	Unclear	Low risk	Unclear	High risk	Unclear	High risk
Jonsson 2009 [80]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Juul-Kristensen et al 2019 [81]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Kachanathu et al 2019 [82]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	High risk
Kang et al 2019 [83]	Low risk	Low risk	High risk	Low risk	High risk	High risk	High risk
Kedia et al 2014 [84]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Ketola et al 2009 [85]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	High risk
Ketola et al 2013 [86]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Kim et al 2017 [87]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Low risk
Kim et al 2020 [88]	Low risk	Low risk	High risk	High risk	Low risk	Unclear	High risk
Knobloch et al 2007 [89]	Low risk	Low risk	Unclear	Unclear	High risk	Unclear	High risk
Knobloch et al 2007 [90]	Unclear	Unclear	High risk	Low risk	Unclear	Unclear	High risk
Knobloch et al 2008 [91]	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	High risk
Koç et al 2020 [92]	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Low risk
Kongsgaard et al 2009 [93]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Kromer et al 2014 [94]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Kromer et al 2013 [95]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kulig et al 2009 [96]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Land et al 2019 [97]	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Low risk
Lee et al 2017 [98]	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	High risk
Lee et al 2014 [99]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Lee et al 2017 [100]	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Littlewood et al 2016 [101]	Low risk	Low risk	High risk	High risk	Unclear	Unclear	High risk
Ludewig et al 2003 [102]	Low risk	Unclear	High risk	Unclear	Low risk	Unclear	Low risk
Luginbuhl et al 2008 [103]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Maenhout et al 2013 [104]	Unclear	High risk	High risk	High risk	Low risk	Unclear	Low risk
Mafi et al 2001 [105]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Manias et al 2006 [106]	High risk	High risk	High risk	High risk	Low risk	Unclear	Unclear
Martinez-Silvestrini et al 2005 [107]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	High risk
Marzetti et al 2014 [108]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mayer et al 2007 [109]	Unclear	Unclear	High risk	High risk	Unclear	Unclear	High risk
McCormack et al 2016 [110]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
McGee et al 1999 [111]	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	High risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
McQueen et al 2020 [112]	High risk	Unclear	Unclear	Unclear	High risk	Unclear	High risk
Melegati et al 2000 [113]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Menek et al 2019 [114]	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Mulligan et al 2016 [115]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
Nazligul et al 2018 [116]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
Nishizuka et al 2017 [117]	Low risk	Low risk	High risk	Unclear	Low risk	Unclear	High risk
Nørregaard et al 2007 [118]	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear	High risk
Notarnicola et al 2014 [119]	Not applicable (quasi)	Not applicable (quasi)	High risk	Unclear	Unclear	Unclear	High risk
Nowotny et al 2018 [120]	Low risk	Unclear	Low risk	Low risk	High risk	Unclear	High risk
Olaussen et al 2015 [121]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Østerås et al 2009 [122]	Low risk	Low risk	Unclear	High risk	Low risk	Unclear	Low risk
Østerås et al 2010 [123]	Low risk	Low risk	High risk	High risk	Low risk	Unclear	High risk
Paavola et al 2018 [124]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Park et al 2010 [125]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Pearson et al 2012 [126]	Unclear	Unclear	High risk	Unclear	Low risk	Unclear	High risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Pearson et al 2018 [127]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
Pekgöz et al 2020 [128]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Pekyavas et al 2016 [129]	Low risk	Low risk	High risk	Low risk	Unclear	Unclear	Low risk
Pérez-Merino et al 2016 [130]	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
Petersen et al 2007 [131]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Peterson et al 2011 [132]	Low risk	Low risk	Unclear	High risk	Low risk	Low risk	Low risk
Peterson et al 2014 [133]	Low risk	Unclear	Low risk	High risk	Low risk	Low risk	Low risk
Polimeni et al 2003 [134]	Unclear	Unclear	High risk	Low risk	Unclear	Unclear	Unclear
Praet et al 2019 [135]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Rabusin et al 2020 [136]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
Ramon et al 2020 [137]	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	High risk
Reyhan et al 2020 [138]	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	High risk
Rhon et al 2014 [139]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Rio et al 2017 [140]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Rodríguez-Huguet et al 2020 [141]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Rodríguez-Huguet et al 2020 [142]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Røe et al 2005 [143]	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Romero-Morales et al 2020 [144]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	High risk
Rompe et al 2007 [145]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Rompe et al 2008 [146]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear
Rompe et al 2009 [147]	Unclear	Low risk	High risk	High risk	Low risk	Unclear	Low risk
Rompe et al 2009 [148]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Roos et al 2004 [149]	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Rosety-Rodriguez et al 2006 [150]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Santamato et al 2016 [151]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	High risk
Scott et al 2019 [152]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Şenbursa et al 2011 [153]	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Seven et al 2017 [154]	Low risk	Low risk	High risk	Low risk	High risk	Unclear	Low risk
Sevier et al 2015 [155]	Low risk	Unclear	High risk	High risk	High risk	Unclear	High risk
Silbernagel et al 2001 [156]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Silbernagel et al 2007 [157]	Low risk	Low risk	High risk	High risk	Low risk	Unclear	Low risk
Şimşek et al 2013 [158]	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Slider et al 2013 [159]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear
Smidt et al 2002 [160]	Low risk	Low risk	High risk	High risk	Low risk	Unclear	Low risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Söderberg et al 2012 [161]	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Stasinopoulos 2013 [162]	High risk	High risk	High risk	Low risk	Low risk	Unclear	High risk
Stasinopoulos et al 2006 [163]	Not applicable (quasi)	Not applicable (quasi)	Unclear	Low risk	Low risk	Unclear	High risk
Stasinopoulos et al 2009 [164]	Not applicable (quasi)	Low risk	High risk	Low risk	Unclear	Unclear	High risk
Stasinopoulos et al 2010 [165]	Not applicable (quasi)	Not applicable (quasi)	Low risk	Low risk	Low risk	Unclear	High risk
Stasinopoulos et al 2017 [166]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	High risk
Stefansson et al 2019 [167]	Low risk	Unclear	High risk	Low risk	High risk	Unclear	Low risk
Stergioulas et al 2007 [168]	Low risk	Low risk	High risk	Low risk	Unclear	Unclear	Unclear
Stergioulas et al 2008 [169]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Steunebrink et al 2013 [170]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Stevens et al 2014 [171]	Unclear	Unclear	High risk	High risk	Unclear	Unclear	High risk
Struijs et al 2004 [172]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	High risk
Svernlov et al 2001 [173]	Not applicable (quasi)	Not applicable (quasi)	Unclear	Unclear	Unclear	Unclear	High risk
Tahran et al 2020 [174]	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Thijs et al 2017 [175]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Tonks 2012 [176]	No Data	No Data	No Data	No Data	No Data	No Data	No Data

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Tonks et al 2007 [177]	Low risk	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Tumilty et al 2012 [178]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Tumilty et al 2016 [179]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Turgut et al 2017 [180]	Low risk	Unclear	Unclear	Unclear	High risk	Unclear	Low risk
Tyler et al 2010 [181]	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	High risk
Vallés-Carrascosa et al 2018 [182]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk
van Der Vlist 2020 [183]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
vanArk et al 2016 [184]	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk
Vinuesa-Montoya et al 2017 [185]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Visnes et al 2005 [186]	Low risk	Low risk	High risk	Low risk	Unclear	Unclear	Unclear
Vuvan et al 2019 [187]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Walther et al 2004 [188]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Warden et al 2008[189]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Wegener et al 2016 [190]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	High risk
Wen et al 2011 [191]	Unclear	Unclear	Low risk	Unclear	High risk	Unclear	High risk
Werner et al 2002 [192]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Wiedmann et al 2017 [193]	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear	High risk

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants /personnel	Blinding of outcome assessment	Incomplete outcome bias	Selective reporting	Other bias
Yazmalar et al 2016[194]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Yeldan et al 2009[195]	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk
Yelland et al 2011 [196]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Low risk
Yerlikaya et al 2018 [197]	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	High risk
Young et al 2005 [198]	Unclear	Unclear	High risk	Low risk	High risk	Unclear	High risk
Yu et al 2013 [199]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear
Yuruk et al 2014 [200]	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear