

**EFFICACY OF CONSERVATIVE TREATMENTS FOR HAND OSTEOARTHRITIS:  
AN UMBRELLA REVIEW OF INTERVENTION STUDIES**

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## ABSTRACT

**Background:** Hand osteoarthritis (OA) is common, but the efficacy/safety of treatment interventions aimed to improve health outcomes in this population are not well understood. Therefore, the aim of this study was to map and grade the effect of interventions for health outcomes in hand OA.

**Methods:** Umbrella review of systematic reviews with meta-analyses of randomized controlled trials (RCTs) using placebo/no intervention as control group. For outcomes with a p-value <0.05, the certainty of the evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment.

**Results:** From 189 abstracts, 9 meta-analyses (24 outcomes) were included, with eight reporting significant summary results. The use of splints was associated with reduced pain at medium term in thumb carpometacarpal OA (standardized mean difference, SMD=-0.70; 95% confidence intervals, CI: -1.05 to -0.35; low certainty), reduced pain in long follow-up RCTs in symptomatic hand OA (SMD=-0.80; 95%CI: -1.16; -0.45; moderate certainty), and better function (SMD=0.42; 95%CI: 0.08; 0.70; low certainty). The use of resistance training (SMD=-0.27; 95%CI: -0.47; -0.07) or physical exercise (SMD=-0.23; 95%CI: -0.42; -0.04) in improving hand pain and in improving finger joint stiffness (SMD=-0.36; 95%CI: -0.58; -0.15) was supported by a moderate certainty of evidence. The use of intra-articular hyaluronic acid in improving function (MD=1.12; 95%CI: 0.61; 1.64; moderate certainty of evidence) was the only pharmacological intervention statistically significant.

**Conclusion:** Only some non-pharmacological interventions are effective in improving health outcomes in hand OA and this evidence is supported by a moderate/low certainty, indicating the necessity of further intervention research.

**Key words:** hand osteoarthritis; physical activity; splint; randomized controlled trial; umbrella review.

## INTRODUCTION

Hand osteoarthritis (OA) is a common condition in adults and older people. It is widely known that the presence of hand OA linearly increases with age, with women having rates than men, especially after menopause. [1] In an American study comparing the incidence of different forms of OA in a population living around Boston, the authors, using only radiological information found that the highest incidence was found for knee OA (240/100 000 person-years), with intermediate rates for hand OA (100/100000 person-years) and lowest observed rates for hip OA (88/100000 person-years). [2] These figures were overall confirmed in other surveys, such as in Europe. [3]

Hand OA seems to be associated with several negative outcomes including a high rate of disability [4], poor quality of life [5], whilst the association between hand OA and cardiovascular disease [6] or mortality [7] is less clear. However, hand OA is characterized by a high presence of pain, stiffness and finally limited function making this condition very relevant from a clinical point of view. [8] Despite the clinical importance of hand OA, a few treatments are approved for treating the symptoms (pain, stiffness, poor function) associated with this condition.[9] In 2007, the European League Against Rheumatism (EULAR) proposed some non-pharmacological and pharmacological interventions based on experts' opinion [10], whilst in 2018 other authors updated these recommendations, even if the evidence was mainly based on single randomized controlled trials (RCTs) credibility.[11]

Given this background, we aimed to capture the breadth of outcomes associated with interventions in people affected by hand OA and systematically assess the quality, strength and credibility of these associations. We used the umbrella review methodology to combine evidence from a wide range of outcomes and populations including only RCTs.

## MATERIALS AND METHODS

### *Data sources and searches*

We conducted an umbrella review [12], searching MEDLINE, Scopus, Embase databases until 31<sup>st</sup> December 2019 with: “(Meta-Analysis[ptyp] OR metaanaly\*[tiab] OR meta-analy\*[tiab] OR Systematic review [ptyp] OR “systematic review” [tiab]) AND (hand osteoarthritis [tiab])”. In addition, we hand-searched the reference lists of eligible and other relevant articles.

### *Study selection*

For the aims of this work, we included formal systematic reviews with meta-analyses of intervention studies, which investigated the effect of any kind of interventions (except surgical ones) for the treatment of hand OA. Two authors (JD, NV) performed title and abstract screening, with another independent author (LS) available if needed. Full-texts of all potentially eligible articles were then retrieved by the same two authors and any disagreement was resolved with another independent author (LS).

We included meta-analyses that investigated people affected by hand OA and including RCTs, with at least one group taking placebo or no active intervention, exploring the association of any kind of intervention with any health-related outcome. The type of interventions was consequently categorized as pharmacological and non-pharmacological depending on their nature. Nutritional supplementations were included among the pharmacological interventions. Meta-analyses were included only if they reported study-specific information (i.e. effect size, 95% confidence intervals [CIs], sample size) or such information could be inferred from the presented data.

### ***Data extraction***

Two independent investigators (JD, NV), extracted key information for each meta-analysis: first author name; publication year; type of intervention; comparison group; hand OA definition; outcome of interest; follow-up (in months); number of people randomized to active intervention and those randomized to placebo/no intervention. We also extracted the study-specific estimated relative risk for health outcome (mean difference, MD; standardized mean difference, SMD) and 95% confidence intervals (CIs). We finally extracted the data for the Assessment of Multiple Systematic Reviews (AMSTAR)-2 tool. [13]

When more than one meta-analysis on the same research question was identified, the one with the largest number of participants was selected.

### ***Quality assessment***

We assessed the methodological quality of the included meta-analyses using AMSTAR-2 [13, 14] that ranks the quality of a meta-analysis from critically low to high according to 16 predefined items.

### ***Data synthesis and analysis***

For each meta-analysis, we re-calculated the summary effect size and its 95% CI by using the random-effects DerSimonian and Laird. [15] We also estimated the prediction interval (PIs) and its 95% CI, which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association.[16, 17] Between-study inconsistency was estimated with the  $I^2$  metric, with values  $\geq 50\%$  indicative of high heterogeneity.[18]

We then calculated the evidence of small-study effects (i.e. whether small studies inflated effect sizes).

We used the regression asymmetry test [19], using a p-value  $< 0.10$  with more conservative effects in larger studies as indicative of small-study effects.[20]

All the analyses were conducted with STATA 13.0 (Stata Corp LP, College station, Texas).

### ***Grading the evidence***

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value  $<0.05$  as the threshold for statistical significance, as recently proposed.[21, 22] For significant outcomes, we evaluated the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment.[23] We also considered 95% PIs (excluding the null or not), small study effects ( $P>0.10$ ), and if the largest study was statistically significant or not, as possible indicators of bias in the available evidence.

## RESULTS

As shown in **Figure 1**, we identified 189 unique works in three major databases, with 9 meta-analyses (corresponding to 24 different outcomes) finally included in our umbrella review. [24-32]

### *Meta-analyses of RCTs (vs. placebo/no treatment)*

As reported in **Supplementary Table 1**, the median number of RCTs meta-analyses for each outcome was only 2 (range 2-6), the median number of participants was 164 (130 to 702). Overall, 18/24 of the interventions were ranked as non-pharmacological, and the most frequent intervention regarded physical exercise (n=6 outcomes) and the use of splints (n=10). Regarding the site of hand OA affected, eight outcomes included all types of hand OA and subtypes, six only symptomatic forms, the other 10 thumb-carpometacarpal, only thumb or trapeziometacarpal forms. Finally, 14 outcomes included evaluation of pain, followed by 8 investigating function as outcome, one handgrip strength and another one stiffness.

Overall, one third of the outcomes included (8/24) reported nominally significant summary results ( $p < 0.05$ ). **Table 1** shows the strength of the association between proposed interventions and selected outcomes in people affected by hand OA, using the GRADE. Among seven non-pharmacological interventions, the use of splints was associated with reduced pain sensation at medium term in thumb carpometacarpal OA (SMD=-0.70; 95%CI: -1.05 to -0.35; low certainty of evidence), reduced pain in long follow-up RCTs in symptomatic forms of hand OA (SMD=-0.80; 95%CI: -1.16; -0.45; moderate certainty of evidence) and a better function (SMD=0.42; 95%CI: 0.08; 0.70; low certainty of evidence), in two RCTs for each outcome. The certainty of evidence was mainly given by the small sample sizes included in these RCTs.

A moderate certainty of evidence supported the use of resistance training (5 RCTs, SMD=-0.27; 95%CI: -0.47; -0.07) or physical exercise (5 RCTs, SMD=-0.23; 95%CI: -0.42; -0.04) in improving hand pain and the use of physical exercise in improving finger joint stiffness (4 RCTs, SMD=-0.36; 95%CI: -0.58; -0.15) (**Table 1**). Conversely, the use of a multimodal intervention was associated with an improvement in pain in trapeziometacarpal OA supported by a very low certainty of evidence.

The only pharmacological intervention associated with a significant outcome was the use of intra-articular hyaluronic acid in improving function in people affected by thumb OA (MD=1.12; 95%CI: 0.61; 1.64; moderate certainty of evidence).

**Supplementary Table 1** shows other analyses commonly used in the umbrella review methodology. Three outcomes reported a small-study effect, in six outcomes the largest study, in terms of participants, was statistically significant, and only one outcome reported the PIs not including the null value.

As reported in **Supplementary Table 2**, four meta-analyses were rated “High” according to the AMSTAR-2 criteria, whilst 3 other meta-analyses were rated as “Low” and 2 as “Critically low”.

## DISCUSSION

With this work, we provide a comprehensive overview of the potential pharmacological and non-pharmacological interventions in people affected by hand OA, incorporating evidence from nine meta-analyses. In this regard, we assessed the evidence of RCTs using the GRADE assessment, in order to increase the transparency of these evidences. Overall, we found that, among 24 different interventions investigated, only eight were supported by a statistical significance and of these, five reached a moderate certainty of the evidence. The AMSTAR-2 indicated that works included were accurate in describing risk of bias in studies included in meta-analysis. Moreover, meta-analysis included often presented and followed pre-established protocols and reporting models like PRISMA.

Our umbrella review shows that the large majority of the interventions for hand OA regard non-pharmacological interventions, in particular splints. Using the most common categorization for SMD (i.e. small, moderate, or large effect, if the SMD was 0.2–0.5, 0.5-0.7, and  $\geq 0.7$ , respectively) [33], we observed that splints are able to significantly reduce pain in thumb carpometacarpal and in symptomatic OA with a large effect, even if this evidence is supported only by a low/moderate certainty of evidence, using the GRADE. From a clinical point of view, it seems that splints might provide a material support of inflamed joints, finally reducing inflammation with a consequent reduction in pain.[24, 34, 35] A similar effect was suggested for improving function: in our umbrella review, the improvement in function was moderate according to the SMD, but again suffered on the presence of bias and of limited sample size included. Among non-pharmacological interventions the other that we found to be significant is physical exercise.[36] In this case, physical exercise, in particular resistance training, decreased pain with a small effect and, again, the effect of biases and imprecision is unfortunately of importance, even if it is a topic of great importance. Further specific research is needed regarding the importance of physical exercise in improving hand OA outcomes.

In our umbrella review, the only pharmacological intervention statistically superior to placebo was intra-articular hyaluronic acid in improving function in people specifically affected by thumb OA, in agreement with a robust review regarding this topic.[37] This is somewhat surprising since several medications are commonly used for improving pain and function in hand OA, including topical and oral non-steroidal anti-inflammatory drugs, paracetamol, glucocorticoids, intra-articular medications and many others. [11, 38-41] In this regard, the most common guidelines for hand OA [10, 11] recognize that very limited research is available for this specific condition regarding medications that are commonly used for types of OA, such as knee OA. [42] Our work further supports the need for high-quality RCTs for hand OA, also due its clinical and epidemiological importance. [8]

The findings of our work should be interpreted within its limitations. First, we used evidence assessment criteria, which were based on already established tools for evaluating the current evidence that can be biased for their nature.[43] Moreover, meta-analyses included studies with relevant differences in design, population and other basic characteristics, that can increase the risk of high heterogeneity. In order to overcome this problem, we used an  $I^2 < 50\%$  as one of the domains of the GRADE. Second, another common limitation of an umbrella review approach is the use of existing meta-analyses that are related to choices made about what estimates to select from each primary study and how to represent them in the meta-analysis. Third, in this umbrella review a half of the outcomes included only two RCTs and most of the RCTs included small sample sizes strongly limiting our results. It is noteworthy, for example, that only one outcome (i.e. the use of physical exercise in reducing pain) had 95% PIs excluding the null value.

In conclusion, our umbrella review including nine meta-analyses and 24 different outcomes in people affected by hand OA, found that only a few non-pharmacological interventions are potentially effective

in improving health outcomes and this evidence is supported by a moderate/low certainty of evidence according to the GRADE. Our work further encourages specific research of high quality RCTs in order to increase the availability of interventions for improving outcomes in people affected by hand OA.

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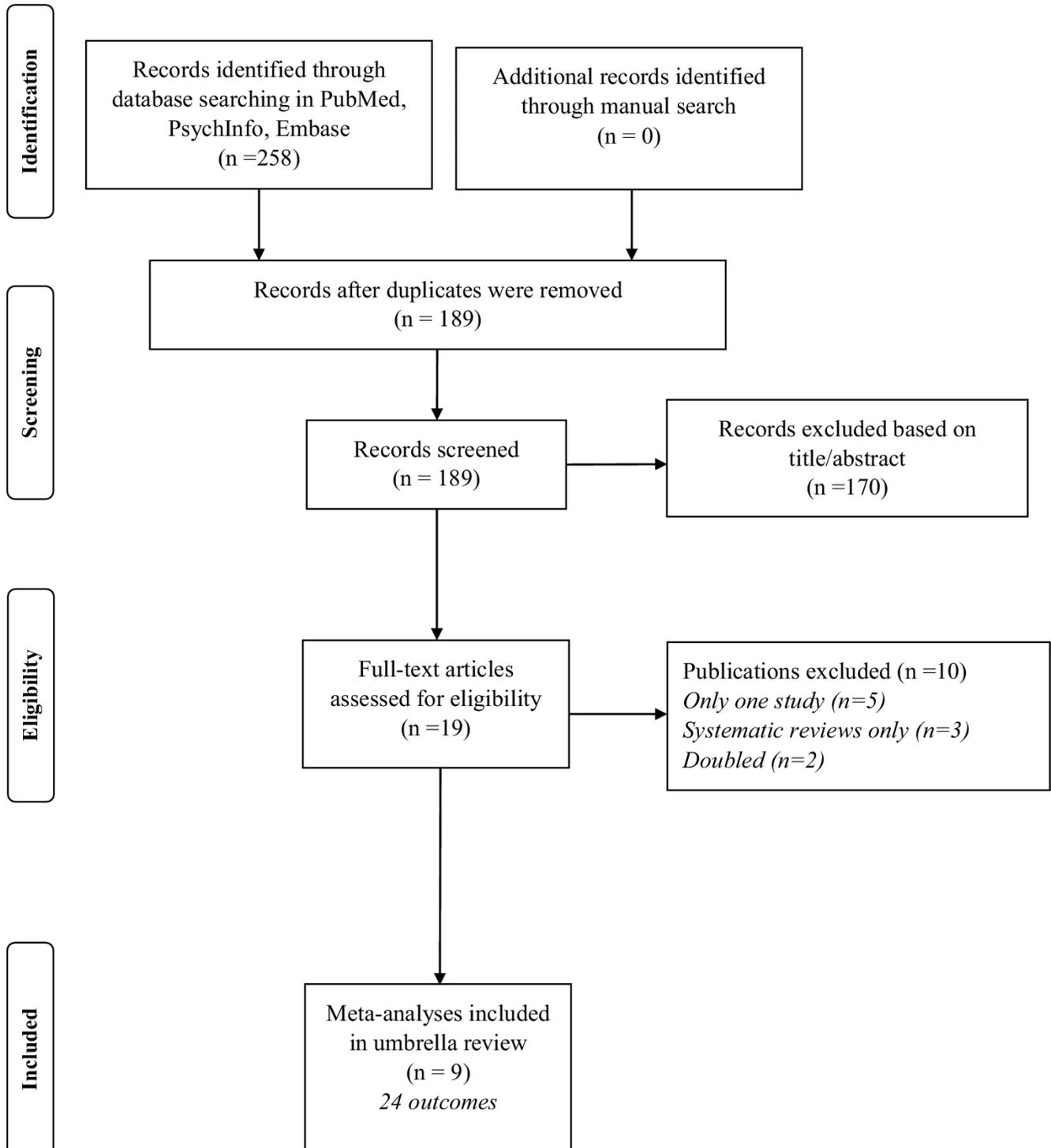
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## FIGURE LEGEND

Figure 1. PRISMA flow-chart



**TABLE 1**

**Table 1 - GRADE evidence of randomized controlled trials using nonpharmacological and pharmacological interventions for hand osteoarthritis**

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Type of intervention (vs. control group)	Anticipated absolute effects	
							With no intervention	With intervention		Risk with no intervention	Risk difference with intervention
<i>Pain (medium follow-up, 3–12 months) in thumb carpometacarpal osteoarthritis</i>											
137 (2 RCTs)	Serious <sup>a</sup>	Not serious	Not serious	Serious <sup>b</sup>	None	⊕⊕○○ LOW	65	72	Splints (vs. no splints)	–	SMD –0.70 (–1.05 to –0.35)
<i>Function (medium follow-up, 3–12 months) in thumb carpometacarpal osteoarthritis</i>											
135 (2 RCTs)	Serious <sup>a</sup>	Not serious	Not serious	Serious <sup>b</sup>	None	⊕⊕○○ LOW	66	69	Splints (vs. no splints)	–	SMD 0.42 (0.08–0.77)
<i>Pain (long follow-up) in symptomatic hand osteoarthritis</i>											
152 (2 RCTs)	Not serious	Not serious	Not serious <sup>b</sup>	Serious <sup>b</sup>	None	⊕⊕⊕○ MODERATE	75	77	Splints (vs. no splints)	–	SMD –0.80 (–1.16 to –0.45)
<i>Hand pain</i>											
381 (5 RCTs)	Serious <sup>c</sup>	Not serious	Not serious	Not serious	None	⊕⊕⊕○ MODERATE	193	188	Resistance training (vs. no resistance training)	–	SMD –0.27 (–0.47 to –0.07)
<i>Finger joint stiffness</i>											
368 (4 RCTs)	Serious <sup>c</sup>	Not serious	Not serious	Not serious	None	⊕⊕⊕○ MODERATE	188	180	Physical exercise (vs. no exercise)	–	SMD –0.36 (–0.58 to –0.15)
<i>Pain in hand osteoarthritis</i>											

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Type of intervention (vs. control group)	Anticipated absolute effects	
							With no intervention	With intervention		Risk with no intervention	Risk difference with intervention
492 (5 RCTs)	Serious <sup>c</sup>	Not serious	Not serious	Not serious	None	⊕⊕⊕○ MODERATE	246	246	Physical exercise (vs. no exercise)	–	SMD –0.23 (–0.42 to –0.04)
<i>Pain in trapeziometacarpal osteoarthritis</i>											
185 (4 RCTs)	Not serious	Very serious <sup>d</sup>	Not serious	Serious <sup>b</sup>	Publication bias strongly suspected <sup>e</sup>	⊕○○○ VERY LOW	91	94	Physical and occupational therapy (multimodal) (vs. no intervention)	–	MD –3.17 (–5.63 to –0.71)
<i>Function in thumb osteoarthritis</i>											
148 (2 RCTs)	Not serious	Not serious	Not serious <sup>b</sup>	Serious <sup>b</sup>	None	⊕⊕⊕○ MODERATE	74	74	IAHA (vs. placebo)	–	MD 1.12 (0.61–1.64)

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**SUPPLEMENTARY INFORMATION**

**Supplementary Table 1. Descriptive characteristics (and additional analyses) for the outcomes included**

Intervention	Comparison group	Hand OA definition	Outcome	Number of studies	Cases	Controls	Sample size	Type of metric	Mean ES (RE)	P	I <sup>2</sup>
CS	placebo	thumb	pain	2	82	82	164	MD	-1.12 (-3.69; 1.29)	0.35	96.6
DMARDS	placebo	all types	pain	6	347	355	702	ES	0.1 (-0.05; 0.24)	0.19	0
exercise	no exercise	all types	pain	4	188	193	381	SMD	-0.27 (-0.47; -0.07)	0.00005	7.2
exercise	no exercise	all types	stiffness	4	180	188	368	SMD	-0.36 (-0.58; -0.15)	0.001	7.6
exercise	no exercise	all types	function	4	181	188	369	SMD	-0.28 (-0.59; 0.02)	0.06	51
hyaluronic	placebo	thumb	function	2	74	74	148	MD	-1.12 (-1.64; -0.61)	0.00002	26.5
hyaluronic	placebo	thumb	pain	2	74	74	148	MD	-0.95 (-3.78; 1.97)	0.52	96
intra-articular CS	placebo	thumb-base	pain	2	85	81	166	MD	-3.56 (-13.9; 6.75)	0.5	50.7
physical and occupational therapy	none	trapeziometacarpal	pain	4	94	91	185	MD	-3.17 (-5.63; -0.71)	0.01	97.3
(multimodal) physical and occupational therapy	none	trapeziometacarpal	function	3	65	65	130	SMD	-0.66 (-1.55; 0.23)	0.15	82.9
(multimodal) resistance training	no resistance training	all types	pain	5	246	246	492	SMD	-0.23 (-0.42; -0.04)	0.02	0
resistance training	no resistance training	all types	grip strength	4	246	246	492	MD	1.35 (-0.84; 3.53)	0.23	49.9
resistance training	no resistance training	all types	function	4	246	246	492	SMD	-0.10 (-0.33; 0.13)	0.39	27.4
splints	no splints	symptomatic	pain long fu	2	77	75	152	SMD	-0.80 (-1.16; -0.45)	7.17E-06	0
splints	no splints	thumb carpometacarpal	pain medium fu	2	72	65	137	SMD	-0.70 (-1.05; -0.35)	8.00E-05	0
splints	no splints	thumb carpometacarpal	function medium fu	2	69	66	135	SMD	-0.42 (-0.77; -0.08)	0.02	0
splints	no splints	symptomatic	pinch short fu	2	77	75	152	SMD	0.26 (-0.08; 0.59)	0.13	0
splints	no splints	symptomatic	function short fu	2	77	75	152	SMD	0.25 (-0.08; 0.58)	0.14	0
splints	no splints	symptomatic	pinch long fu	2	77	75	152	SMD	0.23 (-0.10; 0.57)	0.17	0
splints	no splints	symptomatic	function long fu	2	77	75	152	SMD	-0.22 (-0.56; 0.12)	0.2	0
splints	no splints	thumb carpometacarpal	pain short fu	4	119	102	221	SMD	-0.23 (-0.59; 0.13)	0.2	38.1
splints	no splints	symptomatic	pain short fu	2	77	75	152	SMD	0.63 (-0.51; 1.78)	0.28	88.3
splints	no splints	thumb carpometacarpal	function short fu	4	118	103	221	SMD	0.12 (-0.15; 0.38)	0.39	0
topical NSAIDS	placebo	all types	pain	2	218	207	425	SMD	0.48 (-0.83; 1.80)	0.47	0

**Abbreviations:**

CI: Confidence interval; SMD: Standardised mean difference; MD: Mean difference; ES: Effect size; NA: not available; OA: osteoarthritis; NSAIDS: non steroidal anti-inflammatory drugs; DMARDS: disease modifying anti-rheumatoid drugs.

**Supplementary Table 2. AMSTAR 2 quality assessment of meta-analyses of RCTs**

Author, Year [Reference]	AMSTAR 2 items <sup>a, c</sup>																Overall rating (based on critical domains) <sup>d</sup>
	1	2 <sup>b</sup>	3	4 <sup>b</sup>	5	6	7 <sup>b</sup>	8	9 <sup>b</sup>	10	11 <sup>b</sup>	12	13 <sup>b</sup>	14	15 <sup>b</sup>	16	
Østeras 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Magni 2017	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Aebischer 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Kroon 2016	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Kjeken 2011	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	Critically low
Buhler 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Persson 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Persson 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Trellu 2015	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Critically low

<sup>a</sup> Yes, No, Other

<sup>b</sup> Critical Domains

<sup>c</sup> AMSTAR 2 items:

- 1. Did the research questions and inclusion criteria for the review include the components of PICO (Population, Intervention, Comparator group, Outcome)?** YES/NO. For yes, must have all four.
- 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?** YES, PARTIAL YES, NO. For Partial YES: the authors state that they had a written protocol or guide that included ALL the following (review question(s), a search strategy, inclusion/exclusion criteria, a risk of bias assessment). For YES: as for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, and a plan for investigating causes of heterogeneity, justification for any deviations from the protocol.
- 3. Did the review authors explain their selection of the study designs for inclusion in the review?** YES/NO. For YES, the review should satisfy one of the following: explanation for including only RCTs, or explanation for including only NRSI, or explanation for including both RCTs and NRSI.
- 4. Did the review authors use a comprehensive literature search strategy?** YES, PARTIAL YES, NO. for PARTIAL YES must have all of the following: searched at least 2 databases (relevant to research question), provided key word and/or search strategy, justified publication restrictions (eg. Language). For YES should also have all of the following: searched the reference lists/biographies of included studies, searched trial/study registries, included/consulted content experts in the field, searched for grey literature where relevant, conducted search within 24 months of completion of the review.
- 5. Did the review authors perform study selection in duplicate?** YES/NO. for YES, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder selected by one reviewer.
- 6. Did the review authors perform data extraction in duplicate?** YES/NO. For YES, either one of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder extracted by one reviewer.

7. **Did the review authors provide a list of excluded studies to justify the exclusions?** YES, PARTIAL YES, NO. For partial yes must provide a list of all potentially relevant studies that were read in full text form but excluded from the review. For YES must also have justified the exclusion from the review of each potentially relevant study.
8. **Did the review authors describe the included studies in adequate detail?** YES, PARTIAL YES, NO. For PARTIAL YES, must describe all of the following: populations, interventions, comparators, outcomes, research designs. For YES should also have all of the following: described populations in detail, described intervention and comparator in detail (including doses where relevant), described study setting, timeframe or follow-up.
9. **Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?** For RCTs: YES, PARTIAL YES, NO, INCLUDES ONLY NRSI. For PARTIAL YES must have assessed RoB from unconcealed allocation and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality); for YES must also have assessed RoB from allocation sequence that was not truly random and selection of the reported result from among multiple measurements or analyses of a specified outcome. For NRSI (Non Randomized Studies of Intervention): YES, PARTIAL YES, NO, INCLUDES ONLY RCTs. For PARTIAL YES must have assessed RoB from confounding and from selection bias. For YES, must also have assessed methods used to ascertain exposures and outcomes, and selection of the reported results from among multiple measurements or analyses of a specified outcome.
10. **Did the review authors report on the sources of funding for the studies included in the review?** YES/NO. For YES: must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies
11. **If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?** For RCTs: YES, NO, NO META-ANALYSIS. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present and investigated the causes of heterogeneity. For NRSI: YES, NO, NO META-ANALYSIS CONDUCTED. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present, and they statistically combined effects estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available, and they reported separate summary estimates for RCTs and NRSI separately when both were included in the review.
12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** YES, NO, NO META-ANALYSIS INCLUDED. For YES: included only low risk of bias RCTs or, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analysis to investigate possible impact of RoB on summary estimates of effect.
13. **Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?** YES/NO. for YES: included only low risk of bias RCTs or, if RCTs with moderate or high RoB, or NRSI were included, the review provided a discussion of the key impact of RoB on the results
14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** YES/NO. For Yes: there was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review
15. **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** YES, NO, NO META-ANALYSIS CONDUCTED. For YES: performed graphical statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias
16. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** YES/NO. For Yes: the authors reported no competing interests OR the authors described their funding sources and how they managed potential conflicts of interest.

<sup>d</sup> Rating overall confidence in the results of the review:

HIGH: *no on one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

MODERATE: *more than one non critical weakness* (multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence): the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

LOW: *one critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

CRITICALLY LOW: *more than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies