Comparative effectiveness of different placebos and comparator groups for hand osteoarthritis exploring the impact of contextual factors: a systematic review and meta-analysis of randomised trials

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Review

Comparative effectiveness of different placebos and comparator groups for hand osteoarthritis exploring the impact of contextual factors: A systematic review and meta-analysis of randomised trials

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SUMMARY

Objective: To examine the pain relief effects of comparators (placebos and untreated control groups) in hand osteoarthritis trials and the impact of contextual factors.
Methods: We systematically searched PubMed, EMBASE and CENTRAL from inception to December 26, 2021. We included randomised controlled trials of people with hand osteoarthritis with a placebo or an untreated control group. We assessed the Risk of Bias with Cochrane Risk-of-Bias tool version 2. Each comparator was contrasted with a null-arm, imputed as having a zero change from baseline with the same standard deviation as the comparator. We combined the standardised mean differences with a random effects meta-analysis. The contextual factors' effect was explored in meta-regression and stratified models with pain as the dependent variable.
Results: 84 trials (7262 participants) were eligible for quantitative synthesis, of which 76 (6462 participants) were eligible for the stratified analyses. Placebos were superior to their matched null-arms in relieving pain with an effect size of −0.51 (95% confidence interval −0.61 to −0.42), while untreated control groups were not. When analysing all comparators, blinded trial designs and low risk of bias were associated with higher pain relief compared to an open-label trial design and some concern or high risk of bias.
Conclusion: The placebo response on pain for people with hand osteoarthritis was increased by appropriate blinding and a lower risk of bias assessment. Placebos were superior to a null-arm, while untreated control groups were not. Results emphasise the importance of using appropriate comparators in clinical trials.
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Introduction

Osteoarthritis is a common disease affecting synovial joints. Hand osteoarthritis causes pain and reduces function.[1] Treatment options are limited, with only modest effects and no disease-modifying agents.[2] In hand osteoarthritis trials, there is a repeated failure of experimental interventions, despite treatment response, which could be due to a high placebo response, especially in pain.[3] Placebo can be described as an effect for which no empirically supported theory for its mechanisms of action exists and as an incidental factor of treatment.[4,5] The *placebo response* refers to the overall change observed after administering a placebo comparator. In contrast, the *placebo effect* is found by subtracting the effect seen in an untreated parallel group from the effect of a placebo treatment (i.e., placebo response),[6] thereby accounting for the natural course of the disease, the regression towards the mean, and other non-specific effects. The *nocebo response* refers to a negative expectation leading to a negative realisation.[7] The placebo response could be influenced by contextual factors, leading to variability across trials.[8]

A contextual factor is a '*variable that is not an outcome of the study but needs to be recognised (and measured) to understand the study results. This includes potential confounders and effect modifiers*' and was first introduced in the Outcome Measures in Rheumatology (OMERACT) process in 2012.[9] In trials, where the effect size for a placebo intervention has been found to be effective for pain in osteoarthritis patients, the effect size was largely influenced by the strength of the active treatment, the baseline disease severity, the delivery route, and the study's sample size.[3] In addition, a recent study found that high baseline pain and female sex were associated with a clinically significant placebo response in hand osteoarthritis patients, suggesting an influence of contextual factors in hand osteoarthritis trials.[10]

Understanding the extent of the placebo response for different comparators, and the contextual factors which may impact it is important when designing and estimating clinical trials to avoid over- or underestimation of the active treatment. This study aimed to determine the pain relief effects and safety of comparators i.e. placebos and untreated control groups and to explore the possible determinants of the anticipated placebo response on pain by quantitatively analysing contextual factors among trial settings.

Methods

We define *comparators* as any control group in a clinical trial, whose role it is to be a comparison to the active treatment which is being studied. We define *placebos and shams* as innate drugs or treatments, that are developed to appear as an active treatment. We define *untreated control groups* as comparators that do not receive an active treatment or a placebo, in this meta-analysis this includes no treatment, care as usual, waiting list and education comparator groups. In our method, we refer to a *null-arm,* which is a hypothetical group that represents a zero change from the baseline. This term is explained further in the section 'Data analysis'.

Protocol and registration

The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022298984) before initiating the study. The study protocol is available in Appendix 1**.** We adhere to the PRISMA guideline for reporting.[11]

Search strategy and information sources

A systematic search of MEDLINE (via PubMed), EMBASE (via Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted from inception to 26 December 2021 (see Appendix 1). The search strategy was built on that of a previous systematic review of hand osteoarthritis interventions.[2] We hand-searched reference lists of systematic literature reviews and meta-analyses concerning hand osteoarthritis, and reference lists of included studies. Authors of eligible studies were contacted when no pain data for the comparator group was available.

Study selection and data extraction

References were assessed independently by two reviewers (AD and IMB) using Covidence.[12] All randomised trials studying people with hand osteoarthritis were assessed for full-text screening. Diagnostic criteria for hand osteoarthritis were defined by the trials. We included trials with at least one non-pharmacological, pharmacological, or surgical intervention, with the comparator being either a placebo, care as usual, waiting list, education as a comparator or no treatment, excluding trials in which the only comparator was an active treatment. We excluded studies not written in Danish, Swedish, Norwegian, German, French, Dutch, Italian, Spanish, or English. Studies with hand osteoarthritis reporting outcome efficacy data on pain, function, patient global assessment and hand strength or safety data on withdrawals, withdrawals due to adverse events and serious adverse events were included in the quantitative synthesis. If hand osteoarthritis was part of multi-site osteoarthritis, studies were only included if separate outcome data for hand osteoarthritis was available for analysis. Multi-arm trials could be included if meeting all other criteria. Trials with within-person randomisation were excluded from the quantitative synthesis. Cross-over studies were included in the analysis if separate data was available from the time of the cross-over or excluded if only lumped data was available. The following data were extracted in a systematic standardised way using a customised data extraction sheet by two independent reviewers: study characteristics, description of placebo intervention or other comparator groups, contextual factors, efficacy outcomes and safety outcomes. The full list of collected data items and contextual factors can be found in Appendix 1. Articles in languages other than English were translated by one reviewer before being assessed by a second reviewer. Reviewers resolved disagreements by discussion or consultation with a third reviewer.

Risk of Bias assessment

Two reviewers independently assessed the risk of bias using version 2 of the Cochrane risk-of-bias tool for randomised trials.[13] The assessment was related to outcome reports on pain. The judged domains were the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Each domain was judged as high, low, or some concern. In addition, information on funding sources was extracted, as a Cochrane review has previously demonstrated more favourable efficacy results in industry-sponsored studies compared to non-industry-sponsored studies.[14] Funnel plots were generated for each efficacy outcome to assess publication bias by visual inspection.[15]

Patient research partners

In agreement with European Alliance of Associations for Rheumatology (EULAR) recommendations, two Patient Research Partners identified at the Parker Institute's outpatient clinic were invited to comment on the entire protocol and study design, make suggestions and contributions to the design of the study, as well as participate in a discussion of the results prospectively and contribute to the core publication.[16] One Patient Research Partner participated in the discussion, and qualified for co-authorship but declined this.

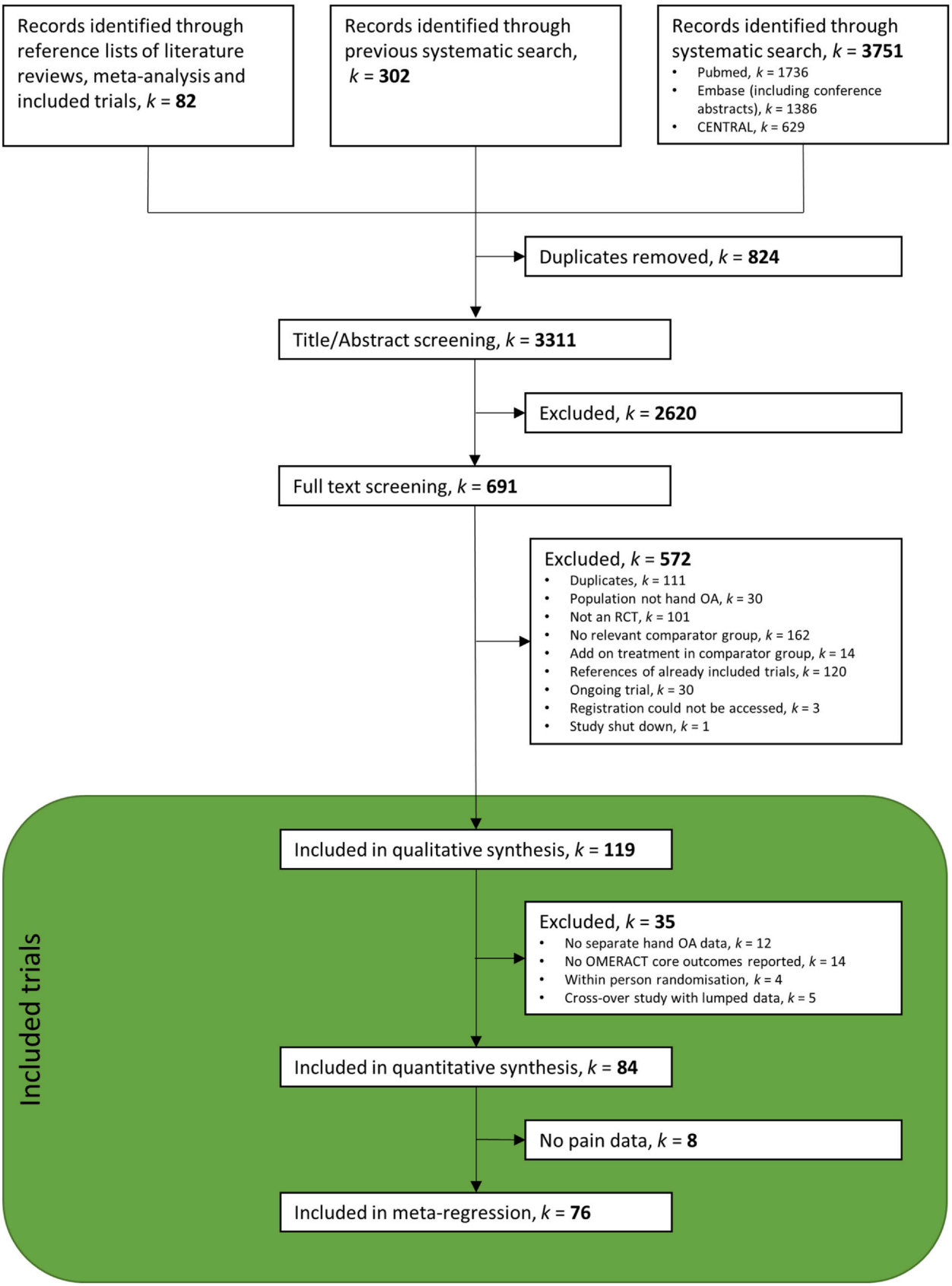


Fig. 1

Osteoarthritis and Cartilage

Flow chart for study selection.

Characteristics	RCTs (k = 84)
Sample size trial, n, median (IQR)	65 (43-103)
Sample size comparator group, n, median (IQR)	30 (20-47)
Publication year, k (%)	
2020 or later	17 (20%)
2010-2019	45 (54%)
2000-2009	12 (14%)
1990-1999	6 (7%)
1980-1989	4 (5%)
Trial population, k (%)	
Thumb osteoarthritis	19 (23%)
Finger osteoarthritis	15 (18%)
Thumb and finger osteoarthritis	50 (60%)
Comparator arm, k (%)	
No treatment	2 (2%)
Care as usual	13 (15%)
Waiting list	1 (1%)
Education* as comparator	8 (10%)
Placebo/sham comparator	60 (71%)
Outcome domain reported,† k (%)	
Pain	76 (90%)
Function	51 (61%)
Patient global assessment	17 (20%)
Health-related quality of life	13 (15%)
Hand strength	33 (39%)
Withdrawals‡	67 (80%)
Withdrawals due to adverse events‡	63 (75%)
Serious adverse events‡	47 (56%)

k: number of trials with this characteristic.
%: percentage of trials with this characteristic.
IQR, Interquartile range; k, number of trials; n, number of participants; RCTs, randomised controlled trials.
* Education as comparator refers to education sessions, oral information, leaflets and advice (please see Appendix 2).
† Each study may report more outcome domains, so the sum will not add up to 100%.
‡ Refer to the number of trials reporting values for withdrawals, withdrawals due to adverse events and serious adverse events.

Table I Osteoarthritis and Cartilage

Characteristics of the trials quantitatively included in this study.

The Patient Research Partner supported the clinical importance of investigating placebo. The Patient Research Partner agreed to appear in the acknowledgements of this article.

Data analysis

We calculated effect sizes, representing the pain relief effect and secondary efficacy outcomes (function, patient global assessment, health related quality of life and hand strength) as the standardised mean difference (SMD) to unify results when different scales were used for the same outcome domain, using data from baseline and endpoint from the comparator groups only. The pain relief effect was estimated for both the comparator groups using an actual placebo or sham treatment as well as for untreated control groups (care as usual, waiting list, education as comparator or no treatment). Unlike a typical meta-analysis, the treatment effect of being allocated to the comparator group of a randomised controlled trial could not be estimated directly, as no comparison was available. Thus, for comparison to the comparator groups, it was assumed that a null-arm was available, representing a scenario of no clinical attention.[17] This counterfactual null-effects approach was manually imputed as having an average zero change from baseline, with the same standard deviation (SD) and the same number of participants as collected for the actual comparator group.[17] We then calculated the SMD based on the mean difference (difference in mean values for change from baseline between the comparator and null-arm divided by the corresponding pooled SD). For studies not reporting a SD to the mean difference, we calculated an SD within a logarithmic model using data from the included studies. We used Review Manager to perform standard arm-based meta-analyses and a random-effects meta-analysis per default for combining comparators across trials.[18] For sensitivity analysis, we used fixed effect analyses for each efficacy outcome. We generated forest plots for each outcome.

The different comparators were subgrouped into either no treatment, care as usual, waiting list, education comparator or placebo/sham. Placebo/sham comparators were further subgrouped according to the administration of the placebo or sham treatment. The effect sizes of each subgroups were combined, representing the combined pain relief effect of the subgroup. The subgroups were then compared with each other in a forest plot.

Among the secondary outcomes, we assessed safety of the placebo comparator versus the null-arm using Peto's odds ratio method and the corresponding 95% confidence interval (CI), to estimate a possible nocebo response.[19] For the null-arm, it was assumed that no safety events occurred with a similar sample size as in the comparator (i.e., zero withdrawals, zero withdrawals due to adverse events, and zero serious adverse events). An odds ratio above one corresponds to a harmful effect of the comparator.

We assessed heterogeneity in the meta-analysis visually and by using I^2 inconsistency index with values > 50% interpreted as substantial heterogeneity.[20] While the actual between-trial variation was quantified using an estimate for τ^2 (communicated in SD-units). We analysed the association between each contextual factor and the efficacy of the comparator using stratified meta-regression analysis. Each contextual factor was explored as the independent variable, using the SMD for pain reduction as the dependent variable. The association was explored in two analyses: one including all comparator groups and one including comparator groups using a placebo or sham treatment only.

Results

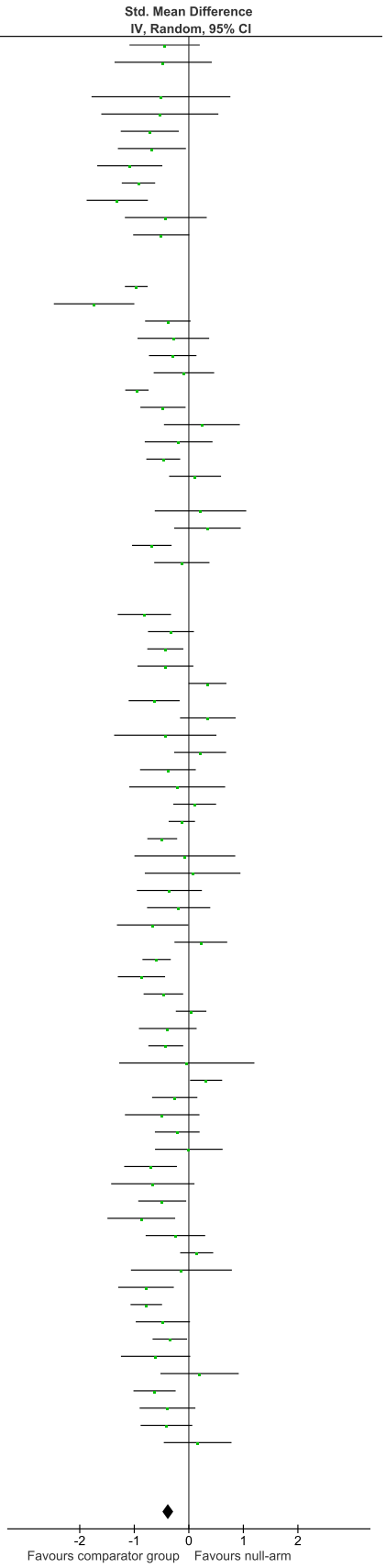
A total of 3311 studies were screened by title and abstract. From these, we assessed 691 potentially eligible studies through full-text reading; 119 trials were included for qualitative analysis. Of these, 84 studies (including 6462 to 1298 participants for analysis depending on outcome) reported outcome data and were eligible for quantitative synthesis. The 76 trials (3231 participants in the comparator groups, 6462 participants in the analysis) that reported data on pain were further included in the meta-regression, see flowchart Fig. 1. The median sample size for the comparator groups was 30 participants, and most trial reports were published between 2010–2019 or after 2020. Table I presents the characteristics of the included trials; individual trial characteristics can be found in Appendix 2.

Efficacy of comparators

The overall effect of all comparators for pain was −0.38 (95% CI −0.47 to −0.28), indicating a beneficial effect of the comparators in terms of pain compared to a null-arm representing the scenario of no attention (Fig. 2). Overall, comparator groups using a placebo or sham treatment were superior to untreated control groups in reducing pain (Fig. 3). The difference in effect sizes (SMDs) between placebo (or sham) treatments and untreated control groups were −0.59 (95% CI −1.23 to 0.05) for no treatment, −0.55 (95% CI −0.74 to −0.36) for care as usual, −0.71 (95% CI −1.44 to 0.02) for waiting list and −0.24 (95% CI −0.53 to 0.05) for education as comparator (Table III, Appendix 3). Topical placebo showed the largest effect size for pain relief, however, CIs did overlap with other placebos (Fig. 3). There was no statistically significant effect on pain reduction of no

Study or Subgroup	Comparator group Mean	SD	Total	Null-arm Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Seiler 1983	-4.1	9.04277	19	0	9.04277	19	1.1%	-0.44 [-1.09, 0.20]	1983
Willner 1985	-5.2	10.5833	10	0	10.5833	10	0.8%	-0.47 [-1.36, 0.42]	1985
Basford 1987	0	0	0	0	0	0		Not estimable	1987
Dickens 1989	-20	35.34	5	0	35.34	5	0.5%	-0.51 [-1.78, 0.76]	1989
McCarthy 1992	-18	31.7	7	0	31.7	7	0.6%	-0.53 [-1.60, 0.54]	1992
Dreiser 1993	-16.5	22.7276	29	0	22.7276	29	1.3%	-0.72 [-1.25, -0.18]	1993
Schnitzer 1994	-14.2	20.5778	21	0	20.5778	21	1.1%	-0.68 [-1.30, -0.05]	1994
Rothacker 1994	-1.1	1	25	0	1	25	1.2%	-1.08 [-1.68, -0.49]	1994
Dougados 1995	-34	36.6763	91	0	36.6763	91	1.8%	-0.92 [-1.23, -0.62]	1995
Rothacker 1998	-2.38	1.79	30	0	1.79	30	1.2%	-1.31 [-1.87, -0.75]	1998
Reeves 2000	-0.6	1.38	14	0	1.38	14	0.9%	-0.42 [-1.17, 0.33]	2000
McKendry 2001	-11.9	23.2	30	0	23.2	30	1.3%	-0.51 [-1.02, 0.01]	2001
Stamm 2002	0	0	0	0	0	0		Not estimable	2002
Verbruggen 2002	0	0	0	0	0	0		Not estimable	2002
Grifka 2004	-19.3	20	196	0	20	196	1.9%	-0.96 [-1.17, -0.75]	2004
Meenagh 2004	-14	7.9	20	0	7.9	20	1.0%	-1.74 [-2.48, -1.00]	2004
Brosseau 2005	-0.26	0.67	45	0	0.67	45	1.5%	-0.38 [-0.80, 0.03]	2005
Heyworth 2008	-1.1	3.78528	18	0	3.78528	18	1.1%	-0.28 [-0.94, 0.37]	2008
Kvien 2008	-6.3	21.13	41	0	21.13	41	1.5%	-0.30 [-0.73, 0.14]	2008
Vander Cruyssen 2008	-0.17	1.86	25	0	1.86	25	1.3%	-0.09 [-0.64, 0.46]	2008
Altman 2009	-26.7	28	187	0	28	187	1.9%	-0.95 [-1.17, -0.74]	2009
Rannou 2009	-10.7	22.38	46	0	22.38	46	1.5%	-0.47 [-0.89, -0.06]	2009
Hansson 2010	0.67	2.726	16	0	2.726	16	1.0%	0.24 [-0.46, 0.94]	2010
Smith 2010	-0.4	2.1	20	0	2.1	20	1.1%	-0.19 [-0.81, 0.43]	2010
Gabay 2011	-11.3	24	82	0	24	82	1.8%	-0.47 [-0.78, -0.16]	2011
Kjeken 2011	0.1	0.86	34	0	0.86	34	1.4%	0.11 [-0.36, 0.59]	2011
Villafañe 2011	0	0	0	0	0	0		Not estimable	2011
Bani 2012	0.5	2.2462	11	0	2.2462	11	0.8%	0.21 [-0.62, 1.05]	2012
Kovács 2012	1.88	5.39716	21	0	5.39716	21	1.2%	0.34 [-0.27, 0.95]	2012
Mandl 2012	-14.2	20.8	62	0	20.8	62	1.6%	-0.68 [-1.04, -0.32]	2012
Verbruggen 2012	-1.7	13.1	30	0	13.1	30	1.3%	-0.13 [-0.63, 0.38]	2012
Villafañe 2012a	0	0	0	0	0	0		Not estimable	2012
Villafañe 2012b	0	0	0	0	0	0		Not estimable	2012
Wenham 2012	-16.8	20.38	35	0	20.38	35	1.4%	-0.82 [-1.30, -0.33]	2012
Shin 2013	-7.8	23.6	44	0	23.6	44	1.5%	-0.33 [-0.75, 0.09]	2013
Stukstette 2013	-1.2	2.77	72	0	2.77	72	1.7%	-0.43 [-0.76, -0.10]	2013
Villafañe 2013	-0.6	1.38	30	0	1.38	30	1.3%	-0.43 [-0.94, 0.08]	2013
Østerås 2014	0.5	1.45	65	0	1.45	65	1.7%	0.34 [-0.00, 0.69]	2014
Chevalier 2014	-16.8	26.16	37	0	26.16	37	1.4%	-0.64 [-1.10, -0.17]	2014
Fiorvanti 2014	1.97	5.56682	30	0	5.56682	30	1.3%	0.35 [-0.16, 0.86]	2014
Rech 2014	-10.78	23.77	9	0	23.77	9	0.7%	-0.43 [-1.37, 0.51]	2014
Hennig 2015	0.3	1.43	34	0	1.43	34	1.4%	0.21 [-0.27, 0.68]	2015
Paschoal 2015	-2.6	6.68915	30	0	6.68915	30	1.3%	-0.38 [-0.89, 0.13]	2015
Sanders 2015	-0.5	2.2462	10	0	2.2462	10	0.8%	-0.21 [-1.09, 0.67]	2015
Van Velden 2015	0.06	0.55202	50	0	0.55202	50	1.6%	0.11 [-0.28, 0.50]	2015
Moe 2016	-0.17	1.32	132	0	1.32	132	1.9%	-0.13 [-0.37, 0.11]	2016
Park 2016	-2.2	4.5	106	0	4.5	106	1.8%	-0.49 [-0.76, -0.21]	2016
Arazpour 2017	-0.11	1.44	9	0	1.44	9	0.7%	-0.07 [-1.00, 0.85]	2017
Saviola 2017	0.48	6.6	10	0	6.6	10	0.8%	0.07 [-0.81, 0.95]	2017
Sofat 2017	-0.9	2.48	22	0	2.48	22	1.2%	-0.36 [-0.95, 0.24]	2017
Aitken 2018	-5	26.38	23	0	26.38	23	1.2%	-0.19 [-0.77, 0.39]	2018
Amaral 2018	-13.42	19.8225	19	0	19.8225	19	1.1%	-0.66 [-1.32, -0.01]	2018
Jamison 2018	0.5	2.2462	33	0	2.2462	33	1.4%	0.22 [-0.26, 0.70]	2018
Kingsbury 2018	-1.31	2.21	119	0	2.21	119	1.9%	-0.59 [-0.85, -0.33]	2018
Kloppenburg 2018a	-21.9	25	45	0	25	45	1.5%	-0.87 [-1.30, -0.44]	2018
Kloppenburg 2018b	-2	4.26	60	0	4.26	60	1.6%	-0.47 [-0.83, -0.10]	2018
Lee 2018	1.1	26.44	98	0	26.44	98	1.8%	0.04 [-0.24, 0.32]	2018
Minten 2018	-0.9	2.3	28	0	2.3	28	1.3%	-0.39 [-0.91, 0.14]	2018
Stoffer-Marx 2018	-0.9	2.12	77	0	2.12	77	1.7%	-0.42 [-0.74, -0.10]	2018
Wade 2018	-0.1	2.42	5	0	2.42	5	0.5%	-0.04 [-1.28, 1.20]	2018
Wang 2018	1.01	3.17	90	0	3.17	90	1.8%	0.32 [0.02, 0.61]	2018
Wilkens 2019	-0.8	3.06588	45	0	3.06588	45	1.5%	-0.26 [-0.67, 0.16]	2019
Cantero-Téllez 2019	-0.1	0.2	17	0	0.2	17	1.0%	-0.49 [-1.17, 0.20]	2019
Kroon 2019	-5.2	24.3	46	0	24.3	46	1.5%	-0.21 [-0.62, 0.20]	2019
Savaş 2019	0	0.03673	20	0	0.03673	20	1.1%	0.00 [-0.62, 0.62]	2019
Barnard 2020	-17	23.96	35	0	23.96	35	1.4%	-0.70 [-1.19, -0.22]	2020
Patru 2020	-13.6	20.0011	14	0	20.0011	14	0.9%	-0.66 [-1.42, 0.10]	2020
Richette 2020	-9.9	20.1	41	0	20.1	41	1.5%	-0.49 [-0.93, -0.05]	2020
Schett 2020	-1.34	1.51	22	0	1.51	22	1.1%	-0.87 [-1.49, -0.25]	2020
Silva 2020	-0.7	2.80653	26	0	2.80653	26	1.3%	-0.25 [-0.79, 0.30]	2020
Tveter 2020	0.3	2.07	84	0	2.07	84	1.8%	0.14 [-0.16, 0.45]	2020
Boada-Pladellorens 2021	-0.25	1.75	9	0	1.75	9	0.7%	-0.14 [-1.06, 0.79]	2021
Davis 2021	-18	22.65	32	0	22.65	32	1.3%	-0.79 [-1.29, -0.28]	2021
Deveza 2021	-17.3	22.1	99	0	22.1	99	1.8%	-0.78 [-1.07, -0.49]	2021
Ferrero 2021	-11.7	24.3	32	0	24.3	32	1.4%	-0.48 [-0.97, 0.02]	2021
Kedor 2021	-4.2	12	78	0	12	78	1.7%	-0.35 [-0.66, -0.03]	2021
Kim 2021	-1.1	1.77	20	0	1.77	20	1.1%	-0.61 [-1.24, 0.03]	2021
Leonard 2021	0.38	1.87309	15	0	1.87309	15	1.0%	0.20 [-0.52, 0.92]	2021
Liu 2021	-14.63	23.118	54	0	23.118	54	1.6%	-0.63 [-1.02, -0.24]	2021
Nery 2021	-1.03	2.6	30	0	2.6	30	1.3%	-0.39 [-0.90, 0.12]	2021
Vela 2021	-1.12	2.7	35	0	2.7	35	1.4%	-0.41 [-0.88, 0.06]	2021
Magni 2022	0.3	1.82	20	0	1.82	20	1.1%	0.16 [-0.46, 0.78]	2022
NCT01683396 NA	0	0	0	0	0	0		Not estimable	NA
NCT01882491 NA	0	0	0	0	0	0		Not estimable	NA
Total (95% CI)			**3231**			**3231**	**100.0%**	**-0.38 [-0.47, -0.28]**	

Heterogeneity: Tau² = 0.11; Chi² = 249.01, df = 75 (P < 0.00001); I² = 70%
Test for overall effect: Z = 7.61 (P < 0.00001)



(caption on next page)

Fig. 2 Osteoarthritis and Cartilage

Forest plot showing the effect of all comparators on pain compared to no clinical attention – random effects model.

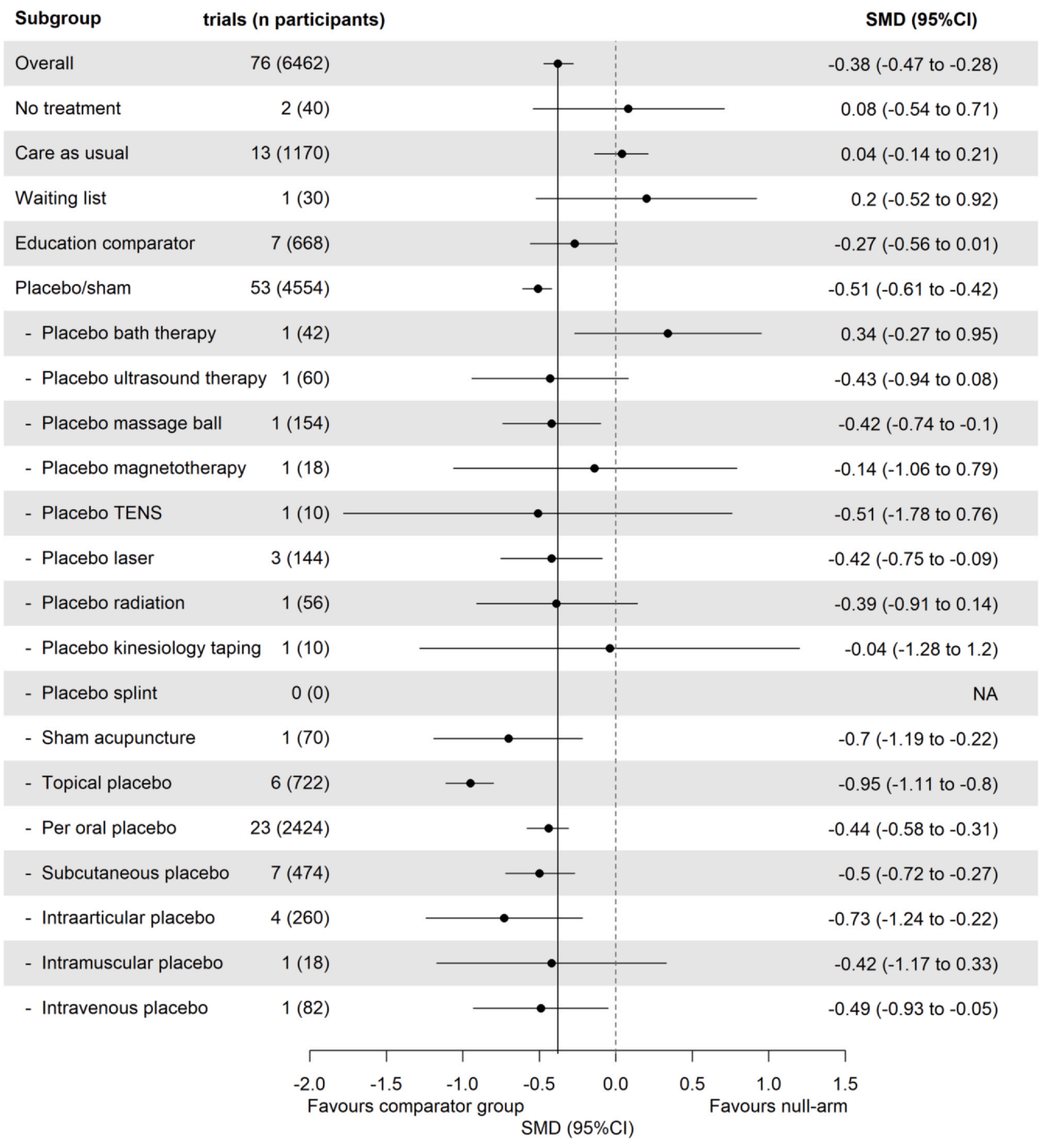


Fig. 3 Osteoarthritis and Cartilage

Comparative effectiveness of comparators for pain illustrated by their stratified subgroups. Forest plot showing the comparative effectiveness of the comparator groups. Solid line indicates the overall effect of all groups. Dashed line is equal to an effect size of zero, with comparator groups crossing this line showing no effect. No pain data was available for the placebo splint subgroup. TENS, transcutaneous electrical nerve stimulation; NA, not available.

Population characteristics	Trials	Summary*	Association with outcome†	τ^2	p Value
Overall	k = 76	-	SMD, −0.38 (−0.47 to −0.28)	0.100	-
Age (years)	k = 66	63.0 (50.2 to 83.0)	β, 0.07 (−0.14 to 0.28)‡	0.097	0.518
Women (%)	k = 67	84.0 (40.0 to 100.0)	β, 0.09 (−0.00 to 0.18)‡	0.085	0.055
BMI (kg/m^2)	k = 32	27.0 (20.7 to 30.0)	β, −0.02 (−0.10 to 0.06)	0.101	0.609
Weight (kg)	k = 14	67.6 (58.5 to 80.4)	β, −0.02 (−0.04 to 0.01)	0.077	0.237
Height (cm)	k = 11	165.0 (156.1 to 168.3)	β, −0.00 (−0.07 to 0.06)	0.109	0.886
Classification criteria	k = 60			0.263	0.767
ACR		44 (74.6%)	SMD, −0.36 (−0.48 to −0.24)		
Other		15 (25.4%)	SMD, −0.40 (−0.62 to −0.17)		
Hand OA subset	k = 76			0.247	0.817
Erosive		6 (7.9%)	SMD, −0.34 (−0.68 to 0.01)		
Inflammatory		5 (6.6%)	SMD, −0.49 (−0.86 to −0.13)		
Other		65 (85.5%)	SMD, −0.37 (−0.47 to −0.27)		
Hand OA affection	k = 76			0.245	0.721
Both		47 (61.8%)	SMD, −0.32 (−0.43 to −0.20)		
Fingers		14 (18.4%)	SMD, −0.54 (−0.76 to −0.31)		
Thumb		15 (19.7%)	SMD, −0.44 (−0.66 to −0.22)		
Disease duration (years)	k = 37	5.4 (1.5 to 14.4)	β, 0.16 (−0.23 to 0.54)‡	0.095	0.425
Knee OA (%)	k = 6	49.9 (10.0 to 63.1)	β, −0.03 (−0.23 to 0.16)‡	0.176	0.733
Hip OA (%)	k = 5	25.0 (9.1 to 46.0)	β, 0.20 (−0.10 to 0.51)‡	0.140	0.188
Concomitant training/physiotherapy	k = 12			0.000	0.942
No		6 (50.0%)	SMD, −0.35 (−0.56 to −0.14)		
Yes		6 (50.0%)	SMD, −0.36 (−0.53 to −0.18)		
Concomitant orthoses	k = 10			0.213	0.198
No		4 (40.0%)	SMD, −0.05 (−0.62 to 0.52)		
Yes		6 (60.0%)	SMD, −0.52 (−0.97 to −0.08)		
Concomitant paracetamol	k = 40			0.073	0.353
No		3 (7.5%)	SMD, −0.64 (−1.09 to −0.18)		
Yes		37 (92.5%)	SMD, −0.42 (−0.53 to −0.30)		
Concomitant topical NSAID	k = 36			0.067	0.323
No		18 (50.0%)	SMD, −0.45 (−0.61 to −0.29)		
Yes		18 (50.0%)	SMD, −0.33 (−0.50 to −0.16)		
Concomitant per oral NSAID	k = 45			0.076	0.368
No		20 (44.4%)	SMD, −0.47 (−0.62 to −0.31)		
Yes		25 (55.6%)	SMD, −0.37 (−0.52 to −0.22)		
Concomitant steroid injections	k = 45			0.095	0.376
No		39 (86.7%)	SMD, −0.38 (−0.51 to −0.25)		
Yes		6 (13.3%)	SMD, −0.22 (−0.54 to 0.10)		
Concomitant systemic steroid	k = 29			0.070	0.555
No		23 (79.3%)	SMD, −0.50 (−0.65 to −0.35)		
Yes		6 (20.7%)	SMD, −0.39 (−0.71 to −0.08)		
Other rheumatic diseases (%)	k = 29	0.0 (0.0 to 43.4)	β, 0.07 (−0.08 to 0.21)‡	0.058	0.388
White race (%)	k = 17	96.0 (0.0 to 100.0)	β, −0.04 (−0.11 to 0.03)‡	0.074	0.232
Affected joints at baseline (No.)	k = 21	6.8 (3.0 to 13.9)	β, −0.01 (−0.05 to 0.03)	0.038	0.523
Radiographic Kellgren-Lawrence score	k = 4	40.8 (23.2 to 51.0)	β, 0.01 (−0.02 to 0.04)	0.022	0.626
CRP (mg/L)	k = 9	2.3 (0.1 to 3.6)	β, 0.07 (−0.09 to 0.22)	0.030	0.385
Number of study visits	k = 71	4.0 (1.0 to 26.0)	β, 0.00 (−0.02 to 0.02)	0.094	0.769
Open label	k = 75			0.068	< 0.001
No		51 (68.0%)	SMD, −0.51 (−0.62 to −0.41)		
Yes		24 (32.0%)	SMD, −0.10 (−0.24 to 0.05)		
Treatment duration (weeks)	k = 75	8.0 (0.1 to 52.0)	β, 0.06 (−0.01 to 0.12)‡	0.093	0.073
Overall risk of bias	k = 76			0.089	0.043
High		42 (55.3%)	SMD, −0.30 (−0.42 to −0.17)		
Some concern		26 (34.2%)	SMD, 0.39 (−0.54 to −0.24)		
Low		8 (10.5%)	SMD, −0.65 (−0.90 to −0.40)		
Funding	k = 76			0.091	0.130
Only pharmaceutical or device company funding		15 (19.7%)	SMD, −0.53 (−0.72 to −0.34)		
Only non-industry funding		30 (39.5%)	SMD, −0.29 (−0.43 to −0.15)		
Mixed funding		8 (10.5%)	SMD, −0.63 (−0.94 to −0.31)		
Free provision of drug or device		1 (1.3%)	SMD, −0.07 (−1.17 to 1.02)		
Undisclosed funding		22 (28.9%)	SMD, −0.32 (−0.50 to −0.15)		

BMI, Body Mass Index; ACR, American College of Rheumatology; OA, osteoarthritis; NSAID, Non-Steroidal Anti-Inflammatory Drugs; CRP, C-reactive protein.
Outcomes for previous musculoskeletal surgery, other musculoskeletal diseases, cardiac diseases, kidney diseases, neurological diseases, endocrinological diseases, lung diseases, gastrointestinal diseases, local inflammation, and inflammation reported by erythrocyte sedimentation rate could not be calculated due to insufficient reporting in the included trials.

* Data are no. (%) trials, median percentage (range of percentages), or median of means (range of means) for aggregated data.

† To investigate the association between each of the population characteristics and the effect sizes (i.e., the SMD for difference in mean change in pain), separate restricted maximum likelihood-based meta-regression models with random effects, including a factor for the characteristic were performed. The slope β should be interpreted as the increase (or decrease) in the SMD per 1 unit increase in the characteristic. Population characteristics for which less than three trials reported data were not analysed. For reference, an SMD of 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect[23] – in this case the equal negative amount.

‡ The association indicates the increase (or decrease) in the SMD per pr. 10 units (i.e., pr. 10 years/percent/weeks).

Table II

The association between contextual factors and placebo response on pain.

Osteoarthritis and Cartilage

treatment, care as usual, waiting list comparators, education as comparator, placebo bath therapy, placebo ultrasound therapy, placebo magnetotherapy, placebo transcutaneous electrical nerve stimulation, placebo radiation, placebo kinesiology taping, or intramuscular placebo compared to the null-arm (Fig. 3).

The function of the participants in the comparator groups improved as well with an SMD of −0.22 (95% CI −0.32 to −0.12), as did the patient global assessment with an SMD of −0.63 (95% CI −0.87 to −0.38). Comparators did not significantly improve quality of life (SMD of 0.03, [95% CI −0.15 to 0.21]) or hand strength (SMD of 0.07, [95% CI −0.05 to 0.19]) compared to the null-arm. Forest plots for all outcomes are available in Appendix 3. Substantial heterogeneity was seen across trials on all efficacy domains (I^2 53–87%). Sensitivity analyses using fixed effects showed similar results. The funnel plot for pain was symmetrical. Fixed effects models and funnel plots for efficacy outcomes are available in Appendix 3.

Harms associated with comparators

Forest plots for the safety outcomes are available in Appendix 3. The odds ratio of withdrawals from studies was 9.03 (95% CI 7.04 to 11.56), indicating a substantial rate of withdrawals from the comparator groups of the included studies compared to the null-arm. The odds ratio for withdrawals due to adverse events was 7.69 (95% CI 4.37 to 13.53), and the odds ratio for serious adverse events was 8.07 (95% CI 4.68 to 13.93), indicating a possible harmful effect of comparator interventions. When looking at the untreated control groups only (no treatment, care as usual, waiting list and education comparators), 17 trials reported values for withdrawals with a median of 3 withdrawals (interquartile range: 1–3), 13 trials reported values for withdrawals due to adverse events, one of which reported 1 withdrawal due to adverse events and the rest reporting zero, and 5 trials reported values for serious adverse events, all of which reported zero serious adverse events.

Influence of contextual factors on the placebo response to pain

The association between contextual factors and placebo response on pain for all comparators is presented in Table II. Open-label trial design and overall risk of bias explained some of the between-trial variation. Closed-label trials gave a higher placebo response than open-label trials. For risk of bias assessment, a low risk of bias yielded the largest placebo response, followed by some concern risk of bias, and a high risk of bias (Table II). A secondary analysis only including data from the comparator groups using a placebo or sham treatment showed no significant difference between open or closed-label designs, overall risk of bias, or any other measured contextual factor in terms of association with the placebo response on pain (Appendix 3).

Discussion

This meta-analysis found comparators for hand osteoarthritis apparently effective for pain, function, and patient global assessment. When comparing untreated control groups separately to the null-arm (i.e., no treatment, care as usual, waiting list comparator groups, and education as comparator), there was no improvement for the participants of the trials in terms of pain. Pain reduction in the various placebo groups is, therefore, likely due to the placebo interventions. Our results emphasise the importance of choosing an appropriate comparator. If an active treatment yields a placebo response on top of a possible actual response (e.g., by topical administration), the effect of the treatment would be positively exaggerated if compared to a comparator without a placebo response. The difference in the size of the placebo response for pain across the different types of placebos indicates the importance of the method of treatment administration on the response, which was also found in another meta-analysis exploring the determinants of the placebo response on pain in osteoarthritis in general.[3]

Interestingly, comparator groups were not effective for health-related quality of life or hand strength. Generally, continuous subjective outcomes are expected to yield a placebo response, as opposed to objective outcomes, which supports the ineffectiveness of comparators on the outcome hand strength.[21] Health-related quality of life was the least reported outcome, which could have affected the results.

Topical placebo had the greatest effect size, although overlapping in CIs with other placebos (Fig. 3). In previous research exploring the placebo response in osteoarthritis, intraarticular hyaluronan and acupuncture were found to have above average effects.[3] Previous research analysing the placebo response in knee osteoarthritis found greater effect sizes for intra-articular placebo and topical placebo than oral placebo.[22] We also found intraarticular placebo and acupuncture to have an effect, although fewer trials were available for these subgroups than for topical placebo, which may explain some of the difference (Fig. 3). Thus, caution should be made when interpreting these results.

Although considered an inert treatment, the placebo strategies seem more harmful than no attention, represented by the null-arm. This suggests a possible nocebo effect but may also be due to the handling of the placebo intervention, e.g. administration via a needle can lead to adverse events whether the content is inert or not. Also, some of the withdrawals, adverse events and serious adverse events could be unrelated to the comparator interventions, which cannot be accounted for when compared to a theoretical scenario of zero safety events.

Whether the trials were open-label or not and the overall risk of bias assessment both influenced the placebo response when analysing all comparator groups, which could suggest rigorous methodology and blinding improves pain reduction. This might influence the contrast for which a comparator group represents, leading to a larger contrast for the active treatment in trials with a high risk of bias or open-label design. However, this was not confirmed when restricting the analysis to trials using a placebo or sham comparator, meaning that for the trials included in this study, a similar placebo response for pain could be found regardless of the risk of bias assessment or trial design, as long as a placebo or sham treatment was given to the comparator group. This is similar to the results of a recent meta-analysis exploring the placebo response of oral placebos for osteoarthritis patients, which also found no significant association between risk of bias assessment and pain decrease.[23] The results of the meta-regressions analysis, including all comparator groups might therefore be affected by the number of non-placebo or sham treatment comparator groups which were open-label trials or assessed to have a high risk of bias.

This study has two main strengths. Searching the reference lists of included studies allowed us to include relevant trials not identified in the systematic search. Secondly, contacting study authors allowed us to include unpublished data from three additional trials, both contribute to minimising publication bias. A key limitation is that we could not conclude anything about the true placebo effect of the comparator interventions for the outcomes through the data synthesis and thus could not account for the natural course of the disease, regression towards the mean or other variables believed to influence the placebo response.[6] By contrasting the comparators with a null-arm and assuming this contrast to be a zero change from baseline, the placebo response observed in the comparator group might be greater due to the regression towards the mean and not the comparator itself. The true placebo effect might be calculated in a meta-analysis of three armed trials with both an inert treatment and

a non-treatment group. Unfortunately, such trials are rare in hand osteoarthritis research. Thus, the part of the overall placebo response attributable to the true placebo effect remains unknown. Our study is also limited by the completion of reporting, which varied across trials, leading to little data for patient global assessment and health-related quality of life. Lastly, since multiple tests were conducted, there is an increased risk of false-positive results (i.e., type I error) from the meta-regression analyses.

In conclusion, a significant placebo response was found for pain, function, and patient global assessment in trials of hand osteoarthritis treatments. No significant placebo response was found for health-related quality of life or hand strength. The placebo response for pain differed between different types of comparator interventions and was largest for topical placebo. We found no pain relief effect for untreated groups (i.e. no treatment, care as usual, waiting list or education as comparator). Closed-label trial design and low risk of bias were associated with a higher placebo response for pain compared to an open-labelled trial design and some concern or high risk of bias when analysing all comparator groups, but not when analysing comparator groups using placebo or sham treatments separately. Safety outcomes favoured the null-arm over comparator groups, indicating a higher risk of harmful effects of the comparator interventions.

Ethics

No ethical approval was required for this study.

Role of the funding source

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Author contributions

IMB, AD and RC conceived and designed the study and contributed to the development of the protocol. AD developed the search strategy. AD and IMB sorted the references. AD, IMB, JIB, and LUD extracted all data. IMB and SMN conducted statistical analyses. All authors assisted in the final manuscript and agreed to its final approval before submission.

Conflict of interest

Interests disclosed in the International Committee of Medical Journal Editors (ICMJE) conflict of interest forms are as follows: MH is supported by a core grant to his institution from the Oak Foundation (OCAY-18-774-OFIL); has received travel support for conference participation from Contura International A/S; is on the advisory board for Thuasne Group; and is associate editor of Osteoarthritis & Cartilage. MK has received grants from IMI-APPROACH and the Dutch Arthritis Society; royalties or licences from Wolters Kluwer and Springer Verlag; consulting fees for consultancy/advisory boards by Pfizer, Galapagos, CHDR, Novartis, and UCB; payment or honoraria from Galapagos and Jansen; and is an OARSI board member (2017–2022), EULAR council, and president of the Dutch Society for Rheumatology. DJH is supported by an NHMRC Investigator Grant Leadership 2 (#1194737); received consulting fees for consulting advice on the scientific advisory boards for Pfizer, Lilly, TLCBio and Novartis; is editor in chief of Osteoarthritis and Cartilage; is section editor of osteoarthritis, UpToDate; is on data safety monitoring board for Success trial for spinal stenosis (ACTRN12617000884303) and ICM-203 for knee OA (NCT04875754); and is an Osteoarthritis Research Society International Board Member. AD has received support for congress attendance from the Danish Rheumatism Organization; and is president of the Danish Association of Junior Rheumatologists. IMB, SMN, RC, LUD, JIB, ST, FK, WZ, and HB have no conflicts of interest.

Data sharing

Template data collection forms, extracted data, data used for analysis, and analytic code are not publicly available. Extracted data that underlie the results reported in this article and analytic code will be available from Robin Christensen (robin.christensen@regionh.dk) once all planned analyses have been completed and published. We will consider the request on an individual basis. We will not share unpublished data explicitly provided for this study. In these cases, we recommend contacting the authors of the original work.

Transparency

The corresponding author (AD) and first author (IMB) affirm that the manuscript is an honest, accurate, and transparent account of the reported study. No aspects of the study have been omitted, and discrepancies from the study as initially planned have been explained.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2024.02.947.

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