

Assessing bias in osteoarthritis trials included in Cochrane reviews: A meta-epidemiological study

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Main results

- Bias associated with study characteristics such as trials size, blinding of personnel and patients, center status, and funding may lead to exaggeration of intervention effect estimates and increases the between-trial heterogeneity in trials reporting subjectively assessed outcomes.
- Results of OA trials may be affected by other domains (i.e., trial size, center status, and source of funding) than those already included in the Cochrane risk of bias tool.

Main results

- Bias associated with study characteristics such as trials size, blinding of personnel and patients, center status, and funding may lead to exaggeration of intervention effect estimates and increases the between-trial heterogeneity in trials reporting subjectively assessed outcomes.
- Results of osteoarthritis (OA) trials may be affected by other domains (i.e., trial size, center status, and source of funding) than those already included in the Cochrane risk of bias tool.

Introduction

The validity of systematic reviews and meta-analyses is depending on the methodological quality of trials.

Bias in trials can lead to underestimation or overestimation of the true intervention effect (1).

Regardless of tools used to assess risk of bias, the methods for assessing and summarising potential bias and incorporating bias assessments into meta-analyses vary greatly (2;3)

¹Gluud LL. Bias in clinical intervention research. Am J Epidemiol 2006 Mar 15;163(6):493-501

²Lundh A, Gotzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. BMC Med Res 2008;8:22.

³Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ2011;343 :d5928



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Objective

Our objective was to evaluate the association of estimates of treatment effects with different bias related study characteristics in meta-analyses of interventions used for treating pain in osteoarthritis (OA).



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Methods

Eligibility criteria

- Only reviews of randomized or controlled trials in patients with OA
- Patient reported pain outcome
- Compared with sham, placebo, or no intervention control

Data was eligible from the trials, which were included in eligible meta-analyses.

Search in Cochrane Library

Pain estimates were abstracted from overall pain reported in the Cochrane review's

Bias items



Original Cochrane items

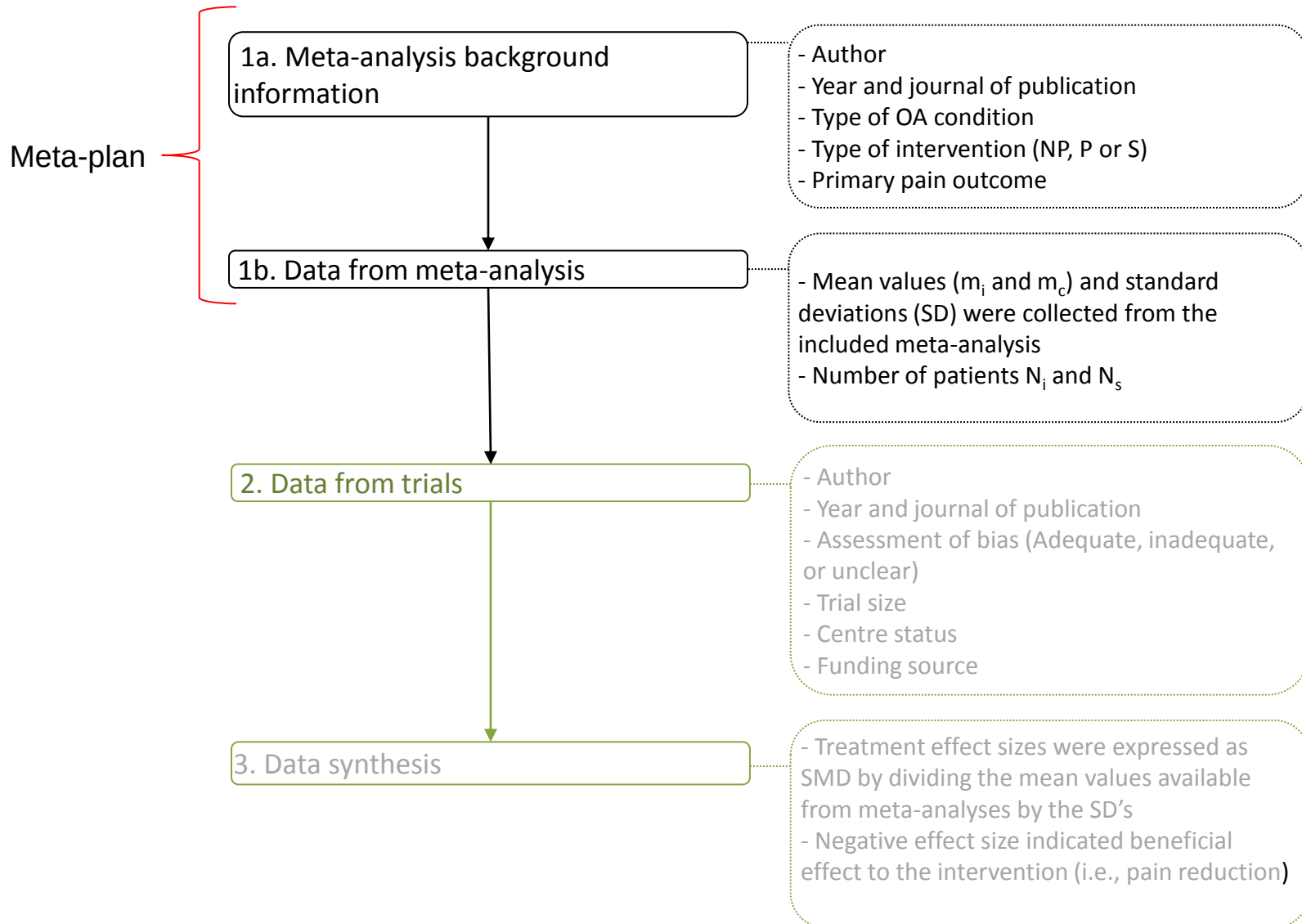
- Sequence generation
- Allocation concealment
- Blinding of participants
- Blinding of personnel
- Incomplete outcome data

New items

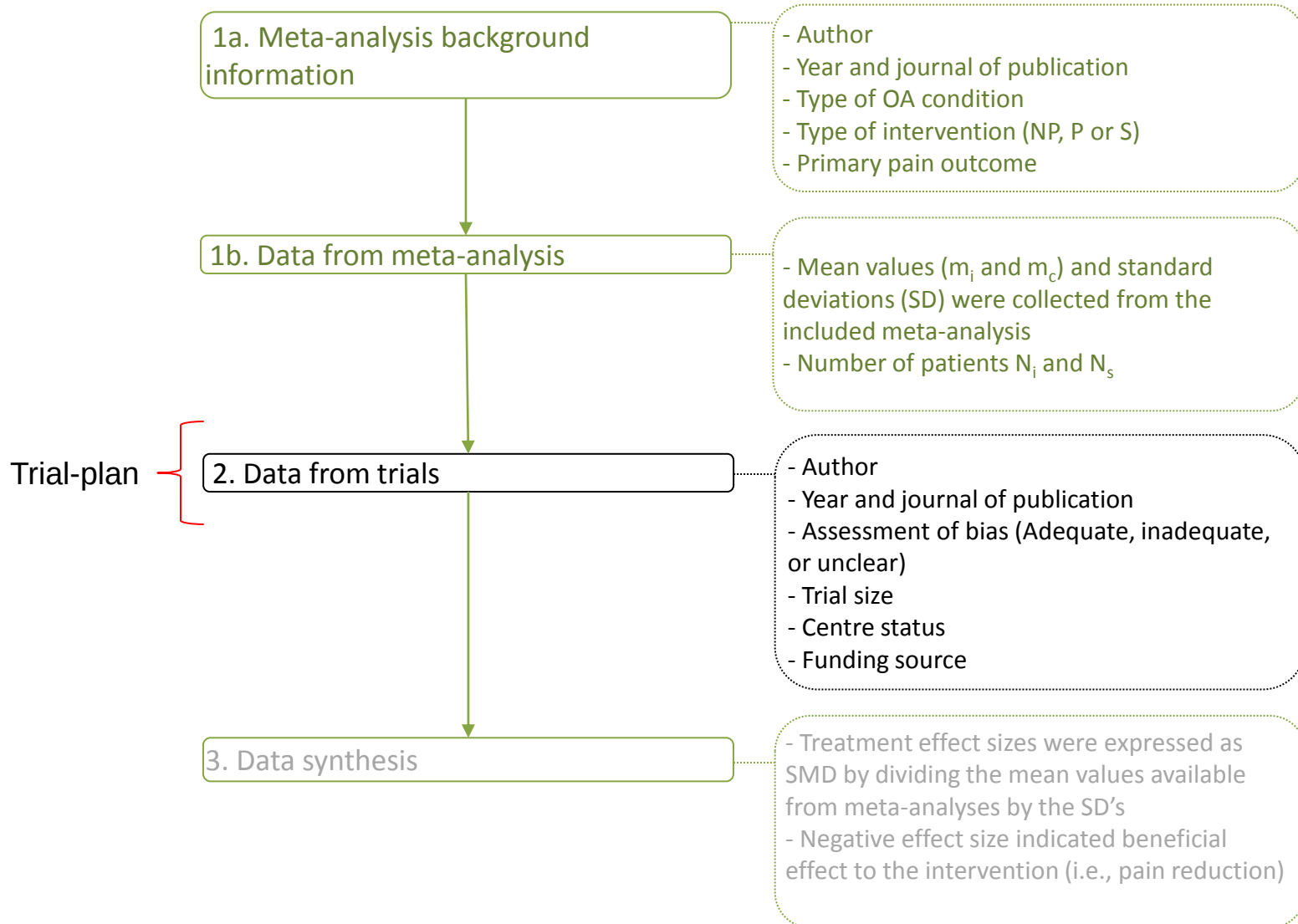
- Centre status
- Trials size
- Source of funding



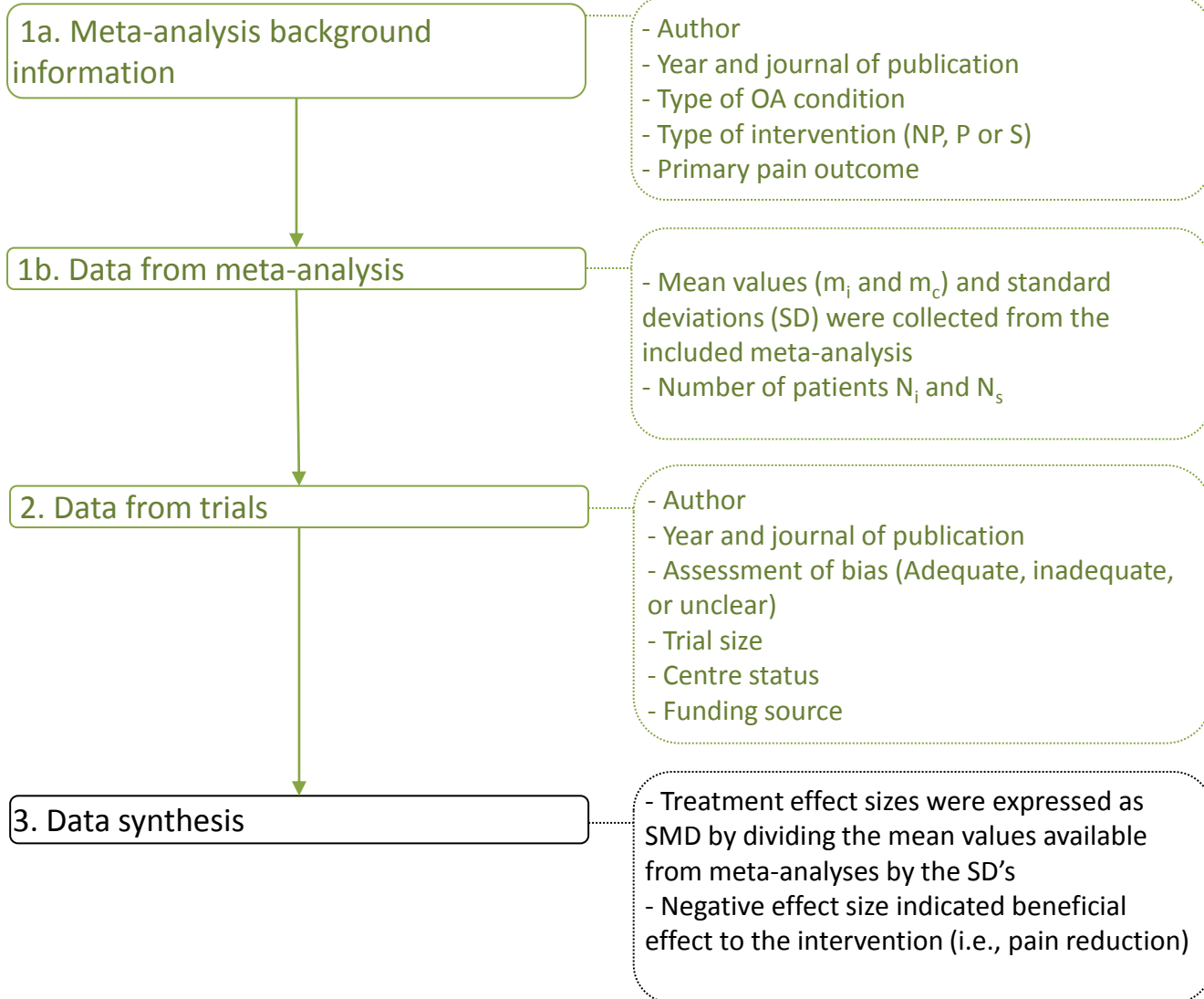
Data extraction



Data extraction



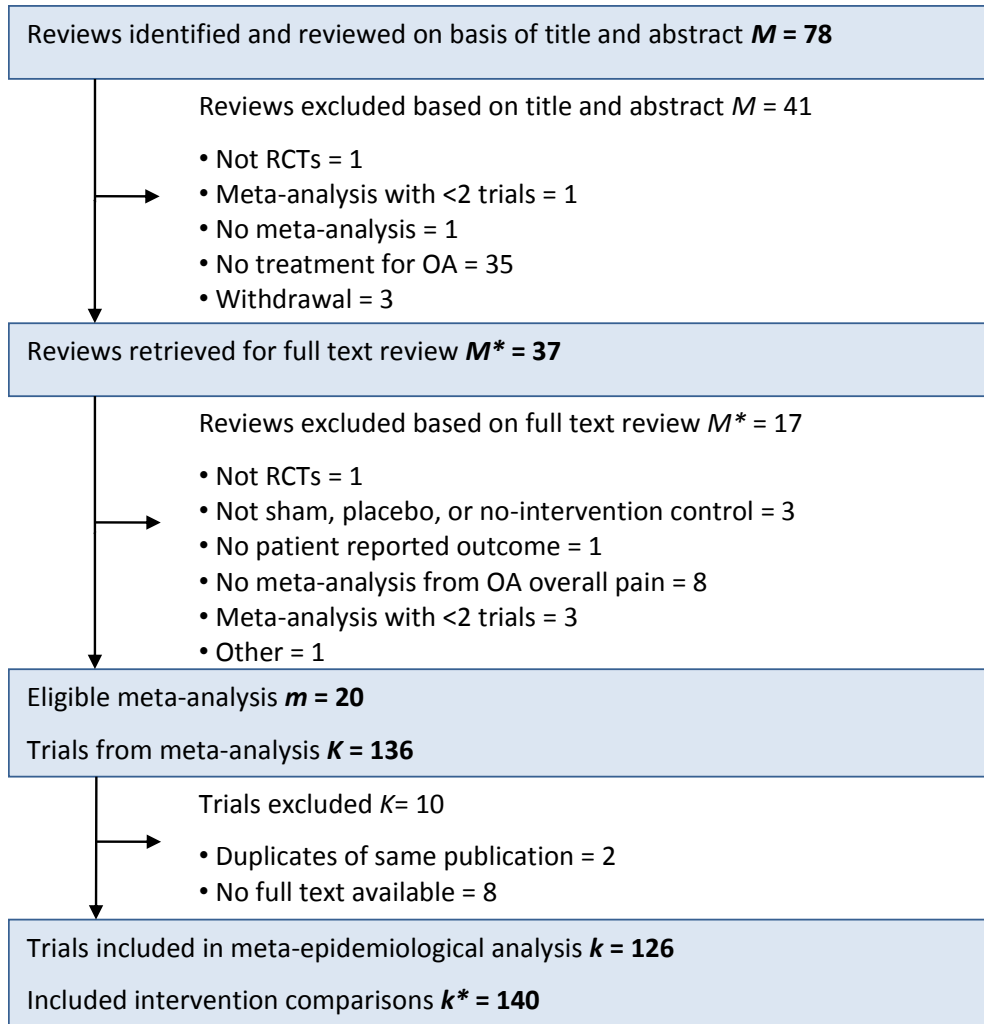
Data synthesis



Methods

- Meta-epidemiology: explore the influence of the study characteristics on treatment effect estimates
- The difference between the pooled estimates from the meta-analyses were combined to measure the variability in bias estimates, expressed in τ^2
- Random effect models with fixed factor for review and trial characteristics
- The primary outcome domain was pain - negative effect indicated beneficial effect of experimental intervention).

Results



Flowchart

M = identified Cochrane Reviews;

M* = Possible eligible Cochrane reviews;

m = included meta-analysis;

K = Trials from included Cochrane reviews;

k = Trials included in meta-analysis;

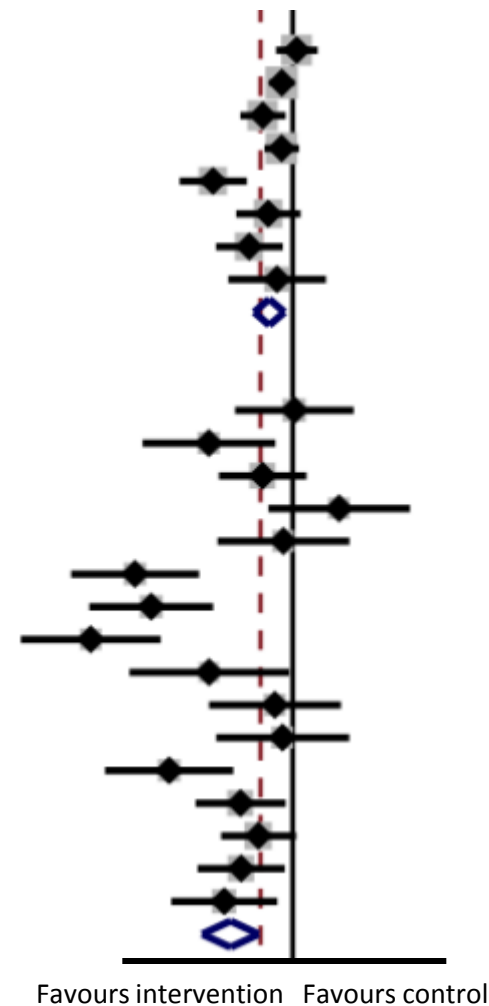
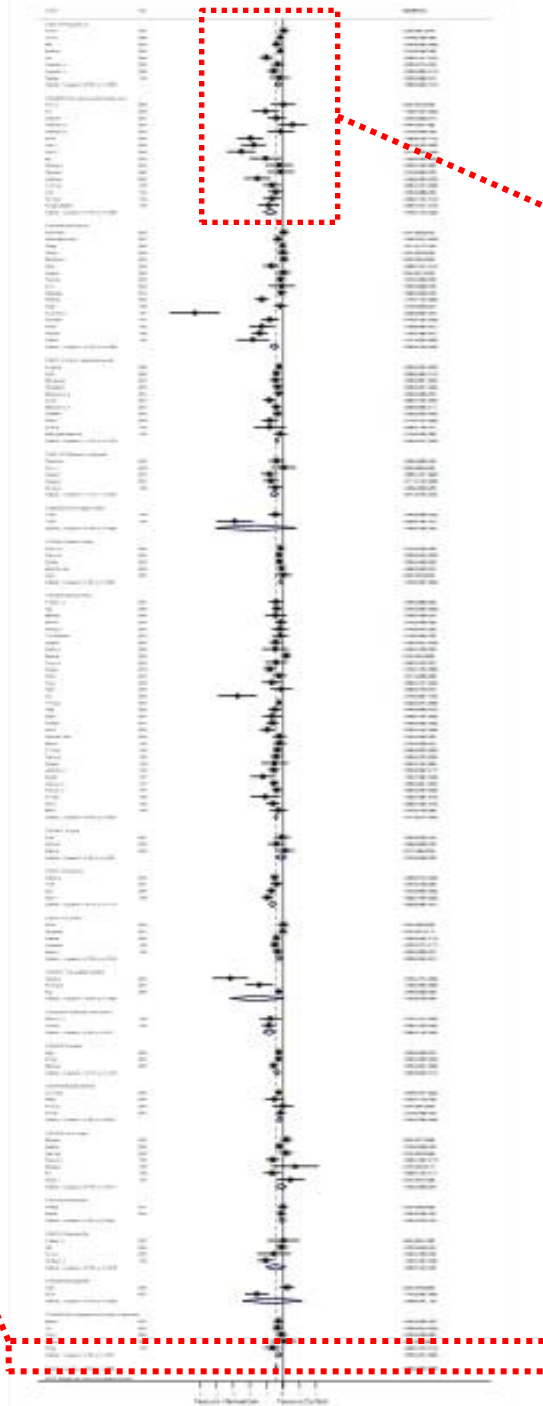
k* = Intervention comparisons.



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Results

Overall meta-analysis:
ES = -0.40,
95%CI (-0.46 to -0.34)
 $I^2 = 73.3\%$



Results

Statistical significant difference in effect estimates:
between small (<128 participants) and large trials

Variable		Trials*	ES	95% CI	Tau ²	Change of Tau ² (%)	P-value for interaction
Overall		140	-0.40	(-0.46 to -0.34)	0.1272	-	-
Trial size					0.1082	-14.93	0.003
	Large	53	-0.31	(-0.43 to -0.19)			
	Small	87	-0.57	(-0.69 to -0.44)			

Results

Other factors that could reduce heterogeneity were (prioritised): *Blinding of personnel, Blinding of patients, Centre status, Funding source.*

Table 2 – Results of the stratified Meta-analysis

Variable		Trials*	ES	95% CI	Tau ²	Change of Tau ² (%)	P-value for interaction
Overall		140	-0.40	(-0.46 to -0.34)	0.1272	-	-
Blinding (Patients)					0.1137	-10.61	0.004
	Adequate	73	-0.33	(-0.44 to -0.21)			
	Unclear	16	-0.71	(-0.94 to -0.48)			
	Inadequate	51	-0.61	(-0.81 to -0.40)			
Blinding (Personnel)					0.1125	-11.56	0.005
	Adequate	87	-0.35	(-0.46 to -0.25)			
	Unclear	46	-0.65	(-0.80 to -0.50)			
	Inadequate	7	-0.28	(-0.61 to 0.04)			
Centre status					0.1211	-4.80	0.026
	Multi	64	-0.35	(-0.47 to -0.22)			
	Single	76	-0.56	(-0.69 to -0.42)			
Funding					0.1213	-4.64	0.020
	Non-profit	51	-0.45	(-0.63 to -0.28)			
	Unclear	40	-0.62	(-0.80 to -0.45)			
	For-profit	49	-0.31	(-0.45 to -0.16)			

Results



Original Cochrane items

- Sequence generation
- Allocation concealment
- Blinding of participants
- Blinding of personnel
- Incomplete outcome data

New items

- Centre status
- Trials size
- Source of funding



Discussion

- Strengths and limitations
 - Single reviewer data extraction
- Comparison with other studies
 - Trials size (Nüesch et al 2010)
- Future research
 - Confirmation of these findings
 - Additive effect



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Take home message

Results of OA trials may be affected by other domains* than those already included in the Cochrane risk of bias tool.

**i.e., trial size, center status,
and source of funding*