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 summarise 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.	1
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*.	2
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
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.	3
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).*	3
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.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
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).	3
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.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
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 summarised for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	4
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.	4
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*.	3-4
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*.	3-4
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.	4
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).	4
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)*.	3-4

Section/Topic	Item #	Checklist item	Reported on Page #
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.	4
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	4
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 randomised 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.	4
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.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	4
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*.	4-5
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 summarise pairwise comparisons*. If additional summary measures were explored (such as treatment rankings), these should also be presented.	4-5
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.	4-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	4
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).	5
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).	5-6
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).*	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			2
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.	

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.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling.
In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches*. Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

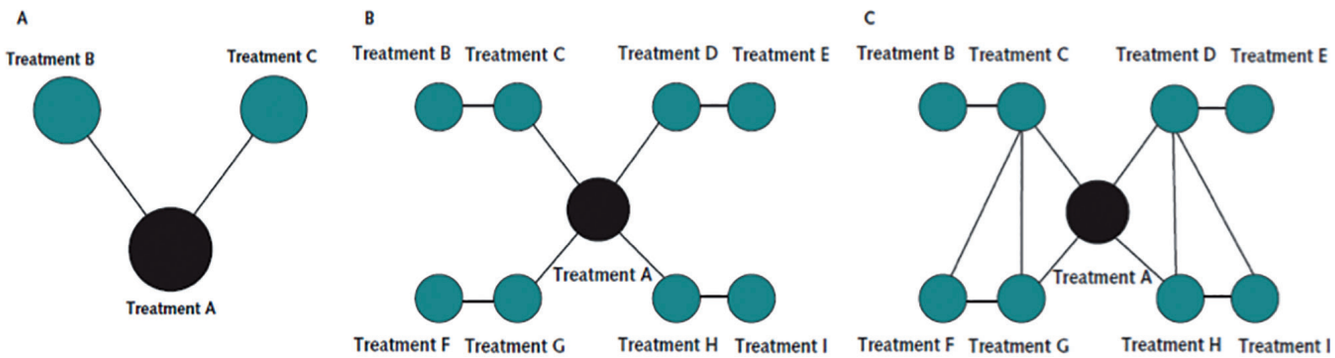
The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

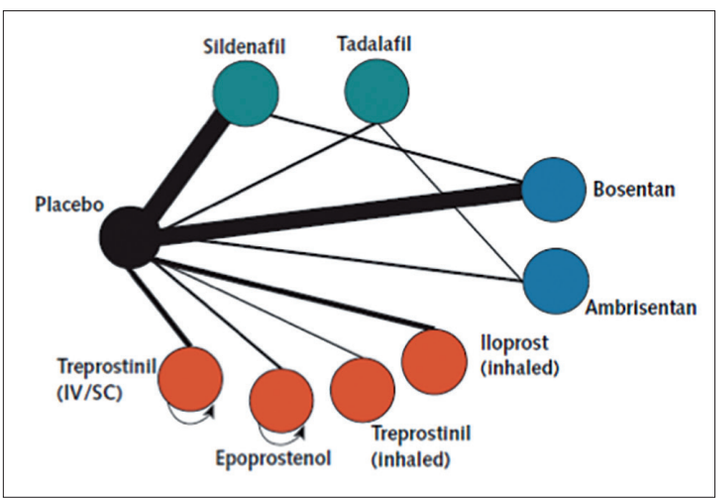
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.



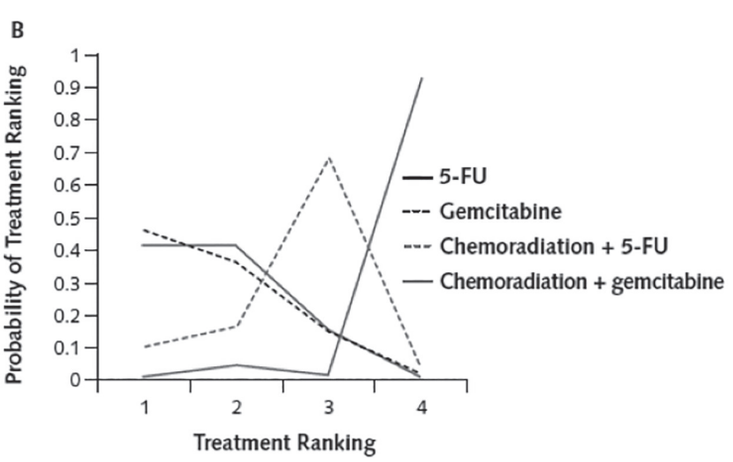
Appendix Figure 1A-1C

Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Cooresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93



Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/or hip osteoarthritis: network meta-analysis

Supplementary File 1

Table S1. Baseline characteristics of the included studies for knee and/or hip osteoarthritis

Study characteristics			Treatment		Patient characteristics					
Study, year	Country	Study design	Intervention	Daily dosage (mg)	Number of patient	Mean age (*y*)	Female (%)	BMI	OA grade	Joint affected
Altman 2007 (1)	USA	RCT	Acetaminophen	3900	160	61.70	71.30	NA	I-III	Knee/Hip
			Placebo	— —	165	61.80	71.50			
Bensen 1999 (2)	USA	RCT	Celecoxib	200	197	62.00	73.10	NA	I-III	Knee
			Placebo	— —	203	62.00	74.88			
Bingham 2007 a (3)	USA	RCT	Celecoxib	200	241	62.50	69.71	NA	I-III	Knee/Hip
			Placebo	— —	127	62.80	65.35			
Bingham 2007 b (3)	USA	RCT	Celecoxib	200	247	62.20	61.94	NA	I-III	Knee/Hip
			Placebo	— —	117	60.90	64.96			
Bourgeois 1998 (4)	France	RCT	Chondroitin	1200	83	63.00	72.29	NA	I-III	Knee
			Placebo	— —	44	64.00	84.09			
Braham 2003 (5)	Australia	RCT	Glucosamine	2000	24	41.60	29.17	NA	I-III	Knee
			Placebo	— —	22	43.80	27.27			
Bucsi 1999 (6)	France	RCT	Chondroitin	800	39	60.60	56.41	29.20	I-III	Knee
			Placebo	— —	46	59.40	63.04	29.10		
Case 2003 (7)	USA	RCT	Acetaminophen	4000	29	62.10	51.72	26.4	NA	Knee/Hip
			Placebo	— —	28	61.70	39.29	27		
Chopra 2013 (8)	India	RCT	Glucosamine	2000	108	55.51	NA	27.46	NA	Knee/Hip
			Celecoxib	200	105	56.60		27.44		
Cibere 2004 (9)	Canada	RCT	Glucosamine	1500	71	64.00	43.66	NA	>=2	Knee
			Placebo	— —	66	65.00	69.70			
Clegg 2006 (10)	USA	RCT	Glucosamine	1500	317	58.60	62.78	31.8	II-III	Knee
			Chondroitin	1200	318	58.20	64.47	32		
			G+C	1500+1200	317	58.60	62.78	31.5		
			Celecoxib	200	318	59.40	66.67	31.5		
			Placebo	— —	313	58.20	63.90	31.9		
Conaghan 2013 (11)	UK	RCT	Celecoxib	200	233	62.00	66.95	NA	I-III	Knee
			Placebo	— —	227	61.30	66.08			
DeLemos 2011 (12)	Canada	RCT	Celecoxib	200	202	60.00	64.85	NA	I-III	Knee/Hip
			Placebo	— —	200	58.90	68.05			
Dougados 2007 (13)	France	RCT	Celecoxib	200	813	61.60	65.81	31.1	NA	Knee
			Placebo	— —	806	61.30	66.87	31.1		
Essex 2012 (14)	USA	RCT	Celecoxib	200	127	58.00	80.31	NA	I-III	Knee
			Placebo	— —	67	58.00	76.12			
Essex 2014 (15)	USA	RCT	Celecoxib	200	127	59.60	72.44	NA	I-III	Knee
			Placebo	— —	62	61.70	59.68			
Essex 2016 (16)	USA	RCT	Celecoxib	200	145	65.90	66.90	NA	I-III	Knee
			Placebo	— —	78	63.90	66.67			
Fleischmann 2006 (17)	USA	RCT	Celecoxib	200	444	61.30	67.12	31.9	NA	Knee
			Placebo	— —	231	61.50	66.23	31.6		
Fransen 2015 (18)	Australia	RCT	Glucosamine	1500	152	61.20	84.21	28.4	NA	Knee
			Chondroitin	800	151	59.50	85.43	29.6		
			G+C	1500+800	151	60.70	89.40	28.8		
			Placebo	— —	151	60.60	81.46	29.1		
Geba 2002 (19)	USA	RCT	Celecoxib	200	97	62.60	64.95	29	I-III	Knee
			Acetaminophen	4000	94	63.10	70.21	29		
Gibofsky 2003 (20)	USA	RCT	Celecoxib	200	189	62.20	68.78	NA	I-III	Knee
			Placebo	— —	98	63.10	65.31			
Giordano 2009 (21)	Italy	RCT	Glucosamine	1500	30	57.20	70.00	22	I-III	Knee
			Placebo	— —	30	58.09	70.00	23		
Herrero-Beaumont 2007 (22)	Spain	RCT	Glucosamine	1500	106	63.40	90.57	27.7	II-III	Knee
			Acetaminophen	3000	108	63.80	86.11	27.9		
			Placebo	— —	104	64.50	85.58	27.6		
Hochberg 2011 a (23)	USA	RCT	Celecoxib	200	242	61.50	61.16	33.2	I-III	Knee
			Placebo	— —	124	61.60	66.13	32.7		
Hochberg 2011 b (23)	USA	RCT	Celecoxib	200	244	62.30	62.70	33	I-III	Knee
			Placebo	— —	122	61.60	63.11	33		
Hochberg 2016 (24)	USA	RCT	G+C	1500+1200	264	62.20	86.74	31.1	II-III	Knee
			Celecoxib	200	258	63.20	81.01	30.9		
Holt 2015 (25)	USA	RCT	Celecoxib	200	486	61.90	61.93	33.1	I-III	Knee
			Placebo	— —	246	61.60	64.63	32.8		
Houpt 1999(26)	Canada	RCT	Glucosamine	1500	58	64.10	63.79	NA	NA	Knee
			Placebo	— —	60	64.80	60.00			
Kahan 2009(27)	France	RCT	Chondroitin	800	309	62.90	69.90	28.5	I-III	Knee/Hip
			Placebo	— —	313	61.80	66.77	29		

Study characteristics			Treatment		Patient characteristics					
Study, year	Country	Study design	Intervention	Daily dosage (mg)	Number of patient	Mean age (*y*)	Female (%)	BMI	OA grade	Joint affected
Kivitz 2001(28)	USA	RCT	Celecoxib	200	207	62.00	65.00	NA	I-III	Knee
			Placebo	— —	218	64.00	67.00			
Kowh 2014(29)	Germany	RCT	Glucosamine	1500	98	52.17	52.04	28.81	I-IV	Knee
			Placebo	— —	103	52.29	45.63	28.99		
Lehmann 2005(30)	Germany	RCT	Celecoxib	200	420	62.90	68.33	29.7	NA	Knee
			Placebo	— —	424	61.70	71.93	29.7		
Lugo 2016(31)	USA	RCT	G+C	1500+1200	65	52.60	56.92	25.5	II-III	Knee
			Placebo	— —	58	53.10	51.72	24.7		
Mazieres 2001(32)	France	RCT	Chondroitin	1000	63	67.30	71.43	29.2	II-III	Knee
			Placebo	— —	67	66.90	77.61	28.9		
Mazieres 2007(33)	France	RCT	Chondroitin	1000	153	66.00	71.24	28.8	II-III	Knee
			Placebo	— —	154	66.00	68.83	28.8		
McAlindon 2004(34)	USA	RCT	Glucosamine	1500	101	NA	57.43	31	NA	Knee
			Placebo	— —	104		71.15	34.1		
McKenna 2001 a(35)	UK	RCT	Celecoxib	200	201	61.90	68.16	NA	NA	Knee
			Placebo	— —	200	60.40	66.00			
McKenna 2001 b(36)	UK	RCT	Celecoxib	200	63	62.00	67.00	NA	I-III	Knee
			Placebo	— —	60	63.20	75.00			
Miceli-Richard 2004(37)	France	RCT	Acetaminophen	4000	405	69.00	72.10	29	NA	Knee
			Placebo	— —	374	70.00	77.81	29		
Michel 2005(38)	Switzerland	RCT	Chondroitin	800	150	62.50	50.67	27.7	I-III	Knee
			Placebo	— —	150	63.10	52.00	28.1		
Noack 1994(39)	Italy	RCT	Glucosamine	1500	126	55.00	58.73	26.6	I-III	Knee
			Placebo	— —	126	55.00	61.90	26.2		
Pavelka 2002(40)	Italy	RCT	Glucosamine	1500	101	61.20	79.21	25.7	II-III	Knee
			Placebo	— —	101	63.50	76.24	25.7		
Pincus 2004 a(41)	USA	RCT	Celecoxib	200	181	63.00	62.00	NA	II-IV	Knee/Hip
			Acetaminophen	4000	171					
			Placebo	— —	172					
Pincus 2004 b(41)	USA	RCT	Celecoxib	200	189	63.00	66.00	NA	II-IV	Knee/Hip
			Acetaminophen	4000	185					
			Placebo	— —	182					
Prior 2014(42)	USA	RCT	Acetaminophen	3900	267	61.70	77.53	NA	II-III	Knee/Hip
			Placebo	— —	275	61.70	71.27			
Reginster 2001(43)	UK	RCT	Glucosamine	1500	106	66.00	74.53	27.3	II-III	Knee
			Placebo	— —	106	65.50	78.30	27.4		
Rother 2007(44)	Germany	RCT	Celecoxib	200	132	62.40	62.12	NA	I-IV	Knee
			Placebo	— —	127	62.80	62.99			
Rozendaal 2008(45)	Netherlands	RCT	Glucosamine	1500	111	63.10	68.47	27.9	>=2	Hip
			Placebo	— —	111	63.70	70.27	28		
Schnitzer 2005(46)	USA	RCT	Celecoxib	200	523	61.40	68.07	NA	I-III	Knee
			Acetaminophen	4000	269	61.90	66.17			
Schnitzer 2011(47)	USA	RCT	Celecoxib	200	419	61.70	61.34	30.2	NA	Hip
			Placebo	— —	416	61.40	60.58	29.7		
Sheldon 2005(48)	USA	RCT	Celecoxib	200	393	60.20	63.10	32.5	NA	Knee
			Placebo	— —	382	60.80	61.26	32.6		
Smugar 2006 a(49)	USA	RCT	Celecoxib	200	456	61.80	67.54	NA	I-III	Knee/Hip
			Placebo	— —	150	61.80	68.67			
Smugar 2006 b(49)	USA	RCT	Celecoxib	200	460	62.00	65.65	NA	I-III	Knee/Hip
			Placebo	— —	151	62.50	67.55			
Tannenbaum 2004(50)	Canada	RCT	Celecoxib	200	481	64.10	69.23	30	NA	Knee
			Placebo	— —	243	64.60	67.08	29.6		
Uebelhart 1998(51)	France	RCT	Chondroitin	800	23	60.00	47.83	NA	I-III	Knee
			Placebo	— —	23	57.00	56.52			
Uebelhart 2004(52)	Switzerland	RCT	Chondroitin	800	54	63.20	79.63	NA	I-III	Knee
			Placebo	— —	56	63.70	82.14			
Usha 2004(53)	India	RCT	Glucosamine	1500	30	52.00	NA	26.62	I-III	Knee
			Placebo	— —	28	50.00		25.39		
Wildi 2011(54)	France	RCT	Chondroitin	800	35	59.70	60.00	30.4	I-III	Knee
			Placebo	— —	34	64.90	58.82	31.5		
Williams 2000(55)	USA	RCT	Celecoxib	200	454	62.90	66.30	31.14	I-III	Knee
			Placebo	— —	232	62.60	66.81	31.96		
Williams 2001(56)	USA	RCT	Celecoxib	200	474	61.70	68.78	32.5	I-III	Knee
			Placebo	— —	244	61.30	72.95	32		
Zegels 2013(57)	Belgium	RCT	Chondroitin	1200	236	65.30	63.14	28.6	NA	Knee
			Placebo	— —	117	64.90	67.52	28.6		
Zhao 1999(58)	Canada	RCT	Celecoxib	200	197	62.00	72.59	31.2	I-III	Knee
			Placebo	— —	204	62.00	75.49	31.4		

NA: not available; G+C: glucosamine + chondroitin.

References of included studies

1. ALTMAN RD, ZINSENHEIM JR, TEMPLE AR, SCHWEINLE JE: Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study. *Osteoarthritis Cartilage* 2007; 15: 454-61.
2. BENSEN WG, FIECHTNER JJ, MCMILLEN JI *et al*.: Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; 74: 1095-105.
3. BINGHAM CO, 3RD, SEBBA AI, RUBIN BR *et al*.: Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology* (Oxford) 2007; 46: 496-507.
4. BOURGEOIS P, CHALES G, DEHAIS J, DELCAMBRE B, KUNTZ JL, ROZENBERG S: Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. *Osteoarthritis Cartilage* 1998; 6 Suppl A: 25-30.
5. BRAHAM R, DAWSON B, GOODMAN C: The effect of glucosamine supplementation on people experiencing regular knee pain. *Br J Sports Med* 2003; 37: 45.
6. BUCSI L, POÓR G: Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis §. *Osteoarthritis Cartilage* 1998; 6 Suppl. A: 31-36.
7. CASE JP, BALIUNAS AJ, BLOCK JA: Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003; 163: 169.
8. CHOPRA A, SALUJA M, TILLU G *et al*.: Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis: a randomized, double-blind, controlled equivalence drug trial. *Rheumatology* (Oxford) 2013; 52: 1408-17.
9. CIBERE J, KOPEC JA, THORNE A *et al*.: Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. *Arthritis Rheum* 2004; 51: 738-45.
10. CLEGG DO, REDA DJ, HARRIS CL *et al*.: Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; 354: 795-808.
11. CONAGHAN PG, DICKSON J, BOLTEN W, CEVC G, ROTHER M: A multicentre, randomized, placebo- and active-controlled trial comparing the efficacy and safety of topical ketoprofen in Transfersome gel (IDEA-033) with ketoprofen-free vehicle (TDT 064) and oral celecoxib for knee pain associated with osteoarthritis. *Rheumatology* (Oxford) 2013; 52: 1303-12.
12. DELEMOS BP, XIANG J, BENSON C *et al*.: Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. *Am J Ther* 2011; 18: 216-26.
13. DOUGADOS M, MOORE A, YU S, GITTON X: Evaluation of the patient acceptable symptom state in a pooled analysis of two multicentre, randomised, double-blind, placebo-controlled studies evaluating lumiracoxib and celecoxib in patients with osteoarthritis. *Arthritis Res Ther* 2007; 9: R11.
14. ESSEX MN, O'CONNELL M, BHADRA BROWN P: Response to nonsteroidal anti-inflammatory drugs in African Americans with osteoarthritis of the knee. *J Int Med Res* 2012; 40: 2251-66.
15. ESSEX MN, BEHAR R, O'CONNELL MA, BROWN PB: Efficacy and tolerability of celecoxib and naproxen versus placebo in Hispanic patients with knee osteoarthritis. *Int J Gen Med* 2014; 7: 227-35.
16. ESSEX MN, O'CONNELL MA, BEHAR R, BAO W: Efficacy and safety of nonsteroidal anti-inflammatory drugs in Asian patients with knee osteoarthritis: summary of a randomized, placebo-controlled study. *Int J Rheum Dis* 2016; 19: 262-70.
17. FLEISCHMANN R, SHELDON E, MALDONADOCOCCO J, DUTTA D, YU S, SLOAN VS: Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. *Clin Rheumatol* 2006; 25: 42-53.
18. FRANSEN M, AGALIOTIS M, NAIRN L *et al*.: Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis* 2015; 74: 851-8.
19. GEBA GP, WEAVER AL, POLIS AB, DIXON ME, SCHNITZER TJ, VIOXX ACTG: Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002; 287: 64-71.
20. GIBOFSKY A, WILLIAMS GW, MCKENNA F, FORT JG: Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design considerations and results of a randomized, placebo-controlled trial. *Arthritis Rheum* 2003; 48: 3102-11.
21. GIORDANO N, FIORAVANTI A, PAPAKOSTAS P, MONTELLA A, GIORGI G, NUTI R: The efficacy and tolerability of glucosamine sulfate in the treatment of knee osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Curr Ther Res* 2009; 70: 185-96.
22. HERRERO-BEAUMONT G, IVORRA JAR, TRABADO MDC *et al*.: Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: A randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum* 2007; 56: 555-67.
23. HOCHBERG MC, FORT JG, SVENSSON O, HWANG C, SOSTEK M: Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials. *Curr Med Res Opin* 2011; 27: 1243-53.
24. HOCHBERG MC, MARTELPELLETIER J, MONFORT J *et al*.: Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis* 2016; 75: 37-44.
25. HOLT RJ, FORT JG, GRAHN AY, KENT JD, BELLO AE: Onset and durability of pain relief in knee osteoarthritis: Pooled results from two placebo trials of naproxen/esomeprazole combination and celecoxib. *Phys Sportsmed* 2015; 43: 200-12.
26. HOUPT JB, MCMILLAN R, WEIN C, PAGETDELLIO SD: Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. *J Rheumatol* 1999; 26: 2423-30.
27. KAHAN A, UEBELHART D, DE VF, DELMAS PD, REGINSTER JY: Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: The study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2009; 60:524-33.
28. KIVITZ AJ, MOSKOWITZ RW, WOODS E *et al*.: Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J Int Med Res* 2001; 29: 467-79.
29. KWOH CK, ROEMER FW, HANNON MJ *et al*.: Effect of oral glucosamine on joint structure in individuals with chronic knee pain: a randomized, placebo-controlled clinical trial. *Arthritis Rheumatol* 2014; 66: 930-9.
30. LEHMANN R, BRZOSKO M, KOPSA P *et al*.: Efficacy and tolerability of lumiracoxib 100 mg once daily in knee osteoarthritis: a 13-week, randomized, double-blind study vs. placebo and celecoxib. *Curr Med Res Opin* 2005; 21: 517-26.
31. LUGO JP, SAIYED ZM, LANE NE: Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. *Nutr J* 2016; 15: 14.
32. MAZIERES B, COMBE B, VAN AP, TONDUT J, GRYNFELTT M: Chondroitin sulfate in osteoarthritis of the knee: a prospective, double blind, placebo controlled multicenter clinical study. *J Rheumatol* 2001; 28: 173-81.
33. MAZIERES B, HUCHER M, ZAIM M, GARNERO P: Effect of chondroitin sulphate in symptomatic knee osteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2007; 66: 639-45.
34. MCALINDON T, FORMICA M, LAVALLEY M, LEHMER M, KABBARA K: Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an internet-based randomized double-blind controlled trial. *Am J Med* 2004; 117: 643-9.
35. MCKENNA F, BORENSTEIN D, WENDT H, WALLEMARK C, LEFKOWITH JB, GEIS GS: Celecoxib versus diclofenac in the management of osteoarthritis of the knee. *Scand J Rheumatol* 2001; 30: 11-8.
36. MCKENNA F, WEAVER A, FIECHTNER JJ, BELLO AE, FORT JG: COX-2 specific inhibitors in the management of osteoarthritis of the knee: a placebo-controlled, randomized, double-blind study. *J Clin Rheumatol* 2001; 7: 151-9.
37. MICELI-RICHARD C, LE BARS M, SCHMIDELY N, DOUGADOS M: Paracetamol in osteoar-

thritis of the knee. *Ann Rheum Dis* 2004; 63: 923-30.

38. MICHEL BA, STUCKI G, FREY D *et al*.: Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum* 2005; 52: 779-86.
39. NOACK W, FISCHER M, FORSTER KK, ROVATI LC, SETNIKAR I: Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1994; 2: 51-9.
40. PAVELKÁ K, GATTEROVÁ J, OLEJAROVÁ M, MACHACEK S, GIACOVELLI G, ROVATI LC: Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002; 162: 2113-23.
41. PINCUS T, KOCH G, LEI H *et al*.: Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004; 63: 931-9.
42. PRIOR MJ, HARRISON DD, FRUSTACI ME: A randomized, double-blind, placebo-controlled 12 week trial of acetaminophen extended release for the treatment of signs and symptoms of osteoarthritis. *Curr Med Res Opin* 2014; 30: 2377-87.
43. REGINSTER JY, DEROISY R, ROVATI LC *et al*.: Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; 357: 251-6.
44. ROTHER M, LAVINS BJ, KNEER W, LEHNHARDT K, SEIDEL EJ, MAZGAREANU S: Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. *Ann Rheum Dis* 2007; 66: 1178-83.
45. ROZENDAAL RM, KOES BW, VAN OSCH GJ *et al*.: Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008; 148: 268-77.
46. SCHNITZER TJ, WEAVER AL, POLIS AB, PETRUSCHKE RA, GEBA GP: Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee. A combined analysis of the VACT studies. *J Rheumatol* 2005; 32: 1093-105.
47. SCHNITZER TJ, DATTANI ID, SERIOLO B *et al*.: A 13-week, multicenter, randomized, double-blind study of lumiracoxib in hip osteoarthritis. *Clin Rheumatol* 2011; 30: 1433-46.
48. SHELDON E, BEAULIEU A, PASTER Z, DUTTA D, YU S, SLOAN VS: Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005; 27: 64-77.
49. SMUGAR SS, SCHNITZER TJ, WEAVER AL, RUBIN BR, POLIS AB, TERSHAKOVEC AM: Rofecoxib 12.5 mg, rofecoxib 25 mg, and celecoxib 200 mg in the treatment of symptomatic osteoarthritis: results of two similarly designed studies. *Curr Med Res Opin* 2006; 22: 1353-67.
50. TANNENBAUM H, BERENBAUM F, REGINSTER JY *et al*.: Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13 week, randomised, double blind study versus placebo and celecoxib. *Ann Rheum Dis* 2004; 63: 1419-26.
51. UEBELHART D, THONAR EJ, DELMAS PD, CHANTRAINE A, VIGNON E: Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage* 1998; 6 Suppl A: 39-46.
52. UEBELHART D, MALAISE M, MARCOLONGO R *et al*.: Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. *Osteoarthritis Cartilage* 2004; 12: 269-76.
53. USHA PR, NAIDU MU: Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Investig* 2004; 24: 353-63.
54. WILDI LM, RAYNAULD JP, MARTELPELLETIER J *et al*.: Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis* 2011; 70: 982-9.
55. WILLIAMS GW, ETTLINGER RE, RUDERMAN EM *et al*.: Treatment of osteoarthritis with a once-daily dosing regimen of celecoxib: a randomized, controlled trial. *J Clin Rheumatol* 2000; 6: 65-74.
56. WILLIAMS GW, HUBBARD RC, YU SS, ZHAO W, GEIS GS: Comparison of once-daily and twice-daily administration of celecoxib for the treatment of osteoarthritis of the knee. *Clin Ther* 2001; 23: 213-27.
57. ZEGELS B, CROZES P, UEBELHART D, BRUYERE O, REGINSTER JY: Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. *Osteoarthritis Cartilage* 2013; 21: 22-7.
58. ZHAO SZ, MCMILLEN JI, MARKENSON JA *et al*.: Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. *Pharmacotherapy* 1999; 19: 1269-78.

Table S2. The methodological quality of the included studies.

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias	Loss of following-up	Intent-to-treat analysis
Altman 2007 (1)	low	unclear	low(double blinding)	low	low	low	Y	Y
Bensen 1999 (2)	low	unclear	low(double blinding)	low	low	low	Y	Y
Bingham 2007 a (3)	low	unclear	low(double blinding)	low	low	low	Y	Y
Bingham 2007 b (3)	low	unclear	low(double blinding)	low	low	low	Y	Y
Bourgeois 1998 (4)	low	unclear	low(double blinding)	low	unclear	High	NA	NA
Braham 2003 (5)	low	unclear	low(double blinding)	low	low	low	NA	NA
Bucsi 1999 (6)	low	unclear	low(double blinding)	low	unclear	High	Y	NA
Case 2003 (7)	low	unclear	low(double blinding)	low	unclear	unclear	Y	Y
Chopra 2013 (8)	low	unclear	low(double blinding)	low	low	unclear	Y	Y
Cibere 2004 (9)	low	unclear	low(double blinding)	low	low	unclear	Y	Y
Clegg 2006 (10)	unclear	unclear	low(double blinding)	low	low	unclear	Y	Y
Conaghan 2013 (11)	low	unclear	low(double blinding)	low	low	low	Y	Y
DeLemos (12)	unclear	unclear	low(double blinding)	low	low	low	Y	Y
Dougados 2007 (13)	low	unclear	low(double blinding)	low	unclear	low	NA	Y
Essex 2012 (14)	unclear	unclear	low(double blinding)	low	low	low	Y	Y
Essex 2014 (15)	unclear	unclear	low(double blinding)	low	low	low	Y	Y
Essex 2016 (16)	low	unclear	low(double blinding)	low	low	low	Y	Y
Fleischmann 2005 (17)	low	unclear	low(double blinding)	low	low	low	Y	Y
Fransen 2014 (18)	low	unclear	low(double blinding)	low	low	low	Y	N
Geba 2002 (19)	unclear	unclear	low(double blinding)	low	low	unclear	Y	N
Gibofsky 2003 (20)	unclear	unclear	low(double blinding)	low	unclear	High	Y	Y
Giordano 2009 (21)	low	unclear	low(double blinding)	low	unclear	High	Y	Y
Herrero-Beaumont 2007 (22)	low	unclear	low(double blinding)	low	low	unclear	Y	Y
Hochberg 2011 a (23)	low	unclear	low(double blinding)	low	unclear	unclear	Y	Y
Hochberg 2011 b (23)	low	unclear	low(double blinding)	low	unclear	unclear	Y	Y
Hochberg 2014 (24)	low	unclear	low(double blinding)	low	low	unclear	Y	Y
Holt 2015 (25)	low	unclear	low(double blinding)	low	low	low	NA	Y
Houpt 1999 (26)	unclear	unclear	low(double blinding)	low	low	low	NA	Y
Kahan 2009 (27)	unclear	unclear	low(double blinding)	low	low	low	Y	Y
Kivitz 2001 (28)	low	unclear	low(double blinding)	low	low	low	Y	Y
Kowh 2014 (29)	low	unclear	low(double blinding)	low	low	unclear	Y	N
Lehmann 2005 (30)	low	unclear	low(double blinding)	low	low	low	Y	Y
Lugo 2016 (31)	low	unclear	low(double blinding)	low	low	low	Y	Y
Mazieres 2001 (32)	low	unclear	low(double blinding)	low	low	low	Y	Y
Mazieres 2006 (33)	low	unclear	low(double blinding)	low	low	low	Y	Y
McAlindon 2004 (34)	low	unclear	low(double blinding)	low	low	low	Y	Y
McKenna 2001 a (35)	low	unclear	low(double blinding)	low	low	low	Y	NA
McKenna 2001 b (36)	low	unclear	low(double blinding)	low	low	low	Y	NA
Miceli-Richard 2004 (37)	unclear	unclear	low(double blinding)	low	low	low	Y	Y
Michel 2005 (38)	low	unclear	low(double blinding)	low	low	low	Y	Y
Noack 1994 (39)	low	unclear	low(double blinding)	low	low	low	Y	Y
Pavelka 2002 (40)	low	unclear	low(double blinding)	low	low	low	Y	Y
Pincus 2004 a (41)	low	unclear	low(double blinding)	low	low	low	NA	Y
Pincus 2004 b (41)	low	unclear	low(double blinding)	low	low	low	NA	Y
Prior 2014 (42)	low	unclear	low(double blinding)	low	low	low	Y	N
Reginster 2001 (43)	unclear	unclear	low(double blinding)	low	low	low	Y	Y
Rother 2005 (44)	low	unclear	low(double blinding)	low	low	low	Y	Y
Rozendaal 2008 (45)	low	unclear	low(double blinding)	low	low	low	Y	N
Schnitzer 2005 (46)	unclear	unclear	low(double blinding)	low	unclear	unclear	Y	Y
Schnitzer 2011 (47)	low	unclear	low(double blinding)	low	low	low	Y	NA
Sheldon 2005 (48)	low	unclear	low(double blinding)	low	low	low	Y	Y
Smugar 2006 a (49)	unclear	unclear	low(double blinding)	low	unclear	High	Y	Y
Smugar 2006 b (49)	unclear	unclear	low(double blinding)	low	unclear	High	Y	Y
Tannenbaum 2004 (50)	low	unclear	low(double blinding)	low	low	low	Y	Y
Uebelhart 1998 (51)	low	unclear	low(double blinding)	low	low	low	NA	NA
Uebelhart 2004 (52)	low	unclear	low(double blinding)	low	unclear	High	Y	Y
Usha 2004 (53)	low	unclear	low(double blinding)	low	low	low	Y	NA
Wildi 2011 (54)	low	unclear	low(double blinding)	low	low	unclear	Y	NA
Williams 2000 (55)	unclear	unclear	low(double blinding)	low	low	low	NA	Y
Williams 2001 (56)	low	unclear	low(double blinding)	low	low	low	Y	Y
Zegels 2013 (57)	low	unclear	low(double blinding)	low	low	low	Y	Y
Zhao 1999 (58)	low	unclear	low(double blinding)	low	low	low	Y	Y

Y: Yes; NA: Not available.
The reference numbers correspond to the references of Table S1 in Additional File 1.

Table S3. The quality of evidence on pain.

Outcomes	GRADE					
	Quality of the evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
Glucosamine vs. Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine vs. Glucosamine+Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine vs. Celecoxib	Moderate⊕⊕⊕⊗	no	serious (-1)[1]	no	no	undetected
Glucosamine vs. Acetaminophen	Low ⊕⊕⊗⊗	no	serious (-1)[1]	no	serious (-1)[3]	undetected
Glucosamine vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Glucosamine+Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs.Celecoxb	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Acetaminophen	Moderate ⊕⊕⊕⊗	no	no	serious (-1) [2]	no	undetected
Chondroitin vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine+Chondroitin vs. Celecoxib	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine+Chondroitin vs. Acetaminophen	Moderate⊕⊕⊕⊗	no	no	serious (-1)[2]	no	undetected
Glucosamine+Chondroitin vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Celecoxib vs. Acetaminophen	High ⊕⊕⊕⊕	no	no	no	no	undetected
Celecoxib vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Acetaminophen vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected

[1]The direct estimate is inconsistent with the indirect estimate; [2]The estimates are based on indirect comparisons; [3]The sample size is less than 500.

Table S4. The quality of evidence on function.

Outcomes	GRADE					
	Quality of the evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
Glucosamine vs. Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine vs. Glucosamine+Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine vs. Celecoxib	Moderate ⊕⊕⊕⊗	no	serious (-1)[1]	no	no	undetected
Glucosamine vs. Acetaminophen	Moderate ⊕⊕⊕⊗	no	no	no	serious (-1)[3]	undetected
Glucosamine vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Glucosamine+Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Celecoxib	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Acetaminophen	Moderate⊕⊕⊕⊗	no	no	serious (-1)[2]	no	undetected
Chondroitin vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine+Chondroitin vs. Celecoxib	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine+Chondroitin vs. Acetaminophen	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine+Chondroitin vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Celecoxib vs. Acetaminophen	Low ⊕⊕⊗⊗	no	no	serious (-1)[2]	serious(-1)[3]	undetected
Celecoxib vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Acetaminophen vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected

[1]The direct estimate is inconsistent with the indirect estimate; [2]The estimates are based on indirect comparisons; [3]The sample size is less than 500.

Table S5. The quality of evidence on stiffness.

Outcomes	GRADE					
	Quality of the evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
Glucosamine vs. Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine vs. Glucosamine+Chondroitin	Moderate ⊕⊕⊕⊗	no	serious (-1)[1]	no	no	undetected
Glucosamine vs. Celecoxib	Moderate ⊕⊕⊕⊗	no	serious (-1)[1]	no	no	undetected
Glucosamine vs. Acetaminophen	Moderate ⊕⊕⊕⊗	no	no	serious (-1)[2]	no	undetected
Glucosamine vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Glucosamine+Chondroitin	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Celecoxib	High ⊕⊕⊕⊕	no	no	no	no	undetected
Chondroitin vs. Acetaminophen	Moderate ⊕⊕⊕⊗	no	no	serious (-1)[2]	no	undetected
Chondroitin vs. Placebo	Moderate ⊕⊕⊕⊗	no	serious (-1)[1]	no	no	undetected
Glucosamine+Chondroitin vs. Celecoxib	High ⊕⊕⊕⊕	no	no	no	no	undetected
Glucosamine+Chondroitin vs. Acetaminophen	Moderate ⊕⊕⊕⊗	no	no	serious (-1)[2]	no	undetected
Glucosamine+Chondroitin vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Celecoxib vs. Acetaminophen	Moderate ⊕⊕⊕⊗	no	no	no	serious (-1)[3]	undetected
Celecoxib vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected
Acetaminophen vs. Placebo	High ⊕⊕⊕⊕	no	no	no	no	undetected

[1]The direct estimate is inconsistent with the indirect estimate; [2]The estimates are based on indirect comparisons; [3]The sample size is less than 500.

Table S6. Network meta-analysis results of the sensitivity analysis.

Intervention	Sensitivity analysis (>100patient per arm)	Sensitivity analysis (>50patients per arm)	Sensitivity analysis (quality of included study)
pain			
Glucosamine vs Chondroitin	0.02 (-0.10,0.14)	0.06 (-0.06,0.17)	0.05 (-0.05, 0.15)
Glucosamine vs Glucosamine+Chondroitin	0.11 (-0.04,0.25)	0.13 (-0.01,0.26)	0.13 (0.01, 0.24)
Glucosamine vs Celecoxib	0.21 (0.11,0.31)	0.23 (0.14,0.32)	0.22 (0.14, 0.30)
Glucosamine vs Acetaminophen	0.03 (-0.09,0.16)	0.05 (-0.07,0.17)	0.05 (-0.05, 0.15)
Glucosamine vs Placebo	-0.10 (-0.19,-0.01)	-0.08 (-0.16,0.00)	-0.07 (-0.14, 0.00)
Chondroitin vs Glucosamine+Chondroitin	0.09 (-0.06,0.22)	0.07 (-0.07,0.20)	0.08 (-0.04, 0.20)
Chondroitin vs Celecoxib	0.19 (0.09,0.29)	0.17 (0.07,0.27)	0.17 (0.09, 0.26)
Chondroitin vs Acetaminophen	0.01 (-0.12,0.15)	-0.01 (-0.13,0.12)	0.00 (-0.11, 0.11)
Chondroitin vs Placebo	-0.12 (-0.21,-0.02)	-0.14 (-0.23,-0.05)	-0.12 (-0.20, -0.04)
Glucosamine+Chondroitin vs Celecoxib	0.11 (-0.02,0.23)	0.10 (-0.01,0.22)	0.09 (-0.01, 0.20)
Glucosamine+Chondroitin vs Acetaminophen	-0.07 (-0.23,0.08)	-0.08 (-0.22,0.07)	-0.08 (-0.21,0.05)
Glucosamine+Chondroitin vs Placebo	-0.20 (-0.33,-0.08)	-0.21 (-0.32,-0.09)	-0.20 (-0.30,-0.10)
Celecoxib vs Acetaminophen	-0.18 (-0.28,-0.08)	-0.18 (-0.27,-0.08)	-0.17 (-0.25, -0.08)
Celecoxib vs Placebo	-0.31 (-0.36,-0.26)	-0.31 (-0.36,-0.26)	-0.29 (-0.33, -0.25)
Acetaminophen vs Placebo	-0.13 (-0.23,-0.04)	-0.13 (-0.22,-0.04)	-0.12 (-0.20, -0.04)
Function			
Glucosamine vs Chondroitin	0.03 (-0.09,0.14)	0.03 (-0.09,0.14)	0.03 (-0.09,0.14)
Glucosamine vs Glucosamine+Chondroitin	0.07 (-0.06,0.21)	0.07 (-0.06,0.21)	0.07 (-0.06,0.21)
Glucosamine vs Celecoxib	0.16 (0.06,0.25)	0.16 (0.06,0.25)	0.16 (0.06,0.25)
Glucosamine vs Acetaminophen	0.00 (-0.13,0.15)	0.00 (-0.13,0.15)	0.00 (-0.13,0.15)
Glucosamine vs Placebo	-0.13 (-0.21,-0.05)	-0.13 (-0.21,-0.05)	-0.13 (-0.21,-0.05)
Chondroitin vs Glucosamine+Chondroitin	0.05 (-0.09,0.18)	0.05 (-0.09,0.18)	0.05 (-0.09,0.18)
Chondroitin vs Celecoxib	0.13 (0.03,0.23)	0.13 (0.03,0.23)	0.13 (0.03,0.23)
Chondroitin vs Acetaminophen	-0.02 (-0.17,0.11)	-0.02 (-0.17,0.11)	-0.02 (-0.17,0.11)
Chondroitin vs Placebo	-0.15 (-0.25,-0.06)	-0.15 (-0.25,-0.06)	-0.15 (-0.25,-0.06)
Glucosamine+Chondroitin vs Celecoxib	0.09 (-0.04,0.21)	0.09 (-0.04,0.21)	0.09 (-0.04,0.21)
Glucosamine+Chondroitin vs Acetaminophen	-0.07 (-0.23,0.09)	-0.07 (-0.23,0.09)	-0.07 (-0.23,0.09)
Glucosamine+Chondroitin vs Placebo	-0.20 (-0.32,-0.08)	-0.20 (-0.32,-0.08)	-0.20 (-0.32,-0.08)
Celecoxib vs Acetaminophen	-0.16 (-0.28,-0.04)	-0.16 (-0.28,-0.04)	-0.16 (-0.28,-0.04)
Celecoxib vs Placebo	-0.29 (-0.34,-0.23)	-0.29 (-0.34,-0.23)	-0.29 (-0.34,-0.23)
Acetaminophen vs Placebo	-0.13 (-0.25,-0.02)	-0.13 (-0.25,-0.02)	-0.13 (-0.25,-0.02)
Stiffness			
Glucosamine vs Chondroitin	-0.08 (-0.25,0.10)	-0.08 (-0.25,0.10)	-0.08 (-0.25,0.10)
Glucosamine vs Glucosamine+Chondroitin	0.09 (-0.09,0.27)	0.09 (-0.09,0.27)	0.09 (-0.09,0.27)
Glucosamine vs Celecoxib	0.19 (0.06,0.33)	0.19 (0.06,0.33)	0.19 (0.06,0.33)
Glucosamine vs Acetaminophen	0.05 (-0.15,0.25)	0.05 (-0.15,0.25)	0.05 (-0.15,0.25)
Glucosamine vs Placebo	-0.09 (-0.21,0.03)	-0.09 (-0.21,0.03)	-0.09 (-0.21,0.03)
Chondroitin vs Glucosamine+Chondroitin	0.17 (-0.02,0.36)	0.17 (-0.02,0.36)	0.17 (-0.02,0.36)
Chondroitin vs Celecoxib	0.27 (0.12,0.42)	0.27 (0.12,0.42)	0.27 (0.12,0.42)
Chondroitin vs Acetaminophen	0.13 (-0.09,0.34)	0.13 (-0.09,0.34)	0.13 (-0.09,0.34)
Chondroitin vs Placebo	-0.01 (-0.15,0.13)	-0.01 (-0.15,0.13)	-0.01 (-0.15,0.13)
Glucosamine+Chondroitin vs Celecoxib	0.10 (-0.05,0.26)	0.10 (-0.05,0.26)	0.10 (-0.05,0.26)
Glucosamine+Chondroitin vs Acetaminophen	-0.04 (-0.26,0.18)	-0.04 (-0.26,0.18)	-0.04 (-0.26,0.18)
Glucosamine+Chondroitin vs Placebo	-0.18 (-0.33,-0.02)	-0.18 (-0.33,-0.02)	-0.18 (-0.33,-0.02)
Celecoxib vs Acetaminophen	-0.14 (-0.32,0.02)	-0.14 (-0.32,0.02)	-0.14 (-0.32,0.02)
Celecoxib vs Placebo	-0.28 (-0.35,-0.21)	-0.28 (-0.35,-0.21)	-0.28 (-0.35,-0.21)
Acetaminophen vs Placebo	-0.14 (-0.30,0.03)	-0.14 (-0.30,0.03)	-0.14 (-0.30,0.03)

Data was pooled as the standard mean difference (SMD) and its related 95% CI (credibility interval).

Table S7. The rank of the competing treatments.

Intervention	SUCRA(95%CI)		
	Pain	Function	Stiffness
Glucosamine	0.35 (0.20, 0.80)	0.44 (0.20, 0.80)	0.82 (0.40, 1.00)
Chondroitin	0.64 (0.20, 1.00)	0.62 (0.20, 1.00)	0.31 (0.00, 1.00)
Glucosamine+Chondroitin	0.67 (0.20, 1.00)	0.65 (0.20, 1.00)	0.58 (0.00, 1.00)
Celecoxib	0.96 (0.80, 1.00)	0.96 (0.20, 1.00)	0.73 (0.40, 1.00)
Acetaminophen	0.38 (0.20, 0.80)	0.33 (0.00, 0.80)	0.37 (0.00, 1.00)
Placebo	0.00 (0.00, 0.00)	0.01 (0.00, 0.20)	0.20 (0.00, 0.60)

SUCRA: Surface under the cumulative ranking curve.

Supplementary File 2

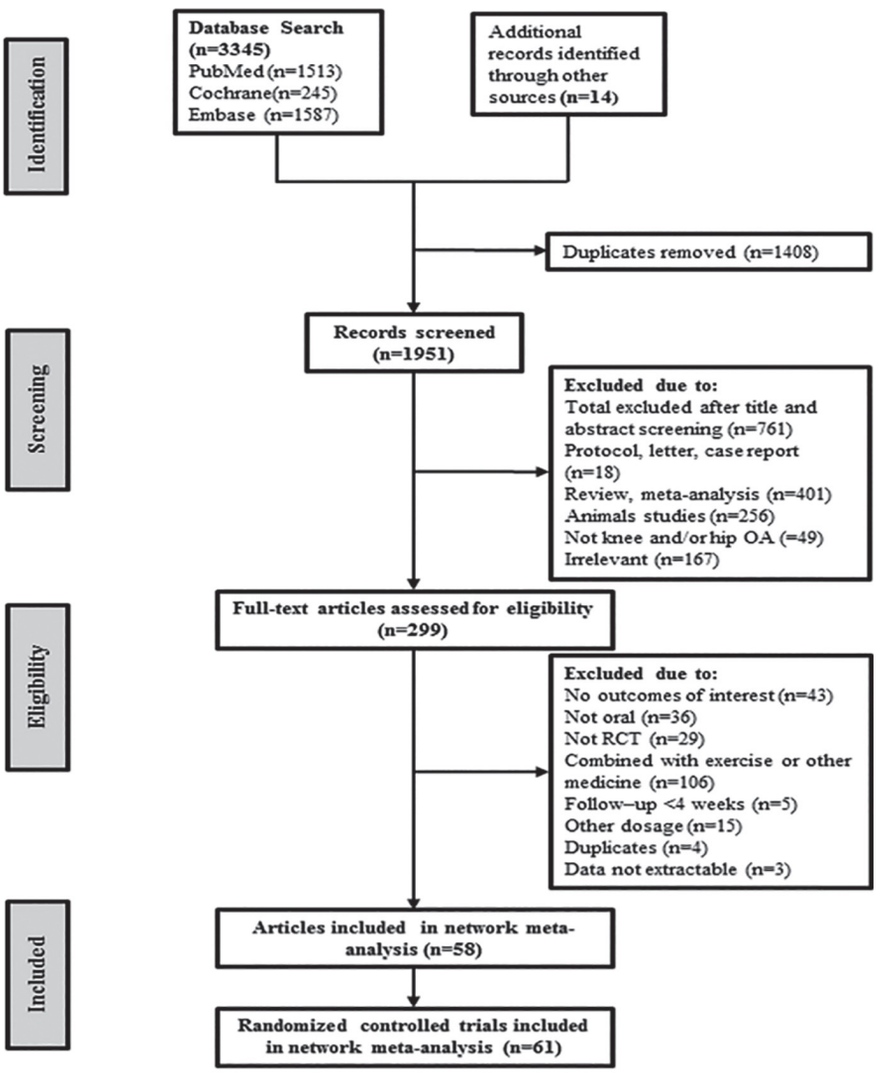


Fig. S1. Summary of the study search and selection.
RCT: Randomised controlled trial.

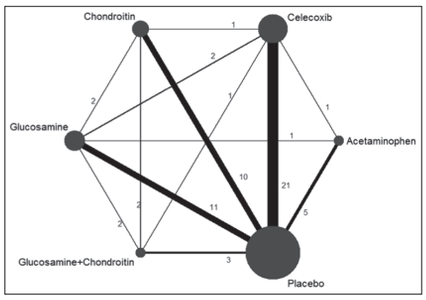


Fig. S2. Network of treatment comparisons included in the analysis for function.

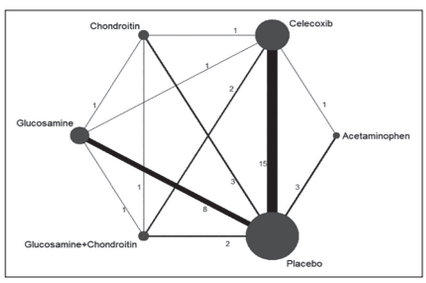


Fig. S3. Network of treatment comparisons included in the analysis for stiffness.

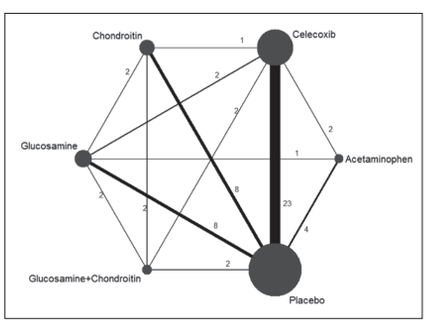


Fig. S4. Network of treatment comparisons included in the analysis for adverse effects.

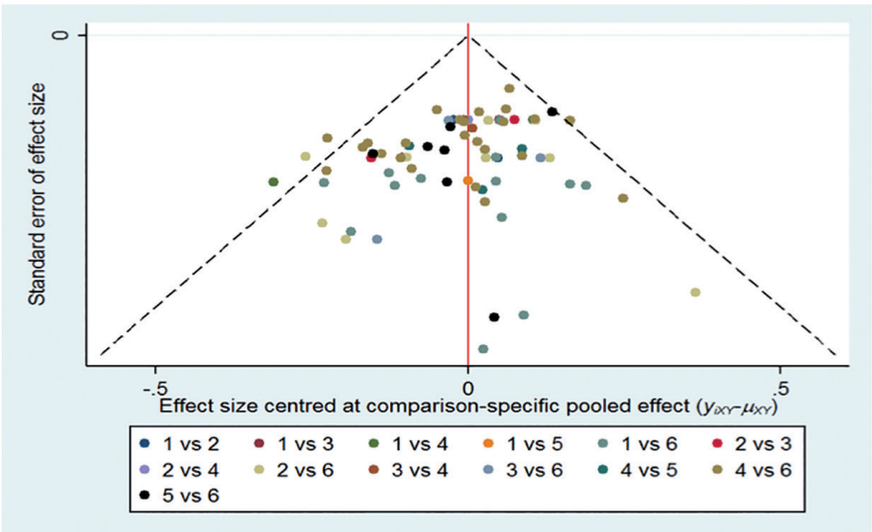


Fig. S5. Comparison adjusted funnel plot for the outcome pain.
1: Glucosamine; 2: Chondroitin; 3: Combination of glucosamine and chondroitin; 4: Celecoxib; 5: Acetaminophen; 6: Placebo.

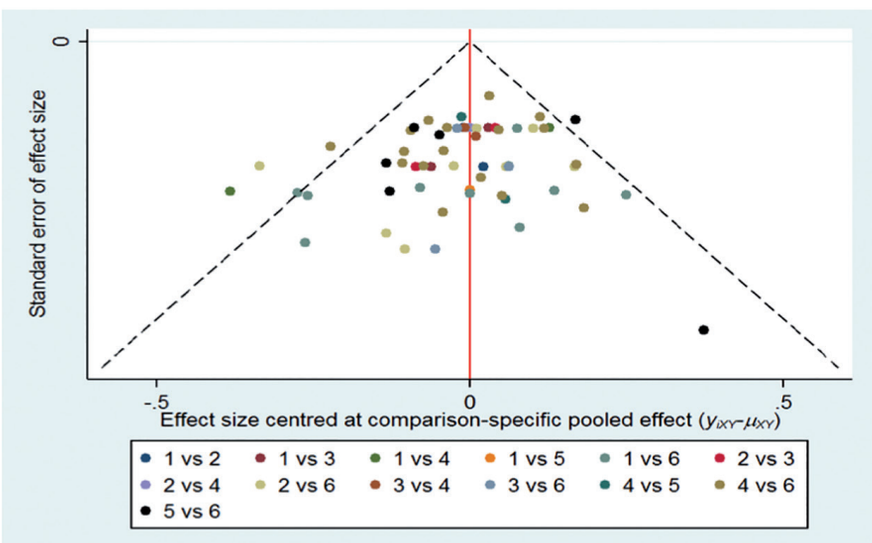


Fig. S6. Comparison adjusted funnel plot for the outcome function
1: Glucosamine; 2: Chondroitin; 3: Combination of glucosamine and chondroitin; 4: Celecoxib; 5: Acetaminophen; 6: Placebo.

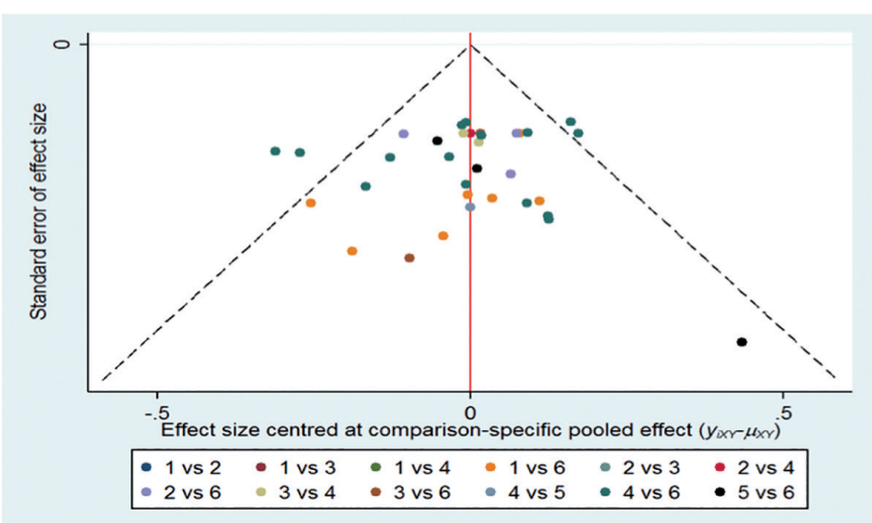


Fig. S7. Comparison adjusted funnel plot for the outcome stiffness.
1: Glucosamine; 2: Chondroitin; 3: Combination of glucosamine and chondroitin; 4: Celecoxib; 5: Acetaminophen; 6: Placebo.

Fig. S8. Inconsistency factors for the outcome pain.
1: Glucosamine; 2: Chondroitin; 3: Combination of glucosamine and chondroitin; 4: Celecoxib; 5: Acetaminophen; 6: Placebo.

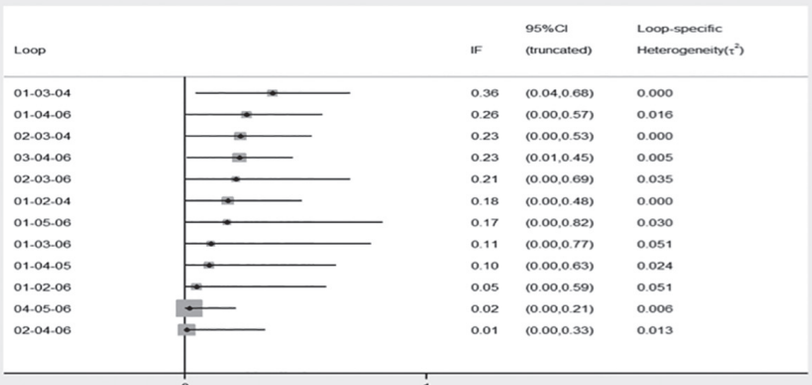


Fig. S9. Inconsistency factors for the outcome function.
1: Glucosamine; 2: Chondroitin; 3: Combination of glucosamine and chondroitin; 4: Celecoxib; 5: Acetaminophen; 6: Placebo.

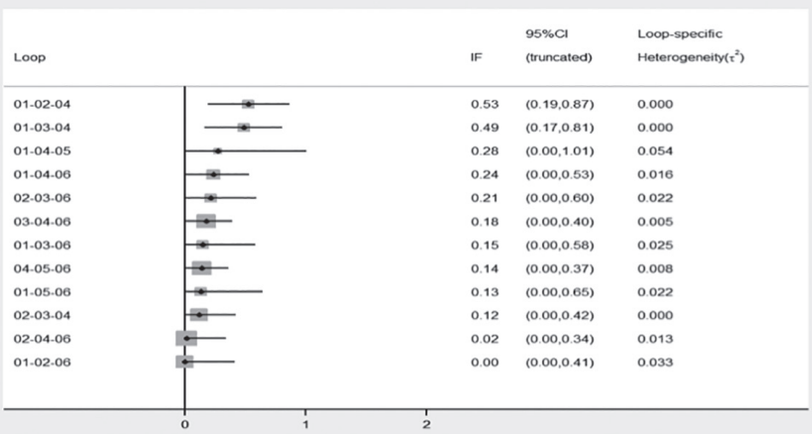
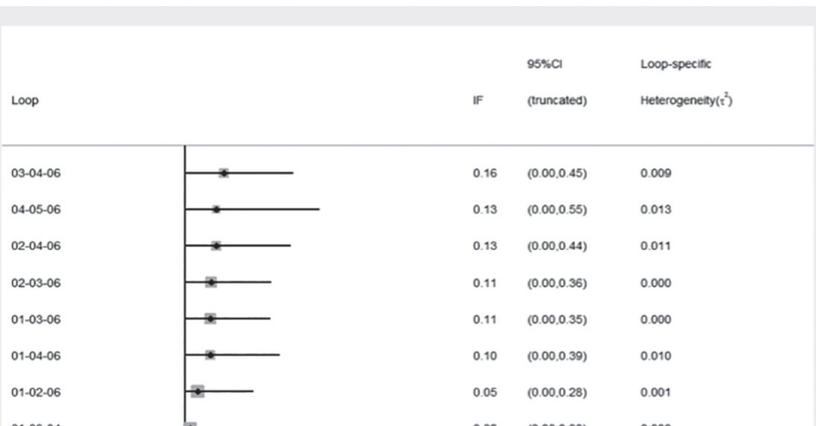


Fig. S10. Inconsistency factors for the outcome stiffness.
1: Glucosamine; 2: Chondroitin; 3: Combination of glucosamine and chondroitin; 4: Celecoxib; 5: Acetaminophen; 6: Placebo.



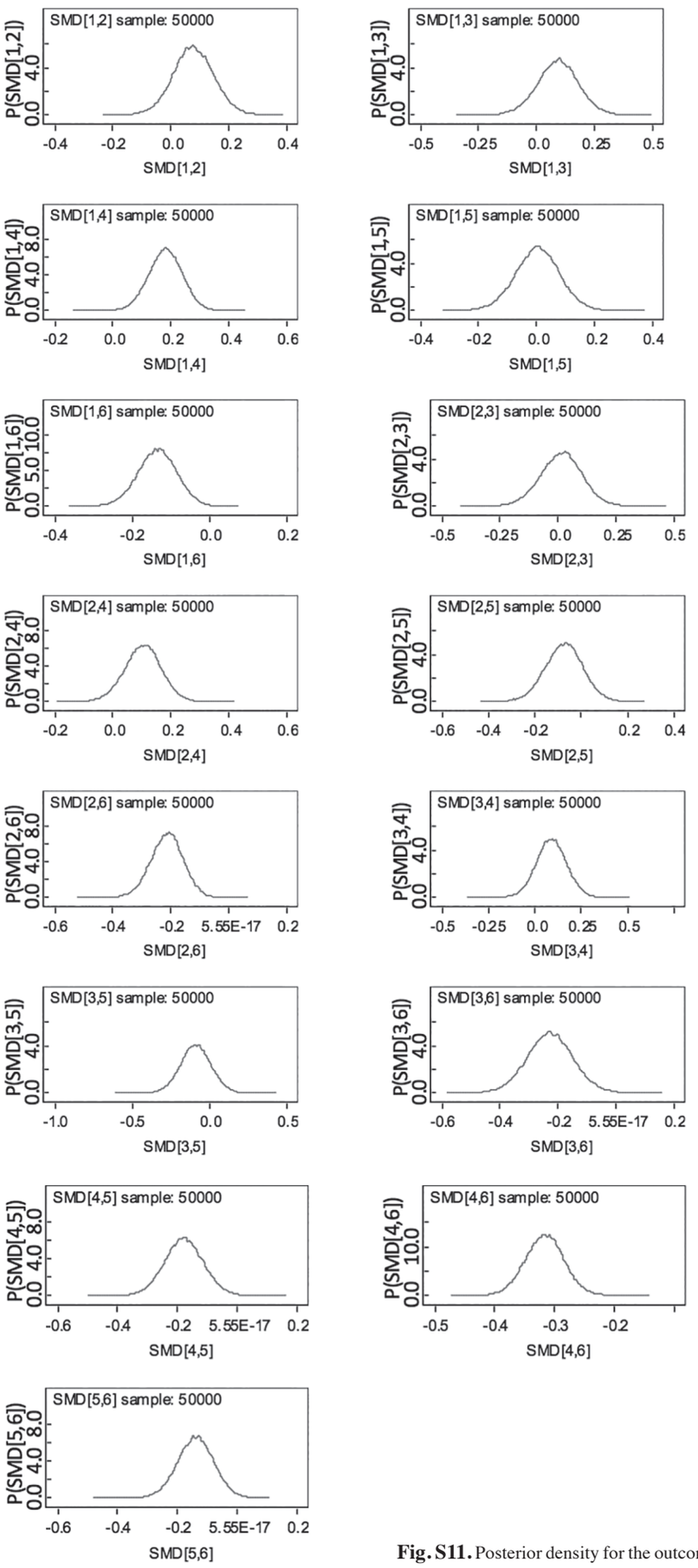


Fig. S11. Posterior density for the outcome pain.

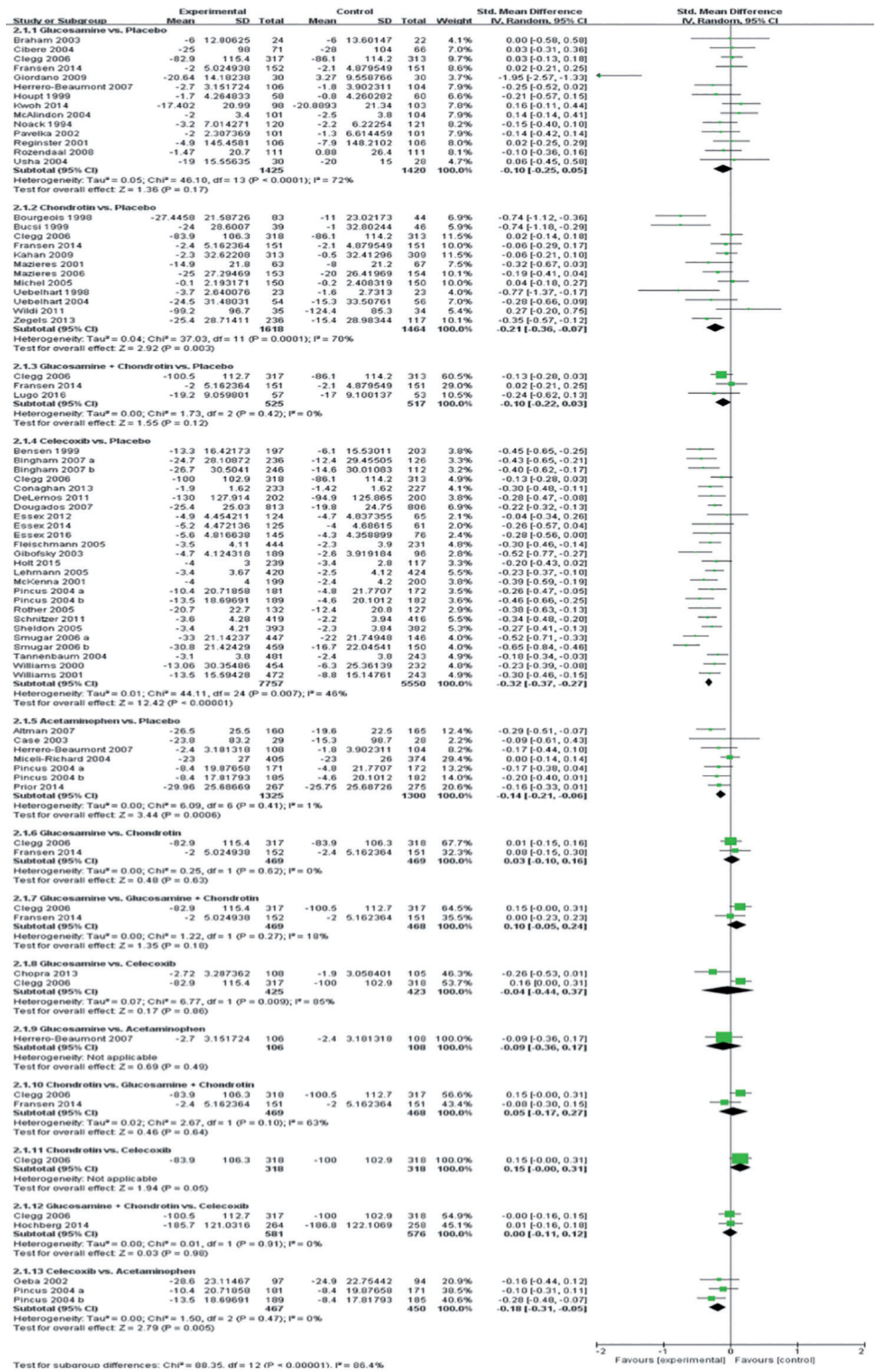


Fig. S12. Traditional meta-analysis results for pain.

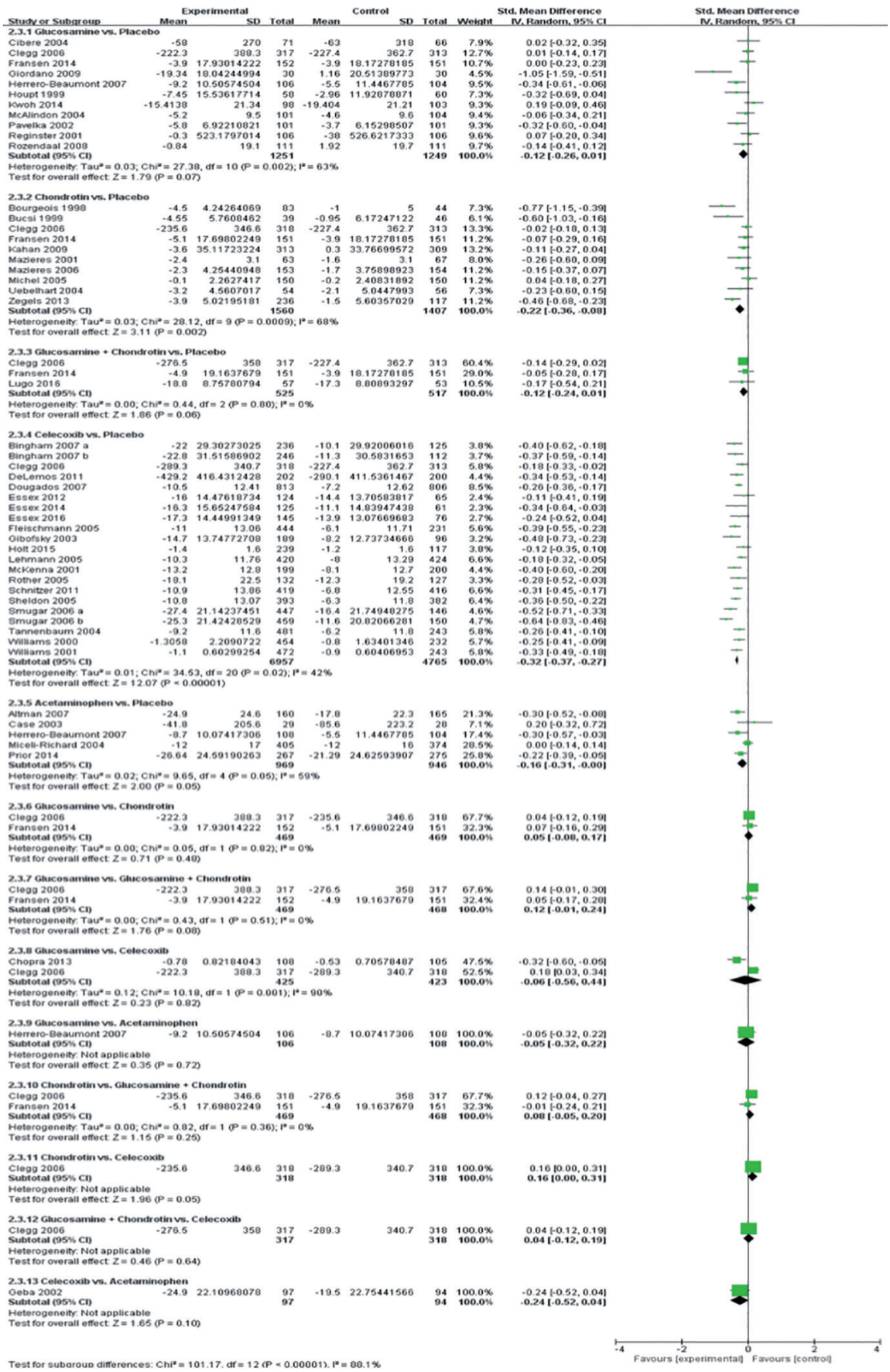


Fig. S13. Traditional meta-analysis results for function

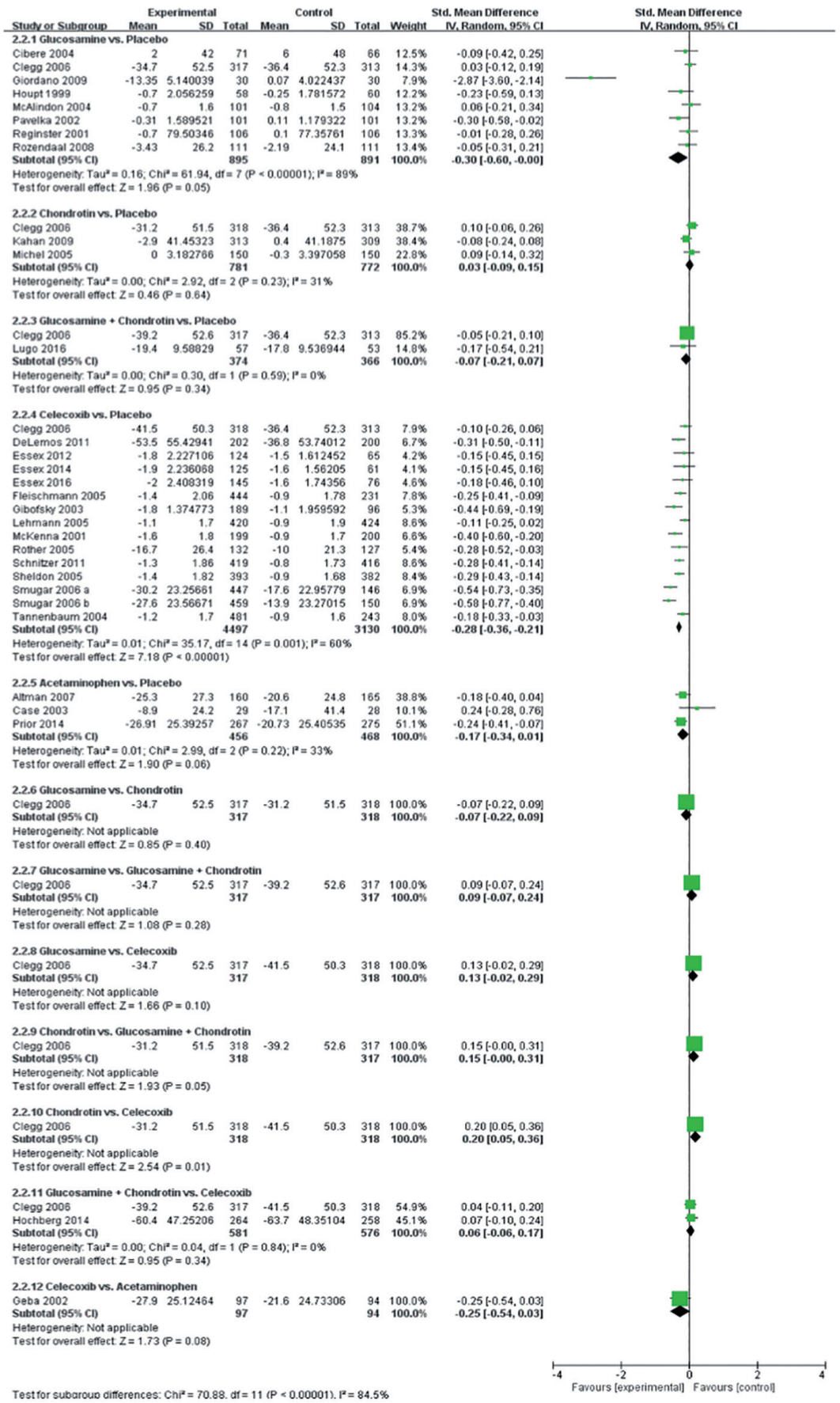


Fig. S14. Traditional meta-analysis results for stiffness.