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	1
		 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. 	
INTRODUCTION	2		2
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention</i> 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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	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: <i>Handling of multi-arm trials;</i> <i>Selection of variance structure;</i> <i>Selection of prior distributions in Bayesian analyses; and</i> <i>Assessment of model fit.</i> 	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

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 #
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	S 3	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. <i>Modified approaches may be needed to deal with information from larger networks</i> .	4-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>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</i> . 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, <i>P</i> -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 analyse	s 23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied</i> , <i>alternative choice of prior distributions for Bayesian analyses</i> , 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). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry</i> (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.

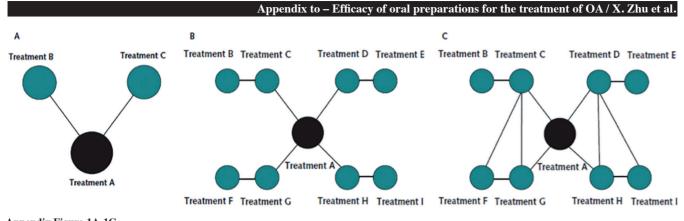
The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, 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.

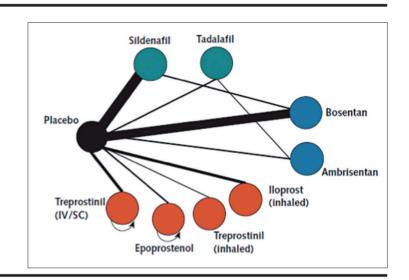
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

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.



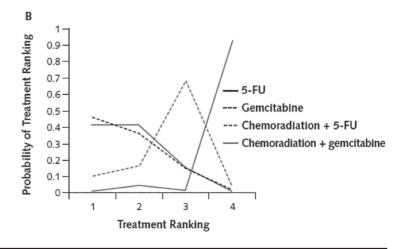
Appendix Figure 1A-1C

Appendix Figure 3



Appendix Figure 6

	Treat	tment and Coo Grade 3 o	responding Rankin r 4 Hematologic To	ig Probabilities exicity
Ranking	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			Trea	atment			Patier	nt charact	eristics	
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
Bensen 1999 (2)	USA	RCT	Placebo Celecoxib	200	165 197 203	61.80 62.00 62.00	71.50 73.10 74.88	NA	I-III	Knee
Bingham 2007 a (3)	USA	RCT	Placebo Celecoxib Placebo	200	203 241 127	62.00 62.50 62.80	69.71 65.35	NA	I-III	Knee/Hip
Bingham 2007 b (3)	USA	RCT	Celecoxib Placebo	200	247 117	62.20 60.90	61.94 64.96	NA	I-III	Knee/Hip
Bourgeois 1998 (4)	France	RCT	Chondroitin Placebo	1200	83 44	63.00 64.00	72.29 84.09	NA	I-III	Knee
Braham 2003 (5)	Australia	RCT	Glucosamine Placebo	2000	24 22	41.60 43.80	29.17 27.27	NA	I-III	Knee
Bucsi 1999 (6)	France	RCT	Chondroitin	800	39	60.60	56.41	29.20	I-III	Knee
Case 2003 (7)	USA	RCT	Placebo Acetaminophen Placebo	4000	46 29 28	59.40 62.10 61.70	63.04 51.72 39.29	29.10 26.4 27	NA	Knee/Hip
Chopra 2013 (8)	India	RCT	Glucosamine	2000	108	55.51	NA	27.46	NA	Knee/Hip
Cibere 2004 (9)	Canada	RCT	Celecoxib Glucosamine	200 1500	105 71	56.60 64.00	43.66	27.44 NA	>=2	Knee
Clegg 2006 (10)	USA	RCT	Placebo Glucosamine	 1500	66	65.00	69.70	31.8	II-III	Knee
Clegg 2006 (10)	USA	KUI	Chondroitin G+C Celecoxib	1200 1500+1200 200	317 318 317 318	58.60 58.20 58.60 59.40	62.78 64.47 62.78 66.67	32 31.5 31.5	11-111	Knee
Conaghan 2013 (11)	UK	RCT	Placebo Celecoxib	200	313 233	58.20 62.00	63.90 66.95	31.9 NA	I-III	Knee
DeLemos 2011 (12)	Canada	RCT	Placebo Celecoxib	200	227 202	61.30 60.00	66.08 64.85	NA	I-III	Knee/Hip
Dougados 2007 (13)	France	RCT	Placebo Celecoxib	200	200 813	58.90 61.60	68.05 65.81	31.1	NA	Knee
Essex 2012 (14)	USA	RCT	Placebo Celecoxib	200	806 127	61.30 58.00	66.87 80.31	31.1 NA	I-III	Knee
Essex 2014 (15)	USA	RCT	Placebo Celecoxib	200	67 127	58.00 59.60	76.12 72.44	NA	I-III	Knee
Essex 2016 (16)	USA	RCT	Placebo Celecoxib	200	62 145	61.70 65.90	59.68 66.90	NA	I-III	Knee
Fleischmann 2006 (17)	USA	RCT	Placebo Celecoxib	200	78 444	63.90 61.30	66.67 67.12	31.9	NA	Knee
Fransen 2015 (18)	Australia	RCT	Placebo Glucosamine Chondroitin G+C	 1500 800 1500+800	231 152 151 151	61.50 61.20 59.50 60.70	66.23 84.21 85.43 89.40	31.6 28.4 29.6 28.8	NA	Knee
Geba 2002 (19)	USA	RCT	Placebo Celecoxib	200	151 97	60.60 62.60	81.46 64.95	29.1 29	I-III	Knee
Gibofsky 2003 (20)	USA	RCT	Acetaminophen Celecoxib	4000 200	94 189	63.10 62.20	70.21 68.78	29 NA	I-III	Knee
Giordano 2009 (21)	Italy	RCT	Placebo Glucosamine	1500	98 30	63.10 57.20	65.31 70.00	22	I-III	Knee
Herrero- Beaumont 2007 (22)	Spain	RCT	Placebo Glucosamine Acetaminophen	 1500 3000	30 106 108	58.09 63.40 63.80	70.00 90.57 86.11	23 27.7 27.9	II-III	Knee
Hochberg 2011 a (23)	USA	RCT	Placebo Celecoxib	200	104 242	64.50 61.50	85.58 61.16	27.6 33.2	I-III	Knee
Hochberg 2011 b (23)	USA	RCT	Placebo Celecoxib	200	124 244	61.60 62.30	66.13 62.70	32.7 33	I-III	Knee
Hochberg 2016 (24)	USA	RCT	Placebo G+C	1500+1200	122 264	61.60 62.20	63.11 86.74	33 31.1	II-III	Knee
Holt 2015 (25)	USA	RCT	Celecoxib Celecoxib	200 200	258 486	63.20 61.90	81.01 61.93	30.9 33.1	I-III	Knee
Houpt 1999(26)	Canada	RCT	Placebo Glucosamine	1500	246 58	61.60 64.10	64.63 63.79	32.8 NA	NA	Knee
Kahan 2009(27)	France	RCT	Placebo Chondroitin Placebo	800	60 309 313	64.80 62.90 61.80	60.00 69.90 66.77	28.5 29	I-III	Knee/Hip

Study characteristics			Trea	atment	-		Patier	nt charact	eristics	
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 Placebo	200	207 218	62.00 64.00	65.00 67.00	NA	I-III	Knee
Kowh 2014(29)	Germany	RCT	Glucosamine Placebo	1500	98 103	52.17 52.29	52.04 45.63	28.81 28.99	I-IV	Knee
Lehmann 2005(30)	Germany	RCT	Celecoxib Placebo	200	420 424	62.90 61.70	68.33 71.93	29.7 29.7	NA	Knee
Lugo 2016(31)	USA	RCT	G+C Placebo	1500+1200	65 58	52.60 53.10	56.92 51.72	25.5 24.7	II-III	Knee
Mazieres 2001(32)	France	RCT	Chondroitin Placebo	1000	63 67	67.30 66.90	71.43 77.61	29.2 28.9	II-III	Knee
Mazieres 2007(33)	France	RCT	Chondroitin Placebo	1000	153 154	66.00 66.00	71.24 68.83	28.8 28.8	II-III	Knee
McAlindon 2004(34)	USA	RCT	Glucosamine Placebo	1500	101 104	NA	57.43 71.15	31 34.1	NA	Knee
McKenna 2001 a(35)	UK	RCT	Celecoxib Placebo	200	201 200	61.90 60.40	68.16 66.00	NA	NA	Knee
McKenna 2001 b(36)	UK	RCT	Celecoxib Placebo	200	63 60	62.00 63.20	67.00 75.00	NA	I-III	Knee
Miceli-Richard 2004(37)	France	RCT	Acetaminophen	4000	405	69.00	72.10	29	NA	Knee
Michel 2005(38)	Switzerland	RCT	Placebo Chondroitin	800	374 150	70.00 62.50	77.81 50.67	29 27.7	I-III	Knee
Noack 1994(39)	Italy	RCT	Placebo Glucosamine	1500	150 126	63.10 55.00	52.00 58.73	28.1 26.6	I-III	Knee
Pavelka 2002(40)	Italy	RCT	Placebo Glucosamine	1500	126 101	55.00 61.20	61.90 79.21	26.2 25.7	II-III	Knee
Pincus 2004 a(41)	USA	RCT	Placebo Celecoxib Acetaminophen	200 4000	101 181 171	63.50 63.00	76.24 62.00	25.7 NA	II-IV	Knee/Hip
Pincus 2004 b(41)	USA	RCT	Placebo Celecoxib Acetaminophen	200 4000	172 189 185	63.00	66.00	NA	II-IV	Knee/Hip
Prior 2014(42)	USA	RCT	Placebo Acetaminophen	3900	182 267	61.70	77.53	NA	II-III	Knee/Hip
Reginster 2001(43)	UK	RCT	Placebo Glucosamine	1500	275 106	61.70 66.00	71.27 74.53	27.3	II-III	Knee
Rother 2007(44)	Germany	RCT	Placebo Celecoxib	200	106 132	65.50 62.40	78.30 62.12	27.4 NA	I-IV	Knee
Rozendaal 2008(45)	Netherlands	RCT	Placebo Glucosamine	1500	127 111	62.80 63.10	62.99 68.47	27.9	>=2	Hip
Schnitzer 2005(46)	USA	RCT	Placebo Celecoxib	200	111 523	63.70 61.40	70.27 68.07	28 NA	I-III	Knee
Schnitzer 2011(47)	USA	RCT	Acetaminophen Celecoxib	4000 200	269 419	61.90 61.70	66.17 61.34	30.2	NA	Hip
Sheldon 2005(48)	USA	RCT	Placebo Celecoxib	200	416 393	61.40 60.20	60.58 63.10	29.7 32.5	NA	Knee
Smugar 2006 a(49)	USA	RCT	Placebo Celecoxib	200	382 456	60.80 61.80	61.26 67.54	32.6 NA	I-III	Knee/Hip
Smugar 2006 b(49)	USA	RCT	Placebo Celecoxib	200	150 460	61.80 62.00	68.67 65.65	NA	I-III	Knee/Hip
Tannenbaum 2004(50)	Canada	RCT	Placebo Celecoxib	200	151 481	62.50 64.10	67.55 69.23	30	NA	Knee
Uebelhart 1998(51)	France	RCT	Placebo Chondroitin	800	243 23	64.60 60.00	67.08 47.83	29.6 NA	I-III	Knee
Uebelhart 2004(52)	Switzerland	RCT	Placebo Chondroitin	800	23 54	57.00 63.20	56.52 79.63	NA	I-III	Knee
Usha 2004(53)	India	RCT	Placebo Glucosamine	1500	56 30	63.70 52.00	82.14 NA	26.62	I-III	Knee
Wildi 2011(54)	France	RCT	Placebo Chondroitin	800	28 35	50.00 59.70	60.00	25.39 30.4	I-III	Knee
Williams 2000(55)	USA	RCT	Placebo Celecoxib	200	34 454	64.90 62.90	58.82 66.30	31.5 31.14	I-III	Knee
Williams 2001(56)	USA	RCT	Placebo Celecoxib	200	232 474	62.60 61.70	66.81 68.78	31.96 32.5	I-III	Knee
Zegels 2013(57)	Belgium	RCT	Placebo Chondroitin	1200	244 236	61.30 65.30	72.95 63.14	32 28.6	NA	Knee
Zhao 1999(58)	Canada	RCT	Placebo Celecoxib	200	117 197 204	64.90 62.00 62.00	67.52 72.59 75.49	28.6 31.2 31.4	I-III	Knee
NA: not available; G+C:	olucosamine	+ chondroi	Placebo		204	02.00	13.49	51.4		

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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-u	Intent-to-treat p 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	Ν
Geba 2002 (19)	unclear	unclear	low(double blinding)	low	low	unclear	Y	Ν
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	Ν
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	Ν
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	Ν
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			GRAD	E		
	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	$\mathrm{Low} \oplus \oplus \otimes \otimes$	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

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

Table S4. The quality of evidence on function.

Outcomes			GRADI	Ξ		
	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	$\operatorname{High} \oplus \oplus \oplus \oplus$	no	no	no	no	undetected

¹The direct estimate is inconsistent with the indirect estimate; ²The estimates are based on indirect comparisons; ³The 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

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

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

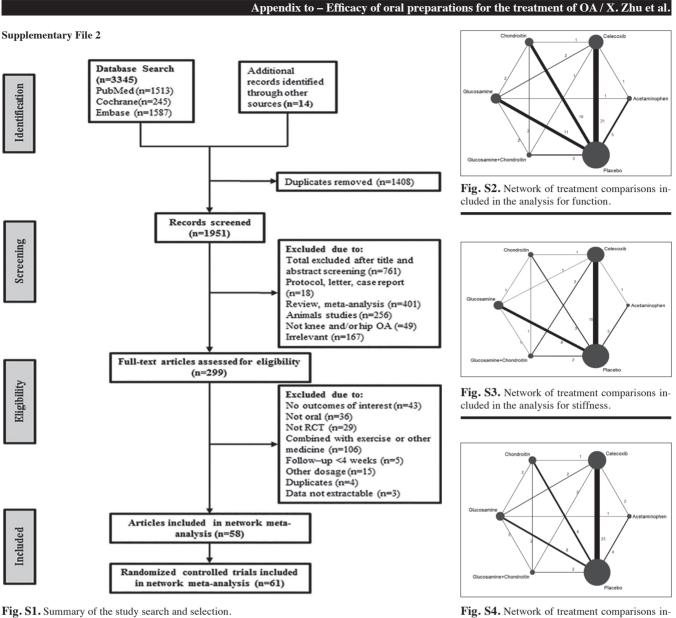
Intervention	Sensitivity analysis (>100patient per arm)	Sensitivity analysis (>50patients per arm)	Sensitivity analysis (quality of included study)
pain			
Glucosamine vs Chondroitin	0.02 (-0.10,0.14)	0.06 (-0.06,0.17)	0.05 (-0.05, 0.15)
Glucosamine vs Glucosamine+Chondroitin	0.11 (-0.04,0.25)	0.13 (-0.01,0.26)	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)
Ilucosamine vs Celecoxib	0.16 (0.06,0.25)	0.16 (0.06,0.25)	0.16 (0.06,0.25)
Ilucosamine vs Acetaminophen	0.00 (-0.13,0.15)	0.00 (-0.13,0.15)	0.00 (-0.13,0.15)
Ilucosamine 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 Chondroitin vs Glucosamine+Chondroitin	-0.09 ($-0.21, 0.03$)	-0.09 (-0.21,0.03)	-0.09 (-0.21,0.03)
	0.17 (-0.02, 0.36) 0.27 (0.12, 0.42)	0.17 (-0.02, 0.36) 0.27 (0.12, 0.42)	0.17 (-0.02, 0.36) 0.27 (0.12, 0.42)
Chondroitin vs Celecoxib	0.27 (0.12, 0.42) 0.13 (0.00, 0.34)	0.27 (0.12, 0.42) 0.13 (0.00, 0.34)	$\begin{array}{c} 0.27 & (0.12, 0.42) \\ 0.13 & (-0.09, 0.34) \end{array}$
Chondroitin vs Acetaminophen Chondroitin vs Placebo	0.13 (-0.09,0.34) -0.01 (-0.15,0.13)	0.13 (-0.09, 0.34) 0.01 (0.15, 0.13)	
Jucosamine+Chondroitin vs Celecoxib		-0.01 (-0.15,0.13) 0.10 (-0.05,0.26)	-0.01 (-0.15,0.13) 0.10 (-0.05,0.26)
Glucosamine+Chondroitin vs Celecoxio	0.10 (-0.05,0.26) -0.04 (-0.26,0.18)	-0.04 (-0.26,0.18)	-0.04 (-0.26,0.18)
Slucosamine+Chondroitin vs Placebo		-0.18 (-0.33,-0.02)	
Celecoxib vs Acetaminophen	-0.18 (-0.33,-0.02) -0.14 (-0.32,0.02)	-0.14 (-0.32,0.02)	-0.18 (-0.33,-0.02) -0.14 (-0.32,0.02)
Celecoxib vs Placebo	-0.14 (-0.32,0.02) -0.28 (-0.35,-0.21)	-0.14 (-0.32,0.02) -0.28 (-0.35,-0.21)	-0.28 (-0.35,-0.21)
Acetaminophen vs Placebo	-0.28 (-0.35,-0.21) -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.



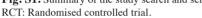


Fig. S4. Network of treatment comparisons included in the analysis for adverse effects.

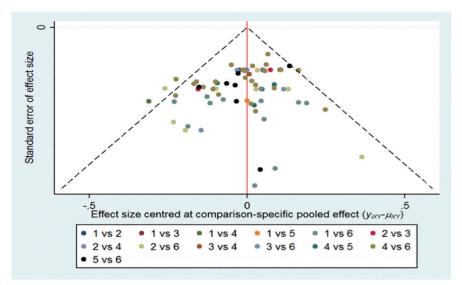


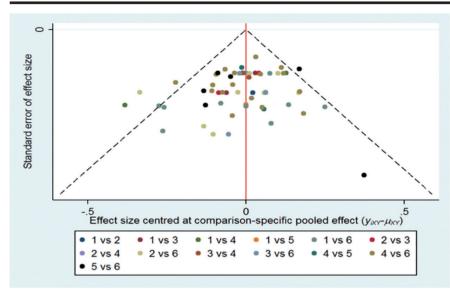
Fig. S5. Comparison adjusted funnel plot for the outcome pain.

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.



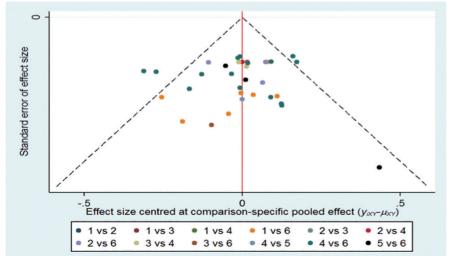


Fig. S7. Comparison adjusted funnel plot for the outcome stiffness.

- 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.

1-04-06 0.26 0. 2-03-04 0.23 0. 3-04-06 0.23 0. 2-03-06 0.23 0. 1-02-04 0.18 0. 1-05-06 0.17 0. 1-03-06 0.11 0.	26 (0.00,0.57) 0.016 23 (0.00,0.53) 0.000 24 (0.00,0.45) 0.005 21 (0.00,0.69) 0.035 28 (0.00,0.48) 0.000 17 (0.00,0.82) 0.035 14 (0.00,0.82) 0.035
1-04-06 0.26 0. 2-03-04 0.23 0. 3-04-06 0.23 0. 2-03-06 0.23 0. 1-02-04 0.18 0. 1-05-06 0.17 0. 1-03-06 0.11 0.	26 (0.00,0.57) 0.016 23 (0.00,0.53) 0.000 24 (0.00,0.45) 0.005 21 (0.00,0.69) 0.035 28 (0.00,0.48) 0.000 17 (0.00,0.82) 0.035 14 (0.00,0.82) 0.035
22.03.04 Image: Constraint of the second of th	23 (0.00,0.53) 0.000 23 (0.01,0.45) 0.005 24 (0.00,0.69) 0.035 18 (0.00,0.48) 0.000 17 (0.00,0.82) 0.030 11 (0.00,0.77) 0.051
33-04-06 Image: Constraint of the second secon	23 (0.01,0.45) 0.005 21 (0.00,0.69) 0.035 18 (0.00,0.48) 0.000 17 (0.00,0.82) 0.030 11 (0.00,0.77) 0.051
02-03-06 0.21 (0. 01-02-04 3 0.18 (0. 01-05-06 0.17 (0. (0. 01-03-06 0.11 (0. (0. 01-04-05 0.10 (0. (0.	21 (0.00,0.69) 0.035 18 (0.00,0.48) 0.000 17 (0.00,0.82) 0.030 11 (0.00,0.77) 0.051
01-02-04 0.18 (0. 01-05-06 0.17 (0. 01-03-06 0.11 (0. 01-04-05 0.10 (0.	18 (0.00,0.48) 0.000 17 (0.00,0.82) 0.030 11 (0.00,0.77) 0.051
01-05-06 0.17 (0. 01-03-06 0.11 (0. 01-04-05 0.10 (0.	17 (0.00,0.82) 0.030 11 (0.00,0.77) 0.051
01-03-06 0.11 (0. 01-04-05 0.10 (0.	0.051
01-04-05 0.10 (0.	
	0 (0 00 0 62) 0 024
0.05 (0.	0.024
	05 (0.00,0.59) 0.051
04-05-06 0.02 (0.	02 (0.00,0.21) 0.006
02-04-06 0.01 (0.	0.013 (0.00,0.33)

Fig. S9. Inconsistency factors for the outcome function.

- 1: Glucosamine; 2: Chondroitin; 3: Combination
- of glucosamine and chondroitin; 4: Celecoxib;

5: Acetaminophen; 6: Placebo.

	IF	(truncated)	Heterogeneity(τ^2)
1-02-04	0.53	(0.19,0.87)	0.000
1-03-04	0.49	(0.17,0.81)	0.000
1-04-05	0.28	(0.00,1.01)	0.054
1-04-06	0.24	(0.00,0.53)	0.016
2-03-06	0.21	(0.00,0.60)	0.022
3-04-06	0.18	(0.00,0.40)	0.005
1-03-06	0.15	(0.00,0.58)	0.025
4-05-06	0.14	(0.00,0.37)	0.008
1-05-06	0.13	(0.00,0.65)	0.022
2-03-04	0.12	(0.00,0.42)	0.000
2-04-06	0.02	(0.00,0.34)	0.013
1-02-06	0.00	(0.00,0.41)	0.033

Fig. S10. Inconsistency factors for the outcome stiffness.

- 1: Glucosamine; 2: Chondroitin; 3: Combination
- of glucosamine and chondroitin; 4: Celecoxib;
- 5: Acetaminophen; 6: Placebo.

			95%CI	Loop-specific
Loop		IF	(truncated)	$Heterogeneity(\tau^2)$
03-04-06		0.16	(0.00,0.45)	0.009
04-05-06		0.13	(0.00,0.55)	0.013
02-04-06	-*	0.13	(0.00,0.44)	0.011
02-03-06		0.11	(0.00,0.36)	0.000
01-03-06		0.11	(0.00,0.35)	0.000
01-04-06		0.10	(0.00,0.39)	0.010
01-02-06		0.05	(0.00,0.28)	0.001
01-03-04	*	0.02	(0.00,0.30)	0.000
02-03-04	*	0.02	(0.00,0.30)	0.000

*** Loop(s) [01-02-03] [01-02-04] are formed only by multi-arm trial(s) - Consistent by definition

0.5

. 0.4

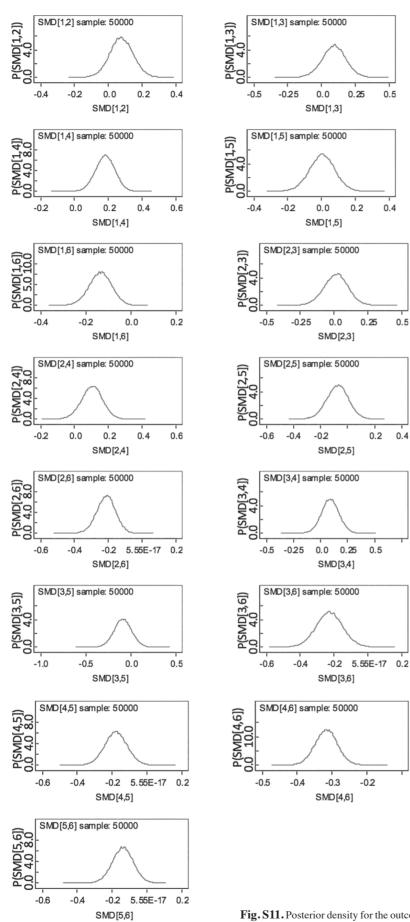
. 0.25

0.2

. 0.5

0.5

0.4





-02

Experimental Study or Subgroup Mean SD	Control Total Mean SD	Std. Mean Difference Total Weight IV, Random, 95% C	Std. Mean Difference IV. Random, 95% Cl
2.1.1 Glucesamine vs. Placebo Braham 2003 -6 12.0662 Cibere 2004 -25 96 Cleog 2006 -82.9 1154. Fransen 2014 -2 5.024933 Oiordano 2009 -2.06 4 11.81724 Houpt 1999 -1.7 3.151724 Houpt 1999 -1.7 4.264032 Kokindon 2004 -2 2.09 McAlindon 2004 -2 2.7 Parelin 2001 -3.2 7.014271 Parelin 2001 -4.9 2.36 4616 Rozendaal 2008 -1.47 20.30 Usha 2004 -19 15.556335 Subtotal (95% Ct) +14etrogenetik: Tau ² = 0.05; Chi ² = 46.10, df= 13 Testfor overall effect Z = 1.36 (P = 0.17) -115	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
2.1.2 Chondrotin vs. Placebo Bourgeois 1998 -27.4458 21.58726 Bucisi 1999 -44 28.6007 Clegg 2006 -9.9 106.5 Fransen 2014 -2.4 51.6236 Kanan 2006 -2.3 2.6200 Mazieres 2001 -2.3 2.6200 Michel 2005 -0.1 2.7165 Michel 2005 -0.1 2.1617 Uebeihart 1998 -3.7 2.64007 Uebeihart 2004 -24.5 31.46031 Vidi 2011 -90.2 96.7 Zegeis 2013 -25.4 28.71411 Subtotal (95% CI) -2.4.2 2.9.03) Testor overall effect Z = 2.9.2 (P = 0.003) 2.4.2	39 -1 32.00244 318 -06.1 114.2 151 -2.1 4.079549 313 -0.5 32.41296 063 -8 21.2 153 -0.2 2.40399 150 -0.2 2.40319 23 -1.6 2.7313 54 -15.3 33.50761 35 -15.4 85.3 236 -15.4 89.8344	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
2.1.3 Glucosamine + Chondrotin vs. Placebo Clegg 2006 100.5 112.7 Transen 2014 -2 5.162.36 Lugo 2016 -19.2 9.059801 Subtotal (95% Cl) Hetrogeneiky: Tau'# 0.00; Chi# 1.73, df = 2 (P Test for overall effect Z = 1.55 (P = 0.12)	151 -2.1 4.879549 57 -17 9.100137 525	151 29.0% 0.02[-0.21, 0.25	
2.1.4 Celecoxib vs. Placebo Bensen 1999 -13.3 16.42173 Bingham 2007 a -24.7 28.1087 Bingham 2007 b -26.7 30.6041 Cleog 2006 -100 102.5 Compone 2011 -10 127.91 Dougados 2007 -26.4 25.00 Essex 2012 -4.9 4.454211 Essex 2014 -5.2 4.873 Essex 2015 -4.4 21.61633 Fleischman 2005 -3.4 3.67 McKenna 2001 -4 22.7 Pincus 2004 b -10.4 20.71856 Pincus 2004 b -3.3 11.42318 McKenna 2005 -3.4 3.67 McKenna 2001 -4 2.7 Sheldon 2005 -3.4 3.67 McKenna 2001 -4 2.7 Smugar 2006 b -3.3 21.42318 Villiams 2001 -4 2.7 Smugar 2006 b -3.3 21.14237 Smugar 2006 b -3.03 21.4227 </td <td>$\begin{array}{cccccccccccccccccccccccccccccccccccc$</td> <td>$\begin{array}{cccccccccccccccccccccccccccccccccccc$</td> <td></td>	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
2.1.5 Acetaminophen vs. Placebo -26.6 25.6 Altman 2007 -26.6 25.6 Case 2003 -22.0 83.3 Herrero-Beaumont 2007 -2.4 3.181316 Miceli-Richard 2004 -2.3 27 Pincus 2004 a -8.4 19.07656 Pincus 2004 b -8.4 17.01792 Prior 2014 -29.96 25.68666 Subtotal (95% Ct) Heterogeneity: Tavef 2.0.00, Chi* = 6.09, df = 6 (P Test for overall effect Z = 3.44 (P = 0.0006) -0.0006)	29 -15.3 98.7 108 -1.8 3.902311 405 -23 26 171 -4.8 21.7707 185 -4.6 20.1012 267 -25.75 25.68726 1325 - -	28 2.2% -0.09 [-0.61, 0.43] 104 8.2% -0.17 [-0.44, 0.10] 374 29.4% 0.00 [-0.14, 0.14] 172 13.2% -0.17 [-0.38, 0.04] 182 14.0% -0.20 [-0.40, 0.01]	
2.1.6 Glucesamine vs. Chondrotin Clegg 2006 -82.9 116.4 Fransen 2014 -2 5.024936 Subtotal (95% Cl) -2 5.024936 Hebrogeneity: Tau ² = 0.00; Ch ² = 0.25, df = 1 (P Test for overall effect. Z = 0.48 (P = 0.63)	152 -2.4 5.162364	318 67.7% 0.01 [-0.15, 0.16 151 32.3% 0.08 [-0.15, 0.30 469 100.0% 0.03 [-0.10, 0.16	
2.1.7 Glucosamine vs. Glucosamine + Chondrol Clegg 2006 -02.9 115.4 Fransen 2014 -2 5.024936 Subtotal (95% CI) -2 5.024936 Heterogeneity: Tau ² = 0.00; Chi ² = 1.22, df = 1 (P Test for overall effect Z = 1.35 (P = 0.10) 100	317 -100.5 112.7 152 -2 5.162364 469		
$\begin{array}{llllllllllllllllllllllllllllllllllll$	317 -100 102.9 425		
2.1.9 Glucosamine vs. Acetaminophen Herrero-Beaumont 2007 -2.7 3.151724 Subtotal (95% C) Heterogeneity: Not applicable Test for overall effect Z = 0.69 (P = 0.49)	106 -2.4 3.101310 106	100 100.0% -0.09 (-0.36, 0.17 108 100.0% -0.09 (-0.36, 0.17	
$\begin{array}{c} \textbf{2.1.10 Chondrotin vs. Glucosamine + Chondroti \\ Clegg 2006 & -03.9 & 106.5 \\ Fransen 2014 & -2.4 & 5.162364 \\ Subtotal (95% Cl) \\ Heterogeneik; Tau'e 0.02; Chia = 2.67, df = 1 (\mathcal{P} \\ Test for overall effect Z = 0.46 (\mathcal{P} = 0.64) \\ \end{array}$	310 -100.5 112.7 151 -2 5.162364 469		
2.1.11 Chondrotin vs. Celecoxib Clegg 2006 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 1.94 (P = 0.05)	318	318 100.0% 0.15 (-0.00, 0.31 318 100.0% 0.15 (-0.00, 0.31	
2.1.12 Glacosamine + Chondrotin vs. Celecoxili Clegg 2006 -100.5 112.7 Hochberg 2014 -185.7 121.0316 Subtotal (95% CI) Heterogeneily: Tau* = 0.00; Chi* = 0.01, df = 1 (P Test for overall effect Z = 0.03 (P = 0.96) 24.13 (Consult).	317 -100 102.9 264 -186.8 122.1069 581		· · · · · · · · · · · · · · · · · · ·
2.1.13 Celecoxib vs. Acctaminophen Oeba 2002 -20.6 23.11467 Pincus 2004 a -10.4 20.71956 Pincus 2004 b -13.5 18.60691 Subtotal (95% CI) Heterogeneity: Tau'e 0.00; Chi* a 1.50, df = 2 (P Test for overall effect Z = 2.79 (P = 0.005)	181 -8.4 19.87658 189 -8.4 17.81793 467	171 38.5% -0.10 [-0.31, 0.11	
Test for subaroup differences: Chi#= 88.35. df=	12 (P ≺ 0.00001). I# = 86.4%		-2 -1 0 1 2 Favours (experimental) Favours (control)

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

Experimental		Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup Mean S 2.3.1 Glucosamine vs. Placebo Cibere 2004 -58 22		-63 318		Weight 7.9%		IV, Random, 95% Cl
Clegg 2006 -222.3 388 Fransen 2014 -3.9 17.930142	.3 317 -2	-03 310 27.4 362.7 -3.9 18.17278185	313	12.7%	0.01 [-0.14, 0.17]	+
Giordano 2009 -19.34 18.042449 Herrero-Beaumont 2007 -9.2 10.5057450	34 30	1.16 20.51389773 -5.5 11.4467785	30	4.5%	-1.05 [-1.59, -0.51]	
Houpt 1999 -7.45 15.536177 kwoh 2014 -15.4138 21.3	4 58 -	2.96 11.92878871 .404 21.21	60	7.3%	-0.32 [-0.69, 0.04] 0.19 [-0.09, 0.46]	
	.5 101	-4.6 9.6 -3.7 6.15298507	104	9.4%	-0.06 [-0.34, 0.21] -0.32 [-0.60, -0.04]	
Reginster 2001 -0.3 523.17970 Rozendaal 2008 -0.84 19	4 106	-38 526.6217333 1.92 19.7	106	9.6% 9.7%	0.07 [-0.20, 0.34]	
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.03; Chi ² = 27.38, df = 10 (P	1251		1249	100.0%		•
Test for overall effect: Z = 1.79 (P = 0.07)						
2.3.2 Chondrotin vs. Placebo Bourgeois 1998 -4.5 4.2426400	39 83	-1 5	44	7.3%		
Bucsi 1999 -4.55 5.760841 Clegg 2006 -235.6 346		0.95 6.17247122 27.4 362.7		6.1% 13.3%		
Fransen 2014 -5.1 17.6980220 Kahan 2009 -3.6 35.117232	19 151	-3.9 18.17278185 0.3 33.76699572	151	11.2%	-0.07 [-0.29, 0.16]	7
	.1 63	-1.6 3.1 -1.7 3.75898923	67	8.0% 11.2%	-0.26 [-0.60, 0.09]	
Michel 2005 -0.1 2.26274 Uebelhart 2004 -3.2 4.56070	17 150	-0.2 2.40831892 -2.1 5.0447993	150	11.2%		
Zegels 2013 -3.9 5.0219511 Subtotal (95% CI)	31 236 1560	-1.5 5.60357029	117 1407	11.2% 100.0%	-0.46 [-0.68, -0.23]	•
Heterogeneity: Tau ^a = 0.03; Chi ^a = 28.12, df = 9 (P = Test for overall effect Z = 3.11 (P = 0.002)	= 0.0009); I ^a = 0	38%				
2.3.3 Glucosamine + Chondrotin vs. Placebo						
Clegg 2006 -276.5 3 Fransen 2014 -4.9 19.16376	79 151	27.4 362.7 -3.9 18.17278185	151	60.4% 29.0%	-0.05 [-0.28, 0.17]	-
Lugo 2016 -18.8 8.7578079 Subtotal (95% Cl)	525	17.3 8.80893297	53 517	10.5% 100.0%	-0.17 [-0.54, 0.21] -0.12 [-0.24, 0.01]	•
Heterogeneity: Tau ^a = 0.00; Chi ^a = 0.44, df = 2 (P = Test for overall effect: Z = 1.86 (P = 0.06)	0.80); I [#] = 0%					
2.3.4 Celecoxib vs. Placebo		10.1 00.0000000				_
Bingham 2007 a -22 29.302730 Bingham 2007 b -22.8 31.5158699	02 246 -	10.1 29.92006016 11.3 30.5831653	112	3.8%	-0.37 [-0.59, -0.14]	
Clegg 2006 -289.3 340 DeLemos 2011 -429.2 416.43124	28 202 -2	27.4 362.7 90.1 411.5361467		5.8%	-0.18 [-0.33, -0.02] -0.34 [-0.53, -0.14]	-
Dougados 2007 -10.5 12. Essex 2012 -16 14.476187:	34 124 -	-7.2 12.62 14.4 13.70583817	65	8.5% 2.4%	-0.11 [-0.41, 0.19]	
Essex 2014 -16.3 15.6524750 Essex 2016 -17.3 14.449913	19 145 -	11.1 14.83947438 13.9 13.07669683	76	2.3% 2.7%	-0.24 [-0.52, 0.04]	
Fleischmann 2005 -11 13.1 Gibofsky 2003 -14.7 13.7477270		-6.1 11.71 -8.2 12.73734666	231	5.6% 3.2%	-0.39 [-0.55, -0.23] -0.48 [-0.73, -0.23]	
Holt 2015 -1.4 1 Lehmann 2005 -10.3 11.3		-1.2 1.6 -8 13.29		3.8% 6.6%	-0.12 [-0.35, 0.10] -0.18 [-0.32, -0.05]	-
McKenna 2001 -13.2 12 Rother 2005 -18.1 22		-8.1 12.7 12.3 19.2		4.4%		
Schnitzer 2011 -10.9 13.0 Sheldon 2005 -10.8 13.0	36 419	-6.8 12.55 -6.3 11.8	416	6.6% 6.4%		-
Smugar 2006 a -27.4 21.142374 Smugar 2006 b -25.3 21.424285		16.4 21.74948275 11.6 20.82066281		4.6%		-
Tannenbaum 2004 -9.2 11 Williams 2000 -1.3058 2.20907		-6.2 11.8 -0.8 1.63401346		5.8% 5.7%		-
Williams 2001 -1.1 0.602992 Subtotal (95% CI)	6957	-0.9 0.60406953	243 4765	5.8% 100.0%		Ŧ
Heterogeneity: Tau [#] = 0.01; Chi [#] = 34.63, df = 20 (P Test for overall effect: Z = 12.07 (P < 0.00001)	$= 0.02$; $I^{a} = 4$;	296				
2.3.5 Acetaminophen vs. Placebo						
Altman 2007 -24.9 24 Case 2003 -41.8 2005	.6 29 -	17.8 22.3 85.6 223.2	28	21.3%	0.20 [-0.32, 0.72]	
	7 405	-5.5 11.4467785 -12 16	374	17.4%	0.00 [-0.14, 0.14]	
Prior 2014 -26.64 24.591902 Subtotal (95% Cl)	969	1.29 24.62593907	276 946	25.8% 100.0%	-0.22 [-0.39, -0.05] -0.16 [-0.31, -0.00]	•
Heterogeneity: Tau [*] = 0.02; Chi [*] = 9.65, df = 4 (P = Test for overall effect $Z = 2.00$ (P = 0.05)	0.05); P = 59%					
2.3.6 Glucosamine vs. Chondrotin Clegg 2006 -222.3 388	3 317 -2	35.6 346.6	318	67.7%	0.04 [-0.12, 0.19]	
Francen 2014 -3.9 17.930142: Subtotal (95% CI)		-5.1 17.69802249		32.3%	0.07 [-0.16, 0.29]	Ŧ
Heterogeneity: Tau [#] = 0.00; Chi [#] = 0.05, df = 1 (P = Test for overall effect: Z = 0.71 (P = 0.40)			405	100/07	0.00 [10.00, 0.11]	Ī
2.3.7 Glucosamine vs. Glucosamine + Chondrotin						
Clegg 2006 -222.3 300 Fransen 2014 -3.9 17.9301422	.3 317 -2	76.5 350 -4.9 19.1637679		67.6% 32.4%	0.14 [-0.01, 0.30] 0.05 [-0.17, 0.28]	
Subtotal (95% Cl) Heterogeneity: Tau* = 0.00; Chi* = 0.43, df = 1 (P =	469	10.1007070		100.0%		•
Test for overall effect: $Z = 1.76$ (P = 0.08)						
2.3.8 Glucosamine vs. Celecoxib Chopra 2013 -0.78 0.821840	3 108 -	0.63 0.70578487	105	47.5%	-0.32 [-0.60, -0.05]	
Clegg 2006 -222.3 388 Subtotal (95% CI)		89.3 340.7		52.5% 100.0%	0.18 [0.03, 0.34]	-
Heterogeneity: Tau ² = 0.12; Chi ² = 10.18, df = 1 (P = Test for overall effect: $Z = 0.23$ (P = 0.82)		9%			-	
2.3.9 Glucosamine vs. Acetaminophen						\perp
Herrero-Beaumont 2007 -9.2 10.5057450 Subtotal (95% CI)	106	-8.7 10.07417306	108	100.0% 100.0%		
Heterogeneity: Not applicable Test for overall effect: $Z = 0.35$ (P = 0.72)						
2.3.10 Chondrotin vs. Glucosamine + Chondrotin						_
Clegg 2006 -235.6 346 Fransen 2014 -5.1 17.698022	19 151	76.5 358 -4.9 19.1637679	161	67.7% 32.3%	-0.01 [-0.24, 0.21]	
Subtotal (95% Cl) Heterogeneity: Tau*= 0.00; Chi*= 0.82, df= 1 (P =	469 0.36); I ^a = 0%		468	100.0%	0.08 [-0.05, 0.20]	Ī
Test for overall effect $Z = 1.15$ (P = 0.25)						
2.3.11 Chondrotin vs. Celecoxib Clegg 2006 -235.6 346		89.3 340.7		100.0%		
Subtotal (95% CI) Heterogeneity: Not applicable	318		318	100.0%	0.16 [0.00, 0.31]	•
Test for overall effect: Z = 1.96 (P = 0.05)						
2.3.12 Glucosamine + Chondrotin vs. Celecoxib Clegg 2006 -276.5 3		89.3 340.7		100.0%	0.04 [-0.12, 0.19]	
Subtotal (95% CI) Heterogeneity: Not applicable	317		318	100.0%	0.04 [-0.12, 0.19]	T
Test for overall effect $Z = 0.46$ (P = 0.64)						
2.3.13 Celecoxib vs. Acetaminophen Geba 2002 -24.9 22.109680		19.5 22.75441566		100.0%		-
Subtotal (95% CI) Heterogeneity: Not applicable	97		94	100.0%	-0.24 [-0.52, 0.04]	7
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subaroup differences: Chi ² = 101.17. df = 1	2 (P < 0.0000	 I[#] = 88.1%. 				-4 -2 0 2 4 Favours (experimental) Favours (control)
the second as differences, one = ror.ry, di = r						

Fig. S13. Traditional meta-analysis results for function

study or Subgroup	Mean		Total	Mean	Control SD	Total	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl
2.2.1 Glucosamine v Cibere 2004	s. Placebo 2	42	71	6	48	66	12.5%	-0.09 [-0.42, 0.25]	
clegg 2006	-34.7	52.5	317	-36.4	52.3	313	14.3%	0.03 [-0.12, 0.19]	+
Biordano 2009		5.140039	30	0.07	4.022437	30	7.9%	-2.87 [-3.60, -2.14]	
loupt 1999		2.056259	58	-0.25	1.781572	60	12.2%	-0.23 [-0.59, 0.13]	
IcAlindon 2004	-0.7	1.6	101	-0.8	1.5	104	13.2%	0.06 [-0.21, 0.34]	+
avelka 2002		1.589521	101	0.11	1.179322	101	13.2%	-0.30 [-0.58, -0.02]	
Reginster 2001		79.50346	106	0.1	77.35761	106	13.3%	-0.01 [-0.28, 0.26]	+
tozendaal 2008	-3.43	26.2	111	-2.19	24.1	111	13.4%	-0.05 [-0.31, 0.21]	
ubtotal (95% CI)	0.48-01-		895	- 0.000	0.011 12 - 0.00	891	100.0%	-0.30 [-0.60, -0.00]	•
leterogeneity: Tau ² = est for overall effect.			II = 7 (P	< 0.000	JO1); I= 89	20			
.2.2 Chondrotin vs.									L
legg 2006	-31.2	51.5	318	-36.4	52.3	313	38.7%	0.10 [-0.06, 0.26]	
Cahan 2009		41.45323	313	0.4	41.1875	309	38.4%	-0.08 [-0.24, 0.08]	1
lichel 2005 ubtotal (95% CI)	0	3.182766	150 781	-0.3	3.397058	150	22.8% 100.0%	0.09 [-0.14, 0.32]	T.
leterogeneity: Tau ^a = est for overall effect.				= 0.23);	I [#] = 31%	112	100.07	0.03 [-0.09, 0.15]	Ī
.2.3 Glucosamine +			abo						
legg 2006	-39.2	52.6	317	-36.4	52.3	313	85.2%	-0.05 [-0.21, 0.10]	
ugo 2016	-19.4	9.58829	57	-17.8	9.536944	53	14.8%	-0.17 [-0.54, 0.21]	
subtotal (95% CI)			374			366	100.0%	-0.07 [-0.21, 0.07]	•
leterogeneity: Tau ² = est for overall effect:			= 1 (P :	= 0.59);	l ^a = 0%				
.2.4 Celecoxib vs. P	lacebo								
legg 2006	-41.5	50.3	318	-36.4	52.3	313	7.9%	-0.10 [-0.26, 0.06]	
eLemos 2011		55.42941	202		53.74012	200	6.7%	-0.31 [-0.50, -0.11]	
ssex 2012		2.227106	124		1.612452	65	4.2%	-0.15 [-0.45, 0.15]	
ssex 2014		2.236068	125	-1.6	1.56205	61	4.1%	-0.15 [-0.45, 0.16]	
ssex 2016		2.408319	145	-1.6	1.74356	76	4.6%	-0.18 [-0.46, 0.10]	
leischmann 2005	-1.4	2.06	444 189	-0.9	1.78	231 96	7.8% 5.3%	-0.25 [-0.41, -0.09] -0.44 [-0.69, -0.19]	
ibofsky 2003 ehmann 2005	-1.8	1.3/4//3	189	-1.1	1.959592	96 424	5.3%	-0.44 [-0.59, -0.19] -0.11 [-0.25, 0.02]	-
enmann 2005 IcKenna 2001	-1.1	1.7	199	-0.9	1.9	200	6.6%	-0.40 [-0.60, -0.20]	-
Rother 2005	-16.7	26.4	132	-10	21.3	127	5.4%	-0.28 [-0.52, -0.03]	
chnitzer 2011	-1.3	1.86	419	-0.8	1.73	416	8.6%	-0.28 [-0.41, -0.14]	+
heldon 2005	-1.4	1.82	393	-0.9	1.68	382	8.4%	-0.29 [-0.43, -0.14]	-
mugar 2006 a	-30.2	23.25661	447	-17.6	22.95779	146	6.9%	-0.54 [-0.73, -0.35]	-
mugar 2006 b	-27.6	23.56671	459	-13.9	23.27015	150	6.9%	-0.58 [-0.77, -0.40]	-
annenbaum 2004	-1.2	1.7	481	-0.9	1.6	243	8.0%	-0.18 [-0.33, -0.03]	
ubtotal (95% CI)			4497			3130	100.0%	-0.28 [-0.36, -0.21]	
leterogeneity: Tau ² =	= 0.01; Chi			P = 0.00	$(11); 1^{*} = 60\%$				
est for overall effect	Z=7.18(P < 0.0000	1)						
			1)						
.2.5 Acetaminopher			1)	-20.6	24.8	165	38.8%	-0.18 [-0.40, 0.041	-
2.2.5 Acetaminopher Itman 2007	-25.3	27.3	160	-20.6	24.8 41.4		38.8% 10.1%	-0.18 [-0.40, 0.04] 0.24 [-0.28, 0.76]	-
2.5 Acetaminopher Numan 2007 Case 2003	n vs. Place -25.3 -8.9	27.3 24.2	160 29	-17.1	41.4	28		0.24 [-0.28, 0.76]	-
2.2.5 Acetaminopher Utman 2007 Case 2003 Prior 2014	n vs. Place -25.3 -8.9	27.3	160	-17.1			10.1%		•
Fest for overall effect 2.2.5 Acetaminopher Mman 2007 Case 2003 Prior 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect	-25.3 -8.9 -26.91 = 0.01; Chi	27.3 24.2 25.39257 ² = 2.99, df	160 29 267 456	-17.1 -20.73	41.4 25.40535	28 275	10.1% 51.1%	0.24 [-0.28, 0.76] -0.24 [-0.41, -0.07]	•
2.2.5 Acetaminopher Vitman 2007 Case 2003 Prior 2014 Subtotal (95% CI) Heterogeneity: Tau ^a = Fest for overall effect.	-25.3 -8.9 -26.91 = 0.01; Chi : Z = 1.90 (27.3 24.2 25.39257 = 2.99, df P = 0.06)	160 29 267 456	-17.1 -20.73	41.4 25.40535	28 275	10.1% 51.1%	0.24 [-0.28, 0.76] -0.24 [-0.41, -0.07]	•
2.2.5 Acetaminopher NIman 2007 Case 2003 Prior 2014 Subtotal (95% CI) Heterogeneity: Tau ² =	-25.3 -8.9 -26.91 = 0.01; Chi : Z = 1.90 (27.3 24.2 25.39257 = 2.99, df P = 0.06)	160 29 267 456	-17.1 -20.73	41.4 25.40535	28 275 468	10.1% 51.1%	0.24 (-0.28, 0.76) -0.24 (-0.41, -0.07) -0.17 (-0.34, 0.01)	•
2.2.5 Acetaminopher Itman 2007 Case 2003 Yrior 2014 Subtotal (95% Cl) teterogeneity: Tau ² = Test for overall effect: 2.2.6 Glucosamine vo Clegg 2006	-25.3 -8.9 -26.91 = 0.01; Chi : Z = 1.90 (s. Chondro	27.3 24.2 25.39257 a = 2.99, df P = 0.06)	160 29 267 456 = 2 (P	-17.1 -20.73 = 0.22);	41.4 26.40535 I ² = 33%	28 275 468	10.1% 51.1% 100.0%	0.24 [+0.28, 0.76] -0.24 [+0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09]	
2.2.5 Acetaminopher Vitman 2007 Case 2003 viror 2014 subtotal (95% CI) Heterogeneity: Tau ² = fest for overall effect 2.2.6 Glucosamine vo Clegg 2006 Subtotal (95% CI) Heterogeneity: Not ap	-25.3 -8.9 -26.91 = 0.01; Chi : Z = 1.90 (s. Chondro -34.7 oplicable	27.3 24.2 25.39257 ^a = 2.99, df P = 0.06) otin 52.5	160 29 267 456 = 2 (P 317	-17.1 -20.73 = 0.22);	41.4 26.40535 I ² = 33%	28 275 468 318	10.1% 51.1% 100.0%	0.24 (-0.28, 0.76) -0.24 (-0.41, -0.07) -0.17 (-0.34, 0.01)	•
2.2.5 Acetaminopher Itman 2007 Case 2003 rior 2014 Subtotal (95% CI) Heterogeneity: Tau ² = fest for overall effect 2.2.6 Glucosamine vo Clegg 2008 Subtotal (95% CI) Heterogeneity: Not ag fest for overall effect	-25.3 -8.9 -26.91 = 0.01; Chi : Z = 1.90 (s. Chondro -34.7 pplicable : Z = 0.85 (27.3 24.2 25.39257 a = 2.99, df P = 0.06) otin 52.5 P = 0.40)	160 29 267 456 = 2 (P 317 317	-17.1 -20.73 = 0.22); -31.2	41.4 26.40535 I ² = 33%	28 275 468 318	10.1% 51.1% 100.0%	0.24 [+0.28, 0.76] -0.24 [+0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09]	•
2.2.5 Acetaminopher Vitman 2007 Case 2003 viror 2014 subtotal (95% CI) Heterogeneity: Tau ² = fest for overall effect 2.2.6 Glucosamine vo Clegg 2006 Subtotal (95% CI) Heterogeneity: Not ap	-25.3 -8.9 -26.91 = 0.01; Chi : Z = 1.90 (s. Chondro -34.7 pplicable : Z = 0.85 (27.3 24.2 25.39257 a = 2.99, df P = 0.06) otin 52.5 P = 0.40)	160 29 267 456 = 2 (P 317 317	-17.1 -20.73 = 0.22); -31.2	41.4 26.40535 I ² = 33%	28 275 468 318 318 318	10.1% 51.1% 100.0%	0.24 [+0.28, 0.76] -0.24 [+0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09]	•
22.5 Acetaminopher Itman 2007 2ase 2003 Ylor 2014 Jubtotal (95% CI) Ieterogeneity: Tau ² = Test for overall effect 2.2.6 Glucosamine vy Legg 2006 Subtotal (95% CI) Ieterogeneity: Not af est for overall effect 2.2.7 Glucosamine vy 2.2.7 Glucosamine vy	n vs. Place -25.3 -8.9 -26.91 = 0.01; Chi Z = 1.90 (s. Chondro -34.7 opticable Z = 0.85 (s. Glucosa	27.3 24.2 25.39257 ^a = 2.99, df P = 0.06) 52.5 P = 0.40) mine + Ch	160 29 267 456 = 2 (P 317 317 317	-17.1 -20.73 = 0.22); -31.2	41.4 25.40535 P= 33% 51.5	28 275 468 318 318 318	10.1% 51.1% 100.0% 100.0% 100.0%	0.24 [-0.28, 0.76] -0.24 [-0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09] -0.07 [-0.22, 0.09]	
22.5 Acetaminopher Itman 2007 ase 2003 rior 2014 Jubtotal (95% CI) ielerogeneity: Tau ² = est for overall effect 2.6 Glucosamine vn legg 2006 Jubtotal (95% CI) ielerogeneity: Not ag legr 2006 Jubtotal (95% CI) ielerogeneity: Not ag	n vs. Place -26.3 -8.9 -26.91 = 0.01; Chi Z = 1.90 (s. Chondro -34.7 oplicable Z = 0.85 (s. Glucosa -34.7 oplicable	ebo 27.3 24.2 25.39257 * = 2.99, df P = 0.06) otin 52.5 P = 0.40) mine + Ch 52.5	160 29 267 456 = 2 (P 317 317 ondrott 317	-17.1 -20.73 = 0.22); -31.2	41.4 25.40535 P= 33% 51.5	28 275 468 318 318 318 318	10.1% 51.1% 100.0% 100.0% 100.0%	0.24 [-0.28, 0.76] -0.24 [-0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09] -0.07 [-0.22, 0.09]	
22.5 Acetaminopher Itman 2007 ase 2003 vitor 2014 subtotal (95% CI) teterogeneity. Tau ² = est for overall effect 2.6 Glucosamine vn vitegg 2008 subtotal (95% CI) teterogeneity. Not ag rest for overall effect 2.2.7 Glucosamine vn vitegg 2006 subtotal (95% CI) teterogeneity. Not ag est for overall effect	n vs. Place -26.3 -8.9 -26.91 = 0.01; Chi Z = 1.90 (s. Chondre -34.7 oplicable Z = 0.85 (s. Glucosa -34.7 oplicable Z = 1.08 (ebo 27.3 24.2 25.39257 ^a = 2.99, df P = 0.06) otin 52.5 P = 0.40) mine + Ch 52.5 P = 0.28)	160 29 267 456 = 2 (P 317 317 ondrott 317	-17.1 -20.73 = 0.22); -31.2	41.4 25.40535 P= 33% 51.5	28 275 468 318 318 318 318	10.1% 51.1% 100.0% 100.0% 100.0%	0.24 [-0.28, 0.76] -0.24 [-0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09] -0.07 [-0.22, 0.09]	•
2.2.5 Acetaminopher Itman 2007 Sase 2003 Prior 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect 2.2.6 Glucosamine vn Subtotal (95% CI) Heterogeneity: Not af Fest for overall effect 2.2.7 Glucosamine vn Slegg 2006 Subtotal (95% CI) Heterogeneity: Not af Fest for overall effect 2.2.8 Glucosamine vn 2.2.8 Glucosamine vn	n vs. Place -26.3 -8.9 -28.91 = 0.01; Chi Z = 1.90 (s. Chondre -34.7 oplicable Z = 0.85 (s. Glucosa -34.7 oplicable Z = 1.08 (s. Celecox	ebo 27.3 24.2 25.39257 * = 2.99, df P = 0.06) otin 52.5 P = 0.40) umine + Ch 52.5 P = 0.28) iib	160 29 267 456 = 2 (P = 317 317 317 317 317	-17.1 -20.73 = 0.22); -31.2 m -39.2	41.4 25.40535 P=33% 51.5 52.6	28 275 468 318 318 318 317 317	10.1% 51.1% 100.0% 100.0% 100.0% 100.0%	0.24 [-0.28] 0.76j -0.24 [-0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09] -0.07 [-0.22, 0.09] -0.07 [-0.22, 0.09] 0.09 [-0.07, 0.24]	•
2.2.5 Acetaminopher Itman 2007 Case 2003 Prior 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2.2.6 Glucosamine vy Clegg 2006 Subtotal (95% CI) Heterogeneity: Not ag Test for overall effect 2.2.7 Glucosamine vy Clegg 2006 Subtotal (95% CI) Heterogeneity: Not ag Test for overall effect 2.2.8 Glucosamine vy Clegg 2006	n vs. Place -26.3 -8.9 -26.91 = 0.01; Chi Z = 1.90 (s. Chondre -34.7 oplicable Z = 0.85 (s. Glucosa -34.7 oplicable Z = 1.08 (ebo 27.3 24.2 25.39257 ^a = 2.99, df P = 0.06) otin 52.5 P = 0.40) mine + Ch 52.5 P = 0.28)	160 29 267 456 = 2 (P 317 317 317 317 317 317	-17.1 -20.73 = 0.22); -31.2	41.4 25.40535 P= 33% 51.5	28 275 468 318 318 317 317 317 317	10.1% 51.1% 100.0% 100.0% 100.0% 100.0%	0.24 [-0.28, 0.76] -0.24 [-0.41, -0.07] -0.17 [-0.34, 0.01] -0.07 [-0.22, 0.09] -0.07 [-0.22, 0.09] 0.09 [-0.07, 0.24] 0.09 [-0.07, 0.24]	
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Fig. S14. Traditional meta-analysis results for stiffness.