Web-appendix

Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis

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Web-appendix 1. Further details about the eligibility criteria and study selection.

Aspect	Definition
Type of control	The control consisted of either placebo intra-articular injection(s), saline or minimal concentrations of hyaluronic acid such as $1/100^{th}$ of active concentration or no intervention.
No intervention trials and co-interventions	Trials in which HA injections were added to another treatment and compared to that other treatment alone (e.g., HA + another treatment vs. that other treatment alone) were termed no intervention controlled trials [1]. The use of co-interventions could be present in any group of the placebo-controlled or no intervention controlled trials.
Cut-off of 75% or more patients with knee osteoarthritis	The threshold was defined *a priori* and compatible with previous systematic reviews on knee osteoarthritis [2-6]. Based on our previous clinical experience, we assumed that 75% or more of patients with confirmed knee OA would be sufficient to provide a treatment response representative of this population. Notably, across 169 trials, only 6 small trials included other types of patients. Among the six small trials with mixed populations, the proportion of patients with clinically or radiologically confirmed knee OA ranged from 78 to 95%. Importantly, all large, placebo-controlled trials (main analysis) enrolled 100% knee OA patients, as shown **Table 1** (main manuscript).

References

1. U.S.Department of Health and Human Services Food and Drug Administration CfDEaRC. Guidance for Industry E 10 Choice of Control Group and Related Issues in Clinical Trials, 2001. Accessed at https://www fda gov/media/71349/download on September 1, 2021 2001.

2. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, Bobos P, Gao L, Kiyomoto HD, Montezuma T, Almeida MO, Cheng PS, Hincapié CA, Hari R, Sutton AJ, Tugwell P, Hawker GA, Jüni P. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ. 2021 Oct 12;375:n2321. doi:

3: da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, Trelle S. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017 Jul 8;390(10090):e21-e33.

4: Jüni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, da Costa BR. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev. 2015 Oct 22;(10):CD005328.

5: da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014 Sep 17;(9):CD003115.

6: Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012 Aug 7;157(3):180-91.

Web-appendix 2. Search strategies

	Search Strategy from MEDLINE (1946 to Present)*
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	random allocation.sh.
4	double blind method.sh.
5	single blind method.sh.
6	clinical trial.pt.
7	exp clinical trial/
8	(clin* adj25 trial*).ti,ab.
9	((singl* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ti,ab.
10	placebos.sh.
11	placebo*.ti,ab.
12	random*.ti,ab.
13	research design.sh.
14	comparative study.sh.
15	exp evaluation studies/
16	follow up studies.sh.
17	prospective studies.sh.
18	(control* or prospectiv* or volunteer*).ti,ab.
19	osteoarthriti$.ti,ab,sh.
20	osteoarthro*.ti,ab,sh.
21	gonarthriti*.ti,ab,sh.
22	gonarthro*.ti,ab,sh.
23	coxarthriti*.ti,ab,sh.
24	coxarthro*.ti,ab,sh.
25	arthros*.ti,ab.
26	arthrot*.ti,ab.
27	((knee* or hip* or joint*) adj3 (pain* or ach* or discomfort*)).ti,ab.
28	((knee* or hip* or joint*) adj3 stiff*).ti,ab.
29	exp osteoarthritis/
30	hyaluron*.mp.
31	hylan*.mp.
32	viscosup*.mp.
33	viskosup*.mp.
34	(visco* adj suppl*).mp.
35	synvisc*.mp.
36	orthovisc*.mp.
37	ostenil*.mp.
38	suplasyn*.mp.
39	arthrum*.mp.
40	synov-hyal*.mp.
41	artz*.mp.
42	biotty*.mp.
43	go-on*.mp.
44	healon*.mp.
45	hya-ject*.mp.

46	hyalgan*.mp.
47	hyalart*.mp.
48	hyalectin*.mp.
49	nuflexxa*.mp.
50	polireumin*.mp.
51	hy-gag*.mp.
52	nrd101*.mp.
53	(nrd adj "101").mp.
54	replasyn*.mp.
55	supartz*.mp.
56	or/1-18
57	or/19-29
58	or/30-55
59	and/56-58
60	animal/
61	animal/ and human/
62	60 not 61
63	59 not 62
64	remove duplicates from 63
65	limit 64 to yr= “2012-Current”

*Search strategy from EMBASE was similar, hence not included.

Search strategy from CENTRAL

#1	MeSH descriptor: [Osteoarthritis] explode all trees
#2	Osteoarthriti* or osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or arthros* or arthrot*
#3	(knee* or joint*) near/3 (pain* or discomfort*)
#4	(knee* or joint*) near/3 stiff*
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Hyaluronic Acid] explode all trees
#7	MeSH descriptor: [Viscosupplementation] explode all trees
#8	#6 or #7
#9	#5 and #8

Web-appendix 3. Data sources, study selection and data extraction

Data sources

The search strategy was based on a previous systematic review [1]. In the original search from 2012 (database inception to January 2012), we manually searched conference proceedings in the area of Rheumatology: European League Against Rheumatism (http://www.abstracts2view.com/eular/sessionindex.php) and American College of Rheumatology (http://acrabstracts.org/search). All meeting abstracts were screened for eligible trials. Besides, we used the Science Citation Index to retrieve reports citing relevant articles, contacted experts in the field of OA, and screened reference lists of all obtained articles, including related reviews. In the current search update (January 2012 to September 2021), we employed in addition Google Scholar to retrieve reports citing at least one of the 89 trials found in the original search (Rutjes et al., 2012 [1]). More specifically, the title of each eligible trial found in 2012 was used as a search query in Google scholar, and we used the option "Cited by" to check all related articles. We used automated translators to screen titles and abstracts of references available in languages other than English during this process. A second investigator rechecked each potential new trial. That strategy was able to identify potentially eligible reports not identified elsewhere, including theses and dissertations, personal communications, books, pamphlets, conference abstracts, trial registries, manufacturer's reports, and regulatory documents.

Furthermore, we retrieved and screened 50 systematic or narrative reviews on the use of viscosupplementation for knee osteoarthritis published since January 2012. Finally, we searched the following clinical trial registries: ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/TrialSearch.aspx), *WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp)* and UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr) to identify ongoing trials and previous trials with available data online. We performed the last

update of the current search on September 11, 2021, and the date of the latest access to all websites was September 11, 2021.

Study selection

Throughout the study selection process, we worked in pairs of investigators. Nine investigators, working in pairs, independently screened the titles, abstracts, and relevant full-text reports. Discrepancies were solved by consensus or consultation of a third reviewer. We performed detailed evaluations to identify duplicate reports.

Data extraction

Non-English reports were extracted by one native-speaker investigator and a second investigator (a non-native speaker) using a machine translator.

Reference

1. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012 Aug 7;157(3):180-91.

Web-appendix 4. Definitions used to classify trials according to methodological characteristics

Domain	Definition
Methodological characteristics	
Quasi-randomized trials	We defined a quasi-randomized trial as a prospective interventional study with two or more treatment groups, in which patients were allocated using pseudo-random methods (e.g., consecutive order, medical record numbers, day of the week) [1].
ITT analysis (incomplete outcome data)	We considered statistical analyses adequate (low risco of bias) if all randomized patients were included in the analysis based on the intention-to-treat principle.
Large trial	A large trial was defined as a trial with ≥100 randomized participants per arm [2]. Nüesch et al. showed that small trials (<100 randomized participants per arm) were associated with more exacerbated treatment effects than large trials due to small-study bias. In the meta-epidemiological study of Nüesch et al., the definition of a large trial was based on a formal sample size calculation for a typical osteoarthritis trial with pain as the primary outcome [2]. Assuming a two-arm trial and a treatment effect equal to a standardized mean difference of -0.4, 100 participants per arm would give the trial 80% power at a two-sided alpha of 0.05.
Treatment duration	Treatment duration refers to the period starting from the first day of the treatment to the last day of treatment. Treatment duration was categorized in weeks where one month is about 4.3 weeks.
Trial size	Trial size refers to the total number of participants randomized for the trial considering all arms.
Trial duration	Trial duration constitutes the period starting at randomization of patients (day 0) to the last day of follow-up.
Endpoint at 3 months	The time point closest to 3 months was defined as our main time point of interest. This pre-specified decision was based on previous evidence suggesting that the most pronounced effects of viscosupplementation on pain intensity are observed between week 5 and 13 after treatment [3-4].
Multi-arm trials	Within multi-arm trials, we combined group-level means at follow-up or mean changes from baseline from different hyaluronic acid preparations/doses using a fixed-effect meta-analysis whenever needed.
Publication-related characteristics	
Published trial	A published trial was defined as any trial published through a formal peer-review process and with a digital object identifier (DOI). However, peer-reviewed trials published in Chinese journals without a DOI were also considered published.
Unpublished trial	An unpublished trial was defined as any trial obtained through clinical trial registries, conference abstracts, and master or doctoral dissertations that have not been subjected to formal academic publishing with a peer-review process.

	Trials produced by commercial and non-commercial bodies without academic publishing and peer-review process were also considered unpublished (government reports, industry reports, and FDA documents).
Funding independent of industry	Any body with a commercial interest in one of the interventions evaluated can be considered a "commercial body", including the pharmaceutical industry and medical device manufacturers.
Language of publication	This refers to the language of publication of the included trials. We categorized languages into English vs others.
Clinical characteristics	
Cycles	Patients are usually given either a single injection or a course of ≥2 to 6 injections. One cycle refers to one such course of treatment.
Follow-up duration	For the main analysis, follow-up duration was defined as the period from the last day of treatment to the last day of follow-up, that is, the time of follow-up after treatment. The follow-up duration was categorized in <3 months, 3-6 months, and >6 months.
Molecular weight	Hyaluronic acid has been categorized according to its molecular weight: • Low (<1500 kDa); • Intermediate (≥1500 and <6000 kDa); • High (≥6000 kDa).
Molecular structure	Hyaluronic acid is a naturally occurring linear glycosaminoglycan composed of repeating disaccharides of glucuronic acid and N-acetylglucosamine. It is usually found in either a cross-linked or a non-cross-linked form.

References

1. Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2019). *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons.

2. Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Jüni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ. 2010 Jul 16;341:c3515.

3. Bellamy, N., Campbell, J., Welch, V., Gee, T. L., Bourne, R., & Wells, G. A. (2006). Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane database of systematic reviews*, (2).

4. Hunter, D. J. (2015). Viscosupplementation for osteoarthritis of the knee. *New England Journal of Medicine*, *372*(11), 1040-1047.

Web-appendix 5. Back-transformation of the minimal clinically important standardized mean difference to visual analog scale (in mm)

For continuous outcomes, we back-transformed standardized mean differences to a 100-mm visual analog scale (VAS). First, we used the median (e.g., "typical") standard deviation of 25 mm derived from large, placebo-controlled OA trials that examined pain on a VAS [1-4]. Second, we multiplied the summary estimates of the continuous outcomes by the "typical" standard deviation value to obtain results in mm.

References

1. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180-191.

2. da Costa BR, Nüesch E, Rutjes AW, et al. Combining follow-up and change data is valid in meta-analyses of continuous outcomes: a meta-epidemiological study. *J Clin Epidemiol*. 2013;66(8):847-855.

3. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev*. 2015;(10):CD005328.

4. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ. 2010 Sep 16;341.

Web-appendix 6. Minimal clinically important difference (MCID)

The minimal clinically important difference was calculated based on the median MCID from four studies in patients with OA [1]. We pre-specified a minimal clinically important between-group difference of 0.37 SD units. The four studies calculated the between-group MCID in osteoarthritis pain based on the difference in mean changes from baseline pain between two groups of patients after treatment: those feeling "slightly better" at follow-up and those reporting "no change" at follow-up [1]. Based on these four primary studies, this difference corresponds approximately to -9 mm on a visual analogue scale (VAS) of 100 mm, representing an SMD of -0.37 SD (assuming a typical standard deviation of approximately 25 on a 0-to-100 mm VAS, as discussed in **web-appendix 5**). This follows the valid anchor-based approach where an external global rating of change is used to anchor change scores according to patients' perspectives on their health status [2]. Of note, between-group MCID (used to define minimally important differences between two groups of patients who received different treatments) needs to be distinguished from minimal important change (MIC) from baseline estimated within a group of patients who experienced a slight improvement. Within-group MIC is used as a threshold to define treatment response in individual patients: if a patient reaches the threshold, they are considered treatment responders.

Further considerations regarding the MCID

Although the MCID is intended to facilitate the interpretation of the magnitude of treatment effects, it should not be applied to distinguish between clinically relevant and irrelevant treatment effects. Treatment effects should be interpreted along a continuum: the closer the treatment effect is to zero and further away from the MCID, the less likely it is that a treatment effect is clinically relevant. Given that the effect of viscosupplementation on osteoarthritis pain is an SMD of -0.08,

which is only 22% of the MCID, it is unlikely that the effect of viscosupplementation surpasses the placebo effect in an appreciable number of patients.

References

1. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ. 2010 Sep 16;341.

2. Bobos, P., Ziebart, C., Furtado, R., Lu, Z., & MacDermid, J. C. (2020). Psychometric properties of the global rating of change scales in patients with low back pain, upper and lower extremity disorders. A systematic review with meta-analysis. *Journal of Orthopaedics*, *21*, 40-48.

Web-appendix 7. Hierarchy of scales

Pain
If a trial presented pain outcomes on more than one scale, we employed the following hierarchical list to extract data from the scale highest on the list [1,2]:
(1) global osteoarthritis pain assessed using visual analog or numeric rating scales;
(2) pain on walking (any scale: visual analog scale, Likert or numeric rating scale);
(3) WOMAC osteoarthritis index pain subscore;
(4) composite pain scores other than WOMAC;
(5) pain on activities other than walking (such as stair climbing);
(6) WOMAC global score;
(7) Lequesne osteoarthritis index score;
(8) other algofunctional composite scores;
(9) patient's global assessment;
(10) physician's global assessment.
Function
Our secondary efficacy outcome was physical function. If a trial presented function outcomes on more than one scale, we used the following hierarchical list to extract data from the scale highest on the list[1]
(1) global osteoarthritis function score;
(2) walking disability (any scale: visual analog scale, Likert or numeric rating scale);
(3) WOMAC osteoarthritis index physical function subscore;
(4) composite physical function scores other than WOMAC;
(5) physical function on activities other than walking (such as stair climbing);
(6) WOMAC global score;
(7) Lequesne osteoarthritis index score;
(8) other algofunctional composite scores;
(9) patient's global assessment;
(10) physician's global assessment.

References

1. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. Best Pract Res Clin Rheumatol 2006; 20: 721–40.

2. da Costa BR, Saadat P, Basciani RM, Agarwal A, Johnston BC, Jüni P. Visual Analogue Scale has higher assay sensitivity than WOMAC pain in detecting between-group differences in treatment effects: A meta-epidemiological study. Osteoarthritis Cartilage 2020; published online Nov 30. DOI:10.1016/j.joca.2020.10.004.

Web-appendix 8. Risk of bias assessment

Upon editorial request, we amended our methods and assessed the risk of bias in large, placebo-controlled trials using the Cochrane risk of bias 2.0 (RoB 2.0) (25 trials). All the other trials were assessed with RoB 1.0, per our pre-specified protocol. For RoB 1.0 assessments, we based our assessments on four domains: sequence generation/allocation concealment (selection bias), blinding of participants (performance bias), blinding of outcome assessors (detection bias), and intention-to-treat analysis (ITT) (attrition bias). We rated the risk of bias for each item as low, high, or unclear [1].

Criteria to judge the risk of bias

Domain	**Criterion**
Allocation concealment	• Low risk of bias: If participants and investigators enrolling participants could not foresee treatment assignment using one of the following, or an equivalent, methods: central allocation, sequentially numbered drug containers of identical appearance, opaque sealed envelopes, and coded syringes. • High risk of bias: If there is evidence of inadequate sequence generation. • Unclear risk of bias: The information about the allocation concealment process was insufficient to permit judgment of "Low risk" or "High risk".
Blinding of patients	• Low risk of bias: If one of the following techniques were used: a) a sham injection was used with a syringe identical in appearance to the control intervention, b) an attempt was made to hide the patient's view from the injected knee using screens or curtains, c) the double-dummy technique was used, or d) the patient was given general anesthesia • High risk of bias: Patients were more likely to be unblinded if no placebo injection was involved. • Unclear risk of bias: The information about blinding of patients was insufficient to permit judgment of "Low risk" or "High risk".
Blinding of assessor	• Low risk of bias: If all of the following conditions were met: a) the extracted outcome was reported using self-assessment instruments b) blinding of patients was considered adequate (see '*Blinding of patients*' above) c) the investigator was not involved in outcome assessment, or investigator and patients were both reported to be blinded • High risk of bias: If pain or function outcome was measured by the physician's global assessment instrument and the assessor was not blinded to patient's allocation.

	• Unclear risk of bias: The information about blinding of outcome assessors was insufficient to permit judgment of "Low risk" or "High risk".
ITT (pain and function)	• Low risk of bias: A trial was considered at low risk of attrition bias when the number of analyzed patients was identical to the number of randomized patients. • High risk of bias: A trial was considered at a high risk of attrition bias when the number of analyzed patients was different from the number of randomized patients. • Unclear risk of bias: A trial was considered at an unclear risk of attrition bias when the number of analyzed patients was unclear. A trial was also considered at unclear risk of attribution bias when the number of randomized patients was unclear.

Cochrane risk of bias 2.0

We based our assessments on the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. We rated the risk of bias for each item as low, high, or some concerns [2].

References

[1] Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ, 343.

[2] Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, *366*.

Web-appendix 9. Imputation of means and standard deviations

We used two different approaches to approximate sample means and standard deviations when this information was not reported directly. We first used Approximate Bayesian Computation (ABC) models to approximate sample means and standard deviations using the available summary statistics. When ABC models were not feasible to estimate standard deviations, we used empirically-derived estimates obtained from large sham-controlled trials. Detailed information is provided below.

Approximate Bayesian computation (ABC) model and empirically-derived standard deviation estimates

Studies reporting only median, interquartile range, and/or min-max cannot be directly used in the traditional meta-analysis. To overcome this issue, we imputed means and standard deviations based on the above-mentioned summary statistics using a flexible ABC model described previously [1]. Briefly, outcomes are considered random variables that follow a specific family distribution (e.g., beta, gamma, or normal). Once the family distribution is chosen either based on clinical grounds or empirical evidence, a large number of similar statistical distributions are generated, but each with a slightly different set of parameters. For each study arm without a reported mean and standard deviation, we generated 100,000 distributions. For each generated distribution, we calculated the Euclidean distance between the real (reported) summary statistics, and the corresponding statistics from the pseudo-data sampled from the distribution thought to be the distribution of unavailable data. The top 0.1% distributions with the smallest Euclidean distances (i.e., 100 distributions) were kept and served as the basis for the estimation of means and standard deviations. This approach has been demonstrated to furnish a reasonable approximation of the posterior distribution via summary statistics provided – given that a tight tolerance level is used (e.g. the 0.1% top distributions with the smallest Euclidean distances). Estimates for the mean and

the standard deviation were computed by the "simulation method", that is, the mean and the standard deviation are the averages of means and standard deviations from the randomly generated data, respectively. Since both pain and function are typically measured on a bounded interval (e.g., 0 to 100 scale), we assumed that these outcomes were approximately distributed as beta random variables. Prior parameters for the beta distributions were assumed to follow a uniform distribution: $\alpha \sim \text{Unif}(0,50)$ and $\beta \sim \text{Unif}(0,50)$.

Empirical distribution (imputation of missing standard deviations)

When summary statistics were insufficient to fit the ABC model, we employed the following imputation approach. First, we constructed an empirical distribution of the ratio of the pooled standard deviation to outcome measurement scale range. This analysis was based on large sham-controlled trials in patients with OA where such information was available. Empirical distributions were constructed for pain (38 trials) and function (23 trials) separately. A large study was defined as a trial with an average sample size ≥100 randomized participants per group [2]. The database containing large placebo-controlled OA trials was assembled from previous investigations by our group [2-4]. Second, the median value for this distribution was estimated. Finally, missing standard deviations were then imputed by the median of the empirical distribution multiplied by the study-specific scale range.

Imputation of atypical standard deviations (SD)

Some trials produced considerably atypical small or large standard deviations, which would influence the magnitude of the SMD, ultimately leading to spurious high or low values of the treatment effect. This is a commonly known fallacy of the SMD [5]. Thus, we used an empirical distribution to replace extremely outlying SDs. Specifically, an SD was flagged as an outlier if the ratio of SD to scale range was below the 2.5^{th} or above the 97.5^{th} percentiles of the empirical

distribution constructed based on large sham-controlled trials as described above. We calculated the ratio SD/scale range for each trial. Trials whose SDs were too low (e.g., the ratio of SD to scale range was below the 2.5th percentile of the empirical distribution) were truncated at the 2.5th empirical percentile. In other words, when SDs were considered to be atypically low, we replaced the observed SD with the 2.5th empirical percentile multiplied by the scale range. Similarly, trials with atypically high SDs had their SDs truncated at the 97.5th percentile of the empirical distribution. Stated differently, when SDs were considered to be atypically high, we replaced the observed SD by the 97.5th empirical percentile multiplied by the scale range (Box 1).

Box 1. Descriptive statistics of SD-to-mean ratio from large sham-controlled arms

Outcome	No. of trials*	Median	2.5th	97.5th percentile
Pain	38	0.227	0.103	0.317
Function	23	0.211	0.097	0.269

For example, assume a hypothetical trial that examined the effect of viscosupplementation on pain levels based on a 0-100 VAS. After 3 months of treatments, the means (SDs) for intervention and control groups were 80 (8.2) and 80 (10.6), respectively. The ratio of SD to scale range were: 0.082 and 0.106, with the first SD considered implausibly low. Hence, the SD of 0.082 was replaced by 0.103 × 100 = 10.3, which represents the 2.5th percentile from the empirical distribution when all scales are standardized to a 0-to-100 range. In this example, the SD from the control group remained unchanged.

References

1. Kwon D, Reis IM. Simulation-based estimation of mean and standard deviation for meta-analysis via Approximate Bayesian Computation (ABC). BMC Med Res Methodol. 2015 Aug 12;15:61.

2. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180-191.

3. da Costa BR, Nüesch E, Rutjes AW, et al. Combining follow-up and change data is valid in meta-analyses of continuous outcomes: a meta-epidemiological study. *J Clin Epidemiol*. 2013;66(8):847-855.

4. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev*. 2015;(10):CD005328.

5. Johnston BC, Alonso-Coello P, Friedrich JO, et al. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. *CMAJ*. 2016;188(1):25-32.

Web-appendix 10. Explanation of cut-offs used for the interpretation of τ^2

Our interpretation of the magnitude of heterogeneity based on τ^2 values as explained below is based on the recommendations of Spiegelhalter et al [1].

Interpretation of tau-squared for continuous outcomes (pain and physical function)

Low heterogeneity

In case of low heterogeneity, τ^2 is approximately 0.04, τ is therefore 0.20, and the median difference in effect sizes between any two randomly selected trials is $1.09 \times \tau$, corresponding to a difference in effect sizes between randomly selected trials of 0.22 SD units. For example, if one randomly selected trial would show an effect size of 0.00 SD units, then the other randomly selected trial would show an effect size of either -0.22 or +0.22 SD units.

The 95% reference range for true effect sizes across all trials in a meta-analysis would be $3.92 \times \tau$, corresponding to a difference between the lower end and the upper end of the 95% reference range of 0.78 SD units. If the pooled effect size were at 0, then 95% of the true effects of included trials would be between -0.39 and +0.39 SD units.

Moderate heterogeneity

In case of moderate heterogeneity, the difference in effect size between any two randomly selected trials of $1.09 \times \tau$ is 0.33 SD units if τ is 0.30 and τ^2 0.09.

The 95% reference range for true effect sizes across all trials in a meta-analysis would be 3.92×0.30, corresponding to a difference between the lower end and the upper end of the 95% reference range of 1.18 SD units. If the pooled effect size were at 0, then 95% of the true effects of included trials would be between -0.59 and +0.59 SD units.

Large heterogeneity

In case of large heterogeneity, the difference in effect size between any two randomly selected trials of 1.09 × τ is 0.44 SD units if τ is 0.40 and τ^2 0.16.

The 95% reference range for true effect sizes across all trials in a meta-analysis would be 3.92 × 0.40, corresponding to a difference between the lower end and the upper end of the 95% reference range of 1.57 SD units. If the pooled effect size were at 0, then 95% of the true effects of included trials would be between -0.785 and +0.785 SD units.

Interpretation of tau-squared for a binary outcome (serious adverse event)

Low heterogeneity

In case of low heterogeneity, τ^2 is approximately 0.04, τ is 0.20, and the 95% reference range for true effect sizes across all trials in a meta-analysis would be 3.92 × τ. If the pooled risk ratio were 1.00, then 95% of the true effects of included trials would be between 0.68 and 1.48.

Moderate heterogeneity

In case of low heterogeneity, τ^2 is 0.16 and τ is 0.40. The 95% reference range for true effect sizes across all trials in a meta-analysis would thus be 3.92 × 0.40. If the pooled risk ratio were 1.00, then 95% of the true effects of included trials would be between 0.46 and 2.19.

Large heterogeneity

In case of low heterogeneity, τ^2 is 0.36 and τ is 0.60. The 95% reference range for true effect sizes across all trials in a meta-analysis would thus be 3.92 × 0.60. If the pooled risk ratio were 1.00, then 95% of the true effects of included trials would be between 0.31 and 3.24.

Reference

1. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health-care evaluation. John Wiley & Sons; 2004 Jan 16, page 169.

Web-appendix 11. Trial sequential analysis

For a review of trial sequential analysis methods and interpretation, see Kang [1] and Wetterslev et al. [2].

Monitoring boundaries were calculated by the alpha spending method [3]. More stringent alpha and power values were used for trial sequential analyses of effectiveness outcomes. For continuous outcomes, the required information size was calculated as the sample size that provided 90% power at a two-sided α=0.005 to detect a standardized mean difference of -0.37 of viscosupplementation compared to placebo in a superiority analysis, and to establish equivalence at margins of -0.20 and 0.20 in an equivalence analysis. For serious adverse events, the required information size was calculated as the sample size that gives a trial 80% power to detect a 50% relative risk increase of serious adverse events, assuming a control event rate of 2.5% and a two-sided α=0.05. The relative risk (RR) of 1.5, a relevant effect, was informed by the summary RR from eight large placebo-controlled trials with blind outcome assessment as reported in a previous review [4]. For the calculation of the required information size, we accounted for between-trial variation using diversity (D^2) index-adjusted sample sizes [2]. We assumed a D^2 of 50% in sample size calculations for both pain and function. For serious adverse events, we assumed a D^2 of 25%. Assumptions for expected heterogeneity are conservative and based on Rutjes et al. [4]

References

1. Kang, H. (2021). Trial sequential analysis: novel approach for meta-analysis. *Anesthesia and Pain Medicine*, *16*(2), 138.

2. Wetterslev, J., Jakobsen, J. C., & Gluud, C. (2017). Trial sequential analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology*, *17*(1), 1-18.

3. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; 35:549-56.

4. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180-191.

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 1/13)

Large, placebo-controlled trials (Cochrane risk of bias 2.0)

Author (year)	Year	Sample size	Bias arising from the randomization process	Bias due to deviations from intended interventions	Pain*			Function*		
					Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results
Shichikawa	1983	228	Some concerns	High	High	Some concerns	Some concerns	-	-	-
Puhl	1993	209	Some concerns	High	High	Low	Some concerns	High	Low	Some concerns
Lohmander	1996	240	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Altman & Moskowitz	1998	332	Some concerns	High	High	Low	Some concerns	High	Low	Some concerns
Brandt‡	2001	226	Low	Low	-	-	-	-	-	-
Seikagaku [UK]	2001	231	Some concerns	Low	Low	Low	High	Low	Low	High
Jubb	2003	408	Low	Low	Low	Low	Some concerns	-	-	-
Altman	2004	347	Some concerns	Low	Low	Low	Low	Low	Low	Low
Day	2004	240	Some concerns	Low	Low	Low	Low	Low	Low	Low
Pham	2004	216	Low	Low	Low	Low	Some concerns	Low	Low	Some concerns
Altman	2009	588	Low	Low	Some concerns	Low	Low	Some concerns	Low	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 2/13)

Large, placebo-controlled trials (Cochrane risk of bias 2.0)

Author (year)	Year	Sample size	Bias arising from the randomization process	Bias due to deviations from intended interventions	Pain*			Function*		
					Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results
Baltzer	2009	242	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Chevalier	2010	253	Low	Low	Low	Low	Low	Low	Low	Low
Jørgensen	2010	337	Low	Low	Low	Low	Low	Low	Low	Low
Huang	2011	200	Some concerns	Low	Low	Low	Low	Low	Low	Low
Strand	2012	379	Low	Low	Low	Low	Low	Low	Low	Low
NCT00988091	2012	596	Some concerns	Low	Low	Low	Low	Low	Low	Low
Arden	2014	218	Low	Low	Low	Low	Low	Low	Low	Low
NCT01372475	2015	800	Low	Low	Low	Low	Low	-	-	-
NCT01934218	2017	814	Low	Low	Low	Low	Low	-	-	-
Hangody	2017	219	Low	Low	Low	Low	Low	Low	Low	Low
Petterson and Plantcher	2018	369	Low	Low	Low	Low	Low	Low	Low	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 3/13)

Large, placebo-controlled trials (Cochrane risk of bias 2.0)

Author (year)	Year	Sample size	Bias arising from the randomization process	Bias due to deviations from intended interventions	Pain*			Function*		
					Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results
NCT02495857*	2018	599	Low	Low	Low	Low	Low	Low	Low	Low
Ke	2021	440	Some concerns	Low	Low	Low	Low	-	-	-
Migliore	2021	692	Some concerns	Low	Low	Low	Low	Low	Low	Low

* Pain and function were assessed separately for the following domains: bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported results. Pain was reported in 24 trials, and function was reported in 19 trials.
‡ Brandt et al. (2001) reported only subgroup analyses for pain and function.

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 4/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Adams	1995	71	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear		
Ardic	2001	20	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	High/unclear		
Aslan	2012	29	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Atay	2008	45	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Bao	2018	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Başar	2021	76	Low	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Bayramoğlu	2003	46	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Belyaeva	2019	70	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Blanco	2008	52	High/unclear	Low	No/unclear	Published	Low	High/unclear	Low	High/unclear
Bragantini	1987	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Bunyaratavej	2001	49	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear		
Bütün	2000	56	High/unclear	High/unclear	No/unclear	Unpublished	Low	High/unclear		

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 5/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Campos	2017	103	High/unclear	High/unclear	yes	Published	High/unclear	High/unclear	High/unclear	High/unclear
Cao	2013	100	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Caracuel	2001	27	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Carrabba	1995	80	High/unclear	Low	No/unclear	Published	Low	Low	Low	Low
Chareancholvanich	2014	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Cohen	1994	39	High/unclear	High/unclear	No/unclear	Unpublished	Low	High/unclear		
Corrado	1995	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Creamer	1994	24	High/unclear	High/unclear	No/unclear	Published	Low	Low		
Cubukçu	2005	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
DeCaria	2012	30	High/unclear	Low	yes	Published	Low	Low	Low	Low
Dhaundiyal	2020	100	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Dickson	2001	110	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	High/unclear	High/unclear
Ding	2017	47	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Diracoglu	2009	63	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	High/unclear	High/unclear
Dixon	1988	63	High/unclear	Low	No/unclear	Published	Low	High/unclear	Low	High/unclear

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 6/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Dong	2012	63	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Dougados	1993	110	Low	Low	No/unclear	Published	High/unclear	High/unclear	Low	High/unclear
Erdem	2007	42	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Fang	2006	160	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Farr	2019	132	Low	Low	No/unclear	Published	Low	High/unclear	Low	High/unclear
Feng	2016	110	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Gang	2015	80	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Ghirardini	1990	10	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	High/unclear		
Giombini	2016	47	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Grecomoro	1987	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Guler	1996	30	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Görmeli	2017	91	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Hamdan	2020	20	High/unclear	High/unclear	yes	Published	High/unclear	Low	High/unclear	Low
Hatipoglu	2002	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
He	2010	226	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Hempfling	2007	80	High/unclear	Low	No/unclear	Published	Low	Low	Low	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 7/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Henderson	1994	91	High/unclear	Low	No/unclear	Published	Low	High/unclear		
Henrotin	2017	81	High/unclear	Low	No/unclear	Published	Low	Low	Low	Low
Hermans	2019	156	High/unclear	High/unclear	yes	Published	High/unclear	Low	High/unclear	Low
Heybeli	2008	67	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Hiemstra	2012	28	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	High/unclear	High/unclear	High/unclear
Hizmetli	2002	50	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Horey	2014	40	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	Low	High/unclear	Low
Hu	2014	270	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Hu	2011	102	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Huang	2005	140	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	Low	High/unclear
Huskisson	1999	100	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	Low	High/unclear
Husni	2017	42	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	Low		
Jacob	2017	51	High/unclear	High/unclear	yes	Published	High/unclear	Low	High/unclear	Low
Jiang	2012	108	High/unclear	High/unclear	No/unclear	Published			High/unclear	Low
Kahan	2003	518	Low	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Kalay	1997	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 8/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Karlsson	2002	246	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	High/unclear	High/unclear
Ke	2016	100	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Kosuwon	2012	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Kotevoglu	2006	59	High/unclear	High/unclear	yes	Published	Low	High/unclear	High/unclear	High/unclear
Kul-Panza	2010	48	High/unclear	High/unclear	yes	Published	Low	High/unclear	High/unclear	High/unclear
Lana	2016	69	High/unclear	High/unclear	yes	Published	High/unclear	High/unclear	High/unclear	High/unclear
Lertwanich	2016	20	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Li	2014	80	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Li	2011	81	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Li	2012	96	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Lin	2017	54	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Lin	2019	56	High/unclear	Low	yes	Published	High/unclear	Low	High/unclear	Low
Listrat	1997	39	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Liu	2014	80	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Luchikhina	2013	82	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Lude	2015	58	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Lundsgaard	2008	168	Low	Low	No/unclear	Published	Low	High/unclear	Low	High/unclear
Maia	2019	28	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 9/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Miltner	2002	86	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Moreland	1993	93	High/unclear	High/unclear	No/unclear	Unpublished	Low	High/unclear	High/unclear	High/unclear
Neustadt	2005	372	Low	High/unclear	No/unclear	Published	Low	High/unclear	Low	High/unclear
Pal	2017	150	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Pan	2011	53	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Pang	2013	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Pereira	2019	22	High/unclear	High/unclear	yes	Published	High/unclear	Low	High/unclear	Low
Petrella	2008	200	High/unclear	Low	No/unclear	Published	Low	Low	Low	Low
Petrella	2002	60	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	Low	High/unclear
Petrella	2009	30	High/unclear	High/unclear	No/unclear	Unpublished	Low	High/unclear	High/unclear	High/unclear
Petrella	2006	106	Low	Low	No/unclear	Published	Low	Low		
Pineda	2017	62	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Qian	2014	66	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Qin	2016	50	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 10/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Qiu	2015	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Rabi'u and Aliyu	2019	52	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Raynauld	2002	255	Low	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Rejaili	2005	20	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Ren	2017	128	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Russell	1992	139	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	High/unclear	High/unclear
Rydell	1972	28	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Saccomanno	2016	110	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Scale	1994	30	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	High/unclear	High/unclear
Scale	1994	50	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear	High/unclear	High/unclear
Schirmeisen	2009	30	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	High/unclear	High/unclear	High/unclear
Schneider	1997	36	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Seikagaku (France)	2001	254	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	High/unclear	High/unclear	High/unclear
Sezgin	2005	41	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Shen	2013	64	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 11/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Shen	2007	84	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Shichikawa	1983	107	Low	High/unclear	No/unclear	Published	Low	High/unclear	Low	High/unclear
Shmidt	2014	18	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Su	2017	80	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Sun	2021	85	Low	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Tamir	2001	49	High/unclear	High/unclear	No/unclear	Published	Low	High/unclear		
Teng	2008	38	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Tetik	2003	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear
Trofimov	2018	61	High/unclear	High/unclear	No/unclear	Published			High/unclear	High/unclear
van Der Weegen	2014	196	Low	Low	No/unclear	Published	Low	Low	Low	Low
Wang	2009	62	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Wang	2009	98	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Wang	2011	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Wang	2013	39	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Wang	2013	70	High/unclear	High/unclear	No/unclear	Published			High/unclear	Low
Wang	2015	92	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 12/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publication status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Wei	2013	120	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Wei	2016	100	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Weiss	1981	32	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Westrich	2009	43	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear		
Wobig	1998	117	High/unclear	Low	No/unclear	Published	Low	High/unclear	Low	High/unclear
Wu	2004	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Xu	2015	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Xu	2020	100	High/unclear	Low	No/unclear	Published	Low	High/unclear	Low	High/unclear
Yang	2010	128	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Yang	2014	80	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Yang	2015	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Ye	2016	90	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
You	2016	60	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Yu	2014	78	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Yuan	2013	110	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low

Web-appendix 12. Risk of bias in the included trials – according to the Cochrane risk of bias tool 2.0 for large, placebo-controlled trials (n = 25) and Cochrane risk of bias 1.0 for the remaining trials (n = 144) (n = 169 trials in total) (part 13/13)

(Cochrane risk of bias 1.0)

Author	Year	Sample size*	Allocation concealment	Blinding of patients	Is funding independent of the industry?	Publications status	Blinding of outcome assessor (pain)	Attrition bias (pain)	Blinding of outcome assessor (function)	Attrition bias (function)
Zang	2011	40	High/unclear	High/unclear	No/unclear	Unpublished	High/unclear	Low	High/unclear	Low
Zeng	2017	90	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Zhang	2009	78	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Zhang	2011	106	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low	High/unclear	Low
Zhao	2010	105	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Zhou	2016	88	High/unclear	High/unclear	No/unclear	Published	High/unclear	Low		
Сорока	2009	40	High/unclear	High/unclear	No/unclear	Published	High/unclear	High/unclear	High/unclear	High/unclear

High denotes high risk of bias
Unclear denotes unclear risk of bias
Low denotes low risk of bias

* The 169 trials included 21,163 randomized participants.

Some domains were not evaluated, because pain or function outcomes may not have been reported (or could not be extracted).

References of the included trials

Adams, M. E., Atkinson, M. H., Lussier, A. J., Schulz, J. I., Siminovitch, K. A., Wade, J. P., & Zummer, M. (1995). The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis and Cartilage*, *3*(4), 213–225.

Altman, R. D., & Moskowitz, R. (1998). Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: A randomized clinical trial. Hyalgan Study Group. *The Journal of Rheumatology*, *25*(11), 2203–2212.

Altman, Roy D., Akermark, C., Beaulieu, A. D., Schnitzer, T., & Durolane International Study Group. (2004). Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis and Cartilage*, *12*(8), 642–649. https://doi.org/10.1016/j.joca.2004.04.010

Altman, Roy D., Rosen, J. E., Bloch, D. A., Hatoum, H. T., & Korner, P. (2009). A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). *Seminars in Arthritis and Rheumatism*, *39*(1), 1–9. https://doi.org/10.1016/j.semarthrit.2009.04.001

Arden, N. K., Åkermark, C., Andersson, M., Todman, M. G., & Altman, R. D. (2014). A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. *Current Medical Research and Opinion*, *30*(2), 279–286. https://doi.org/10.1185/03007995.2013.855631

Ardic, F., Bolulu, D., Topuz, O., & Cubuk﷽u, S. (2001). Efficacy of intra-articular hyaluronic acid injections in knee osteoarthritis [Abstract 75]. *Ann.Rheum.Dis.*, *60*(Suppl 1), 232.

Aslan, A., Kirdemir, V., Atay, T., Baykal, Y. B., Aytekin, O., & Aydogan, F. C. (2012). The efficacy of intra-articular injection of hyaluronic acid with supplemental peroral vitamin E following arthroscopic debridement in the treatment of knee osteoarthritis: A prospective, randomized, controlled study /Diz osteoartritli hastalarda artroskopik debridman sonrasi eklemici hyaluronik asitle birlikte peroral E vitamini tedavisinin etkinligi: prospektif, randomize, kontrollu calisma. *Turkish Journal of Physical Medicine and Rehabilitation*, *58*(3), 199–204.

Atay, T., Aslan, A., Baydar, M. L., Ceylan, B., Baykal, B., & Kirdemir, V. (2008). [The efficacy of low- and high-molecular-weight hyaluronic acid applications after arthroscopic debridement in patients with osteoarthritis of the knee]. *Acta Orthopaedica Et Traumatologica Turcica*, *42*(4), 228–233. https://doi.org/10.3944/aott.2008.228

Baltzer, A. W. A., Moser, C., Jansen, S. A., & Krauspe, R. (2009). Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthritis and Cartilage*, *17*(2), 152–160. https://doi.org/10.1016/j.joca.2008.06.014

Bao, X., Tan, J.-W., Flyzik, M., Ma, X.-C., Liu, H., & Liu, H.-Y. (2018). Effect of therapeutic exercise on knee osteoarthritis after intra-articular injection of botulinum toxin type A, hyaluronate or saline: A randomized controlled trial. *Journal of Rehabilitation Medicine*, *50*(6), 534–541. https://doi.org/10.2340/16501977-2340

Başar, B., Başar, G., Büyükkuşçu, M. Ö., & Başar, H. (2021). Comparison of physical therapy and arthroscopic partial meniscectomy treatments in degenerative meniscus tears and the effect o combined hyaluronic acid injection with these treatments: A randomized clinical trial. *Journal of Back and Musculoskeletal Rehabilitation*, (Preprint), 1-8.

Bayramoğlu, M., Karataş, M., Cetin, N., Akman, N., Sözay, S., & Dilek, A. (2003). Comparison of two different viscosupplements in knee osteoarthritis—A pilot study. *Clinical Rheumatology*, *22*(2), 118–122. https://doi.org/10.1007/s10067-002-0691-0

Belyaeva, E. A., & Avdeeva, O. S. (2019). Эффективность комплексной терапии с применением инъекционной формы хондроитина сульфата и гиалуроната натрия при остеоартрите коленного сустава [The effectiveness of complex therapy using the injectable form of chondroitin sulfate and sodium hyaluronate with osteoarthritis of the knee joint]. *ТЕРАПЕВТИЧЕСКИЙ АРХИВ [Therapeutic Archive]*, *91*(5), 96–102.

Blanco, F. J., Fernández-Sueiro, Pinto-Tasende, J. A., Fernández-López, J. C., Ramallal, M., Freire, A., & Galdo, F. (2008). Intra-Articular Hyaluronan Treatment of Patients with Knee Osteoarthritis Waiting for Replacement Surgery. *The Open Arthritis Journal*, *1*(1). https://doi.org/10.2174/1876539400801010001

Bragantini, A., Cassini, M., DeBastiani, G., & Perbellini, A. (1987). Controlled single-blind trial of intra-articularly injected hyaluronic-acid (Hyalgan) in osteoarthritis of the knee. *Clinical Trials Journal*, *24*(4), 333–340.

Brandt, K.D., Block, J.A., Michalski, J.P., Moreland, L.W., Caldwell, J.R., Lavin, P.T., ORTHOVISC Study Group. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. Clinical Orthopaedics and Related Research®. 2001 Apr 1;385:130-43.

Bunyaratavej, N., Chan, K. M., & Subramanian, N. (2001). Treatment of painful osteoarthritis of the knee with hyaluronic acid. Results of a multicenter Asian study. *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet*, *84 Suppl 2*, S576-581.

Bütün, B., Kaçar, C., & Evcik, D. (2002). Intraarticular injection of sodium hyaluronate in the treatment of knee osteoarthritis. *Rheumatism*, *17*, 31–38.

Campos, A. L. S., E Albuquerque, R. S. P., da Silva, E. B., Fayad, S. G., Acerbi, L. D., de Almeida, F. N., Ooka, N. H. M., Franco, J. S., & Gameiro, V. S. (2017). Viscosupplementation in patients with severe osteoarthritis of the knee: Six month follow-up of a randomized, double-blind clinical trial. *International Orthopaedics*, *41*(11), 2273–2280. https://doi.org/10.1007/s00264-017-3625-9

Cao, G., Hu, J., & Wang, C. (2013). 独活寄生汤加减结合透明质酸钠针关节腔注射治疗膝骨性关节炎 [Clinical efficacy observation of duhuo jisheng decoction combined sodium hyaluronate injection intra-articular cavity injection in treatment of knee osteoarthritis]. *中国实验方剂学杂 [Chinese Journal of Experimental Traditional Medical Formulae]*, *12*(18), 305–308.

Caracuel, M., Muñoz-Villanueva, M., Escudero, A., Veroz, R., Frias, G., Vacas, J., Perez, C., Romero, M., Perez, V., Gonzalez, J., Martinez, F., & Collantes, E. (2001). SAT0091 Effects of joint lavage and hyaluronic acid infiltration in patients with osteoarthritis of the knee. *Annals of the Rheumatic Diseases*, *60*(Suppl 1), A184. https://doi.org/10.1136/annrheumdis-2001.466

Carrabba, M., Paresce, E., Angelini, M., Re, K. A., Torchiana, E. E. M., & Perbellini, A. (1995). The safety and efficacy of different dose schedules of hyaluronic acid in the treatment of painful osteoarthritis of the knee with joint effusion. *European Journal of Rheumatology and Inflammation*, *15*(1), 25–31. EPISTEMONIKOS.

Chareancholvanich, K., Pornrattanamaneewong, C., & Narkbunnam, R. (2014). Increased cartilage volume after injection of hyaluronic acid in osteoarthritis knee patients who underwent high tibial osteotomy. *Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*, *22*(6), 1415–1423. https://doi.org/10.1007/s00167-013-2735-1

Chevalier, X., Jerosch, J., Goupille, P., van Dijk, N., Luyten, F. P., Scott, D. L., Bailleul, F., & Pavelka, K. (2010). Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double-blind, placebo controlled trial. *Annals of the Rheumatic Diseases*, *69*(1), 113–119. https://doi.org/10.1136/ard.2008.094623

Cohen, M., Shiroky, J., Ballachey, M., Neville, C., & Esdaile, J. (1994). *Double-blind randomized trial of intraarticular (I/A) hyaluronate in the treatment of osteoarthritis of the knee*. *37*, R31–R31.

Corrado, E., Peluso, G., Gigliotti, S., Durante, C., Palmieri, D., Savoia, M., Oriani, G., & Tajana, G. (1995). The effects of intra-articular administration of Hyaluronic acid on osteoarthritis of the knee: A clinical study with immunological and biochemical evaluations. *European Journal of Rheumatology and Inflammation*, *15*, 47–56.

Creamer, P., Sharif, M., George, E., Meadows, K., Cushnaghan, J., Shinmei, M., & Dieppe, P. (1994). Intra-articular hyaluronic acid in osteoarthritis of the knee: An investigation into mechanisms of action. *Osteoarthritis and Cartilage*, *2*(2), 133–140. https://doi.org/10.1016/s1063-4584(05)80063-9

Cubukçu, D., Ardiç, F., Karabulut, N., & Topuz, O. (2005). Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: Clinical and MRI assessment. *Clinical Rheumatology*, *24*(4), 336–341. https://doi.org/10.1007/s10067-004-1043-z

Day, R., Brooks, P., Conaghan, P. G., Petersen, M., & Multicenter Trial Group. (2004). A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. *The Journal of Rheumatology*, *31*(4), 775–782.

DeCaria, J. E., Montero-Odasso, M., Wolfe, D., Chesworth, B. M., & Petrella, R. J. (2012). The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: A randomized, controlled study. *Archives of Gerontology and Geriatrics*, *55*(2), 310–315. https://doi.org/10.1016/j.archger.2011.11.007

Dhaundiyal, S., & Joshi, D. (2020). The Role of Intra-Articular Viscosupplementation in Treatment of Early Osteoarthritis of Knee: An Interventional Study. *Journal of Medical Science and Clinical Research*, *8*(8), 268–280.

Dickson, D., Hosie, G., & English, J. (2001). A double-blind, placebo-controlled comparison of hylan GF 20 against diclofenac in knee osteoarthritis. *JOURNAL OF DRUG ASSESSMENT*, *4*(3), 179–190.

Ding, Q., Lv, S., Shen, X., & Tong, P. (2017). 富血小板血浆联合透明质酸钠关节内注射治疗膝骨关节炎的前瞻性随机对照研究 [A prospective randomized controlled study on platelet-rich plasma (PRP)combined with sodium hyaluronate (HA) intra-articular injection in the treatment of knee osteoarthritis]. *Shanghai Medical and Pharmaceutical Journal*, *38*(5), 25–28.

Diracoglu, D., Vural, M., Baskent, A., Dikici, F., & Aksoy, C. (2009). The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. *Journal of Back and Musculoskeletal Rehabilitation*, *22*(1), 1–9. https://doi.org/10.3233/BMR-2009-0207

Dixon, A. S., Jacoby, R. K., Berry, H., & Hamilton, E. B. (1988). Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Current Medical Research and Opinion*, *11*(4), 205–213. https://doi.org/10.1185/03007998809114237

Dong, X., Yang, Y., Zibin, Y., Zhengxiang, W., Qiao, L. V., & Ruan, A. (2012). 关节镜有限清理联合玻璃酸钠治疗老年膝 性关节炎疗效分析 [Analysis of selective arthroscopy debridement combination with sodium hyaluronate in treating elderly knee osteoarthritis]. *中国现代医生 [China Modern Doctor]*, *50*, 41–42.

Dougados, M., Nguyen, M., Listrat, V., & Amor, B. (1993). High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: A 1 year placebo-controlled trial. *Osteoarthritis and Cartilage*, *1*(2), 97–103. https://doi.org/10.1016/s1063-4584(05)80024-x

Erdem, F., & Karatay, S. (2007). Diz Osteoartriti Tedavisinde Hyaluronik Asitin Agri ve Kuadriseps Kasi Agirlik Kaldirma G�c�ne Etkisi [The Effects of Hyaluronic Acid on Pain and Lifting Mass Power of Quadriceps Muscle in Knee Osteoarthritis Treatment]. *The Eurasian Journal of Medicine*, *39*, 28–32.

Fang, Z., Li, F., Xiong, W., & Li, G. (2006). 维骨力联合透明质酸钠关节内注射治疗膝骨性关节炎的疗效观察 [Therapeutic effect of intra—Articular injection of hyaluronic acid and vitamin B vitality on knee osteoarthritis]. *Chinese Journal of Gerontology [中国老年学杂志]*, *26*(7), 871–871.

Farr, J., Gomoll, A. H., Yanke, A. B., Strauss, E. J., Mowry, K. C., & ASA Study Group. (2019). A Randomized Controlled Single-Blind Study Demonstrating Superiority of Amniotic Suspension Allograft Injection Over Hyaluronic Acid and Saline Control for Modification of Knee Osteoarthritis Symptoms. *The Journal of Knee Surgery*, *32*(11), 1143–1154. https://doi.org/10.1055/s-0039-1696672

Feng, Y. (2016). 膝骨关节炎应用玻璃质酸钠与硫酸氨基葡萄糖治疗的效果研究 [Study on the effect of sodium hyaluronate and sulfuric acid amino glucose in the treatment of knee osteoarthritis]. *中国社区医师 [Chinese Community Doctors]*, *32*(35), 38–39.

Ferring Pharmaceuticals. (2012). *A 26 Week, Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Single Intra-Articular Injection 1.2% Sodium Hyaluronate for Treatment of Painful Osteoarthritis of the Knee, With Optional 26-Week Open-Label Safety Extension* (Clinical Trial Registration No. NCT00988091). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT00988091

Fidia Farmaceutici s.p.a. (2014). *A Multi-Centre, Double-Blind, Randomized, Placebo Controlled Study To Evaluate The Safety And Effectiveness Of A New Viscoelastic Hydrogel (Hymovis)*

In The Treatment Of Knee OA With An Open-Label Extension (Clinical Trial Registration No. NCT01372475). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01372475 and https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150010b.pdf (last access: October 21, 2021)

Gang, L., Yang, Y., Hu, S., Huang, P., Liu, Z., & Gao, C. (2015). 补肾活血祛湿除痹法联合玻璃酸钠治疗膝骨性关节炎的临床研究 [Clinical research of bushen huoxue qushi chubi decoction combined with hyaluronic acid in the treatment of knee osteoarthritis]. *J Med Res [医学研究杂志]*, *44*(9), 134–138.

Ghirardin, M., Betelemme, L., & Fatti, L. (1990). Impiego intraarticolare di acido ialuronico estrattivo de orgoteina sia separatamente che in associazione in pazienti affetti da gonartrosi in fase sinovitica [Intra-articular use of orgotein, hyaluronic acid or both in patients suffering from gonarthrosis in the synovitic phase] [Abstract]. *Reumatismo.*, *42*, 132.

Giombini, A., Menotti, F., Di Cesare, A., Giovannangeli, F., Rizzo, M., Moffa, S., & Martinelli, F. (2016). Comparison between intrarticular injection of hyaluronic acid, oxygen ozone, and the combination of both in the treatment of knee osteoarthrosis. *Journal of Biological Regulators and Homeostatic Agents*, *30*(2), 621–625.

Görmeli, G., Görmeli, C. A., Ataoglu, B., Çolak, C., Aslantürk, O., & Ertem, K. (2017). Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*, *25*(3), 958–965. https://doi.org/10.1007/s00167-015-3705-6

Grecomoro, G., Martorana, U., & Di Marco, C. (1987). Intra-articular treatment with sodium hyaluronate in gonarthrosis: A controlled clinical trial versus placebo. *Pharmatherapeutica*, *5*(2), 137–141.

Guler, M., Kuran, B., Parlar, D., Guler, M., Saglam, H., Yapici, S., Guzeloglu, S., Ozgul Mese, F., & Bonveval, F. (1996). *Clinical trial of intra-articular injection of hyaluronic acid in patients with osteoarthritis of the knee*. *29*.

Hamdan, P., Miranda, H., Paula, T., Nicoliche, E., Cossich, V., & Salles Neto, J. (2020). Isokinetic response, viscosupplementation and strength training in gonarthrosis. *Revista Brasileira.de Medicina Do.Esporte.*, *26*(3), 258–261.

Hangody, L., Szody, R., Lukasik, P., Zgadzaj, W., Lénárt, E., Dokoupilova, E., Bichovsk, D., Berta, A., Vasarhelyi, G., & Ficzere, A. (2018). Intraarticular injection of a cross-linked sodium hyaluronate combined with triamcinolone hexacetonide (Cingal) to provide symptomatic relief of osteoarthritis of the knee: A randomized, double-blind, placebo-controlled multicenter clinical trial. *Cartilage*, *9*(3), 276–283.

Hatipoglu, F., Cogalgil, S., & Cerrahoglu, L. (2002). FiziK TEDAVi UYGULANAN GONARTROZLU HASTALARDA iNTRAARTiKULER SODYUM-HYALURONANIN ETKiLERi [The effects of intra-articular sodium-hyaluronan in patients with gonarthrosis treated with physical therapy]. *Journal of Physical Education and Sport Sciences*, *4*(1), 5–11.

He, Z. (2010). 透明质酸钠关节腔内注射治疗膝关节炎临床观察 [The Clinical Observation of Sodium Hyaluronate Injection for Knee Osteoarthritis]. *医学信息: 下旬刊 [Medical Information]*, *23*(6), 61–61.

Hempfling, H. (2007). Intra-articular hyaluronic acid after knee arthroscopy: A two-year study. *Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*, *15*(5), 537–546. https://doi.org/10.1007/s00167-006-0260-1

Henderson, E. B., Smith, E. C., Pegley, F., & Blake, D. R. (1994). Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: A randomised single centre double-blind

placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Annals of the Rheumatic Diseases*, *53*(8), 529–534. https://doi.org/10.1136/ard.53.8.529

Henrotin, Y., Berenbaum, F., Chevalier, X., Marty, M., Richette, P., & Rannou, F. (2017). Reduction of the Serum Levels of a Specific Biomarker of Cartilage Degradation (Coll2-1) by Hyaluronic Acid (KARTILAGE® CROSS) Compared to Placebo in Painful Knee Osteoarthritis Patients: The EPIKART Study, a Pilot Prospective Comparative Randomized Double Blind Trial. *BMC Musculoskeletal Disorders*, *18*(1), 222. https://doi.org/10.1186/s12891-017-1585-2

Hermans, J., Bierma-Zeinstra, S. M. A., Bos, P. K., Niesten, D. D., Verhaar, J. A. N., & Reijman, M. (2019). The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial. *BMC Musculoskeletal Disorders*, *20*(1), 196. https://doi.org/10.1186/s12891-019-2546-8

Heybeli, N., Doral, M. N., Atay, O. A., Leblebicioğlu, G., & Uzümcügil, A. (2008). [Intra-articular sodium hyaluronate injections after arthroscopic debridement for osteoarthritis of the knee: A prospective, randomized, controlled study]. *Acta Orthopaedica Et Traumatologica Turcica*, *42*(4), 221–227. https://doi.org/10.3944/aott.2008.221

Hiemstra, L., Kerslake, S., Heard, M., & Buchko, G. (2012). Postoperative Pain and Function in Patients Having a Knee Arthroscopy With Viscosupplementation or Placebo Injection at the Time of Surgery: A Pilot Study [Additional unpublished data]. *Clin J Sport Med*, *22*(3), 300.

Hizmetli, S., Kocagil, S., Kaptanoglu, E., Elden, H., & Nacitarhan, V. (2002). *The efficacy and safety of intra-articular hyaluronic acid in osteoarthritis of the knee: A prospective, double-blind trial. Pamphlet provided at the European League Against Rheumatism*. 12–15.

Hu, X., & Liu, H. (2011). 臭氧联用透明质酸钠治疗膝关节骨性关节炎疗效[Effects of ozone combined with sodium hyaluronate in the treatment of osteoarthritis of knee]. *中国临床药理学杂志 [Chin J Clin Pharmacol]*, *27*(8), 584–586.

Hu, Z. (2014). 关节镜下清理术联合透明质酸钠注射治疗老年膝骨关节炎疗效观察

[Arthroscopic debridement combined with sodium hyaluronate injection in the treatment of senile knee osteoarthritis]. *Shandong Medical University [山东医药]*, *54*(48), 60–62.

Huang, M.-H., Yang, R.-C., Lee, C.-L., Chen, T.-W., & Wang, M.-C. (2005). Preliminary results of integrated therapy for patients with knee osteoarthritis. *Arthritis and Rheumatism*, *53*(6), 812–820. https://doi.org/10.1002/art.21590

Huang, T.-L., Chang, C.-C., Lee, C.-H., Chen, S.-C., Lai, C.-H., & Tsai, C.-L. (2011). Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee. A randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskeletal Disorders*, *12*, 221. https://doi.org/10.1186/1471-2474-12-221

Huo, L. (2014). 明质酸钠注射配合自体富血小板血浆注射治疗膝骨关节炎的临床及实验研究

[Clinical and experimental study of sodium hyaluronate injection combined with autologous platelet-rich plasma injection for treatment of knee osteoarthritis]. *Doctoral Dissertation, Suzhou University*.

Huskisson, E. C., & Donnelly, S. (1999). Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford, England)*, *38*(7), 602–607. https://doi.org/10.1093/rheumatology/38.7.602

Husni, E. (2017). Optimization of Synvisc-One for Knee OA (NCT02029703). *Clinicaltrials.Gov*.

Jacob, G., Shetty, V., & Shetty, S. (2017). A study assessing intra-articular PRP vs PRP with HMW HA vs PRP with LMW HA in early knee osteoarthritis. *Journal of Arthroscopy and Joint Surgery*, *4*(2), 65–71. https://doi.org/10.1016/j.jajs.2017.08.008

Jiang, D. (2012). 口服盐酸氨基葡萄糖和注射透明质酸钠以及

两者联合治疗膝关节骨性关节炎的临床研究 [A Randomized Controlled Clinical Trial of

Glucosamine Hydrochloride Hyaluronic Acid and Combined Use in the Treatment of Knee Osteoarthritis]. *医学研究杂志 [J Med Res]*, *41*(5), 173–176.

Jørgensen, A., Stengaard-Pedersen, K., Simonsen, O., Pfeiffer-Jensen, M., Eriksen, C., Bliddal, H., Pedersen, N. W., Bødtker, S., Hørslev-Petersen, K., Snerum, L. Ø., Egund, N., & Frimer-Larsen, H. (2010). Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: A multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Annals of the Rheumatic Diseases*, *69*(6), 1097–1102. https://doi.org/10.1136/ard.2009.118042

Jubb, R. W., Piva, S., Beinat, L., Dacre, J., & Gishen, P. (2003). A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. *International Journal of Clinical Practice*, *57*(6), 467–474.

Kahan, A., Lleu, P.-L., & Salin, L. (2003). Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. Conventional treatment in knee osteoarthritis. *Joint Bone Spine*, *70*(4), 276–281. https://doi.org/10.1016/s1297-319x(03)00043-5

Kalay, S. (1997). The effectiveness of intra-articular hyaluronic acid treatment in primary gonarthrosis. *[Specialization Thesis]*.

Karlsson, J., Sjögren, L. S., & Lohmander, L. S. (2002). Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford, England)*, *41*(11), 1240–1248. https://doi.org/10.1093/rheumatology/41.11.1240

Ke, C., Zhang, R., & Xue, J. (2016). 富血小板血浆联合透明质酸关节腔内注射治疗膝骨关节炎疗效分析 [Clinical efficacy of autologous platelet-rich plasma combined

with intra-articular hyaluronic acid injection for knee osteoarthritis]. *中华全科医学 [Chinese Journal of General Practice]*, *14*(11), 1810–1812.

Ke Y., Jiang W., Xu Y., Chen Y., Zhang Q., Xue Q., Lin J., Ngai W., Nian G., Fazeli MS., & Xie Y (2021). Efficacy and safety of a single intra-articular injection of 6 ml Hylan GF 20 Compared to placebo in Chinese patients with symptomatic knee osteoarthritis. *BMC Musculoskeletal Disorders*. 22(1):1-2.

Kosuwon, W., Sirichatiwapee, W., Visanuyotin, T., Jeeravipoolvarn, P., & Laupattarakasem, W. (2012). Determination of cartilage volume using MRI in patients with knee osteoarthritis: Efficacy study of 25 milligrams of sodium hyaluronate (2.5 Ml) versus placebo. *Clin Exp Pharmacol*, *2*(2), 1.

Kotevoglu, N., Iyibozkurt, P. C., Hiz, O., Toktas, H., & Kuran, B. (2006). A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. *Rheumatology International*, *26*(4), 325–330. https://doi.org/10.1007/s00296-005-0611-0

Kul-Panza, E., & Berker, N. (2010). Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. *Minerva Medica*, *101*(2), 63–72.

Lana, J. F. S. D., Weglein, A., Sampson, S. E., Vicente, E. F., Huber, S. C., Souza, C. V., Ambach, M. A., Vincent, H., Urban-Paffaro, A., Onodera, C. M. K., Annichino-Bizzacchi, J. M., Santana, M. H. A., & Belangero, W. D. (2016). Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *Journal of Stem Cells & Regenerative Medicine*, *12*(2), 69–78.

Lertwanich, P., & Lamsam, C. (2016). Efficacy of a Single Intra-Articular Injection of 2% Sodium Hyaluronate Plus 0.5% Mannitol in Patients with Symptomatic Osteoarthritis of the Knee: A

Preliminary Report. *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet*, *99*(10), 1094–1101.

Li, C., Wang, N., Bi, D., Ma, H., & Xu, H. (2014). 关节镜清理术联合透明质酸钠治疗膝关节骨性关节炎的临床疗效研究 [Clinical effect of arthroscopic debridement combined with injection of sodium hyaluronate in articular cavity in the treatment of knee osteoarthritis]. *Journal of Shanxi College of Traditional Chinese Medicine*, *15*, 65–67.

Li, J. (2012). 透明质酸钠联合双氯芬酸钠治疗膝骨性关节炎的临床疗效分析 [Analysis of the clinical efficacy of sodium hyaluronate combined with diclofenac sodium in the treatment of knee osteoarthritis]. *Strait Pharmaceutical Journal [海峡药学]*, *24*(1), 150–152.

Li, Y., Liu, J., Li, Z., & Wang, X. (2011). 关节镜术后加玻璃酸钠治疗膝骨陛关节炎疗效研究 [Arthroscopic surgery with sodium hyaluronate in the treatment of knee osteoarthritis]. *Chin J Postgrad Med*, *34*(8), 36–38.

Lin, K.-Y., Yang, C.-C., Hsu, C.-J., Yeh, M.-L., & Renn, J.-H. (2019). Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. *Arthroscopy : The Journal of Arthroscopic & Related Surgery : Official Publication of the Arthroscopy Association of North America and the International Arthroscopy Association*, *35*(1), 106–117. https://doi.org/10.1016/j.arthro.2018.06.035

Lin, Y., Yu, J., & Li, Z. (2017). 经皮穴位电刺激联合透明质酸钠关节腔内注射治疗膝关节骨性关节炎的疗效 [Efficacy of transcutaneous electric acupoint

stimulation combined with intra-articular sodium hyaluronate in the treatment of patients with knee osteoarthritis]. *实用疼痛学杂志 [Pain Clin J]*, *13*(2), 112–115.

Listrat, V., Ayral, X., Patarnello, F., Bonvarlet, J. P., Simonnet, J., Amor, B., & Dougados, M. (1997). Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis and Cartilage*, *5*(3), 153–160. https://doi.org/10.1016/s1063-4584(97)80010-6

Liu, P., Wang, Q., Qiu, X., Chen, Z., & Li, L. (2014). 滞针温针灸配合玻璃酸钠治疗膝骨关节炎时效性观察 [Efficiency observation of sticking-warm needling plus sodium hyaluronate for knee osteoarthritis]. *Shanghai Acupuncture and Moxibustion [上海针灸杂志]*, *33*(8), 748–752.

Lohmander, L. S., Dalén, N., Englund, G., Hämäläinen, M., Jensen, E. M., Karlsson, K., Odensten, M., Ryd, L., Sernbo, I., Suomalainen, O., & Tegnander, A. (1996). Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Annals of the Rheumatic Diseases*, *55*(7), 424–431. https://doi.org/10.1136/ard.55.7.424

Luchikhina, L. V., Mendel, O. A., & Antonov, D. A. (2013). Внутрисуставное введение препарата гиалуроновой кислоты после артроскопического лаважа коленного сустава – отдаленные результаты [Intra-articular injection of hyaluronic acid after arthroscopic lavage of the knee joint—Long-term results]. *Науч-Практич Ревматол [Scientific and Practical Rheumatol]*, *51*(1), 28–33.

Lude, S. (2015). 关节镜清理术联合透明质酸钠注射治疗膝骨关节炎疗效观察 [Arthroscopic debridement combined with sodium hyaluronate injection in the treatment of knee

osteoarthritis]. *Journal of Clinical Psychosomatic Diseases [临床心身疾病杂志]*, *10*, 61–61.

Lundsgaard, C., Dufour, N., Fallentin, E., Winkel, P., & Gluud, C. (2008). Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: A randomized clinical trial. *Scandinavian Journal of Rheumatology*, *37*(2), 142–150. https://doi.org/10.1080/03009740701813103

Maia, P. A. V., Cossich, V. R. A., Salles-Neto, J. I., Aguiar, D. P., & de Sousa, E. B. (2019). Viscosupplementation improves pain, function and muscle strength, but not proprioception, in patients with knee osteoarthritis: A prospective randomized trial. *Clinics (Sao Paulo, Brazil)*, *74*, e1207. https://doi.org/10.6061/clinics/2019/e1207

Migliore, A., Blicharski, T., Plebanski, R., Zegota, Z., Gyula, G., Rannou, F., & Reginster, J. Y. (2021). Knee Osteoarthritis Pain Management with an Innovative High and Low Molecular Weight Hyaluronic Acid Formulation (HA-HL): A Randomized Clinical Trial. *Rheumatology and Therapy*, 1-20.

Miltner, O., Schneider, U., Siebert, C. H., Niedhart, C., & Niethard, F. U. (2002). Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis—A prospective clinical trial. *Osteoarthritis and Cartilage*, *10*(9), 680–686. https://doi.org/10.1053/joca.2002.0815

Moreland, L., Arnold, W., Saway, A., Savory, C., & Sikes, D. (1993). *Efficacy and safety of intraarticular Hylan GF-20 (Synvisc (r)), a viscoelastic derivative of hyaluronan, in patients with osteoarthritis of the knee*. *36*, S165–S165.

Neustadt, D., Caldwell, J., Bell, M., Wade, J., & Gimbel, J. (2005). Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: A randomized, controlled, multicenter trial. *The Journal of Rheumatology*, *32*(10), 1928–1936.

Pal, C., Sadana, A., & Kumar, P. (2017). Therapeutic efficacy of intra-articular hyaluronic acid in osteoarthritis knee. *Journal of Bone and Joint Diseases.*, *32*(1), 49–49.

Pan, Z., Zhang, T., Liu, Y., Zhang, C., Li, C., & Zhu, X. (2011). 玻璃酸钠对老年膝关节炎患者本体感觉的影响 [Effect of intra-articular injection of hyaluronan on proprioception of the knee joint in elderly patients with osteoarthritis]. *中华老年医学杂志 [Chinese Journal of Geriatrics]*, *30*(6), 488–490.

Pang, Y., Zhao, G., & Zhao, Z. (2013). 关节镜清理术配合透明质酸钠在膝关节骨性关节炎中的应用效果 [Arthroscopic debridement combined with sodium hyaluronate in the treatment of osteoarthritis of the knee]. *临床合理用药杂志 [Chinese Journal of Clinical Rational Drug Use]*, *6*(12), 104–106.

Pereira, L. C., Schweizer, C., Moufarrij, S., Krähenbühl, S. M., Favre, J., Gremion, G., Applegate, L. A., & Jolles, B. M. (2019). Gait analysis following single-shot hyaluronic acid supplementation: A pilot randomized double-blinded controlled trial. *Pilot and Feasibility Studies*, *5*, 56. https://doi.org/10.1186/s40814-019-0443-4

Petterson, S. C., & Plancher, K. D. (2019). Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: a multicenter, double-blind, randomized, placebo-controlled trial. *Knee Surgery, Sports Traumatology, Arthroscopy*, *27*(6), 1992-2002.

Petrella, Robert John, DiSilvestro, M. D., & Hildebrand, C. (2002). Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: A randomized, double-blind, placebo-controlled clinical trial. *Archives of Internal Medicine*, *162*(3), 292–298.

Petrella, Robert J., & Petrella, M. (2006). A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *The Journal of Rheumatology*, *33*(5), 951–956.

Petrella, Robert J., Cogliano, A., & Decaria, J. (2008). Combining two hyaluronic acids in osteoarthritis of the knee: A randomized, double-blind, placebo-controlled trial. *Clinical Rheumatology*, *27*(8), 975–981. https://doi.org/10.1007/s10067-007-0834-4

Petrella, R., Decaria, J., Wolfe, D., Chesworth, B., Shapiro, S., & Montero-Odasso, M. (2009). The effect of hyaluronic acid on gait in knee osteoarthritis patients: Preliminary results for a randomized, double-blind, placebo controlled study [Abstract 375]. *Ann Rheum Dis*, *68*(Suppl 3), 479.

Pham, T., Le Henanff, A., Ravaud, P., Dieppe, P., Paolozzi, L., & Dougados, M. (2004). Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Annals of the Rheumatic Diseases*, *63*(12), 1611–1617. https://doi.org/10.1136/ard.2003.019703

Pineda, M. L., Villegas, M. C., Castro, R. O., Ugalde, P. F., Aguilar, L. B., Medina, C. L., Gasco, R. J., Pérez, L. S., Ruiz, M. C., Contreras, A. E., & Collantes, E. E. (2017). SAT0527 Assessment of short-term effectiveness of five local treatment modalities in patients with symptomatic knee osteoarthritis. *Annals of the Rheumatic Diseases*, *76*(Suppl 2), 975. https://doi.org/10.1136/annrheumdis-2017-eular.3555

Puhl, W., Bernau, A., Greiling, H., Köpcke, W., Pförringer, W., Steck, K. J., Zacher, J., & Scharf, H. P. (1993). Intra-articular sodium hyaluronate in osteoarthritis of the knee: A multicenter, double-blind study. *Osteoarthritis and Cartilage*, *1*(4), 233–241. https://doi.org/10.1016/s1063-4584(05)80329-2

Qian, C., & Bian, X. (2014). 玻璃酸钠注射结合乙哌立松口服治疗 膝骨关节炎的疗效分析 [Efficacy of hyaluronan combined with eperisone hydrochloride in treatment of patients with knee osteoarthritis]. *实用临床医药杂志 [Journal of Clinical Medicine in Practice]*, *18*(7), 44–47.

Qin, Y. (2016). 关节镜清理术联合透明质酸钠治疗膝关节骨性关节炎的临床观察 [Clinical observation on arthroscopic debridement combined with injection of sodium hyaluronate in articular cavity in the treatment of knee osteoarthritis]. *中国卫生标准管理 [China Health Standard Management]*, *7*(11), 34–35.

Qiu, M. (2015). 玻璃酸钠联合硫酸氨基葡萄糖治疗膝骨关节炎的疗效 [Therapeutic effect of sodium hyaluronate and glucosamine sulfate in the treatment of knee osteoarthritis]. *药学与临床 [Pharmacy and Clinical Medicine]*, *9*, 139–140.

Rabi'u, M. B., & Aliyu, D. A. (2019). Effect of Addition of Hyaluronic Acid on Platelet Rich Plasma in Treatment of Chronic Osteoarthritis. *EAS J Orthop Physiother*, *1*(6), 63–67.

Raynauld, J.-P., Torrance, G. W., Band, P. A., Goldsmith, C. H., Tugwell, P., Walker, V., Schultz, M., Bellamy, N., & Canadian Knee OA Study Group. (2002). A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): Clinical results. *Osteoarthritis and Cartilage*, *10*(7), 506–517. https://doi.org/10.1053/joca.2002.0798

Rejaili, W. A., Chueire, A. G., Cordeiro, J. A., Petean, F. C., & Carvalho Filho, G. de. (2005). The evaluation of Hilan GF-20 in the postoperative knee arthroscopies for arthrosis. *Acta Ortopédica Brasileira*, *13*(1), 20–23. https://doi.org/10.1590/S1413-78522005000100005

Ren, Z., Du, G., Ma, J., Yang, Z., Gao, G., & Luo, J. (2017). 复方骨肽注射液联合玻璃酸钠治疗膝关节骨性关节炎的临床研究 [Clinical Study of Compound Ossotide Injection Combined with Sodium Hyaluronate in Treatment of knee osteoarthritis]. *现代药物与临床 [Drugs & Clinic]*, *32*(2), 280–283.

Russell, I., Michalek, J., Lawrence, V., Lessard, J., Briggs, B., & May, G. (1992). *A randomized, placebo (PL) and no-intervention (NI) controlled, trial of intraarticular (IA) 1-percent sodium hyaluronate (HA) in the treatment of knee osteoarthritis*. *35*, S132–S132.

Rydell. (1972). *Personal communication (Rydell, 1972) described in: Peyron JG, Balazs EA.Preliminary clinical assessment of Na-hyaluronate injection into human arthritic joints. Pathol Biol (Paris). 1974;22:731-6. [PMID: 4614175]*.

Saccomanno, M. F., Donati, F., Careri, S., Bartoli, M., Severini, G., & Milano, G. (2016). Efficacy of intra-articular hyaluronic acid injections and exercise-based rehabilitation programme, administered as isolated or integrated therapeutic regimens for the treatment of knee osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*, *24*(5), 1686–1694. https://doi.org/10.1007/s00167-015-3917-9

Scale, D., Wobig, M., & Wolpert, W. (1994a). Viscosupplementation of osteoarthritic knees with hylan: A treatment schedule study (Study A). *Current Therapeutic Research*, *55*(3), 220–232. https://doi.org/10.1016/S0011-393X(05)80166-3

Scale, D., Wobig, M., & Wolpert, W. (1994b). Viscosupplementation of osteoarthritic knees with hylan: A treatment schedule study (Study B). *Current Therapeutic Research*, *55*(3), 220–232. https://doi.org/10.1016/S0011-393X(05)80166-3

Schirmeisen, C. (2009). *Evaluation der klinisch-funktionellen Ergebnisse und der Lebensqualität von Patienten mit Kniegelenksarthrose nach Hyaluronsäurebehandlung [Evaluation of the*

clinical-functional results and the quality of life of patients with osteoarthritis of the knee after hyaluronic acid treatment]. Universitätsklinikum Münster.

Schneider, U., Miltner, O., Graf, J., Thomsen, M., & Niethard, F. U. (1997). [Mechanism of action of hyaluronic acid in gonarthrosis of both knee joints in a right/left comparison. Study with dynamometry, oxygen partial pressure, temperature and Lequesne score]. *Zeitschrift Fur Orthopadie Und Ihre Grenzgebiete*, *135*(4), 341–347. https://doi.org/10.1055/s-2008-1039399

Seikagaku Corporation. (2001a). Summary of safety and effectiveness data: Sodiumhyaluronate. Bethesda, MD. U.S. Food and Drug Administration; 2001. [France]. *FDA Report*. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170016B.pdf (last access: October 21, 2021)

Seikagaku Corporation. (2001b). Summary of safety and effectiveness data: Sodiumhyaluronate. Bethesda, MD. U.S. Food and Drug Administration; 2001. [UK]. *FDA Report*. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170016B.pdf (last access: October 21, 2021)

Seikagaku Corporation. (2017). *A Multi-Center, Randomized, Double-Blind, Phosphate Buffered Saline-Controlled Study to Evaluate Effectiveness and Safety of a Single Intra-Articular Injection of Gel-One® for the Treatment of Osteoarthritis of the Knee With Open-Label Safety Extension* (Clinical Trial Registration No. NCT01934218). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01934218 and https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080020S020B.pdf (last access: October 21, 2021)

Sezgin, M., Demirel, A. C., Karaca, C., Ortancil, O., Ulkar, G. B., Kanik, A., & Cakçi, A. (2005). Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? *Rheumatology International*, *25*(4), 264–269. https://doi.org/10.1007/s00296-003-0428-7

Shen, J., Yang, J., & Wang, T. (2007). 透明质酸钠配合物理疗法治疗膝关节骨性关节炎的临床效果 [Clinical Effect of Sodium Hyaluronate Combined with Physiotherapy on Degenerative Osteoarthritis of Knee]. *中国康复 [Chinese Journal of Rehabilitation]*, *22*(6), 411–412.

Shen, S., Zhang, B., Luo, L., & Liu, J. (2013). 局部与关节腔内注射治疗膝骨关节炎临床观察 [Clinical observation of trigger point injection combined with intra-articular injection in the treatment of knee osteoarthritis]. *实用疼痛学杂志 [Pain Clin J]*, *9*(4), 270–273.

Shichikawa, K, Maeda, A., & Ogawa, N. (1983). [Clinical evaluation of sodium hyaluronate in the treatment of osteoarthritis of the knee]. *Ryumach.*, *23*, 280–290.

Shichikawa, Kanji, IGARASHI, M., SUGAWARA, S., & IWASAKI, Y. (1983). Clinical Evaluation of High Molecular Weight Sodium Hyaluro nate (SPH) on Osteoarthritis of the Knee Multi-Center Well Controlled Comparative Study. *Rinsho Yakuri/Japanese Journal of Clinical Pharmacology and Therapeutics*, *14*(3), 545–558.

Shmidt, Y. I., & Belozerova, I. V. (2014). СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ И ПЕРЕНОСИМОСТЬ НЕОМЫЛЯЕМЫХ СОЕДИНЕНИЙ АВОКАДО/СОЕВЫХ БОБОВ И ИХ СОЧЕТАНИЯ С ВНУТРИСУСТАВНЫМ ВВЕДЕНИЕМ ГИАЛУРОНОВОЙ КИСЛОТЫ У БОЛЬНЫХ ОСТЕОАРТРОЗОМ КОЛЕННЫХ И ТАЗОБЕДРЕННЫХ СУСТАВОВ [Comparative efficacy and tolerability of avocado / soybean unsaponifiables And their combination with intra-articular hyaluronic acid In patients with knee and hip osteoarthrosis]. *Клиницист [Clinician]*, *8*(1), 82–86.

Strand, V., Baraf, H. S. B., Lavin, P. T., Lim, S., & Hosokawa, H. (2012). A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of

the knee. *Osteoarthritis and Cartilage*, *20*(5), 350–356. https://doi.org/10.1016/j.joca.2012.01.013

Su, Y., & Lei, X. (2017). 关节腔内注射透明质酸钠联合塞来昔布治疗早中期膝关节骨关节炎的疗效分析 [Clinical efficacy of intra-articular hyaluronate injection combined with celecoxib in treatment of early and mid stage knee osteoarthritis]. *中华关节外科杂志(电子版) [China J Joint Surg]*, *11*(2), 204–208.

Sun, S.-F., Lin, G.-C., Hsu, C.-W., Lin, H.-S., Liou, I.-H. S., & Wu, S.-Y. (2021). Comparing efficacy of intraarticular single crosslinked Hyaluronan (HYAJOINT Plus) and platelet-rich plasma (PRP) versus PRP alone for treating knee osteoarthritis. *Scientific Reports*, *11*(1), 140. https://doi.org/10.1038/s41598-020-80333-x

Tamir, E., Robinson, D., Koren, R., Agar, G., & Halperin, N. (2001). Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: A randomized, double blind, placebo controlled study. *Clinical and Experimental Rheumatology*, *19*(3), 265–270.

Teng, X., Hu, G., Zhao, Y., Zhou, L., & Li, J. (2008). 林格氏液关节腔灌洗与欣维可腔内注射治疗膝关节骨性关节炎的对比 [Ringer's solution and Synvisc in treatment of knee osteoarthritis: A contrast study]. *山东大学学报(医学版) [Journal of Shandong University (Medical Science)]*, *46*(8), 787–790.

Tetik, S., Öneş, K., & Tetik, C. (2003). Efficacy of intra-articular Hylan G-F 20 on osteoarthritis of the knee. *The Pain Clinic*, *15*(4), 459–466. https://doi.org/10.1163/156856903770196863

Teva Pharmaceuticals. (2020). NCT02495857. A Study of Hyaluronate Injectable Viscosupplement for Treatment of Osteoarthritis of the Knee. Https://Clinicaltrials.Gov/Ct2/Show/NCT02495857 *and*

https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170016B.pdf (last access: October 21, 2021)

Trofimov, E., Trofimova, A., & Mazurov, V. (2018). The effect of different treatments on the clinical course of knee osteoarthritis. *Osteoarthritis.and Cartilage.*, *26*, S306–S307.

van der Weegen, W., Wullems, J. A., Bos, E., Noten, H., & van Drumpt, R. A. (2015). No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: A randomized, controlled, double-blind trial. *The Journal of Arthroplasty*, *30*(5), 754–757.

Wang, J., Yang, Y., Su, Y. T., Zhang, G., Li, J., & Liu, G. (2009). *透明质酸钠配合物理疗法治疗膝关节骨性 节炎的临床效果 [The clinical effects of arthroscopic debridement and intra-articulus sodium hyaluronate injection for treating knee osteoarthritis]*. *31*(6), 545–549.

Wang, J. (2009). 透明玻璃酸钠在膝骨性关节炎关节镜术后的应用 [Sodium hyaluronate in the treatment of knee osteoarthritis after arthroscopy]. *中国现代医药杂志 [Chinese Journal of Modern Medicine]*, *11*(11), 100–101.

Wang, Y. (2011). 透明质酸钠联合硫酸氨基葡萄糖治疗膝骨关节炎的临床观察 [Clinical observation of sodium hyaluronate combined with glucosamine sulfate in the treatment of knee osteoarthritis]. *药物与临床 [China Medical Herald]*, *8*, 121–122.

Wang, S. (2013). 膝关节骨性关节炎非手术治疗的临床观察 [Clinical observation of non-surgical treatment of knee osteoarthritis]. *临床合理用药杂志 [Chinese Journal of Clinical Medicine]*, *6*(31), 32–33.

Wang, L., Dai, E., Liu, T., Wang, G., & Shi, L. (2013). 膝骨性关节炎中医药治疗与髌下脂肪垫CT 改变的相关性研究 [Treating Knee Osteoarthritis by Chinese Medicine and Its Correlation Study with CT Changes of Infrapatellar Fat Pad]. *中国中西医结合杂志 [CJITWM]*, *33*(11), 1494–1499.

Wang, R. (2015). 膝关节镜联合透明质酸钠治疗老年膝关节骨性关节炎疗效观察 [Curative effect observation of arthroscopic debridement combined with sodium hyaluronate in knee osteoarthritis]. *中国社区医师 [Chinese Community Doctors]*, *4*, 52–53.

Wei, H. (2016). 膝关节骨性关节炎盐酸氨基葡萄糖胶囊联合透明质酸钠治疗分析 [Analysis of Knee Joint Osteoarthritis Treated with Glucosamine Hydrochloride Capsule Combined with Sodium Hyaluronate]. *病例讨论 [Case Discussion]*, *11*, 143–143.

Wei, L., Liu, H., & Wang, A. (2013). 腔内注射玻璃酸钠联合康复训练治疗早期膝骨关节炎的疗效观察 [Efficacy of sodium hyaluronate injection combined with rehabilitation on senile knee osteoarthritis]. *Medical Journal of Wuhan University [武汉大学学报: 医学版]*, *34*(1), 86–89.

Weiss, C., Balazs, E. A., Onge, R. S., & Denlinger, J. L. (1981). *Clinical studies of the intraarticular injection of HealonR (sodium hyaluronate) in the treatment of osteoarthritis of human knees*. *11*, 143–144.

Westrich, G., Schaefer, S., Walcott-Sapp, S., & Lyman, S. (2009). Randomized prospective evaluation of adjuvant hyaluronic acid therapy administered after knee arthroscopy. *American Journal of Orthopedics (Belle Mead, N.J.)*, *38*(12), 612–616.

Wobig, M., Dickhut, A., Maier, R., & Vetter, G. (1998). Viscosupplementation with hylan G-F 20: A 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clinical Therapeutics*, *20*(3), 410–423. https://doi.org/10.1016/s0149-2918(98)80052-0

Wu, H. B., Du, J. Y., Yang, S. H., Shao, Z. W., & Xiong, X. Q. (2004). [Evaluation on the effects of hyaluronan combined with different dosages of celecoxib for relieving pain and ankylosis induced by knee osteoarthritis]. *Zhongguo Linchuang Kangfu*, *8*, 5491–5493.

Xu, B., Huo, X., Zhang, H., Wang, Y. S., Shi, X., & Huo, L. (2015). 关节内注射富血小板血浆与玻璃酸钠治疗膝关节骨关节炎的对比研究 [A comparative study of platelet-rich plasma and hyaluronic acid intra-articular injection for knee osteoarthritis]. *中国微创外科杂 [Chin J Min Inv Surg]*, *15*(8), 676–680.

Xu, Z., He, Z., Shu, L., Li, X., Ma, M., & Ye, C. (2021). Intra-articular platelet-rich plasma combined with hyaluronic acid injection for knee osteoarthritis is superior to PRP or HA alone in inhibiting inflammation and improving pain and function. *Arthroscopy*, *37*(3), 903–915.

Yang, J. (2010). 透明质酸钠注射联合针刀闭合性手术治疗膝关节骨关节炎 远缘 65例疗效观察 [Clinical Observation of 65 Cases of Knee Osteoarthritis Surgical Treatment with Sodium Hyaluronate Injection Combined with Needle-knife Closure Surgery]. *Medical Innovation of China [中国医学创新]*, *7*, 51–53.

Yang, S., Xu, G., & Huang, J. (2014). 臭氧灌注配合注射透明质酸钠治疗退行性骨关节炎的临床观察研究 [Clinical observation study of ozone perfusion combined with sodium hyaluronate injection in treatment of degenerative osteoarthritis]. *中华关节外科杂志 [Chinese Journal of Joint Surgery]*, *8*(3), 310–312.

Yang, L., Zhang, J., & Wang, G. (2015). The effect of sodium hyaluronate treating knee osteoarthritis on synovial fluid interleukin -1β and clinical treatment mechanism. *Pakistan Journal of Pharmaceutical Sciences*, *28*(1 Suppl), 407–410.

Ye, Y., & Ma, L. (2016). 膝关节腔臭氧熏洗配合注射透明质酸钠治疗骨关节炎 [Knee Joint Ozone Fumigation Combined with Injection of Sodium Hyaluronate for Treatment of Osteoarthritis]. *今日健康 [Today's Health]*, *15*, 3–4.

You, C., Jia, X., Yan, C., Yang, S., & Liu, H. (2016). 中西医结合治疗阳虚型膝骨牲关节炎30例 [Integrated Chinese and western medicine in treating 30 cases of knee osteoarthritis of Yang deficiency pattern]. *西部中医药 [Western Journal of Traditional Chinese Medicine]*, *29*(12), 96–97.

Yu, X., & Zhang, C. (2014). 氨基葡萄糖联合关节腔内注射透明质酸钠治疗膝骨关节炎 39 例 [Clinical efficacy of glucosamine combined with intra-articular injection of sodium hyaluronate in treating knee osteoarthritis]. *China Pharmaceutical [中国药业]*, *23*(13), 63–64.

Yuan, T., Zhang, Q., & Zhang, Z. (2013). 硫酸氨基葡萄糖联合膝关节腔内注射透明质酸钠治疗膝骨关节炎的研究 [Combination of glucosamine sulfate and intra-articular injection of sodium hyaluronate in treatment of knee osteoarthritis]. *海峡药学 [Strait Pharmaceutical Journal]*, *25*, 110–111.

Zang, J. (2011). *透明质酸钠联合硫酸氨基葡萄糖治疗早中期KOA的临床疗效观察 [Clinical curative effects research on the treatment of the early and medial stages of knee*

osteoarthritis with sodium hyaluronate and glucosamine hydrochloride]. Shandong University Of Traditional Chinese Medicine.

Zeng, W. (2017). 关节镜清理术联合透明质酸钠注射液治疗膝关节骨性关节炎的临床疗效观察 [Clinical efficacy of arthroscopic debridement combined with sodium hyaluronate injection in the treatment of osteoarthritis of the knee]. *医学理论与实践 [Journal of Medical Theory and Practice]*, *30*(2), 234–235.

Zhang, X., He, C., & Liu, F. (2009). 关节镜清理手术结合中西药物治疗膝关节骨性关节炎40例临床观察 [Arthroscopic surgery combined with Western medicine treatment of knee osteoarthritis clinical observation of 40 cases]. *Guiding Journal of Traditional Chinese Medicine and Pharmacy [中医药导报]*, *15*(1), 56–57.

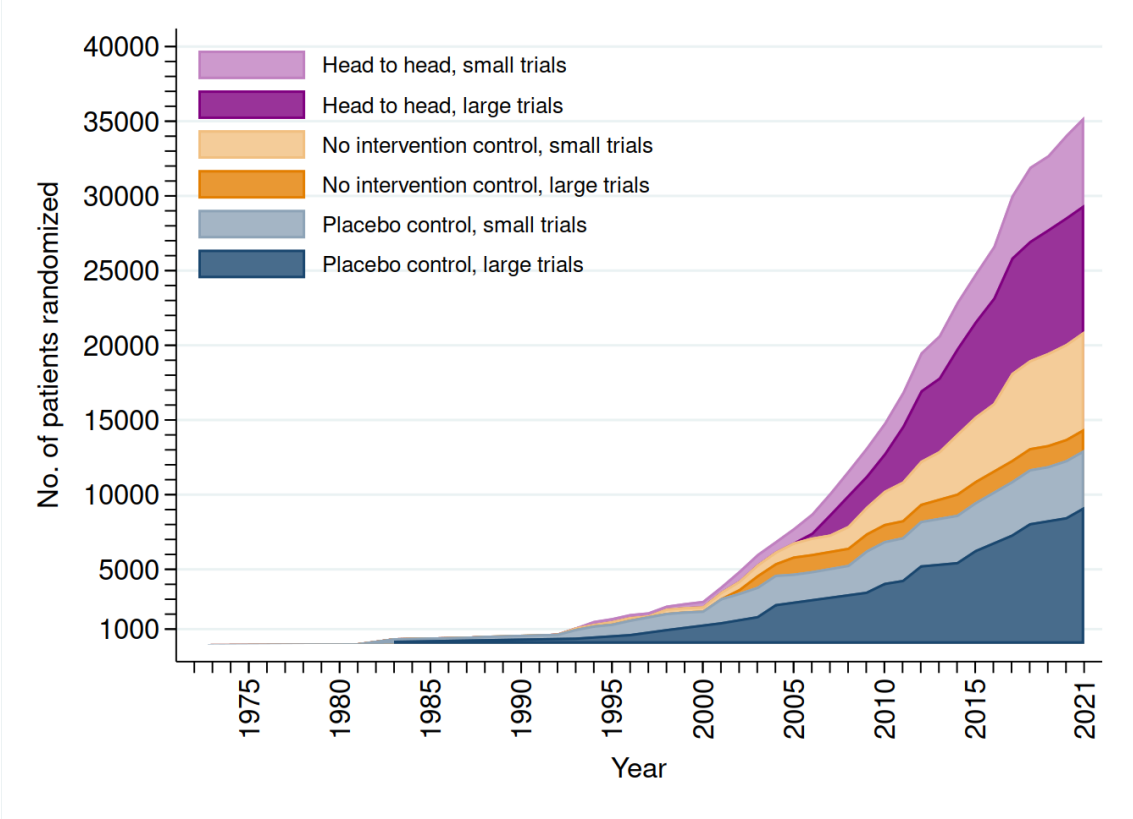
Zhang, Z. (2011). 关节腔内注射联合康复训练治疗膝关节骨性关节炎临床观察. 中华老年医学杂志 [Clinical effect of intra-articular injection of sodium hyaluronate combined with rehabilitation training in treatment of knee osteoarthritis in the elderly]. *空堡鲞生垦堂茎查 [Chin J Geriatr]*, *30*(5), 384–386.

Zhao, X. (2010). 玻璃酸钠关节内注射联合中药外洗治疗膝骨性关节炎的临床研究 [Clinical study of on the curative effect of intra-articular injection of hyaluronic acid combined with external wash of traditional Chinese medicine on knee osteoarthritis]. *Chinese Orthopaedic Medicine [中医正骨]*, *22*(12), 23–25.

Zhou, B. (2016). 膝关节镜联合透明质酸钠治疗老年性膝关节骨性 [Knee arthroscopy combined with sodium hyaluronate in the treatment of senile knee osteoarthritis]. *中国实用医药 [China Practical Medicine]*, *24*, 67–68.

Сорока, Н. Ф. (2009). Клиническая эффективность и безопасность внутрисуставного введения препарата гиалуроновой кислоты “GO-ON” при остеоартрозе коленных суставов [Clinical efficacy and safety of intraarticular administration of the hyaluronic acid preparation “GO-ON” in knee osteoarthritis]. *Здравоохранение [Health Care]*, *4*, 15–19.

Web-appendix 13. Accumulation of randomized patients in viscosupplementation trials (1972-2021).



Web-appendix 13. Evolution of the accrued number of randomized patients over nearly half a century of clinical research on viscosupplementation. Published and unpublished trials were included in this graph (n = 35,535 randomized participants; 255 trials). Also included in the graph are the numbers of randomized participants in head-to-head trials, that is, in trials comparing two or more hyaluronic acid derivatives (n = 86 trials; 14,372 participants). Head-to-head trials were selected using the same searches described in the material and methods section. Numbers are presented separately by large trials (mean ≥ 100 participants per group) and small trials (mean < 100 participants per group). From 2004-2005 onward, there was a shift from placebo-controlled to no intervention control and head-to-head trials. No intervention controlled trials denote open-label studies in which viscosupplementation was given on top of the usual care (e.g., viscosupplementation combined with usual care/other intervention vs. usual care/other intervention).

Web-appendix 14. Summary effects of viscosupplementation on pain intensity (all trials, n = 165 studies that randomized 20,729 participants).

Model	**SMD (95% CI)**	***P***
Random-effects *	-0.56 (-0.64 to -0.48)	< 0.001
Fixed-effect model	-0.35 (-0.38 to -0.32)	< 0.001

SMD denotes standardized mean difference. 95% CI denotes 95% confidence interval.

***** Estimated $\tau^2 = 0.22$ (large heterogeneity). Results based on the fixed-effect model were obtained via the inverse-variance method. [1,2].

References

1. Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research synthesis methods*, *1*(2), 97-111.

2. da Costa, B. R., & Jüni, P. (2014). Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *European Heart Journal*, *35*(47), 3336-3345.

Web-appendix 15. Summary effects of viscosupplementation on function (all trials, n = 133 studies that randomized 16,273 participants).

Model	SMD (95% CI)	*P*
Random-effects *	-0.51 (-0.61 to -0.42)	< 0.001
Fixed-effect model	-0.35 (-0.38 to -0.32)	< 0.001

SMD denotes standardized mean difference. 95% CI denotes 95% confidence interval.

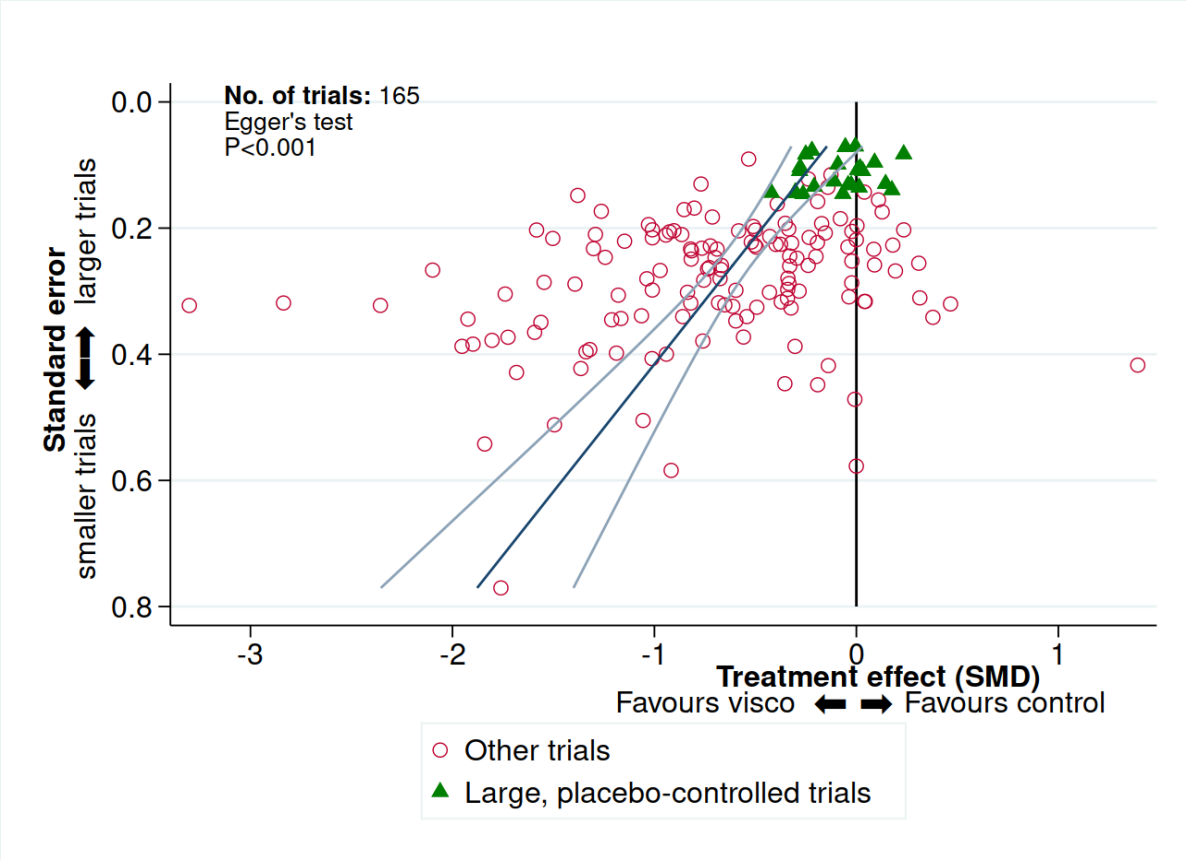
*Estimated τ^2 = 0.25 (large heterogeneity). Results based on the fixed-effect model were obtained via the inverse-variance method. Results based on the fixed-effect model were obtained via the inverse-variance method [1,2].

References

1. Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research synthesis methods*, *1*(2), 97-111.

2. da Costa, B. R., & Jüni, P. (2014). Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *European Heart Journal*, *35*(47), 3336-3345.

Web-appendix 16. Funnel plot of 165 viscosupplementation trials (pain intensity).



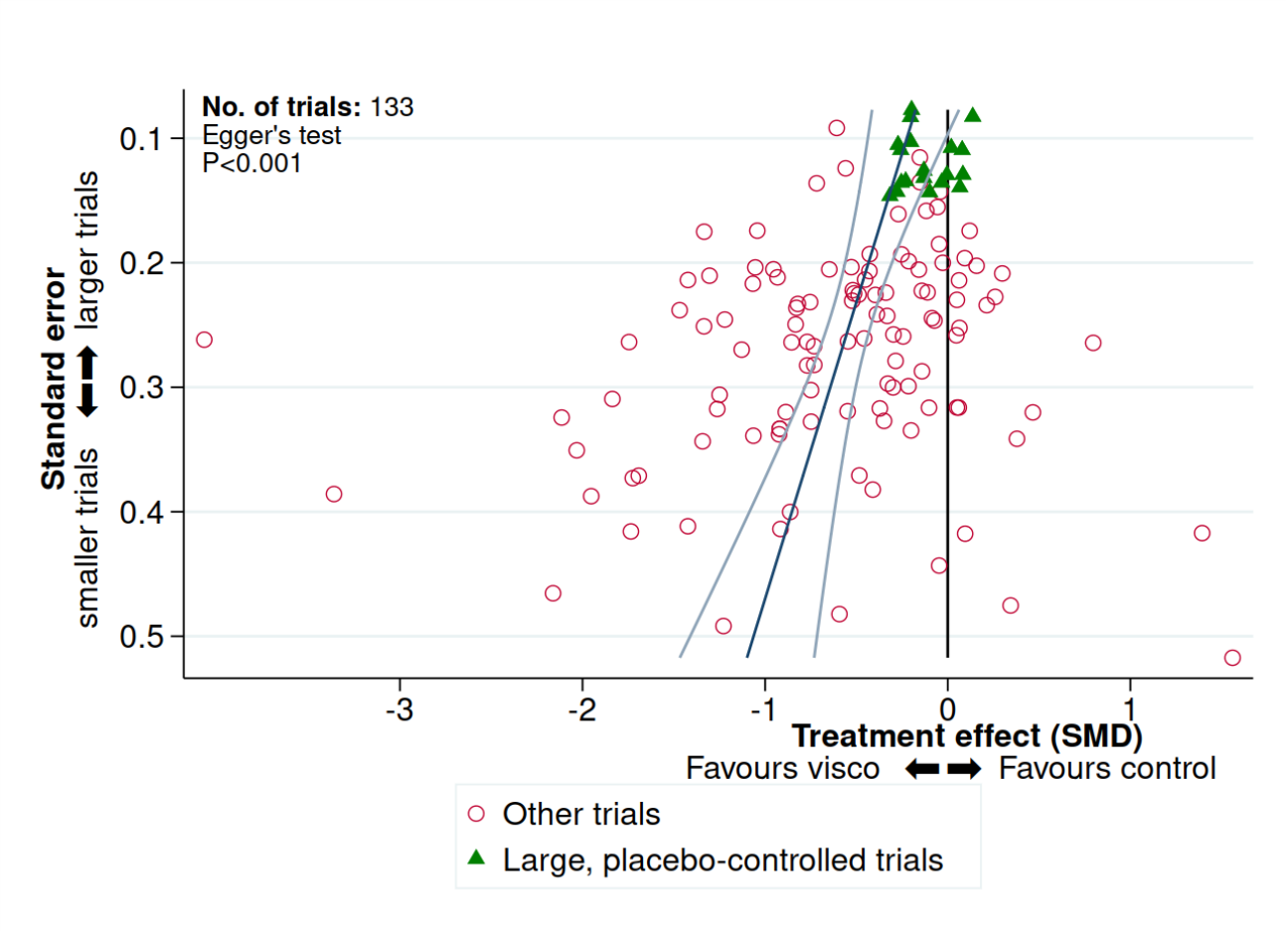
Web-appendix 16. SMD denotes standardized mean difference. All published and unpublished trials are included. The analysis involves data from 20,729 randomized patients. Evidence suggested an association between precision (standard error) and the magnitude of effect sizes, with smaller studies having more impressive estimates of pain reduction than large trials. Most large trials are clustered around the null effect (i.e., SMD = 0). The solid line represents Egger's regression line (i.e., the linear prediction of the treatment effect by the observed standard error) with lighter colored lines denoting the 95% confidence intervals of predicted values. Forty-one (25%) of the 165 trials reported effect sizes for pain outcomes below -1.0 standard deviation. That magnitude of treatment effect can be considered more extreme than the average effect of total knee replacement on knee OA pain [1-2].

References

1. Dusad A, Pedro S, Mikuls TR, Hartman CW, Garvin KL, O'Dell JR et al. Impact of Total Knee Arthroplasty as Assessed Using Patient-Reported Pain and Health-Related Quality of Life Indices: Rheumatoid Arthritis Versus Osteoarthritis. Arthritis Rheumatol 2015; 67:2503-11.

2. Skou ST, Roos EM, Laursen MB, Rathleff MS, rendt-Nielsen L, Simonsen O et al. A Randomized, Controlled Trial of Total Knee Replacement. N Engl J Med 2015; 373:1597-606

Web-appendix 17. Funnel plot of 133 viscosupplementation trials (function).



Web-appendix 17. SMD denotes standardized mean difference. Funnel plot assessing small-study effects and publication bias (knee function). Results are based on both published and unpublished trials (n = 133 trials; 16,273 randomized participants). Evidence suggests an association between precision (standard error) and the magnitude of effect sizes, with smaller studies having more impressive estimates of physical function improvement than large trials. The solid line represents Egger's regression line (i.e., the linear prediction of the treatment effect by the observed standard error) with lighter colored lines denoting the 95% confidence intervals of predicted values.

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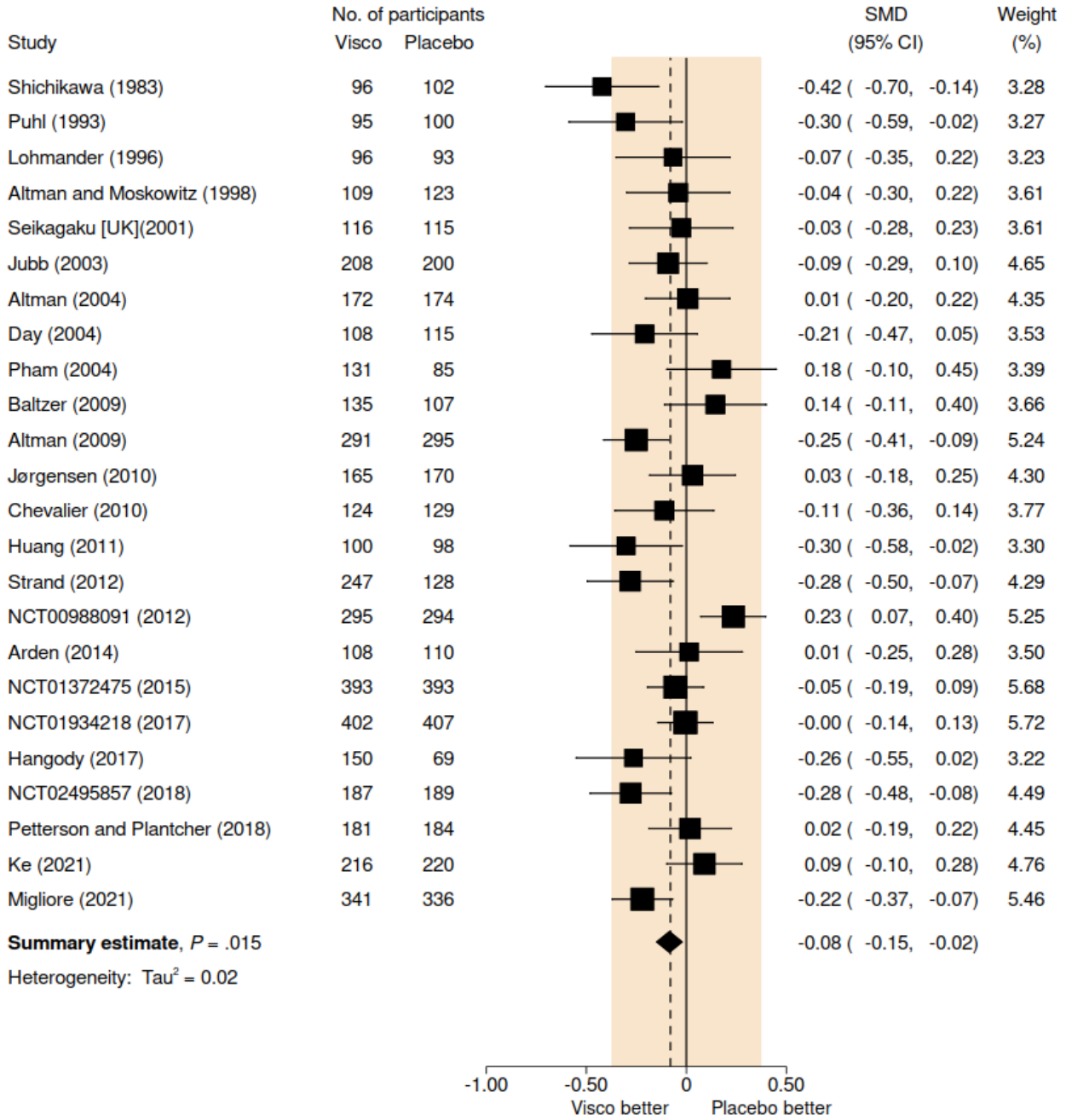
Web-appendix 18. Forest plot of 24 large placebo-controlled trials (pain)



Web-appendix 18. Forest plot of large, placebo-controlled trials (pain). Results are based on published and unpublished trials (n = 24 trials; 8,997 randomized patients). SMD denotes standardized mean difference. 95% CI denotes 95% confidence intervals. Results are based on a random-effects model. The shaded area denotes the area of clinical equivalence smaller than the minimal clinically important difference (-0.37 to 0.37) on both sides. The dashed line represents the

summary (random-effects) estimate. The number of participants analyzed may be smaller than the number of randomized participants.

Web-appendix 19. Further considerations regarding the magnitude of the effect sizes (main analysis – pain intensity)

The standardized mean difference (SMD) of -0.08 observed for viscosupplementation compared to placebo regarding pain intensity in knee OA is among the smallest treatment effects observed for osteoarthritis treatments. It is similar to the also clinically irrelevant but statistically significant effect reported for paracetamol (acetaminophen) when compared to placebo, with an SMD of -0.15 [1]. In contrast, oral and topical non-steroidal anti-inflammatory drugs, when compared to placebo, have an SMD of around -0.60 [1,2].

References

1. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ* 2021; 375:n2321.

2. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials. *Ann Intern Med* 2015; 163:365-72.

Web-appendix 20. Further considerations regarding subgroup effects (main analysis – pain intensity)

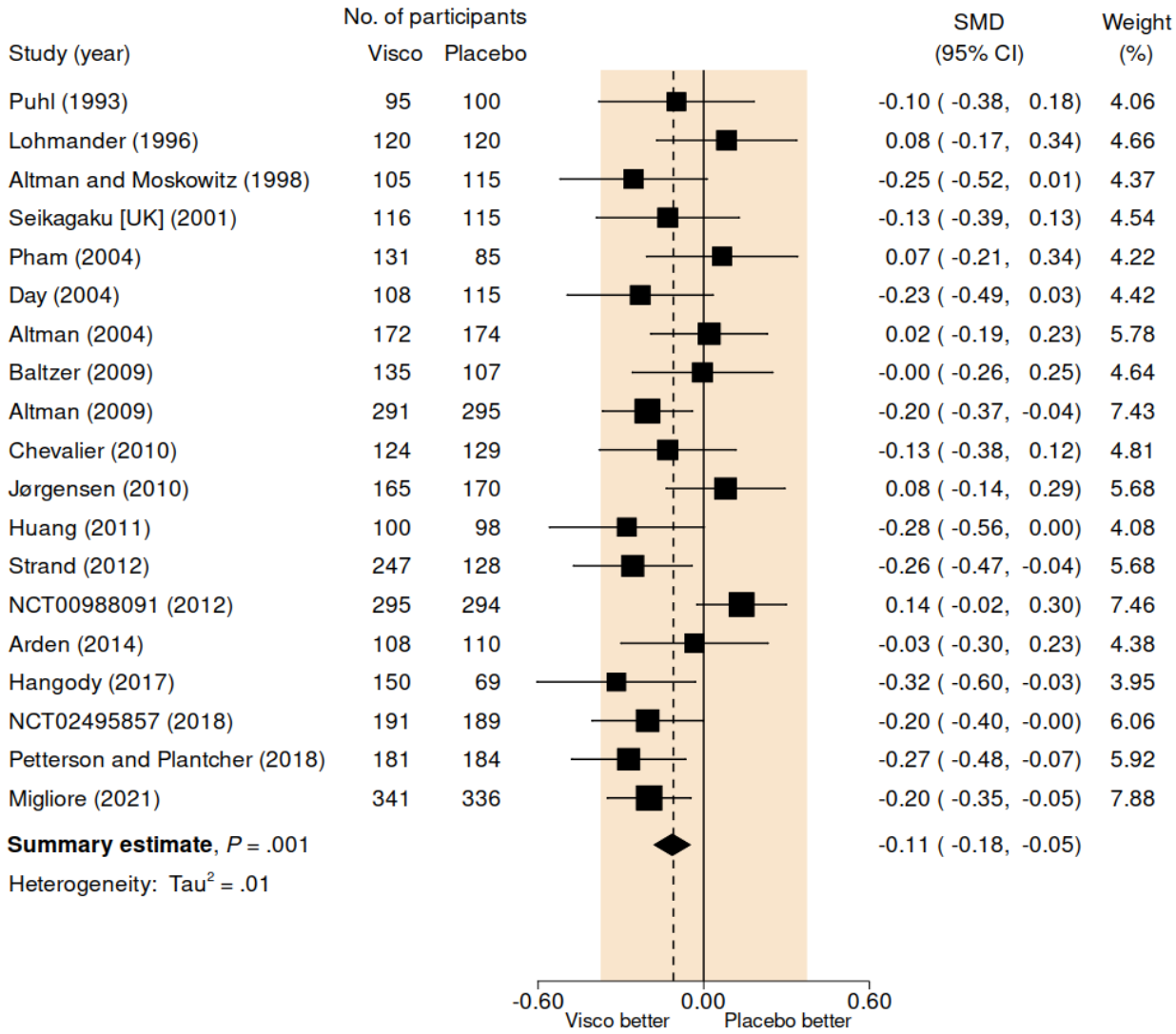
There was evidence that the first, large-placebo-controlled trial (conducted in Japan and reported in Japanese) suggested a more pronounced treatment effect than subsequent trials published in English (P=0.02) [1]. This result is identical to the subgroup considering "bias in the measurement of the outcome" since the Japanese trial [1] was also judged to be at high risk of bias for that domain.

Five unpublished large, placebo-controlled trials (2,840 randomized participants) yielded a pooled summary estimate that was virtually null (-0.02, 95% CI, -0.17 to 0.13, P=0.87, τ^2 =0.02).

Reference

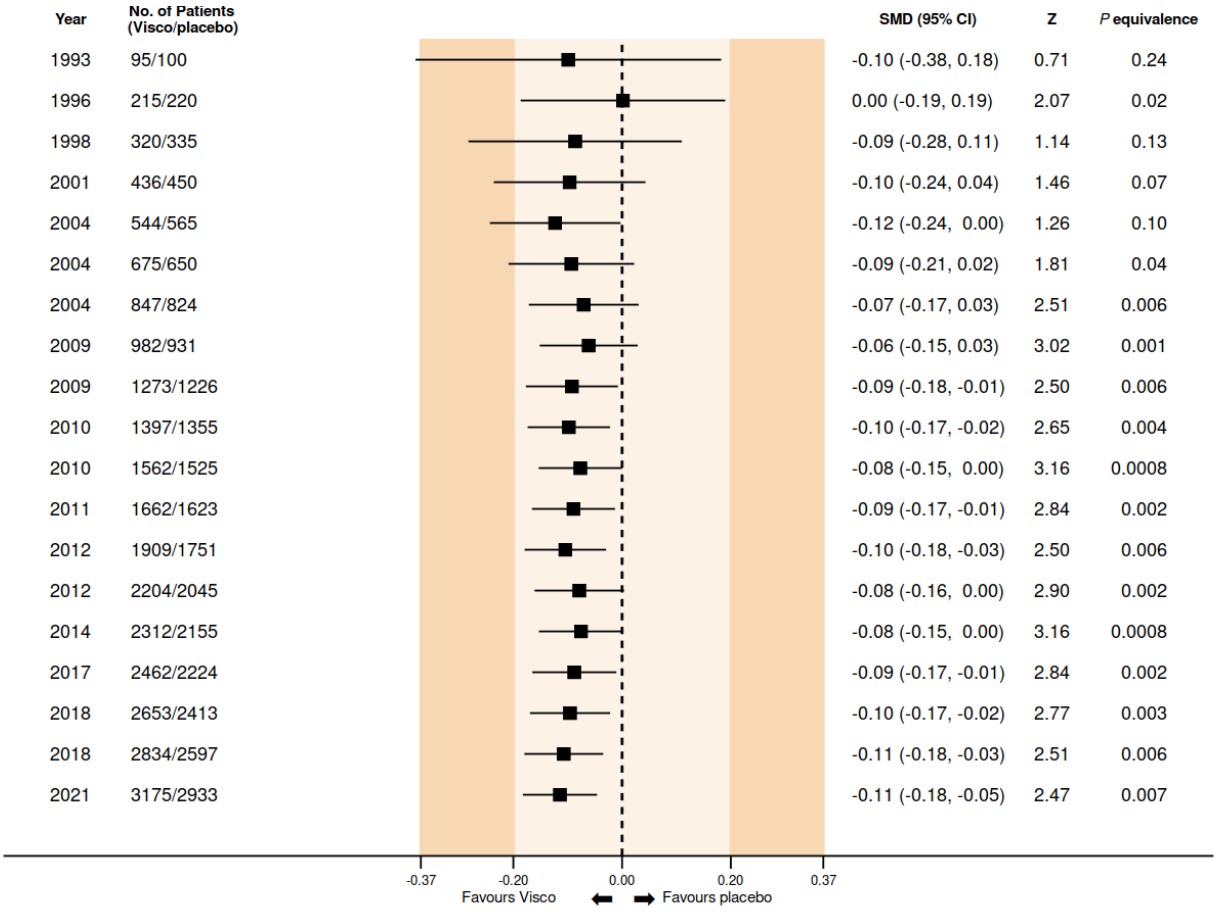
1. Shichikawa, K, Maeda, A., & Ogawa, N. (1983). [Clinical evaluation of sodium hyaluronate in the treatment of osteoarthritis of the knee]. Ryumach., 23, 280–290

Web-appendix 21. Forest plot of 19 large, placebo-controlled trials (function)



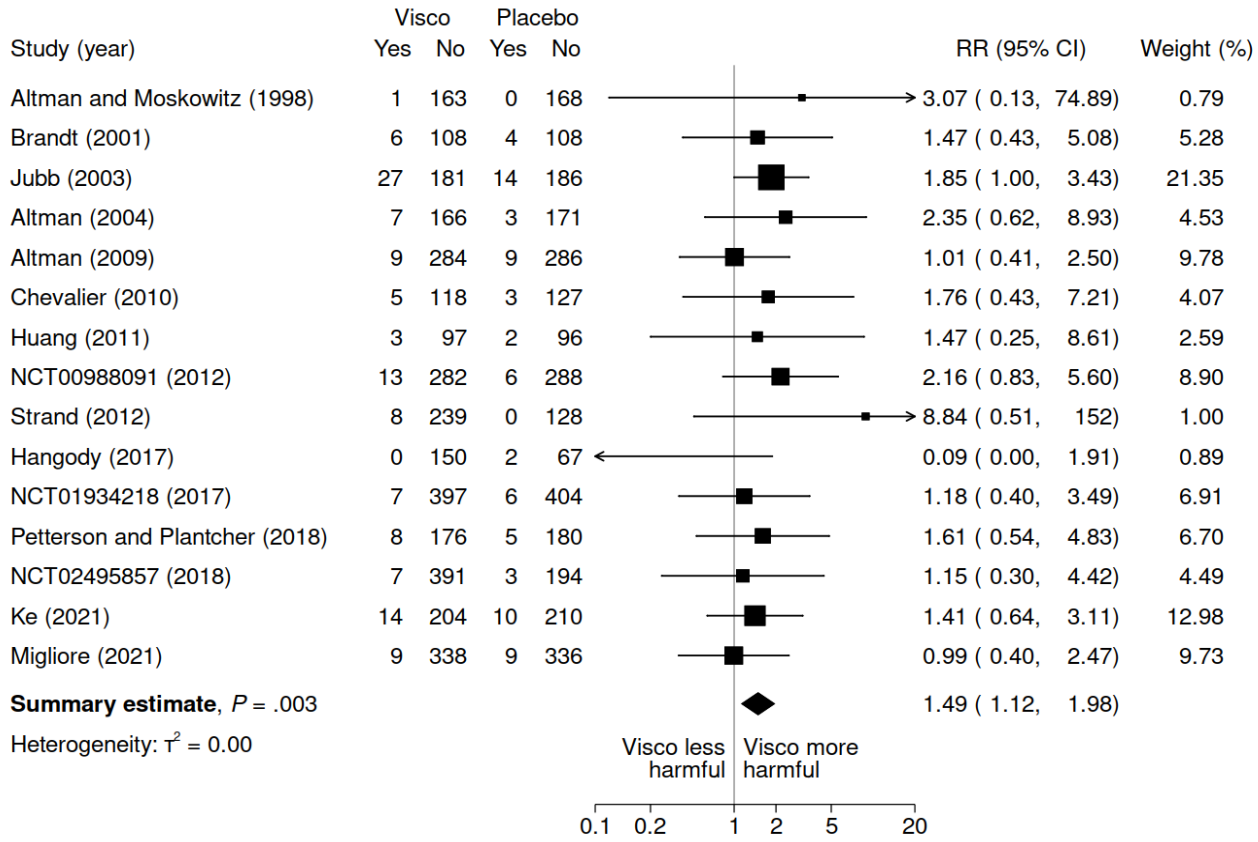
Web-appendix 21. Forest plot of large, placebo-controlled trials (function) including 19 trials; 6,307 randomized patients. SMD denotes standardized mean difference. 95% CI denotes 95% confidence intervals. The dashed line represents the summary (random-effects) estimate. The shaded area denotes the area of clinical equivalence smaller than the minimal clinically important difference (-0.37 to 0.37) on both sides. The number of participants analyzed may be smaller than the number of randomized participants.

Web-appendix 22. Cumulative evidence on the effectiveness of viscosupplementation for knee function based on 19 large, placebo-controlled trials



Web-appendix 22. Cumulative pooled analysis for knee function (n = 19 trials; 6,307 randomized participants). Shading represents the area of clinical equivalence (light areas represent the equivalence |0.2| margins, whereas darker regions represent the 0.37 superiority margin). Results are for the random-effects model. Across years, between-trial variance estimates (τ^2) varied between 0 to 0.02, suggesting low heterogeneity. *P*-values for equivalence are based on two one-sided tests. SMD denotes standardized mean difference. 95% CI denotes 95% confidence intervals. The number of participants analyzed may be smaller than the number of randomized participants.

Web-appendix 23. Serious adverse events based on 15 large, placebo-controlled trials.



Web-appendix 23. Forest plot for serious adverse events. Results are based on 15 large, placebo-controlled trials (6,462 randomized participants). Counts represent the number of participants with an event (Yes) or Non-event (No). Results are based on the random-effects model. For trials with zero events, a continuity correction was used. Harbord's test indicated no evidence of funnel plot asymmetry (P = 0.57). Serious adverse events were typically reported as events resulting in hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality of offspring, life-threatening events, or death. RR denotes relative risk. 95% CI denotes 95% confidence interval. The number of participants analyzed may be smaller than the number of randomized participants. Given the weak association between viscosupplementation with pain reduction in knee osteoarthritis, we considered post-hoc that any increase in the risk of serious adverse events caused by viscosupplementation as compared to placebo can be considered a minimal clinically important increase [1]. Considering the odds ratio as a metric, the summary odds ratio was 1.51 (95% CI = 1.12 to 2.04, P = 0.007, τ^2 = 0).

Reference

[1] Hauber AB, Arden NK, Mohamed AF, et al. A discrete-choice experiment of United Kingdom patients' willingness to risk adverse events for improved function and pain control in osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(2):289-297

Web-appendix 24. List of adverse events reported in large placebo-controlled trials (by trial).

Altman and Moskowitz (1998)

Serious adverse events*	Viscosupplementation (n = 164)	Placebo (n = 168)
No. of subjects affected	**1**	**0**
No. of events	**1**	**0**
Serious adverse events described, No. (%):		
Death**	1 (0.61)	0

* According to the authors: "All serious AEs were considered by the investigators to be the result of primary concomitant disease and not to be drug related."

** Same patient.

Commentary: All other serious adverse events were not described in detail.

Brandt (2001)

Serious adverse events*	Viscosupplementation (n = 114)	Placebo (n = 112)
No. of subjects affected	**6**	**4**
No. of events	**NR**	**NR**
Serious adverse events described, No. (%):		
	NR	NR

* According to the authors: "None of the serious adverse events was thought by the investigators to have been related to treatment." "Adverse events included diverticulitis, esophagitis, cholecystitis, hyperglycemia, atrial fibrillation, congestive heart failure, deep vein thrombosis, pneumonia, asthma, congenital hernia, prostatic disorder, and carcinoma. Only cholecytstitis was reported by more than one patient (n=2)."

Jubb (2003)

Serious adverse events*	Viscosupplementation (n = 208)	Placebo (n = 200)
No. of subjects affected	**27**	**14**
No. of events	**NR**	**NR**
Serious adverse events described, No. (%):		
Myocardial infarction**	1 (0.48)	0
Death**	1 (0.48)	0

* According to the authors: "All serious AEs were considered by the investigators to be the result of primary concomitant disease and not to be drug related."

** Same patient.
Commentary: All other serious adverse events were not described in detail.

Altman (2004)

Serious adverse events*	Viscosupplementation (n = 173)	Placebo (n = 174)
No. of subjects affected	**7**	**3**
No. of events	**NR**	**NR**
Serious adverse events described, No. (%):		
	NR	NR

*According to the authors: "Ten patients […] reported serious adverse events (SAEs), all of which were assessed by the investigator as being unrelated to the study treatment."
Commentary: Serious adverse events were not described in detail.

Altman (2009)

Serious adverse events*	Viscosupplementation (n = 293)	Placebo (n = 295)
No. of subjects affected	**9**	**9**
No. of events	**NR**	**NR**
Serious adverse events described, No. (%):		
Death (motor vehicle accident) ¶	0	1 (0.34)

*According to the authors: "None of the serious TEAE were considered related to study treatment".
¶Not considered to be drug related by the investigators.
Commentary: All other serious adverse events were not described in detail.

Chevalier (2010)

Serious adverse events*	Viscosupplementation (n = 123)	Placebo (n = 130)
No. of subjects affected	**5**	**3**
No. of events	**6**	**3**
Serious adverse events described, No. (%):		
Angina pectoris	1 (0.81)	0
Bradycardia	1 (0.81)	0
Sinus arrest	1 (0.81)	0
Inguinal hernia	1 (0.81)	0
Hernia	1 (0.81)	0
Non-cardiac chest pain	1 (0.81)	0
Radial nerve palsy	0	1 (0.78)
Transitional cell carcinoma	0	1 (0.78)
Femur fracture	0	1 (0.78)

* According to the authors: Quote: "There were no target knee serious AE and no serious AE that were related to the study treatment or the study procedure."

Huang (2011)

Serious adverse events*	Viscosupplementation (n = 100)	Placebo (n = 98)
No. of subjects affected**	**3**	**2**
No. of events**	**3**	**2**
Serious adverse events described, No. (%):		
NR	NR	NR

* According to the authors: Quote: "All were considered to be unrelated to study treatment."
**Assumed to be independent.

Strand (2012)

Serious adverse events*	Viscosupplementation (n = 247)	Placebo (n = 128)
No. of subjects affected	**8**	**0**
No. of events	**19**	**0**
Serious adverse events described, No. (%):		
Ductal carcinoma (Right breast)	1 (0.40)	0
Cardiac arrest	1 (0.40)	0
Respiratory arrest	1 (0.40)	0
Cryptogenic cirrhosis	1 (0.40)	0
Acute bilateral pulmonary edema	1 (0.40)	0
Respiratory failure	1 (0.40)	0
Acute renal failure	1 (0.40)	0
Hypokalemia	1 (0.40)	0
Transient ischemic attack	1 (0.40)	0
Exertional dyspnea	1 (0.40)	0
Transient blurry vision	1 (0.40)	0
Dizziness	1 (0.40)	0
Incarcerated right femoral hernia	1 (0.40)	0
Abdominal pain left side	1 (0.40)	0
Abdominal pain	1 (0.40)	0
Basal cell carcinoma of the face (left eyelid and cheek)	1 (0.40)	0
Malignant melanoma	1 (0.40)	0
Prostate cancer	1 (0.40)	0
Squamous cell carcinoma	1 (0.40)	0

* According to the authors: Quote: "… all judged unrelated to study treatment, including five cancers diagnosed soon after treatment administration. These are consistent with the age of the study population and neither their timing of occurrence nor pre-clinical data would suggest a plausible relationship to administration of Gel-200."

NCT00988091 (2012)

Serious adverse events	Viscosupplementation (n = 295)	Placebo (n = 284)
No. of subjects affected	**13**	**6**
No. of events	**16**	**8**
Serious adverse events described, No. (%):		
Bradycardia	1 (0.34)	0
Cardiac failure congestive	1 (0.34)	0
Myopericarditis	1 (0.34)	0
Angina pectoris	0	1 (0.34)
Atrial fibrillation	0	2 (0.67)
Urethral intrinsic sphincter deficiency	1 (0.34)	0
Chest pain	1 (0.34)	0
Death	1 (0.34)	0
Intraspinal abscess	1 (0.34)	0
Pneumonia	1 (0.34)	0
Femur fracture	1 (0.34)	0
Upper limb fracture	0	1 (0.34)
Heart rate irregular	0	1 (0.34)
Arthralgia	1 (0.34)	0
Osteoarthritis	1 (0.34)	0
Back pain	0	1 (0.34)
Uterine leiomyoma	0	1 (0.34)
Headache	1 (0.34)	0
Syncope	0	1 (0.34)
Urinary incontinence	1 (0.34)	0
Pelvic prolapse	1 (0.34)	0
Nephrectomy	1 (0.34)	0
Spinal fusion surgery	1 (0.34)	0

NCT01934218 (2018)

Serious adverse events	Viscosupplementation (n = 404)	Placebo (n = 410)
No. of subjects affected	**7**	**6**
No. of events	**7**	**7**
Serious adverse events described, No. (%):		
Coronary artery disease	1 (0.25)	0
Acute myocardial infarction	0	1 (0.24)
Aortic valve incompetence	0	1 (0.24)
Chest pain	0	1 (0.24)
Osteomyelitis	1 (0.25)	0
Ankle fracture	0	1 (0.24)
Arthralgia	1 (0.25)	1 (0.24)
Joint effusion	1 (0.25)	0
Basal cell carcinoma	1 (0.25)	0

Oesophageal adenocarcinoma	1 (0.25)	0
Cerebrovascular accident	0	1 (0.24)
Urinary retention	0	1 (0.24)
Deep vein thrombosis	1 (0.25)	0

Hangody (2017)

Serious adverse events*	Viscosupplementation (n = 150)	Placebo (n = 69)
No. of subjects affected	**0**	**2**
No. of events	**NR**	**NR**
Serious adverse events described, No. (%):		
NR	NR	NR

*None of the serious AEs were considered related to treatment and resolved without sequelae. No deaths occurred during the study.

NCT02495857 (2018)

Serious adverse events	Viscosupplementation (n = 199)	Placebo (n = 197)
No. of subjects affected	**5**	**3**
No. of events	**7**	**6**
Serious adverse events described, No. (%):		
Atrioventricular block complete	1 (0.50)	0
Cardiac arrest	0	0
Cardiac failure congestive	1 (0.50)	0
Cardiomyopathy	1 (0.50)	0
Vertigo	1 (0.50)	0
Enteritis	0	1 (0.50)
Gastritis	0	1 (0.50)
Gastrointestinal haemorrhage	0	1 (0.50)
Intestinal ischaemia	0	1 (0.50)
Cholelithiasis	0	1 (0.50)
Muscle spasms	0	0
Osteoarthritis	1 (0.50)	0
Adenocarcinoma of colon	1 (0.50)	0
Prostate cancer	0	1 (0.50)
Nephrolithiasis	1 (0.50)	0

Petterson and Plantcher (2018)

Serious adverse events*	Viscosupplementation (n = 184)	Placebo (n = 185)
No. of subjects affected	**8**	**5**
No. of events	**9**	**5**
Serious adverse events described, No. (%):		
Angina unstable	1 (0.54)	1 (0.54)
Chest pain	0	1 (0.54)
Bronchitis	2 (1.09)	0
Arthralgia	1 (0.54)	0
Synovitis	1 (0.54)	0
Basal cell carcinoma	1 (0.54)	0
Prostate cancer	0	1 (0.54)
Carotid artery stenosis	1 (0.54)	0
Abortion spontaneous	1 (0.54)	0
Suicide attempt	0	1 (0.54)
Rectocele	1 (0.54)	0
Epistaxis	0	1 (0.54)

* According to the authors “None of the SAEs in either of the treatment groups was treatment-related.” SAEs denotes serious adverse events.

Ke (2021)

Serious adverse events*	Viscosupplementation (n = 218)	Placebo (n = 220)
No. of subjects affected	**14**	**10**
No. of events	**17**	**11**
Serious adverse events described, No. (%):		
Arteriosclerosis coronary artery	1 (0.45)	0
Abdominal adhesions	1 (0.45)	0
Bronchitis	1 (0.45)	0
Hepatitis B	0	1 (0.45)
Pneumonia	2 (0.90)	2 (0.90)
Joint injury	0	1 (0.45)
Ligament sprain	1 (0.45)	0
Radius fracture	0	1 (0.45)
Type 2 diabetes mellitus	0	1 (0.45)
Intervertebral disc protrusion	0	1 (0.45)
Lumbar spinal stenosis	1 (0.45)	0
Spinal osteoarthritis	1 (0.45)	1 (0.45)
Colon cancer	1 (0.45)	0
Lung adenocarcinoma	1 (0.45)	0
Ovarian fibroma	1 (0.45)	0
Rectal cancer	1 (0.45)	0
Renal cell carcinoma	1 (0.45)	0
Cerebral infarction	1 (0.45)	1 (0.45)

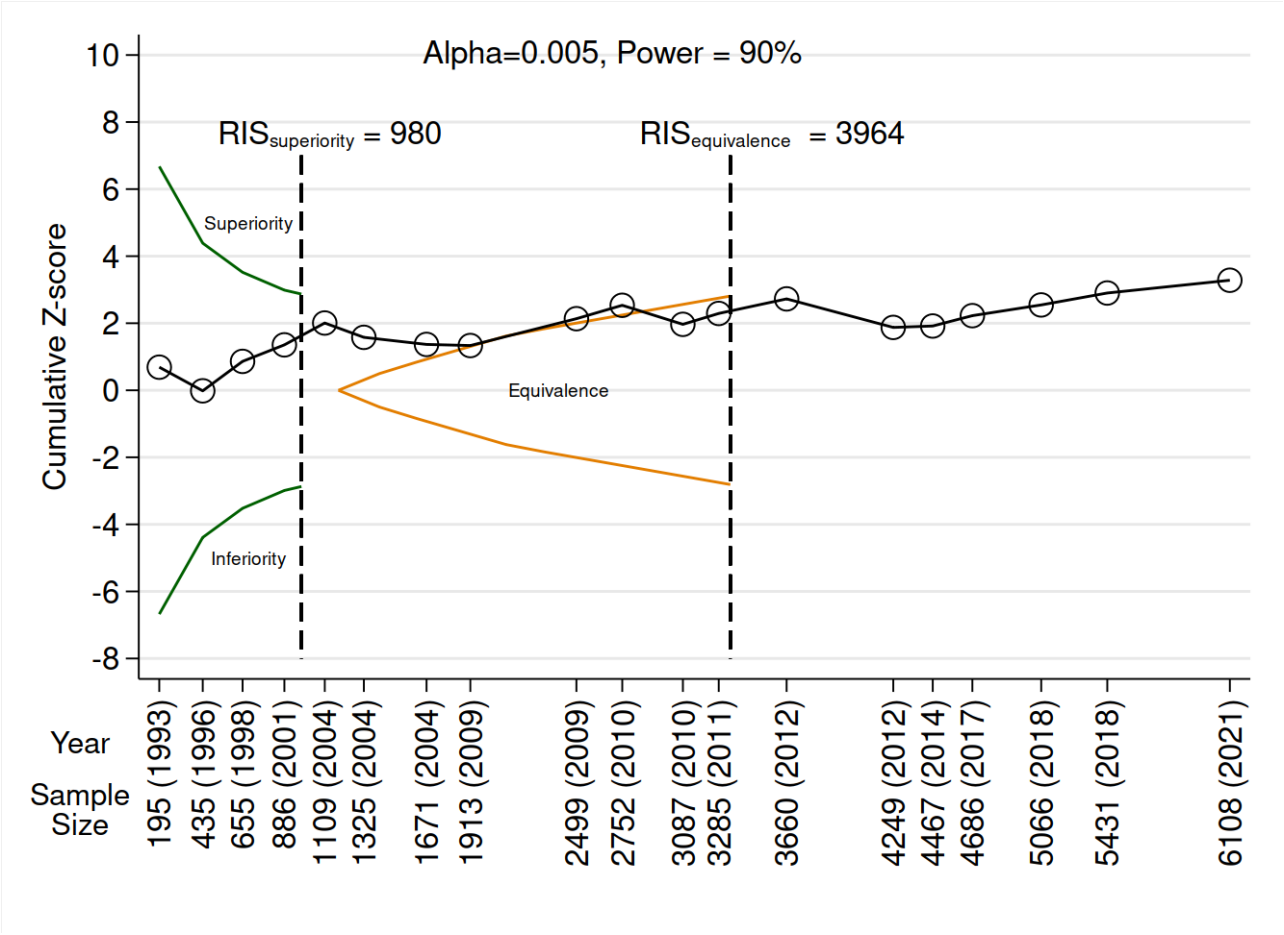
Lacunar infarction	1 (0.45)	0
Uterine polyp	0	1 (0.45)
Hypertension	2 (0.90)	1 (0.45)

Migliore (2021)

Serious adverse events*	Viscosupplementation (n = 347)	Placebo (n = 345)
No. of subjects affected	**9**	**9**
No. of events	**15**	**10**
Serious adverse events described, No. (%):		
NR	NR	NR

***** According to the authors "None of the SAEs in either of the treatment groups was treatment-related." SAEs denotes serious adverse events.

Web-appendix 25. Trial sequential analysis (TSA) for knee function based on 19 large, placebo-controlled trials**.**



Web-appendix 25. Trial sequential analysis for function (secondary analysis). Results are based on 19 large placebo-controlled trials – regardless of publication status (6,307 randomized participants). Cumulative Z-scores are calculated under a random-effects model. The required information size (RIS) was calculated as the sample size that gives a single trial 90% power at a two-sided α=0.005 to detect equivalence assuming limits of equivalence at 0.37 SD units. O'Brien-Fleming monitoring boundaries are represented by green lines. Circles denote the Z score for each additional trial. We accounted for between-trial variation using diversity (D^2) index-adjusted sample sizes. We assumed a D^2 of 50%. Non-peer-reviewed reports had their disclosure year defined as the earliest year in which the document was first officially created (when available within the file), the year of online publication (for instance, "results first posted" date on clinicaltrials.gov), or the date the material

was made available to us. The number of participants analyzed (shown by year) may be smaller than the number of randomized participants.