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Chondroitin for osteoarthritis

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Abstract

Background—Osteoarthritis, a common joint disorder, is one of the leading causes of disability. Chondroitin has emerged as a new treatment. Previous meta-analyses have shown contradictory results on the efficacy of chondroitin. This, in addition to the publication of more trials, necessitates a systematic review.

Objectives—To evaluate the benefit and harm of oral chondroitin for treating osteoarthritis compared with placebo or a comparator oral medication including, but not limited to, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, opioids, and glucosamine or other “herbal” medications.

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Drafting initial review and providing critical revision: SN, JAS
Drafting SoF tables, critical revision: LM
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used the outcomes recommended for summary of findings tables for osteoarthritis reviews based on guidance from the Cochrane Musculoskeletal Editorial Group (allows up to 7 outcomes). Since the original protocol listed pain and WOMAC pain MCII as the co-primary outcomes, we included them in main SOF tables. We used the Cochrane Risk of Bias tool instead of the older system in the protocol. We changed the definition of “short-term” studies to 6 months from 3 months in the protocol. We used the GRADE system to assess the quality of evidence rather than the older grading system described in the protocol.

Search methods—We searched seven databases up to November 2013, including the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, CINAHL, EMBASE, Science Citation Index (Web of Science) and Current Controlled Trials. We searched the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) websites for adverse effects. Trial registers were not searched.

Selection criteria—All randomized or quasi-randomized clinical trials lasting longer than two weeks, studying adults with osteoarthritis in any joint, and comparing chondroitin with placebo, an active control such as NSAIDs, or other "herbal" supplements such as glucosamine.

Data collection and analysis—Two review authors independently performed all title assessments, data extractions, and risk of bias assessments.

Main results—Forty-three randomized controlled trials including 4,962 participants treated with chondroitin and 4,148 participants given placebo or another control were included. The majority of trials were in knee OA, with few in hip and hand OA. Trial duration varied from 1 month to 3 years. Participants treated with chondroitin achieved statistically significantly and clinically meaningful better pain scores (0–100) in studies less than 6 months than those given placebo with an absolute risk difference of 10% lower (95% confidence interval (CI), 15% to 6% lower; number needed to treat (NNT) = 5 (95% CI, 3 to 8; n = 8 trials) (level of evidence, low; risk of bias, high); but there was high heterogeneity between the trials (T^2 = 0.07; I^2 = 70%, which was not easily explained by differences in risk of bias or study sample size). In studies longer than 6 months, the absolute risk difference for pain was 9% lower (95% CI 18% lower to 0%); n = 6 trials; T^2 = 0.18; I^2 = 83%), again with low level of evidence.

For the Western Ontario and McMaster Universities Osteoarthritis Index Minimal Clinically Important Improvement (WOMAC MCII Pain subscale) outcome, a reduction in knee pain by 20% was achieved by 53/100 in the chondroitin group versus 47/100 in the placebo group, an absolute risk difference of 6% (95% CI 1% to 11%), (RR 1.12, 95% CI 1.01 to 1.24; T^2 = 0.00; I^2 = 0%) (n = 2 trials, 1253 participants; level of evidence, high; risk of bias, low).

Differences in Lequesne's index (composite of pain, function and disability) statistically significantly favoured chondroitin as compared with placebo in studies under six months, with an absolute risk difference of 8% lower (95% CI 12% to 5% lower; T^2= 0.78; n = 7 trials) (level of evidence, moderate; risk of bias, unclear), also clinically meaningful. Loss of minimum joint space width in the chondroitin group was statistically significantly less than in the placebo group, with a relative risk difference of 4.7% less (95% CI 1.6% to 7.8% less; n = 2 trials) (level of evidence, high; risk of bias, low). Chondroitin was associated with statistically significantly lower odds of serious adverse events compared with placebo with Peto odds ratio of 0.40 (95% CI 0.19 to 0.82; n = 6 trials) (level of evidence, moderate). Chondroitin did not result in statistically significant numbers of adverse events or withdrawals due to adverse events compared with placebo or another drug. Adverse events were reported in a limited fashion, with some studies providing data and others not.

Comparisons of chondroitin taken alone or in combination with glucosamine or another supplement showed a statistically significant reduction in pain (0–100) when compared with placebo or an active control, with an absolute risk difference of 10% lower (95% CI 14% to 5% lower); NNT = 4 (95% CI 3 to 6); T^2 = 0.33; I^2 = 91%; n = 17 trials) (level of evidence, low). For

physical function, chondroitin in combination with glucosamine or another supplement showed no statistically significant difference from placebo or an active control, with an absolute risk difference of 1% lower (95% CI 6% lower to 3% higher with $T^2 = 0.04$; n = 5 trials) (level of evidence, moderate). Differences in Lequesne's index statistically significantly favoured chondroitin as compared with placebo, with an absolute risk difference of 8% lower (95% CI, 12% to 4% lower; $T^2 = 0.12$; n = 10 trials) (level of evidence, moderate). Chondroitin in combination with glucosamine did not result in statistically significant differences in the numbers of adverse events, withdrawals due to adverse events, or in the numbers of serious adverse events compared with placebo or with an active control.

The beneficial effects of chondroitin in pain and Lequesne's index persisted when evidence was limited to studies with adequate blinding or studies that used appropriate intention to treat (ITT) analyses. These beneficial effects were uncertain when we limited data to studies with appropriate allocation concealment or a large study sample (> 200) or to studies without pharmaceutical funding.

Authors' conclusions—A review of randomized trials of mostly low quality reveals that chondroitin (alone or in combination with glucosamine) was better than placebo in improving pain in participants with osteoarthritis in short-term studies. The benefit was small to moderate with an 8 point greater improvement in pain (range 0 to 100) and a 2 point greater improvement in Lequesne's index (range 0 to 24), both likely clinically meaningful. These differences persisted in some sensitivity analyses and not others. Chondroitin had a lower risk of serious adverse events compared with control. More high-quality studies are needed to explore the role of chondroitin in the treatment of osteoarthritis. The combination of some efficacy and low risk associated with chondroitin may explain its popularity among patients as an over-the-counter supplement.

PLAIN LANGUAGE SUMMARY

Chondroitin for osteoarthritis

We conducted a review of the effects of chondroitin sulfate for people with osteoarthritis. We found 43 studies with 9,110 people after searching for studies up to November 2013. Majority were studies of knee osteoarthritis (few hand, one hip) ranging from 1 month to 3 years. Several studies were funded by makers of chondroitin.

This review shows that in people with osteoarthritis

- Chondroitin may improve pain slightly in the short-term (less than 6 months);
- Chondroitin improves knee pain by 20% in slightly more people;
- Chondroitin probably improves quality of life slightly as measured by Lequesne's index (combined measure of pain, function, and disability);
- Chondroitin has little or no difference in adverse and serious adverse events versus other agents; and
- Chondroitin slightly slows down the narrowing of joint space on X-rays of the affected joint.

We identified a lot of studies in which unsound methods were used to assess the effects of chondroitin. For some outcomes, there was not enough data. In some studies, whose methodological quality was better, chondroitin showed no improvement in pain and in physical function. Other analyses based on different methodological quality criteria reported improvement in pain and physical functionality when chondroitin was given.

What is osteoarthritis and what is chondroitin?—Osteoarthritis is a disease of the joints, such as the knee or hip. When the joint loses cartilage, the bone grows to try to repair the damage, but this bone growth may make the situation worse. This can make the joint painful and unstable, which can affect physical function or ability to use the joint.

Chondroitin is an over-the-counter nutritional supplement made primarily of chondroitin sulfate. It is said to work by stopping the degradation of cartilage and restoring lost cartilage. It also contains sulfur-containing amino acids, which are essential building blocks for cartilage molecules in the human body.

What happens to people with osteoarthritis who take chondroitin?

Pain level after 6 months (lower score is better)

- People who took chondroitin scored 10 points lower on 0 to 100 pain scale than those who took a placebo (10% absolute difference).
- People who took chondroitin rated their pain at 18 on a 0 to 100 scale.
- People who took placebo rated their pain at 28 on a 0 to 100 scale.

In studies longer than 6 months, we are uncertain whether pain is reduced more by chondroitin than placebo.

Reduction in knee pain by 20% (as measured by the WOMAC[1] Pain subscale)

- 6 more people out of 100 experienced improvement of 20% in their knee pain (6% absolute difference).
- 53 people out of 100 who took chondroitin experienced improvement in their knee pain compared to 47 people out of 100 who took placebo.

Lequesne’s index (a combination index of pain and physical function, indicating quality of life) after 6 months

- People who took chondroitin scored 2 points lower (better) on Lequesne’s index (score range 0 to 24).
- People who took chondroitin scored 5 on a scale of 0 to 24 on Lequesne’s index.
- People who took placebo scored 7 on a scale of 0 to 24 on Lequesne’s index.

[1]Western Ontario and McMaster Universities Osteoarthritis Index

Radiographic outcome: reduction in minimum joint space width (mm) (smaller decrease in reduction in minimum joint space width is better) after 2 years

- People who took chondroitin had 0.18 mm less reduction in minimum joint space width than those who took placebo.
- People who took chondroitin had a reduction in minimum joint space width of 0.12 mm.
- People who took placebo had a reduction in minimum joint space width of 0.30 mm.

Serious adverse events

- 3 fewer of 100 people who took chondroitin experienced serious adverse events (such as a serious lung infection or tuberculosis).
- 3 of 100 people experienced a serious adverse event with chondroitin compared to 6 of 100 people who took placebo.

People who dropped out of the studies for adverse events

- People who took chondroitin had no difference in the risk of dropping out of the studies for adverse events than those who took a placebo. This may have happened by chance.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Chondroitin versus placebo for osteoarthritis

Patient or population: patients with osteoarthritis
Settings: international inpatient and outpatient clinics, hospitals, and research centers
Intervention: Chondroitin versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chondroitin versus Placebo				
Pain on a 0 to 100 mm scale - Short-term studies (<6 months)-dose ≥ 800 mg/d	The mean pain on a 0 to 100 scale in the control groups was **28 points**[3]	The mean pain on a 0 to 100 scale in the intervention groups was **10.1 mm lower** (14.6 to 5.7 lower)		1077 (8 studies)	⊕⊕◯◯ **low**[1,2]	Mean Difference −10.14 (95% CI −14.58 to −5.71) Absolute risk difference −10% (95% CI −15% to − 6%) Relative risk difference −36% (95% CI −52% to − 20%) NNTB = 5 (95% CI 3 to 8)

Chondroitin versus placebo for osteoarthritis

Patient or population: patients with osteoarthritis
Settings: international inpatient and outpatient clinics, hospitals, and research centers
Intervention: Chondroitin versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chondroitin versus Placebo				
Pain on a 0 to 100 scale - Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	The mean pain on a 0 to 100 scale in the control groups was **30 points**	The mean pain on a 0 to 100 scale in the intervention groups was **9 points lower** (18 to 0 lower)		989 (6 studies)	⊕⊕◯◯ **low**[1,2]	Mean Difference −9.01 (95% CI −17.68 to −0.34) Absolute risk difference −9% (95% CI −18% to 0%) Relative risk difference −30% (95% CI −60% to 0%) NNTB = n/a
WOMAC MCII Pain sub-scale (reduction in knee pain by 20%) - Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	**471 per 1000**	**528 per 1000** (476 to 584)	**RR 1.12** (1.01 to 1.24)	1253 (2)	⊕⊕⊕⊕ **high**	Absolute risk difference 6% (1% to 11%) Relative risk difference 12% (1% to 24%) NNTB = 16 (9 to 136)
Composite Measure of Pain, Function and Disability as assessed with Lequesne's Index on 0 to 24 scale (lower indicates less pain and disability) - Short-term studies (< 6 months)-dose ≥ 800 mg/d	The mean Lequesne's index on 0 to 24 scale in the control groups was **7. 4 points**	The mean Lequesne's index on 0 to 24 scale in the intervention groups was **1.98 lower** (2.79 to 1.17 lower)		903 (7 studies)	⊕⊕⊕◯ **moderate**[4]	SMD −0.57 (95% CI −0.84 to −0.30) Absolute risk difference − 8% (95% CI −12% to −5%) Relative risk difference − 18% (95% CI −25% to − 10%) NNTB=2 (95% CI 2, 3)
Radiographic Outcome: Reduction in Minimum Joint Space Width (JSW) in mm - Long-term studies (≥ 6	The mean reduction in JSW in the control group was **0.3 mm**	The mean reduction in JSW in the intervention groups was **0.18 mm lower** (0.06 to 0.30 lower)		922 (2 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference not calculable because no range is provided for this measure

Chondroitin versus placebo for osteoarthritis

Patient or population: patients with osteoarthritis
Settings: international inpatient and outpatient clinics, hospitals, and research centers
Intervention: Chondroitin versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chondroitin versus Placebo				
months)-dose ≥ 800 mg/d Scale: millimeters (smaller decrease in reduction in minimum joint space width is better) Follow-up: 3 to 24 months						Relative risk difference: 4. 7% (95% CI, 1.6% to 7. 8%) NNTB = 7 (95% CI 5 to 13)
Withdrawals due to adverse events Follow up: 3 to 24 months	**44 per 1000**	**47 per 1000** (32 to 69)	**RR 1.08** (0.74 to 1.57)	2406 (10 studies)	⊕⊕⊕○ **moderate**[5]	Absolute risk difference: 0% change (−1% to 2%) Relative percentage change: 8% (− 26% to 57%) NNTH = not applicable
Number of serious adverse events Follow-up: 3 to 24 months	**63 per 1000**	**27 per 1000** (13 to 53)	**OR 0.40** (0.19 to 0.82)	954 (6 studies)	⊕⊕⊕○ **moderate**[6]	Absolute risk difference: − 3% (95% CI −6% to −1%) Relative percentage change: −58% (95% CI − 17% to −79%) NNTH was significantly in favor of chondroitin and was 29 (95% CI 22 to 93)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Concerns of risk of bias due to lack of reporting of methods of randomization or allocation concealment or methods were unclear and the majority were sponsored by a manufacturer of chondroitin sulfate.

[2]Significant heterogeneity between study results is evident, with I^2 over 70%, and the studies are split between significant and non significant results from chondroitin. Two studies reporting significant benefit from chondroitin have confidence intervals that do not overlap with those of two studies that report no significant benefit from chondroitin.

[3]This baseline came from Clegg as Sawitzke referenced Clegg and provided both shorter and longer term outcomes

[4]Four of the seven studies reporting on this outcome did not report their methods of randomization, five did not report allocation concealment and seven are sponsored by a manufacturer of chondroitin sulfate or do not report their source of sponsorship. I^2=67%

[5]Downgraded for imprecision; total number of events less than 300 and relative risk increase is larger than 25%

[6]Two of six studies did not report their methods of randomization, five of the six studies did not report their methods of allocation concealment, and all six studies were sponsored by a manufacturer of chondroitin sulfate or did not report their source of funding.

BACKGROUND

Description of the condition

Osteoarthritis, the most common of all joint disorders, is one of the leading causes of disability in the United States (Gabriel 1995; Peyron 1992). Pathologically, osteoarthritis is characterized by softening and degeneration of articular cartilage, formation of new bone at joint margins, and capsular fibrosis. Clinically, osteoarthritis manifests as joint pain, stiffness, deformity, and loss of function. Clinical and radiographic surveys have found that the prevalence of osteoarthritis increases with age, from 1% in people < 30 years to 10% in those < 40 years to more than 50% in individuals > 60 years of age (Felson 1990; van Saase 1989). Autopsy studies show cartilage changes in almost all people above 65 years of age (Felson 1988). Osteoarthritis is equally common in men and women between 45 and 55 years but is more common in women after 55 years of age (Altman 1990). Risk factors for osteoarthritis include obesity, joint dysplasia (abnormal anatomy of the joint due to abnormal growth), trauma, occupational activity, and family history, among others (Solomon 2001). Osteoarthritis is classified as primary or secondary based on the absence or presence of anteceding joint abnormality or injury. Primary osteoarthritis is further classified as generalized or localized to a joint area such as hand, knee, hip, spinal apophyseal joints (between spinal bones/vertebrae), and foot, or to other joints (shoulder, elbow, wrist, and ankle) (Solomon 2001).

Description of the intervention

Treatment of osteoarthritis is primarily directed at relieving pain and improving functional status. Various treatment options are available for patients with osteoarthritis, including the following: (1) oral medications: analgesics such as acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids (Cepeda 2006; Towheed 2006); (2) local therapies (applied as gels or creams): topical NSAIDs and capsaicin; (3) intra-articular therapies: corticosteroid and hyaluronic acid injections (Bellamy 2006); (4) nonpharmacologic methods: physical therapy, aerobic therapy, strengthening exercises, transcutaneous electric nerve stimulation, and wedged insoles (Fransen 2008); and (5)

surgical treatments: joint replacement and arthroscopic debridement of the affected joint (Laupattarakasem 2008). However, frequent side effects, limited efficacy, and variable rates of success limit the use of many non-surgical treatments.

Over the past few years, various nutritional supplements, including chondroitin, glucosamine, avocado/soybean unsaponifiables, and diacerein, have emerged as new treatment options for osteoarthritis (Deal 1999). These supplements are characterized by both slow onset of action over six to eight weeks and a carryover of effect for up to two months after withdrawal (Fajardo 2005). According to recent recommendations from the American College of Rheumatology and the European League Against Rheumatism, drugs for treatment of osteoarthritis are classified as symptom-modifying or structure-modifying drugs, depending on their capacity to interfere with disease progression (Altman 2000; Pendelton 2000). The current body of evidence suggests that chondroitin falls into the symptom-modifying category (i.e., chondroitin has a primary effect on improvement of pain and function), and glucosamine and diacerein into the structure-modifying category (Dougados 2000; Richy 2003) (i.e., they have an effect on progression of arthritis, such as an effect on joint space narrowing as assessed by radiography of the involved joint). One of the main proposed advantages of these medications over traditional medical therapies is their safety profile.

How the intervention might work

Chondroitin sulfate belongs to a family of heteropolysaccharides called *glycosaminoglycans,* or GAGs. Chondroitin sulfate is found in human cartilage, bone, cornea, skin, and arterial wall. Sources of chondroitin used in nutritional supplements include bovine trachea, pork byproducts, shark cartilage, and whale septum (Hendler 2001). Proposed mechanisms of action include restoring the extracellular matrix of cartilage, preventing further cartilage degradation (Johnson 2001), and overcoming a dietary deficiency of sulfur-containing amino acids, which are essential building blocks for cartilage extracellular matrix molecules (Cordoba 2003). A large number of patients with osteoarthritis in the United States and around the world are already using chondroitin alone or in combination with glucosamine for relief of osteoarthritis-related joint pain. Both glucosamine and chondroitin are available over the counter as nutritional supplements, and combination therapy of glucosamine and chondroitin has been used, but it is unclear whether these two supplements produce an additive or a synergistic effect.

Why it is important to do this review

A meta-analysis of glucosamine and chondroitin for treatment of osteoarthritis published in 2000 (McAlindon 2000a) concluded that both supplements were effective for pain relief and functional outcomes with moderate to large effects, but quality issues and publication bias seemed to inflate the effect sizes. The Cochrane review of glucosamine for treating osteoarthritis concluded that studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and function, while studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic osteoarthritis (Towheed 2005). Meta-analyses of chondroitin for osteoarthritis (Leeb 2000) and glucosamine and chondroitin for

knee osteoarthritis (Richy 2003) that included studies up to March 2002 concluded that chondroitin was effective for pain and function compared with placebo. A limitation noted in both of these meta-analyses is that trials included in the analyses allowed coadministration of analgesics or NSAIDs during the study, leading to possible confounding of the results. Publication of additional studies of chondroitin over the past few years since these meta-analyses were published necessitates a new systematic review.

OBJECTIVES

To evaluate the benefit and harm of oral chondroitin for the treatment of osteoarthritis compared with placebo or a comparator oral medication including, but not limited to, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, opioids, and glucosamine or other “herbal” medications.

METHODS

Criteria for considering studies for this review

Types of studies—Randomized controlled trials (RCTs) of two weeks’ duration or longer were included if they reported clinical outcomes data and were published in full. Randomized controlled trials of shorter than two weeks’ duration were excluded because this time frame may be too short to allow assessment of harms and benefits based on biological plausibility.

Types of participants—Adults (age > 18 years) with osteoarthritis of any joint.

Types of interventions—Chondroitin arm:

Use of oral chondroitin alone or in combination with other oral drugs such as glucosamine.

Comparator arm:

Placebo or active medications including NSAIDs, analgesics (e.g., acetaminophen), opioid pain-relieving medications, glucosamine or other “herbal” medications, or other comparator oral medications.

Types of outcome measures

Major outcomes

1. Pain: pain subscale of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy 1988) or Numeric rating scale or Visual Analog Scale; rest pain; pain on motion; pain on walking for index joint; pain in index joint during activities other than walking; or other similar pain scale. A higher score indicates worse pain state in general. Clinically clinically meaningful threshold in pain intensity has been defined as an improvement of 0.9–1.3 cm on a 0–10 cm pain scale (Kelly 1998; Kelly 2001; Todd 1996). This threshold was also endorsed by the The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008). Percent pain responders, defined as the

proportion with minimal clinically important improvement [MCII] on WOMAC (Escobar 2007), was another major outcome of interest.

2. Physical function: both performance-based (e.g., 50-foot walk) and patient-based (WOMAC minimal clinically important improvement, MCII (Escobar 2007); WOMAC total and subscale scores). WOMAC subscale scores are transformed on a scale of 0 to 100, with higher scores indicating worse pain, function, and overall status.

3. Lequesne's index (Lequesne 1997): combines pain, walking ability, and activities of daily living into a composite, with scores ranging from 0 to 24 and higher score indicating worse status of osteoarthritis and disability/quality of life (composite pain, function and disability scale). Clinically meaningful thresholds have not been defined in publications, therefore we used the moderate effect size of 0.5 as meaningful. Personal communications with developer of the scale (Dr. Lequesne) indicated that a change of approximately 2-units for a baseline score of 9–11.5 may be clinically meaningful.

4. Radiographic outcomes: radiologic changes in joint space width or narrowing in millimeters, or other radiographic criteria.

5. Total number of adverse effects or events (AEs).

6. Total number of withdrawals and withdrawals judged to be due to adverse effects in each group.

7. Serious adverse effects (SAEs).

Minor outcomes: Clinical efficacy outcomes:

i. Patient and Physician global assessment, typically on an ordinal scale or a 0 to 100 visual analogue scale (VAS) or a numeric rating scale.

ii. Responders: defined as percentage of participants achieving OMERACT-OARSI response criteria (Dougados 2000; Pham 2004), percentage achieving minimal clinically important improvement (MCII) on WOMAC (Tubach 2005), or percentage achieving responder status based on other validated scales/criteria.

iii. Quality of life as assessed by specific (Health Assessment Questionnaire (HAQ)) and generic questionnaires (Short-Form-36 (SF-36)) and others. Score on HAQ-Disability Index (HAQ-DI) usually ranges from 0 to 3, with a score of 3 indicating worse functional status. SF-36 domain scores range from 0 to 100, with 100 indicating the best health status on each domain score. Summary scores (physical and mental component summary scores) are calculated by combining the eight domains and are norm-based, with mean score of 50 and standard deviation of 10.

iv. Need for joint surgery or arthroscopy.

v. Need for use of concomitant medications for pain relief.

vi. Number of deaths.

vii. Specific adverse effects (gastrointestinal, cardiac, renal, hematologic, and other adverse events).

We searched the US Food and Drug Administration (FDA) website to obtain the adverse effect data.

Pharmacoeconomics: whenever applicable, we attempted to perform analyses by comparing chondroitin with a comparator regarding the cost of drugs per month and the number needed to treat for an additional beneficial outcome (NNTB) to prevent one participant from having an adverse event and the NNTB to have one participant achieve MCII on WOMAC. We analyzed direct medical and non-medical costs as well as indirect medical costs in the analysis and reported indirect costs (productivity losses) separately (Gabriel 2003).

For the 'Summary of findings' (SoF) table, we prespecified seven outcomes as recommended by the Cochrane Musculoskeletal Group (CMSG): pain, WOMAC MCII, Lequesne's index as a measure of overall pain/function/disability/quality of life, radiographic change, total adverse events, withdrawals due to adverse events, and serious adverse events. We decided to present both short- and long-term measures of pain (short- and long-term pain severity); long-term WOMAC MCII for pain, and short-term Lequesne's index.

Search methods for identification of studies

Electronic searches—The trials search coordinator (TSC) carried out the searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, CINAHL, AMED, and Current Controlled Trials updated to November 2013. No language or date restrictions were applied in the search for trials. Please see Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; and Appendix 7 for full search strategies. No trial registers were searched. We searched the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) websites using terms "chondroitin" to obtain the adverse effect data and/or warnings.

Searching other resources—The reference lists of the studies included in the review were searched for additional trials. Because numerous international nutraceutical companies market chondroitin, we anticipated that it would not be feasible to contact each of them for unpublished data. We did not search conference proceedings or journals specifically for the review, as prespecified.

We planned to summarize in our discussion non-randomized, post-marketing surveillance studies if they included 500 or more participants, reported adverse events or safety data, and were of one year's duration or longer because they may be more accurate in detecting rare adverse events.

Data collection and analysis

Selection of studies—We used our predetermined criteria to identify potential trials for inclusion. Two review authors (JAS, SN/KM) independently assessed the methods sections of all identified trials according to the predetermined assessment criteria (*see* "Selection

criteria"). Disagreements were resolved by consensus. For disagreements not resolved by consensus, the third review author (RM) would have served as the referee.

Data extraction and management—Two review authors with the help of research associates (JAS/PF, SN/KM) independently extracted data from the included trials. Extracted data included information such as the population of the study, interventions provided, the number of study centers, funding sources, and outcomes and analyses derived from standardized data extraction forms. When we needed more information, we contacted the authors of the studies. We extracted raw data from the published reports for outcomes of interest such as the standard deviation, the mean for continuous data, and the number of events for dichotomous data to evaluate efficacy. When this was impossible, for example, if data were reported as median scores only, we presented and described them in the "Characteristics of included studies table." When possible, we extracted data on the basis of the intention-to-treat analysis.

Assessment of risk of bias in included studies—Two review authors (JAS, SN) independently assessed the risk of bias for each included trial using The Cochrane Collaboration recommendations for assessment. The main criteria that were applied to measure the risk of bias included the presence of blinding (participants, personnel, and outcome assessors), allocation concealment, random sequence generation, incomplete outcome data, and selective outcome reporting (Higgins 2011). The risk of bias in each study was explicitly judged for each criterion using the following standard: low risk of bias, high risk of bias, or unclear risk of bias (either lack of information or uncertainty over the potential for bias). Disagreements were resolved by discussion between the two review authors.

Measures of treatment effect—We extracted all possibly extractable results from the included trials. For each randomized controlled trial, we calculated point estimates, such as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes. For continuous measures, we calculated mean differences when possible because results presented in this form are more readily interpreted by clinicians. Standardized mean differences were used as measures of treatment effect when outcomes assessed the same construct but used different outcome measures, such as data that used different and inconvertible scales to measure the same construct of interest. In our extraction of pain data, we applied a hierarchy when extracting data on various scales, extracting data on a 0 to 100 scale first, a 0 to 10 cm VAS scale second, a WOMAC pain subscale third, and all other pain outcomes thereafter. Whenever possible, we standardized the data presented to a 0 to 100-mm scale. In our extraction of physical function data, we extracted physical function on a WOMAC scale first and all other physical function measures thereafter. Data on this outcome were standardized to a 0 to 100-mm scale whenever possible.

Unit of analysis issues—For studies with more than two arms being included in the same meta-analysis, the placebo group would be handled so as to not double-count participants.

Dealing with missing data—We decided a priori not to impute any data for missing data. When we reviewed studies with missing data, such as loss of follow-up, or when authors of the study provided mean values on various outcomes but did not provide a standard deviation, we sent email queries to the authors to request the missing data. When data for variability statistics (as standard deviation) could not be obtained, we used the formula in Figure 1 to estimate the standard deviation; however, this was not done for the main analysis but only as part of a sensitivity analysis to facilitate comparisons of our review with reviews that had imputed such missing data.

Assessment of heterogeneity—Factors assessed for clinical homogeneity included duration of osteoarthritis, population demographics, outcomes, and control groups. We performed a Chi^2 test ($P < 0.10$) and used I^2 and T^2 statistics to quantify heterogeneity. As we chose to use the random-effects model, we used T^2 as a measure of heterogeneity between trials. In interpreting the T^2 statistic, a T^2 of 0.04 was prespecified to represent low heterogeneity, 0.09 to represent moderate heterogeneity, and 0.16 to represent high heterogeneity between trials (Spiegelhalter 2004). In interpreting the I^2 statistic, we complied with the recommendations put forth in the *Cochrane Handbook for Systematic Reviews of Interventions*, which determined that 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may indicate considerable heterogeneity (Deeks 2011).

Assessment of reporting biases—To assess reporting biases, we made a funnel plot when performing analyses on 10 or more studies. The funnel plot is a scatter plot that incorporates the sample size on the y-axis and the treatment effect along the x-axis. A good indication of reporting bias or other biases related to small study size is observation of asymmetry in the funnel plot.

Data synthesis—The random-effects model was the default model for pooling outcomes in the meta-analysis. The number needed to treat for an additional beneficial outcome (NNTB) was calculated as the inverse of the absolute risk difference. We used the Wells Calculator, available at the CMSG editorial office, to calculate NNTs for continuous outcomes. The following minimally important clinical differences (MCIDs) were used for the calculator:

Pain: 15 on a 0–100 scale (Farrar 2001)

Lesquene Index: 0.5 SD

Reduction in minimum JSW: 0.4mm (Maillefert 2002)

Standardized mean difference (SMD) was used to calculate the benefit of chondroitin over the comparator group for continuous outcomes such as pain measured on a VAS or other similar scales. Standardized mean difference is very similar to the term “effect size,” which is commonly used in presenting comparisons of active treatment with control. When calculating the SMD, we divided the difference in mean outcome between groups by the standard deviation of the outcome among participants. We obtained the relative difference in the change from baseline (benefit) by dividing the absolute benefit by the baseline mean of the control group. The “Summary of findings” tables included in RevMan 5 was completed

to communicate the key outcomes of the review. We used GRADE Profiler software to develop the tables and the GRADE system which assesses study limitations, indirectness, inconsistency, imprecision and publication bias to provide an overall grading of the quality of the evidence.

Subgroup analysis and investigation of heterogeneity—In this review, we performed subgroup analysis, based on the trials' duration, by the type of treatment arm and the type of control arm. For the main analysis, we divided the studies into short-term trials-those lasting less than six months-and long-term trials-those lasting six months or longer. This was done on the a priori clinical impression that short-term benefits and harms of chondroitin sulfate may differ from long-term benefits and harms. We made a decision that where both long- and short-term effects of chondroitin could be calculated for an outcome (such as pain, physical function etc.), we will present them separately.

We analyzed in one analysis trials that had the same composition in their treatment and control arms. For example, we analyzed in one analysis trials that compared treatment with chondroitin alone versus treatment with placebo alone and in another analysis studies that compared treatment with chondroitin alone versus treatment with an active control.

Sensitivity analysis—Sensitivity analyses were performed to check for the effects of various factors. The sensitivity analyses performed stratified data by allocation concealment, blinding, study size, study sponsorship by a pharmaceutical manufacturer of chondroitin sulfate, publication year, and analyses according to the intention-to-treat principle. Sensitivity analysis was performed on only the top four outcomes of the "Summary of findings tables" (pain, physical function, responders as defined by WOMAC minimal clinically important difference (MCID) or Outcome Measures in Rheuamtology Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) responder, and radiographic progression), under which data from two or more studies were included. If a study provided both short- and long-term data for an outcome (e.g., 3- and 12-month data on pain outcome), we considered only the 12-month outcome for these sensitivity analyses. This was done to allow inclusion of a meaningful number of studies in various subgroups.

RESULTS

Description of studies

Results of the search—Review authors found a total of 187 potential studies in the first search for this systematic review. Of these 187, 57 studies were obtained on 1 January 2006 for further investigation (Figure 2). Of these, 19 studies met the inclusion criteria. The remaining studies were excluded (refer to "Characteristics of excluded studies"). We performed a second search via MEDLINE on 12 September 2006 and identified 26 additional potential studies. Of these 26, two studies qualified for inclusion. We performed another search on 4 June 2007. This search yielded 12 results, of which three qualified for inclusion in our review. We performed another search on 21 May 2008. This time, we identified 15 additional references, of which one study qualified. On 30 June 2009, we performed another search that identified 32 studies. Of the 32 references pulled in the MEDLINE search, 15 were duplicates that had been pulled in the 21 May 2008 search. Of

the remaining 17 new references, six qualified as potential studies for inclusion in the meta-analysis. Of these six studies, two qualified. One of our Russian translators identified two additional studies for inclusion in our review. Later, on 20 July 2011, we performed another search, which yielded 29 results. Of these 29 potential studies, six fit the inclusion criteria. One study (Kahan 2009) was a duplicate from our previous search; therefore, five studies were picked for inclusion. On 12 June 2012, another search was performed to make sure that we included all studies that had been published up to the completion of our meta-analysis. This search yielded 764 results. Of these, sixteen were pulled for further review. Upon examination, five of these studies were deemed to fit the inclusion criteria and were added to our meta-analysis. A review of other meta-analyses performed on chondroitin revealed seven new possible studies for inclusion, of which two fit our inclusion criteria. A final search update was done in November, 2013 that yielded 794 titles/abstracts. An additional 4 studies were included from this search, of which one was a long-term follow-up of a previously included study by Wildi 2011A, but with a different outcome. Overall, therefore, 45 studies were included in our review. One study, Brandao 2009, could not be obtained, and another study, Vertkin 2007, was found to have an obvious mismatch in its data, as reported by the translating abstractor. Both studies were therefore excluded, yielding a total of 43 studies to be included in this systematic review and meta-analysis.

Included studies—See Figure 2 for a flow diagram of the search results. The "Characteristics of included studies table" provides further information about the included studies.

A total of 43 studies with 9,110 participants were included in this review. In all, 4,962 participants were treated with chondroitin (with/without glucosamine, NSAIDs) and 4,148 participants were included in the control group. Trial duration varied 1 month to 3 years. Data were usable from 30 studies in the meta-analysis. Examples of some studies with non-usable data were as follows: the treatment regimens were too different from the cohort of included studies (Alekseeva 2008; Cohen 2003; Magrans-Courtney 2011; Nguyen 2001), or they did not report clinical data (Rovetta 2002; Rovetta 2004).

1. Design: All included studies were randomized trials. Most were also blinded, with very few exceptions (Alekseeva 2005a; Alekseeva 2008; Lila 2005). Most studies were parallel-arm trials.

2. Sample sizes: Sample sizes ranged from ≤ 30 participants in a few trials (e.g., Magrans-Courtney 2011; Rovetta 2002) to 1,583 in the GAIT trial (Clegg 2006). Most studies had a sample size larger than 50 participants; in particular, several studies had sample sizes of 100 or more (Alekseeva 1999; Alekseeva 2005a; Alekseeva 2008; Clegg 2006; Gabay 2011; Kahan 2009; L'Hirondel 1992; Mazieres 2001; Michel 2005; Moller 2010; Morreale 1996; Nasonova 2001; Pavelka 1999; Pavelka 2010; Rai 2004; Sawitzke 2008; Sawitzke 2010; Uebelhart 2004; Fardellone 2013).

3. Setting: Many studies were single-center studies (e.g., Magrans-Courtney 2011; Nakasone 2011; Rovetta 2002; Uebelhart 2004). Other studies were multicenter studies (e.g., Clegg 2006; Uebelhart 2004; Wildi 2011).

4. Participants: Most studies included participants with knee osteoarthritis, with a few exceptions; a few studies included participants with hand osteoarthritis (Gabay 2011; Rovetta 2002; Rovetta 2004; Verbruggen 2002); one study included participants with hip osteoarthritis (Conrozier 1998).

5. Interventions: One study used a cream that included chondroitin (Cohen 2003); this study was not included in the analyses. Other studies administered oral chondroitin. Most studies gave chondroitin at 800 mg daily dose or higher, with notable exceptions such as Kanzaki 2011, Nakasone 2011; Nguyen 2001; Pavelka 1999; Rai 2004, in which a dose of chondroitin < 800 mg/d was used.

6. Outcomes: All studies had pain and function or quality of life as primary or secondary outcome. Two studies examined only radiographic outcomes (Rovetta 2002; Sawitzke 2008).

A summary of studies is provided below.

Alekseeva 1999 was a parallel arm RCT that included 100 patients, 50 each randomzied to chondroitin sulfate and control group in patients aged 45 and older, with knee osteoarthritis diagnosed according to ACR (1986) criteria and with Kellgren-Lawrence X-ray grade II or III. They had moderate to severe pain (> 30 mm on 100-mm VAS), Lequese's index 4 to 11 points, and had taken NSAIDs for at least 30 days over previous three months. Patients received either chondroitin sulfate 1000 mg/d (two capsules of 250 mg twice a day) with meals or ibuprofen up to 1200 mg/d (no rules for dose selection given). Paracetamol was allowed as rescue analgesia. The outcomes included VAS Pain (walking/rest), Lequesne's index, Patient global assessment (% improved), Patient global assessment on VAS and concomitant medication use. The study was sponsored by a manufacturer of chondroitin sulfate. Alekseeva 2005a was a randomized, parallel, independent group study involving 90 participants (45 in the control group, 45 in the active chondroitin sulfate group) that compared 1000 mg and 500 mg of chondroitin sulfate with 100 mg diclofenac daily for six months. Participants were included if they were diagnosed with knee osteoarthritis according to American College of Rheumatology (ACR) 1991 criteria, had a Kellgren-Lawrence X-ray grade II or III, moderate to severe pain on motion assessed on a 0 to 100-mm VAS scale (> 40 mm), and had been taking nonsteroidal anti-inflammatory drugs for at least 30 days in the previous three months. The active group consisted of 45 participants who were treated with 1000 mg of chondroitin sulfate daily for the first month, then with 500 mg of chondroitin sulfate daily for the next five months. The control group was treated with 100 mg diclofenac daily. Outcomes assessed included (1) Total WOMAC score, (2) Patient global assessment, (3) Physician global assessment, and (4) Adverse events.

Alekseeva 2005b was an open-label, randomized, multicenter clinical trial involving 375 participants for six months. Participants were included if they were diagnosed with knee osteoarthritis according to ACR criteria, were in the Kellgren-Lawrence X-ray grade of II or III, had pain on walking of greater than 40 mm on the 0 to 100-mm VAS, and had taken nonsteroidal anti-inflammatory drugs for at least 30 days in the past three months. A total of 203 participants were randomly assigned to the chondroitin sulfate in combination with glucosamine group, and 172 participants to the control group. Participants assigned to the

chondroitin sulfate in combination with glucosamine treatment group received 1000 mg of chondroitin sulfate daily plus 1000 mg of glucosamine daily for the first month, then 500 mg chondroitin sulfate and 500 mg glucosamine daily for the next five months. Participants in the active group were also allowed up to 100 mg diclofenac daily with dose reductions and cessation permitted with restrictions. The control group was treated with 100 mg of diclofenac daily for six months. This group was also allowed dose reduction and cessation of the use of diclofenac without restrictions. Outcomes reported were WOMAC Total, pain, physical function, and stiffness.

Alekseeva 2008 was an open-label, comparative, randomized, independent, parallel-group experimental design clinical trial that compared the effects of intermittent versus constant therapy with chondroitin sulfate and glucosamine. Participants were included in the study if they were diagnosed with RA according to the ACR (1991) criteria, were in the Kellgren-Lawrence X-ray grade II or III, had pain on walking of greater than 40 mm on the 0 to 100-mm VAS, and had taken NSAIDs for at least 30 days over the previous three months. A total of 50 participants were randomly assigned to the active group, which was treated with chondroitin sulfate combined with glucosamine for nine months daily. In the comparator group, chondroitin sulfate and glucosamine were taken for two three-month cycles with a three-month treatment-free interval between cycles. Participants were also allowed 1200 mg of Ibuprofen taken in 400-mg capsules three times daily, with dose reductions permitted at the physician's discretion in both groups. The study reported on the following outcomes: WOMAC pain, performance-based physical function, Patient and Physician global assessments, knee ultrasound, and adverse events.

Artemenko 2005 was a nine-month, open-label, comparative, parallel-design trial that assessed the efficacy of 1000 mg of chondroitin sulfate in combination with 1000 mg of glucosamine for one month, followed by five months of treatment with 500 mg of chondroitin sulfate and 500 mg of glucosamine chloride in comparison with treatment with 50 to 100 mg of diclofenac. A total of 31 participants were randomly assigned to the active arm, and 16 participants were randomly assigned to the control arm. Participants diagnosed with knee osteoarthritis according to ACR criteria, with Kellgren-Lawrence X-ray grade II or III, and with pain on walking greater than 40 mm on the 100-mm VAS were included in the study. Participants with pain on walking less than 40 mm on the 100-mm VAS, with secondary osteoarthritis, or receiving treatment with other "chondroprotective drugs" (not specified) during the six months before commencement of the trial were excluded from the study. Outcomes of interest in this study were pain, stiffness, Total WOMAC scores, rest and motion pain on VAS, Lequesne's index score, and Patient and Physician global assessments.

Bourgeois 1998 was a three-month, phase III, randomized, participant- and investigator-blind, double-dummy, parallel-group clinical trial that assessed the effects of chondroitin sulfate 4&6 in participants with internal or external, femoraltibial knee osteoarthritis. Participants of either sex, aged 45 or older, with femoral tibial, unilateral or bilateral knee osteoarthritis grade I to III diagnosed according to ACR criteria. Participants must have also required stable daily administration of one of the authorized NSAIDs for at least one month before the trial. All participants meeting the inclusion criteria were randomly assigned to one of three groups: chondroitin sulfate 4&6 1200 mg daily (N = 40), CS 4&6 400 mg three

times daily (N = 43), or placebo (N = 44). The primary outcome of interest in the study was Lequesne's index. Secondary outcomes included spontaneous pain on 0 to 100-mm VAS, Patient and Physician global assessments, consumption of NSAIDs, adverse effects, withdrawals, and deaths.

Bucsi 1998 was a randomized, participant- and investigator-blind, placebo-controlled studying involving two centers and lasting six months. A total of 39 and 46 participants were randomly assigned to the active and control groups, respectively. Participants in the chondroitin sulfate group were treated with 400 mg of chondroitin sulfate twice daily for six months. Participants in the control group were given an identical administration of placebo. Participants were included in the study if they were hospitalized patients or outpatients with idiopathic or secondary clinically symptomatic knee osteoarthritis for longer than six months who showed upon entry a Kellgren-Lawrence radiologic score of I to III. The primary end point was spontaneous joint pain on a 0 to 100-mm VAS when pain during daily physical activity was considered. Secondary outcomes were paracetamol consumption, time taken for a 20-m walk on a flat surface, pain, maximal walking distance, discomfort in daily life movements, Lequesne's index, and Patient and Physician global assessment.

Clegg 2006 was a multicenter, participant- and investigator-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT). Participants were included in the trial if they were at least 40 years old, showed clinical and radiographic evidence of osteoarthritis, had a summed pain score of 125 to 400 on the index knee according to WOMAC, and belonged to ARA functional class I, II, or III. Participants were randomly assigned to one of five treatment groups: 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate daily, 200 mg of celecoxib daily, or placebo. A total of 313 participants were assigned to the placebo group, 317 to the glucosamine alone group, 318 to the chondroitin group, 317 to the glucosamine and chondroitin sulfate combination group, and 318 to the celecoxib group. The primary outcome for this study was a 20% decrease in the summed score for the WOMAC pain subscale from baseline to week 24. Secondary outcomes for this study were WOMAC stiffness and physical function subscale scores; Patient and Physician global assessment of response to therapy and pain; presence or absence of soft tissue swelling, effusion, or both in the index knee; SF-36 scores; and analgesic use. Data used for global assessments were Patient and Physician global assessments of "response to therapy scores."

Cohen 2003 was a single-center, randomized, participant- and investigator-blind, placebo-controlled trial lasting eight weeks. The study assessed the effects of chondroitin sulfate preparation cream. Participants diagnosed with osteoarthritis of the knee according to ACR criteria had knee pain due to osteoarthritis greater than 4 cm on a 0 to 10-cm VAS in one or both knees for longer than four weeks. A total of 30 participants were randomly assigned to the active cream group, and 29 were randomly assigned to the inactive cream group. The treatment cream consisted of 30 mg/g of glucosamine sulfate, 50 mg/g of chondroitin sulfate, and 140 mg/g of shark cartilage, of which 10% to 30% is chondroitin sulfate, 32 mg/g is camphor, and 9 mg/g is peppermint oil scent. The inactive cream was a simple conventional cosmetic cream of identical scent and appearance. The primary outcome of this

study was pain on a 0 to 100-mm VAS. Secondary outcomes were pain, stiffness, and physical function on WOMAC and the SF-36 questionnaire.

Conrozier 1992 was a participant- and investigator-blind, placebo-controlled study that took place in France for six months. Participants were included in the study if they were diagnosed with hip joint arthrosis with narrowing but intra-articular space (degree I, II, III) and pain of the hip joint requiring regular analgesics or NSAIDs. A total of 56 participants were randomly assigned to each of the active and treatment groups Participants in the treatment group received three capsules of 400 mg of chondroitin sulfate, and those in the placebo group received an identical administration of placebo capsules. The primary outcomes of the study were Lequesne's index, pain relief on Huskisson's VAS, consumption of analgesics or nonsteroidal antirheumatics (NSARs), and participant evaluation. Secondary outcomes included morning stiffness, maximum walking distance, frequency of waking at night, and intermalleolar distance.

Das 2000 was a randomized, placebo-controlled, participant- and investigator-blind study. Participants were included if they were in grade II, III, or IV of the Kellgren-Lawrence scale, were between the ages of 45 and 75, were able to walk, were symptomatic for longer than six months, and had unilateral or bilateral osteoarthritis. Included participants must have been willing to comply with the protocol. A total of 46 participants were assigned to the chondroitin sulfate and glucosamine group and received two capsules of 500 mg of glucosamine and 400 mg of chondroitin sulfate plus 76 mg of manganese. Those in the placebo group received placebo tablets. The primary outcomes in this study were Lequesne's index, WOMAC score, and Patient global assessment. Secondary outcomes were consumed amounts of rescue pain medications and adverse events.

Debi 2000 was a randomized, participant- and investigator-blind study that compared glucosamine sulfate and chondroitin sulfate versus placebo and lasted one month. The original language of this study was Hebrew; thus we acquired a translator and translated the article. All study participants had osteoarthritis; 36 participants were randomly assigned to the active chondroitin sulfate group and 20 to the inactive group. All patients "suffering from osteoarthritis" were included in the study. Outcomes of the study were Patient global assessment, performance-based physical function, and radiographic changes on X-ray.

Fardellone 2013 was a multicenter, prospective, randomized, double-blind, double-placebo, active-controlled, parallel group study performed in patients with symptomatic knee OA that compared two chondroitin preparations, Structum® 500 mg twice daily or Chondrosulf® 400 mg three times daily over a 24-week duration. Inclusion criteria were as follows: age 50 to 80 years, medial and/or lateral femorotibial OA of the knee according to American College of Rheumatology (ACR) criteria, symptomatic for more than 6 months, with a baseline level of symptoms as follows, global pain score on a Visual Analog Scale (VAS 0 to 100) of at least 40 millimeters (mm), a Lequesne's algofunctional index (LFI 0 to 24) score greater than or equal to 7, radiographic OA as defined by a Kellgren-Lawrence grade II or III on an antero-posterior weight-bearing view of both knees taken. Primary outcome was global pain on 0 to 100 mm VAS. Secondary outcomes included patient's and investigator's global assessment scores (VAS), Osteoarthritis of the knee or hip Quality of Life dimension

score (OAKHQOL), Short-form 12 (SF-12) scores and the use of analgesic medications (paracetamol and/or NSAIDs).

Gabay 2011 was an investigator-initiated, single-center, randomized, participant- and investigator-blind, placebo-controlled clinical trial that examined the efficacy of chondroitin in participants with hand osteoarthritis. Participants were included in the trial if they were at least 40 years old and fulfilled the ACR criteria for the classification of hand osteoarthritis. In addition, radiographic features of hand osteoarthritis affecting at least two joints of the target hand on standard plain films obtained within six months of enrolment and at least two painful flares of osteoarthritis in the finger joints during the previous 12 months were required. The target hand was defined as the participant's most symptomatic hand or, when both hands were equally painful, the participant's dominant hand. To be eligible for the study, participants had to have presented with symptomatic osteoarthritis. Minimum symptoms included joint pain of at least 40 mm on a 0 to 100-mm VAS and a Functional Index for Hand Osteoarthritis (FIHOA) score of at least 6 in the target hand (0 to 30 scale). The study lasted for six months. A total of 80 participants were randomly assigned to receive 800 mg of chondroitin sulfate daily. In all, 82 participants were randomly assigned to receive placebo sachets. The primary outcomes of the study were change in the Patient's assessment of global spontaneous hand pain on VAS and change in Patient's assessment of global spontaneous hand function on the FIHOA score from baseline to month six. Secondary outcomes were grip strength and duration of morning stiffness.

Kahan 2009 is an international, randomized, participant- and investigator-blind, placebo-controlled trial that lasted two years. Participants were included in the trial if they were outpatients between 40 and 80 years old who had been diagnosed with primary knee osteoarthritis of the medial tibiofemoral compartment according to ACR criteria. A total of 309 participants were randomly assigned to the active chondroitin group, which received 800 mg of chondroitin sulfate daily for two years. In all, 313 participants were randomly assigned to the placebo group and received placebo sachets of identical appearance and regimen. The primary outcome of the study was pain modification in the minimum joint space width of the medial compartment of the target tibiofemoral joint. Secondary outcomes included assessment of pain using a 0 to 100-mm VAS, WOMAC Total and subscale scores, Patient and Physician global assessments, cumulative consumption of acetaminophen, and cumulative consumption of NSAIDs. Results and data for joint space width are taken from Kahan's supplementary report, published in 2006, in which results for joint space narrowing were presented for the placebo and chondroitin sulfate groups.

Kanzaki 2011 was a prospective, randomized, placebo-controlled, parallel-group comparative study that was designed to assess the efficacy and safety of a GCQ supplement (that contained chondroitin) for a duration of six months. The study involved two clinical service organization centers that were under the control of two medical investigators in Japan. Male and female Japanese participants between 40 and 85 years of age were diagnosed with knee osteoarthritis, and the presence of knee pain was confirmed by assessment of scores on the "walking" subscale of the Japanese Orthopedic Association (JOA). A total of 20 participants were randomly assigned to receive 1200 mg glucosamine hydrochloride, 300 mg shark cartilage extract (60 mg as chondroitin sulfate), and 45 mg

quercetin glycosides in a daily dose of six tablets in the active group. In all, 20 participants were randomly assigned to the placebo group and received indistinguishable placebo tablets, which were administered identically with six tablets a day. The primary outcomes of the study were Japan Orthopaedic Association subscale scores. Subscales documented walking ability, ascending and descending ability and pain on stairs, range of motion, and degree of joint swelling. The study's secondary outcomes were pain at rest on VAS, pain on walking on VAS, and pain on ascending and descending of stairs on VAS.

L'Hirondel 1992 was a participant- and investigator-blind, parallel-design, randomized study in which orally administered chondroitin sulfate was compared with placebo in participants with tibiofemoral gonarthrosis for six months; the study was conducted in France. Participants were included if they had painful tibiofemoral gonarthrosis with an intra-articular space but without dislocation of the main axis and with or without meniscus calcification. A total of 63 participants were randomly assigned to the active chondroitin sulfate group, and 62 participants were randomly assigned to the placebo group. The chondroitin sulfate group received three sachets of 400 mg chondroitin sulfate daily, and the placebo group received three identical sachets of placebo. Participants were allowed to continue their ongoing treatments through the first two months of the study and were then allowed 500 mg of paracetamol from months 2 to 6, according to their pain intensity. The primary outcomes of this study were Lequesne's index, adverse effects, pain relief on Huskisson's VAS, consumption of analgesics and nonsteroidal antirheumatics, and total efficacy as evaluated by the investigator. Secondary outcomes included extent of flexion and extension of the joint, extent of joint circumference, and verification of a static incident, an abnormal movement, or an intra-articular effusion.

Lila 2005 was a randomized, open efficacy trial that included participants 45 to 75 years of age who were diagnosed with osteoarthritis according to ACR 1987 criteria and were in Kellgren-Lawrence X-ray grade I to III. They had a pain score greater than 40 mm on a VAS (0 to 100 mm) for pain on walking and had daily morning stiffness for at least 30 minutes. A total of 30 participants who fulfilled these criteria were randomly assigned to the active chondroitin sulfate in combination with glucosamine and placebo groups. Those assigned to the active group received 800 mg of chondroitin sulfate in combination with 1000 mg of glucosamine daily for the first month, then 400 mg of chondroitin sulfate plus 500 mg of glucosamine daily for the next two months. The control group received diclofenac 75 mg daily. Outcomes of in the study included WOMAC subscales, rest or motion pain on a 0 to 100-mm VAS, morning stiffness, Patient and Physician global assessments, and adverse events.

Magrans-Courtney 2011 was a randomized, participant- and investigator-blind, placebo-controlled, parallel clinical trial that lasted 14 weeks. Women with physician-diagnosed osteoarthritis between the ages of 18 and 70 years who had a body mass index (BMI) greater than 27 kg/m^2 and no recent participation in a diet or exercise program were included in the study. A total of 16 participants were assigned to the active treatment arm, in which participants received a total of 1500 mg of glucosamine (from d-glucosamine HCL), 1200 mg/d of chondroitin sulfate (from chondroitin sulfate sodium), 120 mg/d of niacin, 120 mg/d of sodium, 45 mg/d of zinc, 900 mg/d of MSM, 300 mg/d of Boswellia serrata extract, 180

mg/d of white willow bark extract, and 15 mg/d of rutin powder. A total of 14 participants were randomly assigned to receive placebo of identical appearance and dosage. All randomly assigned participants also participated in a 14-week circuit-style workout consisting of 14 exercises (e.g., elbow flexion/extension, knee flexion/extension, shoulder press/lat pull, hip abductor/adductor, chest press/seated row, horizontal leg press, squat, abdominal crunch/back extension, pec deck, oblique, shoulder shrug/dip, hip extension, side bends, stepping three times a week). Participants in each treatment group were then randomly assigned to begin a high-protein or high-carbohydrate diet program. Both programs were composed of three phases. During the first phase, which lasted one week, participants were allowed to consume a total of 1200 kcal daily. For the next nine weeks, participants were given 1600 kcal/d. The final four weeks of the diet (Phase III) served as a weight maintenance period. The high-protein (HP) diet regimen was composed of 7% carbohydrate, 63% protein, and 30% fat during Phase I, and 15% carbohydrate, 55% protein, and 30% fat during Phase II. Upon completion of the high-carbohydrate diet program, participants were instructed to consume a diet consisting of 55% carbohydrate, 15% protein, and 30% fat. In the final phase of the diet program, all participants were allowed 55% carbohydrate, 15% protein, and 30% fat. The primary outcomes were measures of pain, including pain on VAS, stiffness, physical function, and Total score on the WOMAC scale. Secondary outcomes included weight loss, body composition, measures of quality of life, changes in energy intake, anthropometrics, body composition, resting energy expenditures, cardiovascular and muscular fitness, balance and functional capacity, serum and whole blood clinical markers, hormonal profiles, pain indices, psychosocial parameters, and knee range of motion and circumference.

Mazieres 1992 was a multicenter, randomized, controlled, parallel, independent, participant- and investigator-blind study that lasted three months; participants were 50 years of age or older; had a pain score of at least 40 mm on a 0 to 100-mm VAS and a score greater than 4 on Lequesne's Index; and were diagnosed with gonarthroses of the femorotibial and internal or external compartment or coxarthrosis. A total of 58 participants were randomly assigned to the active group and received 2000 mg of chondroitin sulfate daily for three months. In all, 56 participants were randomly assigned to the placebo group. Outcomes of interest in the study were rest or motion pain on VAS, Lequesne's index, Patient and Physician global assessments, and NSAID use.

Mazieres 2001 was a participant- and investigator-blind, randomized, parallel-group study that lasted six months. The study included outpatients older than 50 years of age who met the following criteria: (1) clinically and radiographically confirmed osteoarthritis of one or both knees according to the criteria of the ACR; (2) an algofunctional index of Lequesne (AFI) ≥ 4; (3) pain with activity ≥ 30 mm on a 100-mm VAS; (4) regular consumption of NSAIDs for three months; and (5) radiographic grade II to III on the Kellgren-Lawrence scale. In participants with osteoarthritis of both knees, the most painful side was assessed. A total of 67 participants were randomly assigned to the active chondroitin sulfate group and received 500 mg of chondroitin sulfate twice daily for three months. In all, 63 participants were randomly assigned to the placebo treatment group and received placebo sachets. The primary outcome of the study was Lequesne's AFI. Secondary outcomes were pain on physical activity as measured on a 0 to 100-mm VAS, pain on rest as measured on a 0 to

100-mm VAS, self-assessed effect of osteoarthritis on daily activities as measured on a 0 to 100-mm VAS, participant's overall assessment of change as measured on a five-point categorical scale (much better, better, unchanged, somewhat worse, much worse), and daily NSAID and analgesics consumption.

Messier 2007 was a participant- and investigator-blind, placebo-controlled, randomized clinical trial that lasted 12 months, of which six months was applicable to the current review. For the remaining six months, investigators assessed the effect of exercise combined with chondroitin sulfate and glucosamine, and thus the data could not be used. Participants were included if they were 50 years of age or older, had mild to moderate knee osteoarthritis on a Kellgren-Lawrence scale (II or III) according to ACR criteria, and were not currently participating in another study. A total of 45 participants were randomly assigned to the chondroitin sulfate and glucosamine hydrochloride group and received 1200 mg of chondroitin sulfate plus 1500 mg of glucosamine hydrochloride once or three times daily. In all, 44 participants were randomly assigned to the placebo group and received placebo sachets of identical appearance and odor in a blinded fashion. The primary outcome of the study was physical function as measured on the WOMAC. Secondary outcomes were pain on WOMAC, distance walked in six minutes, mental status as measured on the Mini Mental State Examination (MMSE), balance, and strength of concentric extension and flexion in the most affected knee.

Michel 2005 was a randomized, participant- and investigator-blind, placebo-controlled trial that lasted two years and was conducted in Zurich, Switzerland. Participants were included in the study if they were between the ages of 40 and 85 years and had clinically symptomatic knee osteoarthritis (knee pain while standing, walking, and/or on motion for at least 25 or 30 days before study entry, with no required minimum level of pain on the day of entry). Partcipants had to be diagnosed with knee osteoarthritis according to ACR clinical and radiographic criteria for osteoarthritis of the knee. Participants with osteoarthritis of grade I, II or III according to Kellgren-Lawrence (KL) were eligible for study entry. Participants with osteoarthritis of KL grade 4, indicating a greatly narrowed joint space with sclerosis of subchondral bone, were excluded. The target knee was defined as the most symptomatic knee at study entry. A total of 150 participants were randomly assigned to the active chondroitin sulfate group and received 800 mg of chondroitin sulfate once daily for two years. In all, 150 participants were randomly assigned to the placebo group and received placebo sachets. The primary outcome of interest was the minimum and mean joint space width of the more severely affected compartment of the target knee. Secondary outcomes were stiffness and physical function on WOMAC, total consumption of rescue drugs during the trial, average number of tablets of study drug taken per day, and adverse events.

Moller 2010 was a randomized, participant- and investigator-blind, placebo-controlled multicenter study that lasted three months. Participants eligible for the study were men and women 40 years of age or older who had osteoarthritis of the knee as defined by the criteria of the ACR, pain in the affected knee scored as 30 on a continuous 0 to 100-mm Huskisson's VAS, and a confirmatory knee X-ray diagnosis (Kellgren-Lawrence grade I to III) associated with cutaneous plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score of 5. A total of 60 participants were randomly assigned to receive 800 mg of

chondroitin sulfate daily. In all, 56 participants were randomly assigned to receive matched placebo capsules. Primary outcomes were a decrease in pain intensity as assessed by VAS and clinical improvement of psoriasis as determined by PASI score at the end of treatment as compared with baseline. Secondary outcomes were pain relief and function improvement in the knee according to the Lequesne AFI, acetaminophen consumption, histopathologic data, changes in psoriatic lesions according to physician global assessment (PGA), assessment of efficacy by participants and investigators, and quality of life as measured by SF-36.

Morreale 1996 was a six-month, randomized, participant- and investigator-blind, parallel-group study that was conducted at two centers. Participants were between 40 and 75 years of age and had grade I or II monolateral or bilateral knee osteoarthritis; they were not taking NSAIDs or chondroprotective treatment for 15 to 30 days before study initiation. A total of 74 participants were randomly assigned to the chondroitin sulfate group and received 400 mg of chondroitin sulfate three times daily plus three tablets of placebo for the first month, only 400 mg of chondroitin sulfate for the second month, and only placebo tablets from months 3 to 6. A total of 72 participants were randomly assigned to the control group; they received 50 mg of diclofenac sodium three times daily plus three tablets of placebo in the first month of the trial; only three placebo sachets in the second month of the trial, and placebo from months 3 to 6. Only the first month's results were applicable to the study because the treatment setup created dependence over the months of the study and did not allow for stratification of the data into three separate calculable data sets. The primary outcomes of the study were Lequesne's AFI score, spontaneous pain on a 0 to 100-mm VAS, and pain on load on a 4-point scale of absent, light, moderate, and intense. The secondary outcome of interest in the study was paracetamol consumption.

Nakasone 2011 was a randomized, participant- and investigator-blind, placebo-controlled study designed to assess the efficacy and safety of the test supplement in adult participants with symptomatic knee osteoarthritis; the study lasted 16 weeks and was conducted at two clinical service organizations in Yokohama, Japan. All male and female Japanese participants were 40 to 83 years of age and presented with clinical and radiographic evidence of mild knee osteoarthritis, defined by a score of 30 to 75 on a 100-mm VAS and by radiologic severity of affected knee joints mainly graded 1 to 2 on the Kellgren-Lawrence (KL) scale. Participants with diagnosed bilateral knee osteoarthritis were asked to specify the worse affected knee at baseline, and this knee was evaluated throughout the study period. A total of 16 participants were randomly assigned to the treatment group, which received 1200 mg of orally administered glucosamine hydrochloride, 200 mg of shark cartilage (60 mg of chondroitin sulfate), 300 mg of MSM, 105 mg of guava leaf extract, 5.6 μg of vitamin D, and 7.35 mg of vitamin B1 seven times daily; 16 participants were assigned to the inactive placebo group. The primary efficacy outcomes of this study were scores on the Japanese Knee Osteoarthritis Measure subscales of pain/stiffness, conditions of daily life, general conditions, and health conditions. Other reported outcomes were pain on VAS, pain on rest on VAS, pain on walking on VAS, pain on ascending or descending stairs on VAS, synovial inflammation, and cartilage metabolism.

Nguyen 2001 is a three-month, randomized, participant- and investigator-blind pilot study that included participants with pain in one or both temporomandibular joints (TMJs) and

moderate or severe pain on lateral or dorsal palpation of the TMJ. A total of 24 participants were randomly assigned to the chondroitin sulfate group and received two tablets of 250 mg of glucosamine hydrochloride and 200 mg of chondroitin daily. Outcomes of the study were pain on VAS (0 to 100 mm), on the McGill Pain Questionnaire's pain rating scales, and on the mood and functioning questionnaire; tenderness on TMJ palpation; jaw range of motion; daily pain rating on the VAS; analgesic use; and daily change in pain intensity.

Pavelka 1999 was a phase II, randomized, participant- and investigator-blind, dose-effect study. Participants were older than 30 years of age and had femorotibial osteoarthritis of the knee, according to ACR criteria, with clinical symptoms that persisted for at least three months; Lequesne's Index greater than or equal to 8 points; pain on Huskisson's VAS greater than or equal to 40 mm during physical activity; and persistence of some articular joint space as documented on radiography. Participants were randomly assigned to one of four groups. In all, 35 participants were randomly assigned to the 200-mg chondroitin sulfate group and received one sachet of 200 mg chondroitin sulfate; 35 participants to 800 mg of chondroitin sulfate and given one sachet of 800 mg chondroitin sulfate; 35 participants to the 1200-mg chondroitin sulfate group and given one sachet of 1200 mg chondroitin sulfate; and 35 participants to the placebo group and given one placebo sachet. The primary outcome of the study was Lequesne's Index and Spontaneous Pain on Huskisson's VAS on a 0 to 100-mm scale, Patient and Physician Global Efficacy Evaluations, and Paracetamol Consumption from Day 15 to Day 90.

Pavelka 2010 was a six-month, controlled, randomized, multinational, multicenter, participant- and investigator-blind, double-dummy, parallel-group study that was carried out at five centers in the Czech Republic, three in the Slovak Republic, five in Hungary, seven in Poland, and six in Romania. Participants had to be "aged 45 years or above and [to have] femorotibial osteoarthritis of the knees longer than six months with pain and functional discomfort over one month during the past three months, were complying with the clinical and radiologic criteria of the American College of Rheumatology of knee osteoarthritis, had a Lequesne's index between 5 and 13 and a radiologic score of grade I, II or III of the modified Kellgren-Lawrence scale on a frontal image of extended knee, on both knees, the image being not older than six months, had pain on movement and/or pain at rest in the last 48 hours [of] at least 40 mm evaluated on a VAS, and/or at least 40 mm evaluated on at least two items among the five items n the A-section of the WOMAC Index, with no intake of analgesics for 48 hours and NSAID for 5 days." A total of 142 participants were randomly assigned to receive 300 mg of avocado soybean unsaponifiable daily. In all, 121 participants in the comparator group were randomly assigned to receive 400 mg three times daily. The primary outcome of the study was the change in the WOMAC index from the beginning of the study to the end of treatment. Secondary outcomes were the Lequesne index, pain on active movement and at rest, and global assessment of efficacy.

Rai 2004 was a randomized, participant- and investigator-blind, placebo-controlled trial with participants older than 50 years of age who had primary knee osteoarthritis, mainly on the medial femorotibial compartment, according to the clinical and radiographic criteria of ACR and a Lequesne's index score of 4 or greater. The treatment group (n = 50) received a drug called *kondro* and was compared with a placebo group (n = 50). Kondro is a combination of

chondroitin and glucosamine, although the exact amounts of either were not specified on the pharmaceutical company's website. Outcomes of interest in the study were Lequesne's index scores and joint space narrowing as shown on X-rays.

Railhac 2012 was a randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted in 20 French rheumatology practice centers comparing Structum® 500 mg (chondroitin) or matching placebo, twice daily by oral route as from baseline to week 48. Primary outcomes were pain on VAS (0 to 100) and Lequesne index scores. Secondary outcomes were clinical improvement according to the patient and the investigator and the use of rescue medication (paracetamol and/or NSAIDs). The first author was an employee of the maker of chondroitin product discussed.

Raynauld 2013 was a long-term follow-up study of Wildi 2011, as described above. Four-year outcome of total knee replacement was presented along with its predictors, where one group was treated with chondroitin or placebo once daily for the first 6 months (double-blind phase) followed by 6 months of treatment with 800 mg chondroitin sulfate once daily for both groups (open-label phase). Thirty-five patients were randomized each to chondroitin and placebo, of whom 57 patients were followed for this study. Thirteen patients underwent total knee replacement at 4-years, 9/34 in the placebo and 4/35 in the chondroitin group. Details of inclusion/exclusion criteria are provided in Wildi 2011.

Rovetta 2002 was a 24-month, randomized trial involving 24 "consecutive" participants of both sexes (2 men and 22 women) with a mean age of 53 years who were suffering from osteoarthritis and were showing central erosions of the distal interphalangeal (DIP) and/or proximal interphalangeal (PIP) joints. Participants were randomly assigned to one of two groups: naproxen 500 mg/daily only (Group A) or chondroitin sulfate 800 mg daily plus naproxen 500 mg daily (Group B). The only outcome of interest in the study was the joint count for erosions; results were taken at baseline and at 12 and 24 months.

Rovetta 2004 is the same trial as Rovetta 2002; however, the authors present results on several different outcomes. The outcomes of this study are radiographic joint counts for Heberden and Bouchard nodes; the Dreiser index was used to assess pain and function and Patient and Physician global assessments on a 0 to 10-cm VAS.

Sawitzke 2008 was the follow-up of Clegg 2006 study and presented the mean change in JSW in the medial compartment of the knee over 2 years.

Sawitzke 2010 was a 24-month, participant- and investigator-blind, placebo-controlled study that was conducted at nine sites in the United States ancillary to the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), a follow-up report of Clegg 2006; investigators enrolled 662 participants with knee osteoarthritis who satisfied radiographic criteria (Kellgren-Lawrence (KL) grade II or III changes and baseline joint space width of at least 2 mm). Participants were included in the study if they were at least 40 years old, had been diagnosed with osteoarthritis for at least six months, and showed radiographic evidence of osteoarthritis by KL grade II or III. A total of 134 participants were assigned to receive 500 mg of glucosamine three times daily. In all, 126 participants were assigned to receive 400 mg of chondroitin sulfate three times daily; 129 to receive a combination of the

glucosamine and chondroitin sulfate dosages; 142 to receive 200 mg of celecoxib daily; and 131 to receive a placebo. The study's primary outcome was a 20% reduction in WOMAC pain over 24 months. Secondary outcomes were pain reduction attributable to each treatment WOMAC function subscale and the likelihood of achieving an OMERACT/OARSI response over 24 months.

Uebelhart 1998 was a one-year, randomized, participant- and investigator-blind, controlled pilot study with 46 participants of both sexes between the ages of 35 and 79 who had symptomatic osteoarthritis. The chondroitin active group received 400 mg of chondroitin sulfate twice daily, while the placebo group received placebo sachets. A total of 23 participants were randomly assigned to chondroitin sulfate, and 23 participants were randomly assigned to the placebo group. Primary outcomes of the study were the degree of spontaneous joint pain as measured on VAS (0 to 100 mm) and overall mobility capacity on VAS. Secondary outcomes included the actual joint space measurement taken by X-ray and the levels of biochemical markers of bone and joint metabolism. In our meta-analysis, we subtracted the rating for overall mobility capacity from 100 because the scale for this outcome took 0 as the worst score and 100 as the best score. Because all of the other studies that presented data on this outcome did so on an opposite scale, which took 0 as the best and 100 as the worst, we inverted the scale for this study's outcome of physical function to standardize and incorporate its data.

Uebelhart 2004 was a multicenter, participant- and investigator-blind, placebo-controlled, one-year trial that compared chondroitin sulfate with placebo. Participants 40 years of age or older had stiffness of less than 30, bilateral or monolateral idiopathic knee osteoarthritis according to the ACR, and a Kellgren-Lawrence score of I to III, with a minimum of 25% remaining medial femorotibial joint space. A total of 54 participants were randomly assigned to the chondroitin sulfate group and received 800 mg daily of chondroitin sulfate for two periods of three months (1 to 90 days and 181 to 270 days) over a two-year period. The primary outcome of the study was the score on Lequesne's index. Secondary outcomes were spontaneous pain on a 100-mm VAS, time to walk 20 meters, Patient global assessment of efficacy on a 0 to 4 Scale, consumption of analgesics, joint space narrowing on X-ray, and adverse events.

Verbruggen 2002 was a randomized, participant- and investigator-blind, placebo-controlled trial that assessed the effects of chondroitin sulfate as a disease modifying osteoarthritis drug (DMOAD) at Ghent University Hospital. Participants were included if they were between 40 and 70 years of age and had symptoms producing osteoarthritis of the finger joint that were confirmed according to the presence of osteophytes and/or joint space narrowing, with or without subchondral sclerosis on hand X-rays. The study reported that all participants were Caucasian. A total of 44 participants were randomly assigned to the active chondroitin sulfate group and received 400 mg of chondroitin sulfate three times daily for three years. In all, 48 participants were randomly assigned to the placebo group and received placebo sachets three times daily for three years.

Wildi 2011 was a multicenter, randomized, participant- and investigator-blind, controlled trial that compared chondroitin sulfate with placebo in participants with primary knee

osteoarthritis lasting six months. Participants were included if they were diagnosed with primary osteoarthritis of the knee in accordance with the clinical and radiologic criteria of the ACR and if they had clinical signs of synovitis (warmth, swelling, or effusion), a disease severity grade 2 or 3 based on the Kellgren-Lawrence radiographic system, a minimal medial joint space width (JSW) of 2 mm on standing knee X-ray, and a VAS pain index of at least 40 mm while walking. Participants were required to have no significant laboratory abnormalities. In all, 35 participants were randomly assigned to receive 800 mg of chondroitin sulfate as two capsules of 400 mg once daily. A total of 34 participants were randomly assigned to receive placebo once daily. The primary outcome of the study was synovial membrane thickness. Secondary outcomes were cartilage volume; bone marrow lesions; WOMAC pain, function, stiffness, and total score; pain on VAS; and quality of life as assessed by SF-36.

Zegels 2012 was a multicenter, randomized, double blind, double-dummy study with an allocation ratio of 1:1:1, in 10 centres in Belgium, three in France and two in Switzerland that compared oral sachet of chondroitin sulfate 1200 mg/day, one oral capsule of chondroitin sulfate 400 mg three times a day and placebo. Primary outcome was Lequesne's index and secondary outcomes were Pain VAS, treatment compliance and adverse effects.

Excluded studies—After review of the full texts, 58 studies were excluded, all of which are included in the reference list (Excluded studies). Of these studies, 11 were excluded because they were reviews and 13 because they were not randomized. Six studies were excluded because they did not provide data on any clinical outcomes specified. Two studies were excluded because they were duplicates, 16 because they were abstracts, one because it could not be obtained and the author did not respond to requests to provide the study for review, four because they were commentaries, another four because investigators did not study the efficacy of chondroitin or did not study osteoarthritis, and one because an obvious mismatch was noted in the data provided. Details are given in the excluded studies section (Characteristics of excluded studies).

Risk of bias in included studies

Figure 3 and Figure 4 provide information about the risk of bias assessment performed for each individual study.

Allocation—Risk of bias assessment was performed by two assessors independently (SN, PF/JAS). All disagreements were settled by consensus. Of the 43 studies included in this meta-analysis, 30 did not report methods of randomization adequately (Alekseeva 1999; Alekseeva 2005a; Alekseeva 2005b; Alekseeva 2008; Artemenko 2005; Bourgeois 1998; Bucsi 1998; Cohen 2003; Conrozier 1992; Conrozier 1998; Das 2000; Debi 2000; Kanzaki 2011; L'Hirondel 1992; Lila 2005; Magrans-Courtney 2011; Mazieres 1992; Mazieres 2001; Morreale 1996; Nakasone 2011; Nasonova 2001; Pavelka 1999; Rai 2004; Rovetta 2002; Rovetta 2004; Sawitzke 2010; Uebelhart 1998; Verbruggen 2002; Wildi 2011; Raynauld 2013). There were 13 studies that reported adequate methods of randomization (Clegg 2006; Gabay 2011; Kahan 2009; Messier 2007; Michel 2005; Moller 2010; Nguyen 2001;

Pavelka 2010; Sawitzke 2008; Uebelhart 2004; Fardellone 2013; Railhac 2012; Zegels 2012).

In all, 34 studies did not report the methods of allocation concealment used or had unclear methods of allocation concealment (Alekseeva 1999; Alekseeva 2005a; Alekseeva 2005b; Alekseeva 2008; Artemenko 2005; Bourgeois 1998; Bucsi 1998; Cohen 2003; Conrozier 1992; Conrozier 1998; Debi 2000; Gabay 2011; Kanzaki 2011; L'Hirondel 1992; Lila 2005; Magrans-Courtney 2011; Mazieres 1992; Mazieres 2001; Michel 2005; Morreale 1996; Nakasone 2011; Nasonova 2001; Pavelka 1999; Pavelka 2010; Rai 2004; Rovetta 2002; Rovetta 2004; Sawitzke 2008; Sawitzke 2010; Uebelhart 1998; Verbruggen 2002; Fardellone 2013; Railhac 2012; Zegels 2012). Nine studies reported adequate methods of allocation concealment (Clegg 2006; Das 2000; Kahan 2009; Messier 2007; Moller 2010; Nguyen 2001; Uebelhart 2004; Wildi 2011; Raynauld 2013). For a more detailed description of allocation concealment in the individual studies, refer to the risk of bias tables included under the characteristics of included studies and to Figure 1 and Figure 2.

Blinding—Of the 43 studies included in this meta-analysis, 14 used unclear methods of blinding (Bucsi 1998; Cohen 2003; Conrozier 1998; Debi 2000; Gabay 2011; L'Hirondel 1992; Mazieres 1992; Nakasone 2011; Rai 2004; Sawitzke 2008; Sawitzke 2010; Verbruggen 2002; Wildi 2011;Raynauld 2013). Nine studies did not have participant and investigator blinding (Alekseeva 1999, Alekseeva 2005a, Alekseeva 2005b, Alekseeva 2008, Artemenko 2005, Lila 2005, Nasonova 2001, Rovetta 2004, Rovetta 2002); 20 studies (Bourgeois 1998, Clegg 2006, Conrozier 1992, Das 2000, Kahan 2009, Kanzaki 2011, Magrans-Courtney 2011, Mazieres 2001, Messier 2007, Michel 2005, Moller 2010, Morreale 1996, Nguyen 2001, Pavelka 1999, Pavelka 2010, Uebelhart 1998, Uebelhart 2004; Fardellone 2013; Railhac 2012; Zegels 2012) used investigator and participant blinding and described adequately the methods used.

Incomplete outcome data—Of the 43 studies included in this meta-analysis, 10 used unclear methods in handling missing outcomes (Alekseeva 2005a; Alekseeva 2005b; Alekseeva 2008; Bucsi 1998; Debi 2000; Kanzaki 2011; L'Hirondel 1992; Nakasone 2011; Sawitzke 2010; Uebelhart 1998). Of the remaining 33 studies, 25 were assessed to have adequately handled missing outcome data by accounting for and providing a clear explanation of all dropouts or performing the appropriate statistical methods for handling missing data (Bourgeois 1998; Clegg 2006; Cohen 2003; Conrozier 1992; Conrozier 1998; Das 2000; Gabay 2011; Kahan 2009; Magrans-Courtney 2011; Mazieres 1992; Mazieres 2001; Messier 2007; Michel 2005; Morreale 1996; Pavelka 1999; Pavelka 2010; Rovetta 2002; Rovetta 2004; Sawitzke 2008; Uebelhart 2004; Verbruggen 2002; Fardellone 2013; Railhac 2012; Raynauld 2013; Zegels 2012). The remaining eight studies failed to provide an adequate account of their withdrawals and missing outcome data or to perform the appropriate statistical methods.

Selective reporting—Only one study (Clegg 2006) reported on outcome measures as recommended by the Outcome Measures in Rheumatology (OMERACT) group. Therefore, it was difficult to find commonly reported outcomes across the studies. Furthermore,

because review authors could not gain access to the study protocols, it was difficult to decipher whether the studies reported on all outcomes specified in the study protocol.

Other potential sources of bias—Although no other sources of bias were detected, most of the included studies were funded by a manufacturer of chondroitin, which may qualify as a confounding source. This issue is discussed further in the Discussion section of this review, as the source of funding for trials is not a factor that directly influences the methods used in the analysis. For more information on the source of funding for each study, please refer to the "Characteristics of included studies tables."

Effects of interventions

See: **Summary of findings for the main comparison** Chondroitin versus placebo for osteoarthritis; **Summary of findings 2** Chondroitin with or without glucosamine versus placebo/control for osteoarthritis (studies with estimated SDs not analyzed); **Summary of findings 3** Chondroitin with or without glucosamine versus placebo/control for osteoarthritis (sensitivity analysis including studies with estimated SDs)

Five comparison groups were used for this analysis. We performed the meta-analysis by stratifying the compiled data into the following comparable groups.

1. Chondroitin sulfate versus placebo
2. Chondroitin sulfate versus control
3. Chondroitin sulfate plus glucosamine versus placebo
4. Chondroitin sulfate plus glucosamine versus NSAIDs control
5. Chondroitin sulfate/chondroitin sulfate plus glucosamine/chondroitin sulfate plus other supplement versus placebo or control

Overall, 43 studies were included in this review. Of the 43 studies, 30 provided usable data, since outcomes reported matched with those specified for our systematic review. Several studies provided data for more than one of our comparison arms, such as Clegg 2006, Sawitzke 2008 and Sawitzke 2010, which tested the efficacy of chondroitin alone, in combination with glucosamine, and in comparison with both placebo and an NSAID control. We came across additional studies that were not classifiable into these comparison arms or did not provide usable data. Data from Alekseeva 2008 were not used in the meta-analysis because this study compared intermittent versus constant therapy with chondroitin and glucosamine. This treatment regimen did not fit into any of the comparison arms of the meta-analysis. Data from Nguyen 2001 were not used, except for data on safety, because the study was designed in a before and after design by which all participants received treatment with chondroitin sulfate, which was not compatible with the setup of any other study included in this review. We summarized the results of this study in the discussion section. Data from Magrans-Courtney 2011 were not usable in the meta-analysis because the chondroitin arm was confounded by additional co-treatments, including a diet and exercise program. Findings of this study were also summarized in the discussion section. Moreover, data from Rovetta 2002 and Rovetta 2004 were not included in the data meta-analysis because the authors did not provide the data gathered during their study-only their

conclusions. Data from Cohen 2003 were not used in this meta-analysis because this study compared topical treatment with chondroitin sulfate, not oral treatment with placebo. Data from Fardellone 2013 were summarized but not used in meta-analyses, since the trial compared two different preparations of chondroitin, namely the bovine and the avian chondroitin preparations-these results were summarized in the systematic review. Conrozier 1998, L'Hirondel 1992 and Rai 2004 were not included in the main analysis because they did not provide standard deviations. We included these studies in the sensitivity analysis only when all studies without standard deviations were included after an estimate had been calculated for them. Therefore, results of the studies are summarized in the discussion section. Moreover, although we came to a consensus that data from three-month and 12-month time points from Uebelhart 2004 should be used, the study was based on an intermittent design, by which participants in the chondroitin sulfate group were treated with chondroitin sulfate for the first three months, were not treated for the next three months, were treated again for another three months, and then were no longer treated.

CHONDROITIN SULFATE VERSUS PLACEBO

(See Table 1 under Data and analyses.)

1. Pain

Twelve studies provided data (Bourgeois 1998; Bucsi 1998; Clegg 2006; Mazieres 2001; Morreale 1996; Pavelka 1999; Sawitzke 2010; Uebelhart 1998; Uebelhart 2004; Wildi 2011; Railhac 2012; Zegels 2012) for short-term and/or long-term pain. The difference was statistically significant in the eight short-term studies (Bourgeois 1998; Mazieres 1992; Morreale 1996; Pavelka 1999; Sawitzke 2010; Uebelhart 1998; Uebelhart 2004; Railhac 2012), with a mean difference of −10.14 units (95% CI, −14.58 to −5.71) between chondroitin and placebo arms on a 0 to 100 pain scale. This translated into an absolute risk difference of 10% lower (95% CI, 15% to 6% lower) and a NNT=5 (95% CI 3 to 8) (n=8 trials; level of evidence, low). In six long-term studies (Bucsi 1998; Clegg 2006; Uebelhart 1998; Uebelhart 2004; Wildi 2011; Zegels 2012), chondroitin was associated with a mean difference of −9.00 (95% CI −17.7 to −0.34) on a 0–100 scale, which corresponds to absolute risk difference of 9% lower (95% CI, 18% to 0% lower; p=0.05). Heterogeneity was moderate in both long-term and short-term studies, with T^2 of 0.07 and I^2 of 69% in the short-term and T^2 of 0.12 and I^2 of 83% in the long-term pain studies. Because 12 studies were included for short- or long-term pain outcomes, we created a funnel plot to detect bias. Figure 5 shows the presence of bias, as the plot does not take the shape of a funnel.

Sensitivity analysis showed that the results were robust with respect to blinding and ITT, but not robust with respect to allocation concealment, study size, study sponsorship, or publication year (Analysis 6.1; Analysis 10.1; Analysis 14.1; Analysis 18.1; Analysis 22.1; Analysis 31.1). Studies that were adequately blinded had a similar result to the original estimate, and most studies included in the analyses had adequate blinding. Studies using appropriate ITT analyses had an effect size of −0.46 for pain which was significant, similar to the overall effect, while those with unclear ITT had a larger effect size of −1.00, while 1

study with high risk of bias for ITT analyses had an effect size 0.24, which was insignificant. Most included studies used appropriate ITT analyses.

Among studies that used adequate methods of allocation concealment, no significant difference was reported between placebo and chondroitin while studies that used unclear methods of allocation concealment, participants treated with chondroitin had statistically significantly better scores than those in the placebo group. A difference was seen between the results of studies with large and small sample sizes. Studies with large sample sizes reported no statistically significant difference in pain scores between chondroitin and placebo while studies with small sample sizes reported that pain scores for participants in the chondroitin group were significantly better than those in the placebo group.

Studies funded by chondroitin sulfate manufacturers showed that participants in the chondroitin group had statistically significantly better pain scores than those in the placebo group, and the effect size was −0.52. Studies that did not specify their source of funding or with no pharmaceutical sponsorship did not report a statistically significant difference between participants in the chondroitin group and those in the placebo group, but the effect size was greater at −0.73. Thus, the effect of study sponsorship on findings was mixed.

Studies published before 2000 showed that participants treated with chondroitin had significantly better pain scores than those in the placebo group while studies published after 2000 reported no statistically significant difference between chondroitin and placebo.

2. MCII WOMAC

Two studies provided data (Clegg 2006; Kahan 2009). A significantly greater number of participants in the chondroitin sulfate group experienced an MCII in pain on WOMAC (Risk ratio of 1.12, 95% CI 1.01 to 1.24; P = 0.04) with an absolute difference of 6% (95% CI 1% to 11%) and an NNT= 16 (95% CI 9 to 136). Sensitivity analyses showed the results were robust to study sponsorship.

3. Physical function

Three studies provided data (Clegg 2006; Sawitzke 2010; Uebelhart 1998) in the long-term analysis, and two studies provided data in the short-term analysis (Sawitzke 2010; Uebelhart 1998). Uebelhart 1998 presented data on 0 = best and 100 = worst scale, and the mean score was transformed by subtracting the scores from 100 to make the data compatible with those of the other studies, which presented data on a 0 = best and 100 = worst scale. No statistically significant difference was noted between chondroitin and placebo in the short-term studies (SMD 0.11, 95% CI −0.47 to 0.68; P = 0.72; T^2 = 0.13; moderate level of heterogeneity with an $I^2$of 70%) or long-term studies (SMD −0.20, 95% CI −0.53 to 0.14; P = 0.25; T^2 = 0.06; moderate level of heterogeneity, with an $I^2$of 77%). This equated a mean difference of 2.39 (95% CI, −9.81 to 14.58) in short-term and −4.31 (95% CI, −11.33 to 2.70) in long-term studies, on a 0–100 scale. This equated to an absolute risk difference of 8% lower with chondroitin versus placebo (24% lower to 7% higher; n = 3 trials; level of evidence, moderate) for long-term physical function studies.

Sensitivity analyses demonstrated the results were robust to blinding but not to allocation concealment, sample size, pharmaceutical sponsorship, publication year or ITT analyses (Analysis 6.3; Analysis 10.3; Analysis 14.3; Analysis 18.3; Analysis 18.3; Analysis 22.3; Analysis 31.3). Studies with an unclear allocation, small sample size, with pharmaceutical sponsorship, with publication prior to 1999, and with unclear impact of missing data showed that participants in the chondroitin sulfate group performed statistically significantly better on physical function scales than those in the placebo arm.

4. WOMAC stiffness

One study provided data (Clegg 2006). No significant difference between chondroitin and placebo was noted (P = 0.21).

5. Patient global assessment of good to very good

Three studies provided data (Bourgeois 1998; Bucsi 1998; Pavelka 1999). A total of 68% of participants in the chondroitin sulfate group and 33% of participants in the placebo group reported a good to very good assessment of their status. Participants in the chondroitin sulfate group were twice as likely as those in the placebo group to report good to very good overall assessment with a significant risk ratio (RR) of 2.11 (95% CI 1.49 to 2.99; P < 0.0001) in short-term and RR of 2.04 (95% CI 1.28 to 3.27; P = 0.003) in long-term studies.

6. Patient global assessment on VAS

Three studies provided data (Clegg 2006; Gabay 2011; Kahan 2009). No significant difference was reported between chondroitin and placebo in short- or long-term studies, with SMD of −0.03 (95% CI −0.48 to 0.21; P = 0.45) and 0.01 (95% CI −0.21 to 0.23; P = 0.92), respectively.

7. Physician global assessment of good to very good

Three studies provided data (Bourgeois 1998; Bucsi 1998; Pavelka 1999). A total of 71% of physician global assessments in the chondroitin sulfate group and 36% of those in the placebo group were good to very good assessments, leading to a significant risk in short- or long-term studies, with RR of 1.95 (95% CI 1.42 to 2.69; P < 0.00001) and 2.12 (95% CI 1.33 to 3.38; P = 0.002), respectively.

8. Physician global assessment on VAS

Two studies provided data (Clegg 2006; Kahan 2009). No significant difference was noted between chondroitin and placebo (SMD 0.09, 95% CI −0.05 to 0.23, P = 0.19).

9. Total Knee arthroplasty during follow-up

One study provided data (Raynauld 2013), which was a follow-up of Wildi 2011. No significant difference was noted between chondroitin and placebo, RR was 0.43 (95% CI 0.15 to 1.27; P =0.13).

10. Grip strength (kg/cm^2)

One study provided data (Gabay 2011). No significant difference was noted between chondroitin and placebo, mean difference was 0.90 (95% CI −2.29 to 4.09; see Table 1).

11. Morning stiffness (minutes)

One study provided data (Gabay 2011). No significant difference was reported between chondroitin and placebo −0.60 (95% CI −5.16 to 3.96; P = 0.80; see Table 1).

12. Cartilage volume loss (global)

One study provided data (Wildi 2011). Participants in the chondroitin group had significantly less global cartilage volume loss than those in the placebo group, mean difference was 1.80 (95% CI 0.23 to 3.37; P = 0.02; see Table 1).

13. Cartilage volume loss (lateral compartment)

One study provided data (Wildi 2011). Participants in the chondroitin group had significantly less lateral compartment cartilage volume loss than those in the placebo group, mean difference was 2.19 (95% CI 0.31 to 4.07; P = 0.02; see Table 1).

14. Cartilage volume loss (medial compartment)

One study provided data (Wildi 2011). No significant difference in cartilage volume loss was noted between chondroitin and placebo, mean difference was 1.47 (95% CI −0.88, 3.82; P = 0.22).

15. Cartilage volume loss (condyles)

One study provided data (Wildi 2011). No significant difference in cartilage volume loss was reported between chondroitin and placebo, mean difference was 0.64 (95% CI −1.59, 2.87; P = 0.57; see Table 1).

16. Cartilage volume loss (lateral condyles)

One study provided data (Wildi 2011). No significant difference in cartilage volume loss was noted between chondroitin and placebo, mean difference was 1.84 (95% CI −0.44 to 4.12; P = 0.11; see Table 1).

17. Cartilage volume loss (medial condyles)

One study provided data (Wildi 2011). No significant difference in cartilage volume loss was reported between chondroitin and placebo, mean difference was −0.65 (95% CI −4.14 to 2.84; P = 0.71; see Table 1).

18. Cartilage volume loss (tibial plateaus)

One study provided data (Wildi 2011). Participants in the chondroitin group had significantly less tibial plateau cartilage volume loss than those in the placebo group, mean difference was 2.98 (95% CI 1.15 to 4.81; P = 0.001; see Table 1).

19. Cartilage volume loss (lateral tibial plateaus)

One study provided data (Wildi 2011). No significant difference in cartilage volume loss was reported between chondroitin and placebo, mean difference was 2.31 (95% CI −0.09 to 4.71; P = 0.06; see Table 1).

20. Cartilage volume loss (medial tibial plateaus)

One study provided data (Wildi 2011). Participants in the chondroitin group had significantly less cartilage volume loss in their medial tibial plateaus than those in the placebo group, mean difference was 4.47 (95% CI 1.57 to 7.37; P = 0.003; see Table 1).

21. Cartilage volume loss (trochlea)

One study provided data (Wildi 2011). No significant difference in cartilage volume loss was reported between chondroitin and placebo, mean difference was 0.65 (95% CI −1.79 to 3.09; P = 0.60; see Table 1).

22. Change in bone marrow lesion scores (global)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.07 (95% CI −0.65 to 0.51; Table 1).

23. Change in bone marrow lesion scores (lateral compartment)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.10 (95% CI −0.30 to 0.10; P = 0.32; see Table 1).

24. Change in bone marrow lesion scores (medial compartment)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was 0.02 (95% CI −0.52 to 0.56; P = 0.94; see Table 1).

25. Change in bone marrow lesion scores (condyles)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was 0.02 (95% CI −0.35 to 0.39; P = 0.92; see Table 1).

26. Change in bone marrow lesion scores (lateral condyles)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.04 (95% CI −0.14 to 0.06; P = 0.45; see Table 1).

27. Change in bone marrow lesion scores (medial condyles)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was 0.13 (95% CI −0.22 to 0.48; P = 0.47; see Table 1).

28. Change in bone marrow lesion scores (tibial plateaus)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.10 (95% CI −0.46 to 0.26; P = 0.58; see Table 1).

29. Change in bone marrow lesion scores (lateral tibial plateaus)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.01 (95% CI −0.18 to 0.16; P = 0.91; see Table 1).

30. Change in bone marrow lesion scores (medial tibial plateaus)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.10 (95% CI −0.40 to 0.20; P = 0.22; see Table 1).

31. Change in bone marrow lesion scores (trochlea)

One study provided data (Wildi 2011). No significant difference between chondroitin and placebo was noted across all bone marrow lesion regions, mean difference was −0.16 (95% CI −0.10 to 0.42; P = 0.52; see Table 1).

32. OMERACT-OARSI responder

One study provided data (Clegg 2006). The proportion of participants achieving responder status in the chondroitin sulfate group was not significantly different from that in the placebo group, mean difference was (95% CI; P = 0.09; see Table 1).

33. Lequesne's index score

Nine studies provided data (Bourgeois 1998; Bucsi 1998; Mazieres 2001; Morreale 1996; Moller 2010; Pavelka 1999; Uebelhart 2004; Railhac 2012; Zegels 2012). Lequesne's Index score was significantly lower (better) in chondroitin-treated participants than in placebo-treated participants with (mean difference (MD) −1.98, 95% CI −2.79 to −1.17; P < 0.00001) in short-term studies. This translates into an absolute risk difference of 8.3% lower in chondroitin versus placebo (11.6% lower to 4.9% lower; $T^2 = 0.78$; $I^2 = 67\%$; n = 7 trials; level of evidence, moderate). For long-term studies, SMD was −1.60, (95% CI −3.49 to 0.29; P =0.10; $T^2 = 1.88$; $I^2 = 68\%$;), not statistically significant.

34. HAQ Disability score

One study provided data (Clegg 2006). No significant difference was reported between chondroitin and placebo, mean difference was (P = 0.26).

35. Radiographic-minimum joint space width (mm)

Two studies provided data (Uebelhart 1998; Uebelhart 2004). No significant difference was noted between chondroitin and placebo (MD 0.16, 95% CI −0.16 to 0.48; P = 0.32).

36. Radiographic-reduction in minimum joint space width (mm)

Two studies provided data (Kahan 2009; Michel 2005). Participants in the chondroitin group experienced significantly less reduction in minimum joint space width as compared with those in the placebo group (MD 0.18, 95% CI 0.06 to 0.30; P < 0.0001). This translated into significantly less loss of minimum joint space width in the chondroitin group than in the placebo group, with a relative risk difference of 4.72% less (95% CI 1.58% to 7.87% less; n = 2 trials; level of evidence, high).

37. Radiographic-mean joint space width (mm)

One study provided data (Uebelhart 1998). No significant difference was reported between chondroitin and placebo (MD 0.17, 95% CI −0.47 to 0.81; P = 0.60).

38. Radiographic-change in mean joint space width (mm)

Three studies provided data (Kahan 2009; Michel 2005; Sawitzke 2010). Participants in the chondroitin group experienced significantly less change in their mean joint space width as compared with those in the placebo group (MD 0.13, 95% CI 0.07 to 0.20; P <0.0001).

39. SF-36 (Physical component score)

One study provided data (Moller 2010). No significant difference was reported between chondroitin and placebo (P = 0.81).

40. SF-36 (Mental component score)

One study provided data (Moller 2010). No significant difference was noted between chondroitin and placebo (P = 0.96).

41. All withdrawals

Fifteen studies provided data (Bourgeois 1998; Clegg 2006; Conrozier 1992; Gabay 2011; Kahan 2009; Mazieres 1992; Mazieres 2001; Michel 2005; Moller 2010; Morreale 1996; Pavelka 1999; Uebelhart 1998; Uebelhart 2004; Verbruggen 2002; Wildi 2011). The number of participants who withdrew from the study for any reason did not differ significantly between chondroitin and placebo groups (RR 0.80, 95% CI 0.63 to 1.02; P = 0.07).

42. Withdrawals due to adverse events

Ten studies provided data (Bourgeois 1998; Clegg 2006; Gabay 2011; Kahan 2009; Mazieres 2001; Michel 2005; Moller 2010; Morreale 1996; Uebelhart 2004; Verbruggen 2002), four short-term and 6 long-term studies. No statistically significant difference was reported between placebo and chondroitin sulfate (RR 0.95, 95% CI 0.31 to 2.89; P = 0.70) for short-term or long-term studies, RR of 1.09 [95% CI, 0.73 to 1.63]. The overall RR combining short- and long-term studies was 1.08 (95% CI, 0.74 to 1.57).

43. Withdrawals due to inefficacy

Ten studies provided data (Bourgeois 1998; Clegg 2006; Kahan 2009; Mazieres 2001; Michel 2005; Morreale 1996; Uebelhart 1998; Uebelhart 2004; Verbruggen 2002; Wildi 2011). The number of participants who withdrew from the study because of inefficacy did

not differ significantly between chondroitin and placebo groups (RR 1.22, 95% CI 0.88 to 1.70; P = 0.23).

44. Number of adverse events

Eight studies provided data (Bourgeois 1998; Gabay 2011; Kahan 2009; Mazieres 2001; Moller 2010; Morreale 1996; Pavelka 1999; Wildi 2011). The number of adverse events did not differ significantly between chondroitin and placebo groups (RR 0.96, 95% CI 0.78 to 1.18; P = 0.69).

45. Number of serious adverse events

Six studies provided data (Bourgeois 1998; Gabay 2011; Morreale 1996; Sawitzke 2010; Wildi 2011; Zegels 2012). The risk of serious adverse events was lower with chondroitin compared to placebo in the long-term with an RR of 0.38 (95% CI 0.17 to 0.84; P = 0.01], but not in the short-term studies, RR of 0.50 [95% CI, 0.09 to 2.78]. The overall risk, combining both short- and long-term studies, was 0.40 (95% CI 0.19 to 0.82].

46. Gastrointestinal adverse events

Nine studies provided data (Bourgeois 1998; Gabay 2011; Kahan 2009; Mazieres 1992; Michel 2005; Moller 2010; Uebelhart 2004; Verbruggen 2002; Wildi 2011). The number of gastrointestinal adverse events did not differ significantly between chondroitin and placebo groups (RR 0.68, 95% CI 0.45 to 1.04; P = 0.07).

47. Other adverse events

These were defined as adverse events other than gastrointestinal, cardiac, or hematologic. Six studies provided data (Bourgeois 1998; Gabay 2011; Michel 2005; Moller 2010; Uebelhart 2004; Wildi 2011). The number of other adverse events was not significantly different between chondroitin and placebo groups (RR 0.95, 95% CI 0.79 to 1.15; P = 0.66).

48. Death

Seven studies provided data (Bourgeois 1998; Clegg 2006; Gabay 2011; Moller 2010; Sawitzke 2010; Uebelhart 1998; Wildi 2011). Two deaths were reported in the placebo group and none in the chondroitin group. No significant difference was noted between the two groups (RR 0.34, 95% CI 0.04 to 3.20; P = 0.35).

CHONDROITIN SULFATE VERSUS CONTROL

(See Table 2 under Data and analyses.)

Control treatment was avocado soybean unsaponifiable (ASU) in Pavelka 2010, “regular treatment” of osteoarthritis according to physician’s preferences in Nasonova 2001, and ibuprofen 1200 mg daily in Alekseeva 1999.

1. Pain (0–100 scale)

One study (Pavelka 2010) provided both short- and long-term data. No significant difference was noted between chondroitin and control; SMD was −0.06 [95% CI, −0.26 to 0.15] for

short-term and −0.10 [95% CI, −0.31 to 0.11] for long-term studies. This translates to a mean differences of −1.14 [95% CI, −5.32 to 3.04] and −2.02 [95% CI, −6.12 to 2.08], respectively.

2. WOMAC stiffness

One study (Pavelka 2010) provided both short- and long-term data. No significant difference was reported between chondroitin and control; mean differences in short- and long-terms studies were −1.00 [95% CI, −5.77 to 3.77] and −0.60 [95% CI, −5.25 to 4.05], respectively.

3. WOMAC physical function

One study (Pavelka 2010) provided both short- and long-term data. No significant difference was noted between chondroitin and control; mean differences in short- and long-terms studies were −2.10 [95% CI, −6.44 to 2.24] and −1.56 [95% CI, −5.70 to 2.58], respectively.

4. WOMAC Total

One study (Pavelka 2010) provided both short- and long-term data. No significant difference was reported between chondroitin and control; mean differences in short- and long-terms studies were −1.80 [95% CI, −6.06 to 2.46] and −1.60 [95% CI, −5.69 to 2.49], respectively.

5. Lequesne's index

Two studies provided data (Nasonova 2001; Pavelka 2010). Both were long-term studies. No statistically significant difference was noted between chondroitin and control; mean difference was −1.36 [95% CI, −3.60 to 0.89].

6. Patient global assessment (% with improvement)

Two studies provided data (Nasonova 2001; Pavelka 2010). Both were long-term studies. Investigators found that participants treated with chondroitin sulfate scored better than participants in the control group, with an odds ratio (OR) of 5.04 (95% CI 1.95 to 13.05; P = 0.0008).

7. Physician global assessment (% with improvement)

Two studies provided data (Nasonova 2001; Pavelka 2010). Both were long-term studies. Investigators found that participants treated with chondroitin sulfate scored better than participants in the control group (OR 7.68, 95% CI 4.48 to 13.15; P < 0.00001).

8. NSAID consumption

One study (Pavelka 2010) provided both short- and long-term data. No significant difference was reported between chondroitin and control; mean differences in short- and long-terms studies were −0.02 [95% CI, −0.23 to 0.19] and 0.00 [95% CI, −0.20 to 0.20], respectively.

9. All withdrawals

Three studies provided data (Alekseeva 1999; Nasonova 2001; Pavelka 2010). No significant difference was noted between chondroitin and control (OR 0.39, 95% CI 0.09 to 1.74; P = 0.22).

10. Withdrawals due to adverse events

Two studies provided data (Alekseeva 1999; Pavelka 2010). No significant difference was reported between chondroitin and control (RR 0.27, 95% CI 0.03 to 2.65; P = 0.26).

11. Number of adverse events

Two studies provided data (Alekseeva 1999; Pavelka 2010). No significant difference was noted between chondroitin and control (RR 0.08, 95% CI 0.00 to 4.82; P = 0.22).

12. Number of GI adverse events

Two studies provided data (Alekseeva 1999; Pavelka 2010). No significant difference was reported between chondroitin and control RR 0.51, 95% CI 0.24 to 1.07; P = 0.08).

CHONDROITIN SULFATE PLUS GLUCOSAMINE VERSUS PLACEBO

(See Table 3 under Data and analyses.)

1. Pain

Five studies provided data (Clegg 2006; Kanzaki 2011; Messier 2007; Nakasone 2011; Sawitzke 2010). Three were short-term studies (Kanzaki 2011; Nakasone 2011; Sawitzke 2010), and three were long-term studies (Clegg 2006; Messier 2007; Sawitzke 2010). No statistically significant difference was noted between the chondroitin plus glucosamine group and the placebo group for either the short-term studies (SMD −0.06, 95% CI −0.33 to 0.20; P = 0.63) or the long-term studies (SMD −0.09, 95% CI −0.21 to 0.04; P = 0.17).

Sensitvity analyses were robust to allocation concealment, blinding, study size, study sponsorship, publication year, and impact of true ITT analyses.

2. MCII WOMAC pain

One study provided data (Clegg 2006). No significant difference between active treatment and placebo was reported (P = 0.09).

3. Physical function

Four studies provided data (Clegg 2006; Kanzaki 2011; Messier 2007; Sawitzke 2010). Sawitzke 2010 and Kanzaki 2011 were in the short-term category. The rest of the studies, including Sawitzke 2010 at 24 months, were in the long-term subgroup. No significant difference was noted between active treatment and placebo in the short- (SMD 0.11, 95% CI −0.31 to 0.54; P = 0.60) or long-term subgroups (SMD −0.11, 95% CI −0.24 to 0.01; P = 0.08).

Sensitivity analyses were robust to allocation concealment, blinding, study size, study sponsorship, publication year, and impact of true ITT analyses.

4. Six-minute walk, distance in meters

One study provided data (Messier 2007). No significant difference was reported between active treatment and placebo (P = 0.8); mean difference was −2.90 [95% CI, −24.94 to 19.14].

5. WOMAC stiffness

One study provided data (Clegg 2006). No significant difference was reported between active treatment and placebo (P = 0.25); mean difference was −2.20 [95% CI, −5.97 to 1.57].

6. WOMAC Total

One study provided data (Clegg 2006). Participants treated with chondroitin sulfate in combination with glucosamine had significantly better scores on WOMAC Total (MD −2.60, 95% CI −5.29 to 0.72; P = 0.13). The results for WOMAC Total as reported by Clegg 2006 were presented as normalized WOMAC scores on a 0 to 300 scale, which we then normalized to a 0 to 100 scale.

7. Patient global assessment on VAS

Two studies provided data (Clegg 2006; Das 2000). No significant difference was noted between active treatment and placebo (P = 0.39); mean difference was −1.60 [95% CI, −5.29 to 2.09].

8 Physician global assessment on VAS

One study provided data (Clegg 2006). No significant difference between active treatment and placebo was reported (P = 0.43); mean difference was −1.40 [95% CI, −4.87 to 2.07].

9. OMERACT-OARSI responder

One study provided data (Clegg 2006). The proportion of participants achieving responder status in the chondroitin sulfate in combination with glucosamine group was significantly greater in the active treatment group than in the placebo group (P = 0.03); odds ratio was 1.15 [95% CI, 1.02 to 1.31].

10. HAQ Disability score

One study provided data (Clegg 2006). No significant difference between active treatment and placebo was noted (P = 0.24); mean difference was −0.04 [95% CI, −0.11 to 0.03].

11. Objective joint function (flexion)

Only one study provided data on this outcome (Messier 2007). No significant difference between active treatment and placebo groups was reported (P = 0.96); mean difference was −0.60 [95% CI, −21.54 to 20.34].

12. Objective joint function (extension)

Only one study provided data on this outcome (Messier 2007). No significant difference between active treatment and placebo groups was reported (P = 0.29); mean difference was −25.80 [95% CI, −72.67 to 21.07].

13. Objective joint function (balance)

Only one study provided data on this outcome (Messier 2007). Participants in the active treatment group had significantly lower (better) scores on balance in objective joint function (P = 0.008); mean difference was −0.06 [95% CI, −0.10 to −0.02].

14. All withdrawals

Three studies provided data on this outcome (Clegg 2006; Das 2000; Nguyen 2001). No significant difference between active treatment and placebo groups was noted (Risk Ratio [RR] 1.24, 95% CI 0.40 to 3.85; P = 0.70).

15. Withdrawals due to adverse events

Four studies provided data (Clegg 2006; Das 2000; Nakasone 2011; Nguyen 2001). The numbers of participants who withdrew from the study because of adverse events did not differ significantly between active and placebo groups (RR 1.21, 95% CI 0.57 to 2.55; P = 0.62).

16. Withdrawals due to inefficacy

Three studies provided data (Clegg 2006; Das 2000; Nguyen 2001). No significant difference was noted between chondroitin and placebo in the number of withdrawals due to inefficacy (RR 0.76, 95% CI 0.41 to 1.41; P = 0.39).

17. Number of adverse events

Three studies provided data (Das 2000; Nakasone 2011; Nguyen 2001). No significant difference was noted in the number of adverse events between chondroitin and placebo groups (RR 1.11, 95% CI 0.67 to 1.84; P = 0.68).

18. Number of serious adverse events

Three studies provided data (Das 2000; Nguyen 2001; Sawitzke 2010). No significant difference between placebo and chondroitin groups was reported (RR 1.45, 95% CI 0.77 to 2.75; P = 0.25).

19. Gastrointestinal adverse events

Two studies provided data (Das 2000; Nguyen 2001). No difference between chondroitin and placebo groups was reported (RR 0.68, 95% CI 0.34 to 1.37; P = 0.28).

20. Hematologic adverse events

Two studies provided data (Das 2000; Nguyen 2001). No difference between chondroitin and placebo groups was noted (RR 0.34, 95% CI 0.01 to 8.15; P = 0.51).

21. Other adverse events

These were defined as adverse events other than gastrointestinal, cardiac, or hematologic. Two studies provided data (Das 2000; Nguyen 2001). The number of other adverse events was not significantly different between chondroitin and placebo groups (RR 1.35, 95% CI 0.43 to 4.19; P = 0.61).

22. Death

Four studies provided data (Clegg 2006; Das 2000; Nguyen 2001; Sawitzke 2010). No significant difference between the two groups was reported (RR 0.34, 95% CI 0.01 to 8.23; P = 0.51).

CHONDROITIN SULFATE PLUS GLUCOSAMINE VERSUS NSAIDs CONTROL

(See Table 4 under Data and Anayses.)

1. Pain

Four studies provided data (Artemenko 2005; Clegg 2006; Lila 2005; Sawitzke 2010). Participants in the chondroitin sulfate and glucosamine group had significantly lower pain scores than those in the NSAIDs control group (SMD −1.41, 95% CI −2.18 to −0.63; P = 0.0004). Two studies provided short-term data (Lila 2005; Sawitzke 2010), and four studies provided long-term data (Artemenko 2005; Clegg 2006; Lila 2005; Sawitzke 2010). Short-term studies showed no significant difference between NSAIDs control and chondroitin sulfate in combination with glucosamine (SMD −1.41, 95% CI −4.41 to 1.58; P = 0.35). Heterogeneity was high among these studies (T^2 = 4.60). Long-term studies showed that participants in the chondroitin and glucosamine combination group experienced significantly better pain scores than those in the NSAIDs control group (SMD −1.48, 95% CI −2.51 to −0.44; P = 0.005). Heterogeneity was high (T^2 = 1.02). Sensitivity analyses were robust to study sponsorship and publication year. Results were not robust to allocation concealment, blinding, study size, and impact of true ITT analyses.

In groups with both adequate and unclear methods of allocation concealment the estimate was similar to the original estimate. However, among studies with inadequate methods of allocation concealment and blinding, small studies (N<100), unclear pharmaceutical sponsorship, and high risk of bias due to unclear or non-use of ITT analyses, participants treated with chondroitin sulfate had statistically better pain scores than those in the NSAID group.

2. MCII WOMAC

One study provided data (Clegg 2006). No significant difference was reported between chondroitin sulfate in combination with glucosamine and the NSAIDs control (P = 0.33); 0.85 [0.61, 1.19].

3. Physical function

Two studies provided data (Clegg 2006; Sawitzke 2010). No significant difference was noted between chondroitin sulfate in combination with glucosamine and the NSAIDs control with SMD in short- and long-terms studies of 0.04 [95% CI, −0.20 to 0.28; p=0.35] and 0.02 [95% CI, −0.11 to 0.15; p=0.005], respectively. This translates to mean differences of 0.80 [95% CI, −4.09 to 5.69] and 0.34 [95% CI, −2.46 to 3.14], respectively.

4. WOMAC stiffness

Three studies provided data (Artemenko 2005; Clegg 2006; Lila 2005). Participants in the chondroitin sulfate in combination with glucosamine group achieved significantly better scores in WOMAC Stiffness than those in the NSAID group with mean differences in short- and long-terms studies of −2.50 [95% CI, −4.27 to −.073; p=0.006] and −7.72 [95% CI, −15.36 to −0.08; p=0.05], respectively.

5. WOMAC Total

Three studies provided data (Artemenko 2005; Clegg 2006; Lila 2005). No significant difference between chondroitin sulfate in combination with glucosamine and NSAIDs control was noted (MD −4.77, 95% CI −9.75 to 0.20, P = 0.06). WOMAC Total for Clegg 2006 was presented as a normalized WOMAC score on a 0 to 300 scale, which we normalized further to a 0 to 100 scale.

6. Patient global assessment of good to very good

Three studies provided data (Alekseeva 2005a; Alekseeva 2005b; Lila 2005). Significantly more participants in the chondroitin sulfate in combination with glucosamine group were able to achieve a good to very good global assessment as compared with the NSAIDs control (SMD 1.43, 95% CI 1.29 to 1.58; P < 0.00001).

7. Physician global assessment of good to very good

Three studies provided data (Alekseeva 2005a; Alekseeva 2005b; Lila 2005). Significantly more participants in the chondroitin sulfate in combination with glucosamine group said they were able to achieve a good to very good global assessment as compared with those in the NSAIDs control group (SMD 1.51, 95% CI 1.35 to 1.68; P < 0.00001).

8. OMERACT-OARSI responder

One study provided data (Clegg 2006). The proportion of participants achieving responder status in the chondroitin sulfate group was not significantly different from the proportion in the active treatment group (P = 0.65); RR was 0.93 [95% CI 0.67 to 1.29].

9. HAQ Disability score

One study provided data (Clegg 2006). No significant difference was reported between chondroitin sulfate in combination with glucosamine and NSAIDs control (P = 0.77); mean difference was 0.01 [95% CI −0.06 to 0.08].

10. Radiographic outcome: change in mean JSW

One study provided data (Sawitzke 2010). No difference was noted between chondroitin sulfate in combination with glucosamine and NSAIDs control (P = 0.63); mean difference was 0.08 [95% CI, −0.26 to 0.42].

11. All withdrawals

Five studies provided data on this outcome (Alekseeva 2005a; Alekseeva 2005b; Artemenko 2005; Clegg 2006; Lila 2005). No significant difference between chondroitin sulfate in

combination with glucosamine and active treatment was reported (RR 0.31, 95% CI 0.08 to 1.18; P = 0.09).

12. Withdrawals due to adverse events

One study provided data (Clegg 2006). The number of participants who withdrew from the study because of adverse events did not differ significantly between chondroitin sulfate in combination with glucosamine and NSAIDs control groups (RR 1.72, 95% CI 0.69 to 4.31; P = 0.25).

13. Withdrawals due to inefficacy

One study provided data (Clegg 2006). The number of participants who withdrew from the study because of inefficacy did not differ significantly between chondroitin sulfate in combination with glucosamine and NSAIDs control groups (RR 1.55, 95% CI 0.74 to 3.26; P = 0.25).

14. Adverse events

Four studies provided data (Alekseeva 2005a; Alekseeva 2005b; Lila 2005; Sawitzke 2010). No significant difference was reported in adverse events between chondroitin sulfate in combination with glucosamine and NSAIDs control groups (SMD 0.45, 95% CI 0.17 to 1.21; P = 0.11).

15. Serious adverse events

Two studies provided data (Alekseeva 2005a; Lila 2005). No significant difference was noted between the chondroitin sulfate in combination with glucosamine and NSAIDs control groups (RR 3.00, 95% CI 0.13 to 70.83; P = 0.50).

16. Gastrointestinal adverse events

Three studies provided data (Alekseeva 2005a; Clegg 2006; Lila 2005). No difference was reported between the chondroitin sulfate in combination with glucosamine and NSAIDs control groups (RR 0.54, 95% CI 0.29 to 1.01; P = 0.06).

17. Other adverse events

These were defined as adverse events other than gastrointestinal, cardiac, or hematologic. Two studies provided data (Alekseeva 2005a; Lila 2005). The number of other adverse events was not significantly different between chondroitin sulfate in combination with glucosamine and NSAIDs control groups (RR 0.42, 95% CI 0.16 to 1.13; P = 0.08).

18. Death

One study provided data (Clegg 2006). No deaths were reported in either the chondroitin sulfate in combination with glucosamine group or the NSAIDs control group (not estimable).

CHONDROITIN SULFATE ALONE OR WITH GLUCOSAMINE OR WITH OTHER SUPPLEMENT VERSUS PLACEBO OR CONTROL

(See Table 5 under Data and Anayses.)

In this group, we combined all studies in all comparison arms to assess the overall effect of chondroitin (with or without glucosamine) compared with placebo or control resulting in a greater number of studies for the outcomes of pain and physical function. This decision was clinically relevant because many patients take glucosamine and chondroitin together.

1. Pain (All studies)

Before sensitivity analysis was performed, when all studies were combined into one large overall group, 17 studies were identified (Artemenko 2005; Bourgeois 1998; Bucsi 1998; Clegg 2006; Kanzaki 2011; Lila 2005; Mazieres 2001; Messier 2007: Morreale 1996; Nakasone 2011; Pavelka 1999; Pavelka 2010; Uebelhart 1998; Uebelhart 2004; Wildi 2011; Railhac 2012; Zegels 2012). Participants treated with chondroitin alone and in combination with other supplements such as glucosamine showed significantly better pain scores than those treated with a control or placebo in short- and long-terms studies with an SMD −0.65, 95% CI −0.95 to −0.35; P < 0.0001). This translates into an absolute risk difference of which translated into an absolute risk difference of −9.6 (95% CI −14 to −5.2) on a 0 to 100 scale (absolute percent change 10% lower (14% lower to 5% lower ;T^2 = 0.33; n = 17 trials; level of evidence, low). Because were more than 10 studies were included, we created a funnel plot to detect bias. As Figure 6 shows, the possibility of publication bias is high. Removing one study with a small standard deviation (Lila 2005), reduced the SMD for pain to −0.47 (95% CI −0.70 to −0.23) and I^2 to 84%.

Sensitivity analyses showed that the results were robust to blinding but not robust to allocation concealment, study size, study sponsorship, publication year, and impact of true ITT analyses (Analysis 9.1; Analysis 13.1; Analysis 17.1; Analysis 21.1; Analysis 25.1; Analysis 34.1). Among studies with adequate allocation concealment, sample size greater than 100, no pharmaceutical sponsorship, publication year >2010, and high risk of bias due to the use of non-ITT analyses, there was no statistically significant difference between treatment and control groups.

1.1 Pain - restricted to chondroitin dose ≧ 800 mg/day (therapeutic dose)—14 studies were included in this analysis (Artemenko 2005; Bourgeois 1998; Bucsi 1998; Clegg 2006; Lila 2005; Mazieres 2001; Messier 2007: Morreale 1996; Pavelka 2010; Uebelhart 1998; Uebelhart 2004; Wildi 2011; Railhac 2012; Zegels 2012). Participants treated with chondroitin alone at a therapeutic dose of ≧ 800 mg/day and in combination with other supplements such as glucosamine showed significantly better pain scores than those treated with a control or placebo in short- and long-terms studies with an SMD −0.67, 95% CI −0.99 to −0.34; P < 0.0001); absolute percent change 10% lower (14.6% lower to 5% lower) (Figure 7).

2. Physical function (All studies-physical function)

Overall, before sensitivity analysis was performed, five studies provided data on physical function (Clegg 2006; Kanzaki 2011; Messier 2007; Pavelka 2010; Uebelhart 1998). No significant difference was reported between chondroitin or a combination of chondroitin with other supplements and placebo or control (SMD −0.07, 95% CI −0.31 to 0.17) which equates to an absolute risk difference of −1% lower (−6% lower to 3% higher; level of evidence, moderate). Sensitivity analyses demonstrated that results were robust with respect to allocation concealment, blinding, study size, study sponsor, and impact of use of non-ITT analyses (Analysis 9.2; Analysis 13.2; Analysis 17.2; Analysis 21.2; Analysis 25.2; Analysis 34.2). Results were not robust to publication year, with one study published 1999 showing a statistically significant result for improvement in function in favour of the treatment group.

3. Lequesne's index

10 studies provided data. Chondroitin with or without glucosamine was associated with statistically significantly better score on Lequesne's index compared to control or placebo, with a mean difference of 2.14 lower (95% CI 1.39 lower to 2.88 lower; $p<0.00001$) and SMD of −0.48 (95% CI −0.72 to −0.24).

SUMMARY OF SENSITIVITY ANALYSIS BY RISK OF BIAS AND OTHER CRITERIA

(See Tables 5–25 and Tables 31–34 under Data and Anayses.)

In summary, the beneficial effects of chondroitin on pain severity persisted when evidence was limited to studies with adequate blinding or studies using ITT analyses. On the other hand, pain reduction effects were smaller or were nonexistent when we limited data to studies with appropriate allocation concealment or a large study sample (> 200) or to studies without pharmaceutical funding.

SENSITIVITY ANALYSIS INCLUDING STUDIES WITH AN ESTIMATED STANDARD DEVIATION

(See Tables 26–30 under Data and Anayses.)

In this analysis, along with studies that provided standard deviations in their results section, we included studies for which the standard deviation was not provided and was, therefore, estimated using the estimation method described in the Methods section. This analysis revealed significant differences in the results on the efficacy of chondroitin in several outcomes under each comparison group.

In the chondroitin sulfate versus placebo group, five studies were added when we included estimated standard deviation studies (Conrozier 1992; Conrozier 1998; L'Hirondel 1992; Alekseeva 1999; Alekseeva 2005b) for pain outcome and six studies for Lequesne's index (Conrozier 1992; Conrozier 1998; L'Hirondel 1992; Alekseeva 1999; Das 2000; Rai 2004). The addition of these studies did not affect the results for pain and Lequesne's index.

In the comparison group of chondroitin sulfate versus control, one study was added (Alekseeva 1999). The addition of this study resulted in notable differences in the outcomes of pain and Lequesne's index. For pain, the main analysis revealed no significant difference between chondroitin sulfate and control (SMD −0.08, 95% CI −0.23 to 0.07; P = 0.29); this held true after Alekseeva 1999 was added with an estimated standard deviation (SMD 0.34, 95% CI −0.85 to 0.18; P = 0.20). In the main analysis, Lequesne's index showed no significant difference between control and active treatment with a mean difference of −1.36 (95% CI −3.60 to 0.89; P = 0.24). After Alekseeva 1999 was added to the meta-analysis, however, these results switched with a mean difference of −1.99 (95% CI −3.27 to −0.70; P = 0.002).

The sensitivity analysis revealed no noteworthy difference between active treatment and control in the glucosamine and chondroitin sulfate versus placebo comparison group after studies with estimated standard deviations were added (Das 2000).

In the comparison group of chondroitin sulfate and glucosamine versus NSAIDs, the sensitivity analysis revealed notable changes in physical function, WOMAC stiffness, and WOMAC Total. For physical function, a moderate difference between the results of the main analysis and the results of the sensitivity analysis was observed, with the SMD increasing to −0.17 (95% CI −0.57 to 0.23; P = 0.41). In the outcome of stiffness on WOMAC, a slight difference was noted between the main analysis and the sensitivity analysis, with the mean difference decreasing to −8.49 (95% CI −14.52 to −2.46; P = 0.006). In WOMAC Total, a significant difference was observed, with the results switching from non significant to significant in favor of chondroitin (MD −6.94, 95% CI −12.86 to −1.01; P = 0.02).

In the comparison arm of chondroitin with/without glucosamine versus placebo/control, a moderate difference in the results was noted after the addition of studies with estimated SDs (SMD −0.73, 95% CI −1.00 to −0.46; P < 0.00001 for pain). Removing one study with a small standard deviation (Lila 2005), the SMD was −0.52 (95% CI, −0.71 to 0.33; I^2 = 82%) for pain.

Studies Not Included in Data Analyses

Nguyen 2001 studies the efficacy of chondroitin sulfate and glucosamine hydrochloride in participants diagnosed with capsulitis, disk displacement, disk dislocation, or painful osteoarthritis of the temporomandibular joint (TMJ). This study found no statistically significant decrease in the VAS pain ratings of participants treated with chondroitin sulfate-glucosamine hydrochloride, although it did find that participants in the placebo group experienced a statistically significant decrease in their pain ratings. In the outcome of the McGill Pain Questionnaire (MPQ), again no statistically significant change was observed in the sensory, affective, miscellaneous, total, and number of words pain rating indices in the chondroitin sulfate-glucosamine hydrochloride group. Only in the evaluative Pain Rating index was a significant decrease seen in the pain rating, which changed from 3.4 to 2.4. It is interesting to note that participants in the placebo group again underwent statistically significant changes in sensory, evaluative, miscellaneous, and number of words Pain Rating indices. In the placebo group, the evaluative pain rating also decreased from 3.1 to 2. In summary, this study showed that participants treated with chondroitin sulfate-glucosamine

hydrochloride showed improvement in one scale of the MPQ, and participants treated with placebo experienced statistically significant improvement on four scales of the MPQ. In measures of mood and functioning, the results were again interesting, as participants in the chondroitin sulfate-glucosamine hydrochloride group showed slight worsening of their mood and functioning score, although this decrease was not statistically significant. Participants in the placebo group, on the other hand, showed improvement in their mood and functioning, although this was not significant either. In the outcome of TMJ palpation score, participants in the chondroitin sulfate-glucosamine hydrochloride group showed a statistically significant decrease, and those in the placebo group did not. In the outcome of myofascial pain, no statistically significant improvement was observed in the placebo group or the active group. In the outcome of jaw range of motion, no statistically significant improvement was observed. However, this study did show that chondroitin sulfate-glucosamine hydrochloride participants took statistically significantly less medication per day than those in the placebo group (1.42 in the placebo group vs 0.72 in the active group).

Rovetta 2004 studies the efficacy of chondroitin at 800 mg daily plus naproxen versus naproxen alone in participants with erosive osteoarthritis of the hands. This study found that participants in the active and placebo groups showed worsening in their scores on nearly all outcomes as compared with baseline. In the outcomes of degree of erosion, Heberden and Bouchard nodes, and Dreiser index scores, the treated group showed significant worsening, and the Patient and Physician global assessment showed no significant change. The untreated group also showed significant worsening in degree of erosion, Heberden and Bourchard nodes, Dreiser index, and Physician and Patient global assessment scores. Using the Mann-Whitney test, the authors concluded at the end of the study that the results show less worsening in study outcomes in the treated group than in the placebo group.

Rovetta 2002 is a study conducted to evaluate the effect of 800 mg of chondroitin sulfate in combination with naproxen per day on the joint count for erosions in participants with erosive osteoarthritis of the hands as compared with naproxen alone. In both the active group and the placebo group, the general tendency for the joint count was for erosion to increase over time. Progression of erosion over 24 months, however, was significantly less for participants in the chondroitin sulfate-treated group than for those treated with naproxen alone. After the first year, although 11 of the 12 participants in the chondroitin sulfate group had remained at the same joint erosion count, only six in the placebo group had done so. Although only one participant in the chondroitin sulfate group increased by one erosive joint count, five participants in the naproxen alone group experienced a one-count increase in the number of their erosive joints. The authors concluded that the difference between participants with erosive joint count increases and those without in group B versus group A is statistically significant.

Alekseeva 2008 studied the efficacy of chondroitin sulfate plus glucosamine administered daily for nine months (“constant therapy”) versus the efficacy of the two supplements administered for three-month cycles with a treatment-free cycle between the two treated three-month cycles. The study revealed no significant difference between constant and intermittent treatment groups in WOMAC Total, physical function, pain and stiffness scales, or in the time it took to complete a 10-feet week at the end of the 12-month trial. Magrans-

Courtney 2011 is a study undertaken to evaluate the efficacy of glucosamine and chondroitin sulfate in combination with a 14-week exercise program and one of two different diet programs. All participants participated in a 14-week exercise plan. Simultaneously, participants were randomly assigned to receive a high-protein or a high-carbohydrate diet program. Then, they were randomly assigned to receive a placebo or 1500 mg of glucosamine, 1200 mg of chondroitin, and 900 mg of methylsulfonylmethane (MSM) daily. The study found that participants in all groups experienced improvement in their physical functioning test, as well as on WOMAC, VAS, and quality of life measures. However, the authors do not note any significant correlation between the use of chondroitin sulfate, glucosamine, and MSM and improvement on these scales, stating, “no significant differences [were] observed among diet and supplement groups,” which would indicate such a correlation.

Debi 2000 studied the efficacy of glucosamine sulfate and chondroitin sulfate in participants suffering from osteoarthritis. The authors reported on the outcome of Patient global assessment, finding that participants treated with glucosamine and chondroitin sulfate had significantly better global assessments than those treated with placebo.

Cohen 2003 studied the efficacy of a chondroitin cream versus a cream containing placebo. Participants in the chondroitin sulfate in combination with glucosamine group had significantly lower (better) pain scores on VAS (0 to 100 mm) after eight weeks. Those treated with chondroitin sulfate also had improved scores on pain on the WOMAC and SF-36 scales.

Fardellone 2013 compared two chondroitin preparations, Structum® 500 mg twice daily or Chondrosulf® 400 mg three times daily over a 24-week duration. There was no control group or placebo group.

Raynauld 2013 was a long-term follow-up study of Wildi 2011, that assessed 4-year outcome of total knee replacement. Two groups of patients were treated with chondroitin or placebo once daily for the first 6 months (double-blind phase) followed by 6 months of treatment with 800 mg chondroitin sulfate once daily for both groups (open-label phase). Thirteen patients underwent total knee replacement at 4-years, 9/34 in the placebo and 4/35 in the chondroitin group. However since both patient groups were exposed to chondroitin, data from this study could not be used. However, the rates of arthroplasty seemed to be trending towards a difference between groups.

FDA and EMEA on Chondroitin

The U.S. FDA focused its recent review on the efficacy of chondroitin in reducing the risk of osteoarthritis and “....tentatively concluded that a relationship between glucosamine and chondroitin sulfate and a reduced risk of osteoarthritis is not established“ (FDA 2004b).

In 2004, the FDA reviewed health claims from Weider Nutrition International, Inc., regarding glucosamine and chondroitin sulfate, and osteoarthritis, joint degeneration, cartilage deterioration, and osteoarthritis-related joint pain, tenderness, and swelling (FDA 2004a). The FDA rejected these claims.

The FDA did not evaluate the safety of chondroitin, citing "...the Agency did not perform a full safety review and make its own determination on this issue. It was not necessary for FDA to do so because the Agency is denying the proposed claims for lack of credible evidence, as discussed in section II below." We could not find any other safety data on the FDA website. A similar search on EMEA website revealed a waiver to Bioiberica S.A., Spain, but no information related to adverse events was provided.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Chondroitin sulfate/CSGH versus placebo/control for osteoarthritis						
Patient or population: participants with osteoarthritis Settings: international inpatient and outpatient clinics, hospitals, and research centers Intervention: chondroitin sulfate or chondroitin sulfate with glucosamine versus placebo/control						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Chondroitin sulfate/ chondroitin sulfate with glucosamineversus placebo/control**				
Pain (short- and long-term) Scale from 0 to 100 mm (lower is better) Follow-up: 3 to 24 months	The mean pain (short- and long-term) in the control groups was **30.2 mm**	The mean pain on 0 to 100 scale (short- and long-term studies) in the intervention groups was **9.6 mm lower** (14 mm to 5.2 mm lower)		2262 (17 studies)	⊕⊕◯◯ **low**[1,2]	SMD −0.65 (95% CI −0.95 to −0.35) Absolute risk difference −10% lower (95% CI −14% to −5%) Relative risk difference −20% lower (95% CI −30% to −11%) NNTB = 4 (95% CI 3 to 6)
WOMAC MCII Pain sub-scale (reduction in knee pain by 20%) Long-term studies (≥ 6 months) dose ≥ 800 mg/d	**471 per 1000**	**528 per 1000** (476 to 584)	**RR 1.12** (1.01 to 1.24)	1253 (2)	⊕⊕⊕⊕ **high**	Absolute risk difference 6% (1% to 11%) Relative risk difference 12% (1% to 24%) NNTB = 16 (9 to 136)
Composite Measure of Pain, Function and Disability as assessed through Lequesne's index	The mean Lequesne's index in the control groups was **9.7 points**	The mean Lequesne's index on 0 to 24 scale in the intervention groups was **2 points lower** (3 lower to 1 lower)		1756 (10 studies)	⊕⊕◯◯ **low**[3,4]	SMD −0.48 (95% CI −0.72 to −0.24) Absolute risk difference −8% (95% CI −12% to −4%)

Chondroitin sulfate/CSGH versus placebo/control for osteoarthritis

Patient or population: participants with osteoarthritis
Settings: international inpatient and outpatient clinics, hospitals, and research centers
Intervention: chondroitin sulfate or chondroitin sulfate with glucosamine versus placebo/control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chondroitin sulfate/ chondroitin sulfate with glucosamineversus placebo/control				
Scale from 0 to 24 (lower indicates less pain and disability) Follow-up: 3 to 24 months						Relative risk difference −18% lower (95% CI −26% to −9%) NNTB = 5 (95% CI 3 to 9)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; NNTB: Number needed to treat for an additional beneficial outcome

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]11 of the 17 studies reporting on this outcome did not report their methods of randomization, 13 of the 17 did not report the method of allocation concealment. 16 of the 17 studies were sponsored by a manufacturer of chondroitin sulfate or did not report their source of funding.

[2]Significant heterogeneity among the results is evident, with I^2 of 90%. The confidence intervals did not overlap one another, indicating a high degree of inconsistency in the effects observed in each study.

[3]Significant inconsistency was noted in the results of these studies, with five studies reporting significant benefit from chondroitin and three reporting no significant difference between chondroitin. This inconsistency is made serious by the lack of overlap in the confidence intervals of studies with contradictory results.

[4]Six of the 10 studies did not report their methods of randomization or allocation concealment. All ten studies did not report their source of funding or were sponsored by a manufacturer of chondroitin sulfate.

Chondroitin sulfate/CSGH versus placebo/control for osteoarthritis

Patient or population: participants with osteoarthritis
Settings: international inpatient and outpatient clinics, hospitals, and research centers
Intervention: Chondroitin sulfate or Chondroitin sulfate with glucosamine versus placebo/control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chondroitin sulfate/ Chondroitin sulfate with glucosamineversus placebo/control				
Pain (short- and long-term) Scale from 0 to 100 (lower is better) Follow-up: 3 to 24 months	The mean pain (short- and long-term) in the control groups was **30.2 mm**	The mean pain on 0 to 100 scale (short- and long-term studies) in the intervention groups was **9.5 mm lower** (13mm lower to 6.1 mm lower)		3038 (22 studies)	⊕⊕◯◯ **low**[1,2]	SMD −0.64 (95% CI −0.88 to −0.41) Absolute risk difference −10% (95% CI −13% to −6%) Relative risk difference −20% (95% CI −27% to −13%) NNTB = 4 (95% CI 3 to 6)
Physical function (short- and long-term) Scale from 0 to 100 (lower is better) Follow-up: 3–24 months	The mean physical function (short- and long-term) in the control groups was **31.8 mm**	The mean physical function (short- and long-term) on a 0 to 100 scale (higher is worse) in the intervention groups was **1.3 mm lower** (5.7 mm lower to 3.1 mm higher)		1163 (5 studies)	⊕⊕⊕◯ **moderate**[3]	SMD −0.07 (95% CI −0.31 to 0.17) Absolute risk difference −1% (95% CI −6% to 3%) Relative risk difference −3% (95% CI −13% to 7%) NNTB = not applicable
Composite Measure of Pain, Function and Disability as assessed through Lequesne's index (short- and long-term) Scale from 0 to 24 (lower indicates less pain	The mean Lequesne's index (short- and long-term) in the control groups was **9.7 points**	The mean Lequesne's index on 0 to 24 scale (higher is worse; short- and long-term results combined) in the intervention groups was **2.5 points lower** (3.5 to 1.5 lower)		2334 (16 studies)	⊕⊕⊕◯ **moderate**[4]	SMD −0.57 (95% CI −0.79 to −0.35) Absolute risk difference −10% (95% CI −14% to −6%) Relative risk difference −22% (95% CI −30% to −13%)

Chondroitin sulfate/CSGH versus placebo/control for osteoarthritis						
Patient or population: participants with osteoarthritis Settings: international inpatient and outpatient clinics, hospitals, and research centers Intervention: Chondroitin sulfate or Chondroitin sulfate with glucosamine versus placebo/control						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Chondroitin sulfate/ Chondroitin sulfate with glucosamineversus placebo/control**				
and disability) Follow-up: 3 to 24 months						NNTB = 4 (95% CI 3 to 6)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; NNTB: Number needed to treat for an additional beneficial outcome. NNTB is not applicable when the result is not statistically significant

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 17 of the 23 studies reporting on this outcome did not report their methods of randomization, 19 of the 23 did not report the method of allocation concealment. 22 of the 23 studies were sponsored by a manufacturer of chondroitin sulfate or did not report their source of funding.

2 Significant heterogeneity among the results is evident, with I^2 of 88%. The confidence intervals did not overlap one another, indicating a high degree of inconsistency in the effects observed in each study.

3 Two of the five studies reporting on this outcome did not report their methods of randomization. Three of the five studies did not report their methods of allocation concealment. All five studies were funded by a manufacturer of chondroitin sulfate or did not report their source of funding.

4 13 of the 16 studies did not report their methods of randomization, 14 of the 16 did not describe the method of allocation concealment. All 16 studies did not report their source of funding or were sponsored by a manufacturer of chondroitin sulfate.

DISCUSSION

Summary of main results

Overall, 43 trials were included in this meta-analysis, of which 30 contributed data to meta-analyses for clinical outcomes analyzed. Of these 30 studies, 18 assessed the efficacy of chondroitin sulfate in comparison with placebo, three assessed chondroitin sulfate in comparison with control, seven assessed chondroitin sulfate and glucosamine in comparison with placebo, and eight assessed chondroitin sulfate in combination with glucosamine in comparison with control (some studies had more than one active intervention arm). Three

studies presented data on more than one of the comparison groups in this meta-analysis. Clegg 2006 and Sawitzke 2010 (a follow-up of Clegg 2006) compared the efficacy of chondroitin versus placebo, chondroitin and glucosamine versus placebo, and chondroitin and glucosamine versus active control. Sawitzke 2008 compared the efficacy of chondroitin versus placebo and of chondroitin and glucosamine versus active control. Chondroitin (alone or in combination with glucosamine) seemed to be more effective for pain than the comparator among these studies and seemed to be well tolerated. Even though adverse events reporting by most trials was not very detailed, very few participants in either treatment groups reported adverse events.

Eleven studies (with 12 reports; Sawitzke 2010 was a follow-up of Clegg 2006 provided data on pain for chondroitin versus placebo, the first major outcome. These data showed that those treated with chondroitin sulfate alone had statistically significantly better scores on pain than those treated with placebo with a mean difference of −10.1 mm (95% CI −14.1 to −4.9) between chondroitin and placebo for pain on 0–100 scale in studies less than 6 months. The corresponding standardized mean difference was −0.51 (95% CI, −0.74 to −0.23) and absolute risk difference −9% (95% CI, −14% to −5%) between chondroitin sulfate alone vs. placebo. Standardized mean difference was −0.63 (95% CI, −0.93 to −0.33) for pain for chondroitin with/without glucosamine vs. placebo; this equals mean difference of −9.96 mm (95% CI −15.86 to −0.34). The risk of bias was high and the level of evidence was low. A common statistic used in non-Cochrane literature is effect size, such as Cohen's effect size, which is conceptually similar to standardized mean difference in its depiction of the influence of the effects of the experimental treatment. Cohen's effect size categorizes an effect size of 0.20 as small, 0.50 as medium, and 0.80 as large (Cohen 1992). Based on this categorization, the observed standardized mean difference of −0.51 for pain corresponded to a medium/moderate effect size with chondroitin alone and −0.63 corresponding with medium/moderate effect size with chondroitin with/without glucosamine. Analyses of pain studies has shown a reduction of pain between 0.9–1.3 cm on a 0–10 cm pain scale is clinically meaningful (Kelly 1998; Kelly 2001; Todd 1996), and as expected lower than the thresholds for "much improved" pain thresholds (Farrar 2001; Farrar 2000). The clinically meaningful threshold of 1 cm reduction in pain intensity was also endorsed by the The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008). Using the threshold of 0.9 cm on 0–10 cm scale for a clinical meaningful improvement, chondroitin alone or in combination with glucosamine led to clinically meaningful and statistically significantly improvement in pain, compared to placebo. The absolute improvements shown in the Summary of Findings tables of 9–10% also meet the clinically meaningful change threshold. One should note that the actual improvement with chondroitin alone or in combination with glucosamine was higher, given that 0.9 represents the difference between chondroitin (with/without glucosamine) and placebo/control groups. However, assessments of quality of evidence using GRADE method (see summary of findings table) indicated that several studies reporting on pain suffered from low quality of evidence; thus, we performed further sensitivity analyses to detect the influence of study quality on this observed effect from pain. When stratified by study size, for example, studies with large sample sizes (100 or more) found no statistically significant difference in the pain scores of participants treated with chondroitin and those treated with placebo, but studies

with smaller sample sizes showed a statistically significant difference in favor of chondroitin. With the exception of three studies, most studies had a sample size of fewer than 100. Stratification by study sponsorship further revealed that studies that were not funded by a manufacturer of chondroitin showed no significant difference between chondroitin and placebo, but among studies sponsored by a manufacturer of chondroitin, participants treated with chondroitin showed significantly better pain scores than those treated with placebo. However, sensitivity analysis by the blinding method or the ITT confirmed our initial results in favor of chondroitin, with studies that had adequate blinding methods and those using ITT analyses finding that participants treated with chondroitin sulfate had statistically significantly better pain ratings than those treated with placebo. These sensitivity analyses indicate that the effects of chondroitin are variable in sensitivity analyses that adjust for study quality and/ or funding source. The standardized mean differences varied from small-medium and statistically significant overall in some sensitivity analyses to minimal to nonexistent and statistically insignificant in others. Statistically insignificant results were seen particularly in studies with large sample sizes, independent sources of funding, and adequate methods of allocation concealment that did not show any statistically significant difference between the pain scores of participants treated with chondroitin and those treated with placebo.

The studies also showed better Lequesne's index scores (range 0–24) in patients receiving chondroitin compared to control/placebo with effect sizes of −0.52 with chondroitin and −0.48 with chondroitin with/without glucosamine (2.1 or 1.9 unit difference), compared to placebo. This corresponded to small to medium effect size benefit with chondroitin, and seemed clinically meaningful (though no published MCID threshold, a 2-point difference on this scale corresponds to ~10% or more improvement in one group compared to the other).

Of the 28 studies assessing chondroitin versus placebo, only two provided data for WOMAC MCII (Kahan 2009 and Clegg 2006). This is not surprising because this outcome has been defined recently, and many studies precede the description of this outcome; many others published since then have reported pain on various scales as the primary outcome. When chondroitin was compared with placebo, a significantly greater number of participants treated with chondroitin attained clinically meaningful and statistically significant improvement on WOMAC in pain than those treated with placebo (RR 1.12, 95% CI 1.01 to 1.24; P = 0.04).

Other outcomes that were significantly better in the chondroitin group compared with the placebo group were the patient and physician global assessments. Significantly higher proportions of participants reported very good or excellent on the global assessment in the chondroitin group compared with the placebo group. For a few outcomes, the data reveal that participants treated with chondroitin had statistically significant improvement as compared with those treated with placebo. For instance, participants in the chondroitin sulfate group experienced statistically significantly less loss of cartilage volume in global, lateral compartment, tibial plateaus and medial tibial plateaus, and less reduction in minimal joint space narrowing. However, among studies that found a statistically significantly positive effect with chondroitin for these various outcomes, heterogeneity was moderate, and

factors that affect the study's quality, such as size and independence of funding, were generally low quality.

In nearly all other outcomes, including physical function, stiffness, grip strength, morning stiffness, global assessment on VAS (mm), change in bone marrow lesion scores of several different compartments, OMERACT-OARSI, HAQ Disability, HAQ continuous, HAQ MCID scores, and both mental and physical components of SF-36, no statistically significant difference between chondroitin and placebo was noted.

Of the 43 studies contributing data to this systematic review and meta-analysis, seven studies assessed the efficacy of chondroitin sulfate in combination with glucosamine versus placebo. Among these studies, five provided data on some measure of pain. When data were not stratified by any of our considered factors, the studies showed no statistically significant difference between pain scores for participants in the placebo group compared with those in the chondroitin in combination with glucosamine group. Stratification by blinding, study size, study sponsors, and publication year confirmed these results, showing again no significant difference between chondroitin sulfate in combination with glucosamine and placebo in any of the subgroups. For other outcomes, no significant difference between chondroitin and placebo was reported, except in the number of participants achieving OMERACT-OARSI responder status; significantly more participants achieved OMER-ACT-OARSI responder status in the chondroitin in combination with glucosamine group than in the placebo group and had significantly better scores on balance than those in the placebo group. Few studies provided data on efficacy outcomes in this comparison arm, and only one study reported under many of the outcomes, making the authors' conclusions less reliable than desired.

Of the 43 studies contributing data, eight studies provided data that compared the efficacy of chondroitin in combination with glucosamine (along with NSAIDs) with the efficacy of NSAIDs or another active control alone. These studies allowed for the concomitant use of NSAIDs along with chondroitin and glucosamine and assessed whether the use of chondroitin in combination with glucosamine and NSAIDs was more effective than the use of NSAIDs alone. Four studies provided data on pain in this comparison arm. Participants in the chondroitin sulfate in combination with glucosamine and NSAIDs group had statistically significantly lower pain scores than those in the NSAIDs control group before sensitivity analysis. Heterogeneity was statistically significant among the studies. Sensitivity analysis by blinding method showed that studies that reported adequate blinding did not find a statistically significant difference between the use of NSAIDs in combination with chondroitin and glucosamine and alone. Studies that were not blinded, however, reported that those treated with chondroitin in combination with glucosamine and NSAIDs scored statistically significantly better on pain scales than those taking NSAIDs alone. Moreover, sensitivity analysis by study size revealed that those studies with large sample sizes (more than 100) showed no statistically significant difference between therapy with NSAIDs in combination with chondroitin and glucosamine and NSAIDs alone, and studies with small sample sizes did reveal such a statistically significant difference. This shows again that studies of higher quality (large sample sizes and adequate methods of allocation concealment) detected no statistically significant difference between chondroitin and

placebo. No statistically significant difference was noted between the active and control groups in any other outcomes, except WOMAC stiffness and Patient and Physical global assessments of good to very good, where the studies revealed that participants treated with chondroitin and glucosamine in combination with NSAIDs did have statistically significantly better scores than those treated with NSAIDs alone. However, heterogeneity was high among these studies. Moreover, most outcomes that did not show a significant difference between active treatment and placebo were populated by studies of higher methodological quality, and those that did show a statistically significant difference were populated by studies with significant between-study heterogeneity and typically lower methodological quality.

We also performed data analysis combining all studies that reported on pain and physical function without differentiating between the various compositions of their treatment arms, as long as chondroitin was included in the intervention arm. For pain, this sensitivity analysis revealed that participants treated with chondroitin alone or in combination with another supplement including glucosamine in most instances scored statistically significantly better on pain scales than those treated with placebo or control (SMD −0.65, 95% CI −0.95 to −0.35; P < 0.00001), which translated into an absolute risk difference of −9.6 (95% CI −14 to −5.2) on a 0 to 100 scale (Analysis 5.1). A similar result was found when we restricted the analysis to studies with a dose of chondroitin ≧ 800 mg/day, the therapeutic dose, with an SMD −0.67, 95% CI −0.99 to −0.34; P < 0.0001); absolute percent change 10% lower (14.6% lower to 5% lower). Our previous conclusion was again confirmed in this analysis, when all studies were combined and stratified by study size. Studies that had large sample sizes showed no significant difference between chondroitin and placebo, and studies with small sample sizes showed that participants treated with chondroitin alone or in combination with other supplements scored better on pain scales than those treated with a placebo or control. These results were replicated in our sensitivity analysis by source of funding and allocation concealment, showing that higher-quality studies found no statistically significant difference between participants treated with chondroitin alone or in combination with other supplements such as glucosamine and placebo or control. In the outcome of physical function, no statistically significant difference was noted between participants treated with chondroitin alone or in combination with other supplements such as glucosamine (P = 0.52 before the sensitivity analysis), and these results were confirmed in our sensitivity analysis.

Overall completeness and applicability of evidence

The evidence presented herein is up to date. Furthermore, the data presented here are taken from a large number of studies that span a long range of time for their publication. The review authors compared their list of included studies with those of other published reviews and meta-analyses to ensure the inclusion of all relevant studies. In this process, we discovered several studies, which, although they assessed the efficacy of chondroitin, did not offer data that could be used in our meta-analysis. Cohen 2003 assessed the efficacy of a chondroitin sulfate cream and since chondroitin was not orally administered chondroitin sulfate, the study could not be used. Vertkin 2007 had an obvious mismatch in study data and therefore could not be used. Das 2000 divided its participants by the severity of their osteoarthritis and presented separate data for severe and moderate/mild cases of

osteoarthritis; therefore, we estimated overall scores using these numbers. Nguyen 2001 had a before and after trial design; therefore, only its safety data were used, and the rest of the study results are summarized above, at the end of the Results section. Alekseeva 1999; Conrozier 1992; Conrozier 1998; L'Hirondel 1992; and Rai 2004 did not provide standard deviations in their data reports and could not be used in the main meta-analysis, except with categorical outcomes. As has been done previously in the systematic review and meta-analysis published by Reichenbach 2007, we estimated standard deviations using the formula presented in Figure 1 and performed a sensitivity analysis, in which we included all studies with estimated standard deviations as well.

In studies that were included in the data analysis of this review, we made sure to confirm the accuracy of studies with suspect data, such as data presented that appeared more like standard errors than standard deviations, despite the article's claims that they were standard deviations. In these instances, we contacted the authors of the study to double-check the accuracy of the data and indeed found and corrected several such errors.

Furthermore, because the current review assesses the efficacy of not only chondroitin sulfate in comparison with an inert placebo but also chondroitin sulfate in combination with glucosamine and in comparison with NSAIDs, the evidence applies to a broader range of clinical practice. Additionally, we performed numerous sensitivity analyses to try to more completely understand our results. In fact, as our conclusion suggests, the sensitivity analyses performed offer indispensable insight into the efficacy of chondroitin, as the sensitivity analyses show that studies with higher methodological quality show no significant difference between chondroitin and placebo or control.

Search for unpublished studies—Because (1) the funnel plot suggested publication bias and (2) we noted two radiographic studies, both with positive data, we contacted IBSA, the manufacturer of chondroitin sulfate and a supporter of several of these studies, on July 30, 2013 to request all unpublished radiographic data. In its response, dated July 30, 2013, IBSA provided us with five published studies, all of which had been considered in the screening process. They also responded that no radiographic data related to chondroitin from their studies were unpublished.

Quality of the evidence

The quality of the evidence presented in the various studies here may be limited by the fact that heterogeneity between the studies was rather large, and various subscales of an outcome were normalized and used in one overall outcome. For instance, pain on WOMAC, pain on VAS, and pain on the Japanese Orthopedic Association (JOA) scale were normalized and presented as one overall pain outcome. The decision to combine various subscales of an outcome was made a priori because a high degree of heterogeneity among the studies was suspected for the scales used to present data, thus hindering the execution of a fruitful meta-analysis. Several studies in the past have looked at multiple pain scales including numeric rating scales and visual analogue scales and have determined that they provide similar information and are comparable (Breivik 2008; Ferreira-Valente 2011).

Furthermore, the methodological quality of several studies included in the meta-analysis was low. Although most of the studies reported adequate blinding methods and performed appropriate ITT analyses, these authors did not report adequate methods of allocation concealment or randomization. Moreover, most of the studies were funded by manufacturers of chondroitin sulfate, such as IBSA, Rexall Sundown Inc., etc. The degree to which the involvement of chondroitin manufacturers played a role in these studies was not definitively clear. The quality of the evidence from many of these studies was further compromised because study authors did not clearly describe blinding and allocation concealment. Several other studies with no sponsorship from chondroitin sulfate manufacturers had large sample sizes and minimal amounts of bias, such as Clegg 2006; Kahan 2009; Messier 2007; and Uebelhart 2004. These four studies clearly described adequate methods of randomization, allocation concealment, blinding, and handling of missing outcome data, although the remaining studies are unclear in addressing at least one key source of bias, and in most of the studies, more than half of these factors of bias were not described. Additionally, we did not have access to enough information such as complete study protocols to make definitive judgments regarding the risk of selective reporting. Thus, we performed sensitivity analysis by blinding, study size, publication year, source of funding and ITT to detect the impact of such biases on our main results.

Potential biases in the review process

The quality of the information arrived at in this meta-analysis herein is by and large sound. All data and risk of bias assessments were performed by two independent review authors. The accuracy of the data was cross-checked by two research associates (KM, PF). Furthermore, as noted, possible inaccuracies in any part of the article's presentation of data were inquired about from the authors of the study and, when instructed by these authors, corrected.

Agreements and disagreements with other studies or reviews

In this meta-analysis, most of the published studies detected a statistically significant positive effect on pain. However, sensitivity analyses showed that the effect of chondroitin was persisted in some sensitivity analyses (those with adequate blinding and ITT analyses), but not in other sensitivity analyses. Current guidelines of the ACR, using the GRADE approach, discourage the use of supplements because of lack of evidence from high-quality trials (Hochberg 2012).

Other recently published meta-analyses have reported similar findings, with fewer trials, some with a different interpretation. For instance, in a meta-analysis of 21 studies (Alekseeva 1999; Bourgeois 1998; Bucsi 1998; Clegg 2006; Conrozier 1992; Conrozier 1998; Fleisch 1997; Kerzberg 1987; L'Hirondel 1992; Malaise 1999; Mazieres 1992; Mazieres 2001; Mazieres 2006; Michel 2005; Morreale 1996; Nasonova 2001; Pavelka 1999; Rovetta 1991; Soroka & Chyzh 2002; Uebelhart 1998; Uebelhart 1999) that assessed the efficacy of chondroitin in the treatment of osteoarthritis, published in 2007, Reichenbach 2007 found that "...large-scale, methodologically sound trials indicate that the symptomatic benefit of chondroitin is minimal or nonexistent. Use of chondroitin in routine clinical practice should therefore be discouraged." In this meta-analysis, Reichenbach 2007 included

all ”randomized or quasi-randomized trials which compared chondroitin with either no treatment or placebo.“ The review authors performed sensitivity analyses on the data by concealment of allocation, use of placebo in control, participant blinding, use of ITT, trial size, funding, use of co-intervention, route of administration, and length of follow-up. In so doing, they found that higher-quality studies with adequate concealment of allocation and proper ITT analysis showed small to nonexistent effects from chondroitin. The review authors also found a high degree of heterogeneity between the studies included.

We observed several points of agreement and disagreement between Reichenbach 2007 and our review, as noted in the Methods and Results sections. For instance, Reichenbach 2007 had broader inclusion criteria than we did. They included studies published in abstract form (Fleisch 1997; Kahan 2006; Mazieres 2006; Soroka & Chyzh 2002; Uebelhart 1999), but we decided a priori to include only full publications. In addition, they included studies that assessed the efficacy of chondroitin administered intramuscularly and topically (Cohen 2003; Kerzberg 1987; Rovetta 1991). However, we decided a priori to include only studies that assessed the efficacy of oral chondroitin to limit heterogeneity of effect; therefore, we did not include the results of Cohen 2003 in our meta-analyses but have only summarized them.

Furthermore, we discovered that over the several years that passed between the publishing of Reichenbach 2007 and the preparation of this review, several new published studies had assessed the efficacy of chondroitin sulfate (Alekseeva 2008; Gabay 2011; Kahan 2009; Kanzaki 2011; Magrans-Courtney 2011; Messier 2007; Moller 2010; Nakasone 2011; Pavelka 2010; Sawitzke 2008; Sawitzke 2010; Wildi 2011). We included these studies in our review so we could assess whether the publication of more recent studies had any influence on the previously arrived at conclusions regarding the use of chondroitin.

Moreover, we found that Reichenbach 2007 did not account for the possible clinical effect of heterogeneity arising from combining studies assessing the efficacy of chondroitin alone with those assessing the efficacy of chondroitin in combination with other treatments such as glucosamine or NSAIDs. The inclusion of studies that assess the effects of using a combination of chondroitin with other supplements poses the risk of confounding the observed results. It is difficult to see in such studies whether the observed effect in the active group is due to the presence of chondroitin or to another of the matrix components that was administered along with chondroitin. In our review, therefore, to control for any confounding effects arising from the use of other treatments in combination with chondroitin sulfate, we decided to stratify our data based on the make-up of the active treatment groups; therefore, we have separate comparison arms for studies that used chondroitin alone, studies that used chondroitin in combination with supplements, and studies that used chondroitin in combination with NSAIDs. To facilitate the comparison of our results with those of other reviews, however, we performed a sensitivity on all studies, regardless of whether they included confounding treatments, as long as they had chondroitin in the active arm compared with placebo/control (Analysis 5.1; Analysis 5.2; Analysis 5.3 and associated sensitivity analyses).

Moreover, we discovered that many of the studies included in Reichenbach 2007 had data for which standard deviations were provided in published studies. In such instances, Reichenbach 2007 et al. had estimated the standard deviations. We also therefore performed a sensitivity analysis wherein we included studies for which we estimated standard deviations to allow comparisons. Comparing the results of Reichenbach 2007 with ours, we discovered that both reviews agreed to a large extent regarding what the data showed. Both discovered that chondroitin was more efficacious as compared with placebo for pain-related outcomes; however, with the performance of sensitivity analysis, it became obvious that in some sensitivity analyses, beneficial effects from chondroitin were uncertain, while in others these beneficial effects persisted. This is where our findings differ from Reichenbach 2007. In our study, findings of clinically meaningful benefit with chondroitin compared to placebo for pain and Lequensne's index was robust for sensitivity analyses limited to studies with adequate blinding or studies that used appropriate intention to treat (ITT) analyses, but were uncertain when we limited data to studies with appropriate allocation concealment or a large study sample (> 200) or to studies without pharmaceutical funding.

For pain-related outcomes, 20 of the 22 studies included in Reichenbach 2007 provided data. These included studies for which no standard deviations were available and had to be estimated. Among these studies, the review authors witnessed a large "effect size" of −0.75 (95% CI −0.99 to −0.50). This effect size corresponded to a difference in pain scores of 1.6 cm (on a 10-cm VAS) between chondroitin and placebo groups. However, among studies reporting on this outcome, investigators witnessed an I^2 of 92%, indicating a high degree of between-trial heterogeneity. For pain-related outcomes, we identified a total of 22 studies that provided data; for some of these, we were forced to estimate standard deviations (included only in the sensitivity analysis). To facilitate the most accurate comparison possible between our review and Reichenbach 2007, we used data from Analysis 30.1 Analysis 29.1, which analyzed the results of all studies, including those with estimated standard deviations and those that assessed the efficacy of chondroitin sulfate alone or in combination with other supplements in the active group and in the placebo group, with no treatment or control in the control arm. For the outcome of pain, our analysis revealed an SMD of −0.64 and a 95% CI of −0.88 to −0.41, corresponding to a P-value < 0.0001 and a moderate-large effect size. This SMD corresponded to a 11.2 mm difference in pain scores on a 0 to 100-mm VAS scale. Among these studies, we observed a large degree of between-trial heterogeneity, with an I^2 of 91%. It is clear from these results that before sensitivity analysis was performed, the findings of our study were largely in agreement with the findings of Reichenbach 2007.

Our results also found agreement after the sensitivity analysis was performed. Reichenbach 2007 performed sensitivity analysis by allocation concealment, source of sponsorship, and sample size, among others. The mentioned sensitivity analyses revealed a significant interaction between the presence of adequate allocation concealment and sample size and the effect size of chondroitin. In studies with adequate allocation concealment, chondroitin sulfate showed smaller effects, with a P for interaction of 0.05. Two studies in Reichenbach 2007 had adequate allocation concealment. Among these two studies, the "effect size" decreased to −0.01 with a 95% CI level of −0.12 to 0.10. Our sensitivity analysis by allocation concealment revealed the same conclusion. We identified a total of four studies

that had adequate allocation concealment. These studies showed no significant effect from chondroitin with an SMD of 0.03, a 95% CI of −0.08 to 0.14, and a P value of 0.62. Heterogeneity was also non significant, with an I^2 of 36%. Sensitivity analysis by sample size showed the same conclusion. In Reichenbach 2007, when data were stratified according to sample size, studies with large sample sizes (more than 200) showed a non-significant ”effect size“ of −0.26 with a 95% CI of −0.56 to 0.04. When our data were stratified by sample size, studies with large sample sizes (greater than 100) had a decreased SMD of 0.03, with 95% CI of −0.08 to 0.14. Neither Reichenbach 2007 nor our review discovered any significant difference between chondroitin and control.

Moreover, sensitivity analysis by source of funding again revealed the same conclusion. Reichenbach 2007 stratified results between those funded by nonprofit organizations and those not funded by nonprofit organizations or those with unclear sources of funding. Studies that had nonprofit sponsorship showed no significant effect from chondroitin, with an ”effect size“ of 0.01 and a 95% CI of −0.15 to 0.16. In our review, we stratified our data according to whether the study was sponsored by a manufacturer of chondroitin sulfate or whether the study did not specify its source of funding or was not supported by a manufacturer of chondroitin sulfate. This analysis revealed an SMD of 0.00 with a 95% CI of −0.15 to 0.16 in one study that was not funded by a chondroitin sulfate manufacturer. Studies funded by manufacturers had a smaller effect size of −0.52 compared to −0.75 for studies with unclear funding. Therefore, the results of our meta-analysis and the results of Reichenbach 2007 are in some disagreement in these regards. Richy 2003 is another meta-analysis on the efficacy of chondroitin sulfate. Upon performing a meta-analysis on nine studies, Richy 2003 found that chondroitin was more effective on Lequesne’s index, visual analogue scale for pain, mobility, and responder status. Although the review authors note that the quality of the chondroitin studies included in their review was lower than that of studies reporting on the efficacy of glucosamine, they do not perform sensitivity analyses to discover the effect of low methodological quality on their outcomes. This accounts for the high level of variation between results of our meta-analysis and the results presented in Richy 2003. Our overall conclusion revealed a positive effect from chondroitin in comparison with placebo, as does Richy 2003. However, upon further stratification of the data by factors such as sample size, and source of sponsorship, it became clear that studies with high methodological quality, we found that effects persisted in some, but not all sensitivity analyses.

Other reviews, such as Hochberg 2010 and Lee 2010, studied the efficacy of chondroitin in slowing the progression of joint space width loss. Although the number of studies included in this meta-analysis was small-three in Hochberg 2010 (Kahan 2009; Michel 2005; Sawitzke 2008) and four in Lee 2010 (Kahan 2006; Michel 2005; Uebelhart 1998; Uebelhart 2004)-investigators did detect a small but significant positive effect in the rate of joint space width narrowing in participants treated with chondroitin.

Lee 2010 concludes that chondroitin sulfate ”had a small but significant protective effect on minimum JSN [joint space narrowing] after two years (SMD 0.261, 95% CI 0.131–0.392, $P < 0.001$). This meta-analysis of available data shows that glucosamine and chondroitin sulfate may delay radiologic progression of osteoarthritis of the knee after daily

administration for over 2 or 3 years.“ Hochberg 2010 echoes these results, stating that the analysis results showed ”a small significant effect of chondroitin sulfate on the reduction in rate of decline in minimum joint space width of 0.13 mm [95% confidence interval (CI) 0.06, 0.19] (P < 0.0002) that corresponded to an effect size of 0.23 (95% CI 0.11, 0.35) (P < 0.0001). These results demonstrate that chondroitin sulfate is effective for reducing the rate of decline in minimum joint space width in patients with knee OA.” Our estimates of minimum joint space width changes agree with those of Hochberg 2010 and Lee 2010. What is not known is whether these radiographic differences are clinically meaningful. Moreover, the small number of studies used in the meta-analysis makes it difficult to draw firm conclusions, indicating that more data are needed. Another review, Wandel 2010, studied the efficacy of glucosamine, chondroitin, and glucosamine and chondroitin in combination as compared with placebo in reducing pain and joint space width loss and in ensuring safety. This review includes ten studies (Herrero-Beaumont 2007; Kahan 2009; McAlindon 2004; Novack 1994; Pavelka 2002; Reginster 2011; Rozendaal 2008 in glucosamine vs placebo comparison arm; Kahan 2009; Mazieres 2007; and Michel 2005 in the chondroitin vs placebo comparison arm; and Clegg 2006 for glucosamine and chondroitin combination vs the placebo comparison arm). In their analysis of the three studies comparing chondroitin alone with placebo, the authors found that participants treated with chondroitin did not experience a statistically significant reduction in pain intensity with a 95% confidence interval level of −0.3 cm (−0.7 to 0.0 cm) on a 10-cm visual analogue scale. Treatment with chondroitin alone was shown to have “minute” effects on radiographic joint space width, with a 95% confidence interval level of −0.1 mm (−0.3 to 0.1 mm) in favor of chondroitin. In the safety outcomes, chondroitin was shown to have an odds ratio of 0.99 with a 95% confidence interval level of 0.49 to 2.00 in the number of adverse events and 0.92 with a 95% confidence interval of 0.56 to 1.51 for withdrawals or dropouts due to adverse events. This meta-analysis differed from ours in that it included a much smaller number of studies in both the chondroitin versus placebo comparison arm and the chondroitin and glucosamine combination versus placebo comparison arm, thus limiting the scope of the presented findings. Despite the small number of studies included in each of the comparison arms, Wandel 2010 still found, as did our meta-analysis, that studies with industry sponsorship showed that chondroitin had a greater effect on pain than studies that did not have industry sponsorship. “On average, the estimated differences between supplements and placebo were 0.5 cm less pronounced in industry independent trials compared with industry sponsored trials, and estimated treatment effects in industry independent trials were minute to zero and by no means clinically relevant,” the authors write.

AUTHORS’ CONCLUSIONS

Implications for practice

The improvement in joint pain with chondroitin (alone or in combination with glucosamine) in participants with osteoarthritis was clinically meaningful and statistically significantly better than placebo, based on trials of mostly low quality. Participants reported statistically significantly more favorable ratings on patient and physician global assessment scales, Lequesne’s index (a combination of pain, physical function and disability), which seemed clinically meaningful as well, based on evidence of low to moderate quality. There was

statistically significantly less reduction in minimal joint space width with chondroitin compared to placebo groups, based on evidence of moderate to high quality, but the significance of this radiographic benefit is unclear to us.

Differences in physical function (by WOMAC) and most other clinical and radiographic outcomes were not statistically significant. WOMAC scores were reported in few trials, but Lequesne's index (a pain, physical function and disability composite) was reported by several studies, and was statistically significantly different between chondroitin and control/placebo, and the difference is considered clinically meaningful. It is important to note that the risk of serious side effects was lower in the chondroitin group than in comparator groups. Chondroitin was also tested alone and in combination with glucosamine against placebo or control treatments (NSAIDs), and similar observations were made. These differences in pain with chondroitin (alone or in combination with glucosamine) compared with placebo were attenuated or were no longer significant in some sensitivity analyses, but they persisted in other sensitivity analyses (blinding, ITT). Results were sensitive to trial quality, trial sponsorship, and trial sample size, such that trials with unclear or no allocation concealment, with pharmaceutical sponsorship, and with smaller sample size were more likely to show significant differences between groups, and those not in these categories showed a smaller and/or insignificant difference between chondroitin and comparator. On the other hand, when we limited analysis to studies with adequate blinding and studies using intention-to-treat (ITT) analyses, the differences in pain between chondroitin (alone or in combination with glucosamine) and placebo persisted.

Osteoarthritis is a challenging disease, and at present, very few effective and safe treatment options are available. Frequently used treatments such as NSAIDs are associated with significant adverse events, especially in the elderly. In addition, these medications are not universally effective, and a large proportion of patients fail with these over time. Analgesics such as acetaminophen are not very effective in severe osteoarthritis, and also have potential liver toxicity. The elderly may experience adverse events to narcotics, such as constipation, falls, confusion, etc. which sometimes are used for the treatment of severe osteoarthritis. Thus, a clear need exists for several more effective and safe treatment options.

Chondroitin is available over the counter as a supplement. Chondroitin seems to be well tolerated with no major safety issues, and its efficacy seems to range from small to medium treatment effect. However, most data have come from several small trials of short duration, with most sample sizes < 100. Given the widespread use of this supplement, it is important that we understand its efficacy and role in the treatment of osteoarthritis. At this time, we suggest that patients and physicians discuss the pros and cons of using chondroitin for osteoarthritis and use it in conjunction with other modalities for osteoarthritis treatment, including weight loss and quadriceps strengthening and appropriate pharmacological treatment. We believe that larger high-quality studies of chondroitin in various subgroups of osteoarthritis (early vs late vs end-stage osteoarthritis, mild vs severe osteoarthritis, erosive vs. non-erosive osteoarthritis) are needed.

Implications for research

Most evidence for chondroitin comes from small trials. The National Institutes of Health (NIH) has already sponsored and conducted the GAIT trial (Clegg 2006), which showed no statistically significant difference from placebo. Well-designed high-quality RCTs of chondroitin in participants with early and late osteoarthritis are desirable because they can add valuable information to knowledge gaps in this area. Larger samples and appropriate controls (placebo or NSAIDs) are needed, and trials need to provide longer follow-up and closer monitoring so investigators can see long-term effects and detect any safety concerns.

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* Indicates the major publication for the study

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APPENDICES

Appendix 1. MEDLINE search strategy

1. exp OSTEOARTHRITIS/

2. osteoarthr$.tw.
3. (degenerative adj2 arthritis).tw.
4. or/1–3
5. exp CHONDROITIN/
6. chondroitin.sh,rn,tw.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized controlled trials.sh.
12. random allocation.sh.
13. double blind method.sh.
14. single-blind method.sh.
15. clinical trial.pt.
16. clinical trials.sh.
17. clinical trial.tw.
18. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
19. placebos.sh.
20. placebo$.tw.
21. random$.tw.
22. Research Design/
23. comparative study.sh.
24. evaluation studies.sh.
25. follow-up studies.sh.
26. prospective studies.sh.
27. control$.tw.
28. prospectiv$.tw.
29. volunteer$.tw.
30. or/9–29
31. (animal not human).mp.
32. 30 not 31
33. 8 and 32

Appendix 2. EMBASE search strategy

1. exp osteoarthritis/
2. osteoarthr$.tw.
3. (degenerative adj2 arthritis).tw.
4. or/1–3
5. chondroitin/
6. Chondroitin.tw.
7. 5 or 6
8. 4 and 7
9. (random$ or placebo$).ti,ab.
10. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.
11. controlled clinical trial$.ti,ab.
12. RETRACTED ARTICLE/
13. or/9–12
14. (animal$ not human$).sh,hw.
15. 13 not 14
16. 8 and 15

Appendix 3. The Cochrane Library search strategy

#1 MeSH descriptor Osteoarthritis explode all trees

#2 osteoarthr*:ti,ab

#3 (degenerative near/2 arthritis):ti,ab

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Chondroitin explode all trees

#6 Chondroitin:ti,ab

#7 (#5 OR #6)

#8 (#4 AND #7)

Appendix 4. CINAHL search strategy

S8 S4 and S7

S7 S5 or S6

S6 TI Chondroitin OR AB Chondroitin

S5 (MH “Chondroitin+”)

S4 S1 or S2 or S3

S3 TI degenerative N2 arthritis OR AB degenerative N2 arthritis

S2 TI osteoarthr* OR AB osteoarthr*

S1 (MH “Osteoarthritis”)

Appendix 5. AMED search strategy

1. exp osteoarthritis/
2. osteoarthr$.tw.
3. (degenerative adj2 arthritis).tw.
4. or/1–3
5. Chondroitin.tw.
6. 4 and 5

Appendix 6. ISIWeb of Science search strategy

Topic=(osteoarthr* OR degenerative arthritis) AND Topic=(Chondroitin)

AND Document Type=(ABSTRACT OR CLINICAL TRIAL OR MEETING)

Appendix 7. World Health Organization International Clinical Trials Registry Platform

osteoarthr* in Condition AND

Chondroitin in Intervention

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alekseeva 1999	
Methods	Randomized, parallel, independent group study design
Participants	Age 45 and older, knee osteoarthritis diagnosed according to ACR (1986) criteria, Kellgren-Lawrence X-ray grade II or III, moderate to severe pain (> 30 mm on 100-mm VAS), Lequese’s index 4 to 11 points, NSAIDs taken for at least 30 days over previous three months Chondroitin sulfate: N = 50; Age (mean ± SD) = 59.72; Men/Women = 3/47 Control: N = 50; Age (mean ± SD) = 60.06; Men/Women = 3/47
Interventions	Active: chondroitin sulfate 1000 mg/d (two capsules of 250 mg twice a day) with meals, ibuprofen up to 1200 mg/d (no rules for dose selection given), and paracetamol allowed as rescue analgesia (but no guide for doses, duration is given, and no control is described) Control: ibuprofen up to 1200 mg/d (no rules for dose selection given) and paracetamol allowed as rescue analgesia (but no guide for doses, duration is given, and no control is described)
Outcomes	VAS Pain (walking/rest), Lequesne’s index, Patient global assessment (% improved), Patient global assessment on VAS, Concomitant medication use

Notes	Data analysis performed by a manufacturer of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label, unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy Analysis
Selective reporting (reporting bias)	Unclear risk	Not enough information provided to allow assessment
Alekseeva 2005a		
Methods	Randomized, parallel, independent group study design	
Participants	All participants diagnosed with knee osteoarthritis according to ACR (1991) criteria, Kellgren-Lawrence X-ray grade II or III, Moderate to severe pain on motion (> 40 mm on 100-mm VAS), NSAIDs taken for at least 30 days in previous three months CSG: N = 45; Age (mean ± SD) = 59.35 ± 9.58; Men/Women = 0/45; (I/II/III/IV) = 0/31/14/0 Control: N = 45; Age (mean ± SD) = 60.07 ± 7.6; Men/Women = 0/45; (I/II/III/IV) = 0/29/16/0	
Interventions	1000 mg of chondroitin sulfate daily + 1000 mg of glucosamine daily for the first month, then 500 mg of chondroitin sulfate daily for the next five months; NSAID (diclofenac) started at 100 mg daily, with dose reduction and stopping allowed Diclofenac 100 mg/d for six months	
Outcomes	WOMAC Total score Patient global assessment MD global assessment	
Notes	We decided to include the results of this study in our meta-analyses despite differing administration of doses at six months. Study authors are manufacturers of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of randomization method
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT

Selective reporting (reporting bias)	Unclear risk	Unclear
Alekseeva 2005b		
Methods	Open, randomized, multicenter clinical trial	
Participants	Knee osteoarthritis (ACR), K-L X-ray grade II or III, pain in knees on walking > 40 mm on 100mm VAS, NSAIDs taken for at least 30 days in the past three months Chondroitin sulfate: N = 203; Age (mean ± SD) = 57.63 ± 8.5; (I/II/III/IV) = 0/143/60/0 Placebo: N = 172; Age (mean ± SD) = 61.22 ± 7.94; (I/II/III/IV) = 0/106/66/0	
Interventions	Chondroitin sulfate 1000 mg daily + G 1000 mg daily for first month, then chondroitin sulfate 500 mg daily + G 500 mg daily for next five months. Diclofenac 100 mg daily, with dose reduction and stopping allowed without restriction Diclofenac 100 mg daily for six months, with dose reduction and stopping allowed without restriction	
Outcomes	WOMAC Total score WOMAC physical function WOMAC pain WOMAC stiffness	
Notes	We decided to include the results of this study in our meta-analyses despite differing administration of doses at six months. One author is known to be an employee of a chondroitin sulfate manufacturer	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomization not mentioned
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT analysis but account of withdrawals provided
Selective reporting (reporting bias)	Unclear risk	Unclear
Alekseeva 2008		
Methods	Open, comparative, "randomized," independent, parallel-group experimental design, clinical trial	
Participants	All participants diagnosed with knee osteoarthritis according to ACR (1991) criteria, Kellgren-Lawrence X-ray grade II or III, Pain on walking (> 40 mm on 100-mm VAS), NSAIDs taken for at least 30 days in previous three months Chondroitin sulfate: N = 50; Age (mean ± SD) = 58.0 ± 7.1; Men/Women = 1/49; I/II/III/IV = 0/44/6/0; Disease duration (mean ± SD) = 8.92 ± 7.65; Current NSAIDs, n = 50 Placebo: N = 50; Age (mean ± SD) = 57.7 ± 7.69; Men/Women = 0/50; I/II/III/IV = 0/47/3/0; Disease duration (mean ± SD) = 7.06 ± 5.65; Current NSAIDs, n = 50	
Interventions	Chondroitin sulfate + glucosamine for nine months daily ("constant therapy") Chondroitin sulfate + glucosamine for two three-month cycles with a three-month treatment-free interval between cycles ("intermittent therapy") Concurrent treatment: ibuprofen 1200 mg daily (400 mg 3 times daily), with dose reduction allowed at physician discretion in both groups (no guidelines for dose adjustment given)	
Outcomes	WOMAC Performance-based physical function Patient global assessment MD global assessment	

	Adverse effects Knee ultrasound	
Notes	Advertisement for chondroitin sulfate and article published together	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Unclear risk	Unclear
Artemenko 2005		
Methods	"Randomized" single-center trial in Russia	
Participants	All participants had knee osteoarthritis (according to ACR criteria), Kellgren-Lawrence X-ray grade II or III, Pain on walking > 40 mm on 100-mm VAS, Women/Men = 41/6 Treatment: N = 31; Age (mean ± SD) = 54.79 ± 9.52; Severity/Stage = 0/21/10/0 Placebo: N = 16; Age (mean ± SD) = 65.38 ± 7.88; Severity/Stage = 0/11/5/0	
Interventions	Treatment: Chondroitin sulfate 1000 mg daily + glucosamine 1000 mg daily for first month, chondroitin sulfate 500 mg daily + glucosamine 500 mg daily for the next five months; diclofenac 100 mg daily with dose reduction allowed Control: Diclofenac 50 to 100 mg daily, stopping of diclofenac allowed with treatment effect observed *No formal rules for stopping described for either group	
Outcomes	**Primary** Lequesne's index **Secondary** WOMAC Total score WOMAC pain subscale WOMAC stiffness subscale	
Notes	We decided to include the results of this study in our meta-analyses despite differing administration of doses at six months. Source of funding unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded

Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT analysis performed and reason for dropout in treatment group not mentioned
Selective reporting (reporting bias)	Unclear risk	Unclear; translated article
Bourgeois 1998		
Methods	3-Month phase III, randomized, femoral-tibial knee osteoarthritis, internal or external (according to ACR), participant- and investigator-blind, double-dummy, parallel-group clinical trial in France	
Participants	Outpatients of either sex, Aged > 45, with femoral-tibial knee osteoarthritis (ACR), unilateral or bilateral, of grade I to III, requiring stable daily administration of one of the authorized NSAIDs for at least one month before the trial Chondroitin sulfate 1200: N = 40; Men/Women: 16/26; Age (mean ± SD) = 63 ± 11; Weight (mean ± SD) = 76 ± 14 Chondroitin sulfate 3 × 400: N = 43; Men/Women: 8/34; Age (mean ± SD) = 63 ± 9; Weight (mean ± SD) = 72 ± 13 Placebo: N = 44; Men/Women: 7/37; Age (mean ± SD) = 64 ± 8; Weight (mean ± SD) = 78 ± 16	
Interventions	Chondroitin sulfate: 4 and 6 oral gel 1200 mg once daily Chondroitin sulfate: 4 and 6 capsules 400 mg × 3 daily Placebo	
Outcomes	**Primary** Lequesne's index **Secondary** Spontaneous pain on 100-mm VAS Consumption of NSAIDs Adverse effects Withdrawals/Death	
Notes	Study sponsored by IBSA Switzerland and Genevier, a maker of chondroitin sulfate tablets	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "To preserve the double blind condition of the study, chondroitin sulfate chondroitin sulfate 4&6 oral gel… and placebo oral gel were available in sachets of identical appearance" Comment: sachets of identical appearance; administered identically time and dosage wise
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT (LOCF) analysis; the study did not address or provide reasons for incomplete outcome data or compare the effects of incomplete outcomes across study groups
Selective reporting (reporting bias)	Unclear risk	Unclear
Bucsi 1998		
Methods	Randomized, participant- and investigator-blind, placebo-controlled study involving two centers	
Participants	Chondroitin sulfate: N = 39; Age (mean ± SD) = 60.6 ± 9.6; Men/Women = 17/22; MBI/Body weight (kg) = 83.4 ± 13.9 Placebo: N = 46; Age (mean ± SD) = 59.4 ± 9.0; Men/Women = 17/29; MBI/Body weight = 80.2 ± 16.1	
Interventions	400 mg of chondroitin sulfate and placebo 2 times daily for six months	
Outcomes	**Primary**	

	Spontaneous joint pain-VAS scale of 100 mm considering pain during daily physical activity **Secondary** Paracetamol consumption (total number of tablets) Time taken for a 20-meter walk on flat ground Lequesne index-pain Lequesne index-maximal walking distance Lequesne index-discomfort in daily life movements MD global assessment Patient global assessment	
Notes	Supplement sponsored by ISBA Laboratories, a maker of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Eighty… (36 chondroitin sulfate, chondroitin sulfate/44 placebo, PBO) completed the 6 month treatment period, while five patients (three chondroitin sulfate + two PBO) dropped out after 3 months, three of them (two chondroitin sulfate + one PBO) failing to turn up for follow-up examination; one (chondroitin sulfate) had severe viral infection, one (PBO) had brain tumor surgery, both not correlated to the treatment" Comment: no ITT analysis, but clear account of withdrawals
Selective reporting (reporting bias)	Unclear risk	Unclear
Clegg 2006		
Methods	Multicenter, participant- and investigator-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)	
Participants	Age: at least 40; Clinical evidence and radiographic evidence of osteoarthritis; Patients with a summed pain score of 125 to 400 on the index knee according to WOMAC and ARA functional class I, II, or III Placebo: Age (mean ± SD) = 58.2 ± 9.8; Men/Women = 113/200; Duration Sx: 9.5 ± 9.1; Rad severity (I/II/III/IV) = 0/179/0/0; BMI/Body weight = 31.9 ± 7.3 Glucosamine: Age (mean ± SD) = 58.6 ± 10.2; Men/Women = 118/199; Duration Sx: 10.4 ± 10.5; Rad severity (I/II/III/IV) = 0/173/0/0; BMI/Body weight = 31.8 ± 6.8 Chondroitin: Age (mean ± SD) = 58.2 ± 10.0; Men/Women = 113/205; Duration Sx: 9.7 ± 10.0; Rad severity (I/II/III/IV) = 0/186/0/0; BMI/Body weight = 32.0 ± 7.6 Glucosamine + Chondroitin sulfate: Age (mean ± SD) = 58.6 ± 10.6; Men/Women = 118/199; Duration Sx: 10.1 ± 10.2; Rad severity (I/II/III/IV) = 0/160/0/0; BMI/Body weight = 31.5 ± 6.6 Celecoxib: Age (mean ± SD) = 59.4 ± 11.1; Men/Women = 106/212; Duration Sx: 10. 1 ± 9.2; Rad severity (I/II/III/IV) = 0/177/0/0; BMI/Body weight = 31.5 ± 7.1	
Interventions	1500 mg of glucosamine daily 1200 mg of chondroitin sulfate Both glucosamine and chondroitin sulfate daily 200 mg celecoxib daily Placebo	
Outcomes	**Primary** 20% decrease in summed score for the WOMAC pain subscale (from baseline to week 24) **Secondary** WOMAC stiffness subscale WOMAC function subscale Patient global assessments concerning response to therapy, pain, and disease status on VAS Physician global assessment of disease status on VAS	

	Presence/Absence of soft tissue swelling, effusion, or both in index knee Short Form-36 scores Analgesic use	
Notes	In our data analyses, we used Patient and Physician global assessment of disease status on VAS (0 to 100 mm). McNeil Consumer donated acetaminophen; Bioiberica, S.A., Barcelona donated sodium chondroitin; Ferro Pfanstiehl Laboratories, Waukegan Ill, donated portion of glucosamine hydrochloride. "Drs Bingham, Brandt, Clegg, Hooper, Schnitzer report having received consulting fees or having served on advisory boards for McNeil Consumer and Specialty Pharmaceuticals…"	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Permuted-block randomization was used with random block sizes, stratified according to the 16 clinical centers and baseline WOMAC pain"
Allocation concealment (selection bias)	Low risk	Randomization list generated by Veterans Affairs Cooperative Studies Program Data Coordinating Center
Blinding (performance bias and detection bias) All outcomes	Low risk	"During data collection, neither the clinical centers nor the coordinating center at the University of Utah had access to the randomization codes or statistical summaries of follow-up data"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis for primary outcome; LOCF; Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Unclear
Cohen 2003		
Methods	Single-center, randomized, participant- and investigator-blind, placebo-controlled trial lasting eight weeks	
Participants	Diagnosed with osteoarthritis of the knee (ACR); knee pain due to osteoarthritis rated > 4 cm on 10-cm VAS in one or both knees for > 4 weeks Active cream: N = 30; Age (mean ± SD) = 62.3 ± 8.4; Men/Women = 15/15; Duration disease, years, median (IQ range): 10 (5 to 18) Inactive cream: N = 29; Age (mean ± SD) = 63.2 ± 7.8; Men/Women = 15/15; Duration disease, years, median (IQ range): 12 (6 to 16)	
Interventions	Cream form of chondroitin sulfate used Treatment: GS 30 mg/g, chondroitin sulfate 50 mg/g, shark cartilage 140 mg/g (10% to 30% of which is chondroitin sulfate), camphor (32 mg/g), peppermint oil scent (9 mg/g) versus conventional cosmetic cream of identical scent and appearance	
Outcomes	**Primary** Pain on VAS (0 to 100 mm) **Secondary** WOMAC pain WOMAC stiffness WOMAC physical function SF-36 questionnaire	
Notes	"Supported by grants from Nutrasense Australia Pty. Ltd. and Smart Science Laboratories Inc"	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized in blocks of four but method of randomization list generation not mentioned
Allocation concealment (selection bias)	Unclear risk	Unclear

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Texture and scent similar with "slight differences"- although participants were told not to bring cream to follow-up and investigators were told to not ask about cream
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All analyses were based upon intention to treat, in that subjects who completed follow-up were analyzed according to the group to which they were randomized… Four subjects withdrew (2 after Day 4, one after Day 14, and one after Day 26). Data from 59 patients were analyzed" Comment: clear account of all withdrawals
Selective reporting (reporting bias)	Unclear risk	Unclear
Conrozier 1992		
Methods	Participant- and investigator-blind, randomized, placebo-controlled study taking place in France for six months	
Participants	Hip joint arthrosis with narrowing in intra-articular space (degree I, II, III); Pain of the hip joint, requiring regularly analgesics or NSAIDs Overall population: N = 56; Age = 61.4 years (between 26 and 82 years); Disease duration = 5.5 years	
Interventions	3 capsules of chondroitin sulfate 400 mg Identical placebo	
Outcomes	**Primary** Lequesne's index Huskisson's Analogue Scale (pain relief) Consumption of analgesics or NSARs Patient evaluation **Secondary** Morning stiffness Maximum walking distance Frequency of awaking at night Intermalleolar distance	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Chondroitin sulfate and placebo identical sachets
Incomplete outcome data (attrition bias) All outcomes	Low risk	"24 patients dropped out: 5 were in the chondroitin sulfate group (17.24%), 19 in the placebo group (70.37%). Reasons for dropping out of the placebo group were: lack of compliance (n = 2), lacking efficacy (n = 14) and adverse events (n = 3). There were no adverse events in the placebo group"
Selective reporting (reporting bias)	Unclear risk	Unclear
Conrozier 1998		

Methods	Multicenter, randomized, controlled, parallel independent group, participant- and investigator-blind, with ITT trial	
Participants	Chondroitin sulfate: N = 52 Placebo: N = 52 Patients older than 40 years of age	
Interventions	800 mg of chondroitin sulfate for two periods of three months in one year Identical placebo administered similarly	
Outcomes	Rest/Motion pain (VAS) Lequesne's index Patient global assessment MD global assessment Change in joint space width (mm) femorotibial	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Das 2000		
Methods	Randomized, placebo-controlled, participant- and investigator-blind study	
Participants	Kellgren-Lawrence Grade II to IV; Both genders; Age 45 to 75; Able to walk; Willing to comply with protocol; Symptomatic > 6 months; Bilateral or unilateral osteoarthritis Chondroitin sulfate + G: N = 46; Age (mean ± SD) = 64.5 ± 9.8; Men/Women = 13/33; Disease duration: 5.6 ± 1.3; Severity stage: severe osteoarthritis = 13 (28%); n% with secondary osteoarthritis = 7 (15%); Prior surgery arthroscopy: 7 (15%) Placebo: N = 47; Age (mean ± SD) = 66 ± 1.5; Men/Women = 10/37; Disease duration: 7.4 ± 1.2; Severity stage: severe osteoarthritis = 8(17%); n% with secondary osteoarthritis = 21 (45%); Prior surgery arthroscopy: 6 (13%)	
Interventions	Two capsules of 500 mg glucosamine + 400 mg chondroitin sulfate +76 manganese Placebo	
Outcomes	**Primary** Lequesne's Index WOMAC score Patient global assessment **Secondary** Rescue pain medication Adverse events	
Notes	In part support by Nutramex	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence	High risk	"Randomization schedule was obtained using a computer-based pseudo-random number generator"

generation (selection bias)		
Allocation concealment (selection bias)	Low risk	"Each bottle was given a sequential number (1,2,3…) with the code concealed to the investigator. The sequential numbers were matched with the order of inclusion of eligible patients into the study. Neither the patient, nor the evaluating physician was aware of the treatment assignment"
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The 'intention-to-treat' concept was implemented. In other words, persons assigned to either intervention or placebo groups were analysed as such irrespective of their compliance"
Selective reporting (reporting bias)	Unclear risk	Unclear
Debi 2000		
Methods	Randomized, participant- and investigator-blind study comparing glucosamine sulfate and chondroitin sulfate with placebo lasting one month	
Participants	All participants with osteoarthritis Chondroitin sulfate + G: N = 36; Men/Women = 11/25; Age = 40 to 90 Placebo: N = 20; Men/Women = 4/16; Age = 40 to 90	
Interventions	Glucosamine and chondroitin sulfate 800 to 1600 mg daily according to participant weight Placebo	
Outcomes	Patient global assessment Performance-based physical function X-rays	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of a method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT; no mention of dropouts or side effects
Selective reporting (reporting bias)	Unclear risk	Unclear
Fardellone 2013		
Methods	A multicenter, prospective, randomized, double-blind, double-placebo, active-controlled, parallel group study performed in patients with symptomatic knee OA over a 24-week duration	
Participants	Patients aged 50–80 years, presenting with medial and/or lateral femoro-tibial OA of the knee according to American College of Rheumatology (ACR) criteria, symptomatic for more than 6	

	months, with a baseline level of symptoms as follows, global pain score on a Visual Analog Scale (VAS 0–100) of at least 40 millimeters (mm) and a Lequesne's algofunctional index (LFI 0–24) score greater than or equal to 7. Patients had to show radiographic OA as defined by a Kellgren-Lawrence grade II or III [32] on an antero-posterior weight-bearing view of both knees taken during the 12 months prior to inclusion. 412 were randomized to Structurm and 425 to chondrosulf	
Interventions	Comparison of two chondroitin preparations, Structum® 500 mg bid or Chondrosulf® 400 mg tid	
Outcomes	**Primary:** Global pain experienced during the last 24 hours prior to assessment was rated on a 100 mm VAS Lesquense's index **Secondary:** Mean changes of pain scores (at rest or on motion rated on VAS) Mean changes on patient's and investigator's global assessment scores (VAS, where 0 is the worst and 100 the best assessment), Mean changes of Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF-12 (ranges 0–100) Mean changes of each Osteoarthritis of the knee or hip Quality of Life dimension score (OAKHQOL) Percentages of responders according to the modified Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI responder) Consumption of analgesic medications (paracetamol and/or NSAIDs)	
Notes	Study was funded by Institut de Recherche Pierre Fabre.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were assigned to one of the two groups according to a pre-established computer-generated global randomization list (treatment number) with balanced blocks of 4 treatments
Allocation concealment (selection bias)	Low risk	"The patients were assigned to one of the two groups according to a pre-established computer-generated global randomization list (treatment number) with balanced blocks of 4 treatments
Blinding (performance bias and detection bias) All outcomes	Low risk	"The study was double-blind, double-dummy. Both the patient and the investigator remained blinded throughout the entire study." " All study case report forms recorded only the randomization number to identify the patient"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Both full set and per protocol analyses were provided. Missing data was similar in the two groups and 17% overall. "The primary analysis was conducted on the PP dataset, as recommended by the EMEA guidelines for the conduct of non-inferiority trials."
Selective reporting (reporting bias)	Low risk	Used appropriate outcomes: "EMEA recommendations on clinical investigation of medicinal products used in the treatment of OA, pain relief and functional disability were assessed as the primary efficacy criteria in this study". Also provided results for harms in the two groups
Gabay 2011		
Methods	Investigator-initiated, single-center, randomized, participant- and investigator-blind, placebo-controlled clinical trial in participants with hand osteoarthritis	
Participants	Inclusion criteria: Participants were of either sex, age 40 years or older, and fulfilled the American College of Rheumatology (ACR) criteria for the classification of hand osteoarthritis. In addition, radiographic features of hand osteoarthritis affecting at least two joints of the target hand on standard plain films obtained within six months of enrolment, as well as at least two painful flares of osteoarthritis in the finger joints during the previous 12 months, were required. The target hand was defined as the participant's most symptomatic hand or, when both hands were equally painful, the participant's dominant hand. To be eligible for the study, participants had to present with symptomatic osteoarthritis. The minimal level of symptoms was joint pain of at least 40 mm on a 0 to 100-mm visual analogue scale (VAS) and a Functional Index for Hand osteoarthritis (FIHOA) score of at least 6 in the target hand (0 to 30 scale) Chondroitin sulfate: N = 80; Age (mean ± SD) = 63.9 ± 8.5; Men/Women = 22/58; Disease duration (right hand): 7.1 ± 6.1; Disease duration (left hand): 6.9 ± 6.3 Placebo: N = 82; Age (mean ± SD) = 63.0 ± 7.2; Men/Women = 20/62; Disease duration (right hand) = 6.7 ± 5.7; Disease duration (left hand) = 6.2 ± 5.3	

Interventions	Chondroitin sulfate: 800 mg daily or placebo	
Outcomes	**Primary** Change in Patient's assessment of global spontaneous hand pain on VAS Change in Patient's assessment of global spontaneous hand function on the FIHOA score from baseline to month 6 **Secondary** Grip strength Morning stiffness	
Notes	Study funded by IBSA-maker of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomization list was generated by a computer in blocks of 4 containing 2 placebo and 2 chondroitin sulfate allocations. Patients were assigned a randomization number according to the order of inclusion"
Allocation concealment (selection bias)	Unclear risk	Quote: "The treatment allocation was concealed in sealed envelopes until the end of the study" Comment: unclear whether envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Patients, nurses, the medical team in charge of the patient, the physician performing the assessments, and the statistician performing the analysis were blinded to the treatment allocation" Comment: unclear how the blinding was fulfilled
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The main analysis for efficacy and safety was an intent-to-treat analysis. Missing follow-up assessments were replaced using the last observation carried forward (LOCF) method. Alternative techniques of imputing missing follow-up assessments were performed to test the robustness of this assumption. We performed a sensitivity analysis using linear interpolation (mixed regression model) for missing follow-up assessments. We further performed a per-protocol completer analysis including only patients who completed the planned treatment. Overall, sensitivity analyses yielded qualitatively very similar results to those from the LOCF analysis, suggesting that results were not driven by selective drop-outs or differential missing data"
Selective reporting (reporting bias)	Unclear risk	Not enough information to assess the level of risk
Kahan 2009		
Methods	International, randomized, participant- and investigator-blind, placebo-controlled trial, two-year study	
Participants	Outpatient status, age between 45 and 80, primary knee osteoarthritis of the medial tibiofemoral compartment diagnosed according to ACR Chondroitin sulfate: N = 309; Age (mean ± SD) = 62.9 ± 8.789; Men/Women = 93/216; Duration Sx: Left Knee = 6.1 ±. 5.274; Right Knee = 6.6 ± 7.031 Placebo: N = 313; Age (mean ± SD) = 61.8 ± 8.846; Men/Women = 104/209; Duration Sx: Left Knee = 6.5 ± 7.077; Right Knee = 6.3 ± 7.077	
Interventions	800 mg of chondroitin sulfate daily for two years Placebo administered identically	
Outcomes	**Primary** Minimum JSW of the medial compartment of the target tibiofemoral joint **Secondary** VAS (0 to 100 mm) WOMAC score (total and subscale) Patient global assessment MD global assessment Cumulative consumption of acetaminophen Cumulative consumption of NSAIDs	
Notes	Trial funded by IBSA, a maker of chondroitin sulfate	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization list was generated by the computer in blocks of 4, and patients received their randomization number in chronological order"
Allocation concealment (selection bias)	Low risk	"The principal investigator (AK) was provided with the individual envelopes, each containing patients' codes, thus concealing treatment assignment"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Chondroitin sulfate and placebo were packed in anonymous sachets of identical appearance, containing oral gel with the same aspect, odor, and flavor; both chondroitin sulfate and placebo sachets contained sodium benzoate and potassium sorbate" "At the end of the study, after the data bank was completed, the randomization list was provided to the statistician (FDV), who remained blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The cumulative time distribution of withdrawals was similar in the chondroitin sulfate and placebo groups (P = 0. 4 by log-rank test), without significant differences in reasons for withdrawal" Comment: missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Unclear
Kanzaki 2011		
Methods	A prospective, randomized, placebo-controlled, parallel-group comparative study was designed to assess the efficacy and safety of GCQ supplement of a length of six months, involving two clinical service organization centers under the control of two medical investigators in Japan	
Participants	Inclusion criteria: Male and female Japanese subjects, aged 40 to 85 years, with diagnosed knee osteoarthritis, in whom presence of knee pain was confirmed by the assessment scores for the "walking" subscale of the JOA criteria (25 or lower score for either left or right knee joint) GCQ: N = 20; Age (mean ± SD) = 55.1 ± 10.9; Men/Women = 4/16 Placebo: N = 20; Age (mean ± SD) = 58.3 ± 7.4; Men/Women = 3/17	
Interventions	1200 mg glucosamine hydrochloride, 300 mg shark cartilage extract (60 mg as chondroitin sulfate), and 45 mg quercetin glycosides in a daily dose of six tablets or placebo	
Outcomes	**Primary** Japan Orthopaedic Association subscales Walking ability and painfulness (walking) "Stairs-ascending/descending ability and painfulness (stairs-ascending/descending)" "Range of motion" "Joint swelling" **Secondary** VAS pain at rest VAS pain on walking VAS pain on ascending/descending of stairs	
Notes	no mention of study sponsors.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "All subjects were sequentially assigned based on random number tables to one of the two masked products and randomized (1:1) to GCQ supplement (GCQ group) and dummy placebo (placebo group)" Comment: not clear how the random number tables were created
Allocation concealment (selection bias)	Unclear risk	Not clear how treatment allocation took place

Blinding (performance bias and detection bias) All outcomes	Low risk	The products were masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of ITT analysis or descriptions of withdrawals
Selective reporting (reporting bias)	Unclear risk	Not enough information for assessment of selective reporting
L'Hirondel 1992		
Methods	Clinical, participant- and investigator-blind, parallel-design, randomized study with orally administered chondroitin sulfate versus placebo in participants with tibiofemoral gonarthrosis taking place in France for six months	
Participants	Painful tibiofemoral gonarthrosis with an intra-articular space, without dislocation of the main axis, with or without meniscus calcification Chondroitin sulfate: N = 63 Placebo: N = 62	
Interventions	Three sachets of 400 mg chondroitin sulfate daily versus three sachets of identical placebo Concurrent treatment: up to month 2-same treatment as before; months 2 to 6: 500 mg of paracetamol according to pain intensity allowed	
Outcomes	**Primary** Lequesne's Index Adverse Effects Huskisson Analogue Scale (pain relief) Space between heel and bottom Consumption of analgesics and non-steroid anti-rheumatics Total efficacy evaluated by investigator **Secondary** Extent of flexion and extension of the joint Extent of the joint circumference Verification of a static incident or an abnormal movement or an intra-articularly effusion	
Notes	Trial funded by IBSA, a maker of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Unclear risk	Unclear
Lila 2005		
Methods	Randomized, open, efficacy trial	
Participants	Age 45 to 75, osteoarthritis diagnosed according to ACR (1987) criteria, Kellgren-Lawrence X-ray grade I to III, Pain in knees on walking > 40 mm on 100-mm VAS, morning stiffness < 30 minutes	

	Chondroitin sulfate: N = 30; Age (mean ± SD) = 60.1 ± 11.4; Men/Women = 7/23; Disease duration, years: 8.8 ± 1.1; Rad severity (I/II/III) = 2/19/9/0; Spinal osteoarthritis n (%)=12 (40) Placebo: N = 30; Age (mean ± SD) = 63.2 ± 12.2; Men/Women = 10/20; Disease duration, years = 5 ± 1.4; Rad severity (I/II/III) = 4/15/11/0; Spinal osteoarthritis n (%)= 8(26.7)	
Interventions	Chondroitin sulfate 800 mg daily + glucosamine 1000 mg daily for the first month, then chondroitin sulfate 400 mg daily + glucosamine 500 mg daily for the next two months Diclofenac 75 mg/d	
Outcomes	WOMAC Rest/Motion Pain VAS (0 to 100 mm) Morning stiffness Patient global assessment MD global assessment Adverse effects	
Notes	Possible involvement with pharmaceutical company	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT; withdrawals mentioned but reasons not clearly described
Selective reporting (reporting bias)	Unclear risk Unclear	
Other bias	Unclear risk Concurrent treatments not clarified	
Magrans-Courtney 2011		
Methods	Randomized, participant- and investigator-blind, placebo-controlled, parallel clinical trial lasting 14 weeks	
Participants	Females with physician-diagnosed osteoarthritis between the ages of 18 and 70 years with a body mass index (BMI) greater than 27 kg/m2 and no recent participation in a diet or exercise program were included in the study GHCl + Chondroitin Sulfate + Exercise Plan + Diet Plans: N = 16; Age = 52 ± 10 years Placebo + Exercise Plan + Diet Plans: N = 14; Age = 57 ± 7 years	
Interventions	1500 mg of glucosamine (from d-glucosamine HCL), 1200 mg/d of chondroitin sulfate (from chondroitin sulfate sodium), 120 mg/d of niacin, 120 mg/d of sodium, 45 mg/d of zinc, 900 mg/d of MSM, 300 mg/d of Boswellia serrata extract, 180 mg/d of white willow bark extract, and 15 mg/d of rutin powder + High-Protein Diet + Exercise Plan or 1500 mg of glucosamine (from d-glucosamine HCL), 1200 mg/d of chondroitin sulfate (from chondroitin sulfate sodium), 120 mg/d of niacin, 120 mg/d of sodium, 45 mg/d of zinc, 900 mg/d of MSM, 300 mg/d of Boswellia serrata extract, 180 mg/d of white willow bark extract, and 15 mg/d of rutin powder + High-Carbohydrate Diet + Exercise Plan or Placebo + High-Proten Diet + Exercise Plan or Placebo + High-Carbohydrate Diet + Exercise Plan Exercise Plan: 14-Week circuit-style workout consisting of 14 exercises (e.g., elbow flexion/extension, knee flexion/extension, shoulder press/lat pull, hip abductor/adductor, chest press/seated row, horizontal leg press, squat, abdominal crunch/back extension, pec deck, oblique, shoulder shrug/dip, hip extension, side bends, and stepping three times a week) Diet Plans composed of three phases:	

	• Phase I: lasting one week; intake of a total of 1200 kcal daily • Phase II: after nine weeks, intake of 1600 kcals/d • Phase III: final four weeks; weight maintenance period High-Protein (HP) Diet regimen: 7% carbohydrate, 63% protein, and 30% fat during Phase I, and 15% carbohydrate, 55% protein, and 30% fat during Phase II of the diet High-Carbohydrate Diet regimen: 55% carbohydrate, 15% protein, and 30% fat. In the final phase of the Diet Program, all participants were allowed 55% carbohydrate, 15% protein, and 30% fat
Outcomes	**Primary** Measures of pain, including Pain on VAS Stiffness Physical function Total score on WOMAC scale **Secondary** Weight loss Body composition Measures of quality of life Changes in energy intake Anthropometrics Body composition Resting energy expenditures Cardiovascular and muscular fitness Balance and functional capacity Serum and whole blood clinical markers Hormonal profiles Pain indices Psychosocial parameters Knee range of motion and circumference.
Notes	Quote: "Curves International (Waco, TX, USA) provided funding for this project through an unrestricted research grant to Baylor University when the Principal Investigator and the Exercise & Sport Nutrition Lab were affiliated with that institution and currently provides funding to Texas A&M University to conduct exercise and nutrition related research. All researchers involved independently collected, analyzed, and interpreted the results from this study and have no financial interests concerning the outcome of this investigation" Comment: Other bias due to source of funding improbable; however, unclear whether there could have been bias that resulted from other factors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The supplements were prepared in caplet form and packaged in generic bottles for participant- and investigator-blind administration by Nutra Manufacturing (Greenville, SC). The dextrose placebo was prepared with a similar base material and color coated in order to have a similar appearance and aroma as the GCM supplement" Comment: adequate description of blinding method, which appears to have preserved blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 42 women met initial phone screening criteria and were invited to familiarization sessions. Of these, 32 women met entrance criteria and were medially-cleared to participate in the study by a research nurse and their personal physician. A total of 30 women completed the study. Those who dropped out of the study did so due to time constraints unrelated to the exercise, diet, and/or supplementation program"

		Comment: withdrawals clearly accounted for, and it is likely that the dropouts were due to any factors in either of the treatment groups
Selective reporting (reporting bias)	Unclear risk	Not enough information to make a judgement
Mazieres 1992		
Methods	Multicenter, “randomized,” controlled, parallel, independent, participant- and investigator-blind with ITT	
Participants	Pain greater than or equal to 40 mm on 100-mm VAS; score greater than 4 on Lequesne; Age greater than 50; Gonarthroses femorotibial, internal or external, or coxarthroses Chondroitin sulfate: N = 58; Age (mean ± SD) = 64.5 ± 1.14; Men/Women = 19/39; Disease duration, years: 6.3 ± 0.69 Rad severity (I/II/III) = 12/28/18/0; Unilateral = 42; Bilateral = 16; Coxarthrose = 22; Gonarthrose = 36 Placebo: N = 56; Age (mean ± SD) = 63.3 ± 1.07; Men/Women = 16/40; Disease duration, years: 6.3 ± 0.70 Rad severity (I/II/III) = 14/31/11/0; Unilateral = 43; Bilateral = 13; Coxarthrose = 21; Gonarthrose = 35	
Interventions	2000 mg chondroitin sulfate and placebo daily for three months	
Outcomes	Rest/Motion pain VAS Lequesne’s index Patient/MD global assessment NSAID use	
Notes		
Risk of bias		
Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned by blocks of four but method of randomization not mentioned
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT (LOCF) analysis; description of withdrawals and dropouts provided
Selective reporting (reporting bias)	Unclear risk	Unclear
Mazieres 2001		
Methods	Participant- and investigator-blind, randomized, parallel-group study with ITT for six months	
Participants	Chondroitin sulfate: N = 67; Age (mean ± SD) = 66.9 ± 8; Men/Women = 15/52; Rad severity I/II/III/IV = 0/36/31/0; MBI/Body weight = 28.9 ± 4.8; Unilateral knee osteoarthritis % = 21 Placebo: N = 63; Age (mean ± SD) = 67.3 ± 7.8; Men/Women = 18/45; Rad severity (I/II/III/IV) = 0/37/26/0; MBI/Body weight = 29.2 ± 5.1; Unilateral knee osteoarthritis % = 34	
Interventions	500 mg chondroitin sulfate or placebo two times daily for a three-month period	
Outcomes	**Primary** Lequesne’s Index **Secondary** Pain with physical activity (VAS) Pain at rest (VAS) Self-assessed effect of osteoarthritis on daily activity (VAS) Investigator overall assessment of change (better, unchanged, worse)	

	Patient overall assessment of change (much worse, somewhat worse, unchanged, better, much better) Daily NSAID and analgesic consumption	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "An independent monitoring committee verified from the outset that the study was correctly conducted and that the review at the end of the trial was performed under strictly blind conditions" Comment: adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis Comment: There is a clear explanation of the reasons for dropouts, and the number of dropouts was small enough that it seems unlikely that it affected the results
Selective reporting (reporting bias)	Unclear risk	Unclear
Messier 2007		
Methods	Participant- and investigator-blind, placebo-controlled, randomized clinical trial lasting 12 months (only first six months applicable)	
Participants	Age greater than or equal to 50; mild to moderate knee osteoarthritis KL: II-III (ACR); not currently participating in another study Chondroitin sulfate/GH: N = 45; Age (mean ± SD) = 70.0 ± 8.59; Men/Women = 11/34; Baseline BMI (mean ± SD) = 30.7 ± 6.24 Placebo: N = 44 Age (mean ± SD) = 74.1 ± 8.76; Men/Women = 15/29; Baseline BMI (mean ± SD) = 27.3 ± 4.71	
Interventions	1200/1500 mg CSGH either once or three times daily and placebo of identical appearance with the same frequency	
Outcomes	**Primary** WOMAC physical function **Secondary** WOMAC pain subscale Distance walked in 6 minutes MMSE (mental status) Strength of concentric extension and flexion in most affected knee	
Notes	"Support for this study was provided by a grant from Rexall Sundown Inc."-makers of the chondroitin sulfate used	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All study compound bottles received were numbered with corresponding sealed list including lot numbers and bottle contents"
Allocation concealment (selection bias)	Low risk	"All study compound bottles were numbered with a corresponding sealed list including lot numbers and bottle contents (active or placebo). The study compound was allocated in order at the first healthy lifestyle class"
Blinding (performance bias and detection bias)	Low risk	"The control group took a placebo of identical size, color, and shape at the same frequency"

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis observations method of dealing with missing data
Selective reporting (reporting bias)	Unclear risk	Unclear
Michel 2005		
Methods	Randomized, participant- and investigator-blind, placebo-controlled trial with ITT lasting two years in Zurich Switzerland	
Participants	Chondroitin sulfate: N = 150; Age (mean ± SD) = 62.5 ± 9.1; Men/Women = 74/76; MBI/Body weight (kg/m-squared) = 27.7 ± 5.2 Placebo: N = 150; Age (mean ± SD) = 63.1 ± 10.7; Men/Women = 72/78; MBI/Body weight = 28.1 ± 5.5	
Interventions	800 mg chondroitin sulfate or placebo once daily for two years	
Outcomes	**Primary** Minimum and mean joint space width of the more severely affected compartment of the target knee **Secondary** WOMAC stiffness WOMAC physical function Total consumption of rescue drugs during the trial and the average number of tablets study drug taken per day Adverse Events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was done by computer in blocks of 4. Each patient received a randomization number" Comment: computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	The study used sealed envelopes for randomization numbers according to participants' treatment assignment, and pills were identical. It is not clear who administered the pills and whether they were blinded; no mention of appropriate safeguards
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo sachet; statistician was blinded and radiograph readers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were discussed with no significant difference between the two groups. Both completer and ITT (LOCF) analyses were performed
Selective reporting (reporting bias)	Unclear risk	Unclear
Moller 2010		
Methods	Randomized, participant- and investigator-blind, PBO-controlled multicenter study for a duration of three months	
Participants	Inclusion criteria: Eligible participants were male and female patients 40 years of age or older, with osteoarthritis of the knee as defined by criteria of the American College of Rheumatology, with pain in the affected knee scoring 30 on a continuous 0 to 100-mm Huskisson's VAS and a confirmatory knee X-ray diagnosis (Kellgren-Lawrence grades I to III) associated with cutaneous plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score of 5 Chondroitin sulfate: N = 60; Age (mean ± SD) = 58.6 ± 11.4; Men/Women = 31/29; # (%) with Kellgren-Lawrence grade I = 4 (6.7); # (%) with Kellgren-Lawrence grade II = 47 (78.3); # (%) with Kellgren-Lawrence grade III = 9 (15.0)	

	Placebo: N = 56; Age (mean ± SD) = 61.0 ± 10.4; Men/Women = 24/32; # (%) with Kellgren-Lawrence grade I = 4 (7.1); # (%) with Kellgren-Lawrence grade II = 40 (75. 0); # (%) with Kellgren-Lawrence grade III = 12 (21.4)	
Interventions	Chondroitin sulfate 800 mg daily or placebo	
Outcomes	**Primary** Decrease in pain intensity assessed by VAS **Secondary** Pain relief and function improvement in the knee using the Lequesne algo-functional index 26 Acetaminophen consumption OLS score Histopathologic data Changes in psoriatic lesions according to PGA Assessment of efficacy by patients and investigators and Quality of life measured with SF-36 and DLQI	
Notes	Study funded by Bioiberica, maker of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All eligible participants were sequentially assigned by the researchers to one of the two masked products in a proportion of 1:1 per treatment group according to a pre-established computer-generated global randomization list provided by the statisticians. The randomization schedule was generated using the SAS PROCPLAN programme (Release 9.1.3 Service Pack 2) for a block size of 2 and a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	"All eligible participants were sequentially assigned by the researchers to one of the two masked products in a proportion of 1:1 per treatment group according to a pre-established computer-generated global randomization list provided by the statisticians. The randomization schedule was generated using the SAS PROCPLAN programme (Release 9.1.3 Service Pack 2) for a block size of 2 and a 1:1 ratio"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Subjects were randomly assigned to receive daily either chondroitin sulfate 800mg (two capsules of 400mg each) (Condrosan, chondroitin sulfate Bio-Active TM, Bioibérica, S.A., Barcelona, Spain) or matched PBO capsules"
Incomplete outcome data (attrition bias) All outcomes	High risk	"The efficacy analysis was performed for the intention-to-treat (ITT) population defined as all randomized patients who met the inclusion/exclusion criteria, received the study medication and from which data of the primary endpoints for the baseline visit and at least one follow-up visit were available" Comment: The ITT analysis is inadequate
Selective reporting (reporting bias)	Unclear risk	Not enough information to make a judgment
Morreale 1996		
Methods	Six-month, randomized, participant- and investigator-blind, parallel-group study involving two centers	
Participants	Either sex, between 40 and 75 years of age, with grade I or II monolateral or bilateral knee osteoarthritis; not taking NSAIDs and/or "chondroprotective" treatment for 15/ 30 days before study initiation Chondroitin sulfate: N = 74; Age (mean ± SD) = 55.39 ± 12.21; Men/Women = 31/43; Severity: 0/33/41/0 Placebo: N = 72; Age (mean ± SD) = 56.37 ± 12.08; Men/Women = 39/43; Severity: 0/ 35/37/0	
Interventions	One month chondroitin sulfate 3 × 400 mg + 3 × placebo Two months chondroitin sulfate 3 × 400 mg Three to six months placebo only versus One month diclofenac sodium 3 × 50 mg daily + 3 × placebo Two months placebo 3 × daily	

	Three to six months placebo only	
Outcomes	**Primary** Lequesne's index Spontaneous pain (VAS 0 to 100 mm) Pain on load (absent, light, moderate, intense) **Secondary** Paracetamol Consumption	
Notes	Studies Sponsored by Manufacturer of chondroitin sulfate-IBSA	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "To preserve the double blind condition of the study, the diclofenac sodium tablets and placebo tablets were ground and inserted into capsules of identical appearance" Comment: identical capsules, administration, and # of times taken daily
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The number of withdrawals and the rates and reasons for dropping out were similar in both groups" Comment: missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified
Nakasone 2011		
Methods	A randomized, participant- and investigator-blind, placebo-controlled study designed to assess the efficacy and safety of the test supplement in adult participants with symptomatic knee osteoarthritis lasting 16 weeks in two clinical service organizations in Yokohama, Japan	
Participants	Inclusion criteria: Male and female Japanese participants, aged 40 to 83 years, with clinical and radiographic evidence of mild knee osteoarthritis, were enrolled; 30 to 75 on a 100-mm VAS and radiologic severity of affected knee joints mainly graded 1 to 2 on the Kellgren-Lawrence (K/L) scale. Participants with bilateral diagnosed knee osteoarthritis were asked to specify the worse affected knee at baseline, and this knee was evaluated throughout the study period Chondroitin sulfate + glucosamine: N = 16; Age (mean ± SD) = 56.4 ± 7.7; Men/Women = 2/14; Severity: 94% grade I to II on KL Placebo: N = 16; Age (mean ± SD) = 54.5 ± 9.1; Men/Women = 2/14; Severity: 88% grade I to II on KL	
Interventions	1200 mg glucosamine hydrochloride + 200 mg shark cartilage (60 mg of chondroitin sulfate) + 300 mg of MSM + 105 mg of guava leaf extract + 5.6 μg of vitamin D + 7.35 mg of vitamin B1 seven times daily or placebo	
Outcomes	JKOM subscales: • "pain/stiffness" • "conditions in daily life" • "general conditions" • "health conditions" VAS subscales: • Pain • Pain on rest • Pain on walking • Pain on descending and ascending stairs	

	Cartilage metabolism Synovial Inflammation	
Notes	Source of funding not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding inadequately described-"The test supplement was a commercially available tablet-form preparation containing 1,200 mg of glucosamine hydrochloride, 200 mg of shark cartilage extract, of which approximately 30% (60 mg) is chondroitin sulfate, 300 mg of MSM, 105 mg of guava leaf extract and 5.6 μg of vitamin D, together with 7.35 mg of vitamin B1 and vehicle (comprising lactose, maltitol and crystalline cellulose) at a daily dose of 7 tablets. Subjects were randomly assigned to receive 7 tablets (2,300 mg) of the test supplement (test group), or 7 tablets (2,300 mg) of dummy placebo containing only vehicle (placebo group). All subjects were instructed to take 7 tablets of the test supplement or placebo once daily at any time of the day"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description of withdrawal or participant screening-unclear whether 16 participants were deemed eligible at outset or whether 16 participants remained after withdrawals and dropouts
Selective reporting (reporting bias)	Unclear risk	Not enough information to make a judgment
Nasonova 2001		
Methods	Randomized, parallel, independent group study for a duration of six months	
Participants	Inclusion criteria: knee or hip osteoarthritis diagnosed according to ACR (1991) criteria, Kellgren-Lawrence X-rays grade I to III, moderate to severe pain (> 30 mm on 100-mm VAS), Lequesne's Index 4 to 11 points, NSAIDs taken for at least 30 days in previous three months Chondroitin sulfate: N = 192; Age (mean ± SD) = 55.79 ± 9.01; Men/Women = 30/162 Control: N = 363; Age (mean ± SD) = 57.8 ± 9.7; Men/Women = 82/281	
Interventions	Intervention: chondroitin sulfate 1500 mg/d for the first three weeks, than chondroitin sulfate 1000 mg/d for the next period up to six months Control: no chondroitin sulfate treatment, "regular treatment" of osteoarthritis according to physician's preferences. No formal guidelines for treatment described	
Outcomes	VAS Pain (Rest/Motion) Lequesne's Index Patient and Physician global assessment Withdrawals	
Notes	The study included participants with hip and knee osteoarthritis-We used only data from participants with knee osteoarthritis, representing a sample size of 110. The study authors are manufacturers of and spokespeople for chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization

Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT was not performed, and a large number of participants withdrew from both groups without a clear explanation
Selective reporting (reporting bias)	Unclear risk	Protocol not provided
Nguyen 2001		
Methods	Twelve-week, randomized, participant- and investigator-blind, clinical trial; pilot study	
Participants	Pain in one or both TMJ joints; moderate or severe pain on lateral or dorsal palpation of TMJ Chondroitin sulfate: N = 24; Age, mean (SD) = 43 (13); Men/Women = 3/11; Disease duration, years = 76 ± (81/12); VAS mm = 42 ± 24 Placebo: N = 24; Age, mean (SD) = 46 (15); Men/Women = 19/1; Disease duration, years = 56 ± (65/12); VAS mm = 49 ± 17	
Interventions	Two tablets of 250 mg glucosamine hydrochloride + 200 mg chondroitin taken daily versus placebo	
Outcomes	Pain on VAS McGill Pain Questionnaire's Pain rating scales Mood and Functioning Questionnaire Tenderness on TMJ palpation Jaw range of motion Daily pain rating using VAS Analgesic use Daily change in pain intensity	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated simple consecutive randomization"
Allocation concealment (selection bias)	Low risk	"Computer-generated simple consecutive randomization"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Investigators and subjects were blinded to the contents of the assigned medications throughout the study" Comment: placebo and GHCS-identical-looking tablets; identical bottles
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Although nine subjects dropped out of the active medication group, in three of these the reason for dropping out could be directly attributed to the study medications: a stomachache and two possible allergic reaction[s]. In sum, 14 subjects remained in the active medication group, and 20 subjects remained in the placebo group" Comment: no ITT-reason for missing outcome data likely to be related to true outcome, with imbalance in numbers or reasons for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	Unclear

Pavelka 1999		
Methods	Phase II, randomized, participant- and investigator-blind, dose-effect study	
Participants	Femorotibial osteoarthritis of the knee according to ACR, with clinical symptoms persisting for at least three months; Lequesne's Index greater than or equal to 8 points and pain on Huckisson's VAS greater than or equal to 40 mm (pain during daily physical activity); persistence of some articular joint space documented on radiography; age over 30 years Chondroitin sulfate 200 mg: N = 35; Age (mean ± SD) = 63.9 ± 9.8; Men/Women = 8/ 27; Disease duration, years: 3.7 ± 3.8 Chondroitin sulfate 800 mg: N = 35; Age (mean ± SD) = 65.9 ± 10.6 Men/Women = 9/26; Disease duration, years: 3.9 ± 5.1 Chondroitin sulfate 1200 mg: N = 35; Age (mean ± SD) = 67.1 ± 10.4; Men/Women = 5/30; Disease duration, years: 3.7 ± 3.9	
Interventions	One sachet daily of 200 mg chondroitin sulfate, 800 mg chondroitin sulfate, 1200 mg chondroitin sulfate, or placebo	
Outcomes	**Primary** Lequesne's Index ISK and spontaneous pain on Huskisson VAS (0 to 100 mm) **Secondary** Global efficacy evaluation by participants Global efficacy evaluation by the MD Paracetamol consumption from day 15 to day 90	
Notes	No mention of role of sources of funding or mention of conflicts of interest	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	"The different preparations of chondroitin sulfate and the placebo were indistinguishable and packaged in identical sachets"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were three premature withdrawals from the study in total (1 placebo, 1 chondroitin sulfate 200 mg, and 1 chondroitin sulfate 1200 mg) and no statistical difference was found between the study groups" Comment: no LOCF analysis because no significant difference was noted between study groups as the result of incomplete data
Selective reporting (reporting bias)	Unclear risk	Unclear
Pavelka 2010		
Methods	Controlled, randomized, multinational, multicenter, participant- and investigator-blind, double-dummy, parallel-group study carried out at five centers in Czech Republic, three in Slovak Republic, five in Hungary, seven in Poland, and six in Romania	
Participants	Patients had to be "aged 45 years or above and had femorotibial osteoarthritis of the knees longer than 6 months with pain and functional discomfort over 1 month during the last 3 months, were complying with the clinical and radiological criteria of the American College of Rheumatology of knee osteoarthritis, had a Lequesne index between 5 and 13 and a radiologic score of grade I, II or III of the modified Kellgren/Lawrence scale on a frontal image of extended knee, on both knees, the image being not older than 6 months, had pain on movement and/or pain at rest in the last 48 h at least 40 mm evaluated on a VAS, and/or at least 40 mm evaluated on at least two items among the five items in the A-section of the WOMAC index, with no intake of analgesics for 48 h and NSAID for 5 days" ASU: N = 142; Age (mean ± SD) = 62.3 ± 9.46 Chondroitin sulfate: N = 121; Age (mean ± SD) = 62.2 ± 9.02	

Interventions	Chondroitin sulfate 400 mg three times daily or 300 mg avocado soybean unsaponifiable daily	
Outcomes	WOMAC physical function WOMAC stiffness WOMAC pain WOMAC Total OMERACT-OARSI VAS pain Number of paracetamol tablets taken Lequesne's index	
Notes	Study funded by Laboratoire Expanscience	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using a computer random number generator-Rancode 1.0
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	"Thus, ASU verum and placebo were identical, and chondroitin sulfate verum and placebo were identical. The placebos contained all ingredients of the verum except the active substances. The test medication was packed into blisters according to the following scheme: Blister A contained: one capsule ASU 300 mg and three capsules chondroitin sulfate placebo. Blister B contained: one capsule ASU placebo and three capsules chondroitin sulfate 400 mg. All blisters had an identical batch number and expiry date. Each patient took four capsules per day, two in the morning, one at noon, one in the evening"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'
Rai 2004		
Methods	Single-center, outpatient, randomized, participant- and investigator-blind, placebo-controlled trial lasting one year with 100 participants	
Participants	Age > 50; primary knee osteoarthritis, mainly of medial femorotibial compartment, according to clinical and radiographic criteria of ACR; Lequesne's index ≥ 4 Kondro: N = 50; Age = 54.68; Lequesne's Index = 4.6; JSW = 3.66 mm Placebo: N = 50; Age = 53.9; Lequesne's Index = 4.9; JSW = 3.65 mm	
Interventions	250 mg glucosamine sulfate + 200 mg chondroitin sulfate (Kondro) Placebo	
Outcomes	Lequesne's Index Joint space narrowing (X-ray)	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method

Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding method
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals not clearly accounted for
Selective reporting (reporting bias)	Unclear risk	Unclear
Railhac 2012		
Methods	Randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted in 20 French rheumatology practice centers	
Participants	Patients of either sex, aged 50–75 years with medial and/or lateral femoro-tibial OA of the knee (according to ACR criteria), symptomatic for more than 6 months, with global pain score on a visual analog scale (VAS) of at least 30 mm and radiographic OA, as defined by a Kellgren-Lawrence grade II or III on an antero-posterior weight-bearing view of both knees. They were randomized to Structum (N=22) or placebo (N=21)	
Interventions	Hard capsules of either Structum®500 mg or matching placebo, twice daily by oral route as from baseline to week 48	
Outcomes	Pain related to KOA, on a VAS from 0 to 100; Functional disability evaluated using the Lequesne index Clinical improvement according to the patient and the investigator; Consumption of rescue medication (paracetamol and/or NSAIDs).	
Notes	First author employee of the maker of chondroitin product discussed. Institut de Recherche Pierre Fabre provided financial and material support for the design and concept of the study, data collection, data management, data analysis, and medical writing services of this study.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were randomized to one of the two study groups according to a pre-established computer generated list (treatment number) with balanced blocks of four treatments."
Allocation concealment (selection bias)	Unclear risk	not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"The two medications were identical."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts listed in the consort diagram.
Selective reporting (reporting bias)	Low risk	Attrition explained; selective outcome reporting not suspected
Other bias	Low risk	No baseline imbalance, no interim results
Raynauld 2013		
Methods	Follow-up of Wildi 2011, therefore descriptions are the same as Wildi 2011. Multicenter, randomised, participant- and investigator-blind, controlled trial comparing chondroitin sulfate with placebo in participants with primary knee osteoarthritis with a duration of six months	

Participants	Inclusion criteria: primary osteoarthritis of the knee diagnosed according to clinical and radiologic criteria of the American College of Rheumatology (ACR) with clinical signs of synovitis (warmth, swelling, or effusion), disease severity grade 2 to 3 based on the Kellgren-Lawrence radiographic system Minimal medial joint space width (JSW) of 2 mm on standing knee X-ray, and VAS pain index of at least 40 mm while walking. Concomitant femoropatellar osteoarthritis not quantified on X-ray. Participants required to have no significant laboratory abnormalities. If both knees affected by osteoarthritis, the knee with the more pronounced symptoms selected if within inclusion criteria Chondroitin sulfate: N = 35; Age (mean ± SD) = 59.7 ± 9.4; Men/Women = 14/21 Placebo: N = 34; Age (mean ± SD) = 64.9 ± 9.5; Men/Women = 14/20	
Interventions	800 mg of chondroitin sulfate (two capsules of 400 mg) once daily or placebo once daily X 6-months followed by open-label for 6 months with chondroitin for both groups. This study assessed outcome at 4 year follow-up	
Outcomes	**Primary** Total knee arthroplasty	
Notes	Funding provided by Bioiberica-maker of chondroitin sulfate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Low risk	"Through central randomisation, sealed coded tamper-proof envelopes, specifying the treatment group for each study drug kit number, were provided to each centre. The envelopes were to be opened only in the event of an emergency"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Although allocation of treatments was performed with the use of sealed, coded, tamper-proof envelopes, it is unclear whether the drug kits were themselves identical or informative into the contents of the drug
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was not performed, and significantly more dropouts were seen in the placebo group than in the treatment group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of risk level
Rovetta 2002		
Methods	24 participants, randomly assigned into two groups	
Participants	Inclusion criteria: participants suffering from osteoarthritis and showing central erosions of the distal interphalangeal (DIP) and/or proximal interphalangeal (PIP) joints Total: N = 24; men/women = 2/22; age (mean ± SD) = 53.0 ± 6	
Interventions	800 mg/d chondroitin sulfate + 500 mg/d naproxen 500 mg/d only naproxen	
Outcomes	Joint counts for erosions	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment

Blinding (performance bias and detection bias) All outcomes	High risk	No mention of blinding or blinding method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All the patients completed the planned treatment period" Comment: no missing data
Selective reporting (reporting bias)	Unclear risk	Unclear
Rovetta 2004		
Methods	24 participants, randomly assigned into two groups	
Participants	Inclusion criteria: participants suffering from osteoarthritis and showing central erosions of the distal interphalangeal (DIP) and/or proximal interphalangeal (PIP) joints Total: N = 24; men/women = 2/22; age (mean ± SD) = 53.0 ± 6	
Interventions	800 mg/d chondroitin sulfate + 500 mg/d naproxen 500 mg/d only naproxen	
Outcomes	Radiographic joint counts for Heberden and Bouchard nodes Dreiser index for pain and function Patient and Physician global assessment on a 0 to 10-cm VAS	
Notes	Duplicate trial to Rovetta 2002 but presents new results	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the planned period of treatment" Comment: no participant withdrawal
Selective reporting (reporting bias)	Unclear risk	Not enough information presented to allow assessment
Sawitzke 2008		
Methods	24-Month, participant- and investigator-blind, placebo-controlled study, conducted at nine sites in the United States as part of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT). Participants who were assigned to one of the five groups in GAIT continued to receive treatment for the 24 months	
Participants	Inclusion criteria: at least 40 years of age, with knee pain for at least six months on most days in the month preceding enrolment in the trial, and with Kellgren/Lawrence grade 2 or grade 3 knee osteoarthritis on a screening anteroposterior radiograph, with joint space width (JSW) determined to be 2 mm Glucosamine: N assessable = 77; Male/Female = 30/47; Age (mean ± SD), years = 56.7 ± 10.4; Duration of osteoarthritis (mean ± SD), years = 9.2 ± 9.4 Chondroitin: N = 71; Male/Female = 16/55; Age (mean ± SD), years = 56.4 ± 9.2; Duration of osteoarthritis (mean ± SD), years = 8.8 ± 8.9 Chondroitin + Glucosamine: N = 59; Male/Female = 26/33; Age (mean ± SD), years = 56.5 ± 9.9; Duration of osteoarthritis (mean ± SD), years = 10.5 ± 9.8	

	Celecoxib: N = 80; Male/Female = 29/51; Age (mean ± SD), years = 58.3 ± 10.7; Duration of osteoarthritis (mean ± SD), years = 10.3 ± 9.5 Placebo: N = 70; Male/Female = 25/45; Age (mean ± SD), years = 56.6 ± 8.4; Duration of osteoarthritis (mean ± SD), years = 9.4 ± 8.7	
Interventions	Glucosamine 500 mg three times daily Chondroitin sulfate 400 mg three times daily Combination of the glucosamine and chondroitin sulfate treatments Celecoxib 200 mg daily or Placebo	
Outcomes	**Primary** Mean change in JSW in the medial compartment of the knee over 2 years **Secondary** Percentage of progressors at 2 years (defined as knees with a loss in JSW that exceeded 0.48 mm (three times the SD of the standard error of measurements) when compared with the baseline measurement of JSW	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Approved films were assigned a randomly assigned code from a printed table, with randomization according to the order in which the films were received
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified ITT; clear account of all withdrawals
Selective reporting (reporting bias)	Unclear risk	Not enough information to allow determination
Sawitzke 2010		
Methods	A 24-month, participant- and investigator-blind, placebo-controlled study, conducted at nine sites in the United States ancillary to the Glucosamine/chondroitin Arthritis Intervention Trial; enrolled 662 participants with knee osteoarthritis who satisfied radiographic criteria (Kellgren/Lawrence grade 2 or 3 changes and baseline joint space width of at least 2 mm)	
Participants	At least 40 years old, osteoarthritis at least six months, radiographic evidence of osteoarthritis by KL grade 2 or 3 Glucosamine: N = 134; Age (mean ± SD) = 56.7 ± 10.5; Men/Women = 48/86; Disease duration, years: 9.7 ± 10.3 Chondroitin sulfate: N = 126; Age (mean ± SD) = 56.3 ± 8.8; Men/Women = 34/92; Disease duration, years: 9.0 ± 9.0 Glucosamine + Chondroitin sulfate: N = 129; Age (mean ± SD) = 56.7 ± 10.7; Men/Women = 45/84; Disease duration, years: 10.0 ± 9.4 Celecoxib: N = 142; Age (mean ± SD) = 57.6 ± 10.6; Men/Women = 49/93; Disease duration, years: 10.2 ± 9.2 Placebo: N = 131; Age (mean ± SD) = 56.9 ± 9.8; Men/Women = 45/86; Disease duration, years: 10.1 ± 9.4	
Interventions	Glucosamine 500 mg three times daily Chondroitin sulfate 400 mg three times daily Combination of glucosamine and chondroitin sulfate Celecoxib 200 mg daily Placebo	
Outcomes	**Primary** 20% Reduction in Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain over 24 months **Secondary**	

	Pain reduction attributable to each treatment WOMAC function subscale Likelihood of achieving an OMERACT/OARSI response over 24 months	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Unclear risk	No mention of method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of method of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified intent-to-treat analysis-"Recognising that dropout before the 2-year visit in this study may not be completely at random, we applied selection models as described by Hogan et al using weighted generalised estimating equations to estimate the multiple regression models. This form of repeated measures analysis uses all data collected on this cohort while accounting for potentially non-random dropout"
Selective reporting (reporting bias)	Unclear risk	Not enough information to make an informed judgment on the level of risk
Uebelhart 1998		
Methods	One-year, randomized, participant- and investigator-blind, controlled pilot study	
Participants	42 participants of both sexes; between 35 and 78 years of age, with symptomatic osteoarthritis Chondroitin sulfate: Age (mean ± SD) = 60 ± 13 (35 to 78); Men/Women = 12/11; Rad severity (I/II/III/IV) = 10/11/2/0; MBI/Body weight = 72 ± 11 Placebo: Age (mean ± SD) = Placebo 57 ± 11 (37 to 76); Men/Women = 10/13; Rad severity (I/II/III/IV) = 11/10/2/0; MBI/Body weight = 76 ± 14	
Interventions	Chondroitin sulfate 400 mg twice daily versus placebo	
Outcomes	**Primary** Degree of spontaneous joint pain (VAS) Overall mobility capacity (VAS) **Secondary** Actual joint space measurement (X-ray) Levels of biochemical markers of bone and joint metabolism	
Notes	"This work was supported by a grant from IBSA, Lugano, Switzerland. Supplement sponsored by IBSA (Switzerland)/Laboratoires GENEVRIER (France)"	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of randomization method
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical sachets administered at identical doses and time points

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: “The drop-out rate was 8.7% in both chondroitin sulfate and PBO groups. “ Their reasons for dropping out are equal across groups with one death in the chondroitin sulfate group (n = 23), two people who left the country, and one unsatisfied in the PBO group (n = 23) Comment: missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Unclear
Uebelhart 2004		
Methods	Multicenter, participant- and investigator-blind, ITT-modified, placebo-controlled, one year comparing chondroitin sulfate with placebo	
Participants	Both genders, 40 years of age and older, stiffness < 30, bi-lateral or mono-lateral idiopathic knee osteoarthritis (ACR), Kellgren and Lawrence score of I to III with a minimum of 25% remaining medial femorotibial joint space Chondroitin sulfate: N = 54; Age (mean ± SD) = 63.2 ± 9.1; Men/Women = 11/43; Sx duration = 4.2; Radiographic severity = 7/32/15/0; BMI/Body (weight) = 76.8 (15.8) Placebo: N = 56; Age (mean ± SD) = 63.7 ± 8.1; Men/Women = 10/46; Sx duration = 4.4; Radiographic severity = 6/33/17/0; BMI/Body (weight) = 76.4 (13.8)	
Interventions	800 mg daily of chondroitin sulfate or placebo for two periods of three months in a two-year period: days 1 to 90 and days 181 to 270	
Outcomes	**Primary** Lequesne’s Index **Secondary** Spontaneous pain on 100-mm VAS Time to walk 20 meters Patient global assessment of efficacy (0 to 4 scale) Physician global assessment of efficacy (0 to 4 scale) Analgesic consumption Joint space narrowing (X-ray) Adverse events	
Notes	“The study was supported by a grant from IBSA, Lugano, Switzerland”	
Risk of bias		
Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocks of six according to computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Quote: “Investigators were provided with sealed envelopes, each marked with the corresponding patient number and containing the randomization code of that patient”
Blinding (performance bias and detection bias) All outcomes	Low risk	Sachets of chondroitin sulfate and placebo identical with respect to odor, flavor, and appearance; packed in anonymous bottles
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified ITT Quote: “A total of 10 patients (six chondroitin sulfate and 4 placebo) were lost to follow-up before month 3 (second control visit). Since they did not take any dose of treatment and did not report any data at the following control visit, they were consequently not included in the ITT... A total of 26 patients (11 chondroitin sulfate and 15 PBO) dropped out of the study between months 3 and 12 because of inefficacy, absence of compliance, increasing pain or various side effects. No statistically significant difference was shown between both groups” Comment: missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups

Selective reporting (reporting bias)	Unclear risk	Unclear
Verbruggen 2002		
Methods	Independent, randomized, participant- and investigator-blind, placebo-controlled trials to assess the effects of chondroitin sulfate as DMOAD in Ghent University Hospital	
Participants	Between 40 and 70 years of age; symptom producing osteoarthritis of the finger joint, confirmed according to the presence of osteophytes and/or joint space narrowing with or without subchondral sclerosis on conventional X-rays of the hands; all participants Caucasian Chondroitin sulfate: N = 44; Age (mean ± SD) = 57.6 ± 7.1; Men/Women = 4/40; Disease duration (mean ± SD), years = 5.5 ± 3.5 Placebo: N = 48; Age (mean ± SD) = 55.9 ± 8.9; Men/Women = 6/42; Disease duration (mean ± SD), years = 5.7 ± 3.4	
Interventions	400 mg of chondroitin sulfate or a placebo capsule three times daily for three years	
Outcomes	No data provided	
Notes	Unclear source of funding	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization of the study was done in blocks of four and successive treatment allocation numbers were administered following the order of inclusion"
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization of the study medication was done in blocks of four and successive treatment allocation numbers were given according numbers"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of method blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were no significant differences between the number of and the reasons for the withdrawals from both studies. It is noteworthy that the large majority of withdrawals from the CPS/PI-CPS trial and all those from the chondroitin sulfate/ PI-chondroitin sulfate trial occurred during the first year.....the number of withdrawals for this specific reason was no different in the treated groups and their respective placebo controls" Comment: ITT analysis. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Unclear
Wildi 2011		
Methods	Multicenter, randomised, participant- and investigator-blind, controlled trial comparing chondroitin sulfate with placebo in participants with primary knee osteoarthritis with a duration of six months	
Participants	Inclusion criteria: primary osteoarthritis of the knee diagnosed according to clinical and radiologic criteria of the American College of Rheumatology (ACR) with clinical signs of synovitis (warmth, swelling, or effusion), disease severity grade 2 to 3 based on the Kellgren-Lawrence radiographic system Minimal medial joint space width (JSW) of 2 mm on standing knee X-ray, and VAS pain index of at least 40 mm while walking. Concomitant femoropatellar osteoarthritis not quantified on X-ray. Participants required to have no significant laboratory abnormalities. If both knees affected by osteoarthritis, the knee with the more pronounced symptoms selected if within inclusion criteria Chondroitin sulfate: N = 35; Age (mean ± SD) = 59.7 ± 9.4; Men/Women = 14/21 Placebo: N = 34; Age (mean ± SD) = 64.9 ± 9.5; Men/Women = 14/20	
Interventions	800 mg of chondroitin sulfate (two capsules of 400 mg) once daily or placebo once daily	
Outcomes	**Primary** Synovial membrane thickness	

	Secondary Cartilage Volume Bone marrow lesions WOMAC pain WOMAC function WOMAC stiffness WOMAC Total VAS pain Quality of Life SF-36	
Notes	Funding provided by Bioiberica-maker of chondroitin sulfate. "This study was financed by a research grant from IBSA who also provided, free of charge, all medications....IBSA provided administrative assistance in order to have the protocol written in accordance with the current national and international requirements. Monitoring of the trial was also conducted by IBSA."	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomization
Allocation concealment (selection bias)	Low risk	"Through central randomisation, sealed coded tamper-proof envelopes, specifying the treatment group for each study drug kit number, were provided to each centre. The envelopes were to be opened only in the event of an emergency"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Although allocation of treatments was performed with the use of sealed, coded, tamper-proof envelopes, it is unclear whether the drug kits were themselves identical or informative into the contents of the drug
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was not performed, and significantly more dropouts were seen in the placebo group than in the treatment group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment of risk level
Zegels 2012		
Methods	Multicenter, randomized, double blind, double-dummy study with an allocation ratio of 1:1:1, in 10 centres in Belgium, three in France and two in Switzerland	
Participants	Patients aged over 45 years old with primary knee OA diagnosed according to the clinical and radiographic criteria of the American College of Rheumatology. The symptomatic target knee should have a pain score of at least 40 mm on a 0–100 mm visual analogue scale (VAS) and a score 7 at the Lequesne index (LI). If both knees were symptomatic, the target knee was the most symptomatic knee	
Interventions	Group 1: CS 1200, receiving one oral gel sachet of CS 1200 mg/day & one oral placebo capsule three times a day Group 2: CS 3*400, receiving one oral placebo gel sachet/day & one oral capsule of CS 400 mg three times a day Group 3: the control group, receiving one oral placebo gel sachet/day & one oral placebo capsule three times a day	
Outcomes	**Primary**: Algo-functional Lequesne's index **Secondary**: Global spontaneous pain was measured on a vertical VAS of 100 mm Treatment compliance Adverse events	
Notes	All these drug supplies were provided by the Institut Biochimique SA (IBSA)/Laboratoires Genévrier	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	The three different types of treatment were allocated according to a randomisation list balanced/blocks of three established by the sponsor with a randomisation method starting from a validated SAS software
Allocation concealment (selection bias)	Unclear risk	Treatment was allocated in ascending order as recruitment proceeded, by assigning the first available number
Blinding (performance bias and detection bias) All outcomes	Low risk	All placebos were identical in form and appearance to the real drugs. This study is a multicenter, comparative, randomized, double-blind and double-dummy study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intent-to-treat (ITT) analyses were performed for all randomized patients, using the last observation carried forward approach
Selective reporting (reporting bias)	Low risk	Attrition explained; selective outcome reporting not suspected
Other bias	Low risk	No baseline imbalance

Characteristics of excluded studies *[ordered by study ID]*

Study	**Reason for exclusion**
---, 2000	Short review
---, 2000A	Short review
---, 2000B	NA randomized
---, 2000C	Short review
---, 2000D	No data
---, 2002	No data
Alekseeva 2003	duplicate of Nasonova 2001
Berenbaum 2011	Abstract
Borovkov 2000	NA randomized
Brandao 2009	Author contacted; Study not obtainable
Ciobanu 1994	No clinical outcomes
Cohen 2003A	NA randomized
Derrett-Smith 2006	Review
Edelist 2001	NA randomized
Ernest 2003	Commentary
Escudero 2011	Abstract only
Esenyel 2011	Abstract only
Fleisch 1997	Abstract only
Fujita 2002	Abstract Only
Hochberg 2008	Not original study-summary of observations
Kahan 2006	Abstract only
Kerzberg 1987	Injection, not oral administration of chondroitin sulfate

Study	Reason for exclusion
Lapane 2012	No data on chondroitin sulfate
Leeb 2000	NA randomized
Leffler 1999	Studied patients with DJD not osteoarthritis
Long 2000	Commentary
Longyhore 2003	NA randomized
Malaise 1999	Duplicate results of Uebelhart 2004 Study
Matsuno et al, 2009	No clinical outcomes
Mazieres 2006	Abstract only
McAlindon 2000	Meta analysis
McAlindon 2001	Letter
Monfort 2011	Abstract
Monfort 2011A	Abstract
Oliviero 1991	NA randomized
Orth 2003	NA randomized
Pelletier 2011	Abstract
Povoroznyuk 2011	Abstract
Priebe 2003	Review
Reginster 2011	Abstract
Richy 2003	Meta analysis
Rovetta 1991	Injection rather than oral form of chondroitin sulfate
Schenck 2000	NA randomized
Scroggie 2003	Not osteoarthritis
Shaughnessy 2003	NA randomized
Soroka & Chyzh 2002	Abstract
Townheed 2002	Meta analysis
Treves 1994	NA randomized
Tsvetkova 1992	Review
Uebelhart 1999	Abstract
Vela Marquez 2011	Abstract
Verbruggen 1998	No data
Vertkin 2007	Obvious mismatch in data
Villani 1998	Review
Wagenhauser 1968	Case-series; no control group; no randomization
Wakitani 2007	NA randomized
Walker-Bone 2003	Review
Wildi 2011A	Abstract

DATA AND ANALYSES

Comparison 1

Chondroitin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	8	1077	Std. Mean Difference (IV, Random, 95% CI)	−0.51 [−0.74, −0.28]
1.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	6	989	Std. Mean Difference (IV, Random, 95% CI)	−0.39 [−0.78, 0.00]
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
3 Physical Function on a 0 to 100 scale	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	303	Std. Mean Difference (IV, Random, 95% CI)	0.11 [−0.47, 0.68]
3.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
4 WOMAC Stiffness on a 0 to 100 scale	1	631	Mean Difference (IV, Random, 95% CI)	2.5 [−1.43, 6.43]
4.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	631	Mean Difference (IV, Random, 95% CI)	2.5 [−1.43, 6.43]
5 Patient Global Assessment-rating it good to very good	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	154	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.49, 2.99]
5.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	85	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.28, 3.27]
6 Patient Global Assessment on a VAS 0 to 100-mm scale	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	130	Std. Mean Difference (IV, Random, 95% CI)	−0.13 [−0.48, 0.21]
6.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	1415	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.21, 0.23]
7 MD Global Assessment of good to very good	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	154	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.42, 2.69]
7.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	85	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.33, 3.38]
8 MD Global Assessment on a VAS 0 to 100-mm scale	2	1259	Std. Mean Difference (IV, Random, 95% CI)	0.09 [−0.05, 0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	1259	Std. Mean Difference (IV, Random, 95% CI)	0.09 [−0.05, 0.23]
9 Total Knee Arthroplasty during follow-up	1	69	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.15, 1.27]
10 Grip Strength (kg/cm^2)	1	162	Mean Difference (IV, Random, 95% CI)	0.90 [−2.29, 4.09]
10.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	162	Mean Difference (IV, Random, 95% CI)	0.90 [−2.29, 4.09]
11 Morning Stiffness, minutes	1	162	Mean Difference (IV, Random, 95% CI)	−0.60 [−5.16, 3.96]
11.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	162	Mean Difference (IV, Random, 95% CI)	−0.60 [−5.16, 3.96]
12 Cartilage Volume Loss (global)	1	69	Mean Difference (IV, Random, 95% CI)	1.80 [0.23, 3.37]
12.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	1.80 [0.23, 3.37]
13 Cartilage Volume Loss (lateral compartment)	1	69	Mean Difference (IV, Random, 95% CI)	2.19 [0.31, 4.07]
13.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	2.19 [0.31, 4.07]
14 Cartilage Volume Loss (medial compartment)	1	69	Mean Difference (IV, Random, 95% CI)	1.47 [−0.88, 3.82]
14.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	1.47 [−0.88, 3.82]
15 Cartilage Volume Loss (condyles)	1	69	Mean Difference (IV, Random, 95% CI)	0.64 [−1.59, 2.87]
15.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	0.64 [−1.59, 2.87]
16 Cartilage Volume Loss (lateral condyles)	1	69	Mean Difference (IV, Random, 95% CI)	1.84 [−0.44, 4.12]
16.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	1.84 [−0.44, 4.12]
17 Cartilage Volume Loss (medial condyles)	1	69	Mean Difference (IV, Random, 95% CI)	−0.65 [−4.14, 2.84]
17.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.65 [−4.14, 2.84]
18 Cartilage Volume Loss (tibial plateaus)	1	69	Mean Difference (IV, Random, 95% CI)	2.98 [1.15, 4.81]
18.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	2.98 [1.15, 4.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Cartilage Volume Loss (lateral tibial plateaus)	1	69	Mean Difference (IV, Random, 95% CI)	2.31 [−0.09, 4.71]
19.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	2.31 [−0.09, 4.71]
20 Cartilage Volume Loss (medial tibial plateau)	1	69	Mean Difference (IV, Random, 95% CI)	4.47 [1.57, 7.37]
20.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	4.47 [1.57, 7.37]
21 Cartilage Volume Loss (trochlea)	1	69	Mean Difference (IV, Random, 95% CI)	0.65 [−1.79, 3.09]
21.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	0.65 [−1.79, 3.09]
22 Change in Bone Marrow Lesion Score (global)	1	69	Mean Difference (IV, Random, 95% CI)	−0.07 [−0.65, 0.51]
22.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.07 [−0.65, 0.51]
23 Change in Bone Marrow Lesion Score (lateral compartment)	1	69	Mean Difference (IV, Random, 95% CI)	−0.10 [−0.30, 0.10]
23.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.10 [−0.30, 0.10]
24 Change in Bone Marrow Lesion score (medial compartment)	1	69	Mean Difference (IV, Random, 95% CI)	0.02 [−0.52, 0.56]
24.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	0.02 [−0.52, 0.56]
25 Change in Bone Marrow Lesion score (condyles)	1	69	Mean Difference (IV, Random, 95% CI)	0.02 [−0.35, 0.39]
25.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	0.02 [−0.35, 0.39]
26 Change in Bone Marrow Lesion score (lateral condyles)	1	69	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.14, 0.06]
26.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.14, 0.06]
27 Change in Bone Marrow Lesion score (medial condyles)	1	69	Mean Difference (IV, Random, 95% CI)	0.13 [−0.22, 0.48]
27.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	0.13 [−0.22, 0.48]
28 Change in Bone Marrow Lesion score (tibial plateaus)	1	69	Mean Difference (IV, Random, 95% CI)	−0.1 [−0.46, 0.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.1 [−0.46, 0.26]
29 Change in Bone Marrow Lesion score (lateral tibial plateaus)	1	69	Mean Difference (IV, Random, 95% CI)	−0.01 [−0.18, 0.16]
29.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.01 [−0.18, 0.16]
30 Change in Bone Marrow Lesion score (medial tibial plateau)	1	69	Mean Difference (IV, Random, 95% CI)	−0.1 [−0.40, 0.20]
30.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	−0.1 [−0.40, 0.20]
31 Change in Bone Marrow Lesion score (trochlea)	1	69	Mean Difference (IV, Random, 95% CI)	0.16 [−0.10, 0.42]
31.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	69	Mean Difference (IV, Random, 95% CI)	0.16 [−0.10, 0.42]
32 OMERACT-OARSI Responder	1	631	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.27]
32.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	631	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.27]
33 Lequesne's Index on 0 to 24 scale (higher is worse)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
33.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	7	903	Mean Difference (IV, Random, 95% CI)	−1.98 [−2.79, −1.17]
33.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	243	Mean Difference (IV, Random, 95% CI)	−1.60 [−3.49, 0.29]
34 HAQ Disability Score on 0 to 3 scale (higher is worse)	1	631	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.11, 0.03]
34.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	631	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.11, 0.03]
35 Radiographic Outcome: Minimum JSW in mm	2	156	Mean Difference (IV, Random, 95% CI)	0.19 [−0.27, 0.65]
35.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	156	Mean Difference (IV, Random, 95% CI)	0.19 [−0.27, 0.65]
36 Radiographic Outcome: Reduction in Minimum JSW in mm	2	922	Mean Difference (IV, Random, 95% CI)	0.18 [0.06, 0.30]
36.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	922	Mean Difference (IV, Random, 95% CI)	0.18 [0.06, 0.30]
37 Radiographic Outcome: Mean JSW in mm	2	156	Mean Difference (IV, Random, 95% CI)	0.17 [−0.47, 0.81]
37.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	156	Mean Difference (IV, Random, 95% CI)	0.17 [−0.47, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38 Radiographic Outcome: Change in Mean JSW in mm	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.07, 0.20]
38.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.07, 0.20]
39 SF-36-Physical Component Score	1	129	Mean Difference (IV, Random, 95% CI)	2.76 [−19.84, 25.36]
39.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	129	Mean Difference (IV, Random, 95% CI)	2.76 [−19.84, 25.36]
40 SF-36-Mental Component Summary Score	1	129	Mean Difference (IV, Random, 95% CI)	−0.59 [−24.84, 23. 66]
40.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	129	Mean Difference (IV, Random, 95% CI)	−0.59 [−24.84, 23. 66]
41 All withdrawals	15	2763	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.02]
41.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	6	675	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.09]
41.2 Long-term studies (≥ 6 months)-dose ≥800 mg/d	9	2088	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.09]
42 Withdrawals due to adverse events	10	2406	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.74, 1.57]
42.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	4	489	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.31, 2.89]
42.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	6	1917	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.73, 1.63]
43 Withdrawals due to inefficacy	10	2314	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.88, 1.70]
43.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	3	360	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.15, 2.55]
43.2 Long-term studies (≥ 6 months)-dose ≥800 mg/d	7	1954	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.91, 1.78]
44 Number of adverse events	8	1579	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.14]
44.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	6	795	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.81, 1.34]
44.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	784	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.50, 1.40]
45 Number of serious adverse events	6	954	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.82]
45.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	3	466	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.78]
45.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	488	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.84]
46 GI adverse events	9	1684	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.45, 1.04]
46.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	3	329	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.15, 1.19]
46.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	6	1355	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.47, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47 Other adverse events	5	787	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.15]
47.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	213	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
47.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	574	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.35, 1.96]
48 Deaths	7	1378	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.20]
48.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	213	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
48.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	5	1165	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.20]

Comparison 2

Chondroitin sulfate versus Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on various scales standardized to a 0 to 100 scale	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	357	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.26, 0.15]
1.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	357	Std. Mean Difference (IV, Random, 95% CI)	−0.10 [−0.31, 0.11]
2 WOMAC Stiffness on a 0 to 100 scale	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−1.0 [−5.77, 3.77]
2.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−0.60 [−5.25, 4.05]
3 WOMAC Physical Function on a 0 to 100 scale	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−2.10 [−6.44, 2.24]
3.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−1.56 [−5.70, 2.58]
4 WOMAC Total	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−1.80 [−6.06, 2.46]
4.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−1.60 [−5.69, 2.49]
5 Lequesne's Index (higher is worse)	2	1187	Mean Difference (IV, Random, 95% CI)	−1.36 [−3.60, 0.89]
5.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	0.0 [−2.51, 2.51]
5.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	830	Mean Difference (IV, Random, 95% CI)	−2.02 [−5.06, 1.01]
6 Patient Global Assessment (%with improvement)	2	573	Odds Ratio (M-H, Random, 95% CI)	5.04 [1.95, 13.05]
6.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	573	Odds Ratio (M-H, Random, 95% CI)	5.04 [1.95, 13.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 MD Global Assessment (% with improvement)	1	473	Odds Ratio (M-H, Random, 95% CI)	7.68 [4.48, 13.15]
7.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	473	Odds Ratio (M-H, Random, 95% CI)	7.68 [4.48, 13.15]
8 NSAID consumption	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	−0.02 [−0.23, 0.19]
8.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	357	Mean Difference (IV, Random, 95% CI)	0.0 [−0.20, 0.20]
9 All withdrawals	3	1012	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.09, 1.74]
9.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	1012	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.09, 1.74]
10 Withdrawals due to adverse events	2	457	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.65]
10.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	457	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.65]
11 Number of adverse events	2	457	Odds Ratio (M-H, Random, 95% CI)	0.08 [0.00, 4.82]
11.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	457	Odds Ratio (M-H, Random, 95% CI)	0.08 [0.00, 4.82]
12 GI adverse events	2	457	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.03, 6.60]
12.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	457	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.03, 6.60]

Comparison 3

Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on 0 to 100 scale	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	3	332	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.33, 0.20]
1.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.11 [−0.25, 0.04]
2 WOMAC MCII	1	630	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.96, 1.83]
2.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.96, 1.83]
3 Physical Function on a 0 to 100 scale	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	300	Std. Mean Difference (IV, Random, 95% CI)	0.11 [−0.31, 0.54]
3.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.28, 0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Six-minute walk distance in meters walked	1	89	Mean Difference (IV, Random, 95% CI)	−2.90 [−24.94, 19.14]
4.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	89	Mean Difference (IV, Random, 95% CI)	−2.90 [−24.94, 19.14]
5 WOMAC Stiffness	1	630	Mean Difference (IV, Random, 95% CI)	−2.20 [−5.97, 1.57]
5.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Mean Difference (IV, Random, 95% CI)	−2.20 [−5.97, 1.57]
6 WOMAC Total	1	630	Mean Difference (IV, Random, 95% CI)	−2.60 [−5.92, 0.72]
6.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Mean Difference (IV, Random, 95% CI)	−2.60 [−5.92, 0.72]
7 Patient Global Assessment VAS (0 to 100 mm)	1	630	Mean Difference (IV, Random, 95% CI)	−1.60 [−5.29, 2.09]
7.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Mean Difference (IV, Random, 95% CI)	−1.60 [−5.29, 2.09]
8 MD Global Assessment VAS (0 to 100 mm)	1	630	Mean Difference (IV, Random, 95% CI)	−1.40 [−4.87, 2.07]
8.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Mean Difference (IV, Random, 95% CI)	−1.40 [−4.87, 2.07]
9 OMERACT-OARSI Responders	1	630	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.02, 1.31]
9.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.02, 1.31]
10 HAQ Disability Score	1	630	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.11, 0.03]
10.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	630	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.11, 0.03]
11 Objective Joint Function (Flexion)	1	89	Mean Difference (IV, Random, 95% CI)	−0.60 [−21.54, 20.34]
11.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	89	Mean Difference (IV, Random, 95% CI)	−0.60 [−21.54, 20.34]
12 Objective Joint Function (extension)	1	89	Mean Difference (IV, Random, 95% CI)	−25.80 [−72.67, 21.07]
12.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	89	Mean Difference (IV, Random, 95% CI)	−25.80 [−72.67, 21.07]
13 Objective Joint Function (balance)	1	89	Mean Difference (IV, Random, 95% CI)	−0.06 [−0.10, −0.02]
13.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	89	Mean Difference (IV, Random, 95% CI)	−0.06 [−0.10, −0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 All withdrawals	3	768	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.40, 3.85]
14.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	768	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.40, 3.85]
15 Withdrawals due to adverse events	4	800	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.57, 2.55]
15.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	32	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	768	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.57, 2.55]
16 Withdrawals due to inefficacy	3	768	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.41, 1.41]
16.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	768	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.41, 1.41]
17 Number of adverse events	3	170	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.67, 1.84]
17.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	32	Risk Ratio (M-H, Random, 95% CI)	1.6 [0.67, 3.84]
17.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	138	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.51, 1.72]
18 Serious adverse events	3	398	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.77, 2.75]
18.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	398	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.77, 2.75]
19 GI adverse events	2	138	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.37]
19.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	138	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.37]
20 Hematologic adverse events	2	138	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.15]
20.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	138	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.15]
21 Other adverse events	2	138	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.43, 4.19]
21.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	138	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.43, 4.19]
22 Death	4	1028	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]
22.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	4	1028	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.23]

Comparison 4

Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	2	331	Std. Mean Difference (IV, Random, 95% CI)	−1.41 [−4.41, 1.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
2 WOMAC MCII	1	635	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.61, 1.19]
2.1 Long-term studies (≥6 months)-dose ≥ 800 mg/d	1	635	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.61, 1.19]
3 Physical Function on a 0 to 100 scale	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	271	Std. Mean Difference (IV, Random, 95% CI)	0.04 [−0.20, 0.28]
3.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	635	Std. Mean Difference (IV, Random, 95% CI)	−0.02 [−0.18, 0.13]
4 WOMAC Stiffness	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Short-term studies (< 6 months)-dose ≥ 800 mg/d	1	60	Mean Difference (IV, Random, 95% CI)	−2.5 [−4.27, −0.73]
4.2 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	742	Mean Difference (IV, Random, 95% CI)	−7.72 [−15.36, −0.08]
5 WOMAC Total	3	772	Mean Difference (IV, Random, 95% CI)	−4.77 [−9.75, 0.20]
5.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	772	Mean Difference (IV, Random, 95% CI)	−4.77 [−9.75, 0.20]
6 Percentage with improved Patient Global Assessment	3	525	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.28, 1.57]
6.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	525	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.28, 1.57]
7 Percentage with improved MD Global Assessment	3	525	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.35, 1.68]
7.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	3	525	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.35, 1.68]
8 OMERACT-OARSI	1	635	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.29]
8.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	635	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.29]
9 HAQ Disability Score	1	635	Mean Difference (IV, Random, 95% CI)	0.01 [−0.06, 0.08]
9.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	635	Mean Difference (IV, Random, 95% CI)	0.01 [−0.06, 0.08]
10 Radiographic Outcome: Change in Mean JSW in mm	1	139	Mean Difference (IV, Random, 95% CI)	0.08 [−0.26, 0.42]
10.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	139	Mean Difference (IV, Random, 95% CI)	0.08 [−0.26, 0.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 All withdrawals	5	1207	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.08, 1.18]
11.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	5	1207	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.08, 1.18]
12 Withdrawals due to adverse events	1	635	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.69, 4.31]
12.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	635	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.69, 4.31]
13 Withdrawals due to inefficacy	1	635	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.74, 3.26]
13.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	635	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.74, 3.26]
14 Number of adverse events	4	796	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.17, 1.21]
14.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	4	796	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.17, 1.21]
15 Serious adverse events	2	150	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 70.83]
15.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	150	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 70.83]
16 GI adverse events	3	785	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.29, 1.01]
16.1 Long-term studies (≥ 6 months)-dose ≥800 mg/d	3	785	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.29, 1.01]
17 Other adverse events	2	150	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.16, 1.13]
17.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	150	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.16, 1.13]
18 Death	1	635	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	1	635	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5

Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on 0 to 100 scale (short- and long-term results)	17	2278	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−0.95, −0.35]
2 Physical Function on 0 to 100 scale (short- and long-term results)	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.07 [−0.31, 0.17]
3 Lequesne's Index	10	1756	Std. Mean Difference (IV, Random, 95% CI)	−0.48 [−0.72, −0.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
4.1 Long-term studies (≥ 6 months)-dose ≥ 800 mg/d	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
5 Pain on 0 to 100 scale (short- or long-term) for CS dose >= 800 mg/day	14	2136	Std. Mean Difference (IV, Random, 95% CI)	−0.67 [−0.99, −0.34]

Comparison 6

Sensitivity analysis (blinding): Chondroitin sulfate versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	11	1653	Std. Mean Difference (IV, Random, 95% CI)	−0.50 [−0.76, −0.24]
1.1 Blinding: yes	9	1499	Std. Mean Difference (IV, Random, 95% CI)	−0.52 [−0.80, −0.25]
1.2 Blinding: unclear	2	154	Std. Mean Difference (IV, Random, 95% CI)	−0.35 [−1.48, 0.79]
1.3 Blinding: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 Blinding: yes	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.2 Blinding: unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Blinding: no	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Physical Function on a 0 to 100 scale	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3.1 Blinding: yes	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3.2 Blinding: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Blinding: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Radiographic outcome: Change in Mean JSW in mm	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.03, 0.22]
4.1 Blinding: yes	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.03, 0.22]
4.2 Blinding: unclear	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Blinding: no	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 7

Sensitivity analysis (blinding): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	791	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.26, 0.02]
1.1 Blinding: yes	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.13 [−0.27, 0.02]
1.2 Blinding: unclear	1	32	Std. Mean Difference (IV, Random, 95% CI)	0.11 [−0.59, 0.80]
1.3 Blinding: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Physical Function on a 0 to 100 scale	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.19]
2.1 Blinding: yes	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.19]
2.2 Blinding: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Blinding: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 8

Sensitivity analysis (blinding): Glucosamine + Chondroitin sulfate versus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
1.1 Blinding: yes	1	635	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.13, 0.18]
1.2 Blinding: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Blinding: no	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]

Comparison 9

Sensitivity analysis (blinding): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-Blinding	17	2278	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−0.95, −0.35]
1.1 Blinding: yes	12	1985	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−0.64, −0.19]
1.2 Blinding: unclear	3	186	Std. Mean Difference (IV, Random, 95% CI)	−0.21 [−1.01, 0.59]
1.3 Blinding: no	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Physical Function-Blinding	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.30, 0.19]
2.1 Blinding: yes	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.30, 0.19]
2.2 Blinding: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Blinding: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 10

Sensitivity analysis (study size): Chondroitin sulfate versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	11	1653	Std. Mean Difference (IV, Random, 95% CI)	−0.50 [−0.76, −0.24]
1.1 Studies with n ≥ 100	2	865	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.45, 0.17]
1.2 Studies with n < 100	9	788	Std. Mean Difference (IV, Random, 95% CI)	−0.59 [−0.88, −0.31]
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 Studies with n ≥ 100	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.2 Studies with n < 100	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Physical Function on a 0 to 100 scale	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3.1 Studies with n ≥ 100	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.15, 0.16]
3.2 Studies with n < 100	1	46	Std. Mean Difference (IV, Random, 95% CI)	−0.93 [−1.54, −0.32]
4 Radiographic outcome: Change in Mean JSW in mm	3	1179	Std. Mean Difference (IV, Random, 95% CI)	0.19 [−0.02, 0.40]
4.1 Studies with n ≥ 100	3	1179	Std. Mean Difference (IV, Random, 95% CI)	0.19 [−0.02, 0.40]
4.2 Studies with n < 100	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 11

Sensitivity analysis (study size): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	791	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.26, 0.02]
1.1 Studies with n ≥ 100	1	630	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.28, 0.04]
1.2 Studies with n < 100	3	161	Std. Mean Difference (IV, Random, 95% CI)	−0.10 [−0.42, 0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Physical Function on a 0 to 100 scale	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.19]
2.1 Studies with n ≥ 100	1	630	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.29, 0.02]
2.2 Studies with n < 100	2	129	Std. Mean Difference (IV, Random, 95% CI)	0.10 [−0.46, 0.66]

Comparison 12

Sensitivity analysis (study size): Glucosamine + Chondroitin sulfate versus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
1.1 Studies with n ≥ 100	1	635	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.13, 0.18]
1.2 Studies with n < 100	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]

Comparison 13

Sensitivity analysis (study size): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-study size	17	2154	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−0.96, −0.34]
1.1 Studies with n ≥ 100	2	988	Std. Mean Difference (IV, Random, 95% CI)	0.04 [−0.09, 0.16]
1.2 Studies with n < 100	15	1166	Std. Mean Difference (IV, Random, 95% CI)	−0.78 [−1.15, −0.41]
2 Physical Function-study size	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.30, 0.19]
2.1 Studies with n ≥ 100	2	988	Std. Mean Difference (IV, Random, 95% CI)	0.03 [−0.09, 0.16]
2.2 Studies with n < 100	3	175	Std. Mean Difference (IV, Random, 95% CI)	−0.21 [−0.90, 0.48]

Comparison 14

Sensitivity analysis (study sponsors): Chondroitin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	11	1529	Std. Mean Difference (IV, Random, 95% CI)	−0.50 [−0.77, −0.23]
1.1 Pharmaceutical sponsorship: yes	8	698	Std. Mean Difference (IV, Random, 95% CI)	−0.52 [−0.80, −0.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Pharmaceutical sponsorship: unclear	2	200	Std. Mean Difference (IV, Random, 95% CI)	−0.73 [−1.66, 0.20]
1.3 Pharmaceutical sponsorship: no	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.00 [−0.15, 0.16]
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 Pharmaceutical sponsorship: yes	1	622	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.98, 1.48]
2.2 Pharmaceutical sponsorship: unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Pharmaceutical sponsorship: no	1	631	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.97, 1.23]
3 Physical Function on a 0 to 100 scale	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3.1 Pharmaceutical sponsorship: yes	1	46	Std. Mean Difference (IV, Random, 95% CI)	−0.93 [−1.54, −0.32]
3.2 Pharmaceutical sponsorship: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Pharmaceutical sponsorship: no	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.15, 0.16]
4 Radiographic outcome: Change in Mean JSW in mm	3	1179	Std. Mean Difference (IV, Random, 95% CI)	0.19 [−0.02, 0.40]
4.1 Pharmaceutical sponsorship: yes	1	622	Std. Mean Difference (IV, Random, 95% CI)	0.26 [0.11, 0.42]
4.2 Pharmaceutical sponsorship: unclear	1	300	Std. Mean Difference (IV, Random, 95% CI)	0.33 [0.10, 0.55]
4.3 Pharmaceutical sponsorship: no	1	257	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.18]

Comparison 15

Sensitivity analysis (study sponsors): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	791	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.26, 0.02]
1.1 Pharmaceutical sponsorship: yes	1	89	Std. Mean Difference (IV, Random, 95% CI)	0.0 [−0.42, 0.42]
1.2 Pharmaceutical sponsorship: unclear	2	72	Std. Mean Difference (IV, Random, 95% CI)	−0.21 [−0.80, 0.38]
1.3 Pharmaceutical sponsorship: no	1	630	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.28, 0.04]
2 Physical Function on a 0 to 100 scale	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.19]
2.1 Pharmaceutical sponsorship: yes	1	89	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.55, 0.28]
2.2 Pharmaceutical sponsorship: unclear	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.44 [−0.19, 1.07]
2.3 Pharmaceutical sponsorship: no	1	630	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.29, 0.02]

Comparison 16

Sensitivity analysis (study sponsors): Chondroitin sulfate + Glucosamine versus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
1.1 Pharmaceutical sponsorship: yes	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Pharmaceutical sponsorship: unclear	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]
1.3 Pharmaceutical sponsorship: no	1	635	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.13, 0.18]

Comparison 17

Sensitivity analysis (study sponsors): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Control/Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-study sponsors	17	2154	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−0.96, −0.34]
1.1 Pharmaceutical sponsorship: yes	10	1144	Std. Mean Difference (IV, Random, 95% CI)	−0.39 [−0.67, −0.11]
1.2 Pharmaceutical sponsorship: unclear	6	379	Std. Mean Difference (IV, Random, 95% CI)	−1.39 [−2.41, −0.37]
1.3 Pharmaceutical sponsorship: no	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.00 [−0.15, 0.16]
2 Physical Function-study sponsors	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.30, 0.19]
2.1 Pharmaceutical sponsorship: yes	3	492	Std. Mean Difference (IV, Random, 95% CI)	−0.26 [−0.75, 0.24]
2.2 Pharmaceutical sponsorship: unclear	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.44 [−0.19, 1.07]
2.3 Pharmaceutical sponsorship: no	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.15, 0.16]

Comparison 18

Sensitivity analysis (publication year): Chondroitin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	12	1786	Std. Mean Difference (IV, Random, 95% CI)	−0.45 [−0.69, −0.20]
1.1 1990 < Publication year ≤ 1999	5	431	Std. Mean Difference (IV, Random, 95% CI)	−0.89 [−1.13, −0.66]
1.2 2000 ≤ Publication year ≤ 2009	3	871	Std. Mean Difference (IV, Random, 95% CI)	−0.18 [−0.45, 0.09]
1.3 Publication year ≥ 2010	4	484	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.25, 0.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 1990 < Publication year ≤ 1999	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 2000 ≤ Publication year ≤ 2009	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.3 Publication year ≥ 2010	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Physical Function on a 0 to 100 scale	3	934	Std. Mean Difference (IV, Random, 95% CI)	−0.20 [−0.53, 0.14]
3.1 1990 < Publication year ≤ 1999	1	46	Std. Mean Difference (IV, Random, 95% CI)	−0.93 [−1.54, −0.32]
3.2 2000 ≤ Publication year ≤ 2009	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.15, 0.16]
3.3 Publication year ≥ 2010	1	257	Std. Mean Difference (IV, Random, 95% CI)	−0.07 [−0.32, 0.17]
4 Radiographic outcome: Change in Mean JSW in mm	3	1179	Std. Mean Difference (IV, Random, 95% CI)	0.19 [−0.02, 0.40]
4.1 1990 < Publication year ≤ 1999	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 2000 < Publication year ≤ 2009	2	922	Std. Mean Difference (IV, Random, 95% CI)	0.28 [0.15, 0.41]
4.3 Publication year ≥ 2010	1	257	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.18]

Comparison 19

Sensitivity analysis (publication year): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	5	1051	Std. Mean Difference (IV, Random, 95% CI)	−0.10 [−0.22, 0.02]
1.1 1990 < Publication year ≤ 1999	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 2000 < Publication year ≤ 2009	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.11 [−0.25, 0.04]
1.3 Publication year ≥ 2010	3	332	Std. Mean Difference (IV, Random, 95% CI)	−0.08 [−0.31, 0.14]
2 Physical Function on a 0 to 100 scale	4	1019	Std. Mean Difference (IV, Random, 95% CI)	−0.08 [−0.22, 0.05]
2.1 1990 < Publication year ≤ 1999	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 2000 < Publication year ≤ 2009	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.28, 0.01]
2.3 Publication year ≥ 2010	2	300	Std. Mean Difference (IV, Random, 95% CI)	0.11 [−0.33, 0.55]

Comparison 20

Sensitivity analysis (publication year): Glucosamine + Chondroitin sulfate versus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	1013	Std. Mean Difference (IV, Random, 95% CI)	−1.48 [−2.51, −0.44]
1.1 1990 < Publication year ≤ 1999	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 2000 < Publication year ≤ 2009	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
1.3 Publication year ≥ 2010	1	271	Std. Mean Difference (IV, Random, 95% CI)	0.17 [−0.07, 0.41]

Comparison 21

Sensitivity analysis (publication year): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-publication year	18	2411	Std. Mean Difference (IV, Random, 95% CI)	−0.60 [−0.89, −0.32]
1.1 1990 < Publication year ≤ 1999	5	431	Std. Mean Difference (IV, Random, 95% CI)	−0.89 [−1.13, −0.66]
1.2 2000 ≤ Publication year ≤ 2009	6	1067	Std. Mean Difference (IV, Random, 95% CI)	−1.09 [−1.82, −0.36]
1.3 Publication year ≥ 2010	7	913	Std. Mean Difference (IV, Random, 95% CI)	−0.02 [−0.18, 0.13]
2 Physical Function-publication year	6	1420	Std. Mean Difference (IV, Random, 95% CI)	−0.05 [−0.24, 0.14]
2.1 1990 < Publication year ≤ 1999	1	46	Std. Mean Difference (IV, Random, 95% CI)	−0.93 [−1.54, −0.32]
2.2 2000 ≤ Publication year ≤ 2009	2	720	Std. Mean Difference (IV, Random, 95% CI)	−0.01 [−0.16, 0.14]
2.3 Publication year ≥ 2010	3	654	Std. Mean Difference (IV, Random, 95% CI)	0.05 [−0.14, 0.23]

Comparison 22

Sensitivity analysis (allocation concealment): Chondroitin sulfate versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	11	1529	Std. Mean Difference (IV, Random, 95% CI)	−0.50 [−0.77, −0.23]
1.1 Allocation concealment: yes	3	810	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.37, 0.24]
1.2 Allocation concealment: unclear	8	719	Std. Mean Difference (IV, Random, 95% CI)	−0.67 [−0.93, −0.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Allocation concealment: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 Allocation concealment: yes	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.2 Allocation concealment: unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Allocation concealment: no	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Physical Function on a 0 to 100 scale	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3.1 Allocation concealment: yes	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.15, 0.16]
3.2 Allocation concealment: unclear	1	46	Std. Mean Difference (IV, Random, 95% CI)	−0.93 [−1.54, −0.32]
3.3 Allocation concealment: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Radiographic outcome: Change in Mean JSW in mm	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.03, 0.22]
4.1 Allocation concealment: yes	2	879	Mean Difference (IV, Random, 95% CI)	0.07 [−0.11, 0.26]
4.2 Allocation concealment: unclear	1	300	Mean Difference (IV, Random, 95% CI)	0.19 [0.06, 0.31]
4.3 Allocation concealment: no	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 23

Sensitivity analysis (allocation concealment): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	791	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.26, 0.02]
1.1 Allocation concealment: yes	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.11 [−0.25, 0.04]
1.2 Allocation concealment: unclear	2	72	Std. Mean Difference (IV, Random, 95% CI)	−0.21 [−0.80, 0.38]
1.3 Allocation concealment: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Physical Function on a 0 to 100 scale	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.19]
2.1 Allocation concealment: yes	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.28, 0.01]
2.2 Allocation concealment: unclear	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.44 [−0.19, 1.07]
2.3 Allocation concealment: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 24

Sensitivity analysis (allocation concealment): Chondroitin sulfate + Glucosamine versus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
1.1 Allocation concealment: yes	1	635	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.13, 0.18]
1.2 Allocation concealment: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Allocation concealment: no	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]

Comparison 25

Sensitivity analysis (allocation concealment): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-allocation concealment	17	2154	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−0.96, −0.34]
1.1 Allocation concealment: yes	4	899	Std. Mean Difference (IV, Random, 95% CI)	−0.05 [−0.27, 0.17]
1.2 Allocation concealment: unclear	11	1148	Std. Mean Difference (IV, Random, 95% CI)	−0.52 [−0.81, −0.23]
1.3 Allocation concealment: no	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]
2 Physical Function-allocation concealment	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.30, 0.19]
2.1 Allocation concealment: yes	2	720	Std. Mean Difference (IV, Random, 95% CI)	−0.01 [−0.16, 0.14]
2.2 Allocation concealment: unclear	3	443	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.77, 0.53]
2.3 Allocation concealment: no	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 26

Sensitivity analysis (estimated SD): Chondroitin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	14	1814	Std. Mean Difference (IV, Random, 95% CI)	−0.52 [−0.75, −0.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Physical Function on a 0 to 100 scale	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3 Lequesne's Index	9	929	Std. Mean Difference (IV, Random, 95% CI)	−0.61 [−0.83, −0.39]

Comparison 27

Sensitivity analysis (estimated SD): Chondroitin sulfate versus Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	2	457	Std. Mean Difference (IV, Random, 95% CI)	−0.34 [−0.85, 0.18]
2 Lequesne's Index	3	930	Mean Difference (IV, Random, 95% CI)	−1.99 [−3.27, −0.70]
3 Patient Global Assessment (VAS)	1	100	Mean Difference (IV, Random, 95% CI)	−4.0 [−7.80, −0.20]

Comparison 28

Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	791	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.26, 0.02]
2 WOMAC Total	2	723	Mean Difference (IV, Random, 95% CI)	−2.29 [−5.38, 0.79]
3 Patient Global Assessment VAS (0 to 100 mm)	2	723	Std. Mean Difference (IV, Random, 95% CI)	−0.07 [−0.22, 0.07]
4 Lequesne's Index	2	193	Mean Difference (IV, Random, 95% CI)	−4.46 [−10.97, 2.06]

Comparison 29

Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 100)	4	1117	Std. Mean Difference (IV, Random, 95% CI)	−1.70 [−2.70, −0.70]
2 Physical Function	2	1010	Std. Mean Difference (IV, Random, 95% CI)	−0.30 [−0.85, 0.25]
3 WOMAC Stiffness	4	1117	Mean Difference (IV, Random, 95% CI)	−8.49 [−14.52, −2.46]
4 WOMAC Total	4	1147	Mean Difference (IV, Random, 95% CI)	−6.94 [−12.86, −1.01]

Comparison 30

Sensitivity analysis (estimated SD): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 100)	22	3038	Std. Mean Difference (IV, Random, 95% CI)	−0.64 [−0.88, −0.41]
2 Physical Function on a 0 to 100 scale (short- and long-term results)	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.07 [−0.31, 0.17]
3 Lequesne's Index	16	2334	Std. Mean Difference (IV, Random, 95% CI)	−0.57 [−0.79, −0.35]

Comparison 31

Sensitivity analysis (ITT): Chondroitin sulfate versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	11	1529	Std. Mean Difference (IV, Random, 95% CI)	−0.50 [−0.77, −0.23]
1.1 ITT: low risk	8	1329	Std. Mean Difference (IV, Random, 95% CI)	−0.46 [−0.75, −0.18]
1.2 ITT: unclear risk	2	131	Std. Mean Difference (IV, Random, 95% CI)	−1.00 [−1.37, −0.63]
1.3 ITT: high risk	1	69	Std. Mean Difference (IV, Random, 95% CI)	0.24 [−0.24, 0.71]
2 WOMAC MCII	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.1 ITT: low risk	2	1253	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
2.2 ITT: unclear risk	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 ITT: high risk	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Physical Function on a 0 to 100 scale	2	677	Std. Mean Difference (IV, Random, 95% CI)	−0.41 [−1.33, 0.50]
3.1 ITT: low risk	1	631	Std. Mean Difference (IV, Random, 95% CI)	0.01 [−0.15, 0.16]
3.2 ITT: unclear risk	1	46	Std. Mean Difference (IV, Random, 95% CI)	−0.93 [−1.54, −0.32]
3.3 ITT: high risk	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Radiographic outcome: Change in Mean JSW in mm	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.03, 0.22]
4.1 ITT: low risk	3	1179	Mean Difference (IV, Random, 95% CI)	0.13 [0.03, 0.22]
4.2 ITT: unclear risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 ITT: high risk	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 32

Sensitivity analysis (ITT): Chondroitin sulfate + Glucosamine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	4	791	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.26, 0.02]
1.1 Low risk	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.11 [−0.25, 0.04]
1.2 Unclear risk	2	72	Std. Mean Difference (IV, Random, 95% CI)	−0.21 [−0.80, 0.38]
1.3 High risk	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Physical Function on a 0 to 100 scale	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.31, 0.19]
2.1 Low risk	2	719	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.28, 0.01]
2.2 Unclear risk	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.44 [−0.19, 1.07]
2.3 High risk	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 33

Sensitivity analysis (ITT): Glucosamine + Chondroitin sulfate versus NSAID

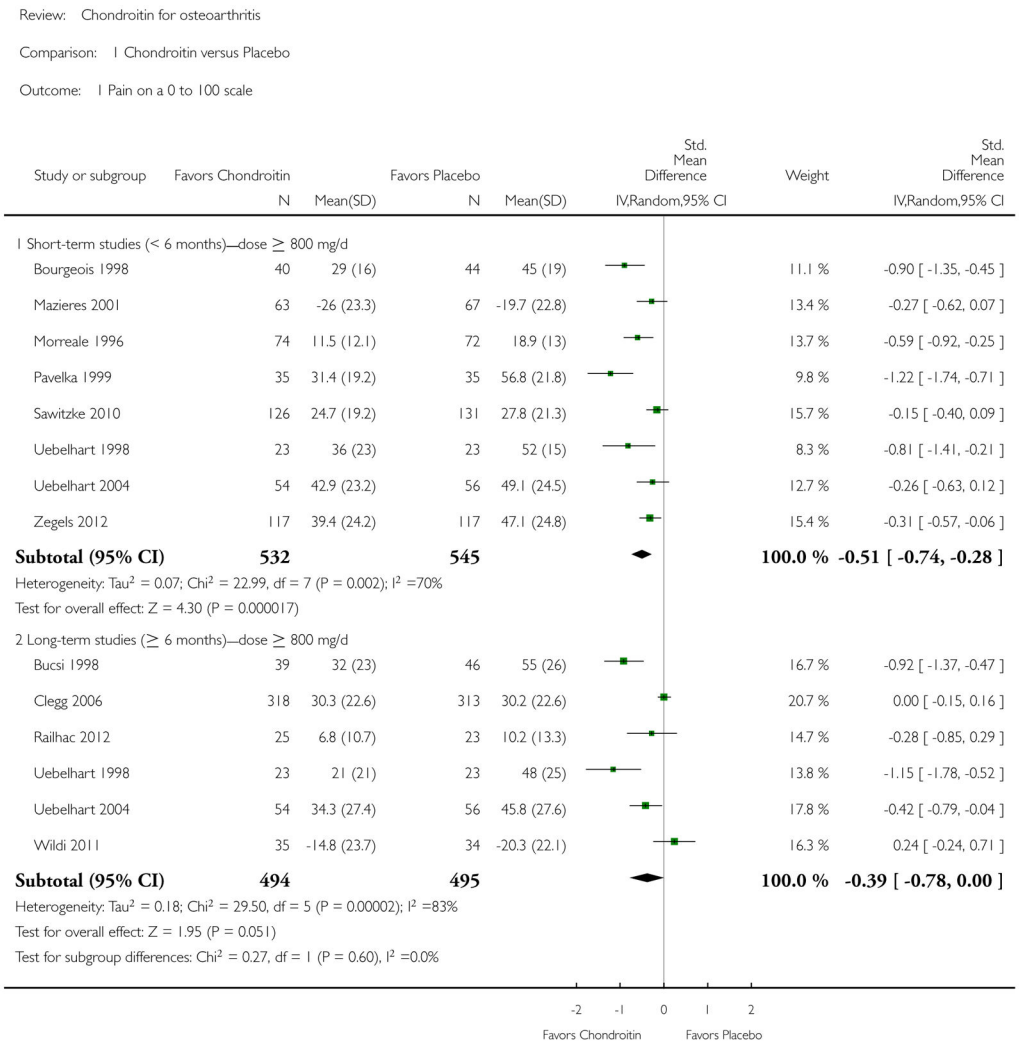
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	3	742	Std. Mean Difference (IV, Random, 95% CI)	−2.22 [−4.87, 0.43]
1.1 ITT: low risk	1	635	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.13, 0.18]
1.2 ITT: unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 ITT: high risk	2	107	Std. Mean Difference (IV, Random, 95% CI)	−3.37 [−5.74, −1.01]

Comparison 34

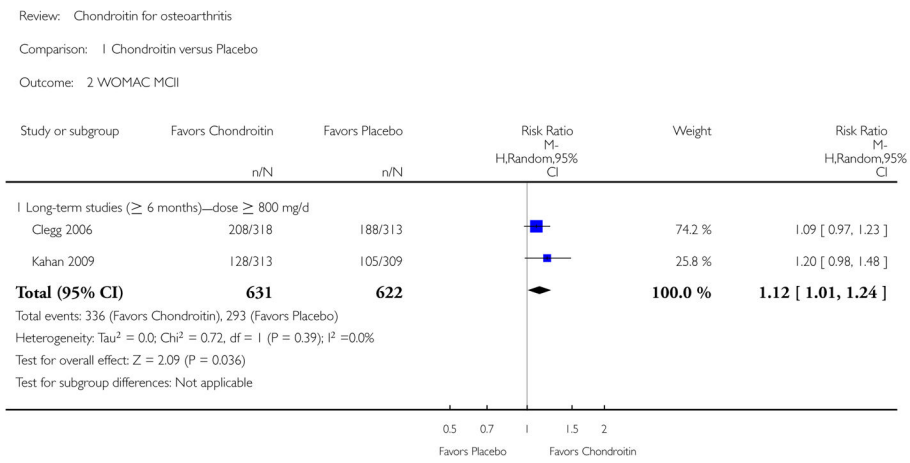
Sensitivity analysis (ITT): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on a 0 to 100 scale	17	2154	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−0.96, −0.34]
1.1 ITT: low risk	10	1775	Std. Mean Difference (IV, Random, 95% CI)	−0.35 [−0.58, −0.11]
1.2 ITT: unclear	4	203	Std. Mean Difference (IV, Random, 95% CI)	−0.65 [−1.15, −0.15]
1.3 ITT: high risk	3	176	Std. Mean Difference (IV, Random, 95% CI)	−2.16 [−4.88, 0.57]

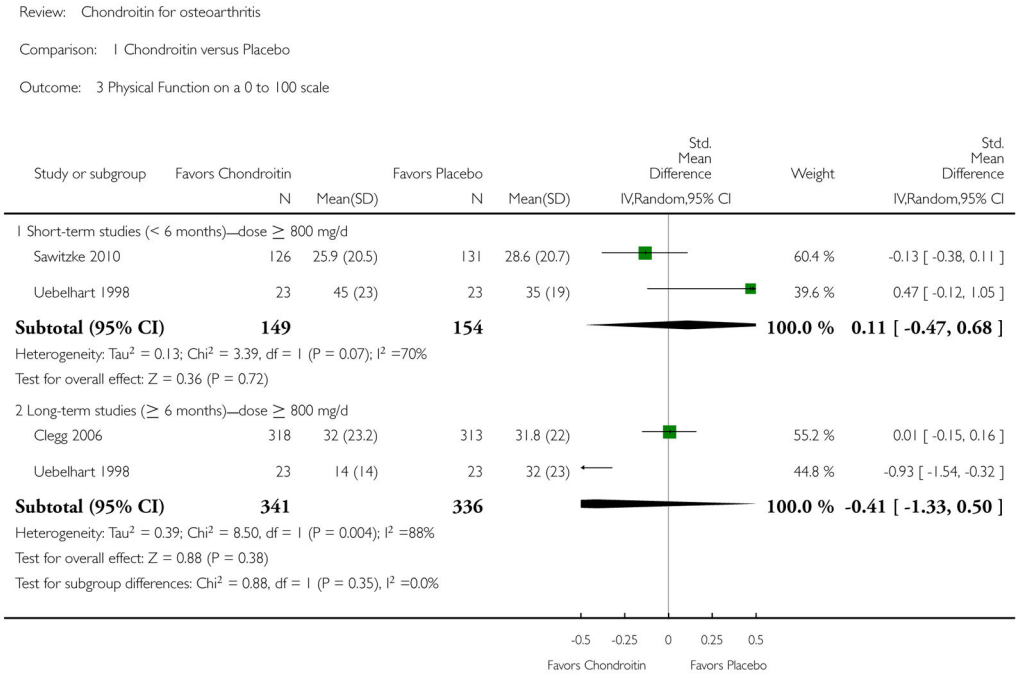
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Physical Function on a 0 to 100 scale	5	1163	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.30, 0.19]
2.1 ITT: low risk	3	1077	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.10, 0.14]
2.2 ITT: unclear	2	86	Std. Mean Difference (IV, Random, 95% CI)	−0.25 [−1.59, 1.10]
2.3 ITT: high risk	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]



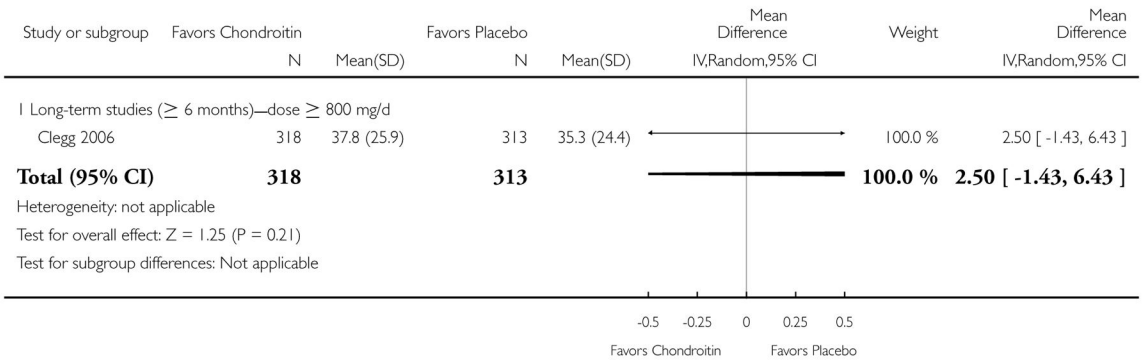
Analysis 1.1.
Comparison 1 Chondroitin versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



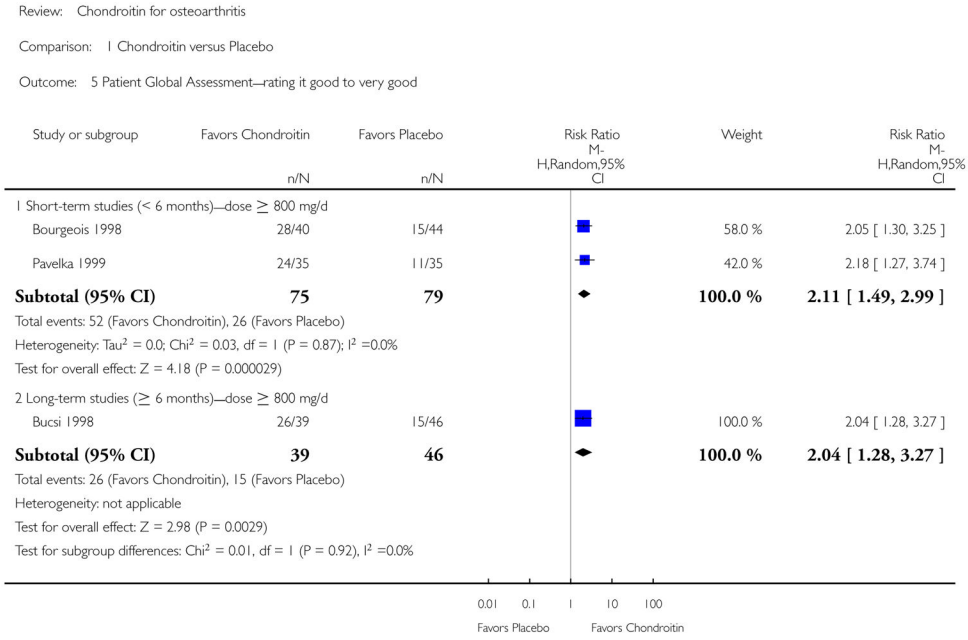
Analysis 1.2.
Comparison 1 Chondroitin versus Placebo, Outcome 2 WOMAC MCII.



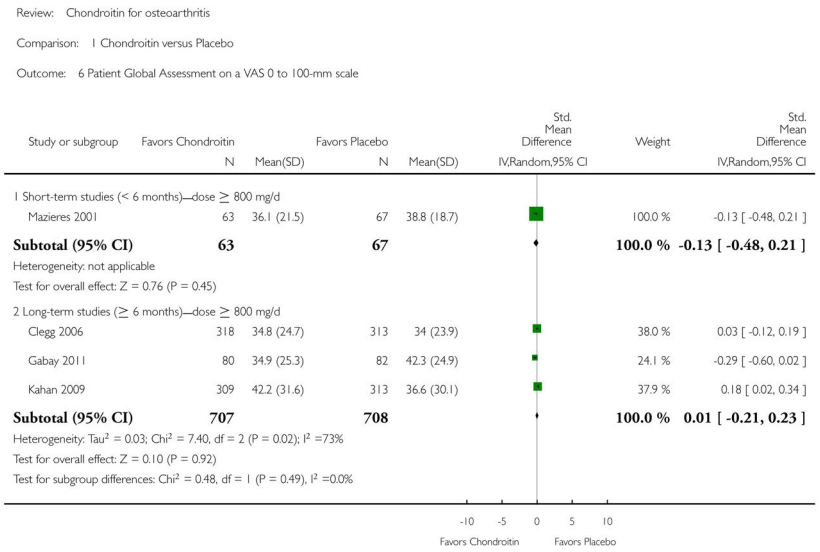
Analysis 1.3.
Comparison 1 Chondroitin versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



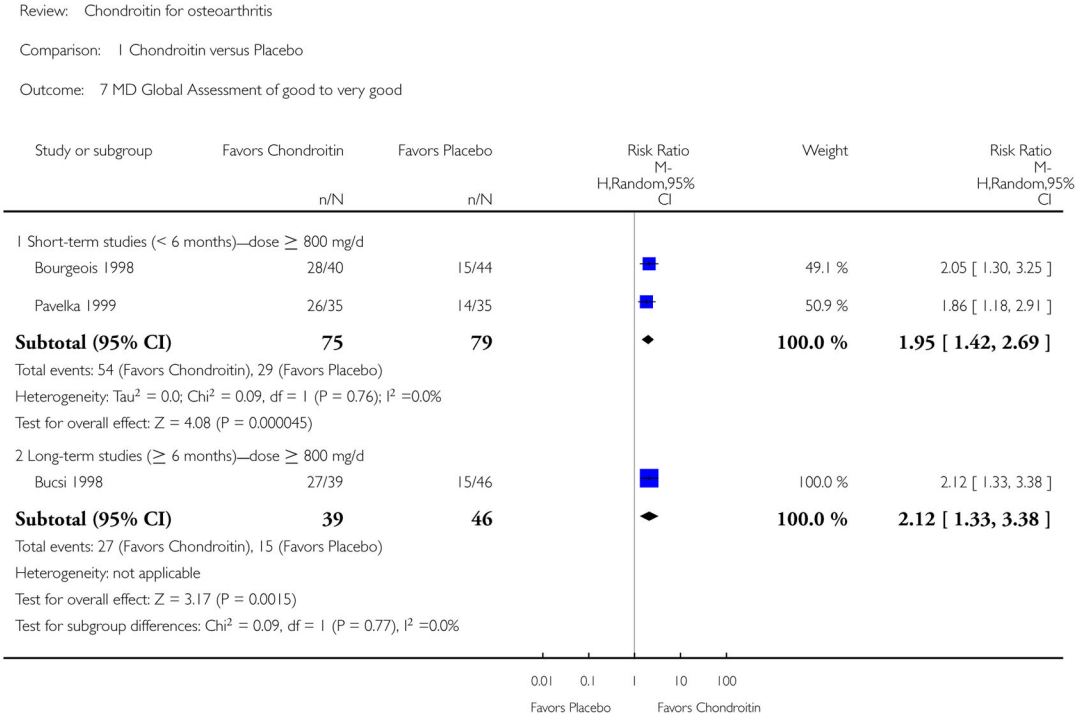
Analysis 1.4.
Comparison 1 Chondroitin versus Placebo, Outcome 4 WOMAC Stiffness on a 0 to 100 scale.



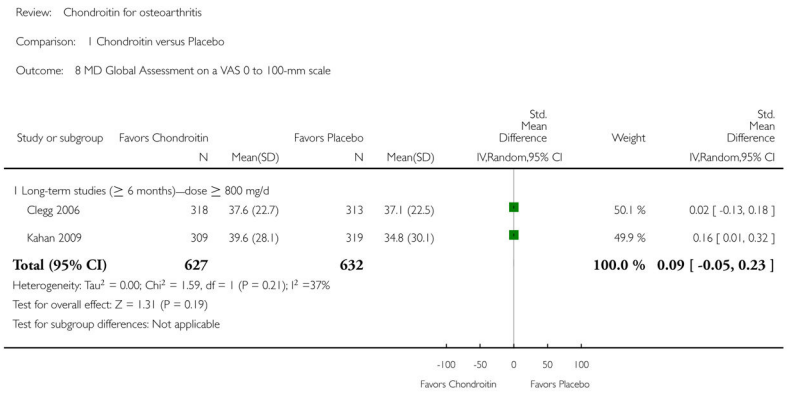
Analysis 1.5.
Comparison 1 Chondroitin versus Placebo, Outcome 5 Patient Global Assessment-rating it good to very good.



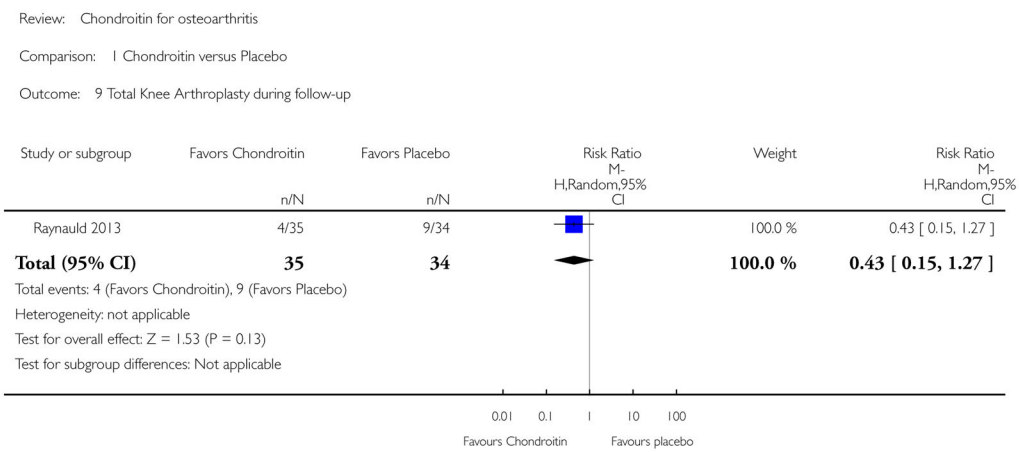
Analysis 1.6.
Comparison 1 Chondroitin versus Placebo, Outcome 6 Patient Global Assessment on a VAS 0 to 100-mm scale.



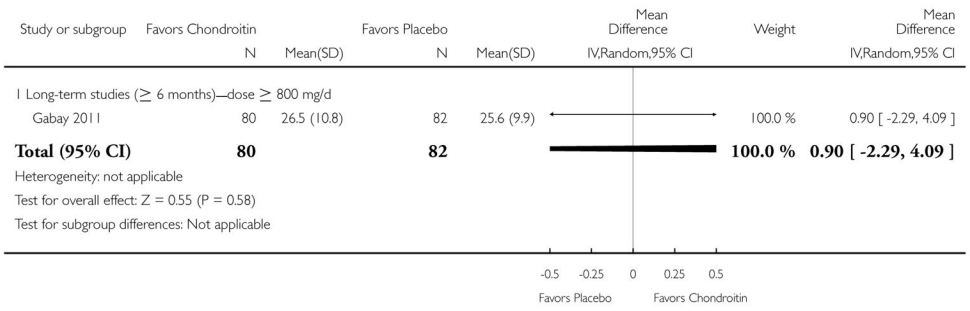
Analysis 1.7.
Comparison 1 Chondroitin versus Placebo, Outcome 7 MD Global Assessment of good to very good.



Analysis 1.8.
Comparison 1 Chondroitin versus Placebo, Outcome 8 MD Global Assessment on a VAS 0 to 100-mm scale.

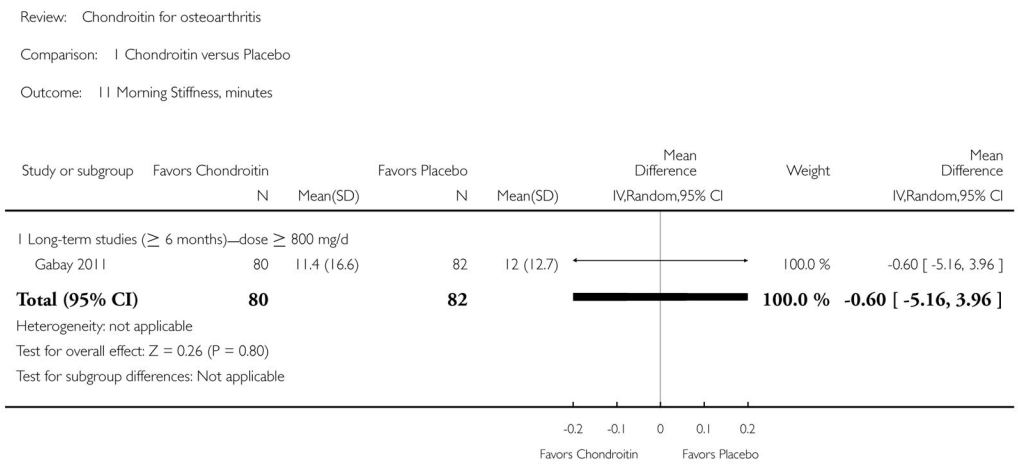


Analysis 1.9.
Comparison 1 Chondroitin versus Placebo, Outcome 9 Total Knee Arthroplasty during follow-up.

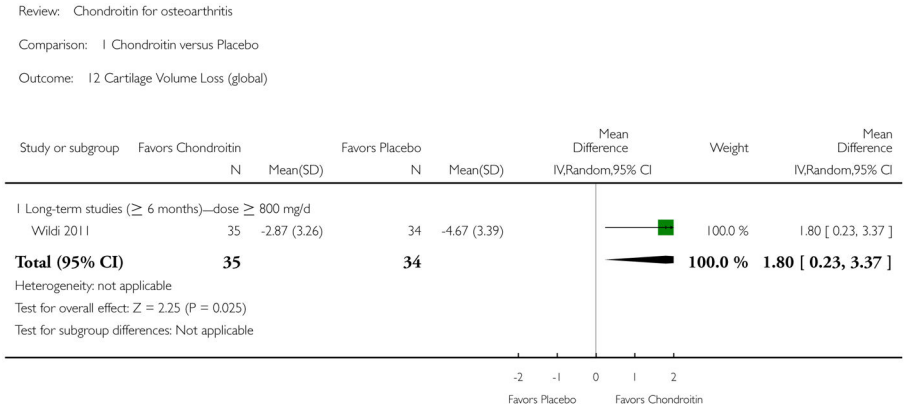


Analysis 1.10.

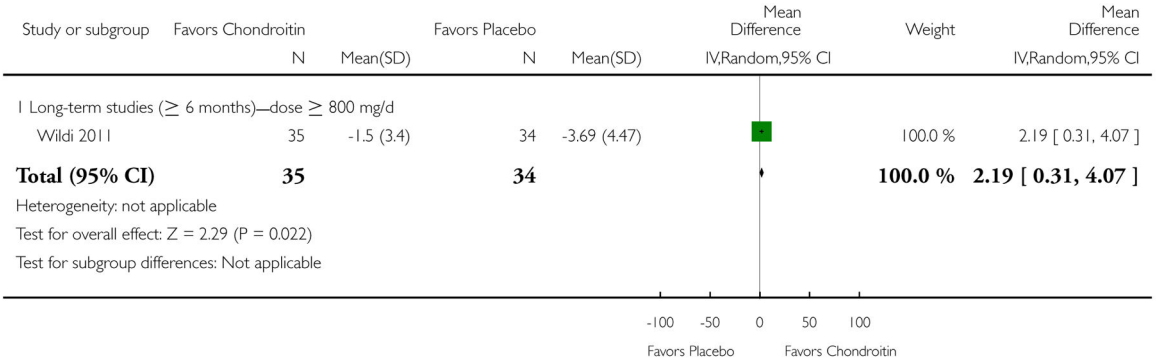
Comparison 1 Chondroitin versus Placebo, Outcome 10 Grip Strength (kg/cm2).



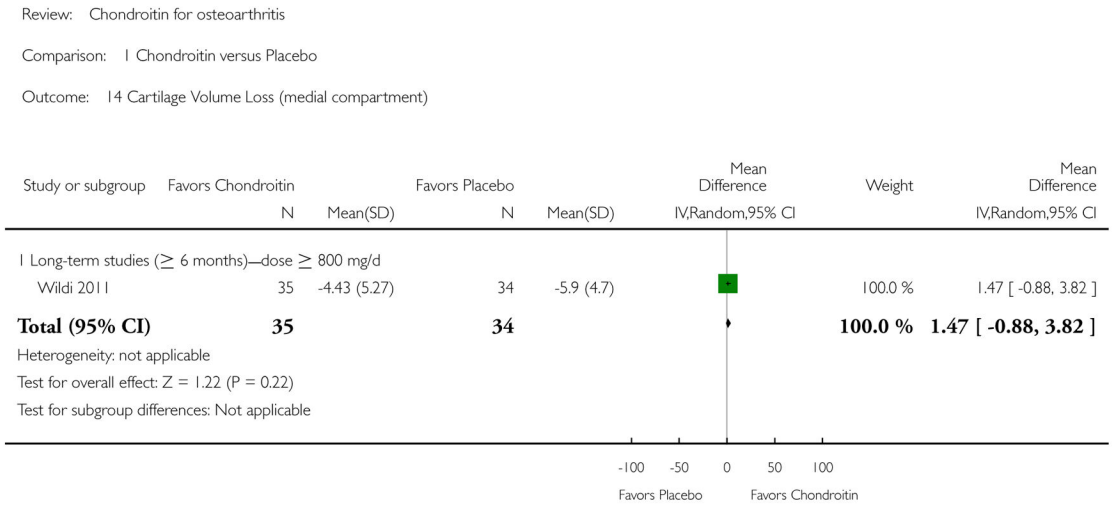
Analysis 1.11.
Comparison 1 Chondroitin versus Placebo, Outcome 11 Morning Stiffness, minutes.



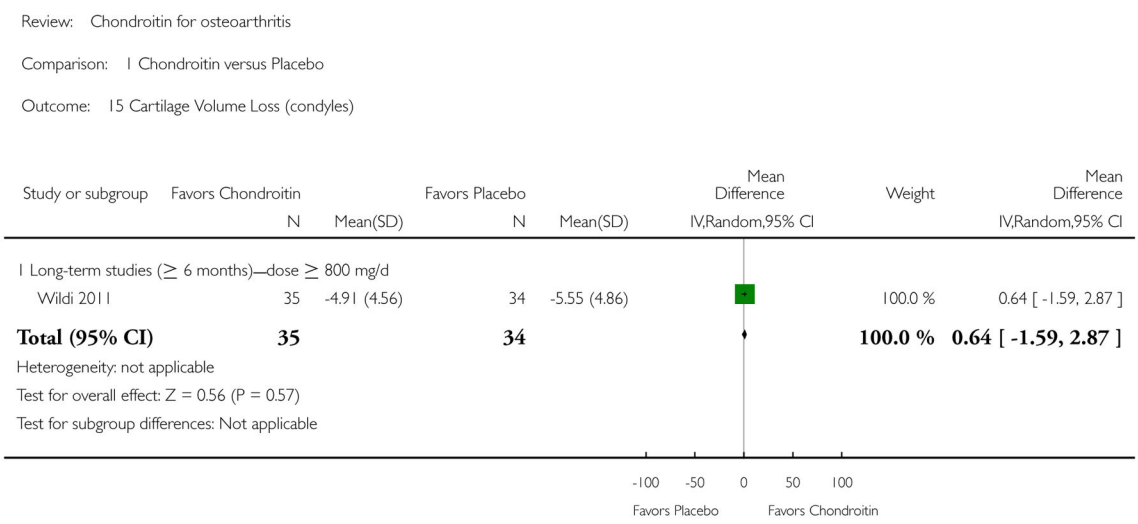
Analysis 1.12.
Comparison 1 Chondroitin versus Placebo, Outcome 12 Cartilage Volume Loss (global).



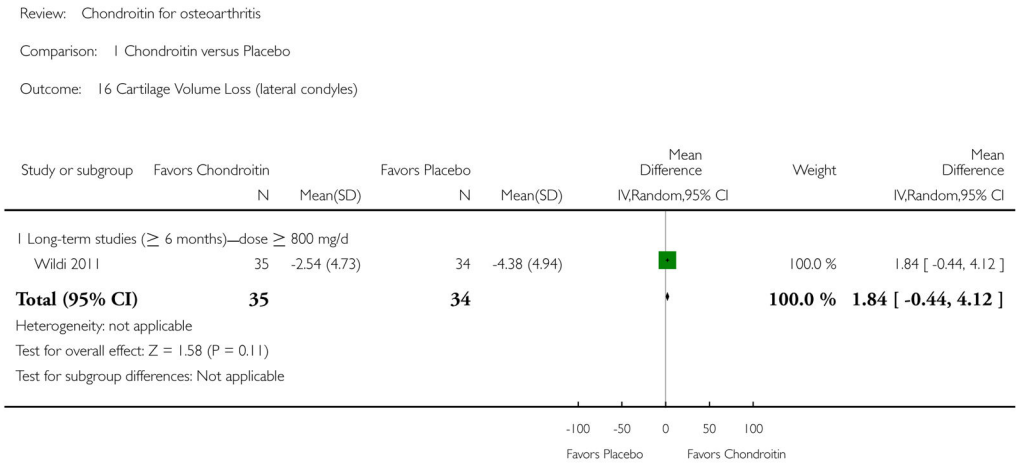
Analysis 1.13.
Comparison 1 Chondroitin versus Placebo, Outcome 13 Cartilage Volume Loss (lateral compartment).



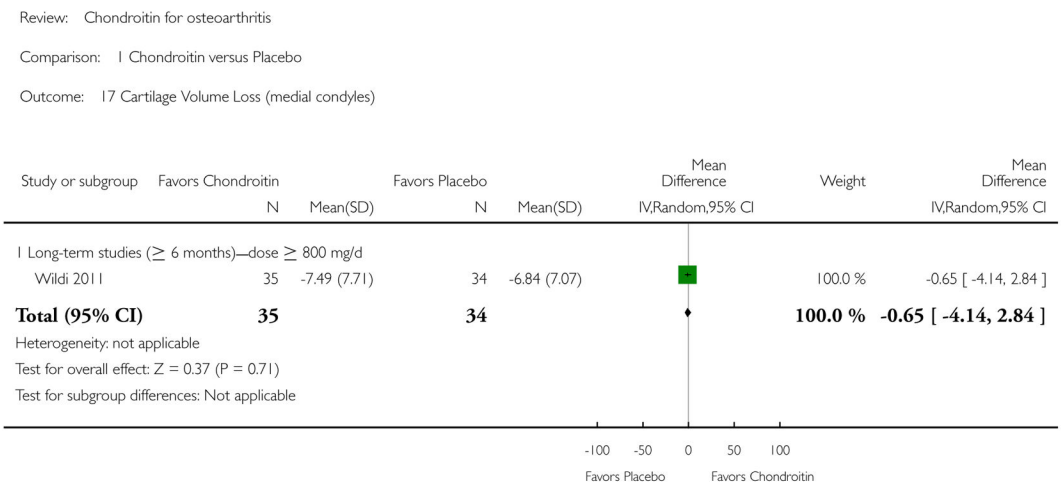
Analysis 1.14.
Comparison 1 Chondroitin versus Placebo, Outcome 14 Cartilage Volume Loss (medial compartment).



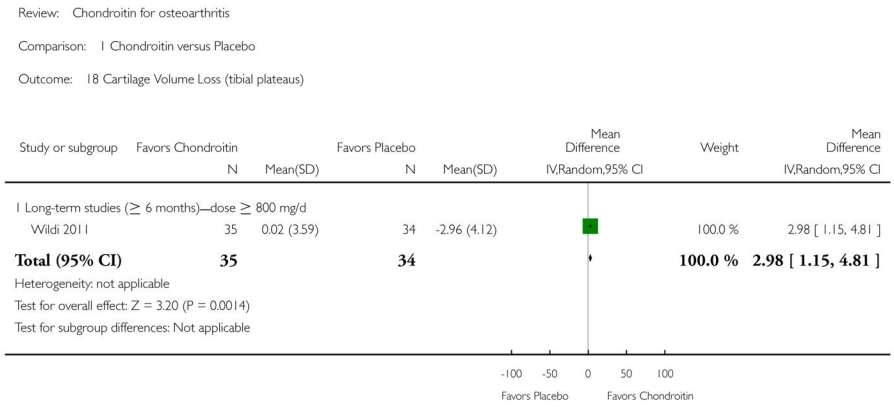
Analysis 1.15.
Comparison 1 Chondroitin versus Placebo, Outcome 15 Cartilage Volume Loss (condyles).



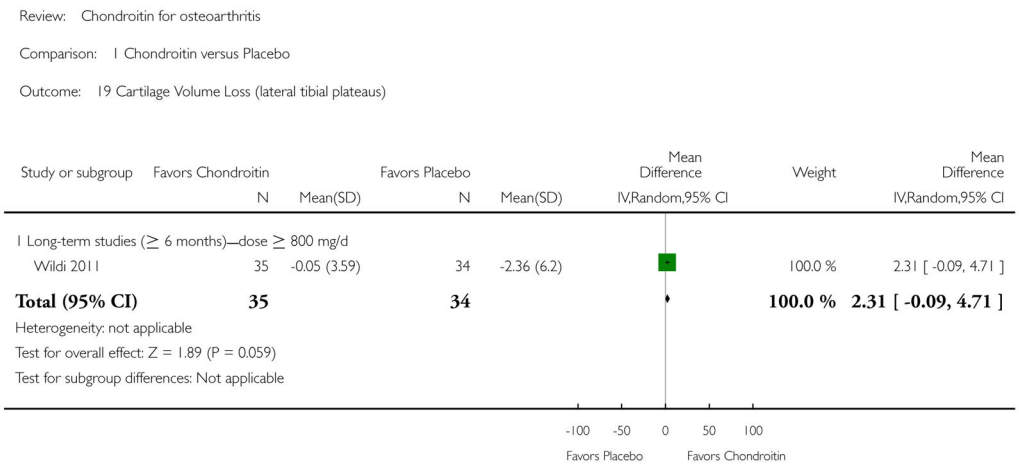
Analysis 1.16.
Comparison 1 Chondroitin versus Placebo, Outcome 16 Cartilage Volume Loss (lateral condyles).



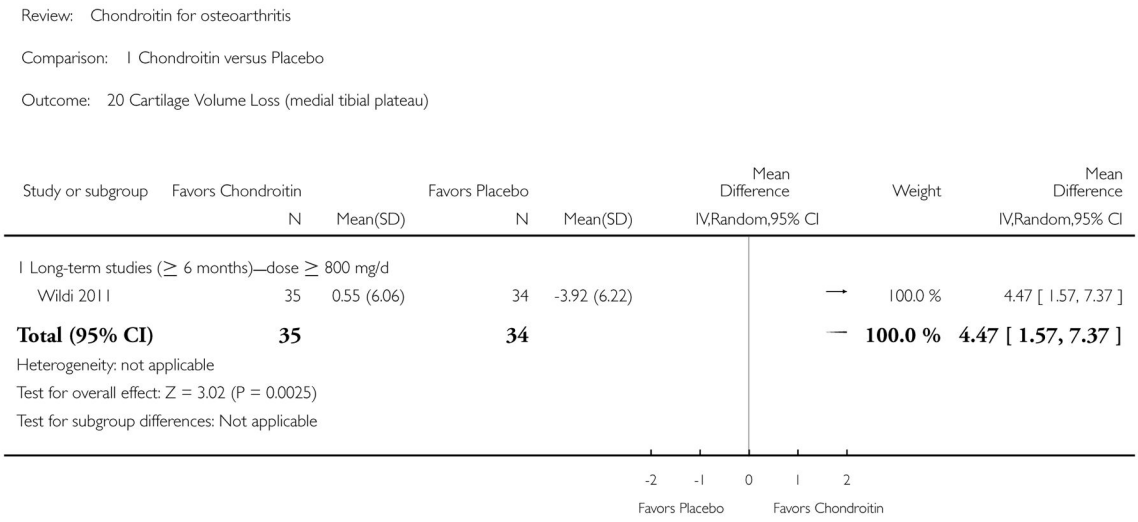
Analysis 1.17.
Comparison 1 Chondroitin versus Placebo, Outcome 17 Cartilage Volume Loss (medial condyles).



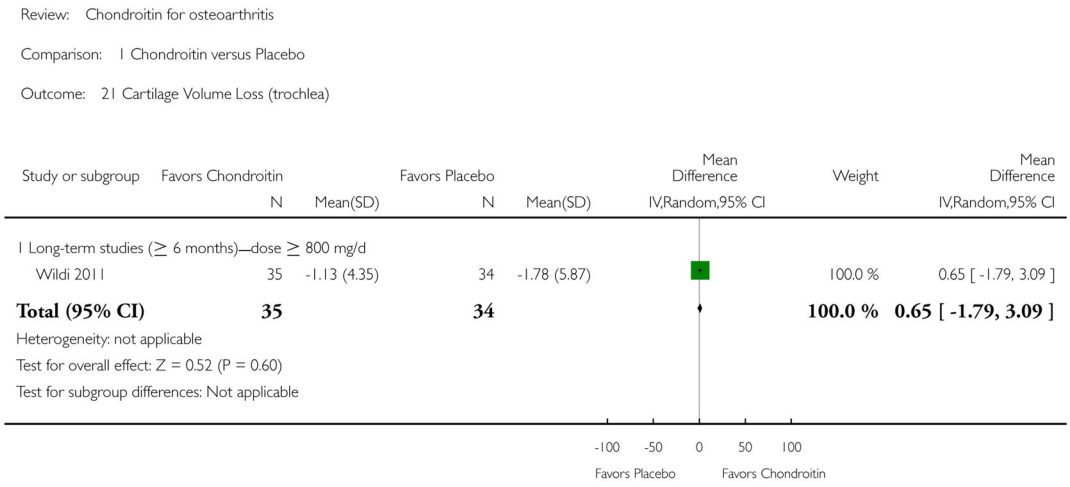
Analysis 1.18.
Comparison 1 Chondroitin versus Placebo, Outcome 18 Cartilage Volume Loss (tibial plateaus).



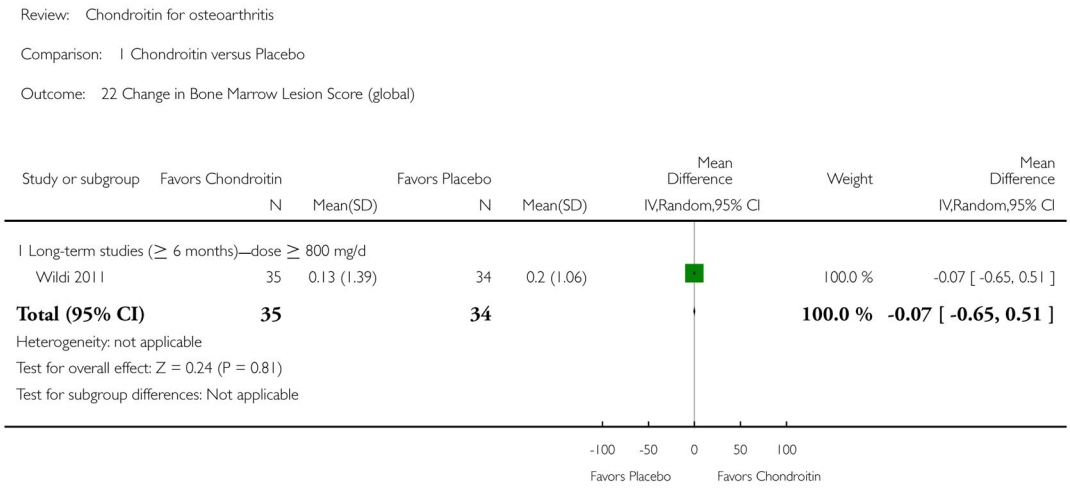
Analysis 1.19.
Comparison 1 Chondroitin versus Placebo, Outcome 19 Cartilage Volume Loss (lateral tibial plateaus).



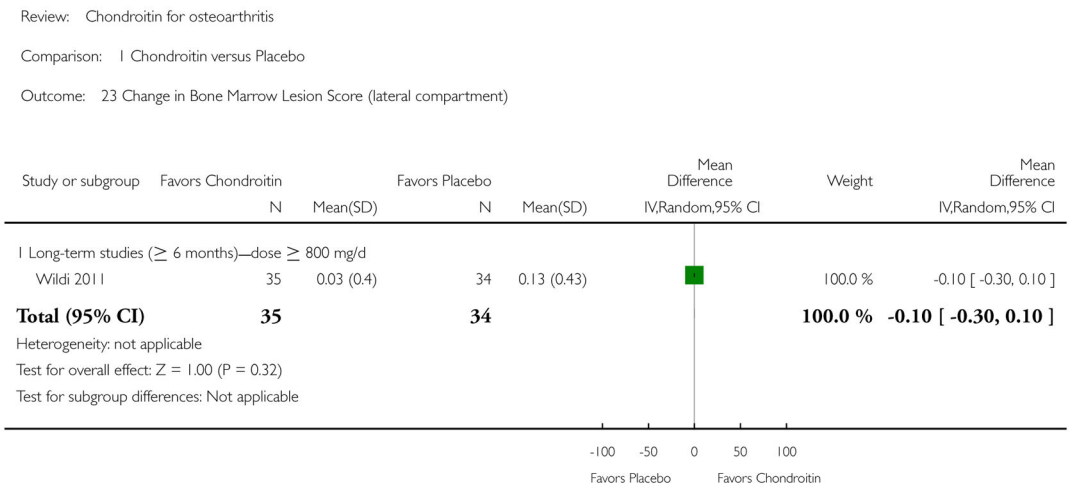
Analysis 1.20.
Comparison 1 Chondroitin versus Placebo, Outcome 20 Cartilage Volume Loss (medial tibial plateau).



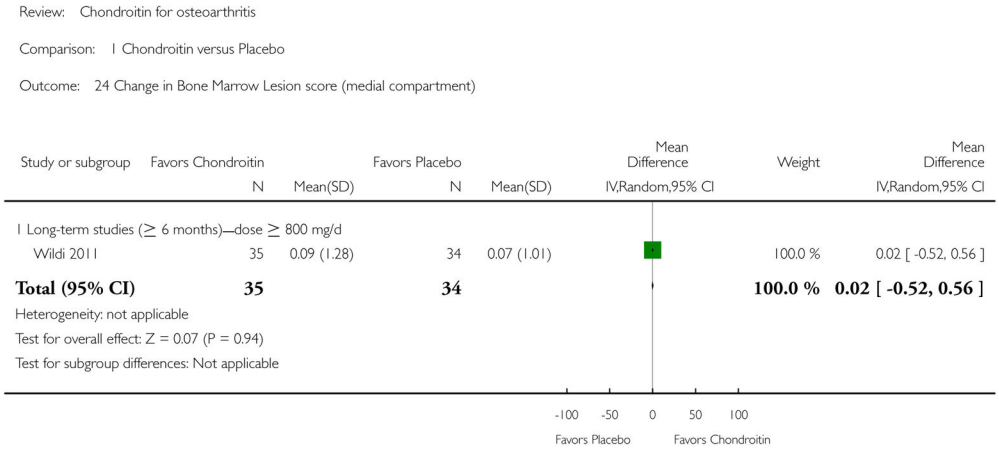
Analysis 1.21.
Comparison 1 Chondroitin versus Placebo, Outcome 21 Cartilage Volume Loss (trochlea).



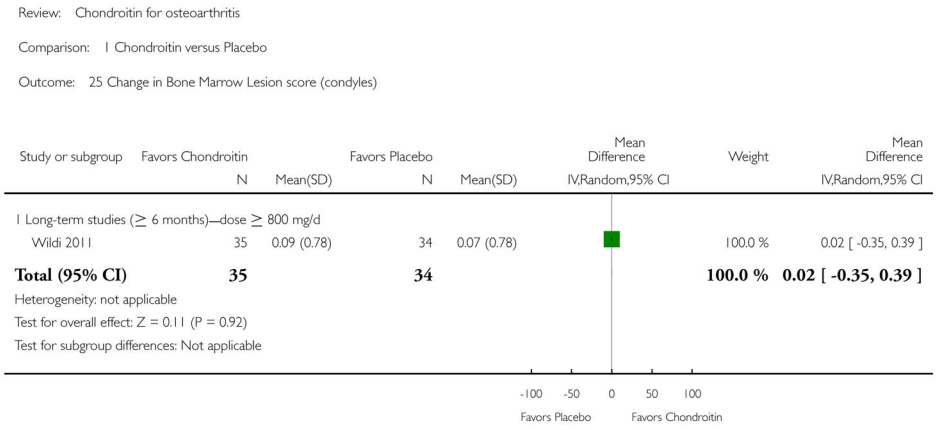
Analysis 1.22.
Comparison 1 Chondroitin versus Placebo, Outcome 22 Change in Bone Marrow Lesion Score (global).



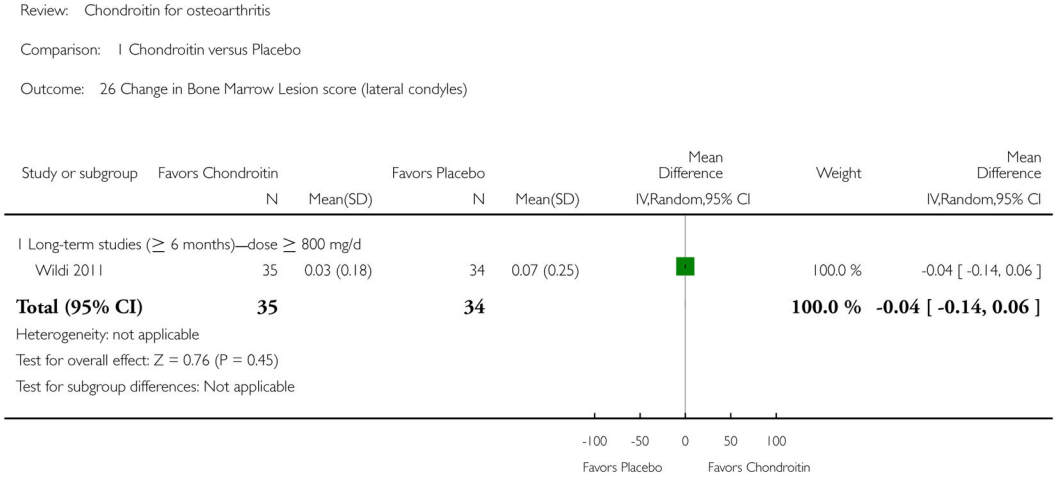
Analysis 1.23.
Comparison 1 Chondroitin versus Placebo, Outcome 23 Change in Bone Marrow Lesion Score (lateral compartment).



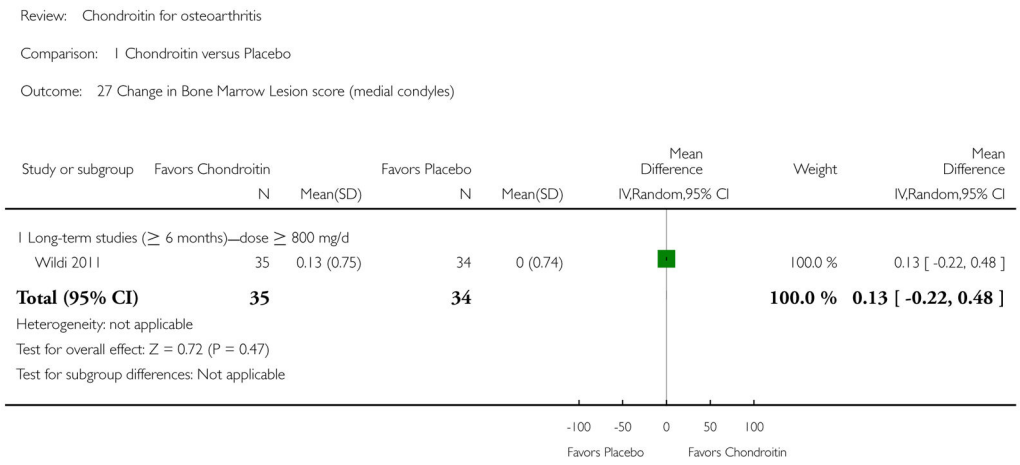
Analysis 1.24.
Comparison 1 Chondroitin versus Placebo, Outcome 24 Change in Bone Marrow Lesion score (medial compartment).



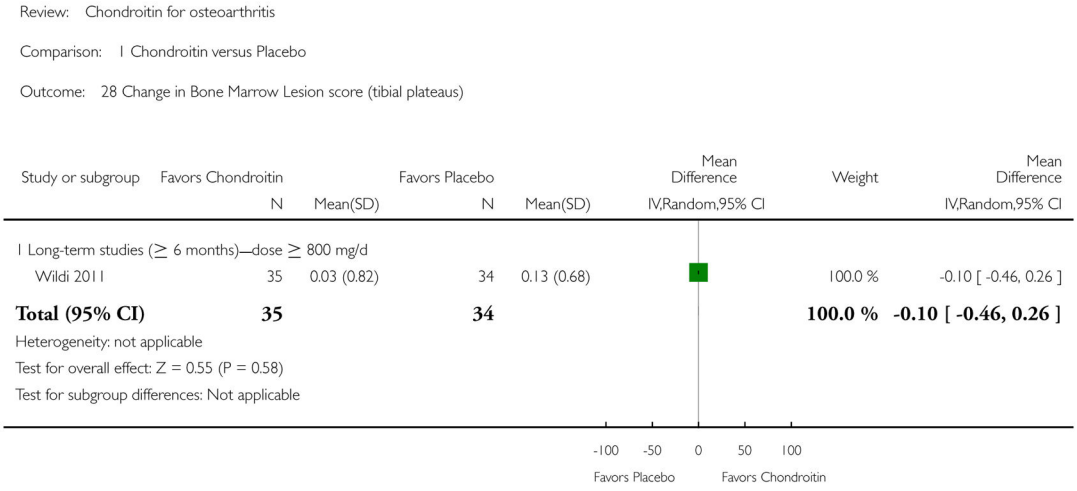
Analysis 1.25.
Comparison 1 Chondroitin versus Placebo, Outcome 25 Change in Bone Marrow Lesion score (condyles).



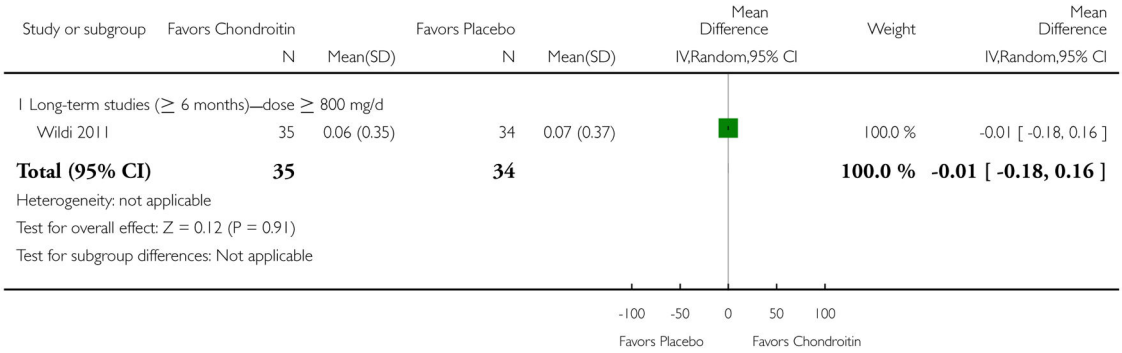
Analysis 1.26.
Comparison 1 Chondroitin versus Placebo, Outcome 26 Change in Bone Marrow Lesion score (lateral condyles).



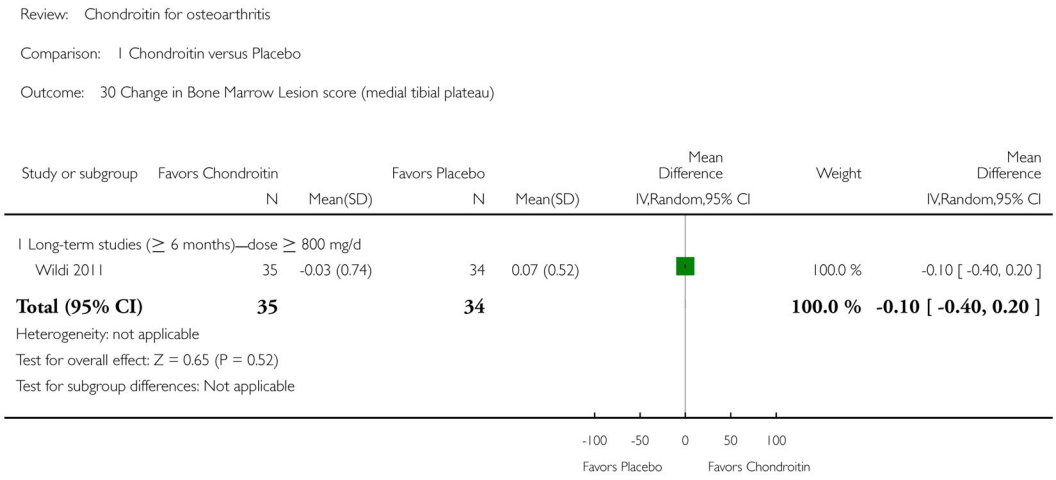
Analysis 1.27.
Comparison 1 Chondroitin versus Placebo, Outcome 27 Change in Bone Marrow Lesion score (medial condyles).



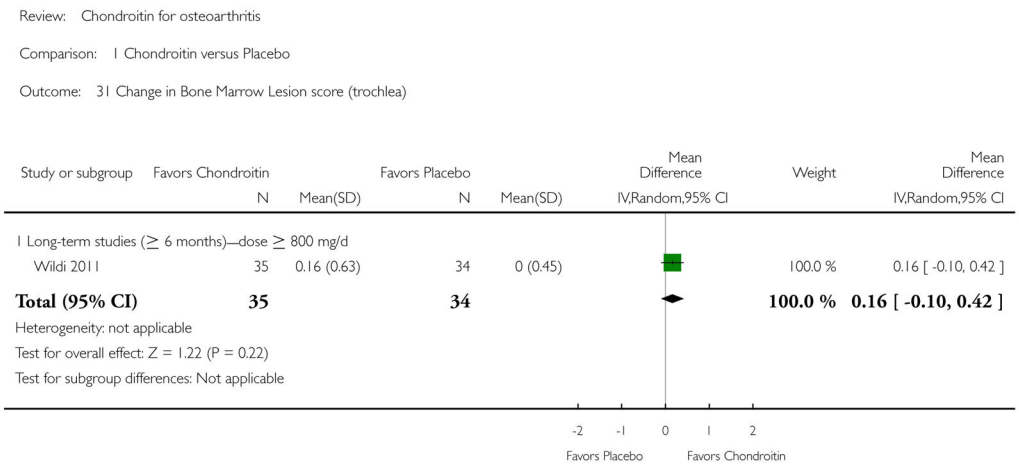
Analysis 1.28.
Comparison 1 Chondroitin versus Placebo, Outcome 28 Change in Bone Marrow Lesion score (tibial plateaus).



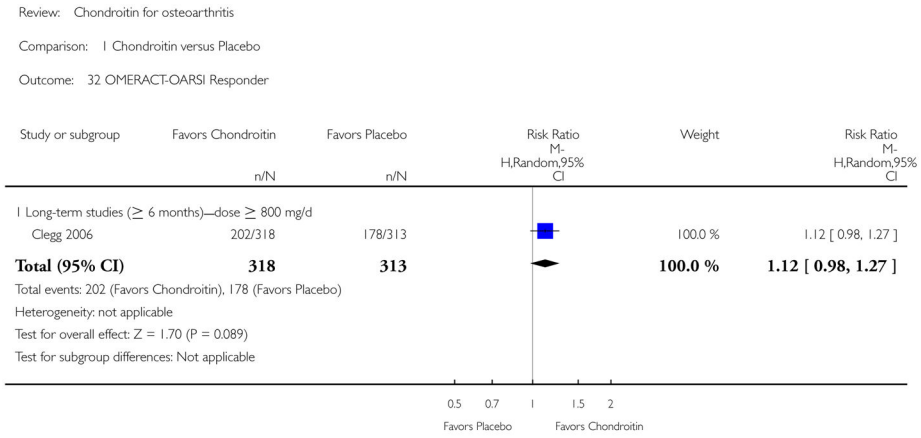
Analysis 1.29.
Comparison 1 Chondroitin versus Placebo, Outcome 29 Change in Bone Marrow Lesion score (lateral tibial plateaus).



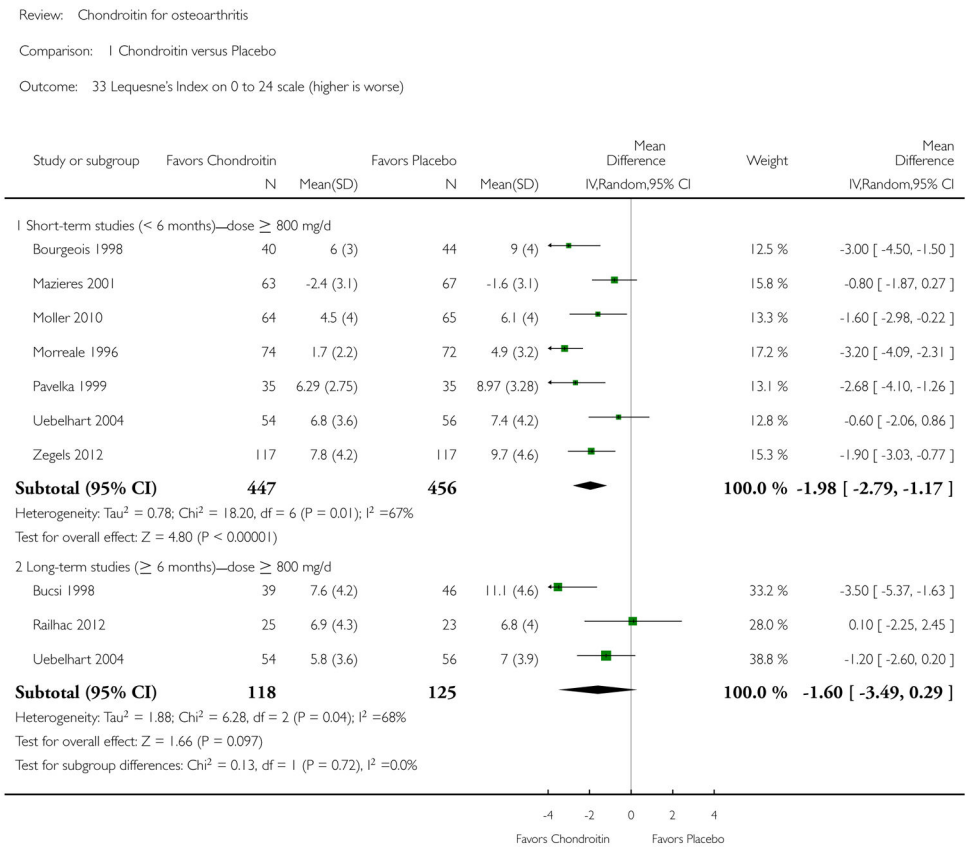
Analysis 1.30.
Comparison 1 Chondroitin versus Placebo, Outcome 30 Change in Bone Marrow Lesion score (medial tibial plateau).



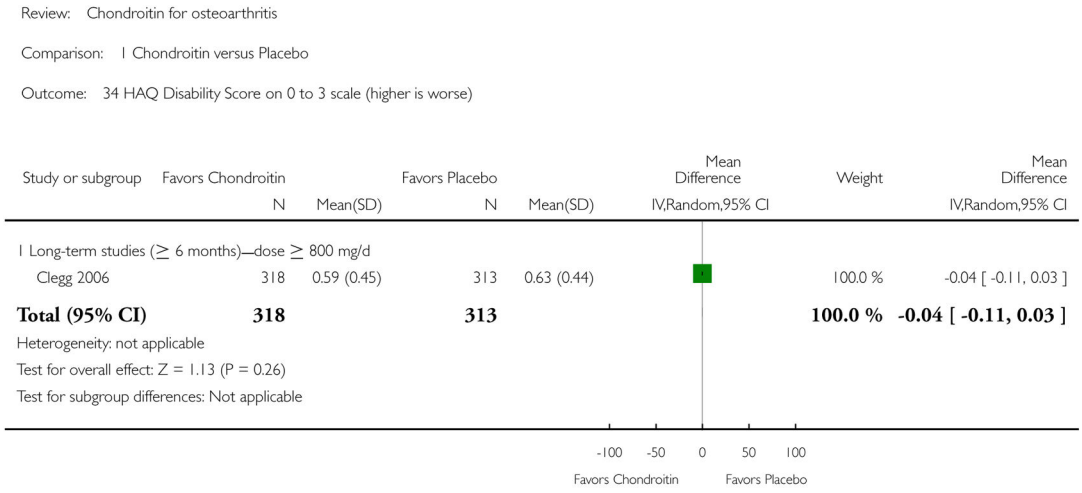
Analysis 1.31.
Comparison 1 Chondroitin versus Placebo, Outcome 31 Change in BoneMarrow Lesion score (trochlea).



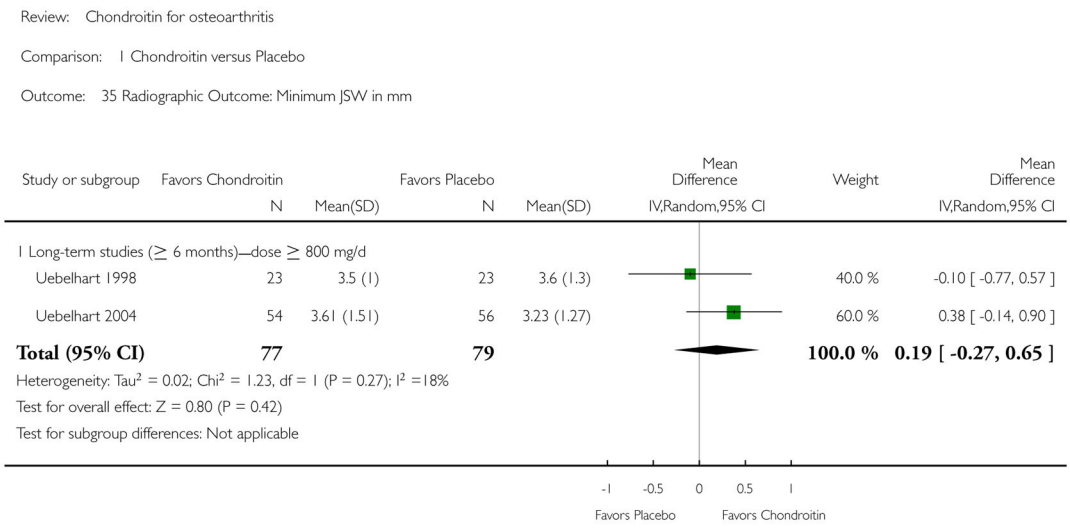
Analysis 1.32.
Comparison 1 Chondroitin versus Placebo, Outcome 32 OMERACT-OARSI Responder.



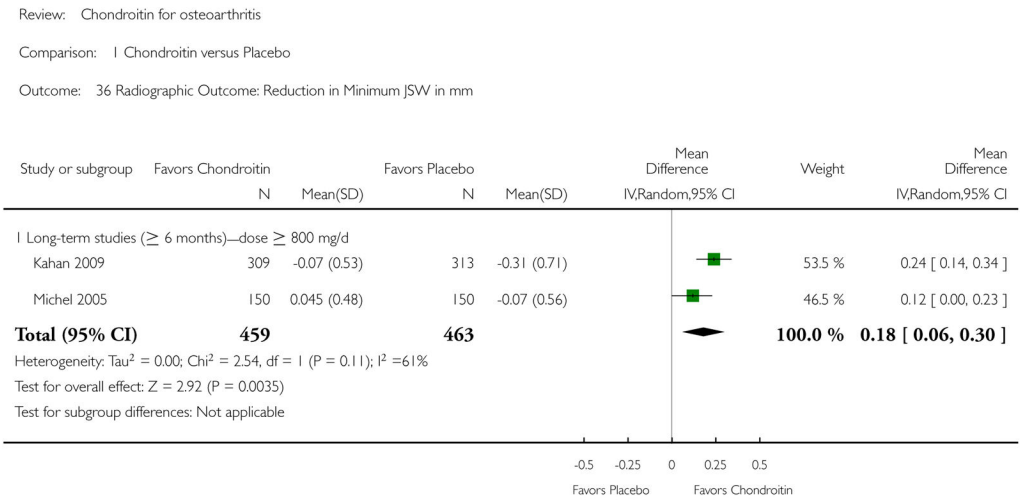
Analysis 1.33.
Comparison 1 Chondroitin versus Placebo, Outcome 33 Lequesne's Index on 0 to 24 scale (higher is worse).



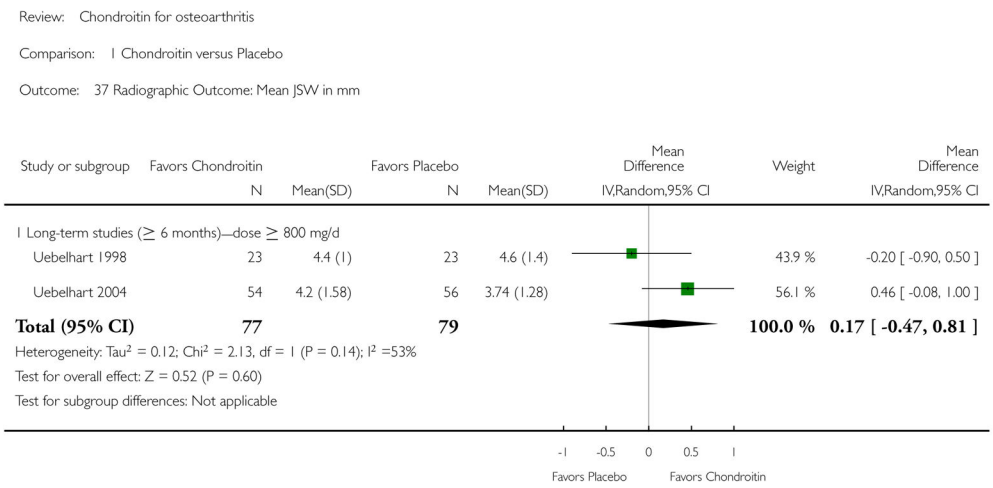
Analysis 1.34.
Comparison 1 Chondroitin versus Placebo, Outcome 34 HAQ Disability Score on 0 to 3 scale (higher is worse).



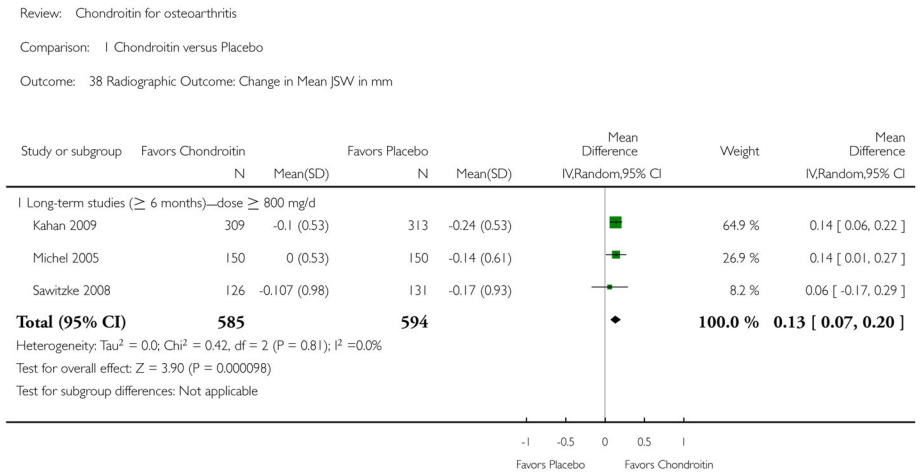
Analysis 1.35.
Comparison 1 Chondroitin versus Placebo, Outcome 35 Radiographic Outcome: Minimum JSW in mm.



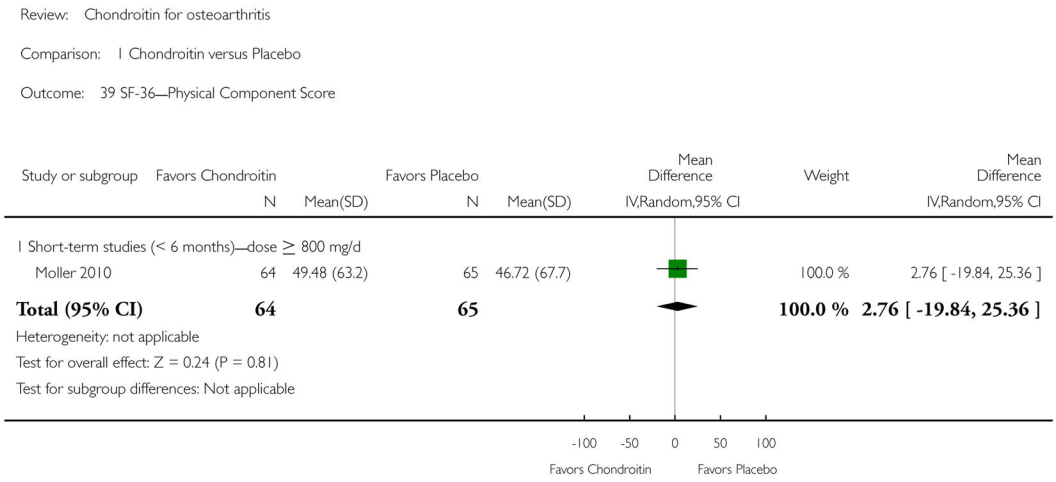
Analysis 1.36.
Comparison 1 Chondroitin versus Placebo, Outcome 36 Radiographic Outcome: Reduction in Minimum JSW in mm.



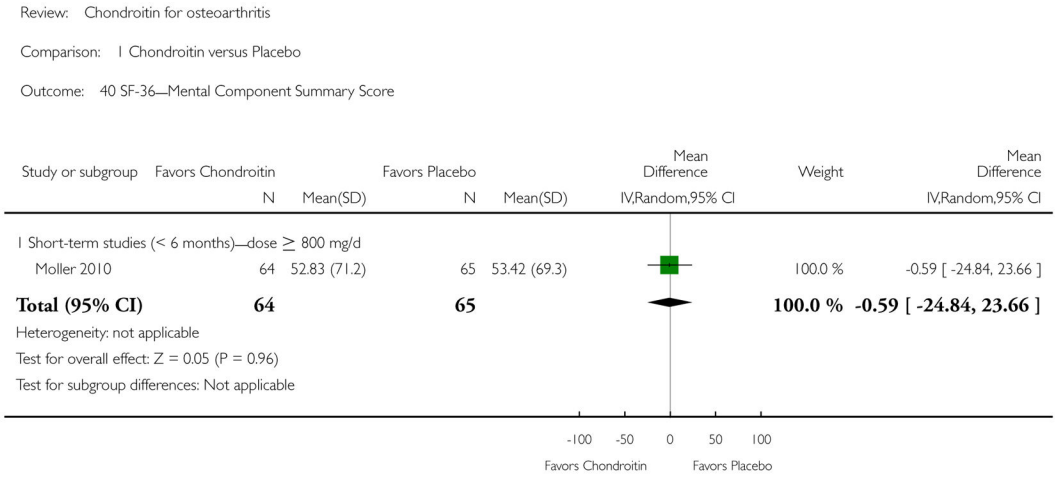
Analysis 1.37.
Comparison 1 Chondroitin versus Placebo, Outcome 37 Radiographic Outcome: Mean JSW in mm.



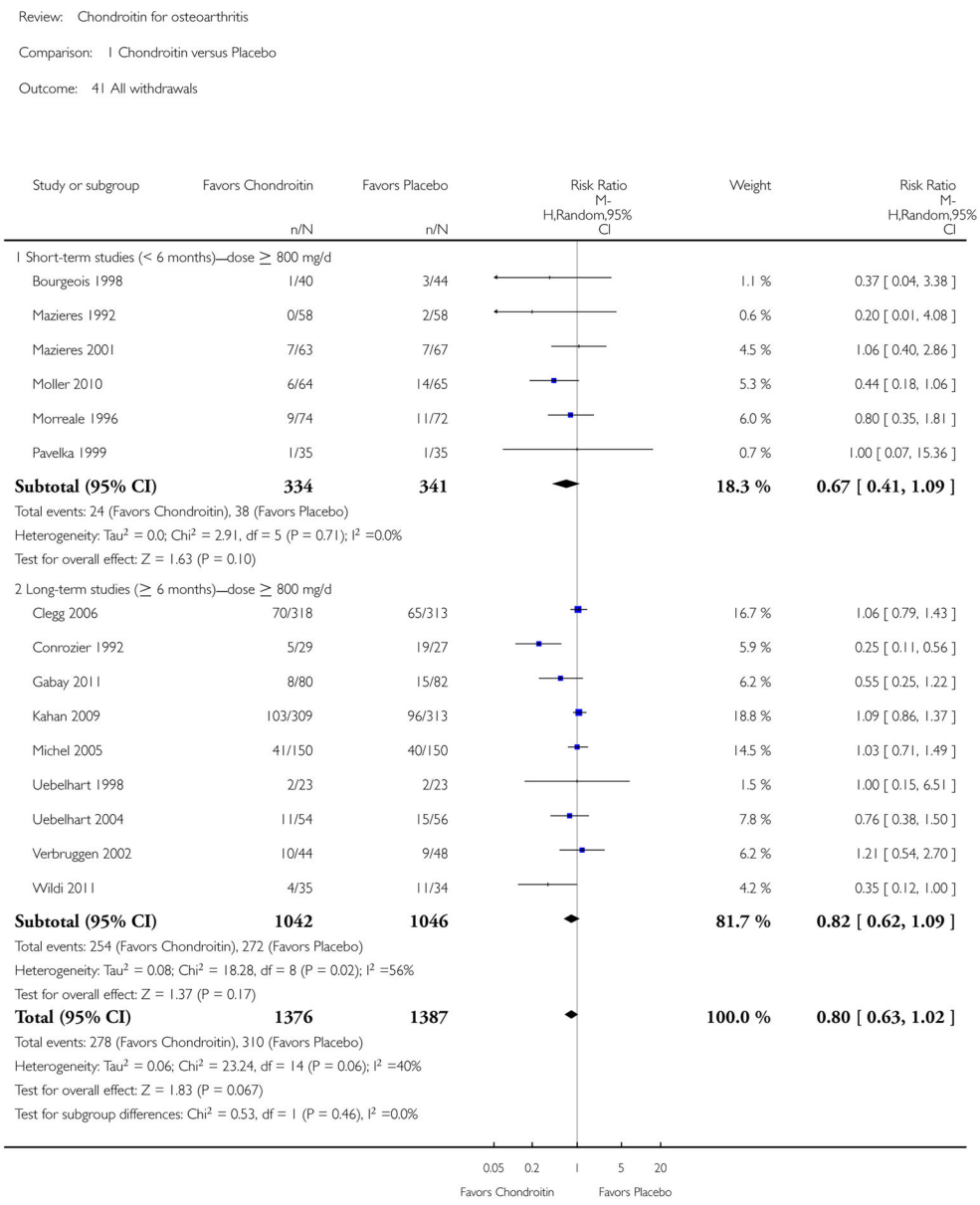
Analysis 1.38.
Comparison 1 Chondroitin versus Placebo, Outcome 38 Radiographic Outcome: Change in Mean JSW in mm.



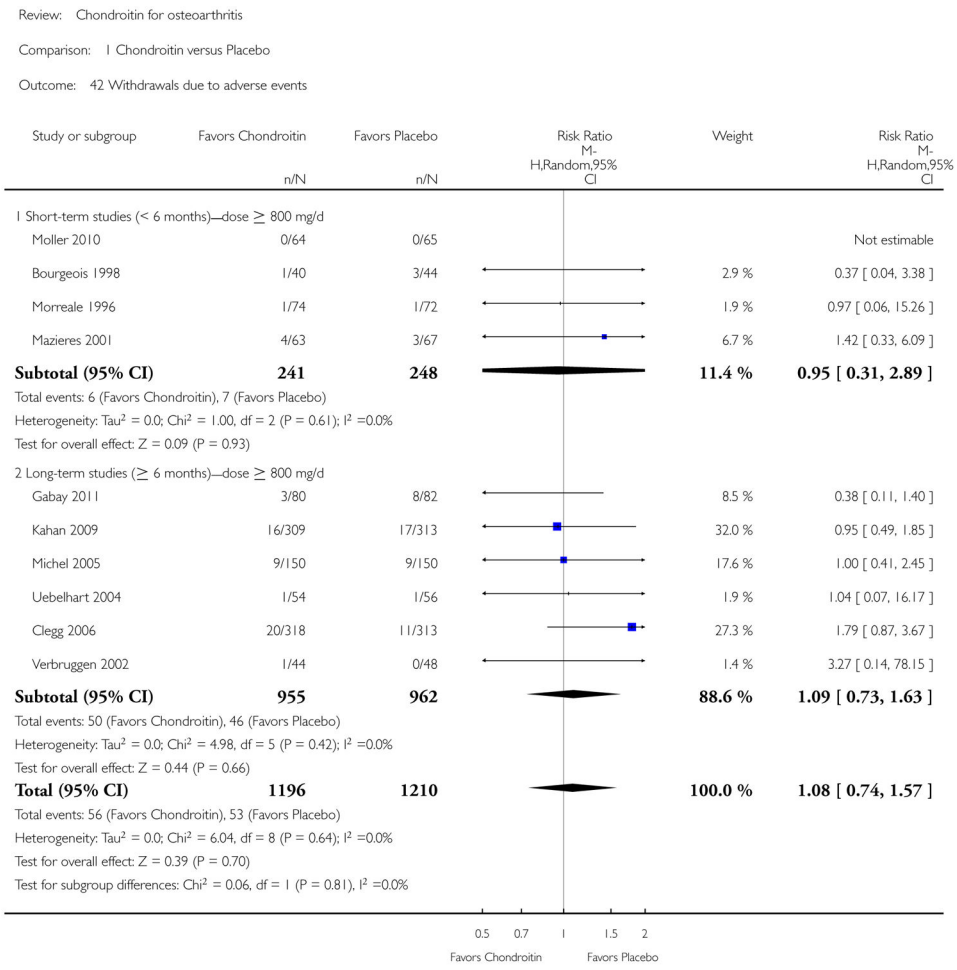
Analysis 1.39.
Comparison 1 Chondroitin versus Placebo, Outcome 39 SF-36-Physical Component Score.



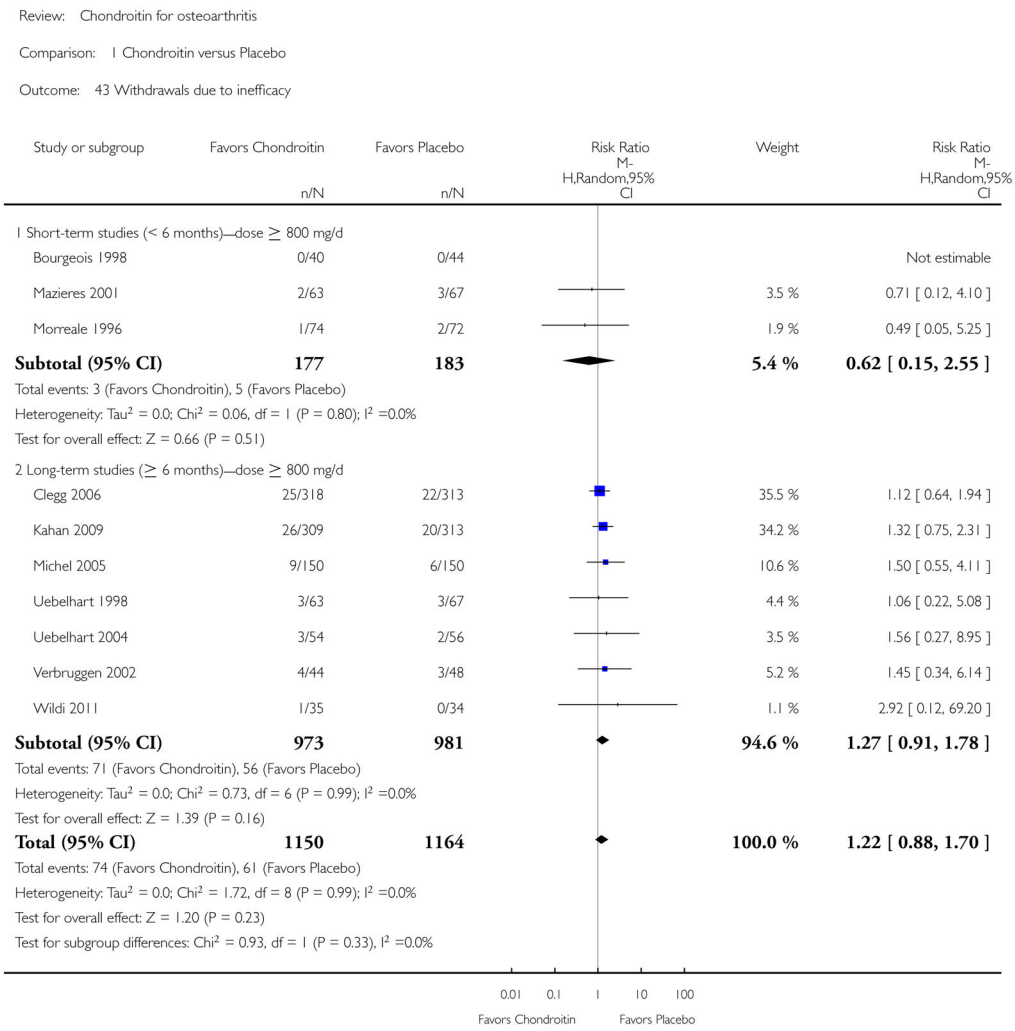
Analysis 1.40.
Comparison 1 Chondroitin versus Placebo, Outcome 40 SF-36-Mental Component Summary Score.



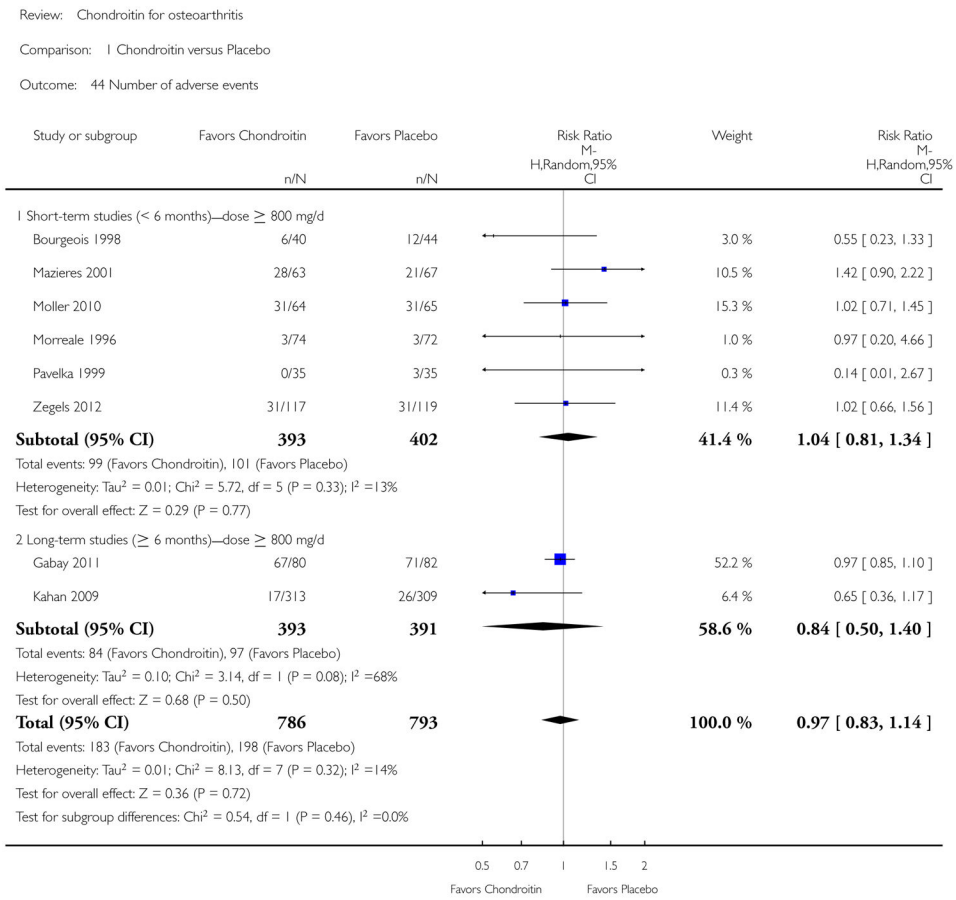
Analysis 1.41.
Comparison 1 Chondroitin versus Placebo, Outcome 41 All withdrawals.



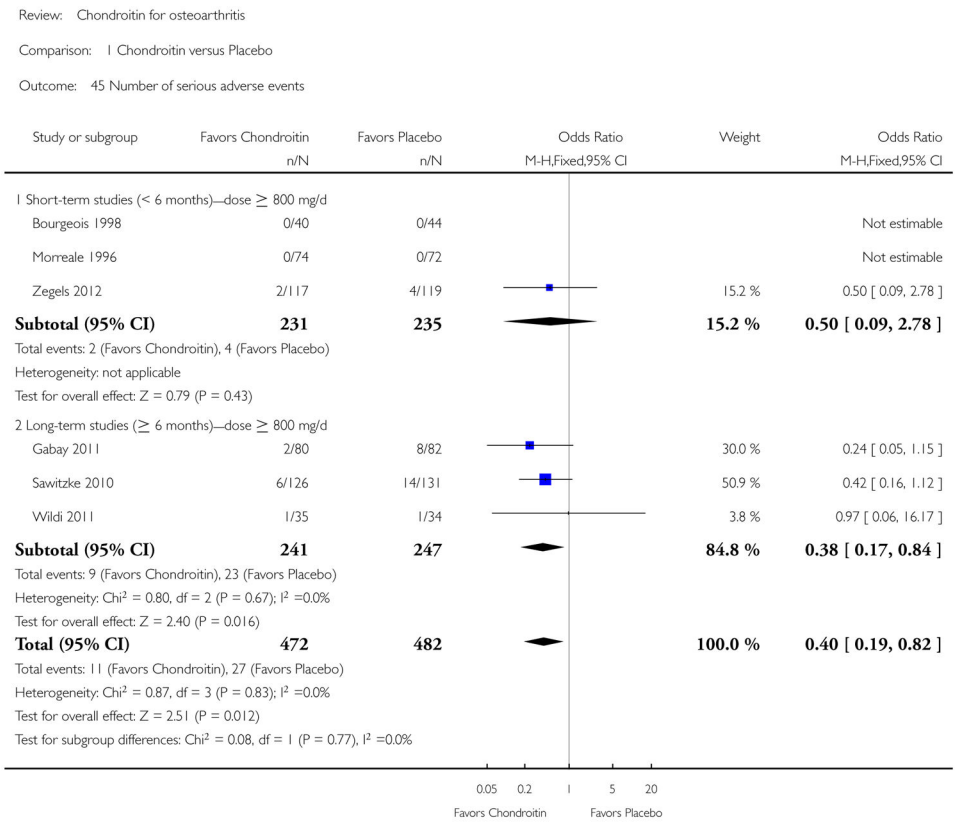
Analysis 1.42.
Comparison 1 Chondroitin versus Placebo, Outcome 42 Withdrawals due to adverse events.



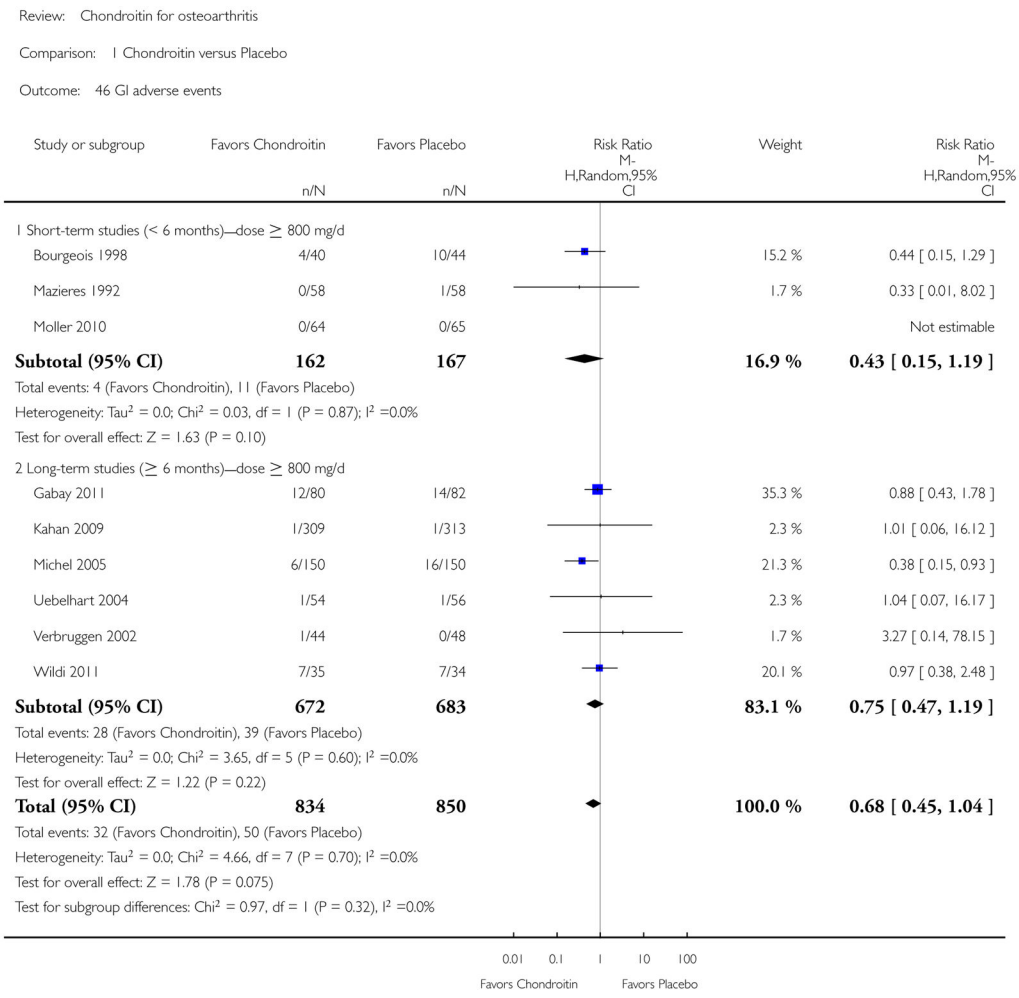
Analysis 1.43.
Comparison 1 Chondroitin versus Placebo, Outcome 43 Withdrawals due to inefficacy.



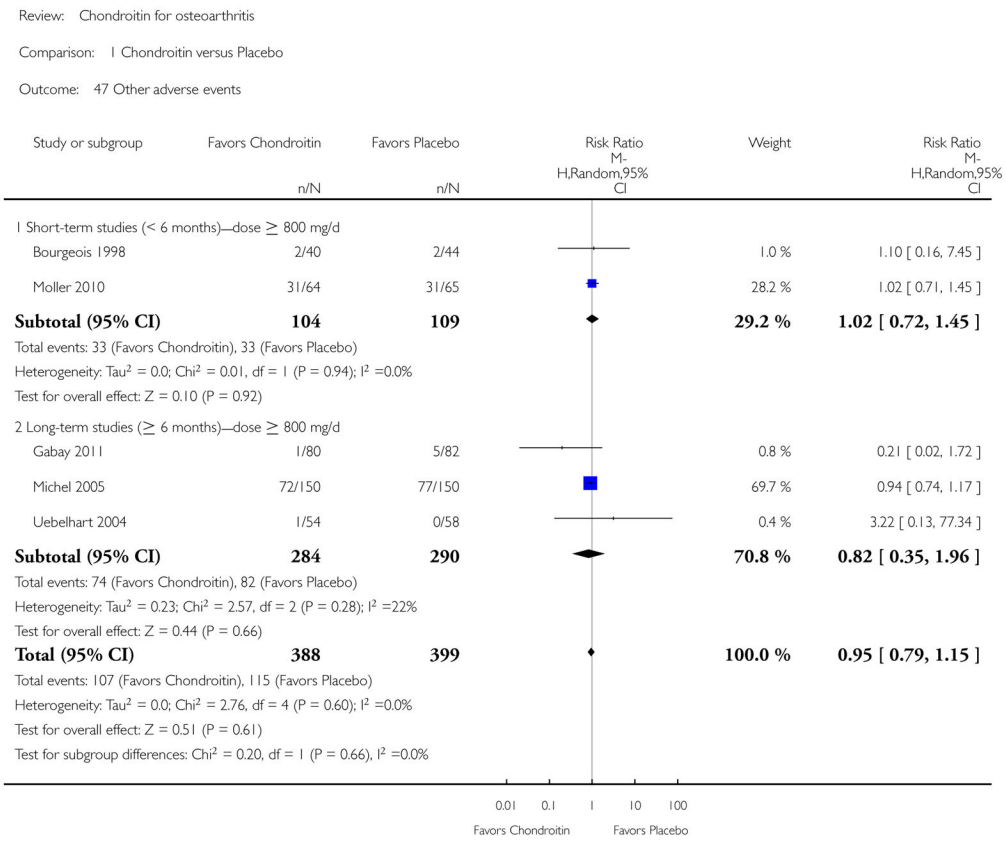
Analysis 1.44.
Comparison 1 Chondroitin versus Placebo, Outcome 44 Number of adverse events.



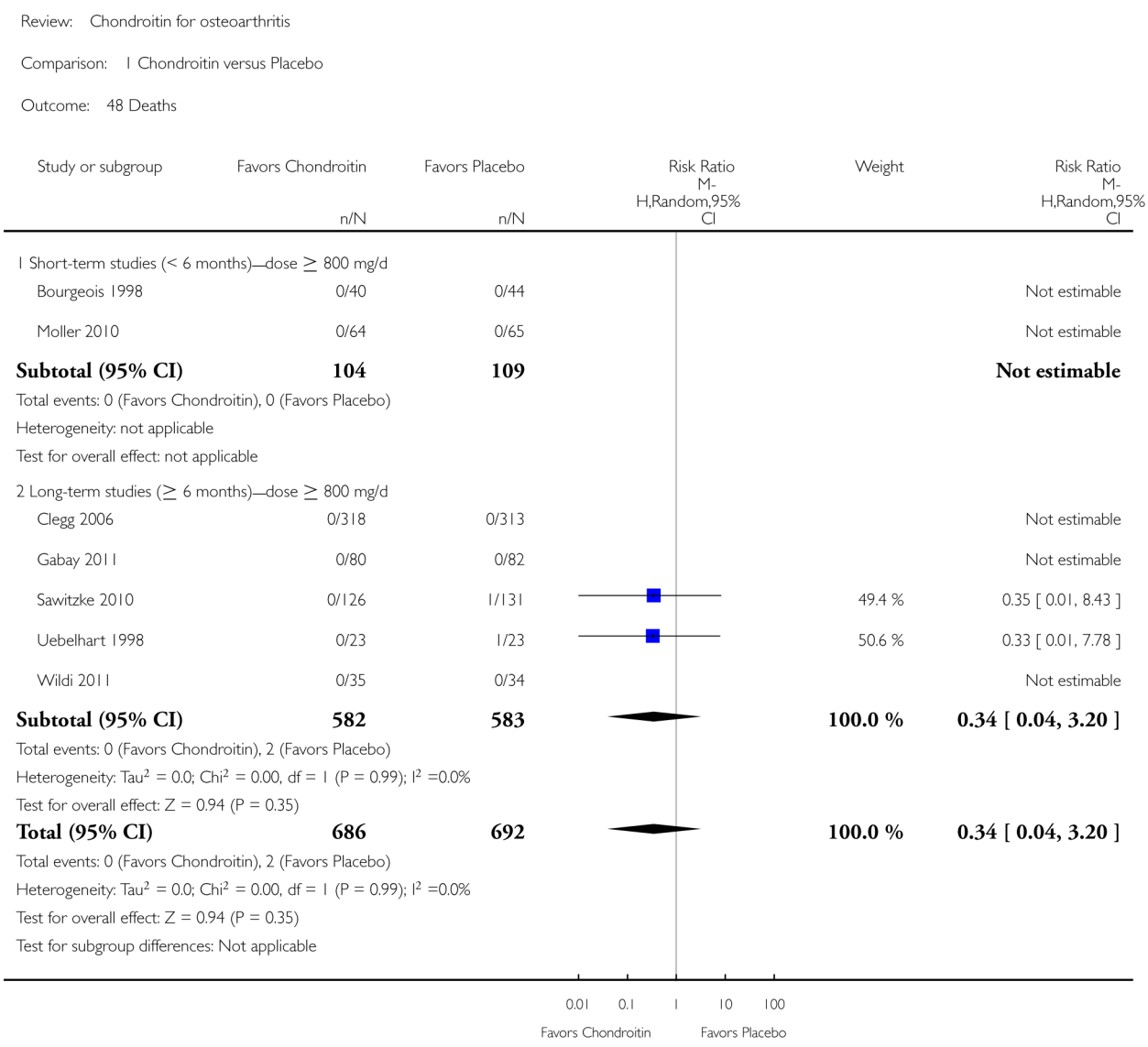
Analysis 1.45.
Comparison 1 Chondroitin versus Placebo, Outcome 45 Number of serious adverse events.



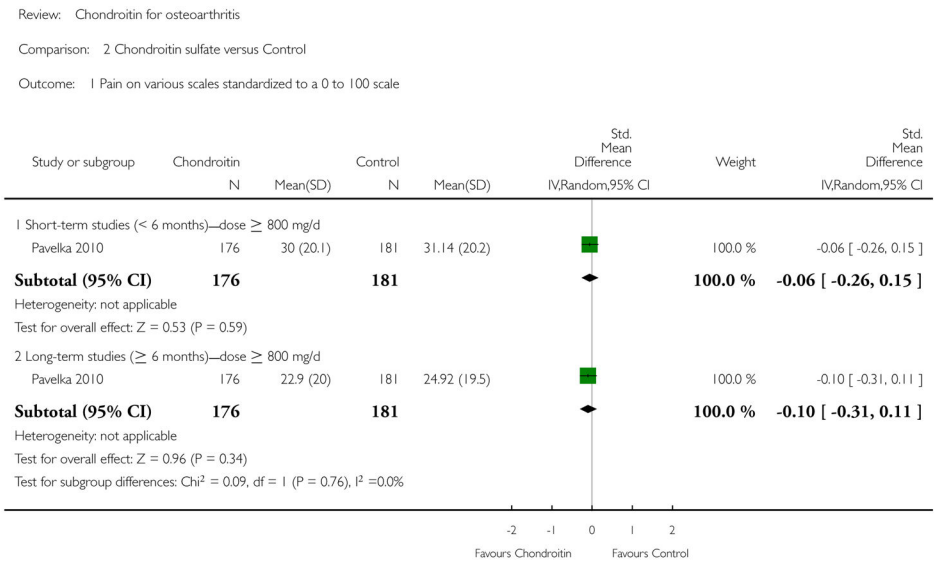
Analysis 1.46.
Comparison 1 Chondroitin versus Placebo, Outcome 46 GI adverse events.



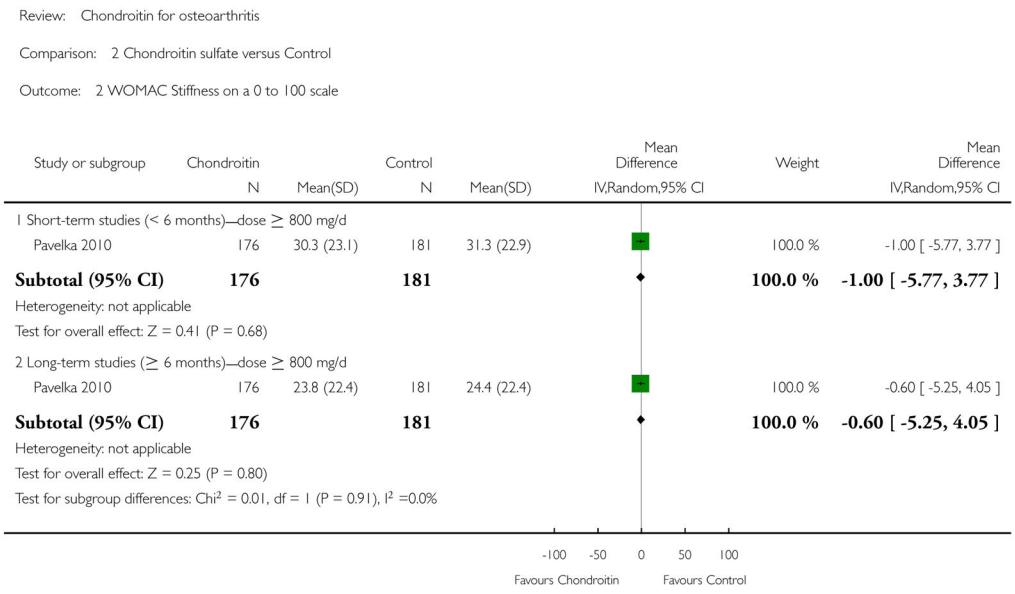
Analysis 1.47.
Comparison 1 Chondroitin versus Placebo, Outcome 47 Other adverse events.



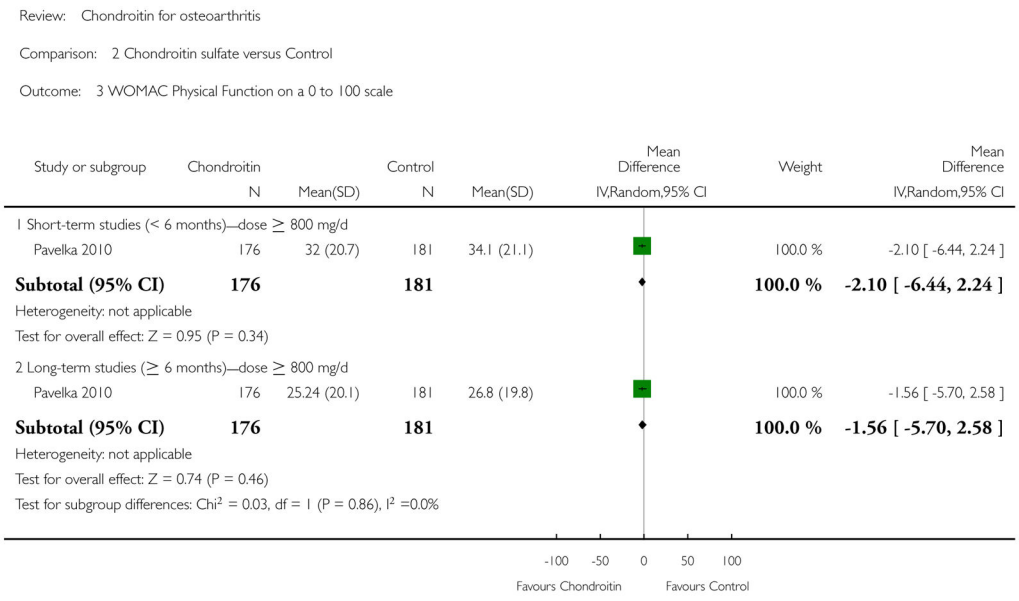
Analysis 1.48.
Comparison 1 Chondroitin versus Placebo, Outcome 48 Deaths.



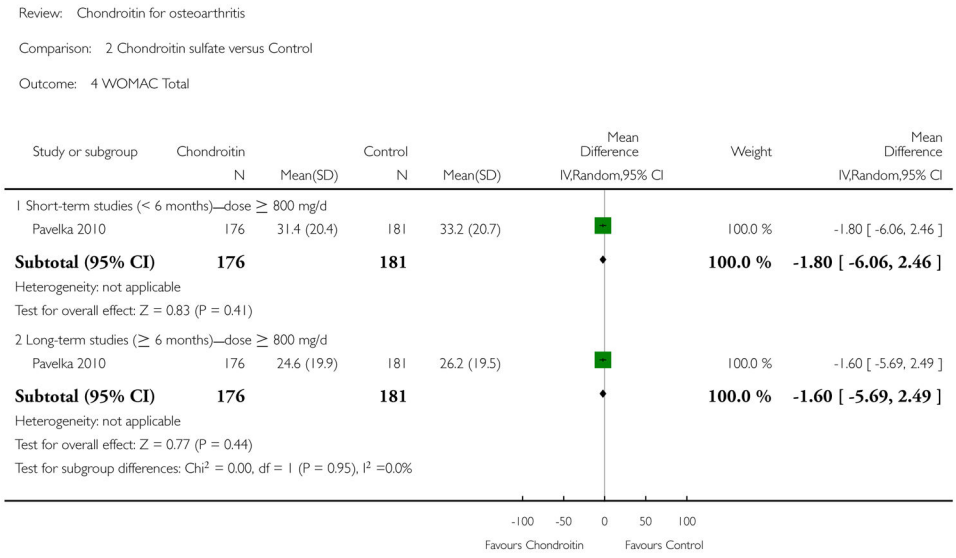
Analysis 2.1.
Comparison 2 Chondroitin sulfate versus Control, Outcome 1 Pain on various scales standardized to a 0 to 100 scale.



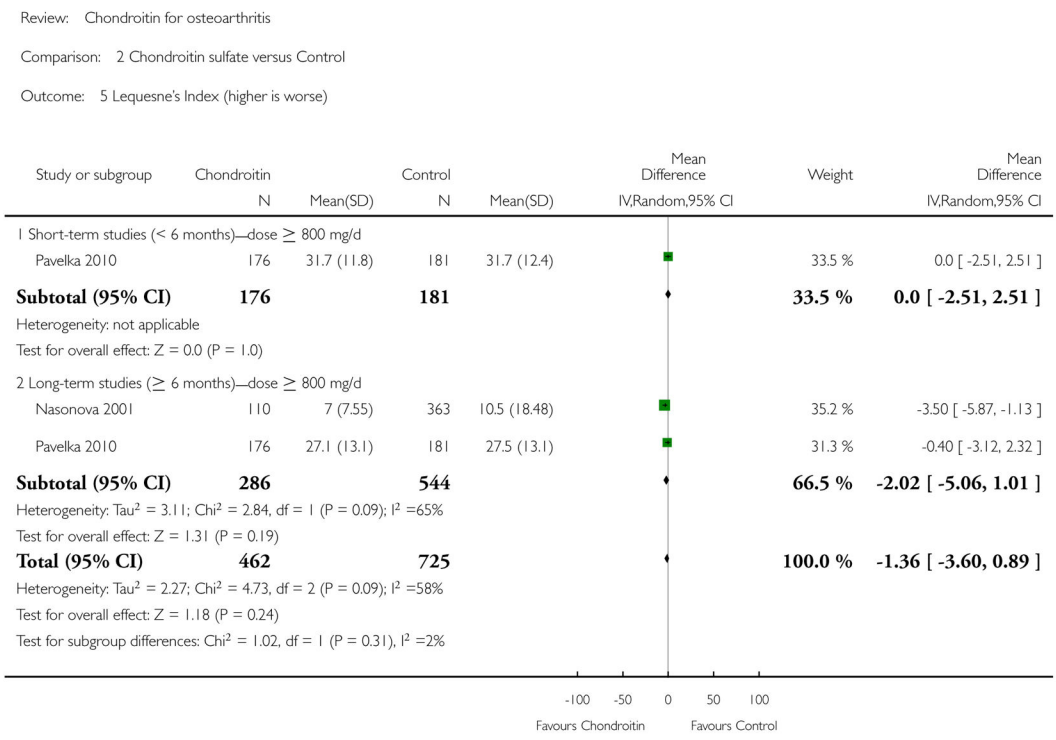
Analysis 2.2.
Comparison 2 Chondroitin sulfate versus Control, Outcome 2 WOMAC Stiffness on a 0 to 100 scale.



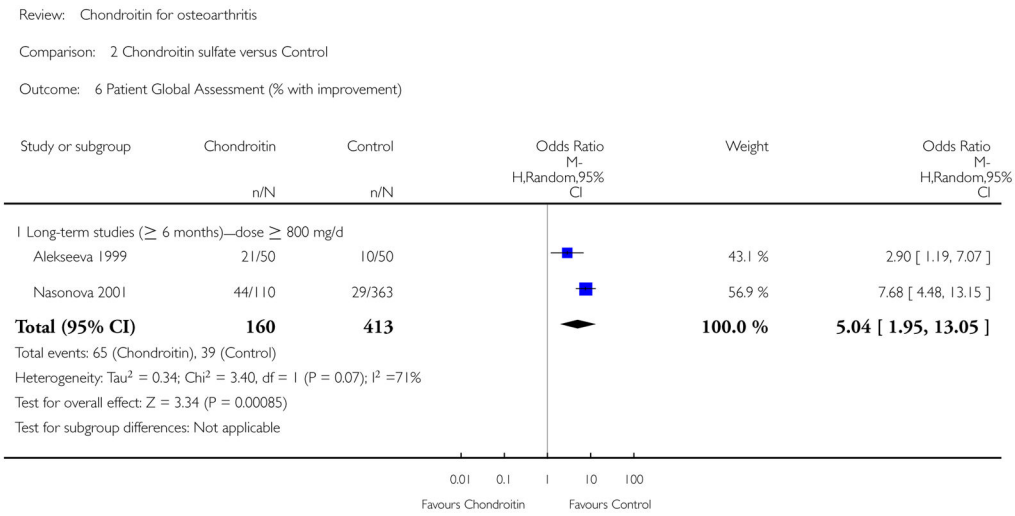
Analysis 2.3.
Comparison 2 Chondroitin sulfate versus Control, Outcome 3 WOMAC Physical Function on a 0 to 100 scale.



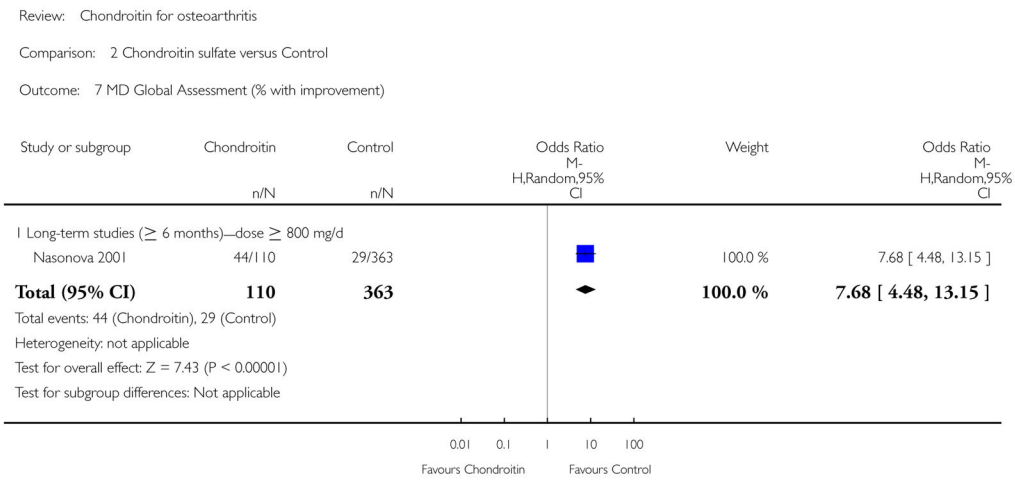
Analysis 2.4.
Comparison 2 Chondroitin sulfate versus Control, Outcome 4 WOMAC Total.



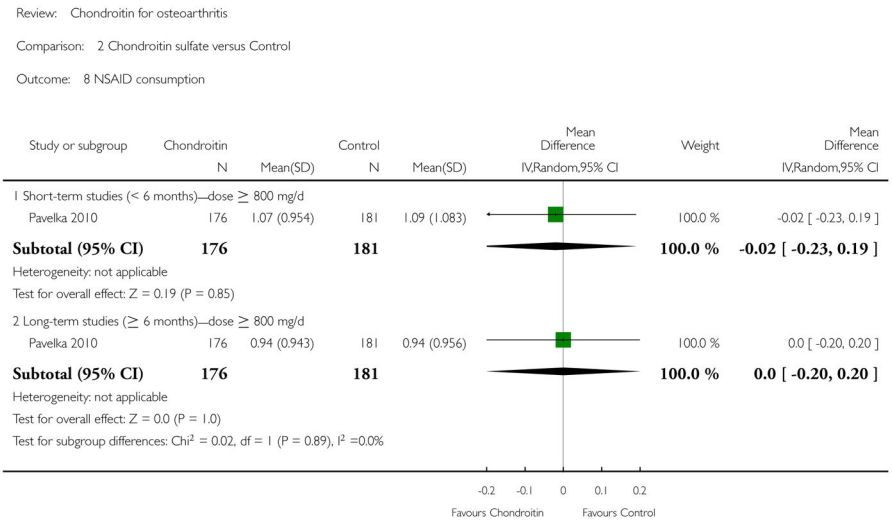
Analysis 2.5.
Comparison 2 Chondroitin sulfate versus Control, Outcome 5 Lequesne's Index (higher is worse).



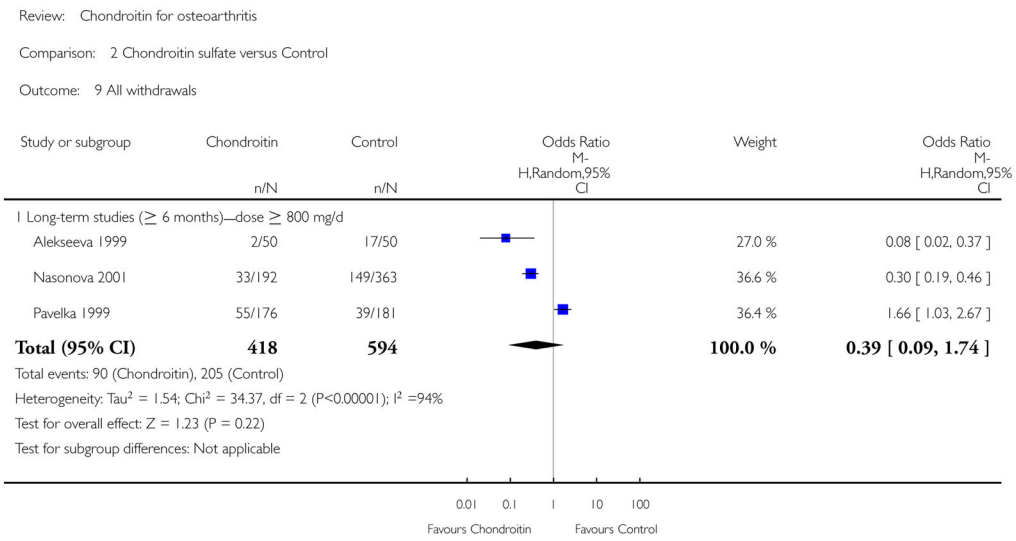
Analysis 2.6.
Comparison 2 Chondroitin sulfate versus Control, Outcome 6 Patient Global Assessment (% with improvement).



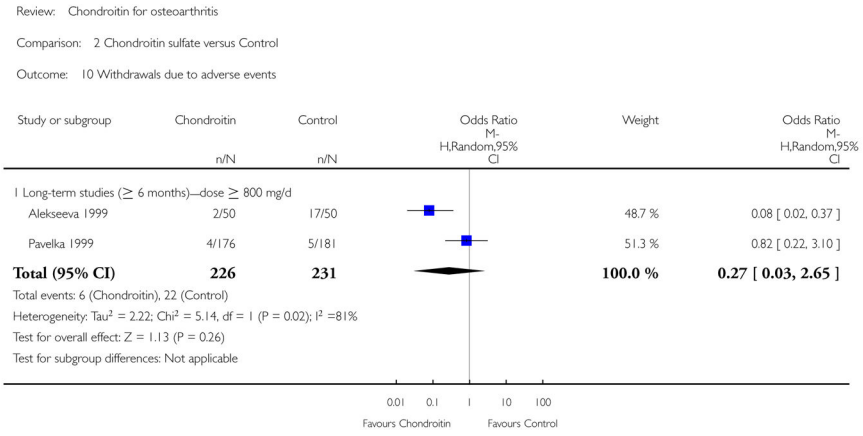
Analysis 2.7.
Comparison 2 Chondroitin sulfate versus Control, Outcome 7 MD Global Assessment (% with improvement).



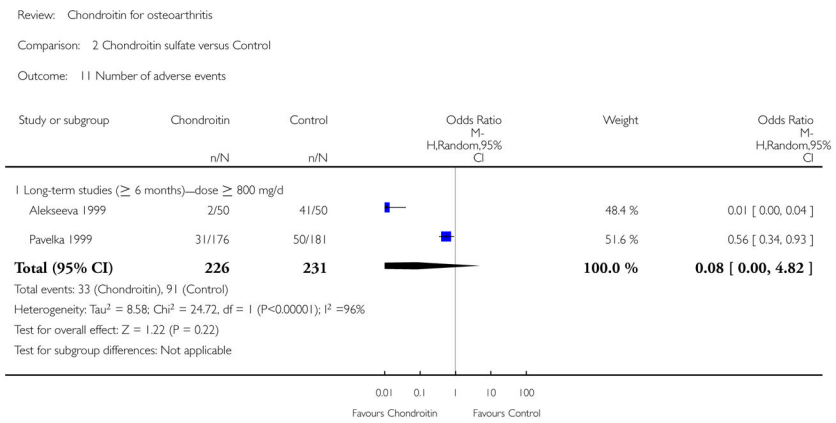
Analysis 2.8.
Comparison 2 Chondroitin sulfate versus Control, Outcome 8 NSAID consumption.



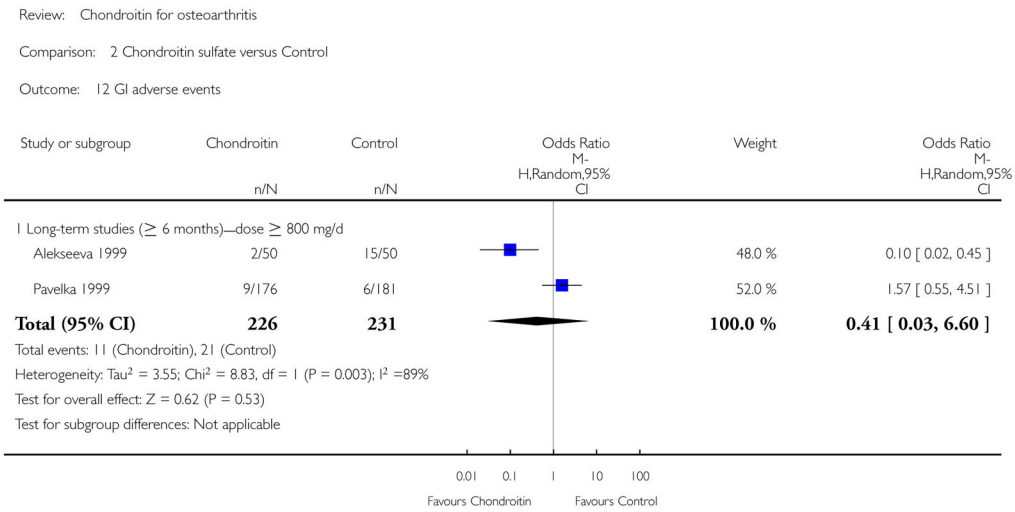
Analysis 2.9.
Comparison 2 Chondroitin sulfate versus Control, Outcome 9 All withdrawals.



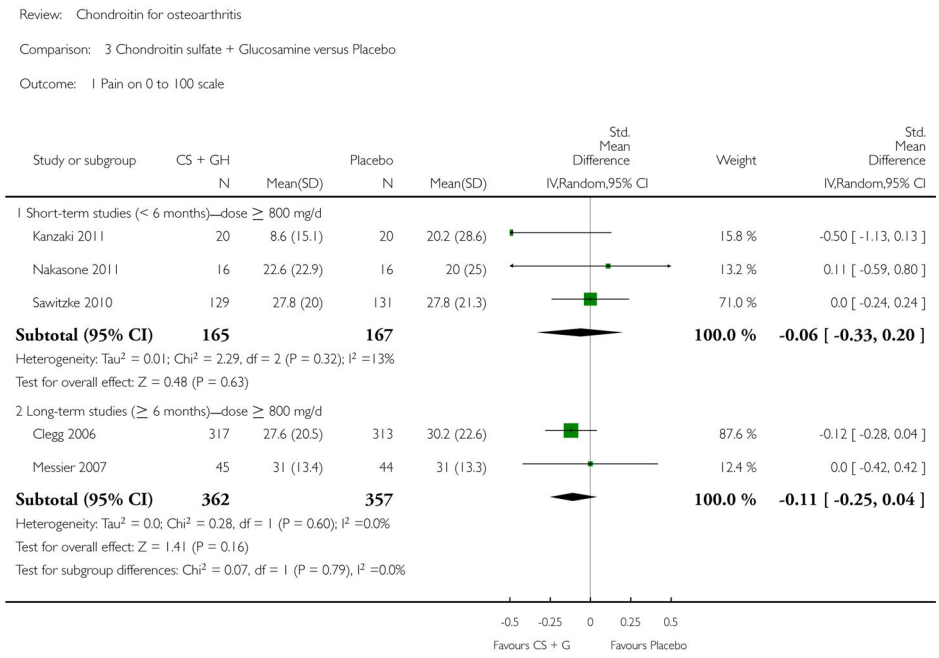
Analysis 2.10.
Comparison 2 Chondroitin sulfate versus Control, Outcome 10 Withdrawals due to adverse events.



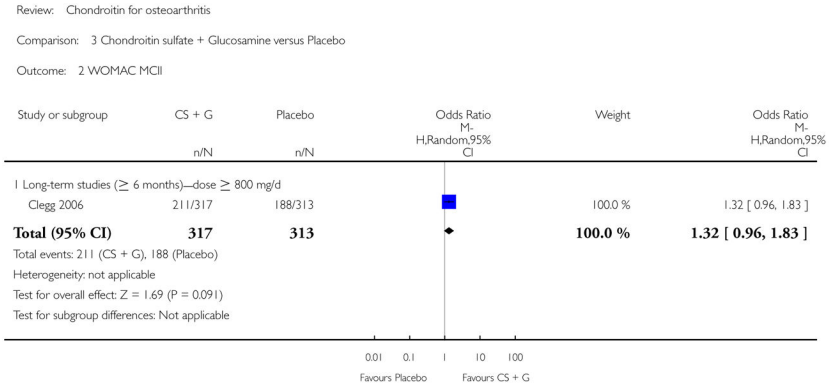
Analysis 2.11.
Comparison 2 Chondroitin sulfate versus Control, Outcome 11 Number of adverse events.



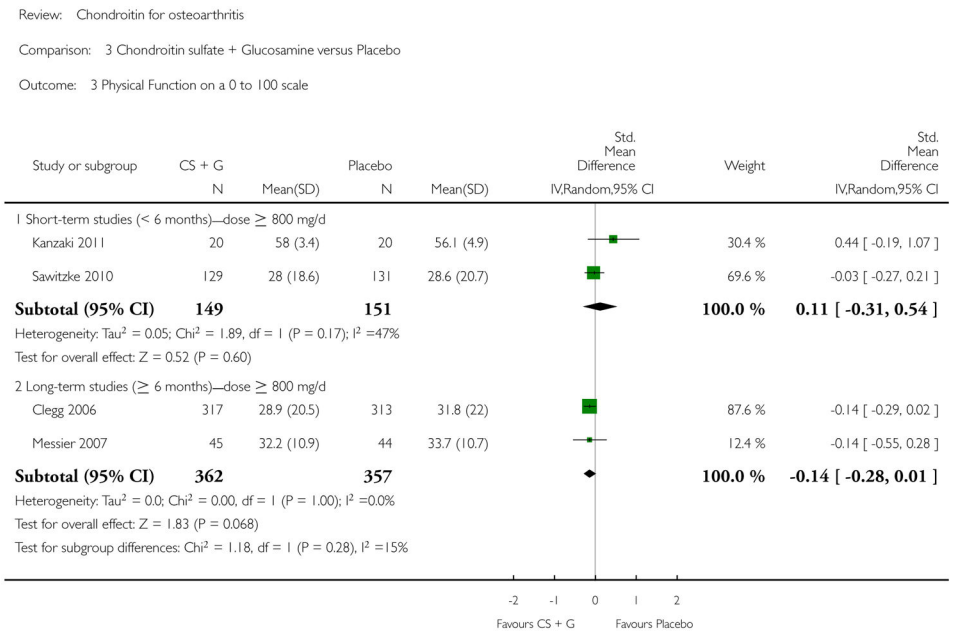
Analysis 2.12.
Comparison 2 Chondroitin sulfate versus Control, Outcome 12 GI adverse events.



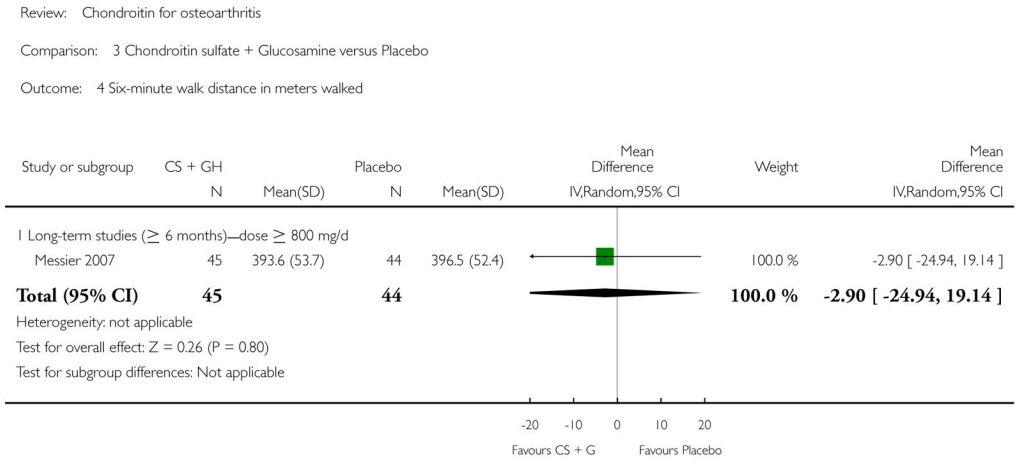
Analysis 3.1.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on 0 to 100 scale.



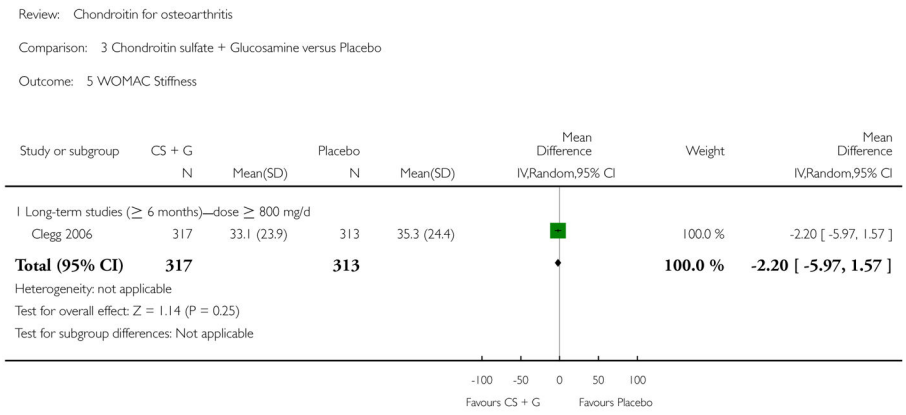
Analysis 3.2.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 WOMAC MCII.



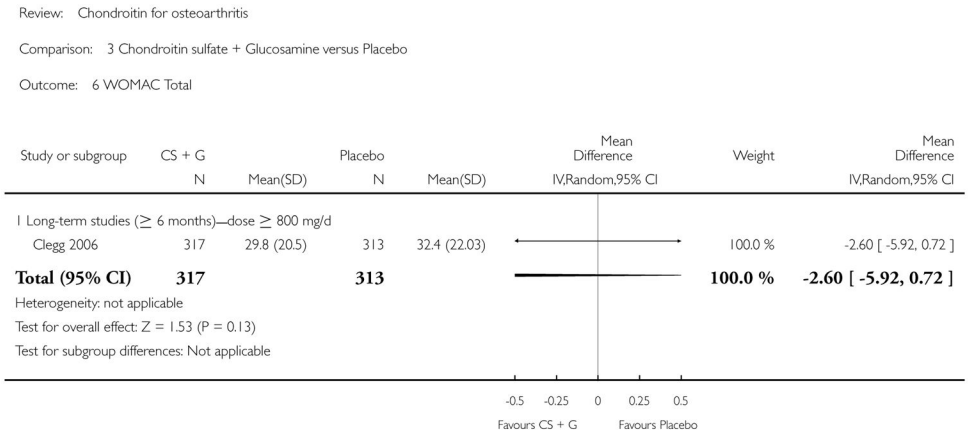
Analysis 3.3.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



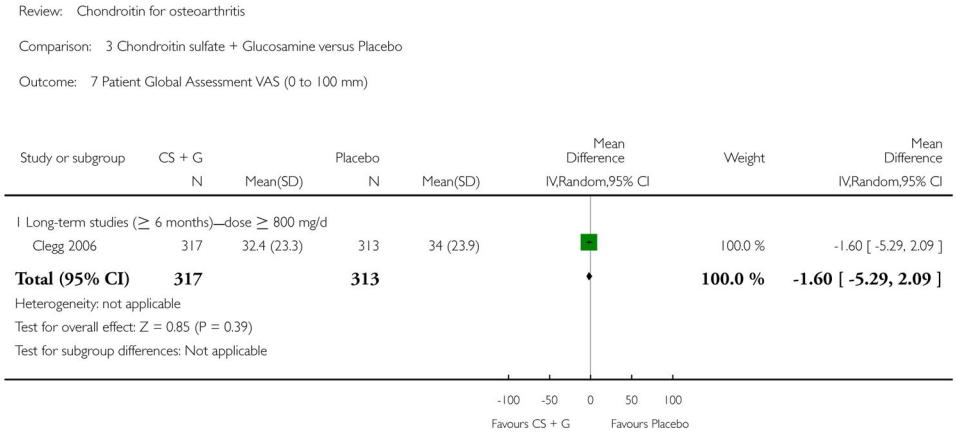
Analysis 3.4.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 4 Six-minute walk distance in meters walked.



Analysis 3.5.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 5 WOMAC Stiffness.

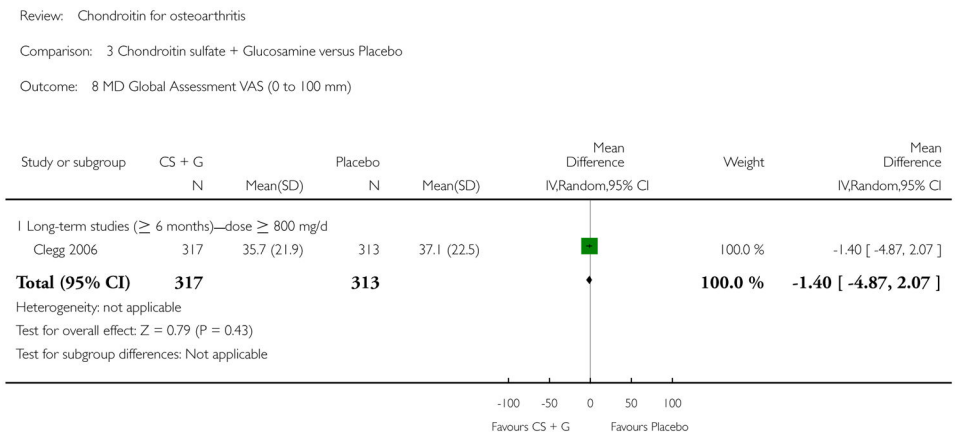


Analysis 3.6.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 6 WOMAC Total.



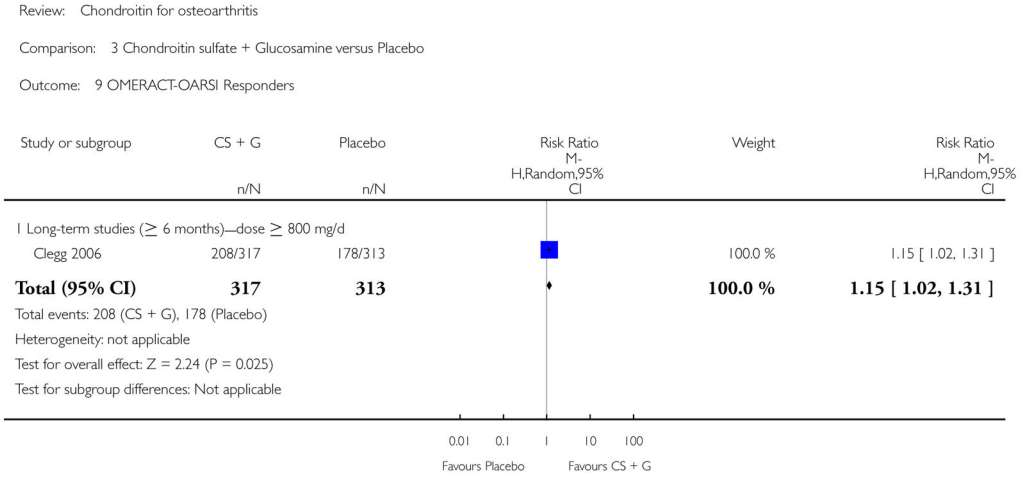
Analysis 3.7.

Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 7 Patient Global Assessment VAS (0 to 100 mm).



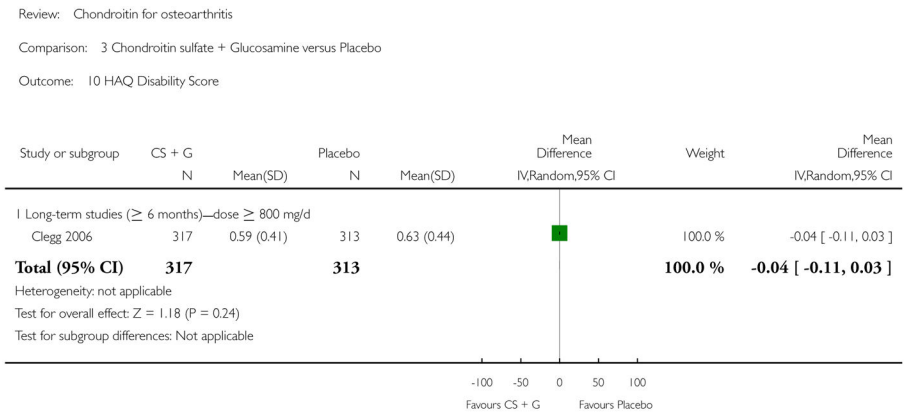
Analysis 3.8.

Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 8 MD Global Assessment VAS (0 to 100 mm).

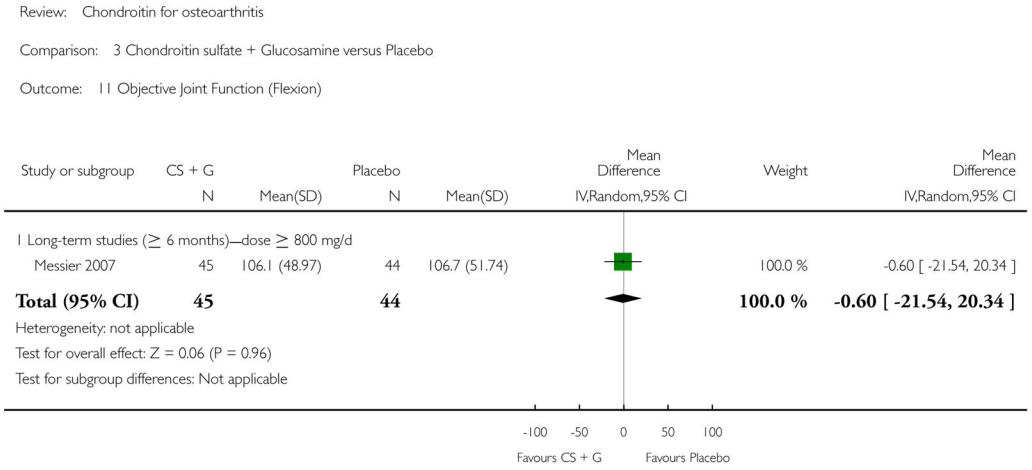


Analysis 3.9.

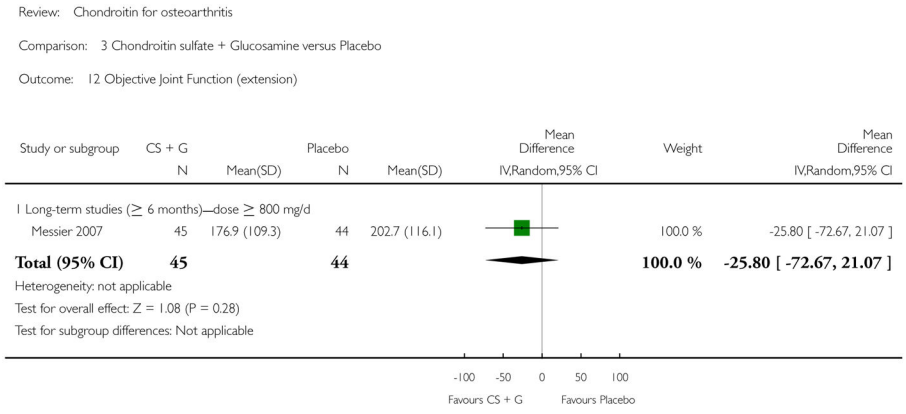
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 9 OMERACT-OARSI Responders.



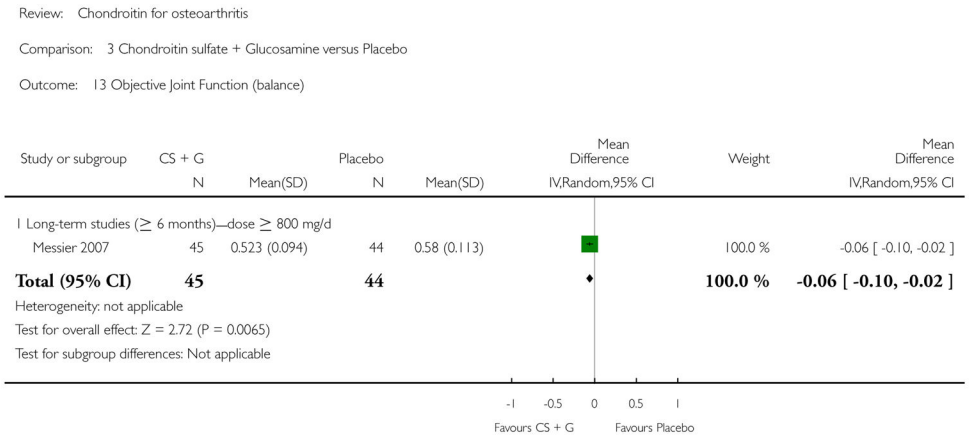
Analysis 3.10.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 10 HAQ Disability Score.



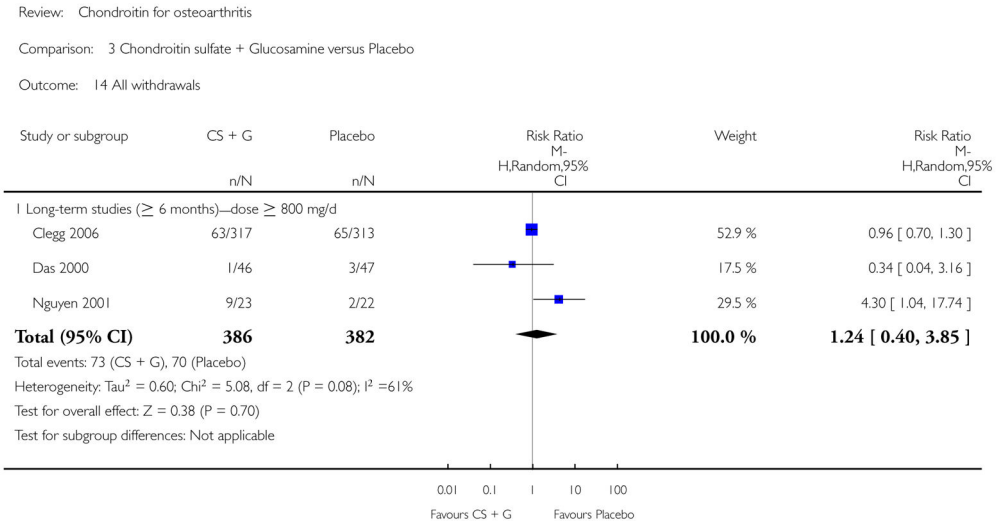
Analysis 3.11.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 11 Objective Joint Function (Flexion).



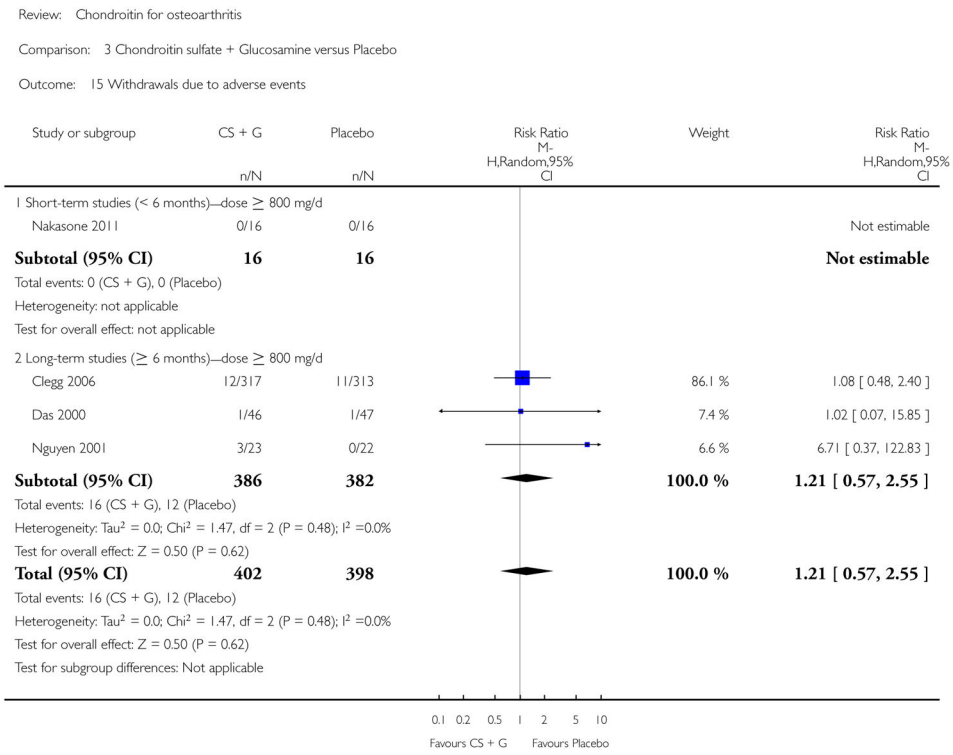
Analysis 3.12.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 12 Objective Joint Function (extension).



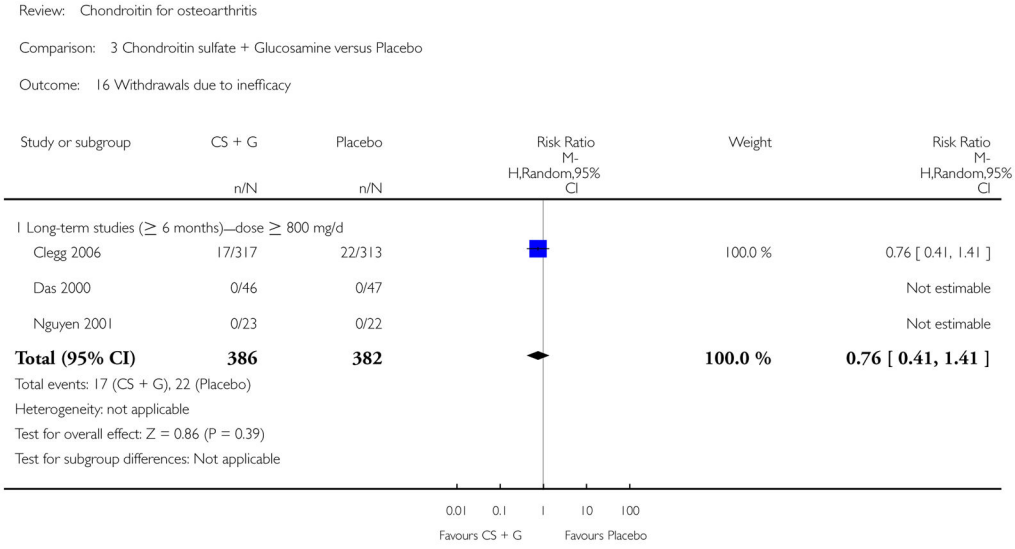
Analysis 3.13.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 13 Objective Joint Function (balance).



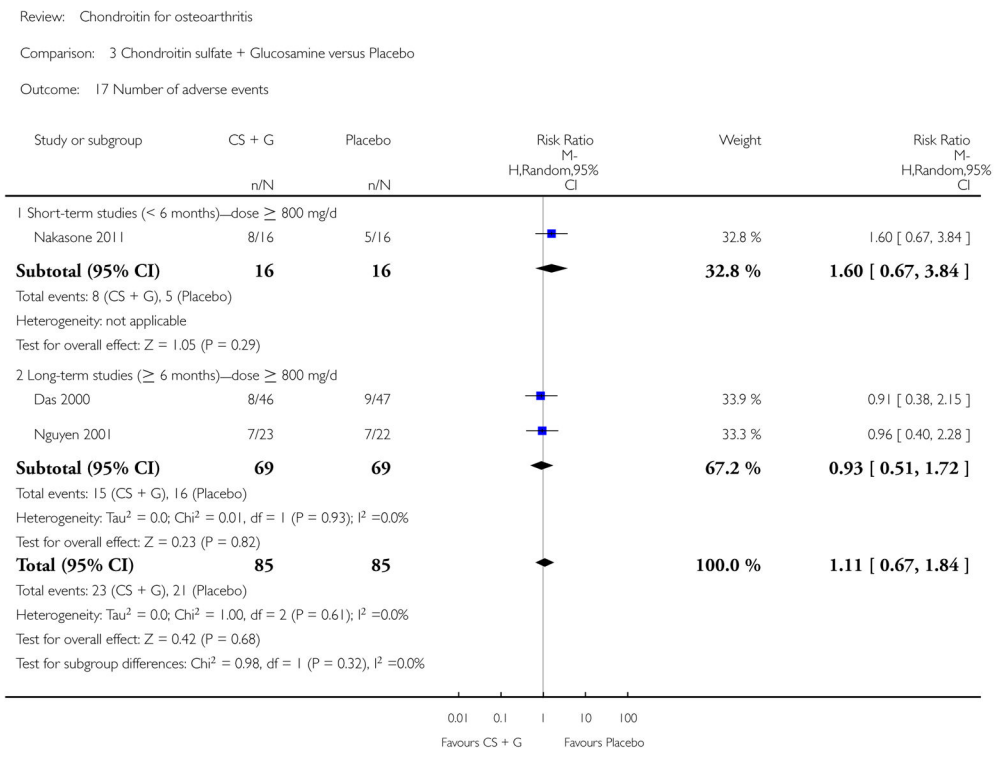
Analysis 3.14.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 14 All withdrawals.



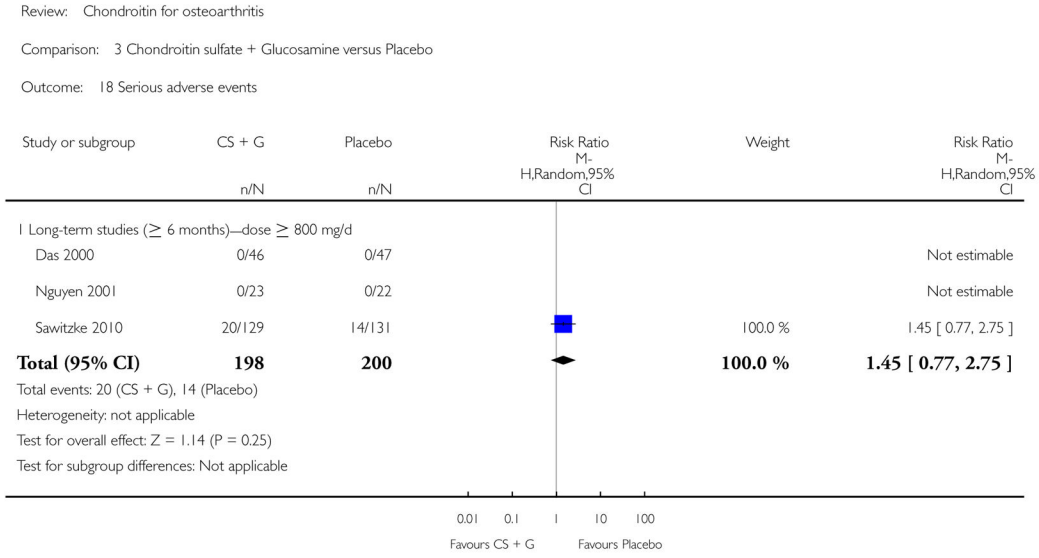
Analysis 3.15.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 15 Withdrawals due to adverse events.



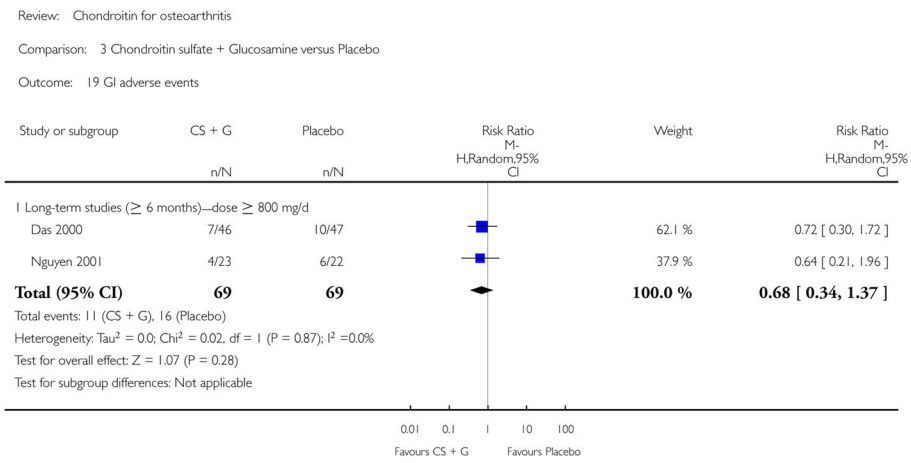
Analysis 3.16.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 16 Withdrawals due to inefficacy.



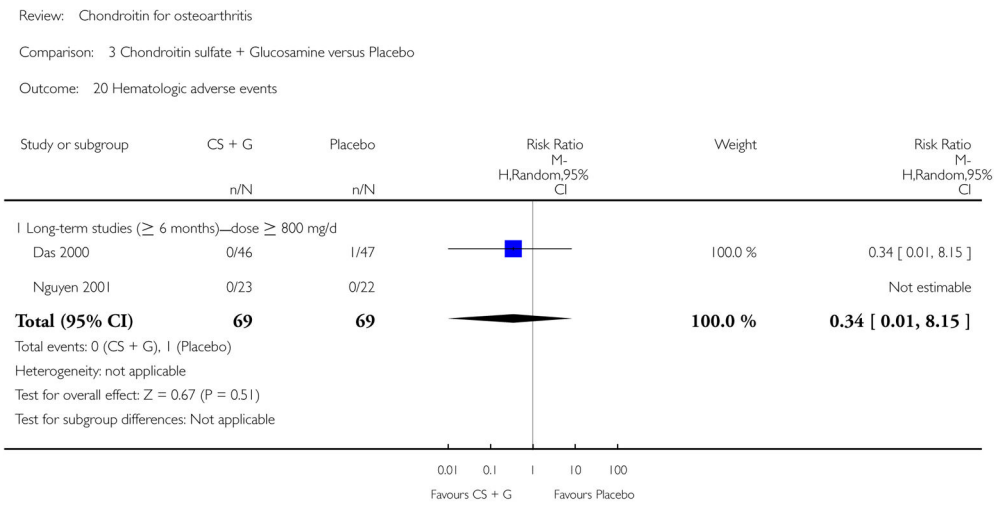
Analysis 3.17.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 17 Number of adverse events.



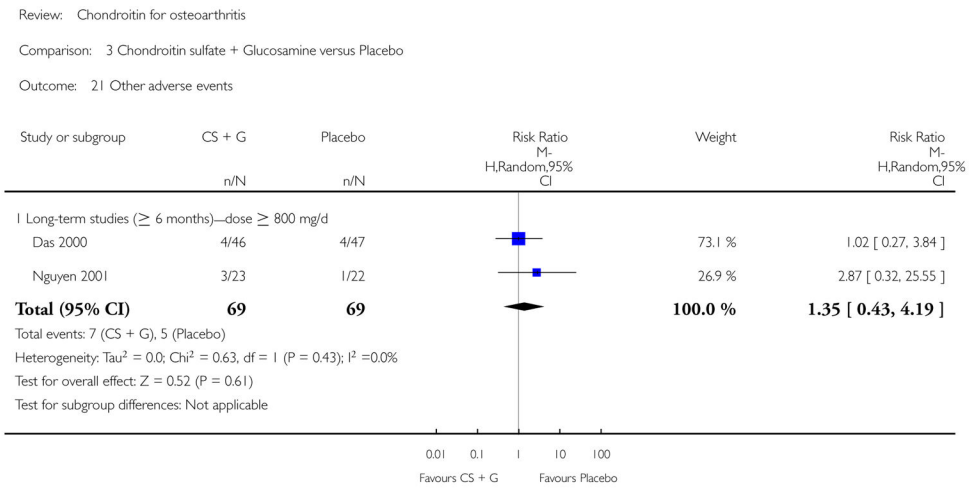
Analysis 3.18.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 18 Serious adverse events.



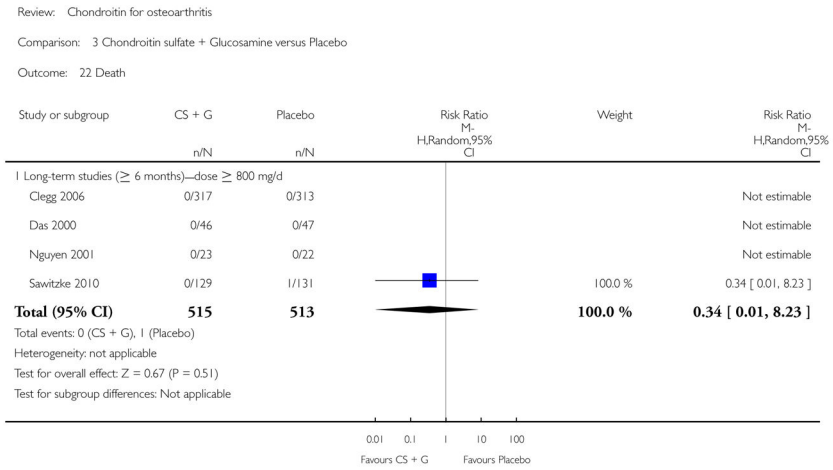
Analysis 3.19.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 19 GI adverse events.



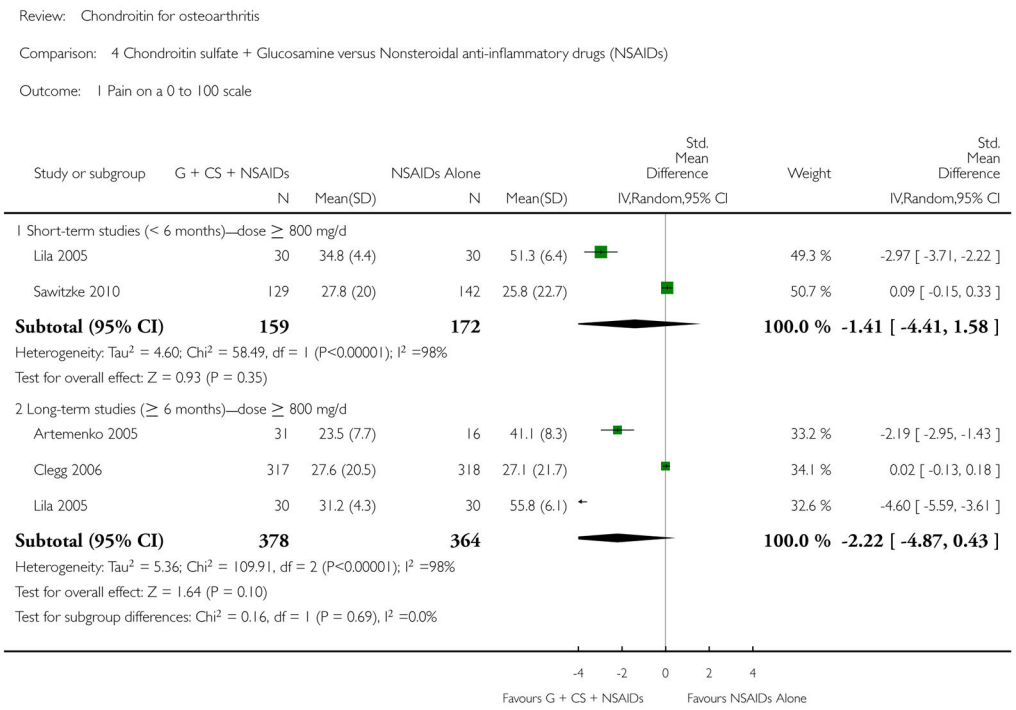
Analysis 3.20.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 20 Hematologic adverse events.



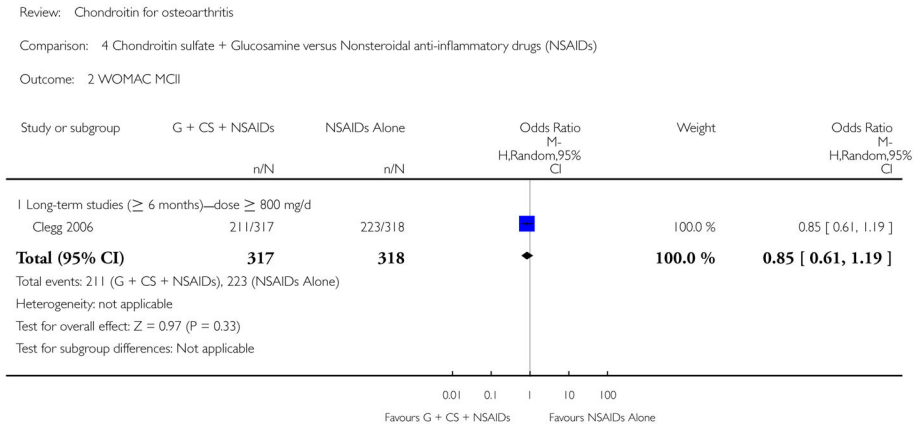
Analysis 3.21.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 21 Other adverse events. 195



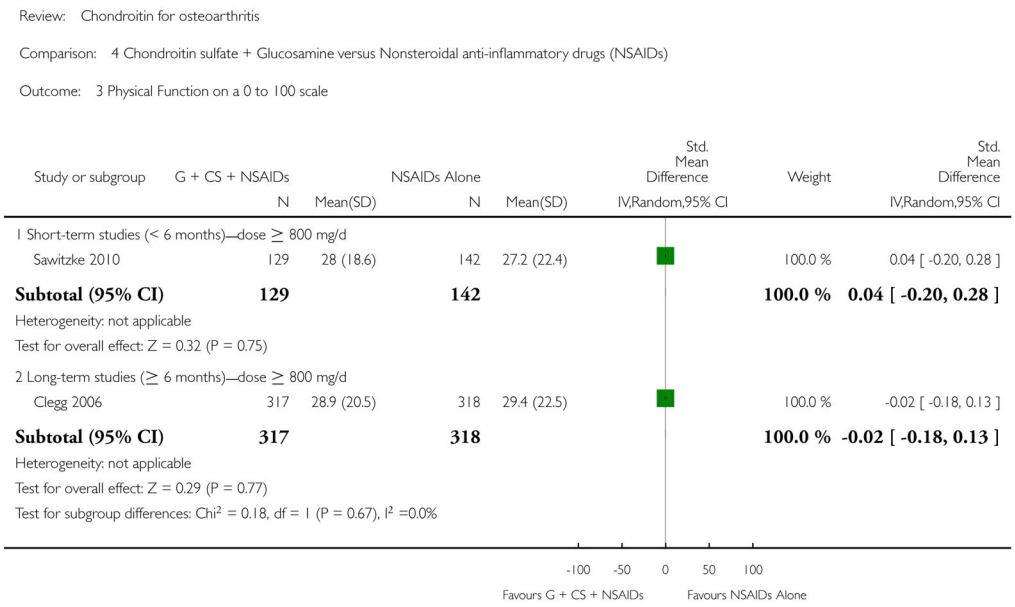
Analysis 3.22.
Comparison 3 Chondroitin sulfate + Glucosamine versus Placebo, Outcome 22 Death.



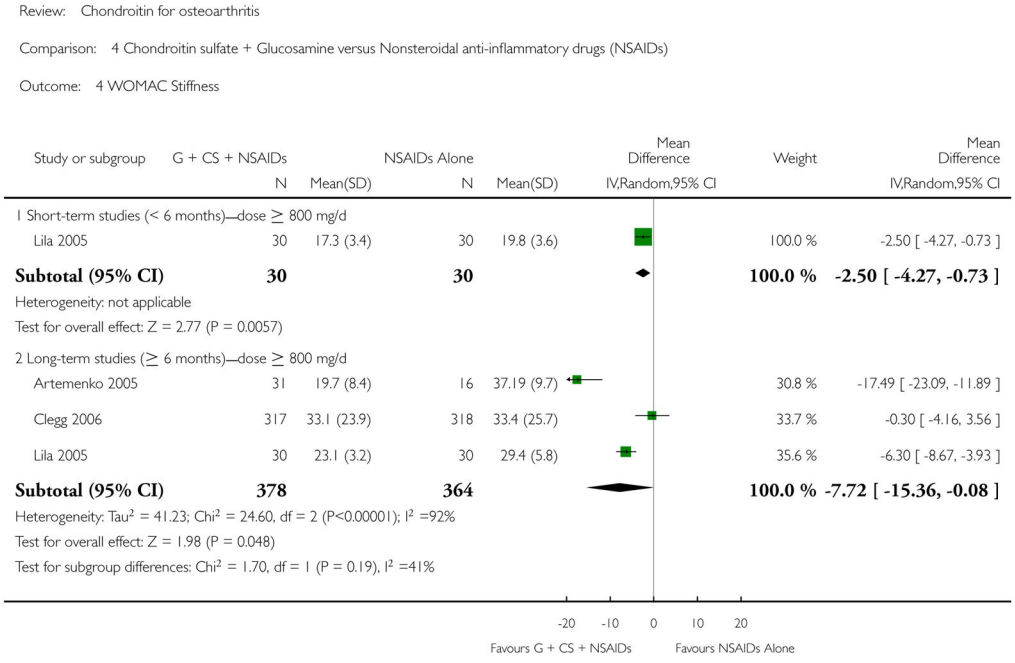
Analysis 4.1.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Pain on a 0 to 100 scale.



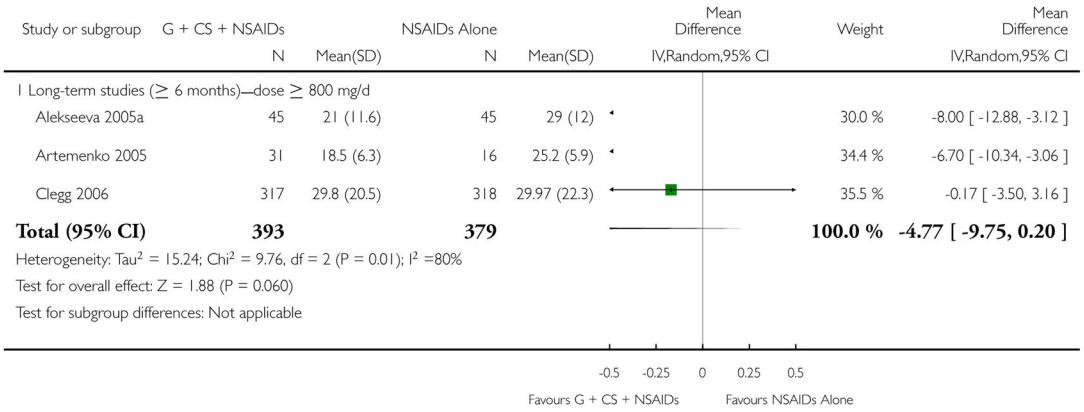
Analysis 4.2.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 2 WOMAC MCII.



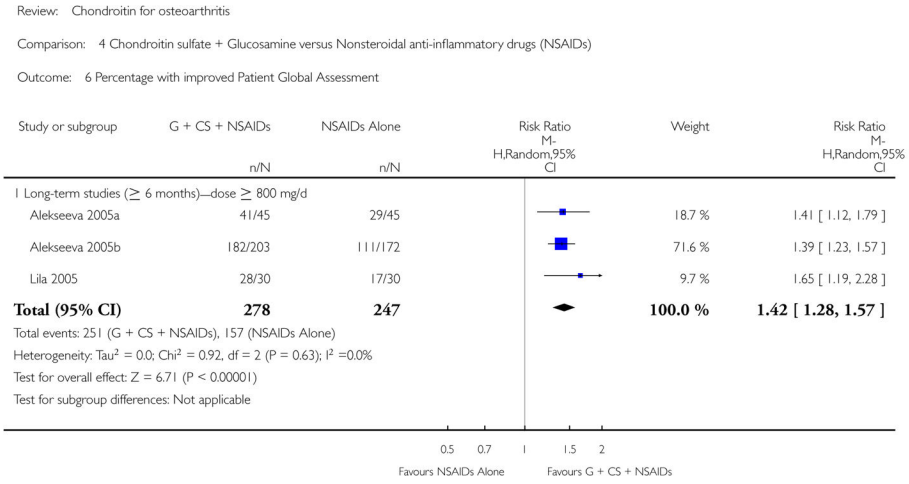
Analysis 4.3.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Physical Function on a 0 to 100 scale.



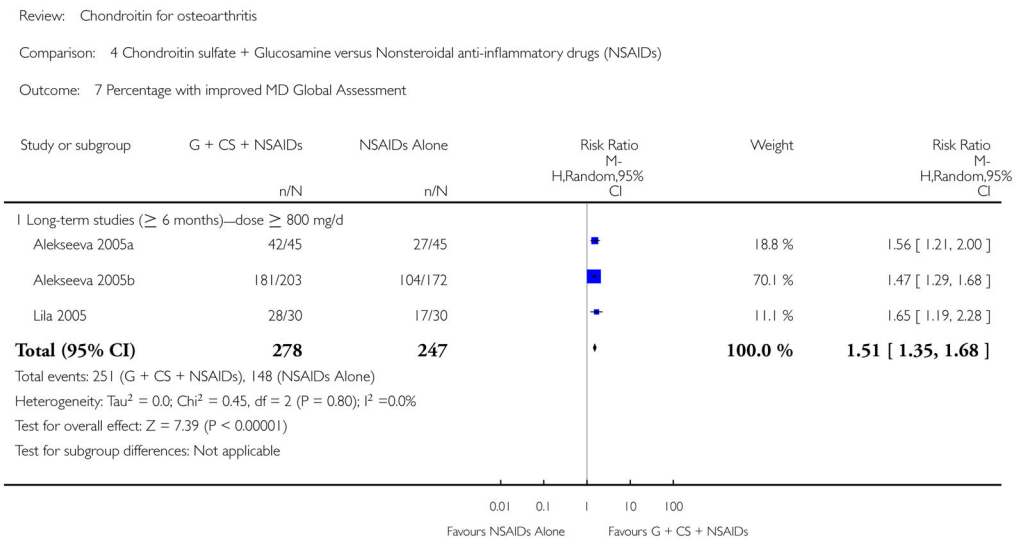
Analysis 4.4.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 4 WOMAC Stiffness.



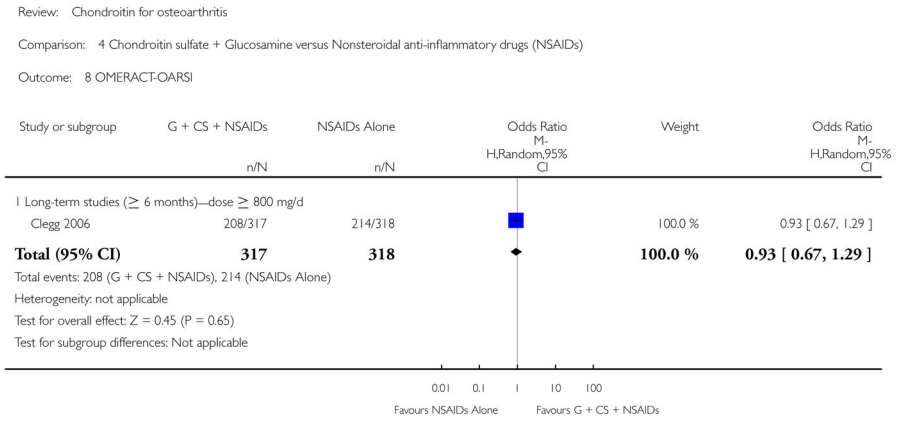
Analysis 4.5.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 5 WOMAC Total.



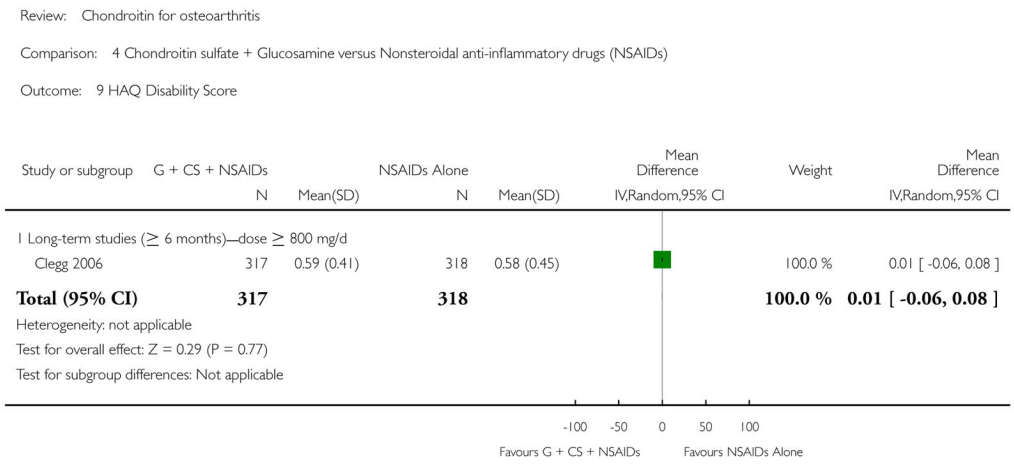
Analysis 4.6.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 6 Percentage with improved Patient Global Assessment.



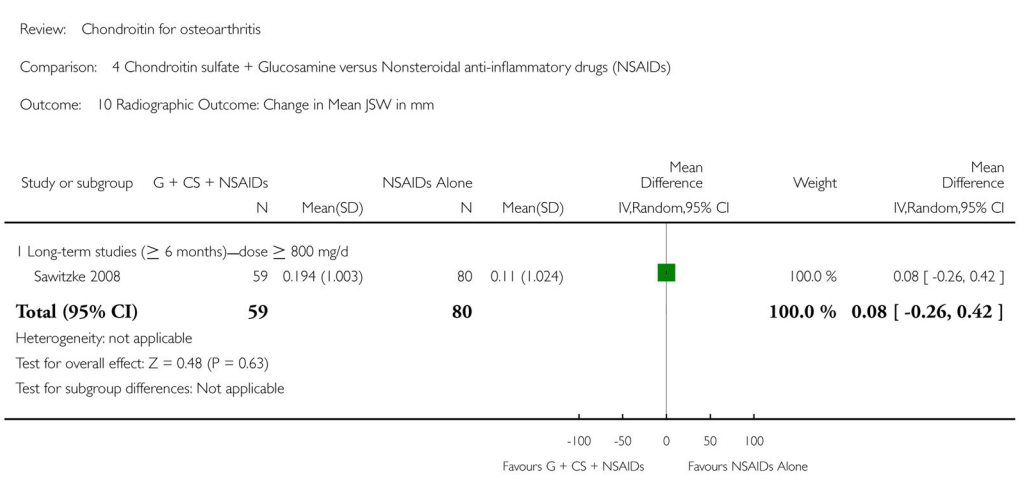
Analysis 4.7.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 7 Percentage with improved MD Global Assessment.



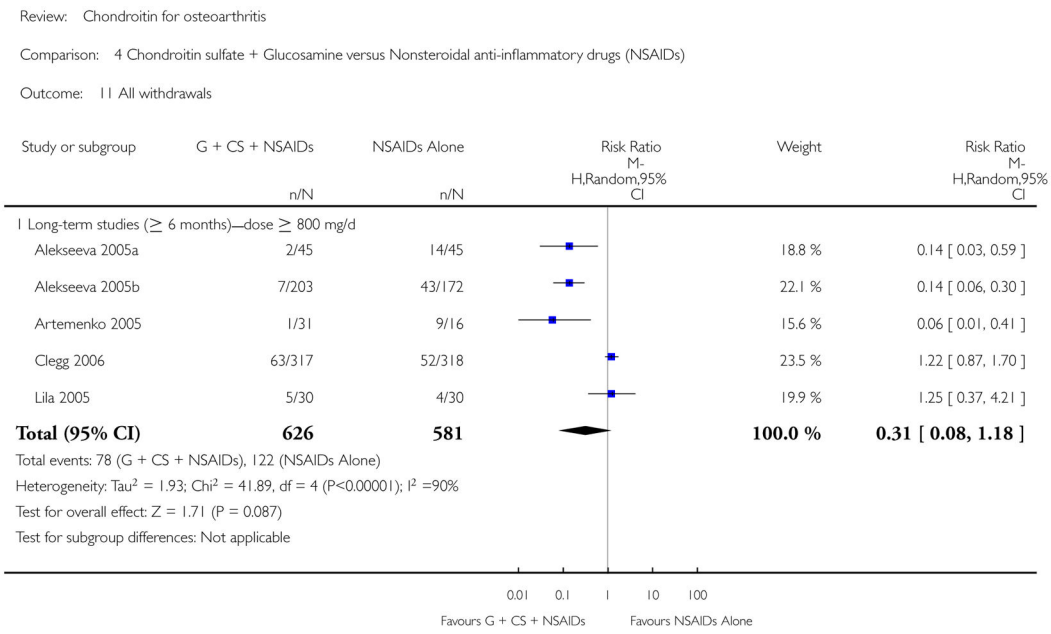
Analysis 4.8.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 8 OMERACT-OARSI.



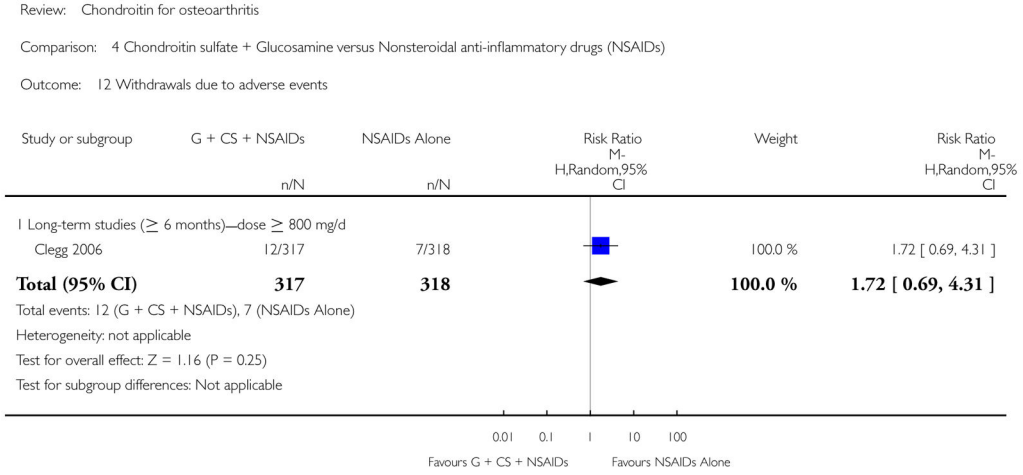
Analysis 4.9.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 9 HAQ Disability Score.



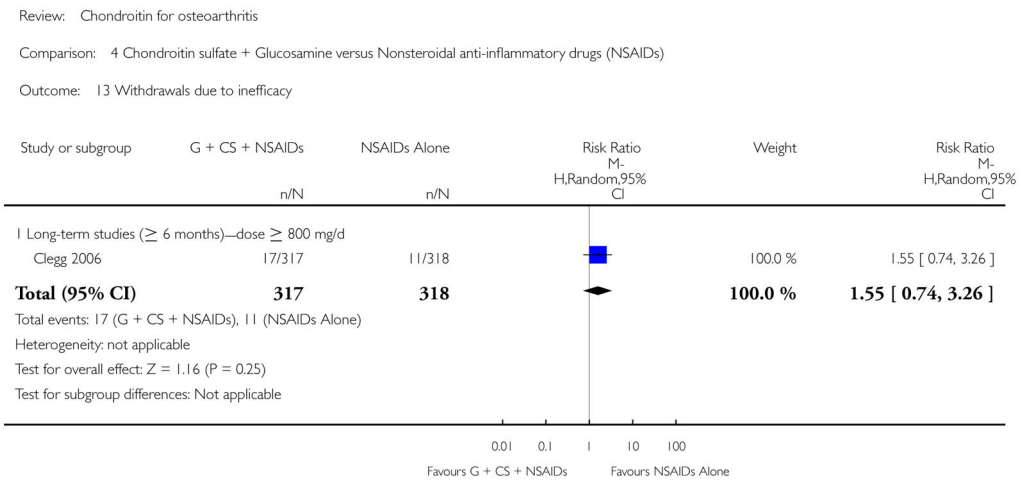
Analysis 4.10.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 10 Radiographic Outcome: Change in Mean JSW in mm.



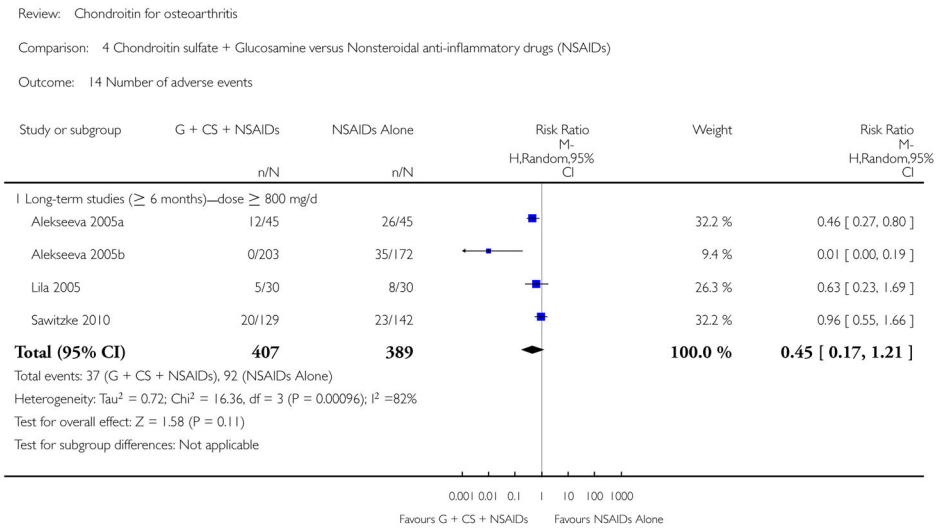
Analysis 4.11.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 11 All withdrawals.



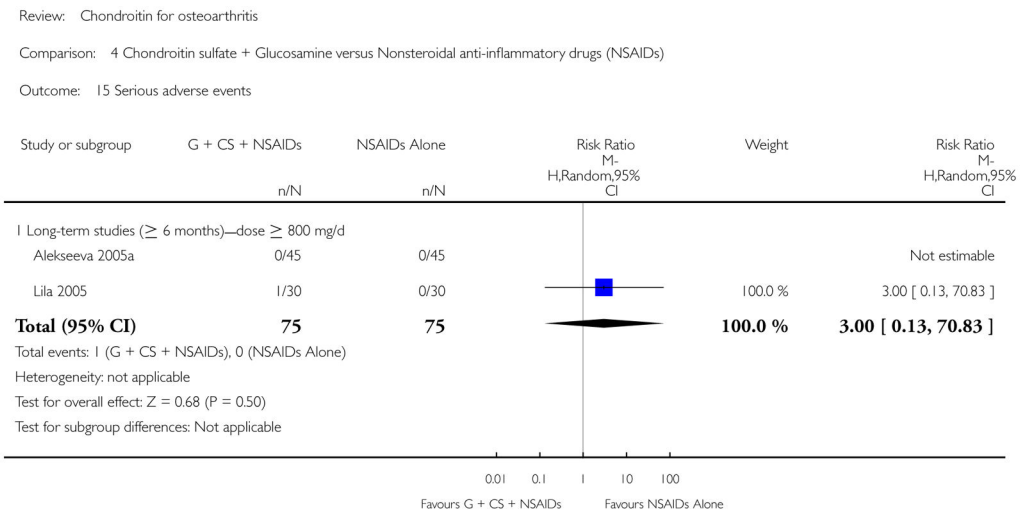
Analysis 4.12.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 12 Withdrawals due to adverse events.



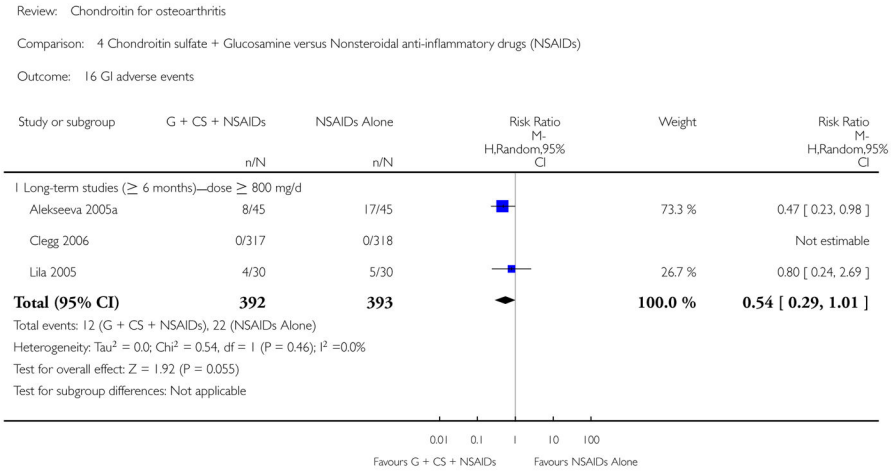
Analysis 4.13.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 13 Withdrawals due to inefficacy.



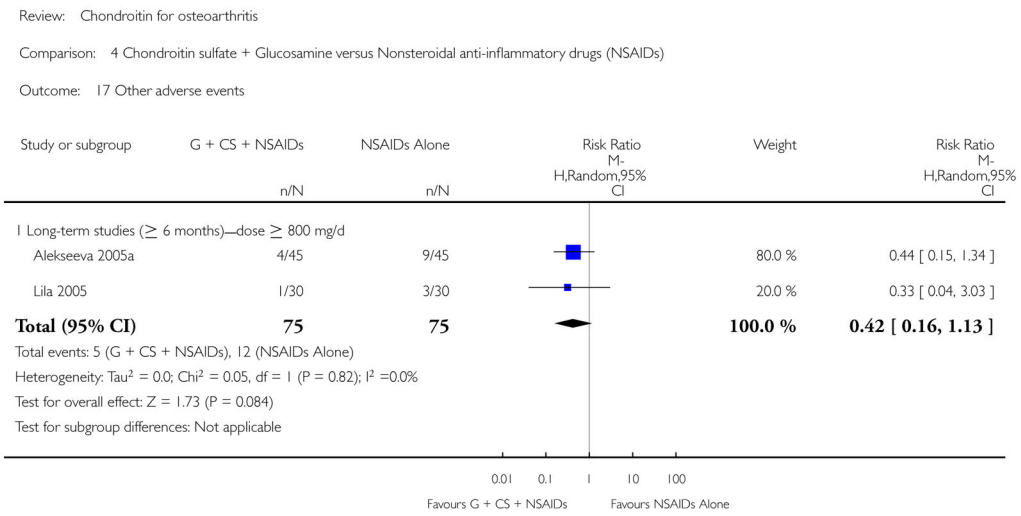
Analysis 4.14.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 14 Number of adverse events.



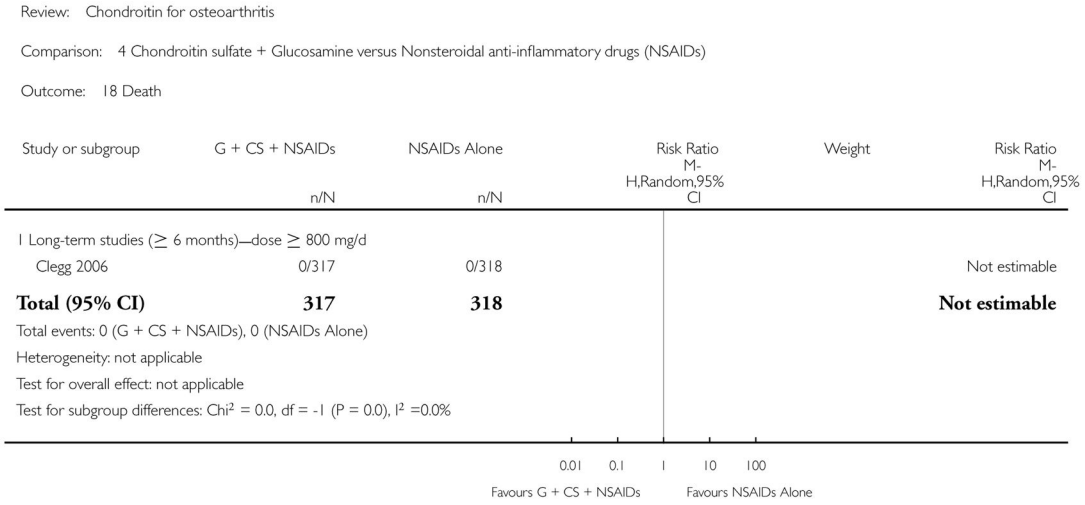
Analysis 4.15.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 15 Serious adverse events.



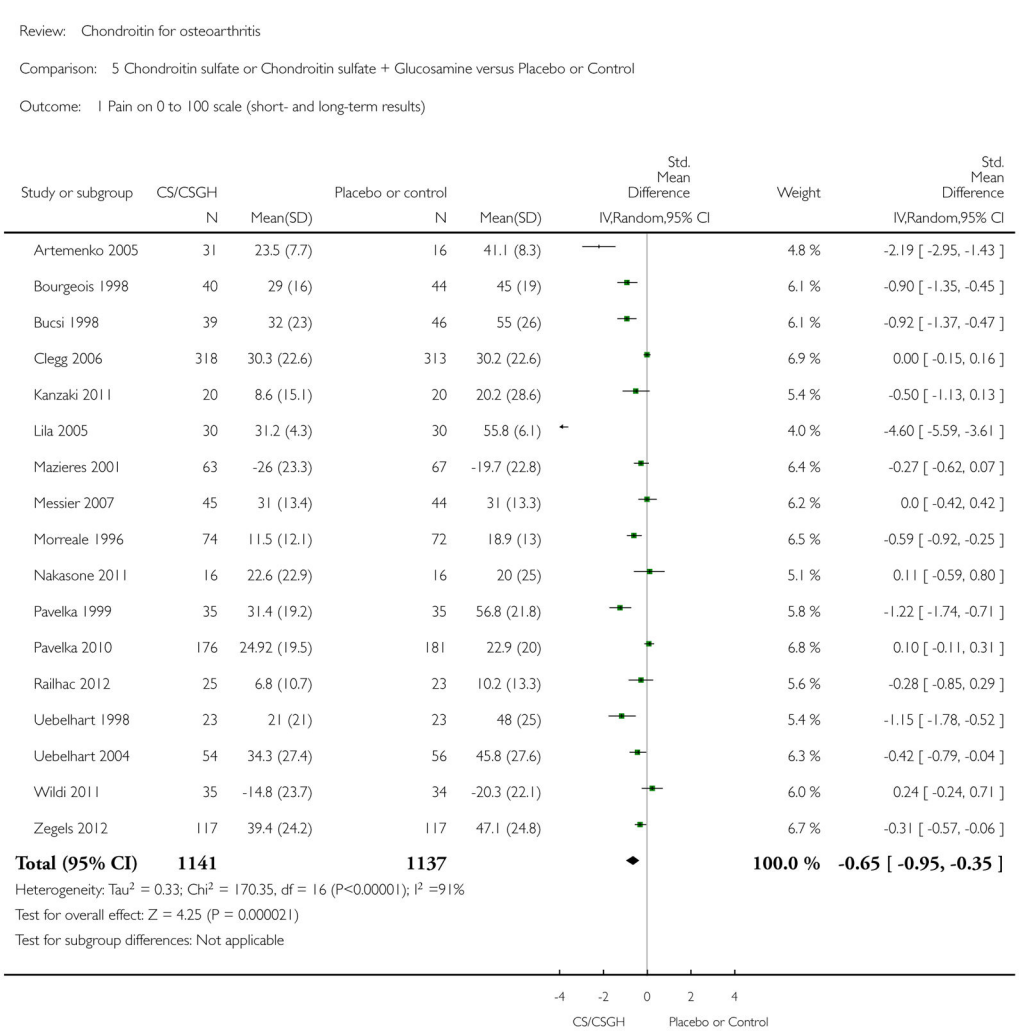
Analysis 4.16.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 16 GI adverse events.



Analysis 4.17.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 17 Other adverse events.

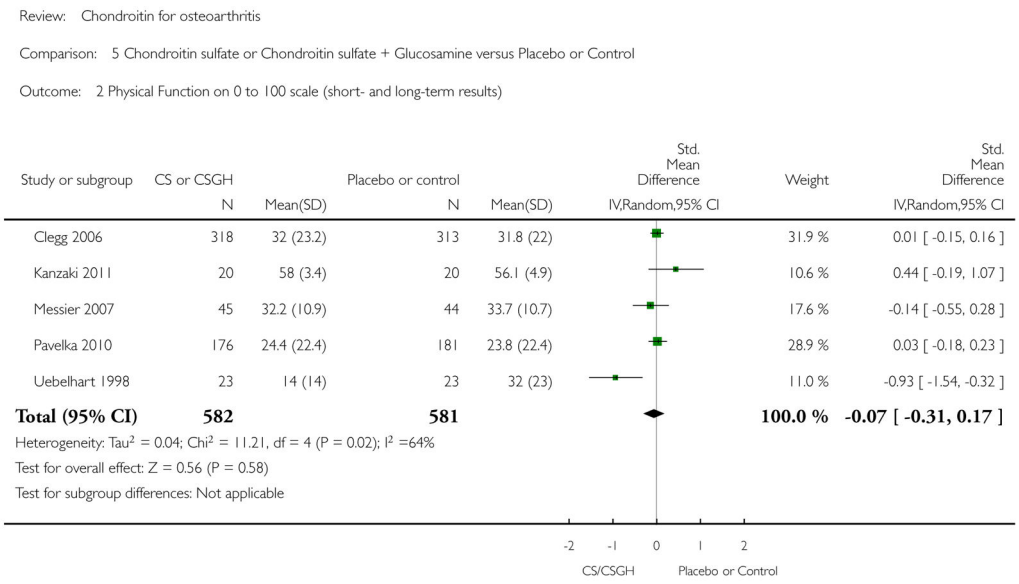


Analysis 4.18.
Comparison 4 Chondroitin sulfate + Glucosamine versus Nonsteroidal anti-inflammatory drugs (NSAIDs), Outcome 18 Death.



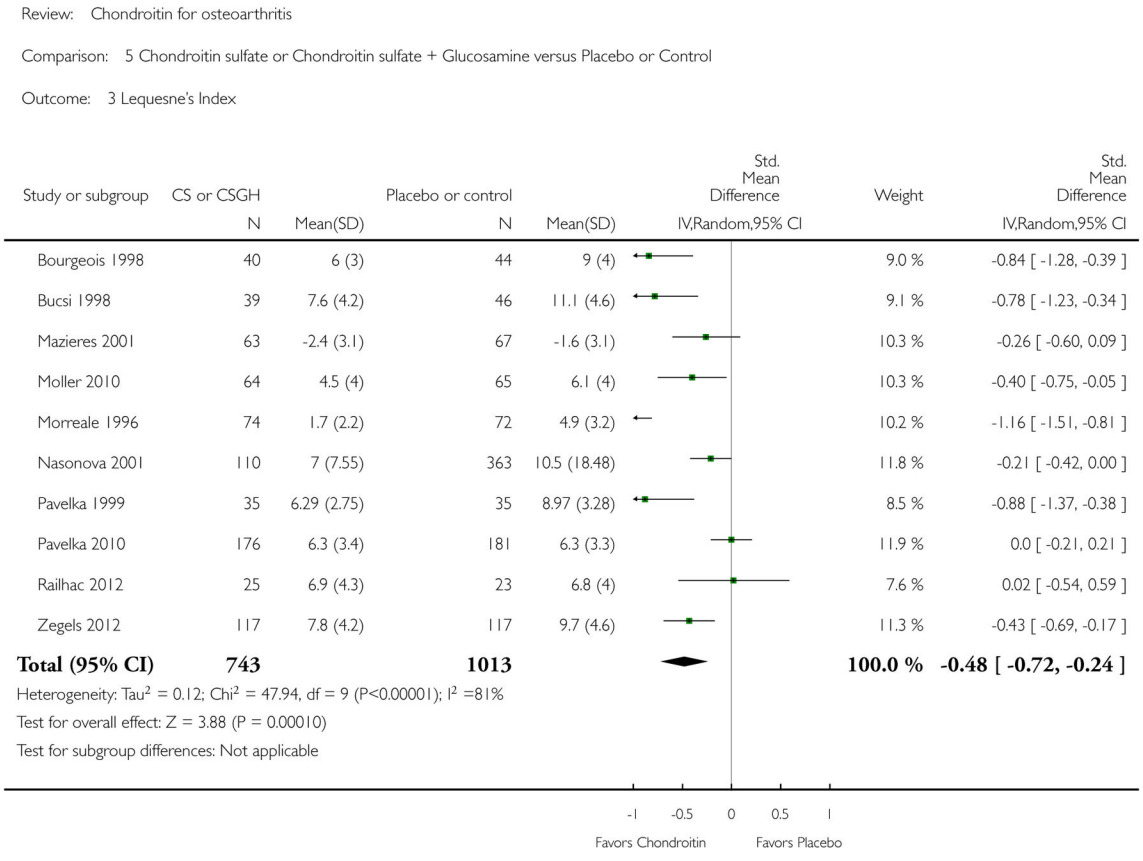
Analysis 5.1.

Comparison 5 Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control, Outcome 1 Pain on 0 to 100 scale (short- and long-term results).



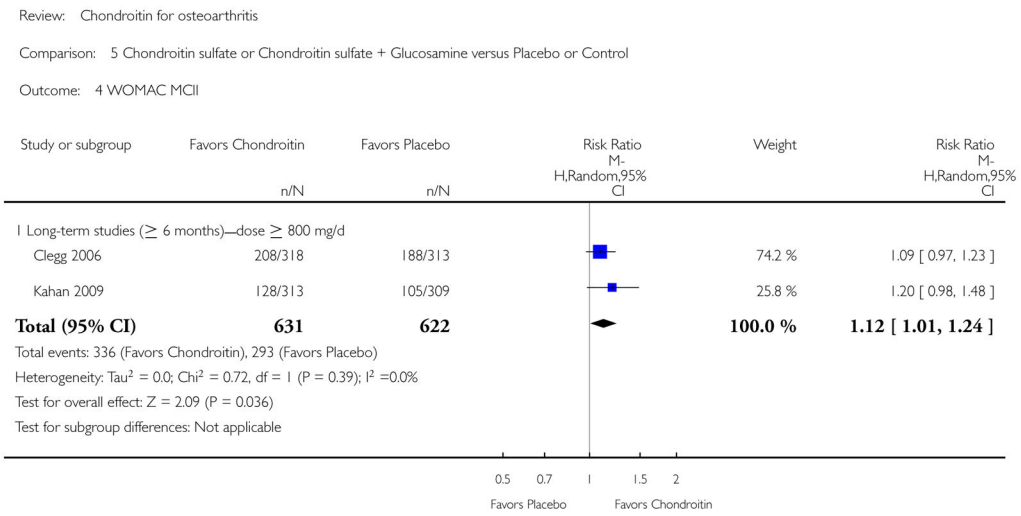
Analysis 5.2.

Comparison 5 Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control, Outcome 2 Physical Function on 0 to 100 scale (short- and long-term results).

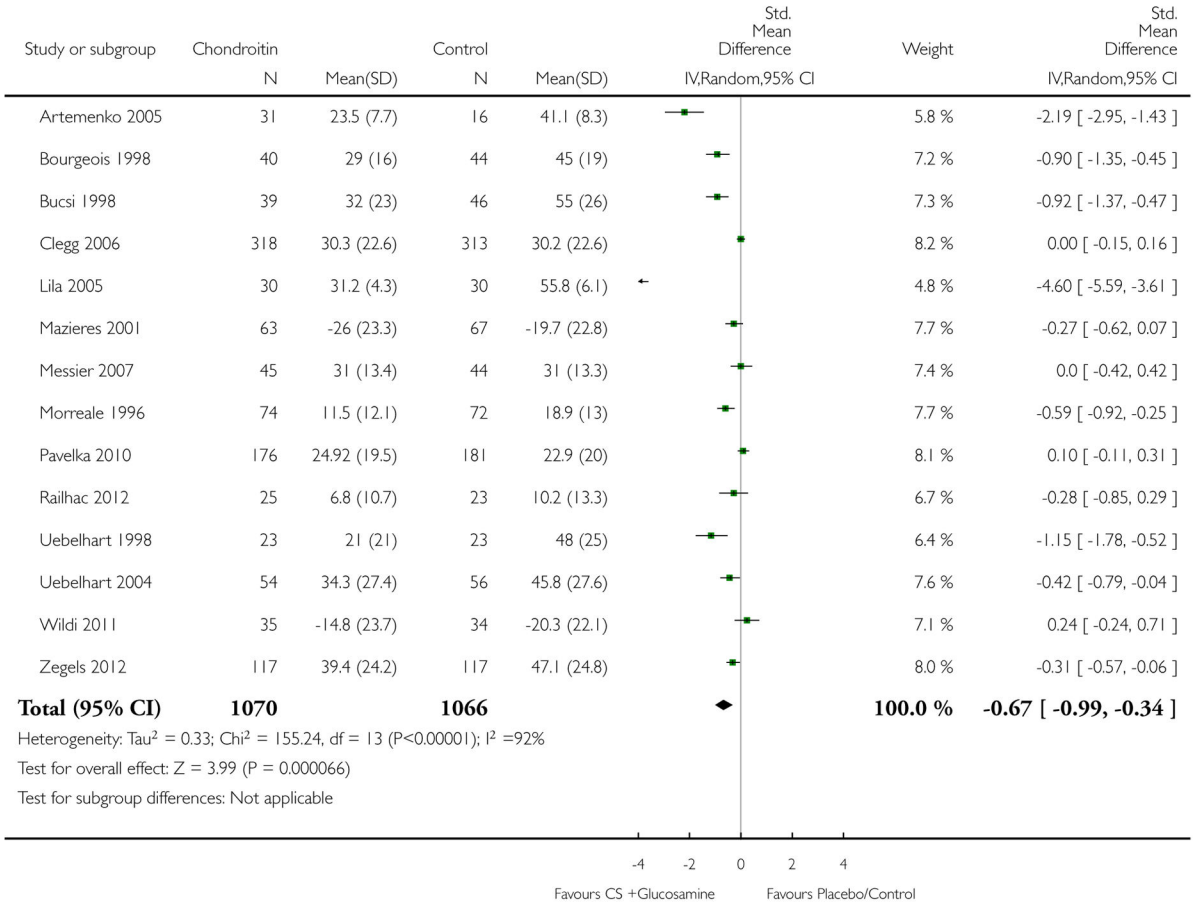


Analysis 5.3.

Comparison 5 Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control, Outcome 3 Lequesne's Index.

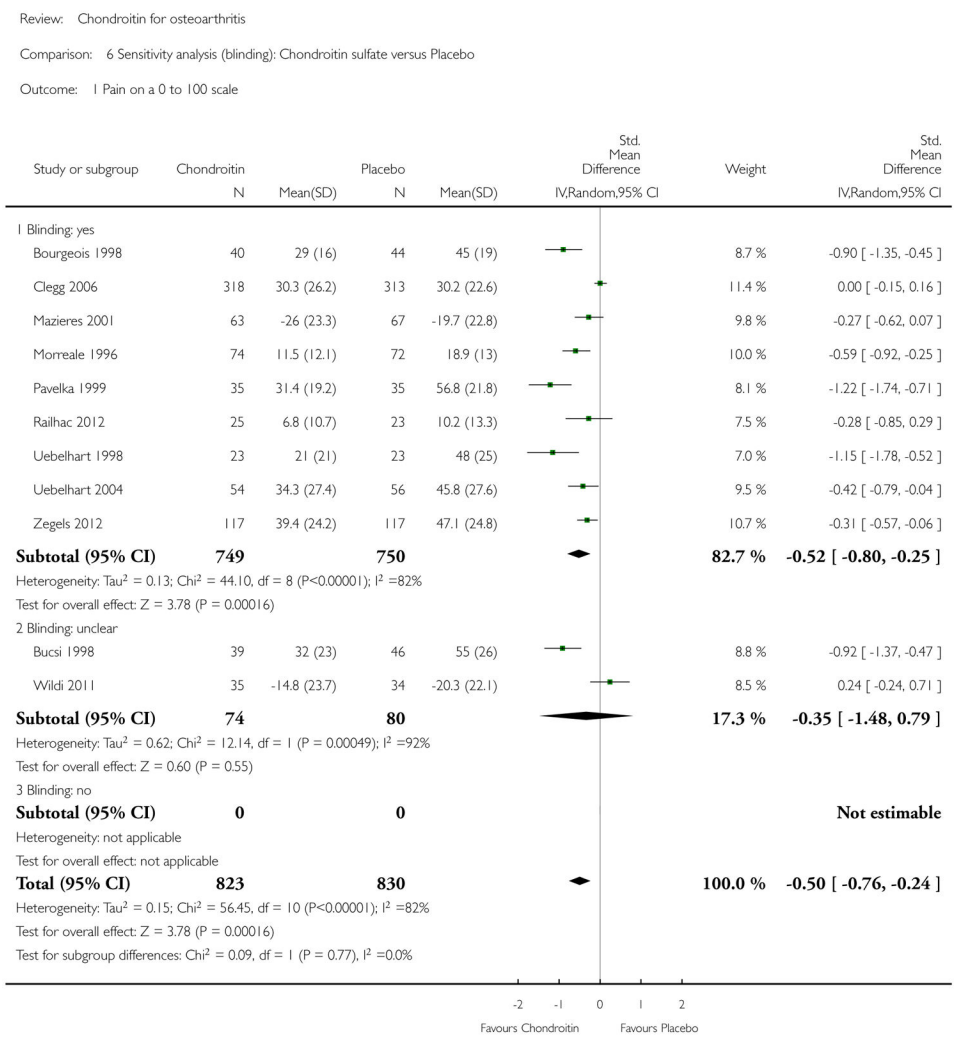


Analysis 5.4.
Comparison 5 Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control, Outcome 4 WOMAC MCII.



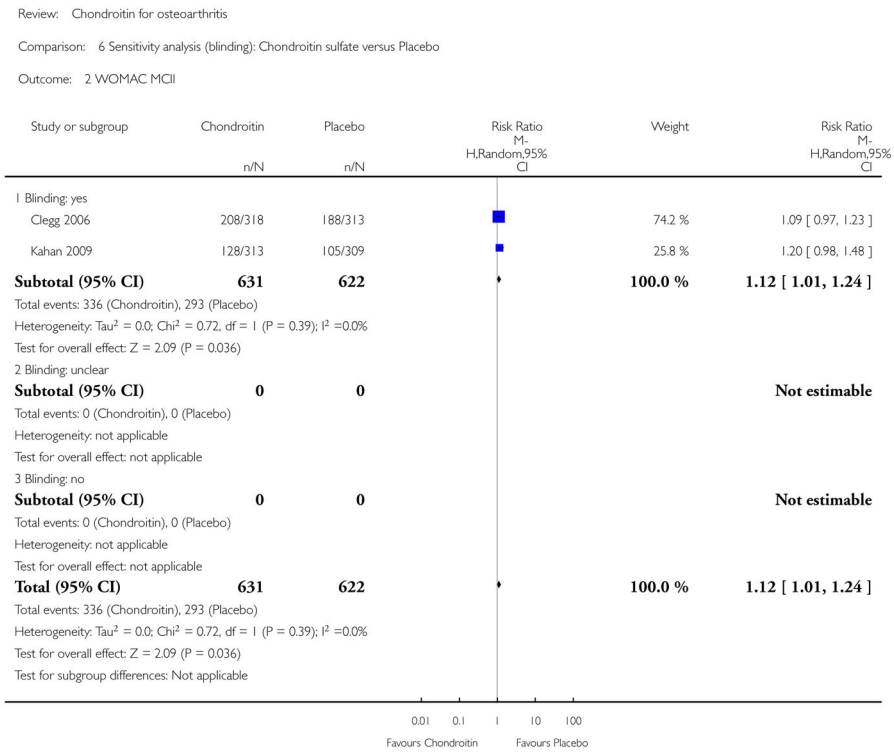
Analysis 5.5.

Comparison 5 Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control, Outcome 5 Pain on 0 to 100 scale (short- or long-term) for CS dose >= 800 mg/day.

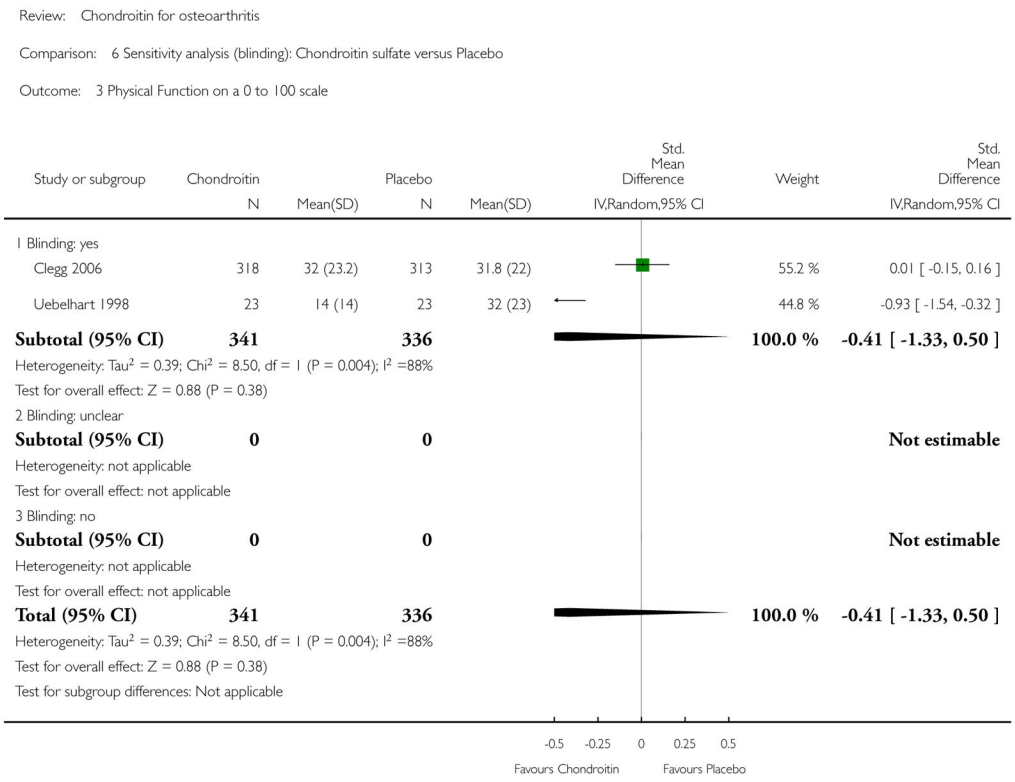


Analysis 6.1.

Comparison 6 Sensitivity analysis (blinding): Chondroitin sulfate versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

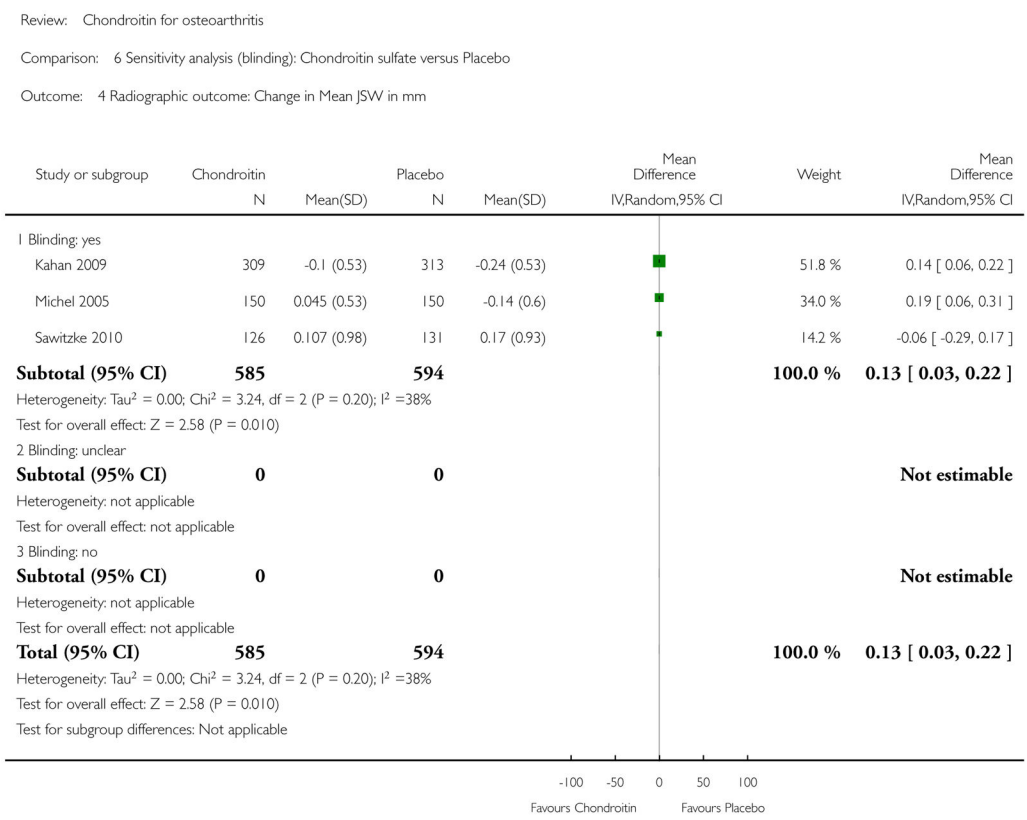


Analysis 6.2.
Comparison 6 Sensitivity analysis (blinding): Chondroitin sulfate versus Placebo, Outcome 2 WOMAC MCII.



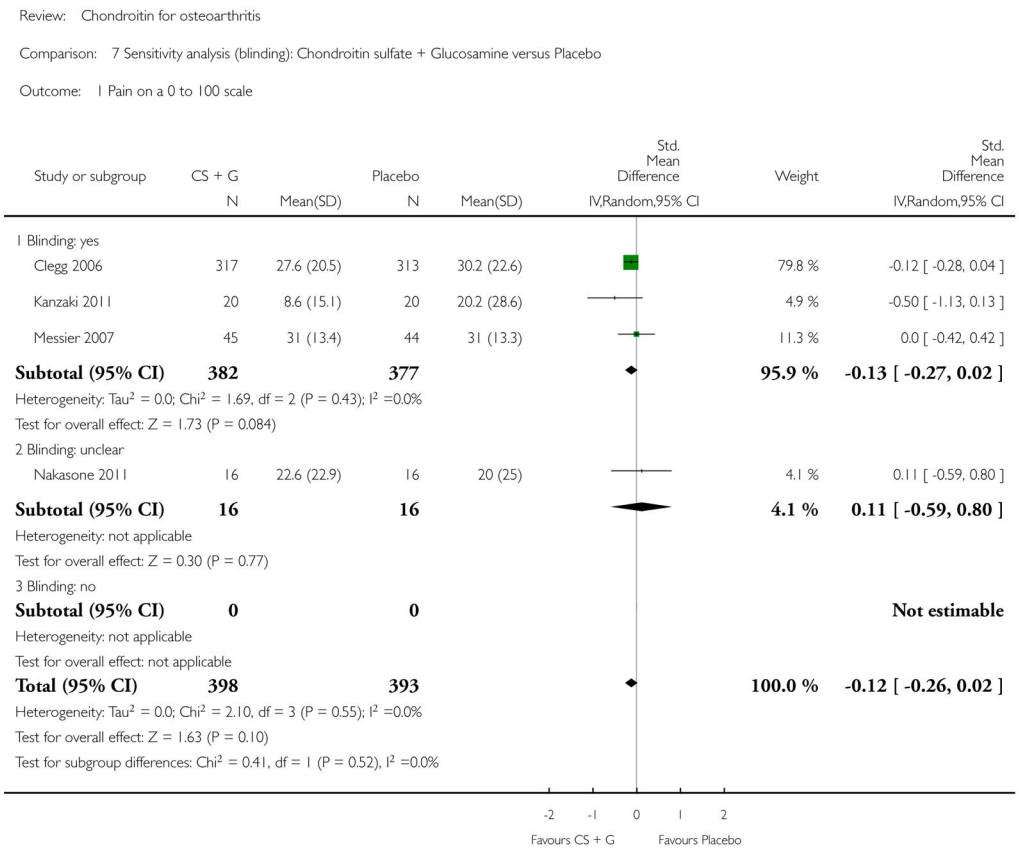
Analysis 6.3.

Comparison 6 Sensitivity analysis (blinding): Chondroitin sulfate versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



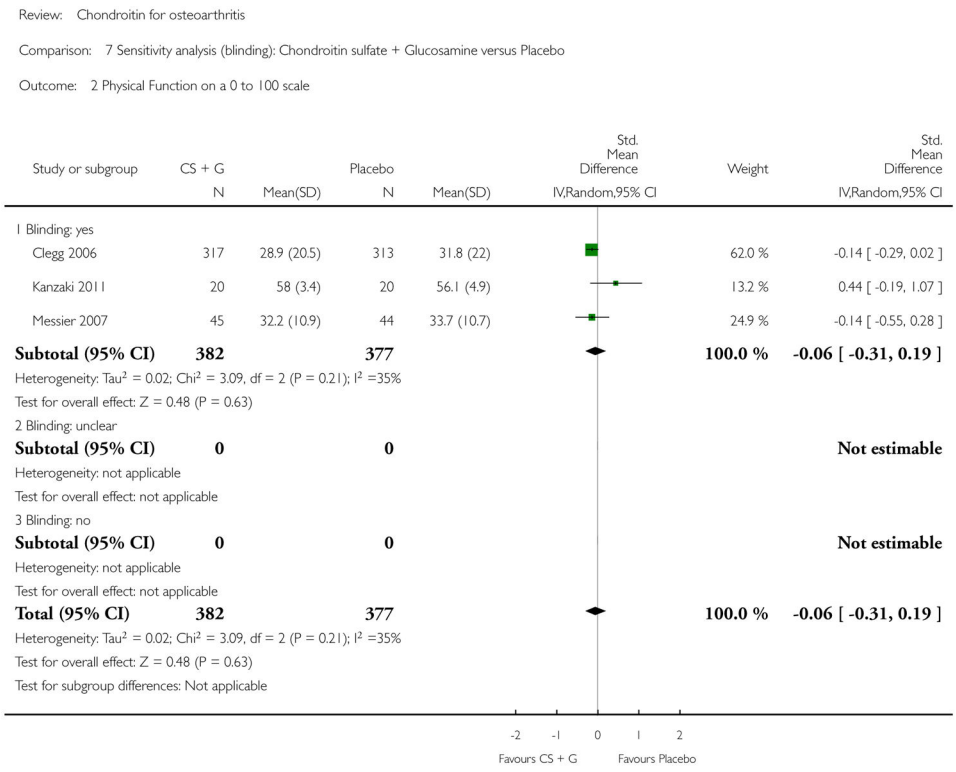
Analysis 6.4.

Comparison 6 Sensitivity analysis (blinding): Chondroitin sulfate versus Placebo, Outcome 4 Radiographic outcome: Change in Mean JSW in mm.

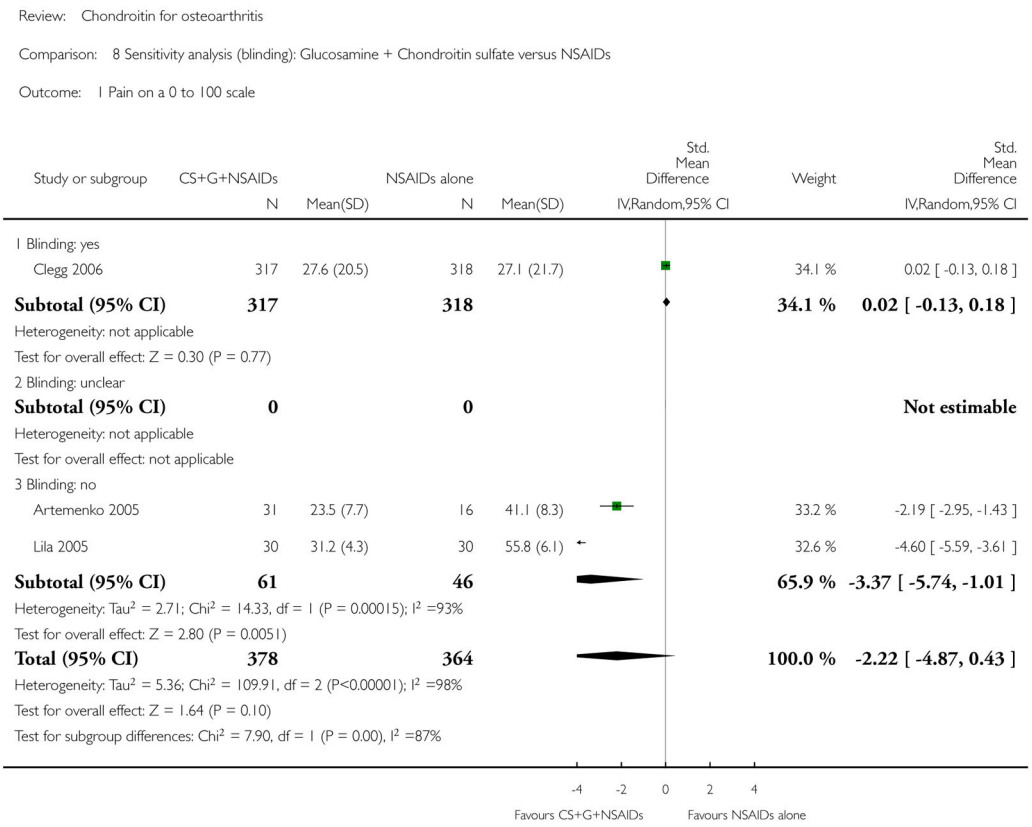


Analysis 7.1.

Comparison 7 Sensitivity analysis (blinding): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

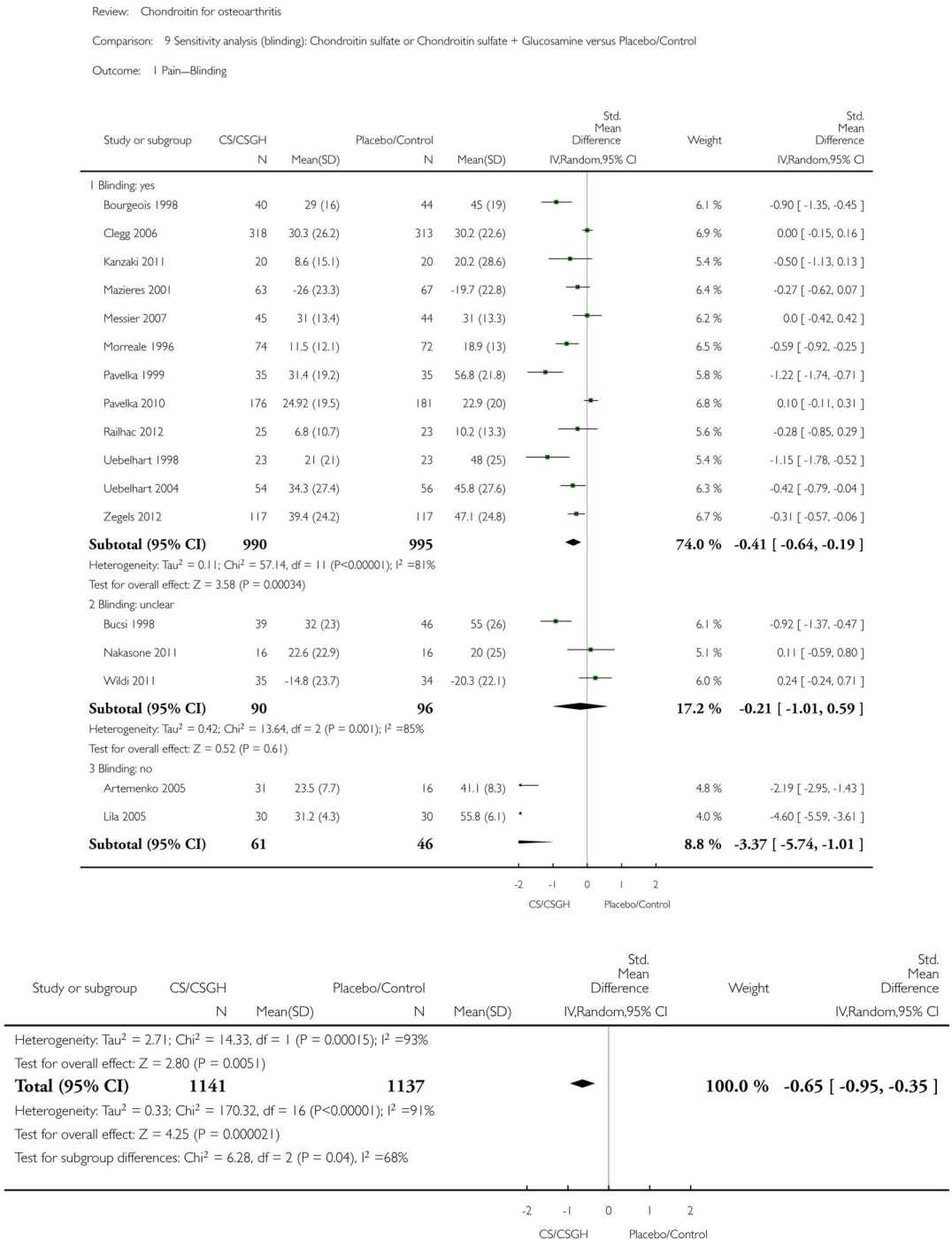


Analysis 7.2.
Comparison 7 Sensitivity analysis (blinding): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



Analysis 8.1.

Comparison 8 Sensitivity analysis (blinding): Glucosamine + Chondroitin sulfate versus NSAIDs, Outcome 1 Pain on a 0 to 100 scale.



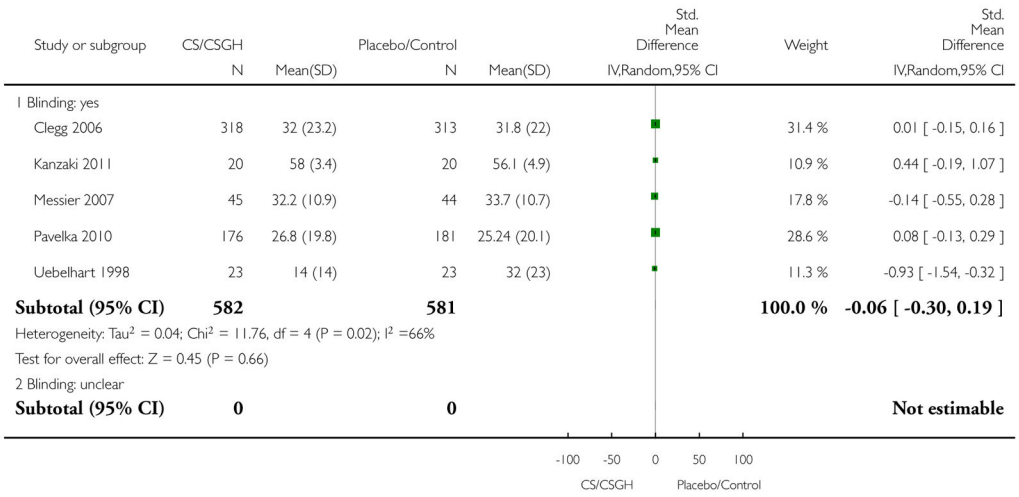
Analysis 9.1.

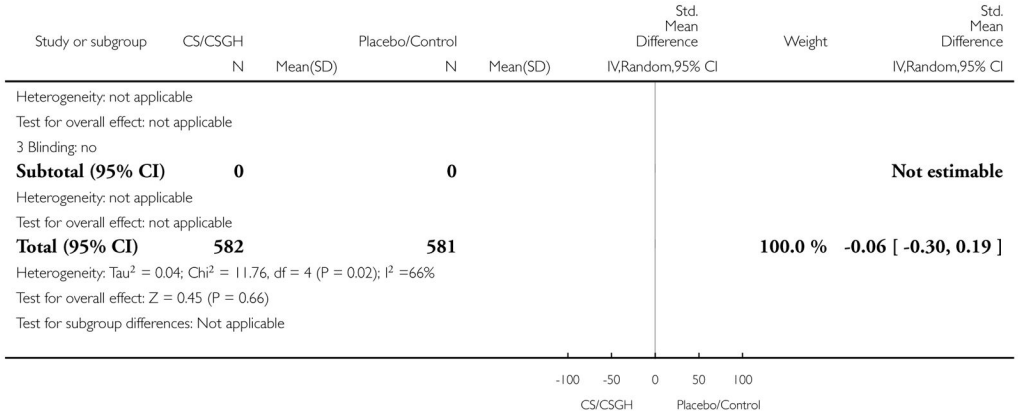
Comparison 9 Sensitivity analysis (blinding): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 1 Pain-Blinding.

Review: Chondroitin for osteoarthritis

Comparison: 9 Sensitivity analysis (blinding): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

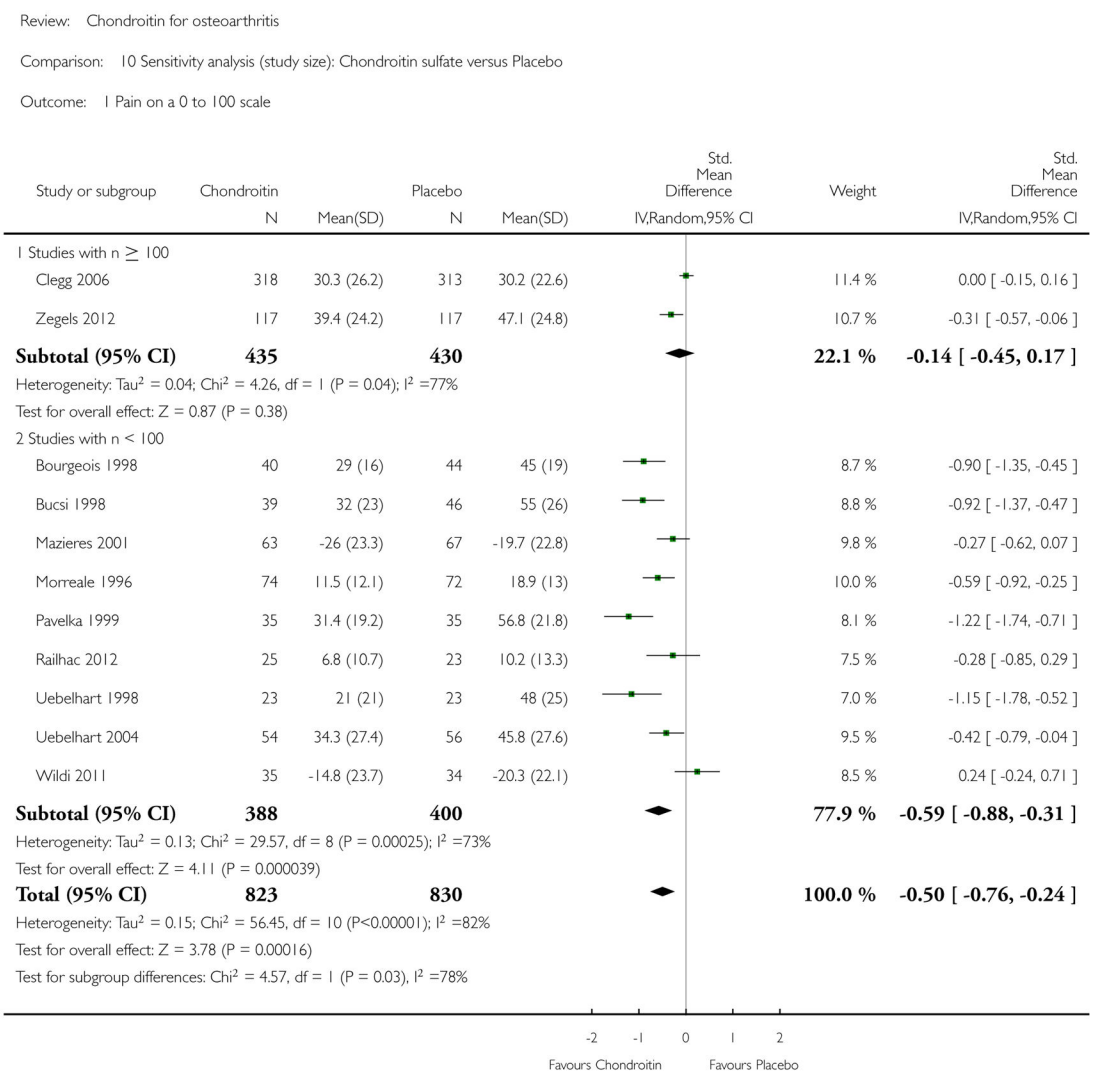
Outcome: 2 Physical Function—Blinding





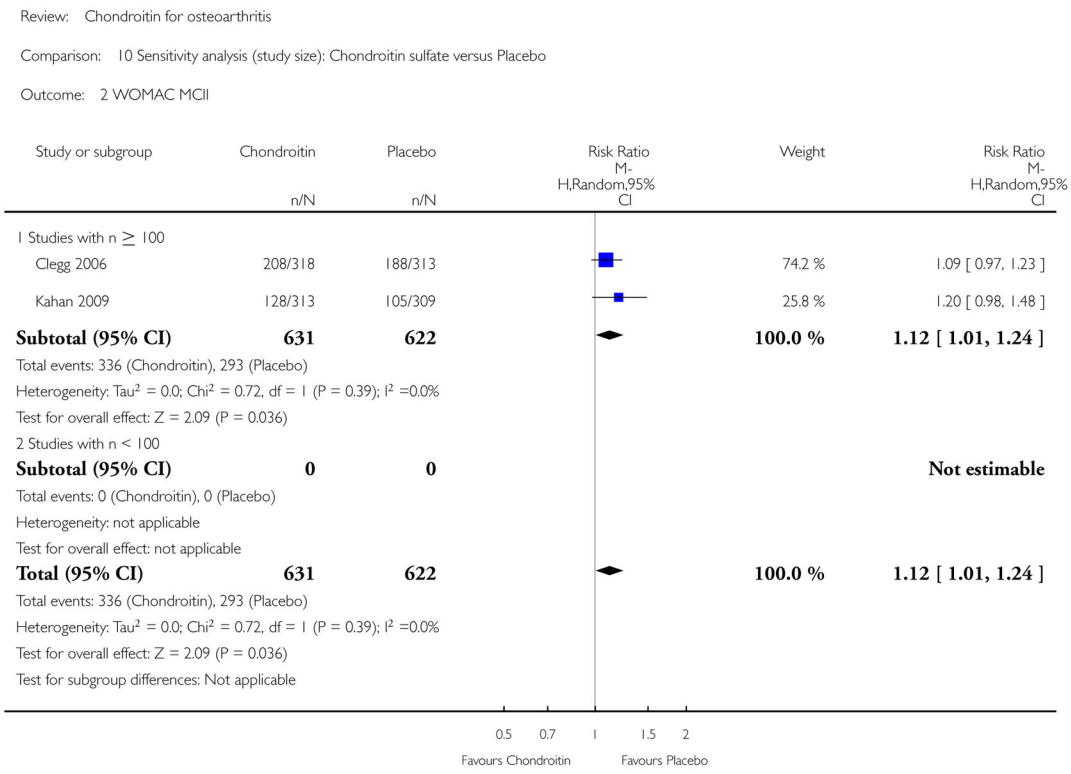
Analysis 9.2.

Comparison 9 Sensitivity analysis (blinding): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 2 Physical Function-Blinding.

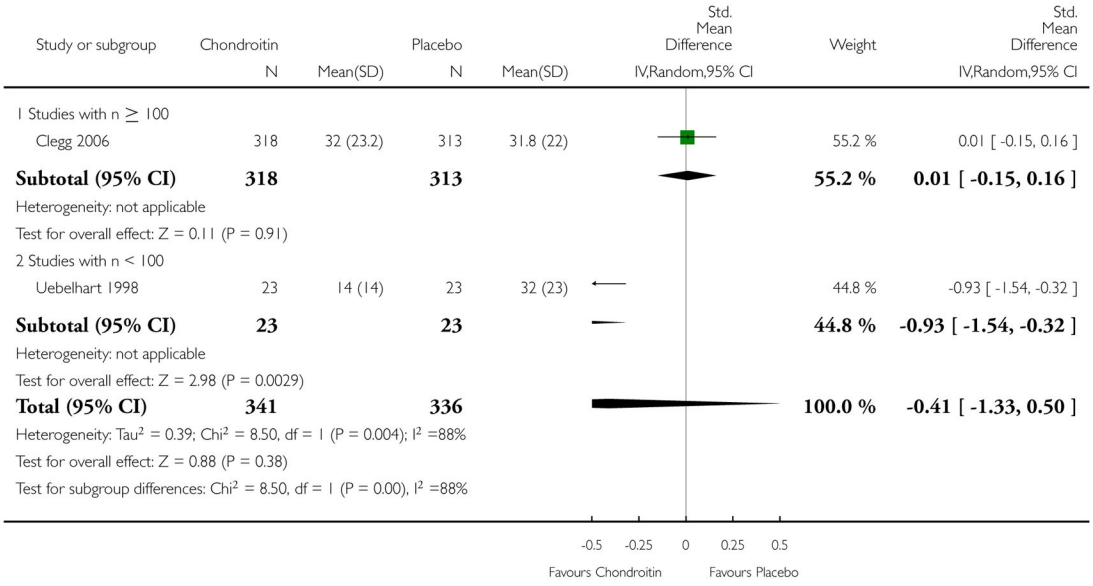


Analysis 10.1.

Comparison 10 Sensitivity analysis (study size): Chondroitin sulfate versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

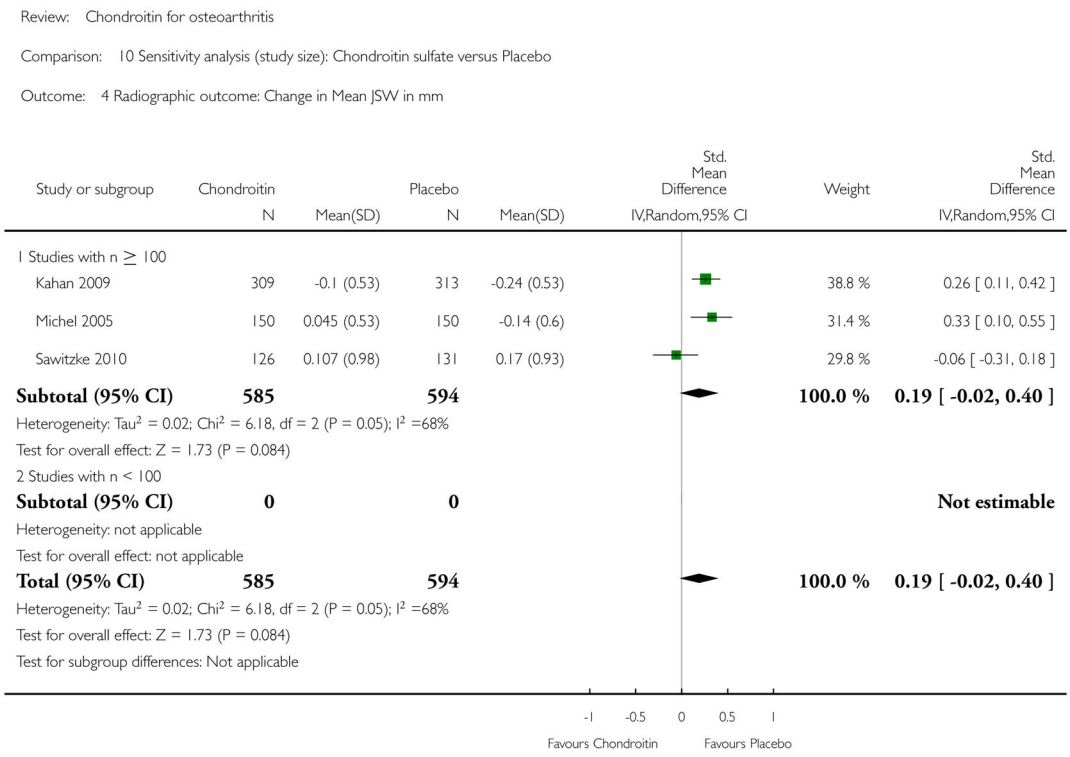


Analysis 10.2.
Comparison 10 Sensitivity analysis (study size): Chondroitin sulfate versus Placebo, Outcome 2 WOMAC MCII.



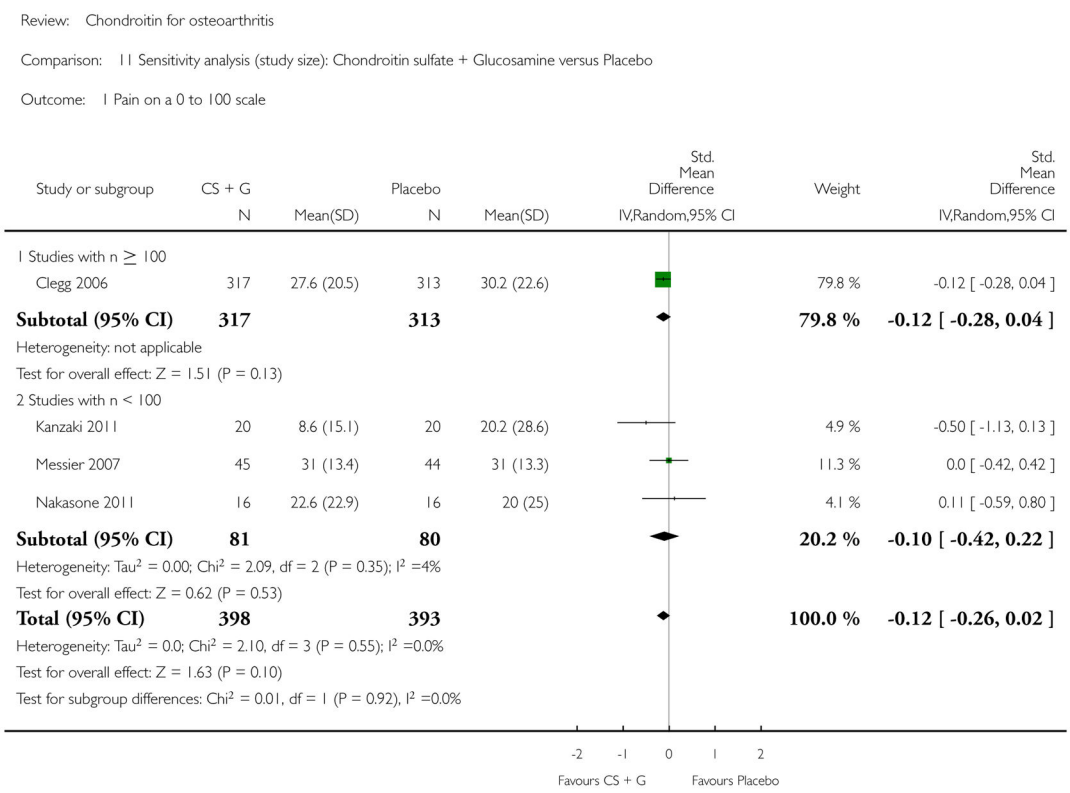
Analysis 10.3.

Comparison 10 Sensitivity analysis (study size): Chondroitin sulfate versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



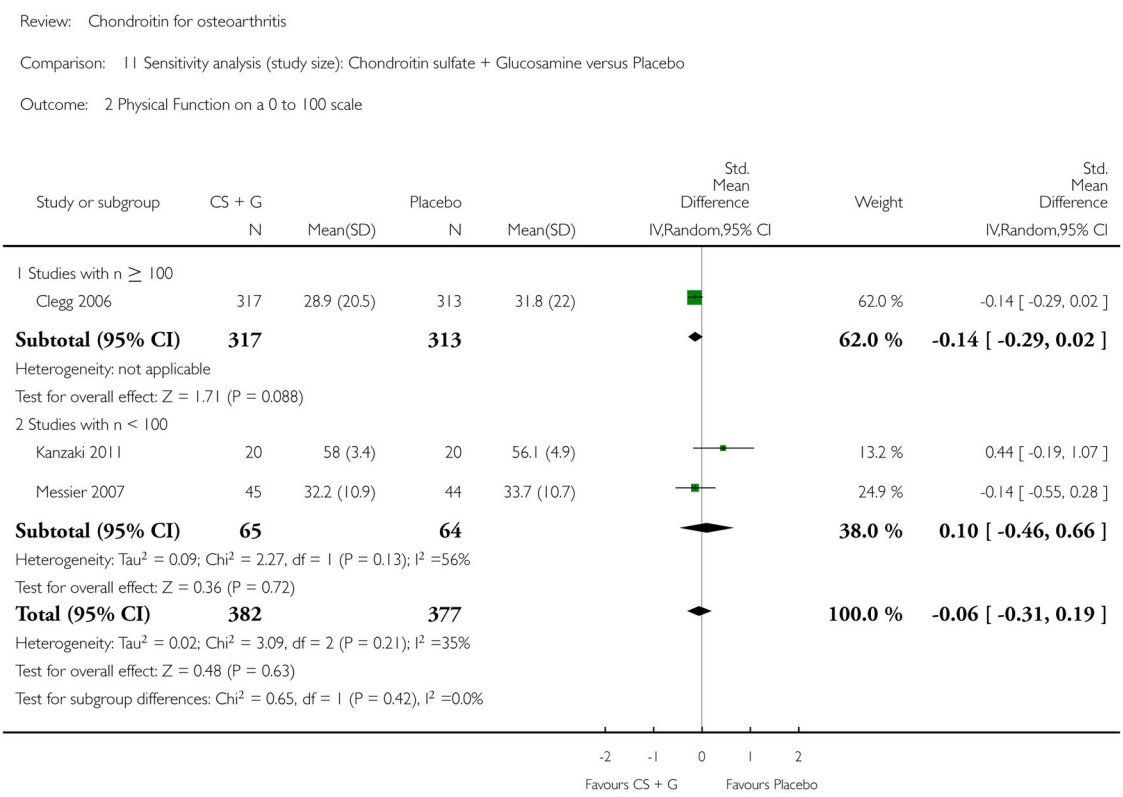
Analysis 10.4.

Comparison 10 Sensitivity analysis (study size): Chondroitin sulfate versus Placebo, Outcome 4 Radiographic outcome: Change in Mean JSW in mm.



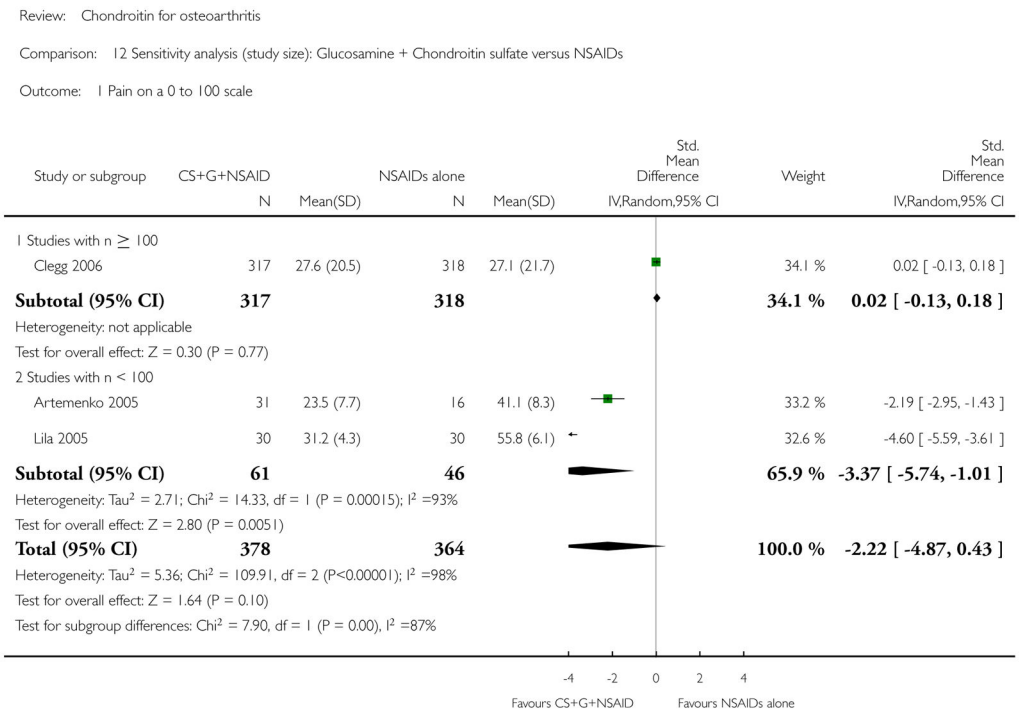
Analysis 11.1.

Comparison 11 Sensitivity analysis (study size): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



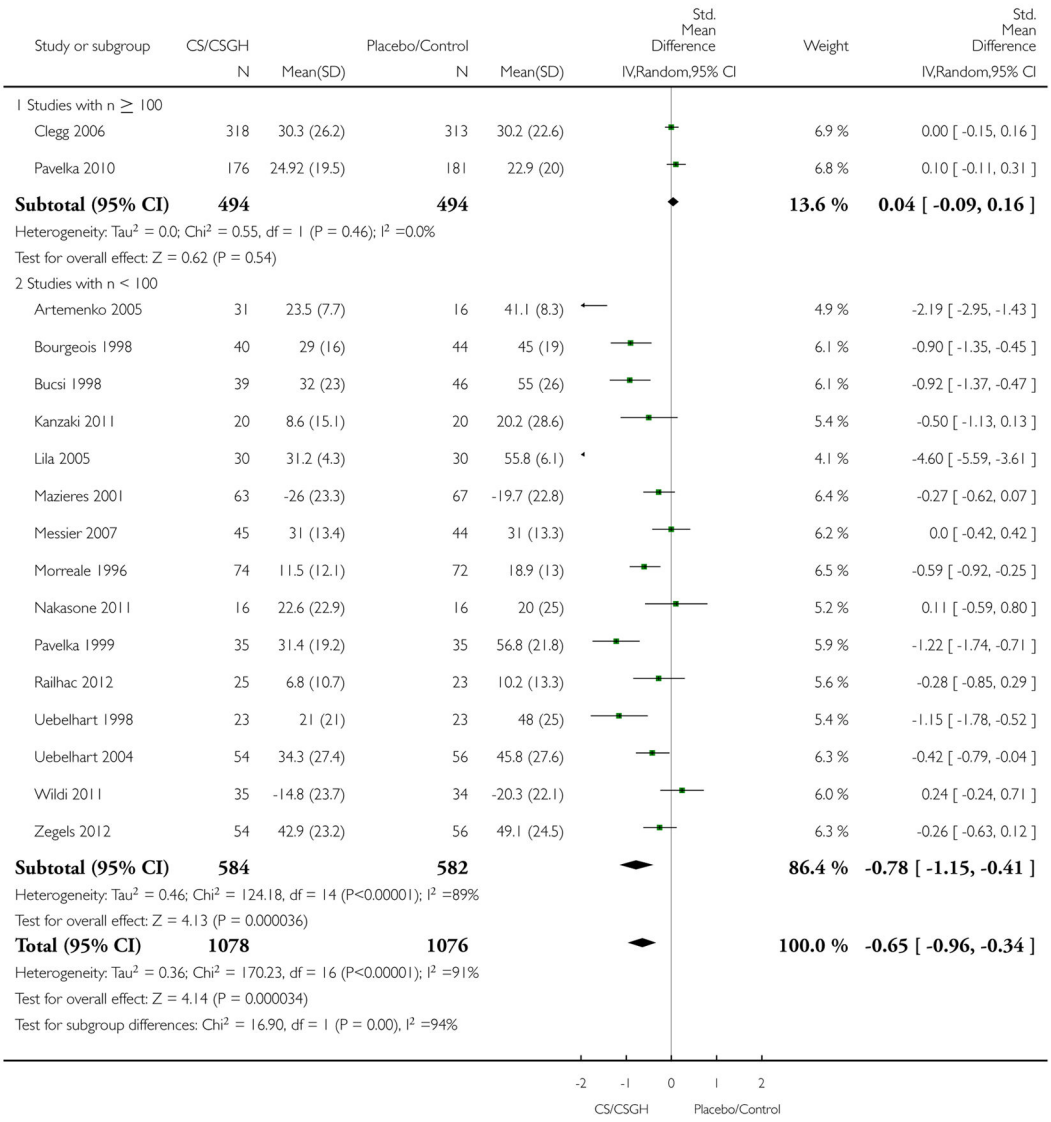
Analysis 11.2.

Comparison 11 Sensitivity analysis (study size): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



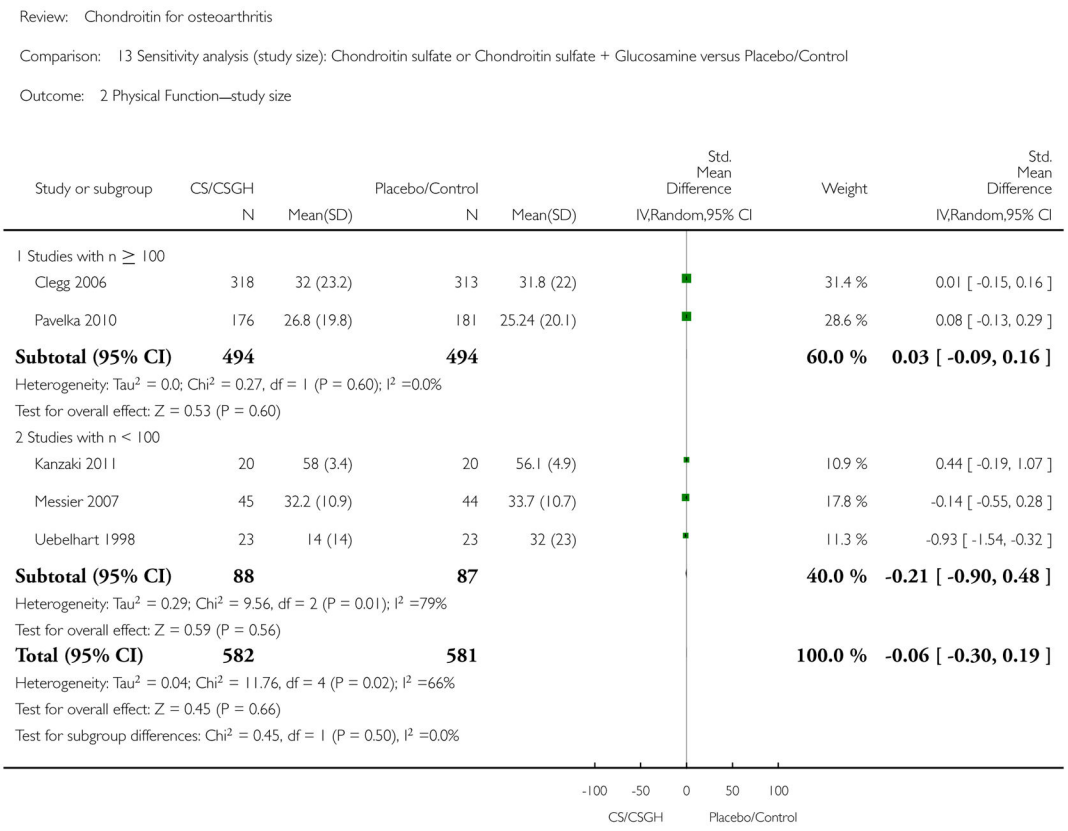
Analysis 12.1.

Comparison 12 Sensitivity analysis (study size): Glucosamine + Chondroitin sulfate versus NSAIDs, Outcome 1 Pain on a 0 to 100 scale.



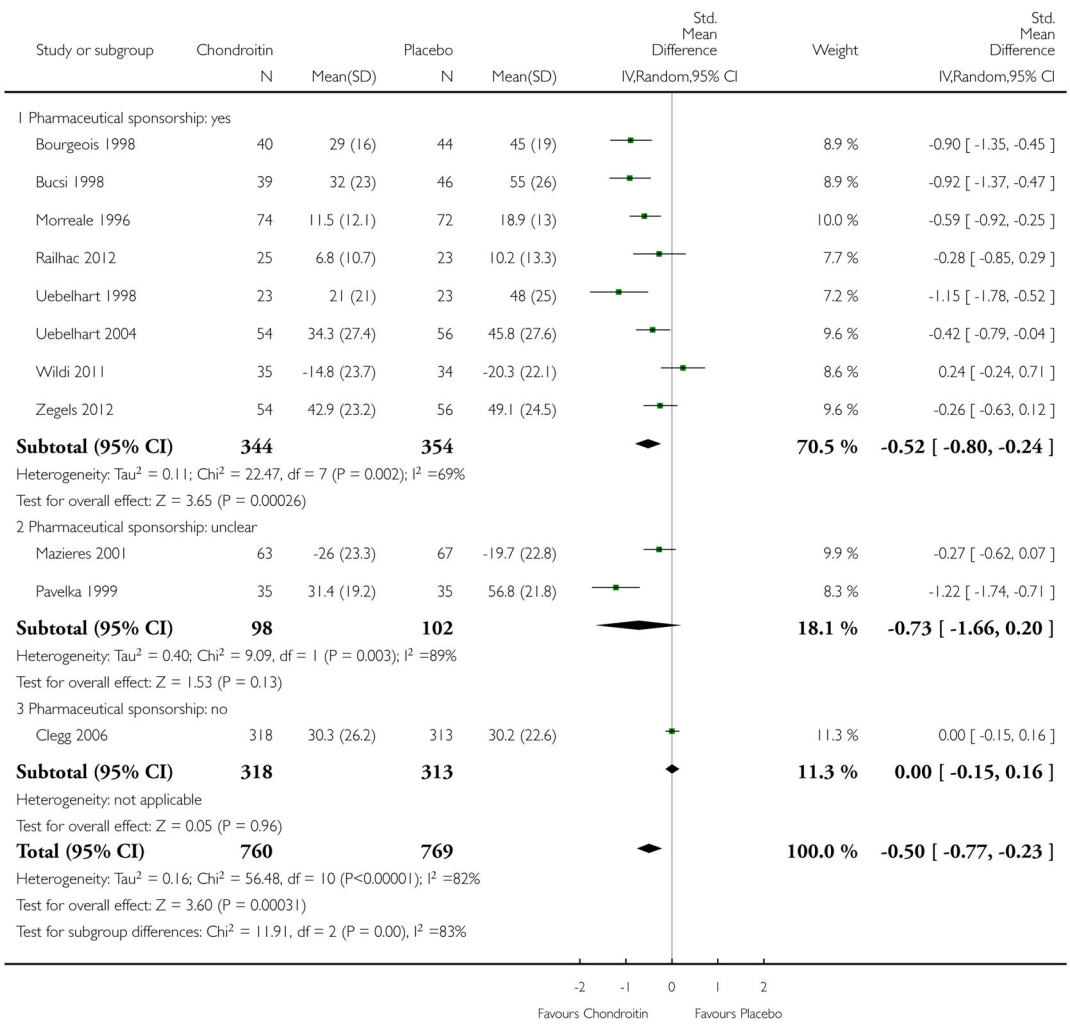
Analysis 13.1.

Comparison 13 Sensitivity analysis (study size): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 1 Pain-study size.



Analysis 13.2.

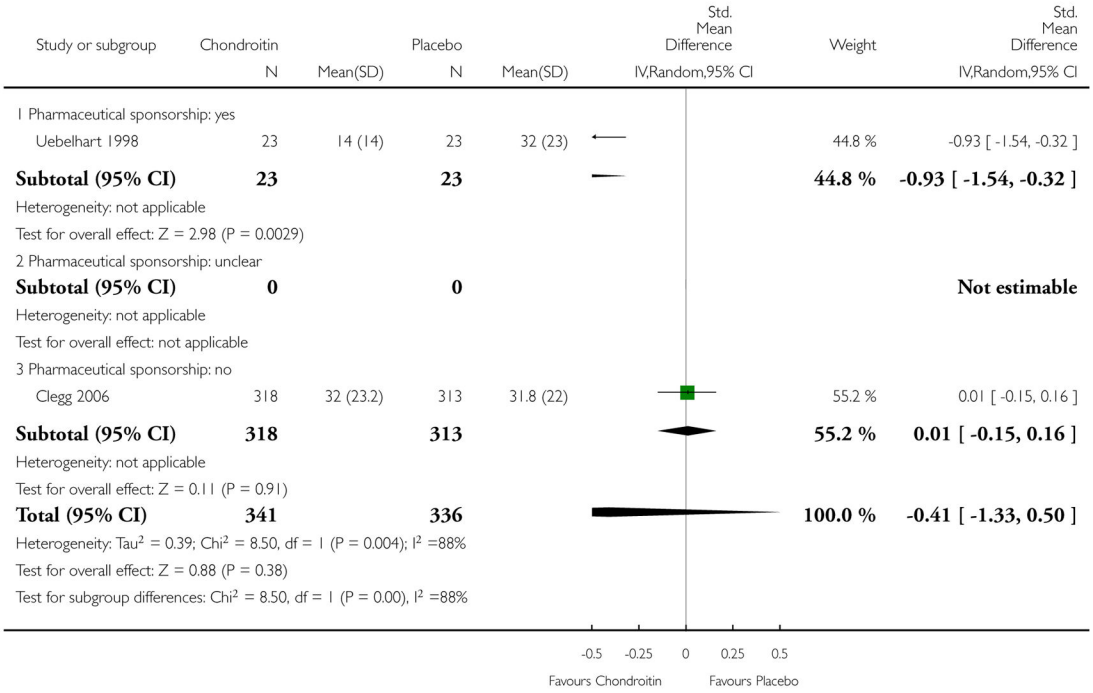
Comparison 13 Sensitivity analysis (study size): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 2 Physical Function-study size.



Analysis 14.1.

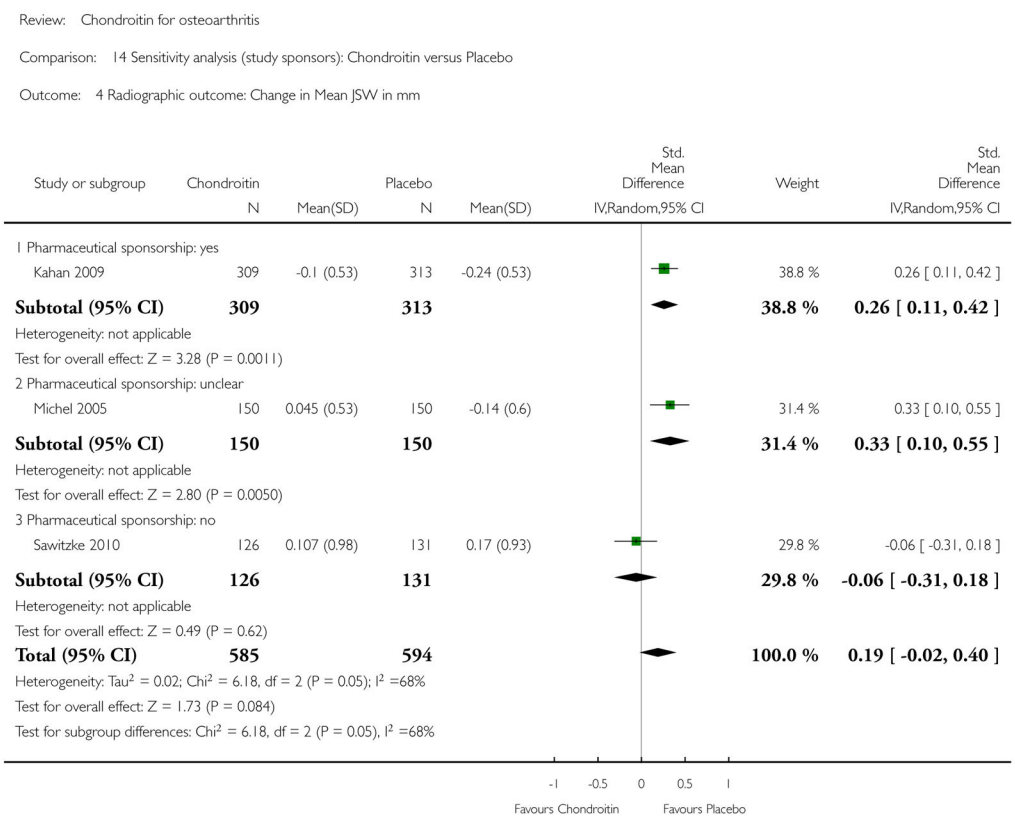
Comparison 14 Sensitivity analysis (study sponsors): Chondroitin versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

Analysis 14.2.
Comparison 14 Sensitivity analysis (study sponsors): Chondroitin versus Placebo, Outcome 2 WOMAC MCII.



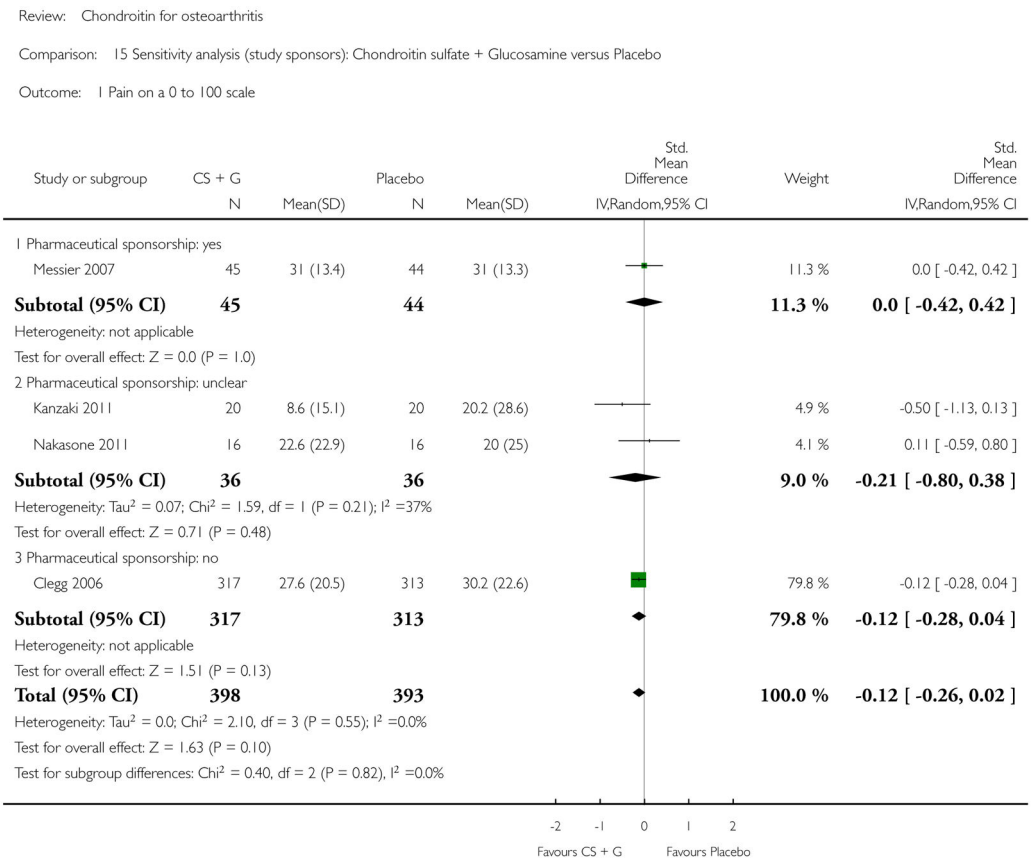
Analysis 14.3.

Comparison 14 Sensitivity analysis (study sponsors): Chondroitin versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



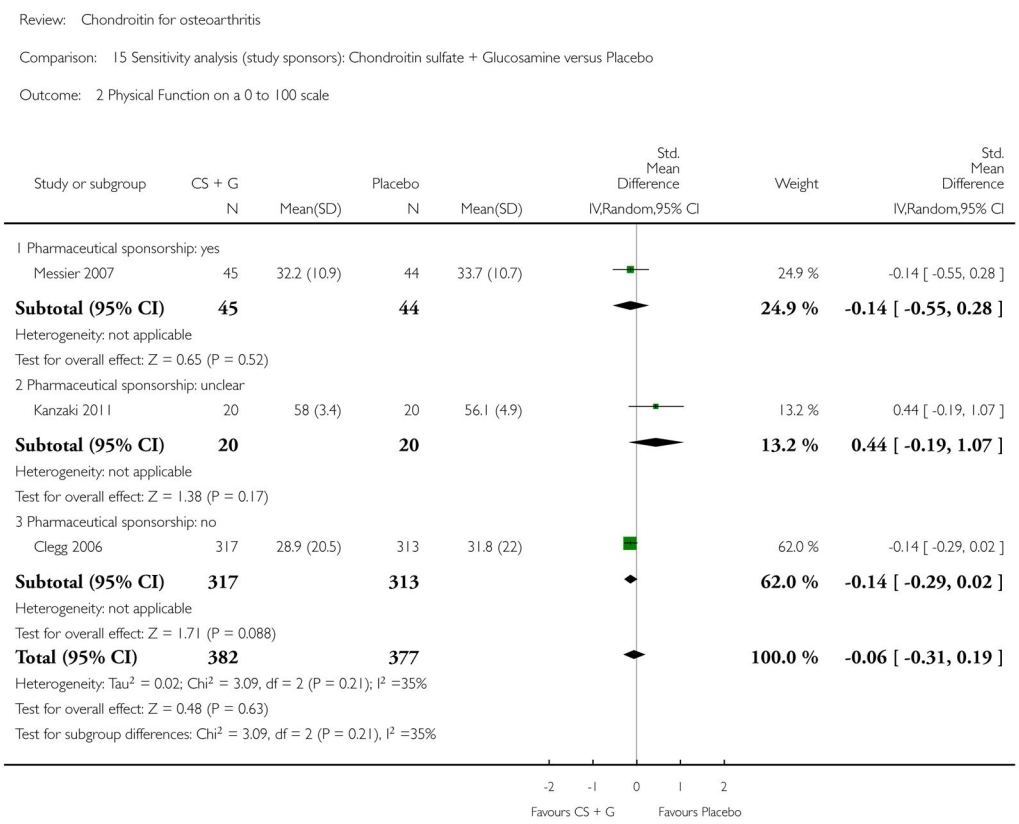
Analysis 14.4.

Comparison 14 Sensitivity analysis (study sponsors): Chondroitin versus Placebo, Outcome 4 Radiographic outcome: Change in Mean JSW in mm.



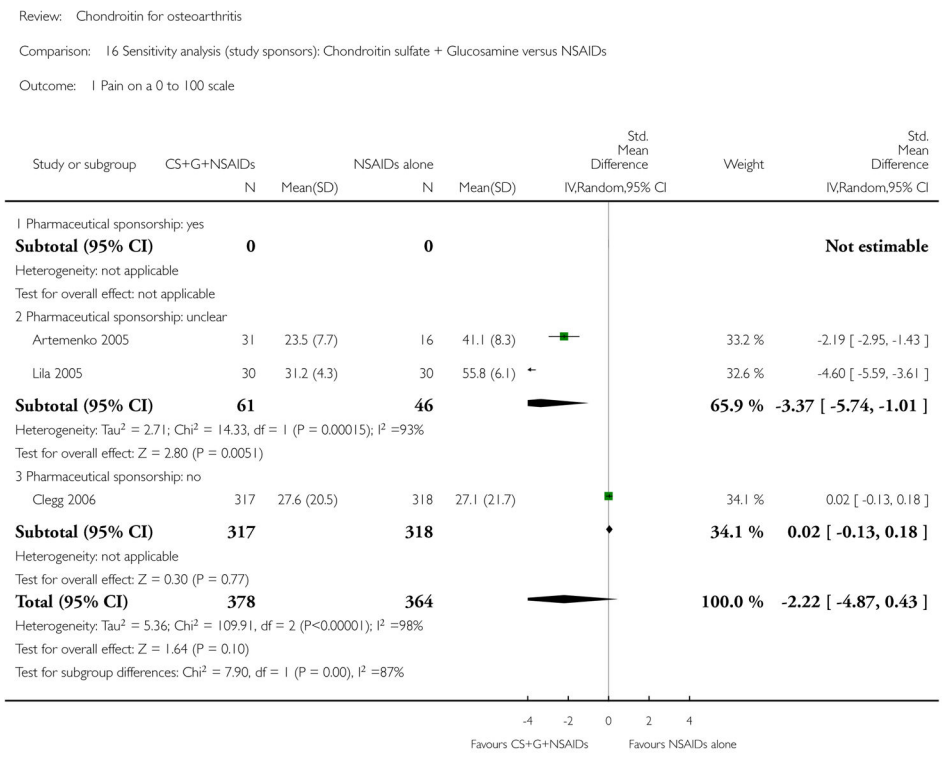
Analysis 15.1.

Comparison 15 Sensitivity analysis (study sponsors): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



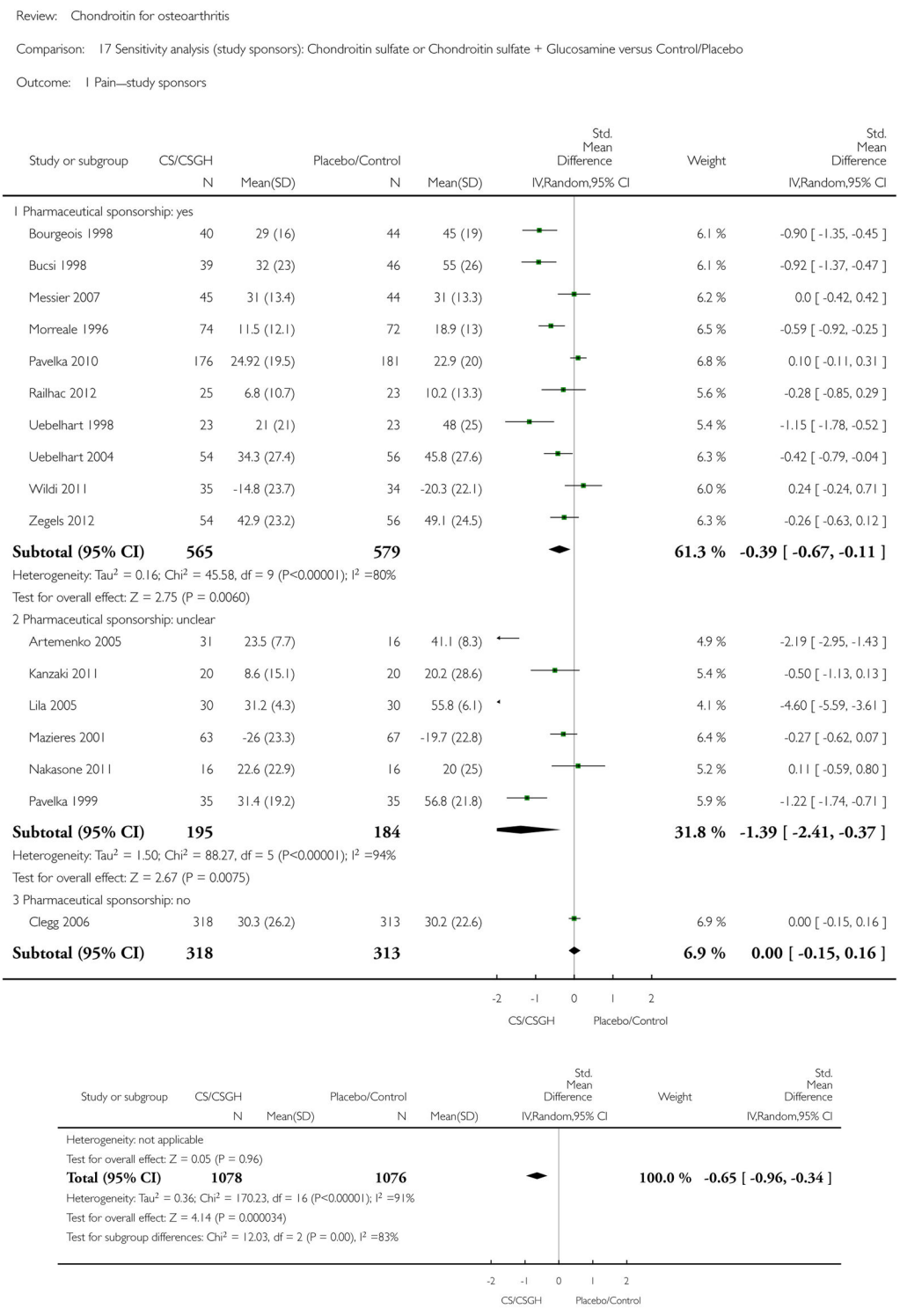
Analysis 15.2.

Comparison 15 Sensitivity analysis (study sponsors): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



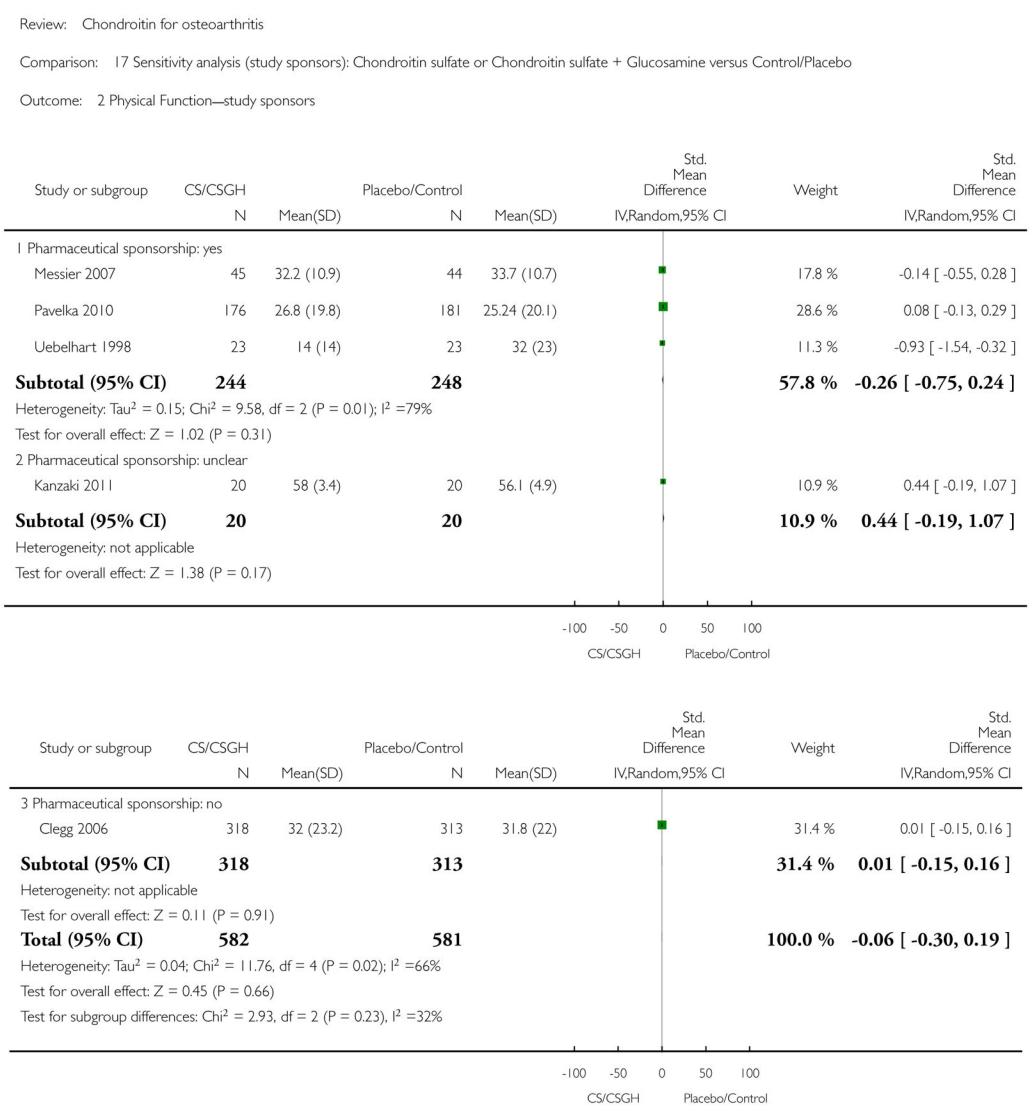
Analysis 16.1.

Comparison 16 Sensitivity analysis (study sponsors): Chondroitin sulfate + Glucosamine versus NSAIDs, Outcome 1 Pain on a 0 to 100 scale.



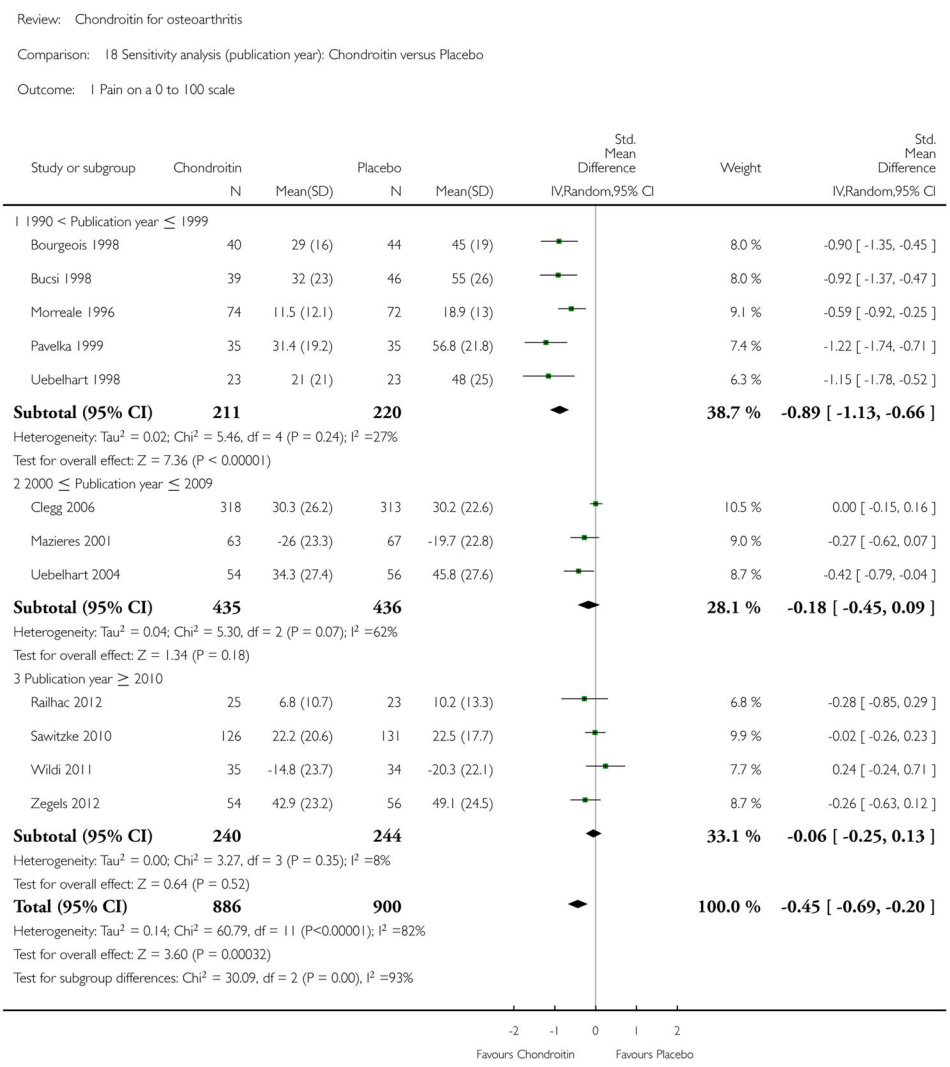
Analysis 17.1.

Comparison 17 Sensitivity analysis (study sponsors): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Control/Placebo, Outcome 1 Pain-study sponsors.



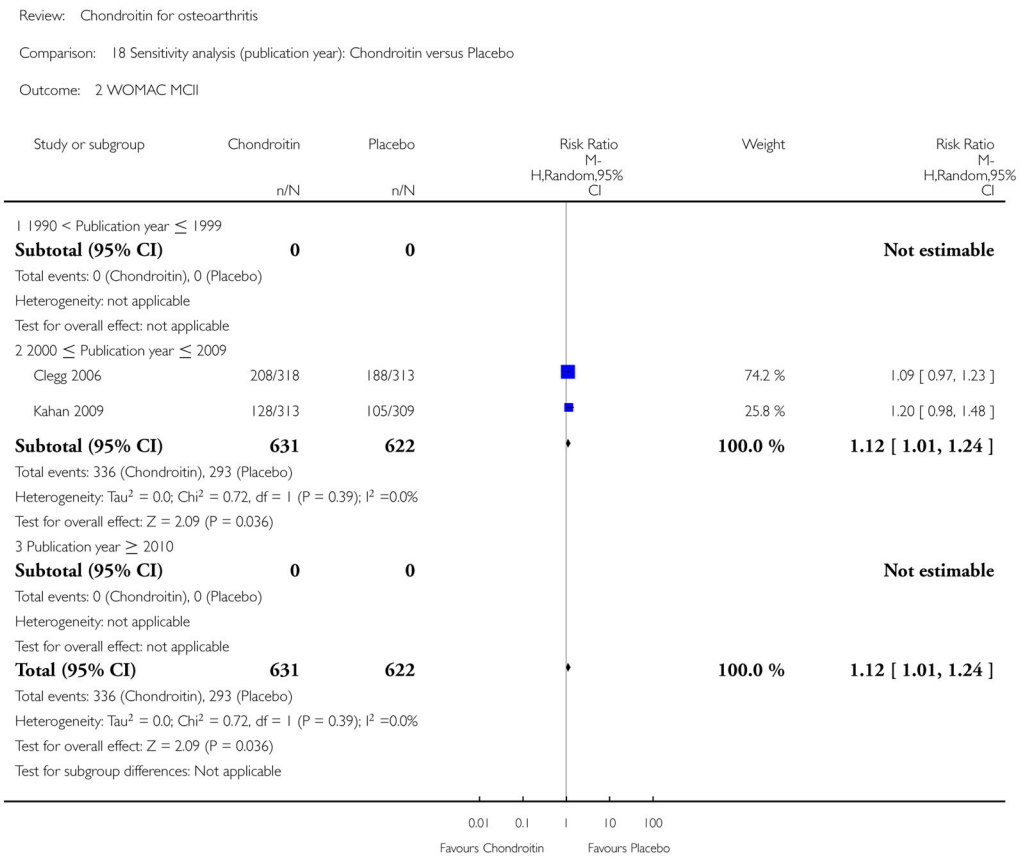
Analysis 17.2.

Comparison 17 Sensitivity analysis (study sponsors): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Control/Placebo, Outcome 2 Physical Function-study sponsors.

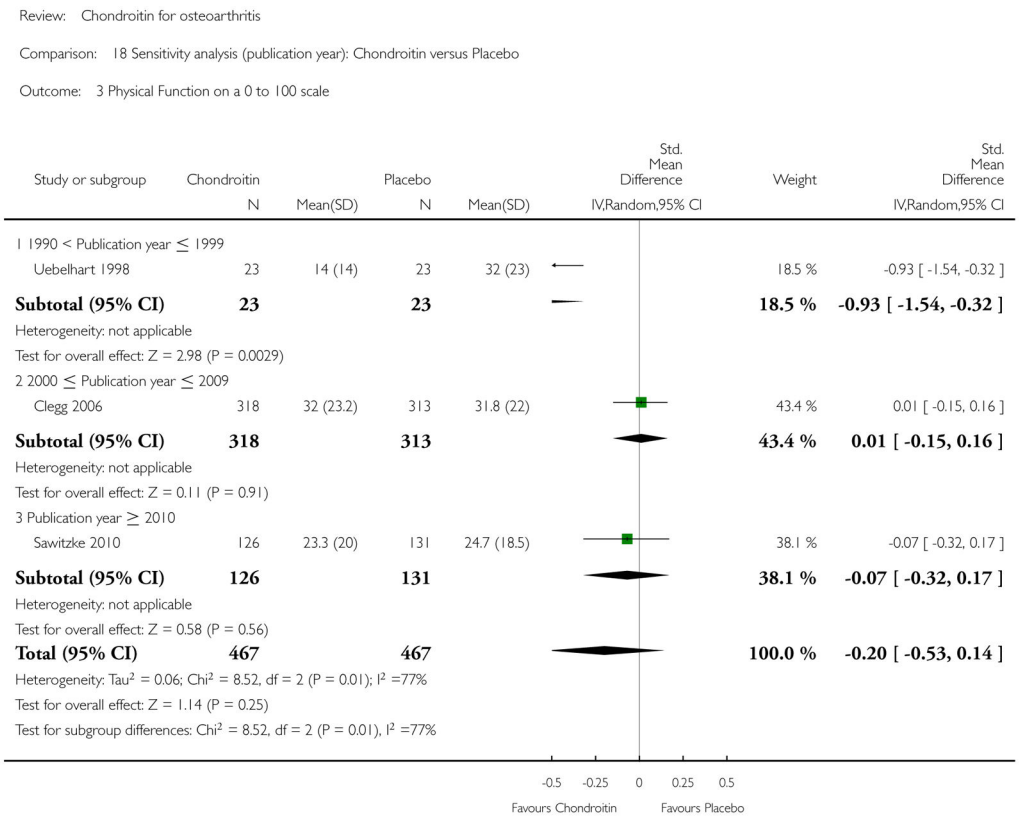


Analysis 18.1.

Comparison 18 Sensitivity analysis (publication year): Chondroitin versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

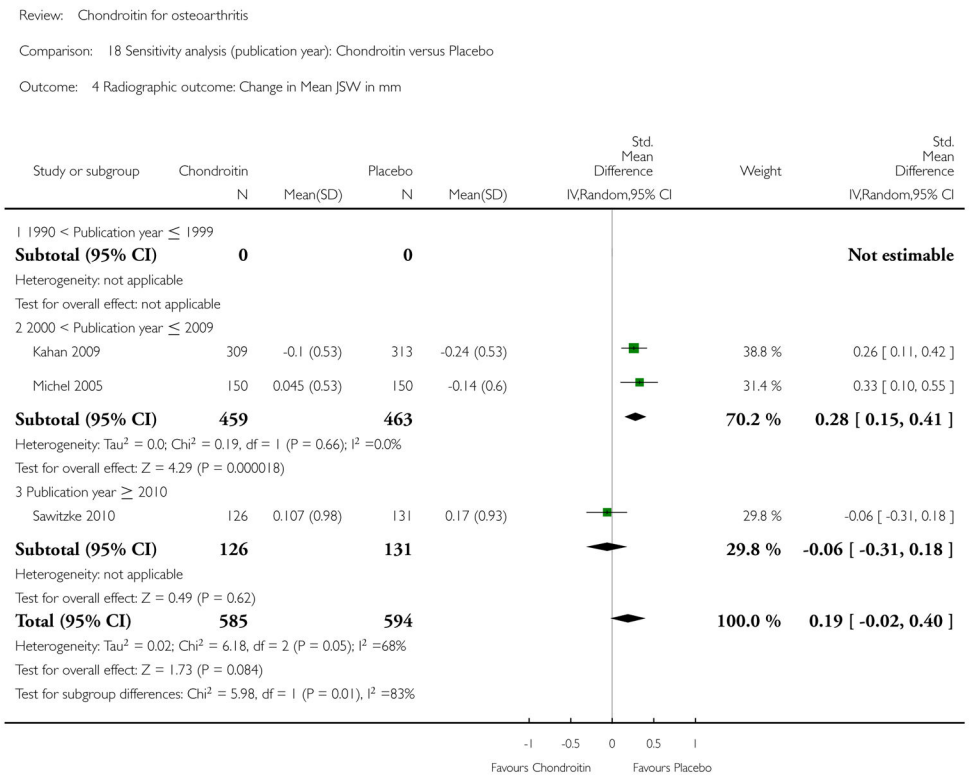


Analysis 18.2.
Comparison 18 Sensitivity analysis (publication year): Chondroitin versus Placebo, Outcome 2 WOMAC MCII.



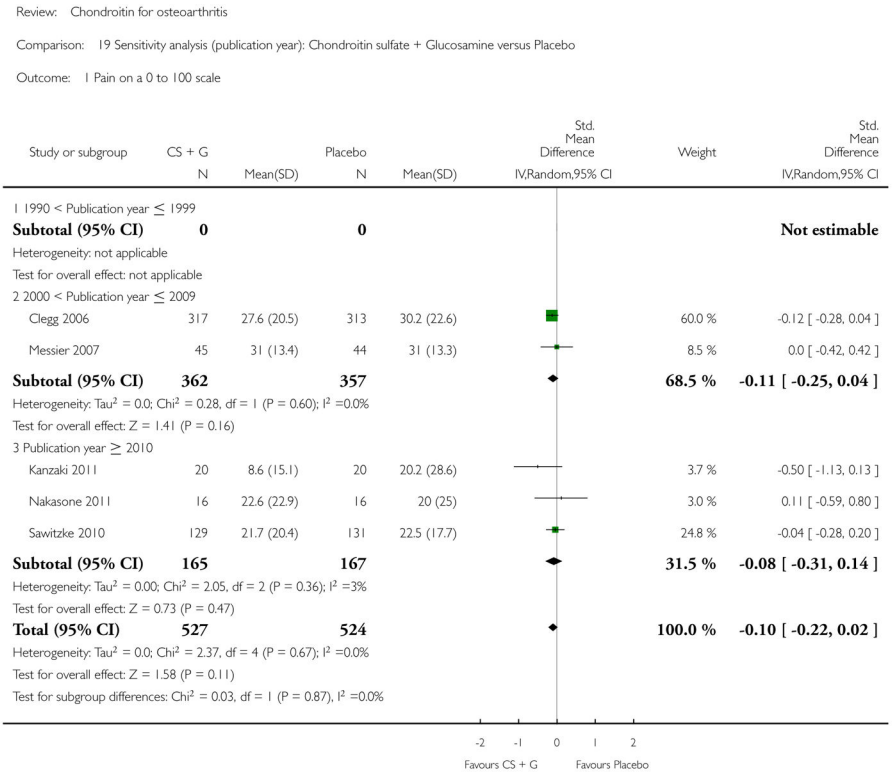
Analysis 18.3.

Comparison 18 Sensitivity analysis (publication year): Chondroitin versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



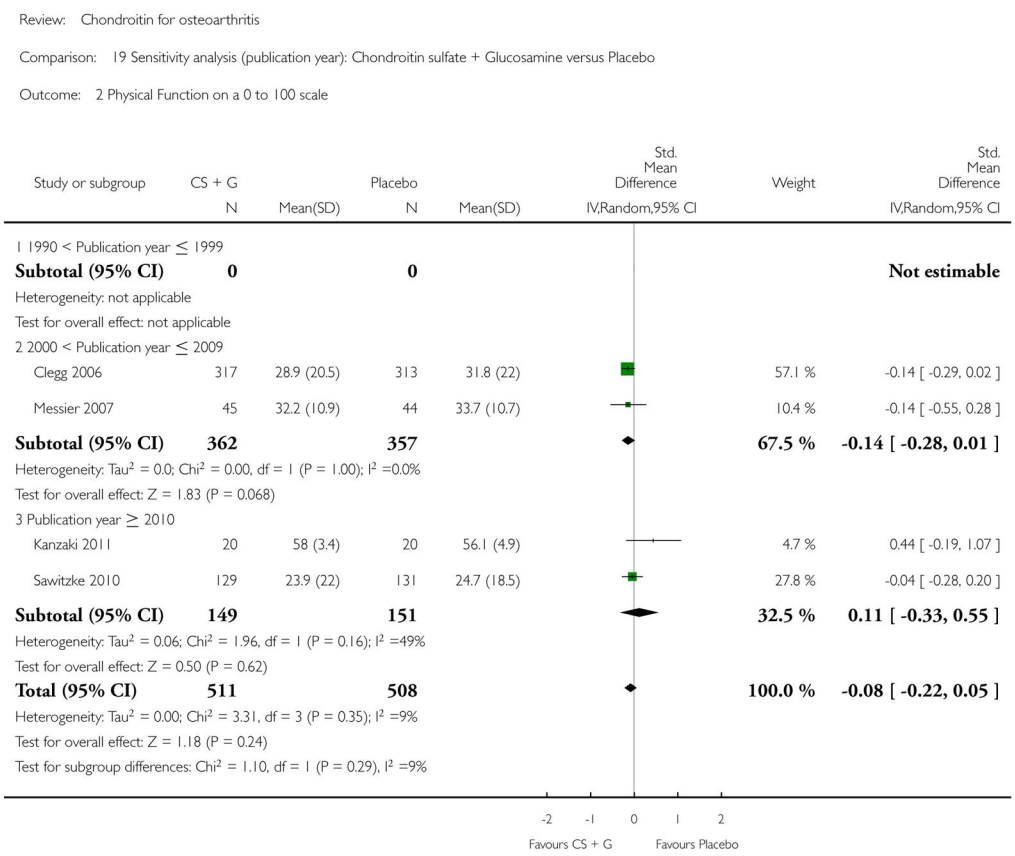
Analysis 18.4.

Comparison 18 Sensitivity analysis (publication year): Chondroitin versus Placebo, Outcome 4 Radiographic outcome: Change in Mean JSW in mm.



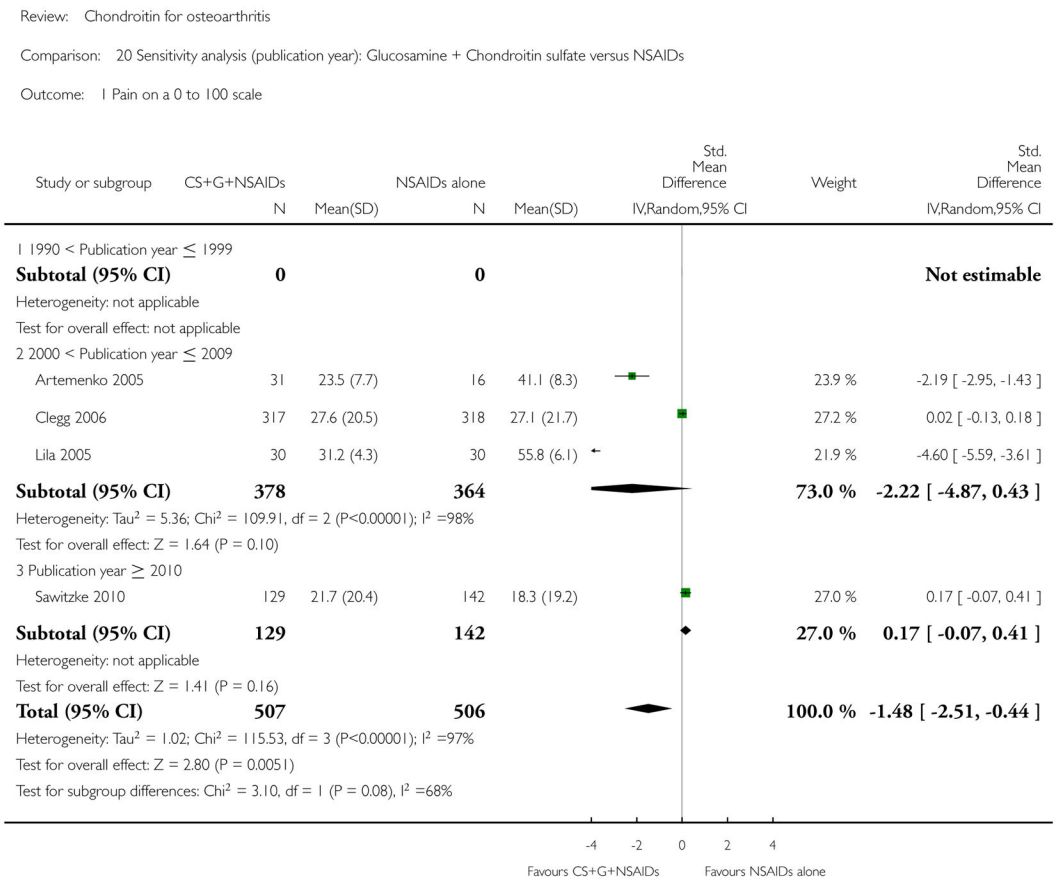
Analysis 19.1.

Comparison 19 Sensitivity analysis (publication year): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



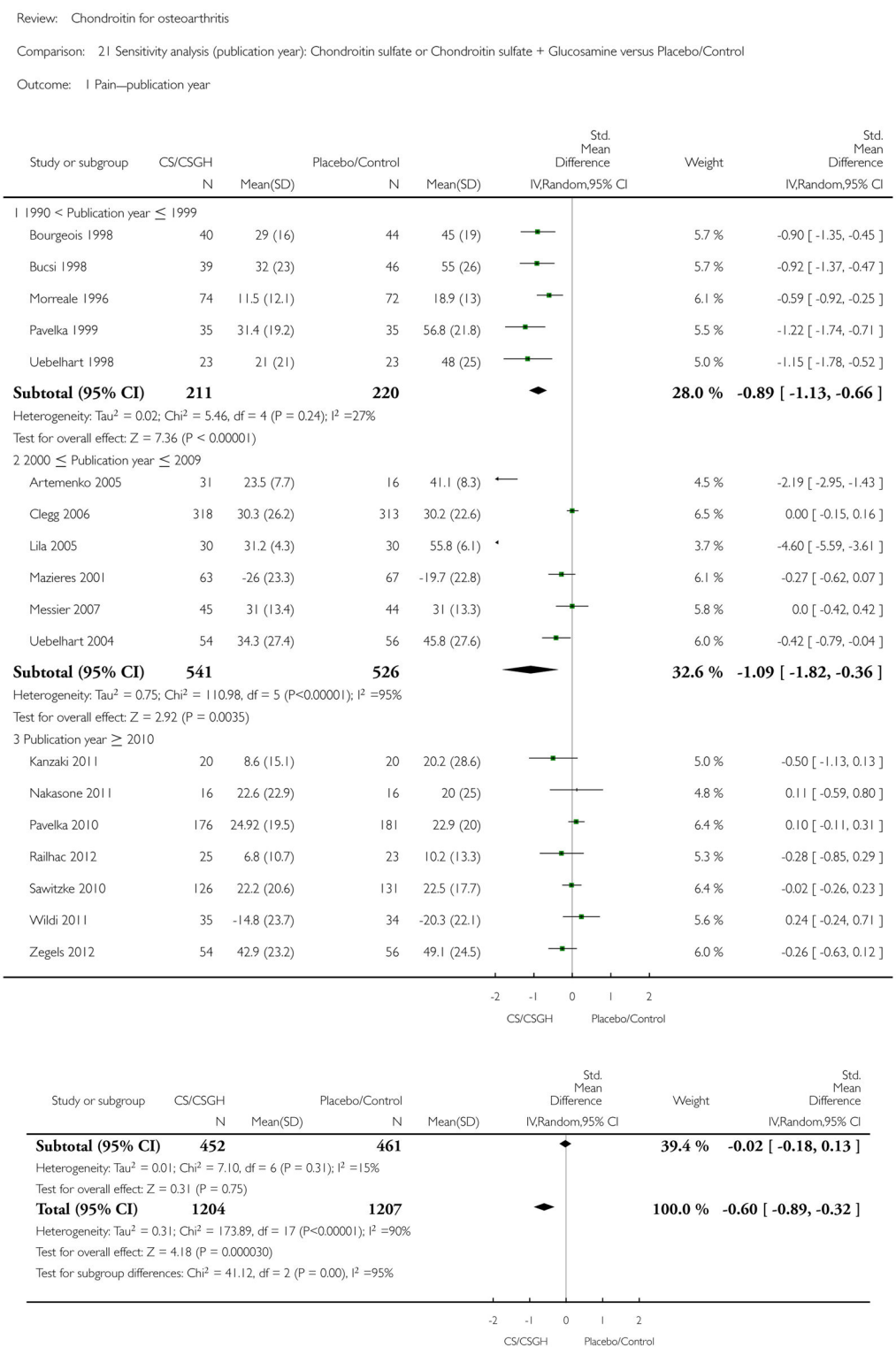
Analysis 19.2.

Comparison 19 Sensitivity analysis (publication year): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



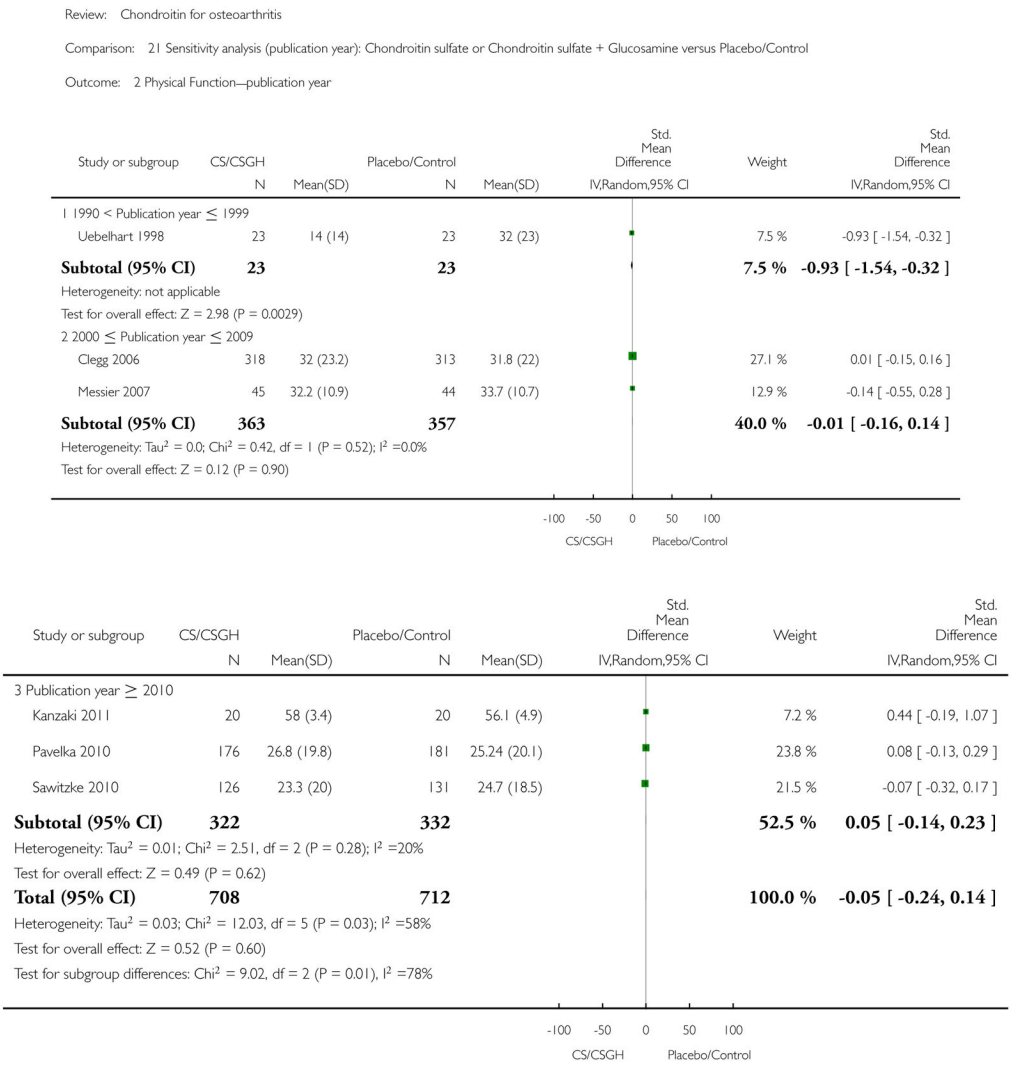
Analysis 20.1.

Comparison 20 Sensitivity analysis (publication year): Glucosamine + Chondroitin sulfate versus NSAIDs, Outcome 1 Pain on a 0 to 100 scale.



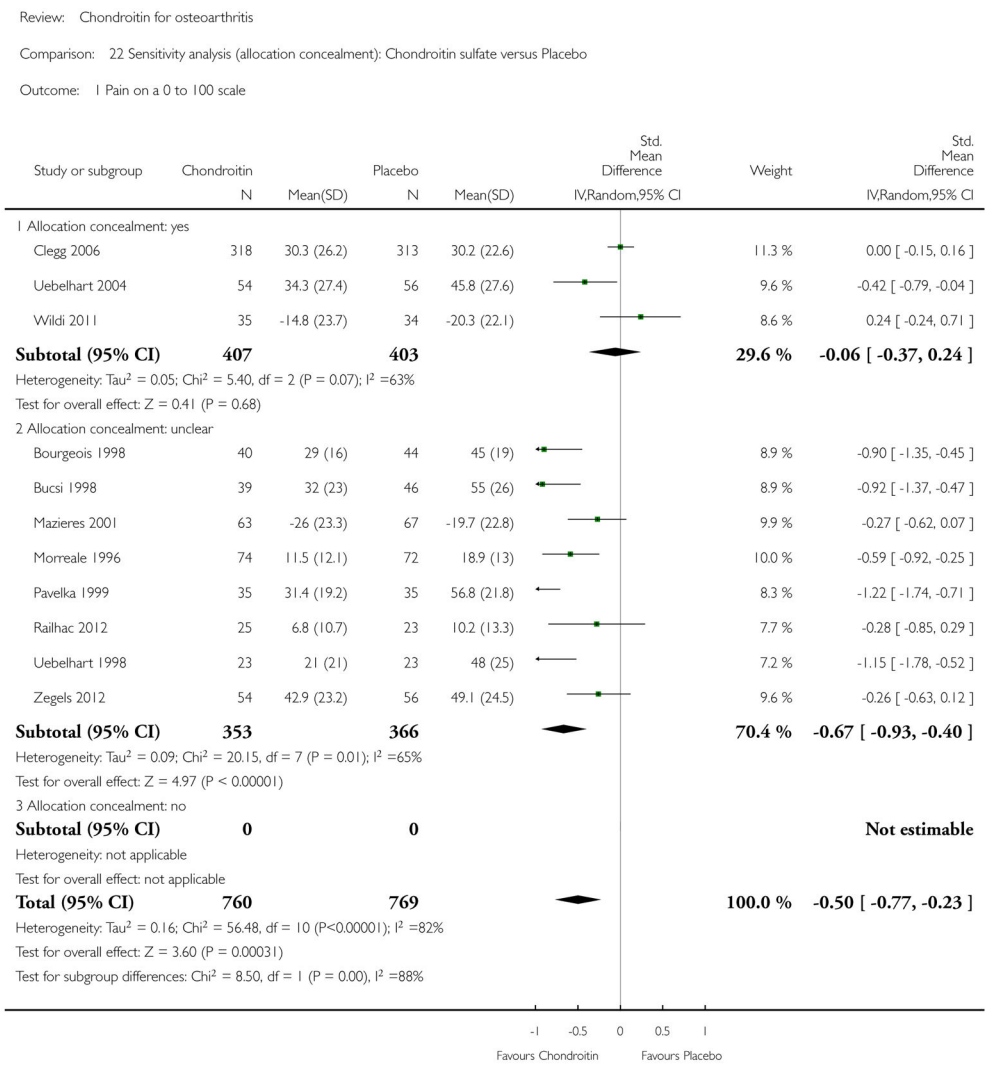
Analysis 21.1.

Comparison 21 Sensitivity analysis (publication year): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 1 Pain-publication year.



Analysis 21.2.

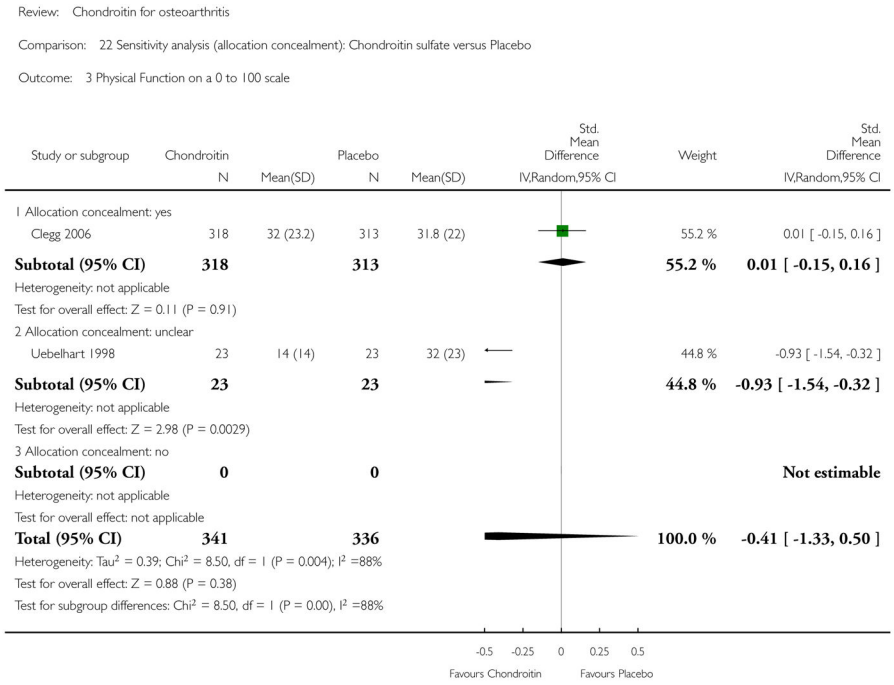
Comparison 21 Sensitivity analysis (publication year): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 2 Physical Function-publication year.



Analysis 22.1.

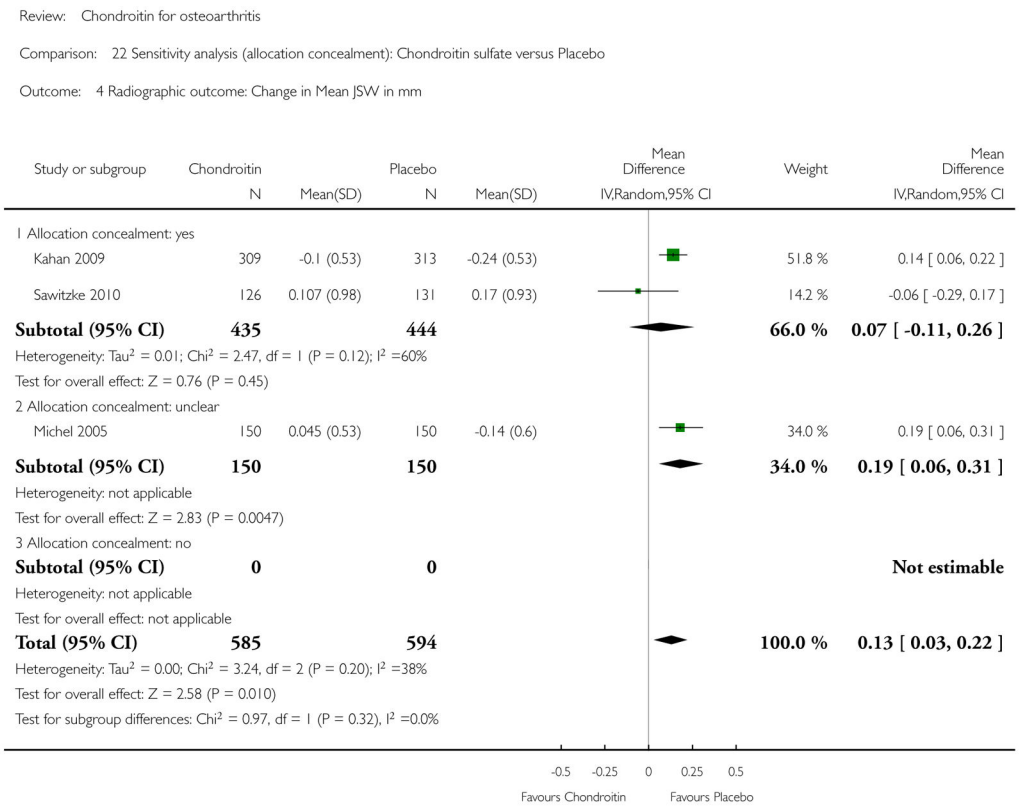
Comparison 22 Sensitivity analysis (allocation concealment): Chondroitin sulfate versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

Analysis 22.2.
Comparison 22 Sensitivity analysis (allocation concealment): Chondroitin sulfate versus Placebo, Outcome 2 WOMAC MCII.



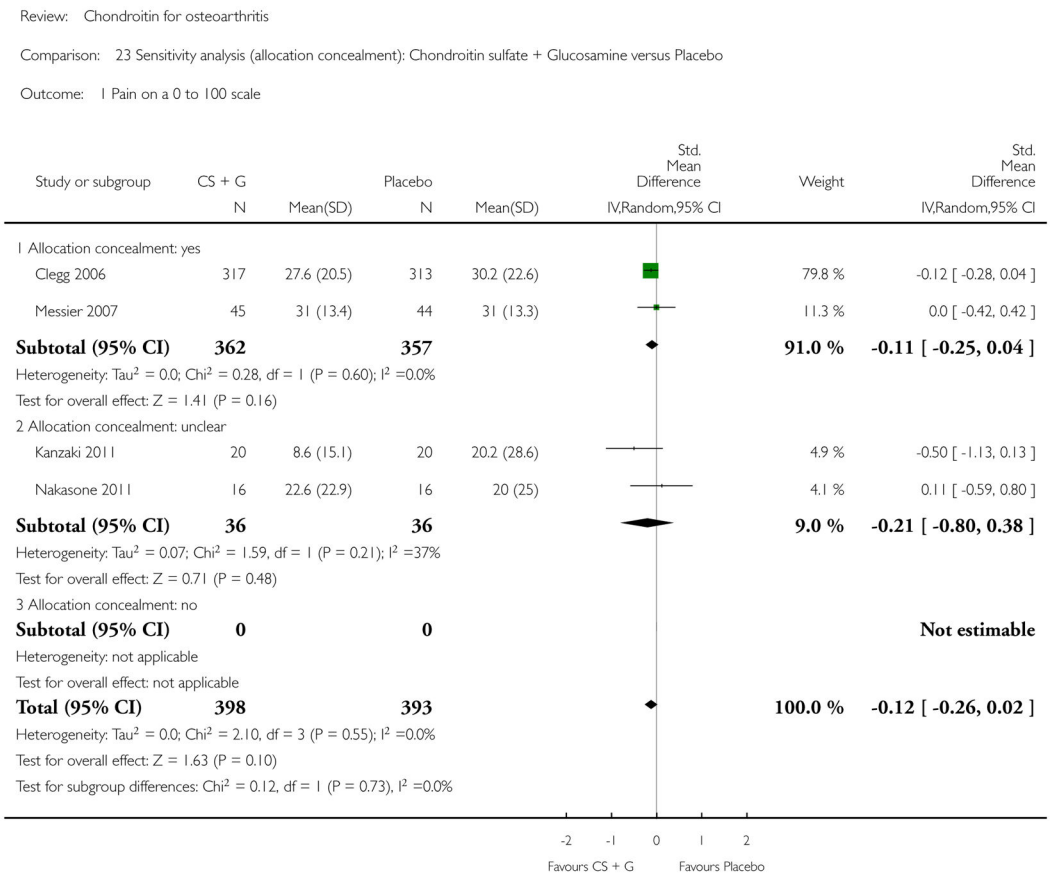
Analysis 22.3.

Comparison 22 Sensitivity analysis (allocation concealment): Chondroitin sulfate versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



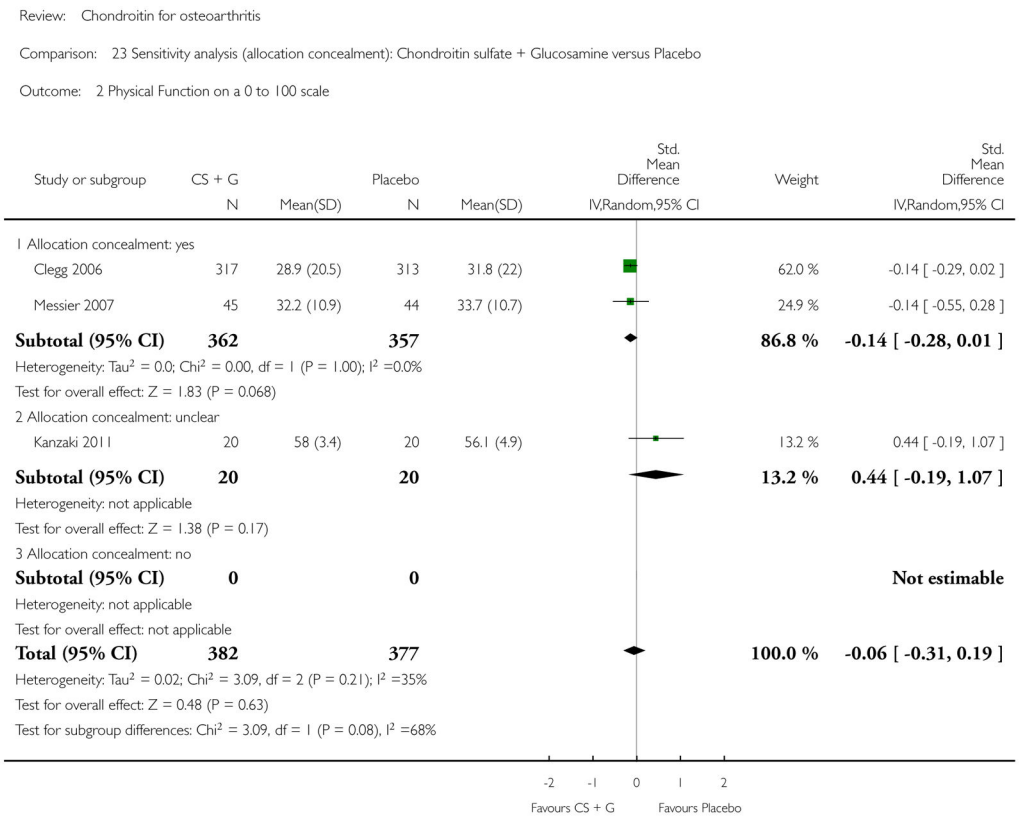
Analysis 22.4.

Comparison 22 Sensitivity analysis (allocation concealment): Chondroitin sulfate versus Placebo, Outcome 4 Radiographic outcome: Change in Mean JSW in mm.



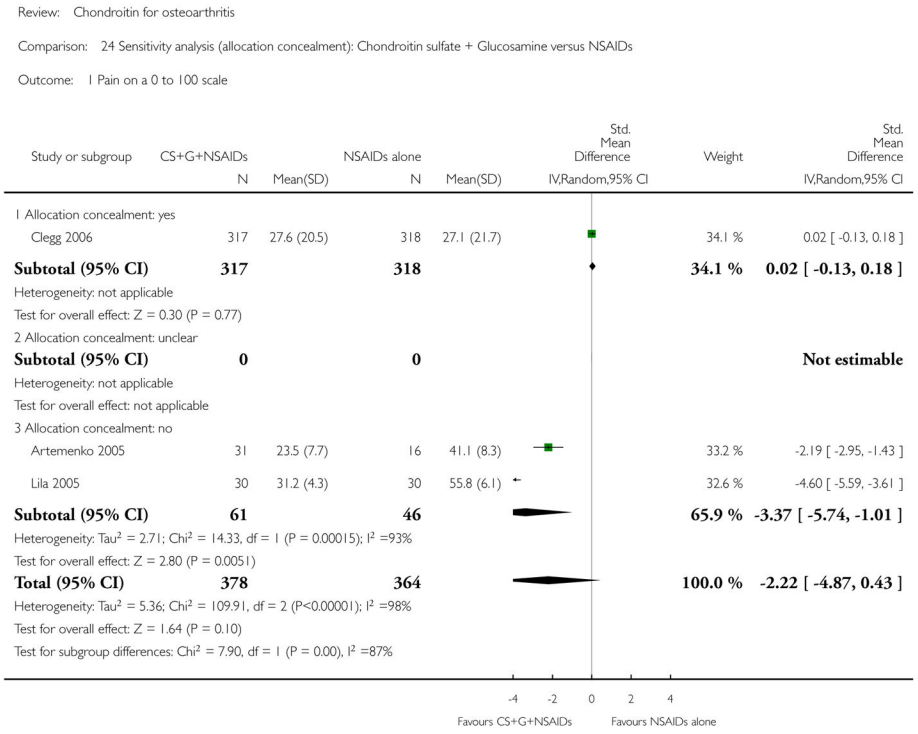
Analysis 23.1.

Comparison 23 Sensitivity analysis (allocation concealment): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



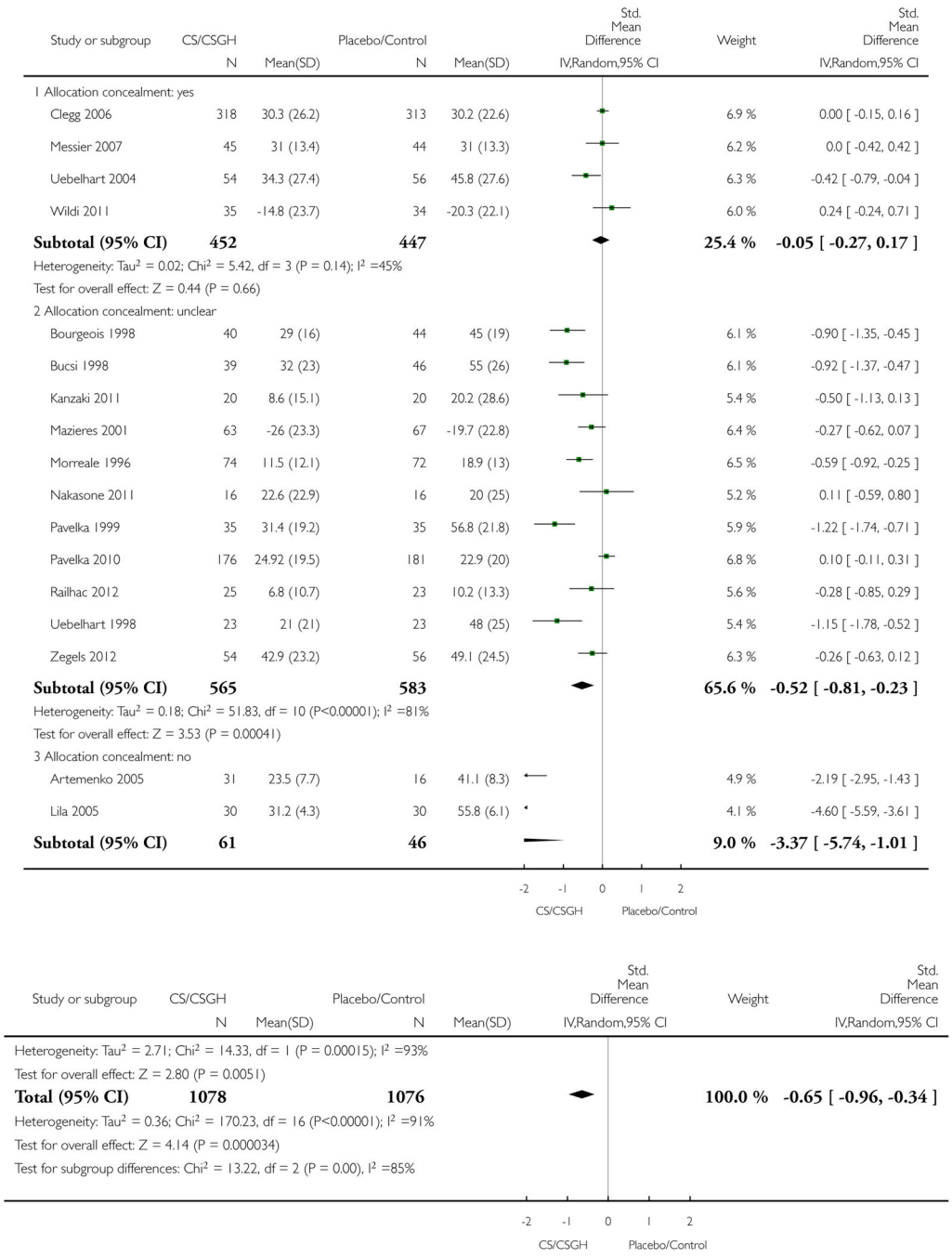
Analysis 23.2.

Comparison 23 Sensitivity analysis (allocation concealment): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



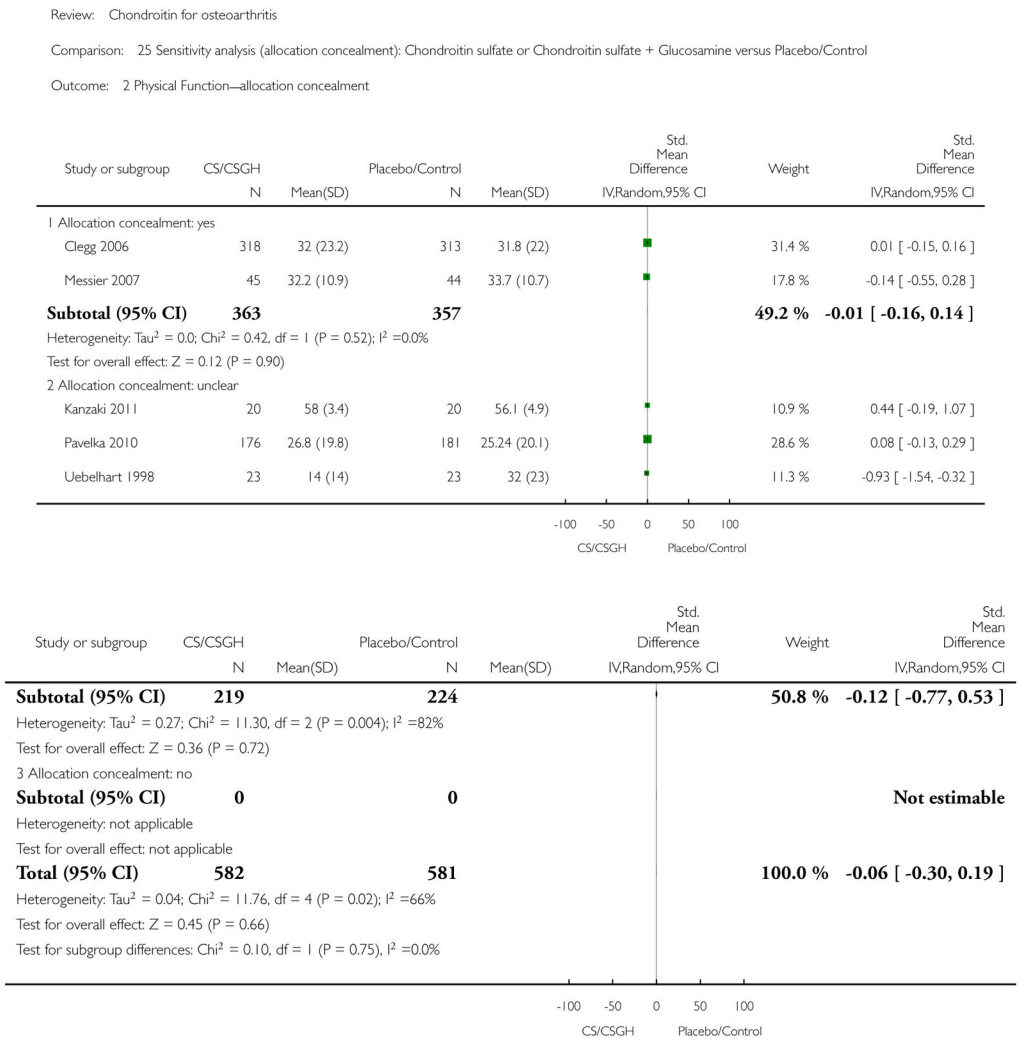
Analysis 24.1.

Comparison 24 Sensitivity analysis (allocation concealment): Chondroitin sulfate + Glucosamine versus NSAIDs, Outcome 1 Pain on a 0 to 100 scale.



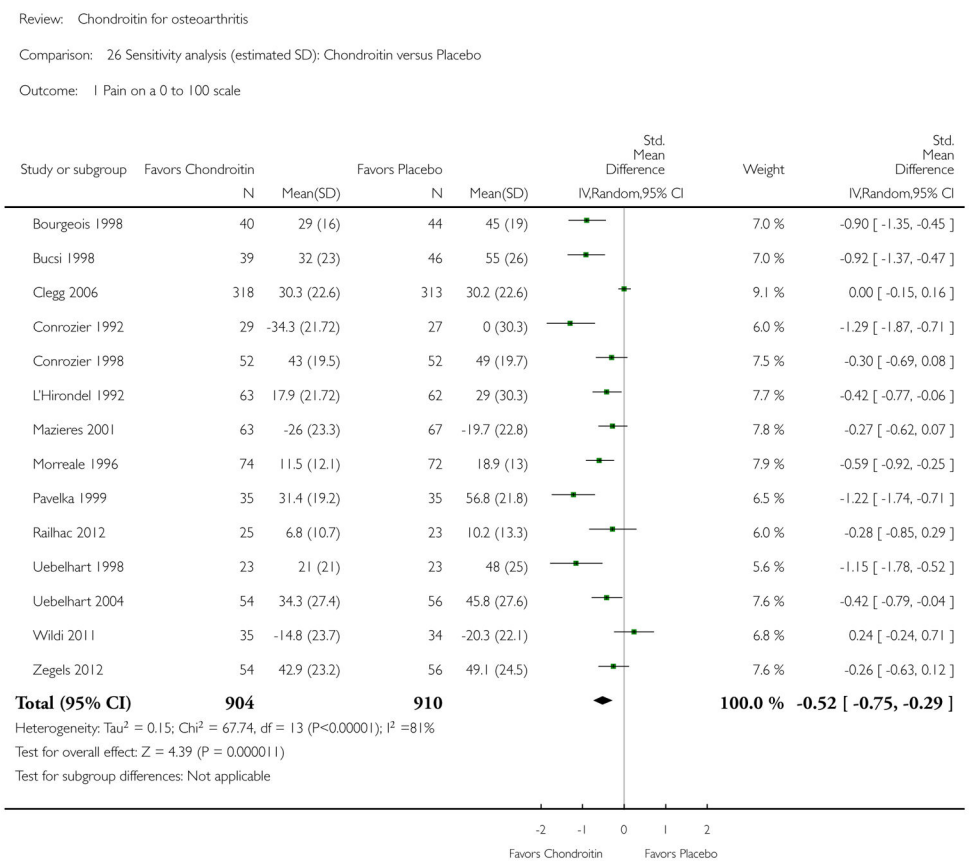
Analysis 25.1.

Comparison 25 Sensitivity analysis (allocation concealment): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 1 Pain-allocation concealment.

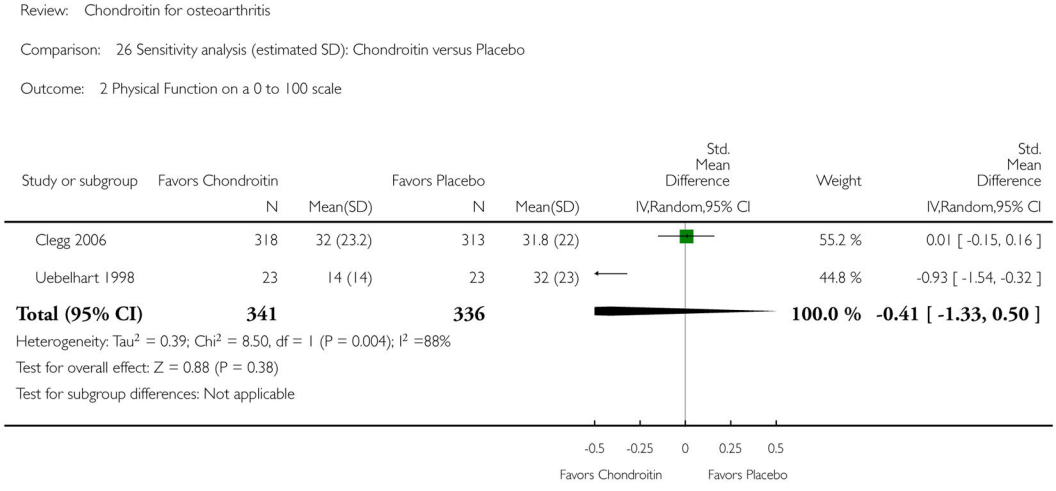


Analysis 25.2.

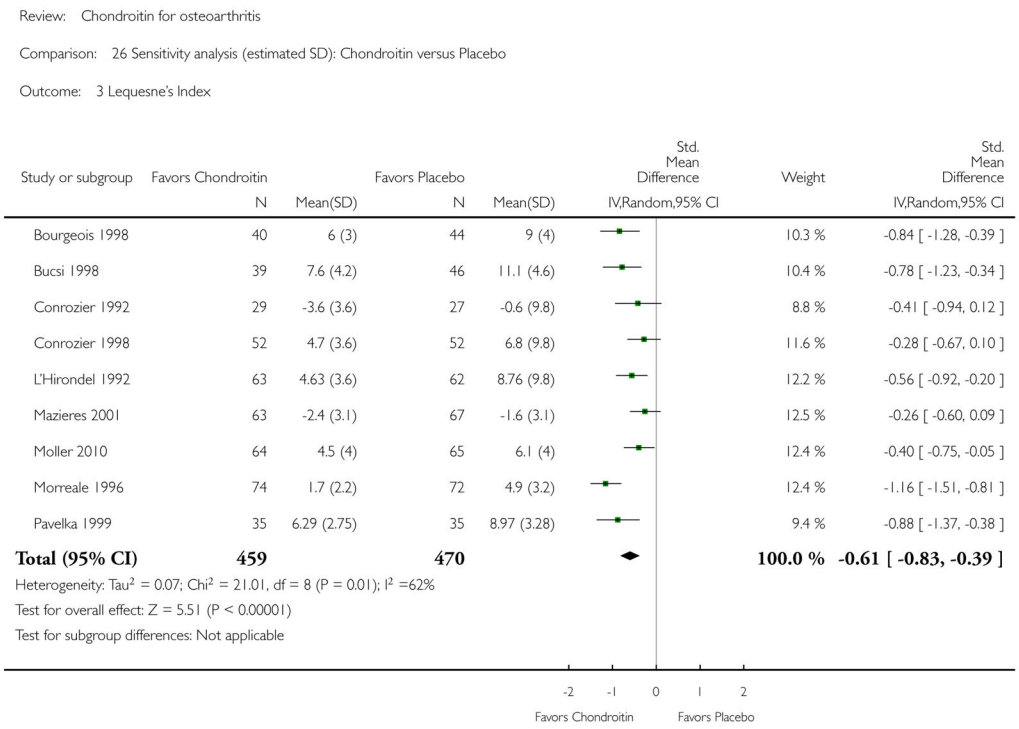
Comparison 25 Sensitivity analysis (allocation concealment): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 2 Physical Function-allocation concealment.



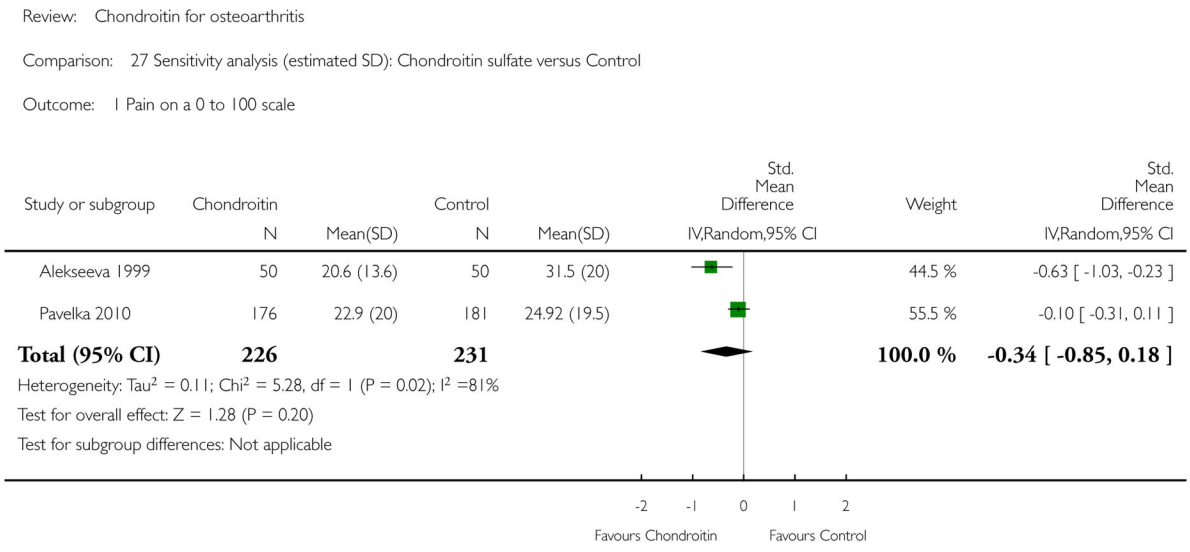
Analysis 26.1.
Comparison 26 Sensitivity analysis (estimated SD): Chondroitin versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



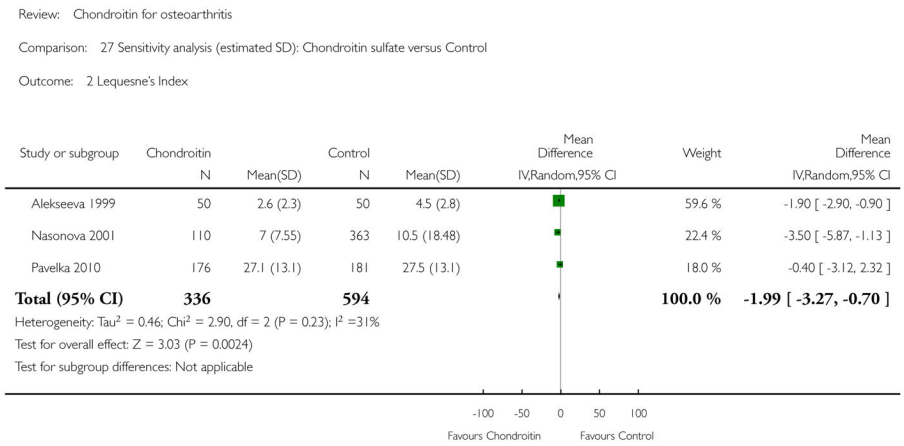
Analysis 26.2.
Comparison 26 Sensitivity analysis (estimated SD): Chondroitin versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



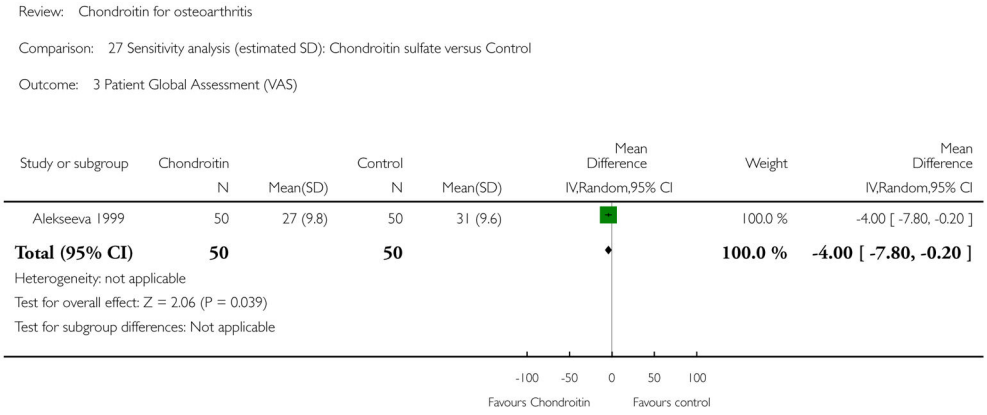
Analysis 26.3.
Comparison 26 Sensitivity analysis (estimated SD): Chondroitin versus Placebo, Outcome 3 Lequesne's Index.



Analysis 27.1.
Comparison 27 Sensitivity analysis (estimated SD): Chondroitin sulfate versus Control, Outcome 1 Pain on a 0 to 100 scale.



Analysis 27.2.
Comparison 27 Sensitivity analysis (estimated SD): Chondroitin sulfate versus Control, Outcome 2 Lequesne's Index.



Analysis 27.3.
Comparison 27 Sensitivity analysis (estimated SD): Chondroitin sulfate versus Control, Outcome 3 Patient Global Assessment (VAS).

Review: Chondroitin for osteoarthritis

Comparison: 28 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo

Outcome: 1 Pain on a 0 to 100 scale

Study or subgroup	Chondroitin Sulfate + Glucosamine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Clegg 2006	317	27.6 (20.5)	313	30.2 (22.6)		79.8 %	-0.12 [-0.28, 0.04]
Kanzaki 2011	20	8.6 (15.1)	20	20.2 (28.6)		4.9 %	-0.50 [-1.13, 0.13]
Messier 2007	45	31 (13.4)	44	31 (13.3)		11.3 %	0.0 [-0.42, 0.42]
Nakasone 2011	16	22.6 (22.9)	16	20 (25)		4.1 %	0.11 [-0.59, 0.80]
Total (95% CI)	**398**		**393**			**100.0 %**	**-0.12 [-0.26, 0.02]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.10$, df = 3 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 1.63 (P = 0.10)

Test for subgroup differences: Not applicable

Analysis 28.1.

Comparison 28 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

Review: Chondroitin for osteoarthritis

Comparison: 28 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo

Outcome: 2 WOMAC Total

Study or subgroup	Chondroitin Sulfate + Glucosamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Clegg 2006	317	29.8 (20.5)	313	32.4 (22.03)		86.2 %	-2.60 [-5.92, 0.72]
Das 2000	46	30.9 (18.46)	47	31.29 (22.25)		13.8 %	-0.39 [-8.69, 7.91]
Total (95% CI)	**363**		**360**			**100.0 %**	**-2.29 [-5.38, 0.79]**

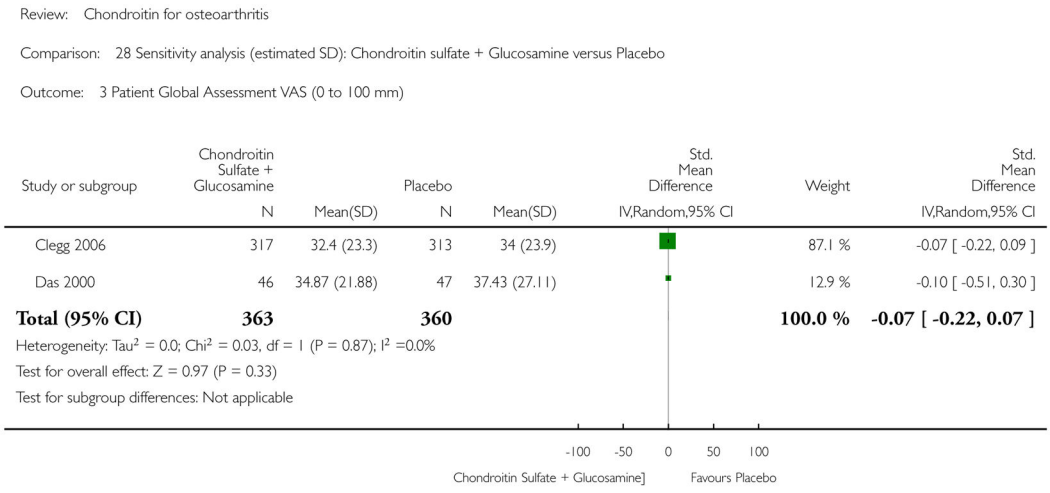
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable

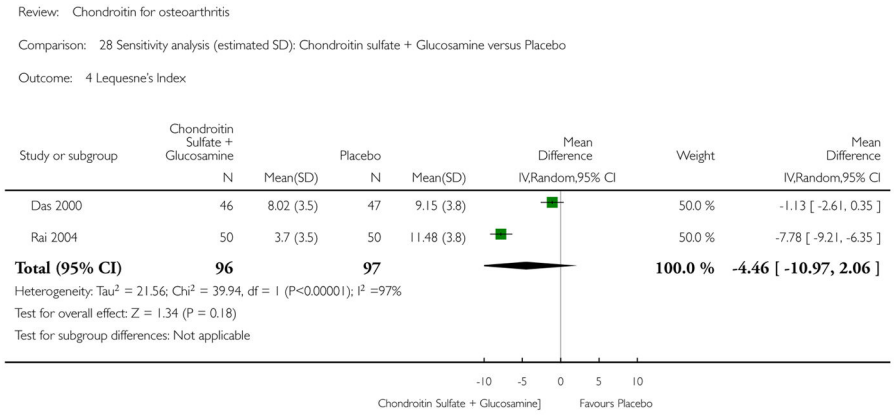
Analysis 28.2.

Comparison 28 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 WOMAC Total.



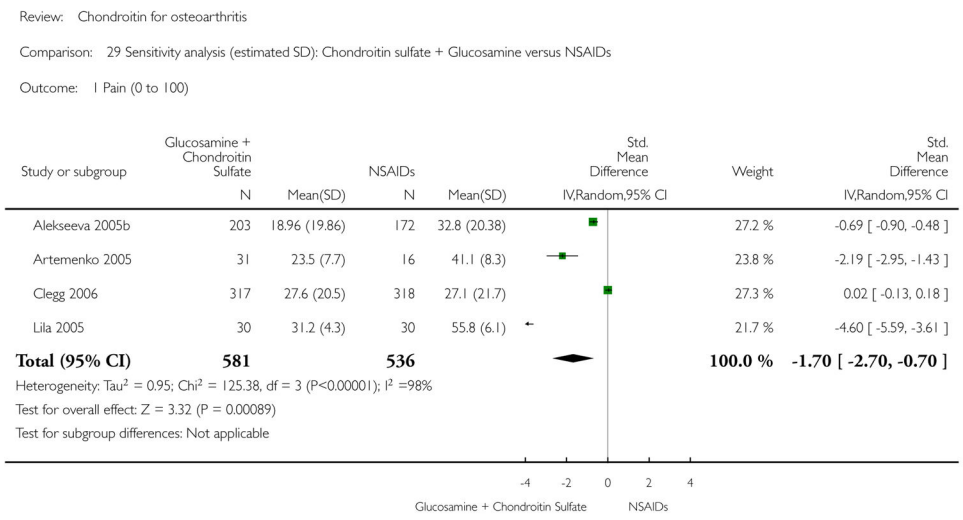
Analysis 28.3.

Comparison 28 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 3 Patient Global Assessment VAS (0 to 100 mm).

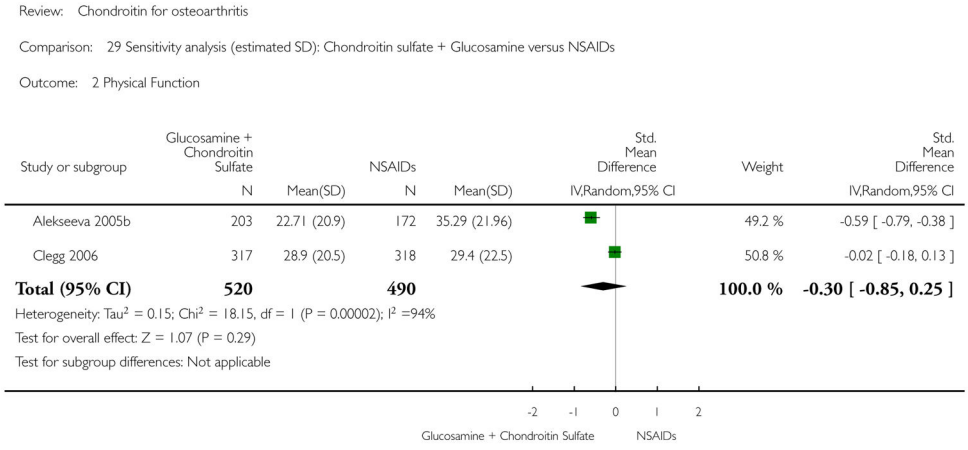


Analysis 28.4.

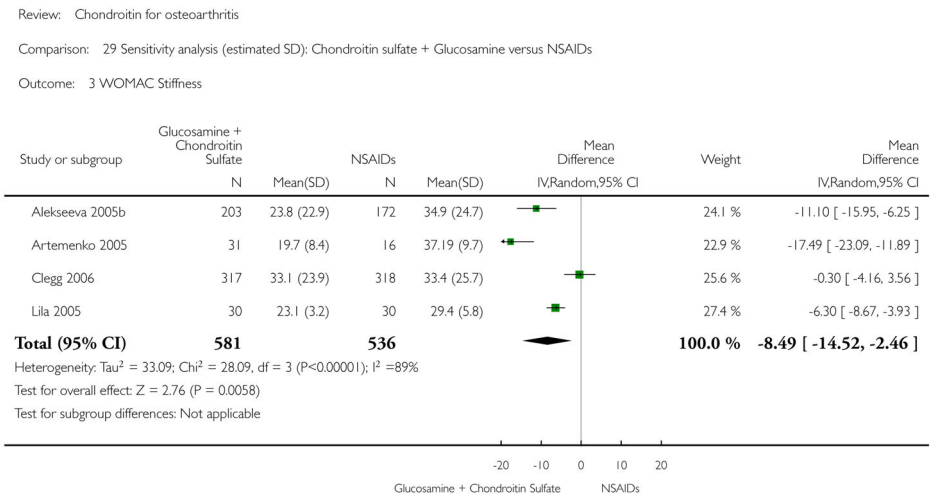
Comparison 28 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 4 Lequesne's Index.



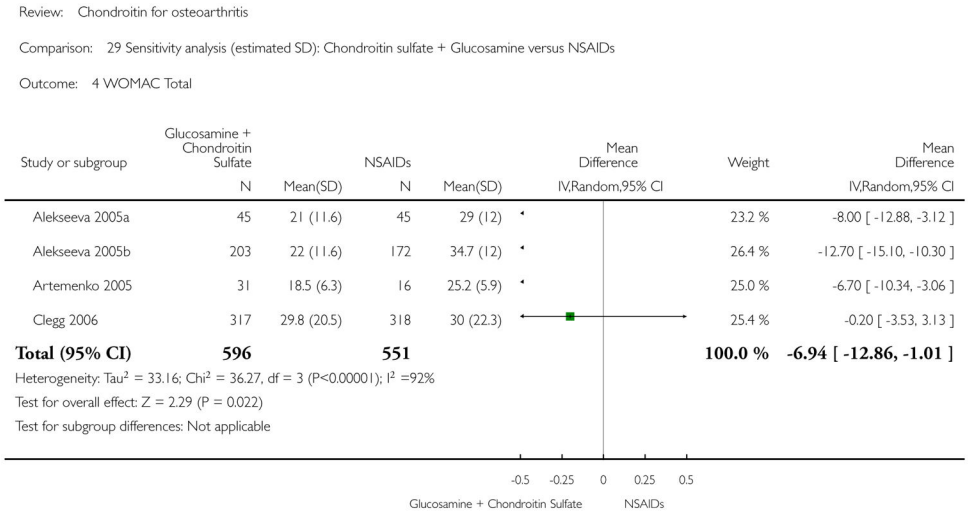
Analysis 29.1.
Comparison 29 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus NSAIDs, Outcome 1 Pain (0 to 100).



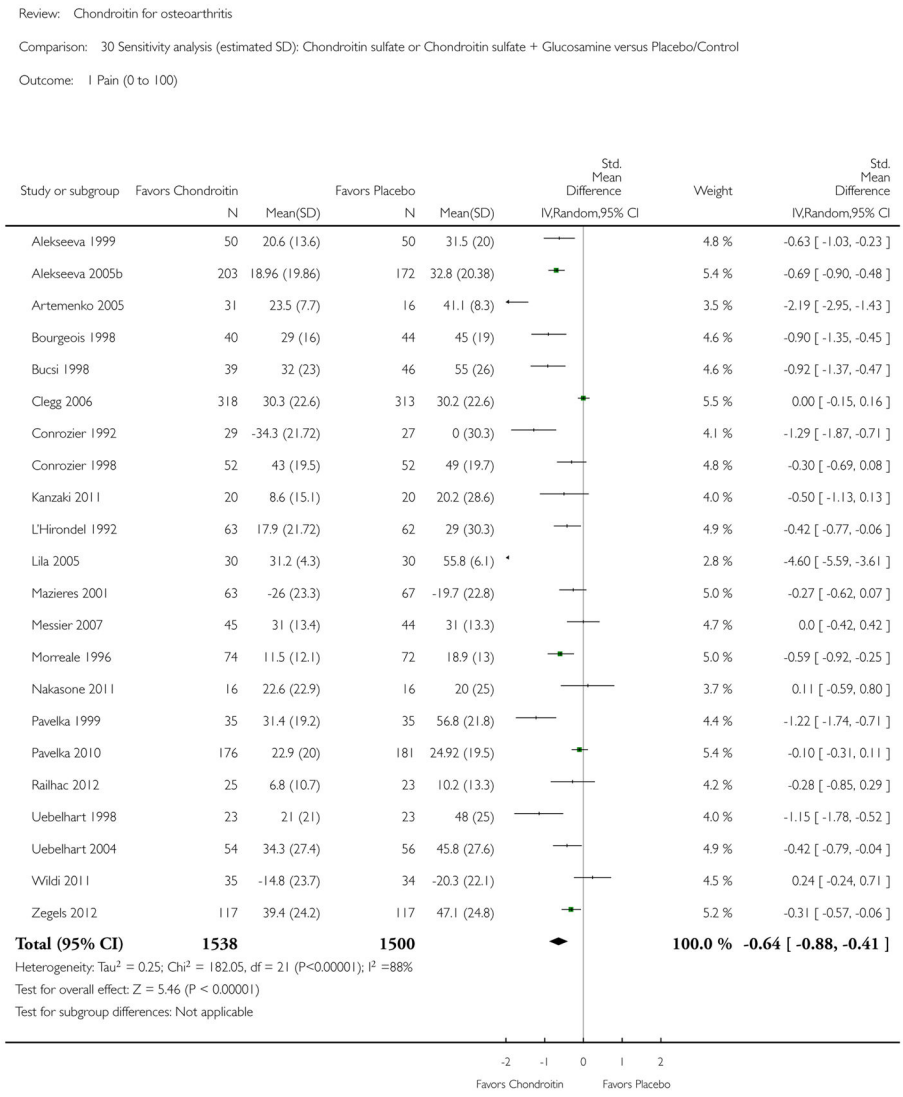
Analysis 29.2.
Comparison 29 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus NSAIDs, Outcome 2 Physical Function.



Analysis 29.3.
Comparison 29 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus NSAIDs, Outcome 3 WOMAC Stiffness.

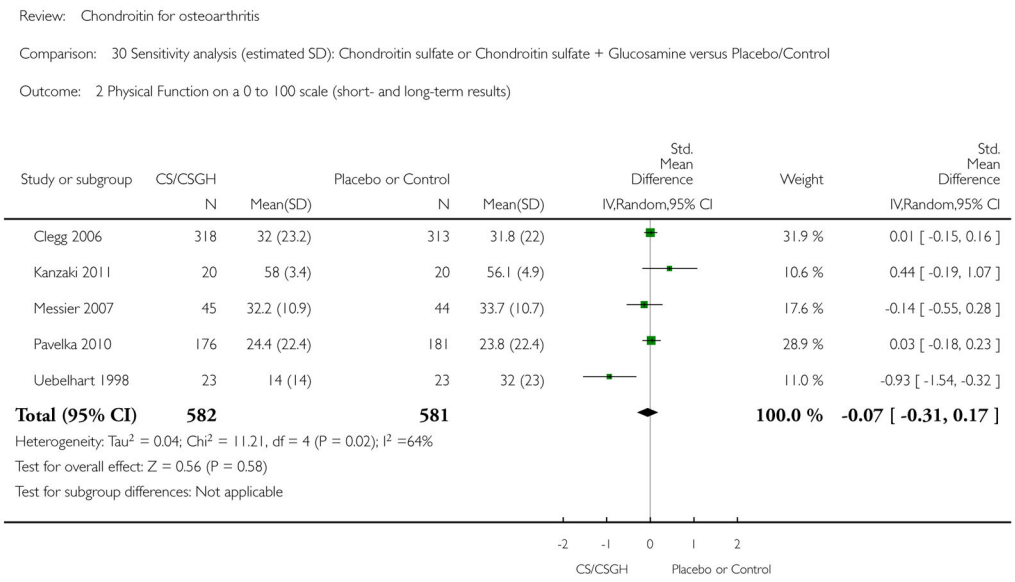


Analysis 29.4.
Comparison 29 Sensitivity analysis (estimated SD): Chondroitin sulfate + Glucosamine versus NSAIDs, Outcome 4 WOMAC Total.



Analysis 30.1.

Comparison 30 Sensitivity analysis (estimated SD): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 1 Pain (0 to 100).



Analysis 30.2.

Comparison 30 Sensitivity analysis (estimated SD): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 2 Physical Function on a 0 to 100 scale (short- and long-term results).

Review: Chondroitin for osteoarthritis

Comparison: 30 Sensitivity analysis (estimated SD): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control

Outcome: 3 Lequesne's Index

Study or subgroup	Favors Chondroitin N	Mean(SD)	Favors Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Alekseeva 1999	50	2.6 (2.3)	50	4.5 (2.8)		6.2 %	-0.74 [-1.14, -0.33]
Bourgeois 1998	40	6 (3)	44	9 (4)		5.9 %	-0.84 [-1.28, -0.39]
Bucsi 1998	39	7.6 (4.2)	46	11.1 (4.6)		5.9 %	-0.78 [-1.23, -0.34]
Conrozier 1992	29	-3.6 (3.6)	27	-0.6 (9.8)		5.4 %	-0.41 [-0.94, 0.12]
Conrozier 1998	52	4.7 (3.6)	52	6.8 (9.8)		6.3 %	-0.28 [-0.67, 0.10]
Das 2000	46	8.02 (3.5)	47	9.15 (3.8)		6.2 %	-0.31 [-0.72, 0.10]
L'Hirondel 1992	63	4.63 (3.6)	62	8.76 (9.8)		6.5 %	-0.56 [-0.92, -0.20]
Mazieres 2001	63	-2.4 (3.1)	67	-1.6 (3.1)		6.5 %	-0.26 [-0.60, 0.09]
Moller 2010	64	4.5 (4)	65	6.1 (4)		6.5 %	-0.40 [-0.75, -0.05]
Morreale 1996	74	1.7 (2.2)	72	4.9 (3.2)		6.5 %	-1.16 [-1.51, -0.81]
Nasonova 2001	110	7 (7.55)	363	10.5 (18.48)		7.2 %	-0.21 [-0.42, 0.00]
Pavelka 1999	35	6.29 (2.75)	35	8.97 (3.28)		5.6 %	-0.88 [-1.37, -0.38]
Pavelka 2010	176	6.5 (3.15)	181	6.6 (3.14)		7.3 %	-0.03 [-0.24, 0.18]
Rai 2004	50	3.7 (3.5)	50	11.48 (3.8)		5.6 %	-2.11 [-2.61, -1.62]
Railhac 2012	25	6.9 (4.3)	23	6.8 (4)		5.2 %	0.02 [-0.54, 0.59]
Zegels 2012	117	7.8 (4.2)	117	9.7 (4.6)		7.0 %	-0.43 [-0.69, -0.17]
Total (95% CI)	**1033**		**1301**			**100.0 %**	**-0.57 [-0.79, -0.35]**

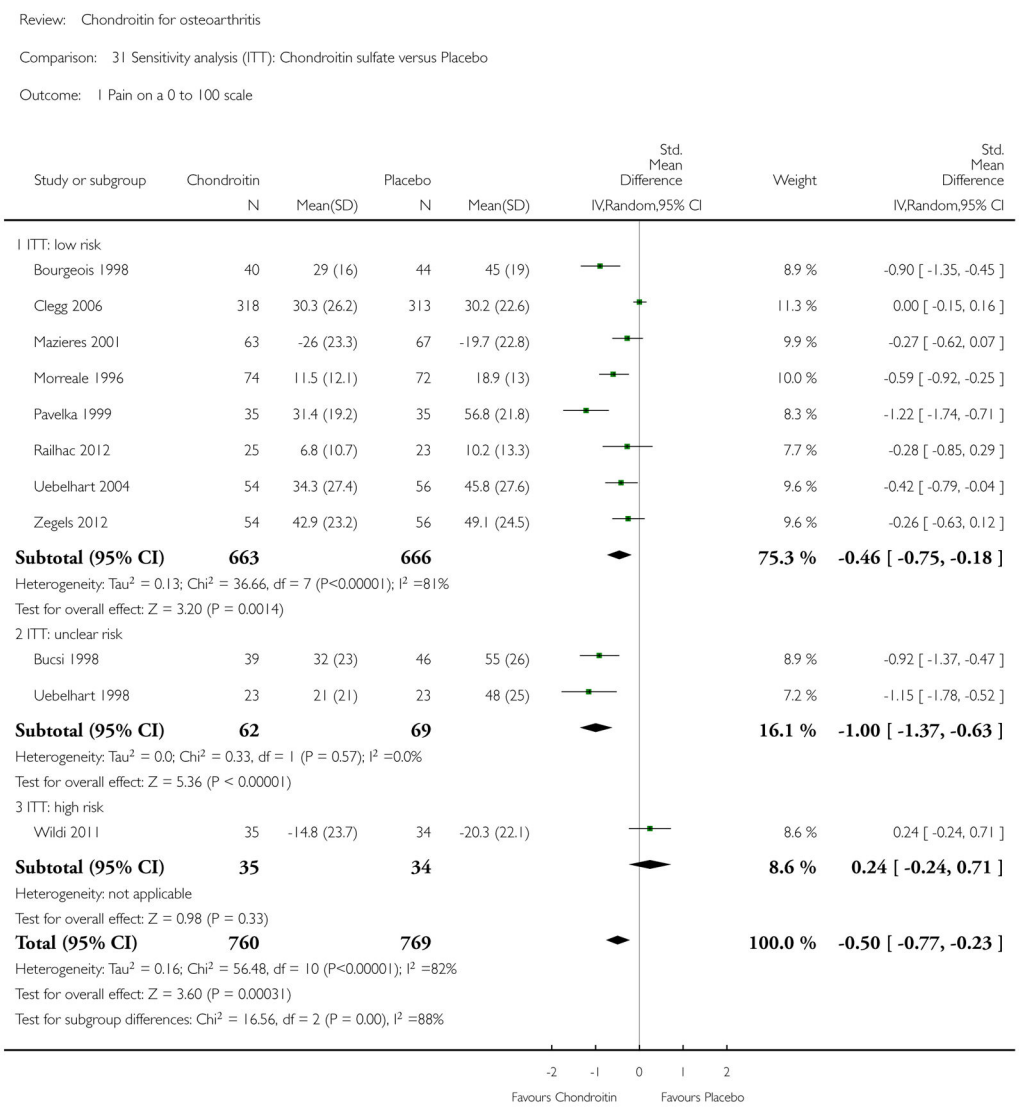
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 95.34$, df = 15 ($P<0.00001$); $I^2 = 84\%$

Test for overall effect: $Z = 4.98$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

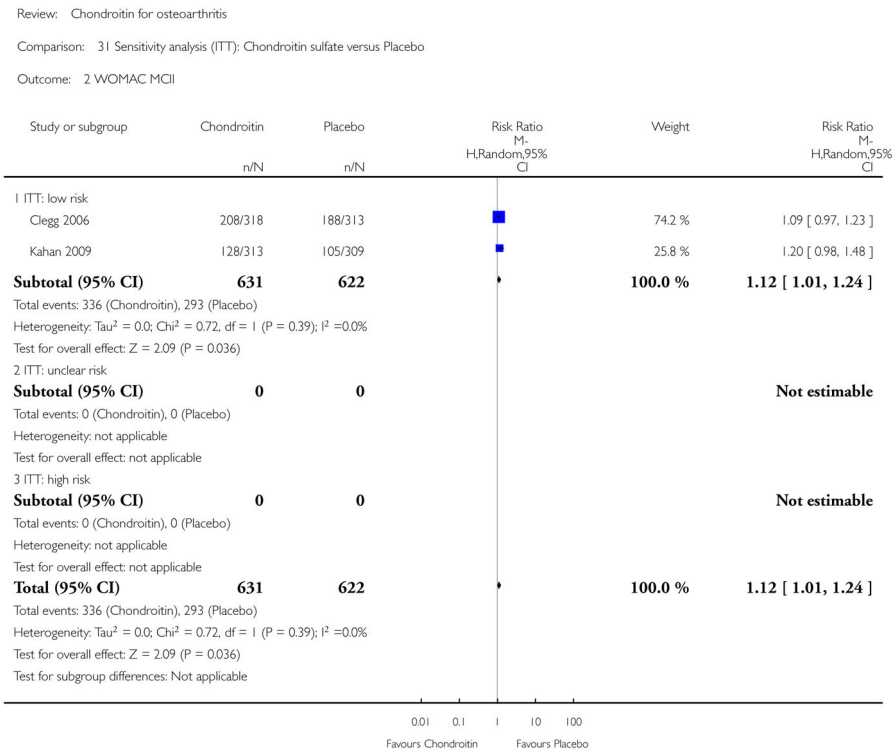
Analysis 30.3.

Comparison 30 Sensitivity analysis (estimated SD): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 3 Lequesne's Index.

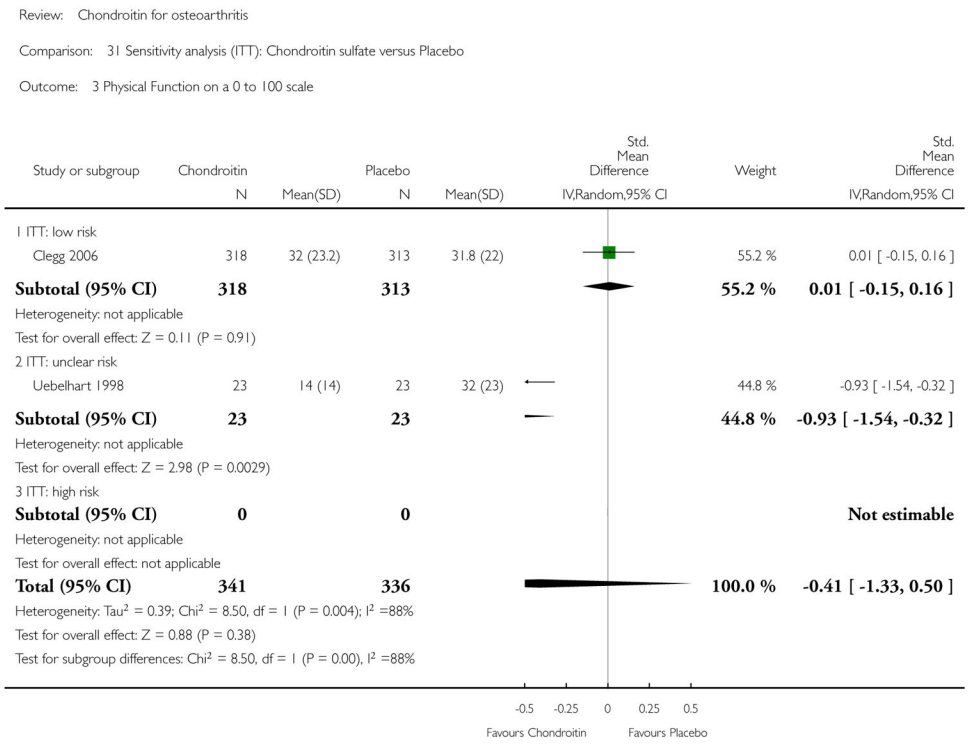


Analysis 31.1.

Comparison 31 Sensitivity analysis (ITT): Chondroitin sulfate versus Placebo, Outcome 1 Pain on a 0 to 100 scale.

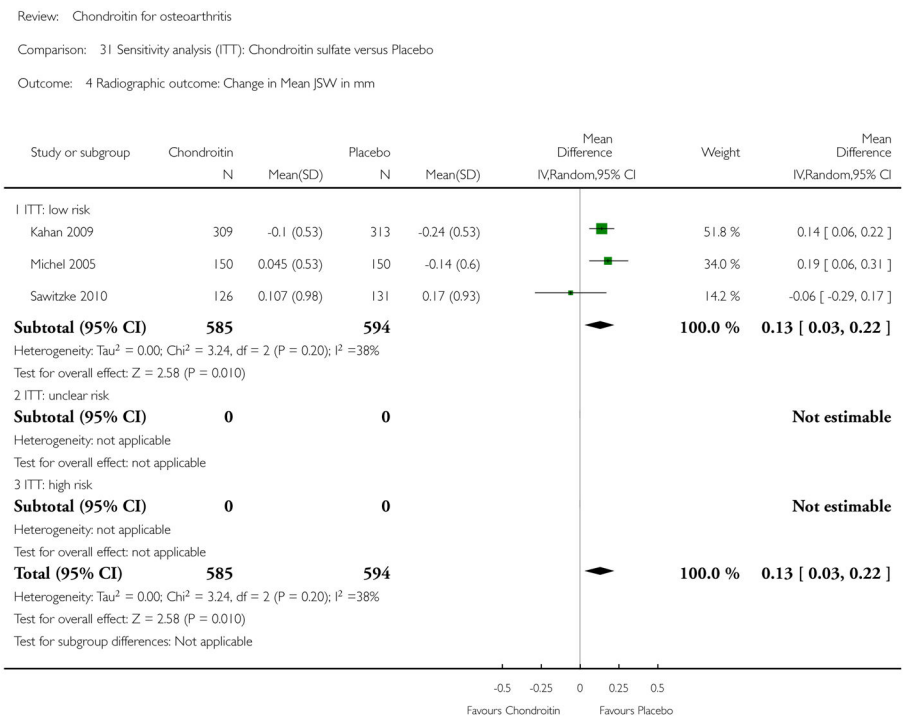


Analysis 31.2.
Comparison 31 Sensitivity analysis (ITT): Chondroitin sulfate versus Placebo, Outcome 2 WOMAC MCII.



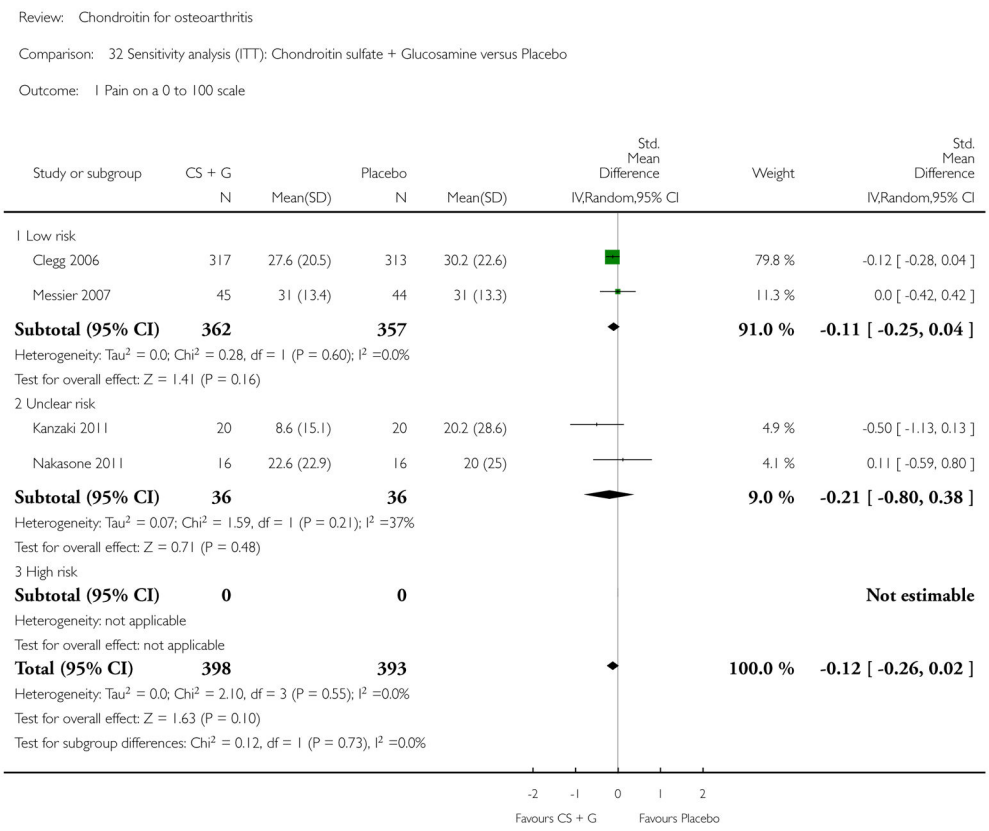
Analysis 31.3.

Comparison 31 Sensitivity analysis (ITT): Chondroitin sulfate versus Placebo, Outcome 3 Physical Function on a 0 to 100 scale.



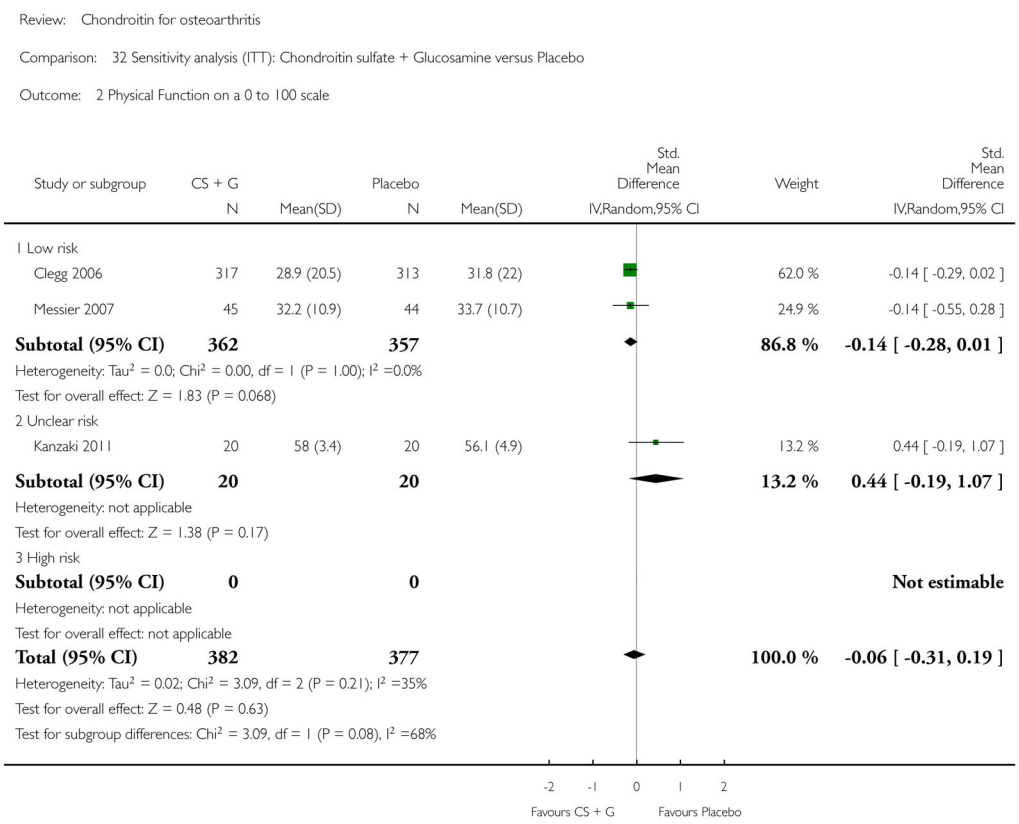
Analysis 31.4.

Comparison 31 Sensitivity analysis (ITT): Chondroitin sulfate versus Placebo, Outcome 4 Radiographic outcome: Change in Mean JSW in mm.



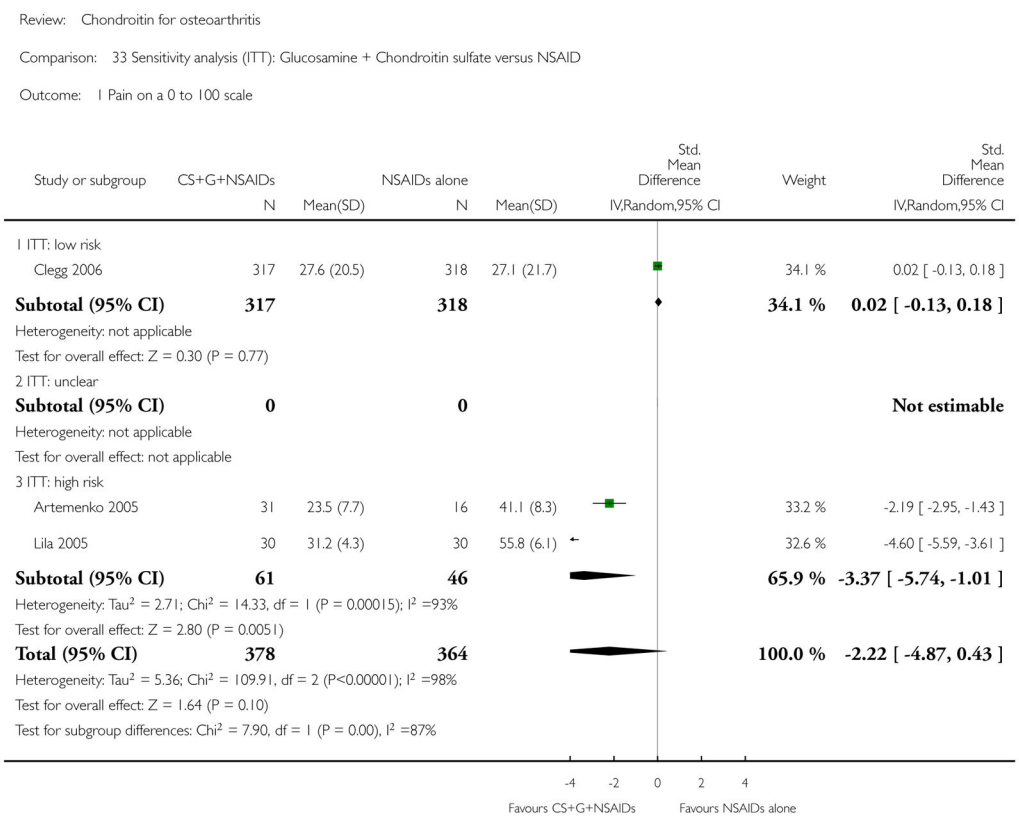
Analysis 32.1.

Comparison 32 Sensitivity analysis (ITT): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 1 Pain on a 0 to 100 scale.



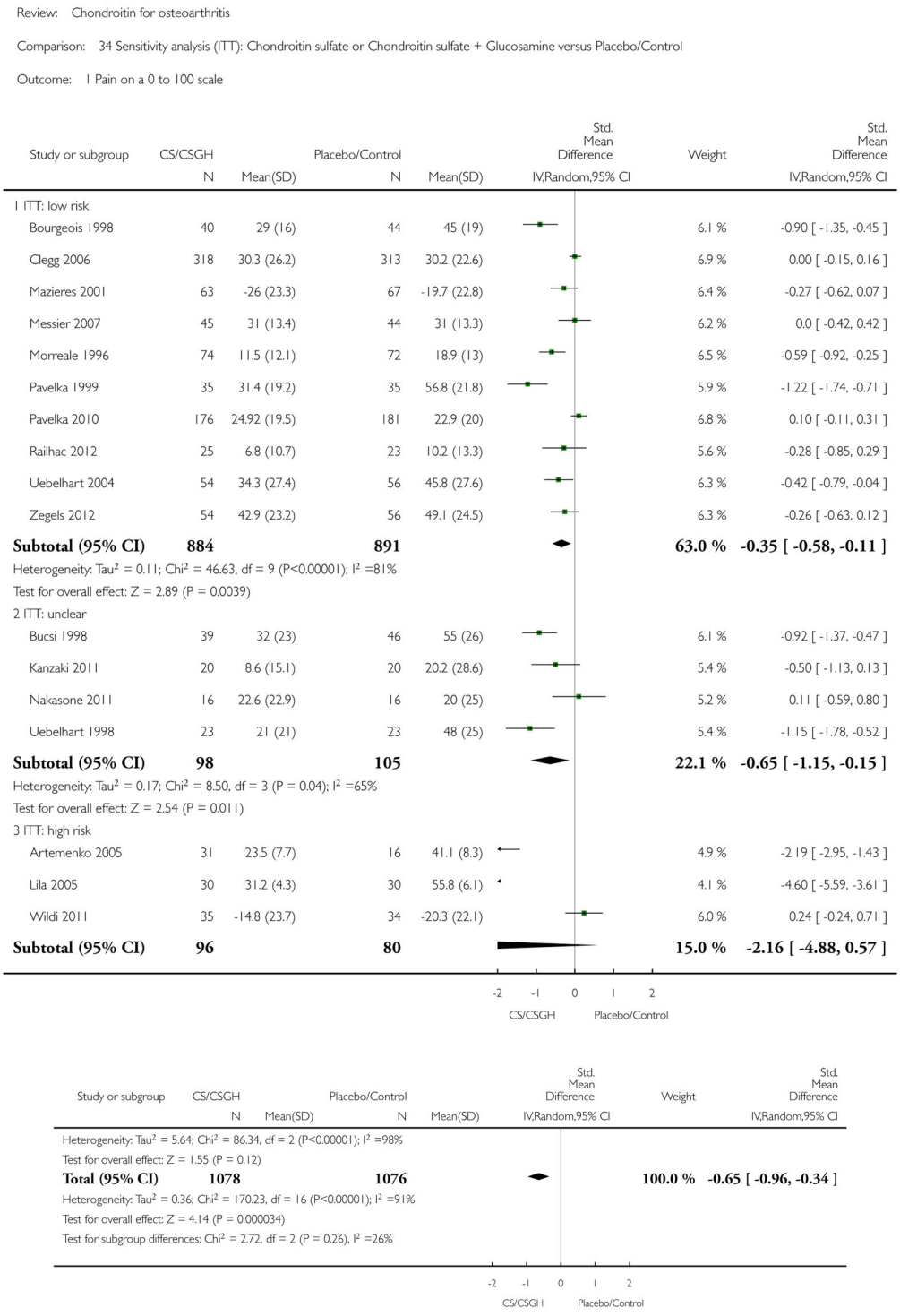
Analysis 32.2.

Comparison 32 Sensitivity analysis (ITT): Chondroitin sulfate + Glucosamine versus Placebo, Outcome 2 Physical Function on a 0 to 100 scale.



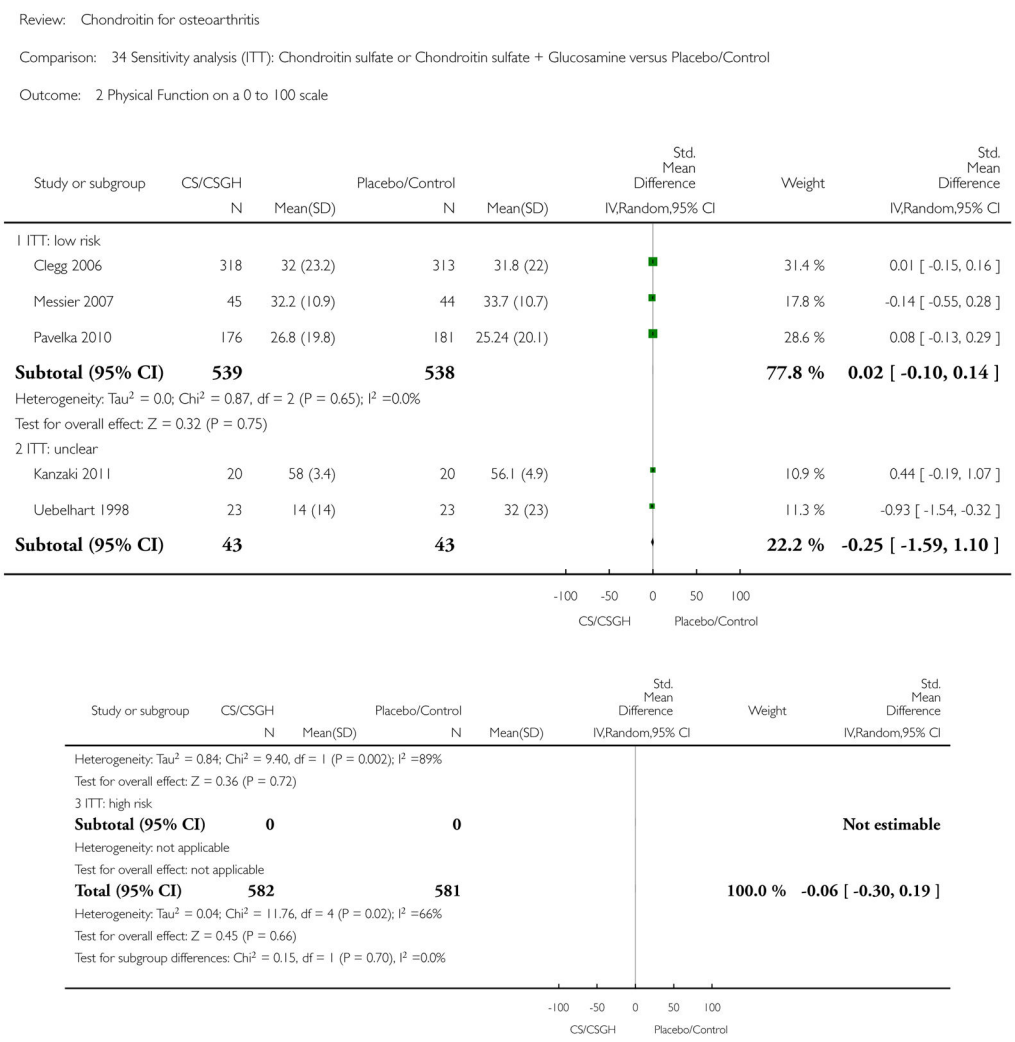
Analysis 33.1.

Comparison 33 Sensitivity analysis (ITT): Glucosamine + Chondroitin sulfate versus NSAID, Outcome 1 Pain on a 0 to 100 scale.



Analysis 34.1.

Comparison 34 Sensitivity analysis (ITT): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 1 Pain on a 0 to 100 scale.



Analysis 34.2.

Comparison 34 Sensitivity analysis (ITT): Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo/Control, Outcome 2 Physical Function on a 0 to 100 scale.

$$\sigma_{est} = \sqrt{\frac{\sigma_1^{\,2}(n_1 - 1) + \sigma_2^{\,2}(n_2 - 1) + \ldots + \sigma_x^{\,2}(n_x - 1)}{(n_1 + n_2 + \ldots + n_x - x)}}$$

Figure 1.
Formula used to estimate standard deviations for studies that did not provide them.

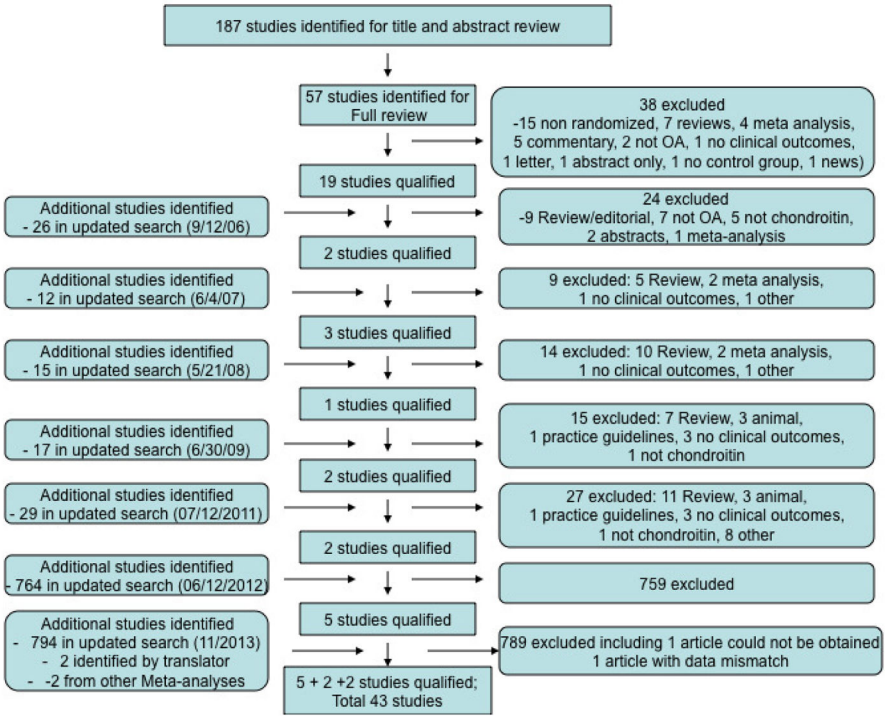


Figure 2.
Study Flow chart

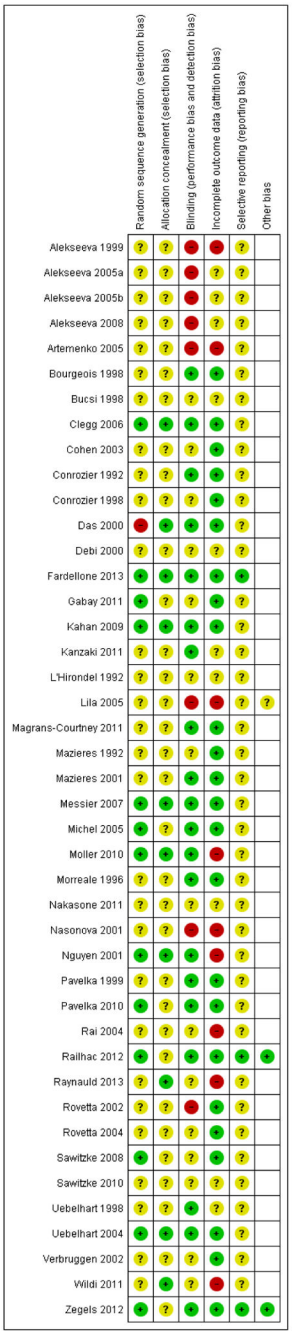


Figure 3.

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

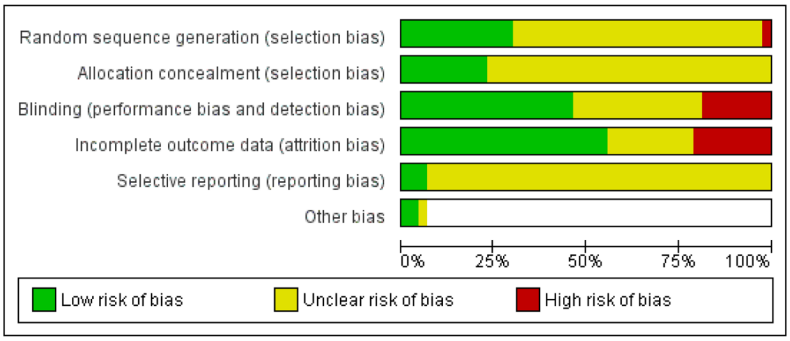


Figure 4.

Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

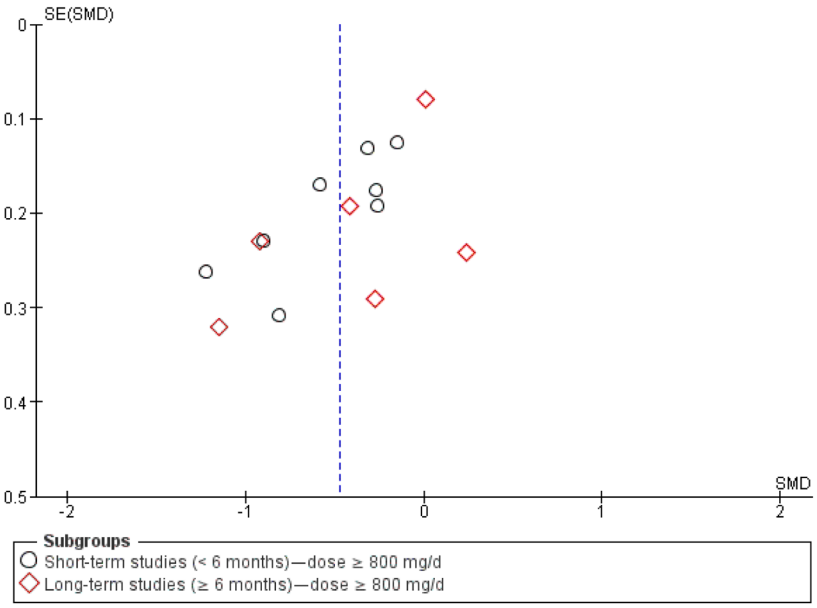


Figure 5.

Funnel plot of comparison: 1 Chondroitin versus placebo, outcome: 1.1 Pain on a 0 to 100 scale.

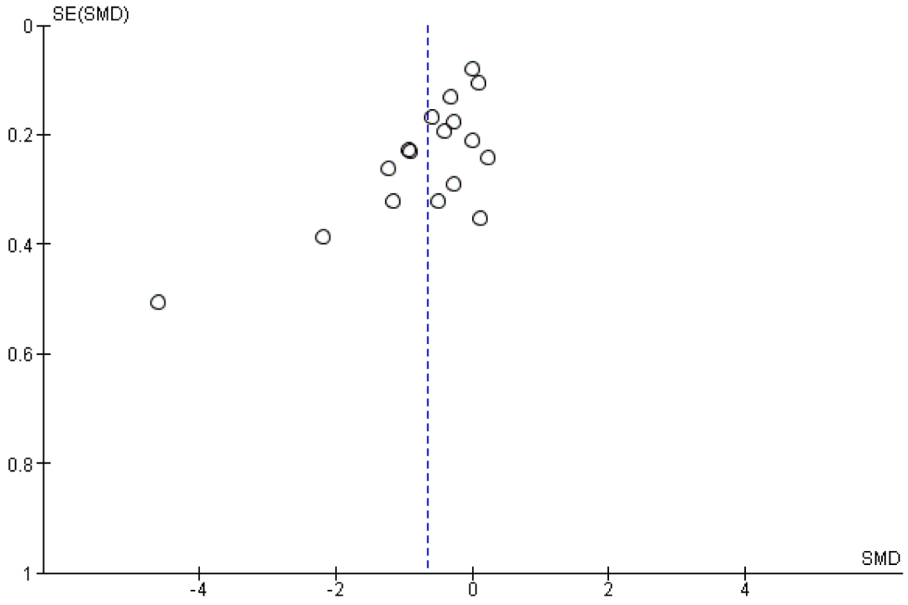


Figure 6.

Funnel plot of comparison: 5 chondroitin sulfate/CSGH versus Placebo/Control, outcome: 5.1 Pain on a 0 to 100 scale (short- and long-term results).

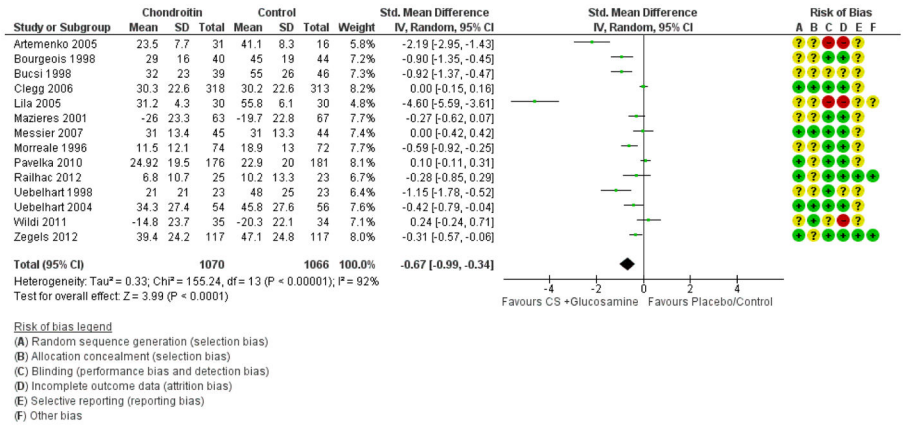


Figure 7.

Forest plot of comparison: 5 Chondroitin sulfate or Chondroitin sulfate + Glucosamine versus Placebo or Control, outcome: 5.5 Pain on 0 to 100 scale (short- or long-term) for CS dose >= 800 mg/day.