# GLUCOSAMINE SULPHATE: AN UMBRELLA REVIEW OF HEALTH OUTCOMES

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# ABSTRACT

**BACKGROUND & AIMS**: Glucosamine sulphate (GS) can be used as background therapy in people affected by knee osteoarthritis (OA). The knowledge regarding the efficacy and safety of GS is of importance since its use worldwide is increasing. Therefore, the present study aimed to map and grade the diverse health outcomes associated with GS using an umbrella review approach.

**METHODS**: Medline, Cinhal and Embase databases were searched until 01st April 2020. An umbrella review of systematic reviews and meta-analyses of randomized controlled trials (RCTs) was carried out. The evidence from RCTs was graded using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool.

**RESULTS**: From 140 articles returned, 11 systematic reviews, for a total of 21 outcomes (37 RCTs; 3,949 participants; almost all using 1,500 mg/day), were included. No systematic reviews/meta-analyses of observational studies were included. Regarding the findings of the meta-analyses, 9/17 outcomes were statistically significant, indicating that GS is more effective than placebo. A high certainty of evidence, as assessed by the GRADE, supported the use of GS (vs. placebo), in improving the Lequesne index, joint space width change, joint space width change after 3 years of follow-up, joint space narrowing and OA progression. No difference in terms of adverse effects was found between GS and placebo. In systematic reviews, GS was associated with a better glucose profile and a better physical function performance than placebo.

**CONCLUSIONS**: GS, when used as prescription drug (i.e. crystalline glucosamine sulfate) at 1,500mg daily dosage, can positively affect the cartilage structure, reduce pain, improve function and glucose metabolism in people with knee OA, without having a greater incidence of adverse effects than placebo.

**Key words**: glucosamine sulphate; osteoarthritis; umbrella review.

# INTRODUCTION

Osteoarthritis (OA) is among the most common diseases in older people, defined here as those greater than or equal to 65 years. This condition is traditionally characterized by joint pain and stiffness, with relevant consequences on functional decline/disability and finally loss in quality of life.[[Woolf *et al.*, 2003](#_ENREF_73), [Murray *et al.*, 2012](#_ENREF_48)] In this regard, knee OA is the most common localization within the symptomatic forms of OA, affecting more than approximately 250 million people worldwide, with symptomatic forms occurring in 10% of men and 13% of women aged 60 years or older.[[Corti *et al.*, 2003](#_ENREF_15), [Vos *et al.*, 2012](#_ENREF_72)]

Currently, there is no definitive treatment for knee OA. The current therapeutic approach combines non-pharmacological and pharmacological strategies that aim to improve function, decrease pain and, if possible, improve structural aspects, with limited adverse events.[[Bruyere *et al.*, 2016](#_ENREF_5)] In this regard, symptomatic slow-acting drugs for OA (SYSADOAs) (such as chondroitin sulfate, glucosamine sulfate (GS), hyaluronic acid and diacerein) [[Reginster *et al.*, 2020](#_ENREF_53)] are an important background therapy for people affected by knee OA.[[Bruyère *et al.*, 2014](#_ENREF_4), [Bruyere *et al.*, 2016](#_ENREF_5), [Bruyère *et al.*, 2019](#_ENREF_6)] In this class of medications, however, different drugs exist exhibiting different pharmacological profiles.

Glucosamine is a natural compound, present in different preparations. Briefly, glucosamine hydrochloride (GHCl) is used as nutraceutical or over-the counter (OTC) products. [[De Wan *et al.*, 1998](#_ENREF_16)] In contrast, glucosamine sulfate (GS) is obtained only by a proprietary semi-synthetic route and stabilization process.[[De Wan *et al.*, 1998](#_ENREF_16)] GS is used only as a prescription drug product, prescription crystalline glucosamine sulfate (pCGS).[[De Wan *et al.*, 1998](#_ENREF_16)] However, multiple formulations of GS are available[[Bruyère *et al.*, 2018](#_ENREF_3)], both as prescription-grade products and OTC, with the latter having small/varying amounts of glucosamine.[[Russell *et al.*, 2002](#_ENREF_59)] Moreover, GS is not available as a prescription-grade product in all countries. Importantly, there is extensive and increasing literature supporting the idea that only pCGS is able to deliver consistently high glucosamine bioavailability and plasma concentration in humans. [[Persiani *et al.*, 2005](#_ENREF_51), [Persiani *et al.*, 2007](#_ENREF_52)] In these experimental studies, the measurement of glucosamine concentration in patients affected by knee OA was also made as a plasma peak (7.17µM) and as a site of action concentration (synovial fluid) equal to 4.34µM. [[Persiani *et al.*, 2007](#_ENREF_52)] Plasma and synovial pCGS concentrations are highly correlated and both are in the 10 µM, a cut-off that seems important for some actions of pCGS, such as anti-inflammatory effect [[Chiusaroli *et al.*, 2011](#_ENREF_12)] that finally results in clinical efficacy.[[Reginster *et al.*, 2001](#_ENREF_55), [Pavelka *et al.*, 2002](#_ENREF_49), [Herrero-Beaumont *et al.*, 2007](#_ENREF_27), [Reginster, 2007](#_ENREF_54), [Towheed *et al.*, 2009](#_ENREF_69), [Eriksen *et al.*, 2014](#_ENREF_20), [Bruyere *et al.*, 2016](#_ENREF_2), [Kucharz *et al.*, 2016](#_ENREF_39)]

In addition to the use of GS for people affected with knee OA, GS may be an appropriate treatment for other conditions. For example, GS is used in hip OA[[Bruyère *et al.*, 2007](#_ENREF_8), [Rozendaal *et al.*, 2009](#_ENREF_58)] or in other forms of OA.[[Towheed, 1998](#_ENREF_67), [Towheed *et al.*, 2005](#_ENREF_68), [Tenti *et al.*, 2019](#_ENREF_65)] Moreover, the difference in efficacy and adverse effects incidence by prescription and OTC doses is still unclear.

The aim of the present work is to evaluate, through an umbrella review, the strength and credibility of the evidence derived from systematic reviews and meta-analyses of observational and/or intervention studies (i.e. randomized controlled trials, RCTs) and obtain a general summary of their importance relative to health outcomes and adverse effects, in order to inform policies on the use of GS in humans.

# METHODS

This work followed a pre-planned protocol (PROSPERO link: CRD42020179570). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[[Moher *et al.*, 2009](#_ENREF_47)] recommendations and specific guidelines regarding how to conduct an umbrella review[[Aromataris *et al.*, 2015](#_ENREF_1)] were followed for the reporting of this study.

## Data sources and searches

An umbrella review was carried out[[Ioannidis, 2009](#_ENREF_36)], systematically searching the Medline, Cinhal and Embase databases from inception until 01st April 2020, using the terms “systematic reviews/meta-analyses” and “glucosamine”, as free vocabulary words and/or controlled terms specific to each database, on a central platform hosted at Anglia Ruskin University. Reference lists of eligible articles and reviews in this field were also searched, including systematic reviews and meta-analyses under process.

## Eligibility and selection criteria

We included systematic reviews with or without formal meta-analysis of RCTs in which at least one group used GS and one placebo reporting on health outcomes, in both terms of efficacy and safety. Only subjects taking only GS (not in combination with other medications) versus those not taking GS, independently from the length of treatment (i.e. no requirement that RCTs should be of a certain length was a priori set), were included. We included systematic reviews (with or without formal meta-analysis) that evaluated observational studies with longitudinal (prospective or retrospective) designs. We excluded studies comparing GS with another similar medication (e.g. chondroitin sulphate) or when GS was used together with another active medication (e.g. chondroitin sulphate).

Two reviewers (NV, JD) independently screened title/abstracts and full-texts for eligibility, and when a consensus was not reached a third reviewer (SM) was consulted.

## Data extraction

The following information was extracted: PMID/DOI, first author’s name, year of publication, study design (cohort, case-control, RCT), number of included studies in each systematic review, the specific population under investigation (i.e., general population, subjects with OA and its location, etc.), the dosage of GS, the health outcome(s), the median follow-up period (in months), and for RCTs the risk of bias in included studies, according to the Cochrane review indications (high, unclear, low).[[Higgins *et al.*, 2019](#_ENREF_29)] If an article presented separate meta-analyses on more than one reported outcome, each one was assessed separately.

Next, the RCT-specific estimated estimates for any adverse effects or negative outcome for both systematic reviews and meta-analyses outcomes (risk ratio [RR], odds ratio [OR], hazard ratio [HR], incident risk ratio, standardized mean differences [SMDs], mean differences [MDs]), along with their 95% CIs, were extracted.

## Outcomes

Any efficacy/effectiveness outcome, adverse events or adverse effects potentially associated to GS use was included.

## Risk of bias assessment

The methodological quality of each included systematic review was assessed using the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at https://amstar.ca/Amstar-2.php), which is a recent update of AMSTAR, [[Shea *et al.*, 2017](#_ENREF_62)] by two independent investigators (JD, NV). The AMSTAR2 ranks the quality of a systematic review from critically low to high according to 16 predefined items.

## Data synthesis and analysis

For each meta-analysis, we re-estimated the summary effect size and its 95% CIs under the assumption of a random-effects model. If the re-calculated effect size differed from the published effect size (e.g. in case of the use of fixed-effects model instead of random-effects model), we keep the re-calculated estimations. After the data extraction, we re-calculated the overall summary effect size, double checking with the original published ones. We also estimated the prediction interval (PIs), which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association.[[Higgins *et al.*, 2009](#_ENREF_31), [Inthout *et al.*, 2016](#_ENREF_35), [Serghiou *et al.*, 2018](#_ENREF_61)] Between-study inconsistency was estimated with the *I2* metric, with values > 50% indicative of high heterogeneity and > 75% very large heterogeneity. [[Higgins *et al.*, 2002](#_ENREF_30)] We calculated the evidence of small-study effects (i.e. whether small studies inflated effect sizes) using the regression asymmetry test [[Egger *et al.*, 1997](#_ENREF_19)] with a p-value < 0**.**10.[[Carvalho *et al.*, 2016](#_ENREF_10)] We considered the effect size of the largest RCT included for each outcome, determining if it was statistically significant (p-value <0.05) or not.

All statistical analyses were conducted in Stata, version 14.0 (StataCorp).

## Grading the evidence

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0**.**05 as the threshold for statistical significance. When the p-value for the random effects model was <0**.**05, we evaluated the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment.[[Guyatt *et al.*, 2008](#_ENREF_26)] Full details regarding the GRADE assessment are reported in **Supplementary Table 1**. We also reported 95% PIs (excluding the null or not), the presence of large heterogeneity (I2 >50%), small study effects (P<0**.**10), if the largest RCT in terms of participants, and excess significance (P>0**.**10) as possible indicators of quality of the available evidence.

## Sensitivity analyses

For outcomes of observational studies having a class I/II evidence, it was planned to conduct sensitivity analyses including only cohort studies. Moreover, for the outcomes of RCTs, it was planned to stratify analyses for risk of bias of the RCTs included using the original data if possible or evaluating the risk of bias using the Cochrane tool for Risk of Bias if not available in the original meta-analysis. Finally, it was planned to stratify the analyses of RCTs by prescription and not prescription doses. However, no observational studies were included and only prescription doses (i.e. >750 mg/day)[[Hsu *et al.*, 2019](#_ENREF_34)] were used. Only for one outcome (pain in OA) it was possible to run a sensitivity analysis, removing the RCTs at high risk of bias.

# RESULTS

## Literature review

The initial search yielded 180 articles. After removing the duplicates, study selection commenced and 140 papers were evaluated, with 47 assessed as full text. As reported in the PRISMA flow-chart (**Figure 1**), 11 articles were finally included[[Richy *et al.*, 2003](#_ENREF_57), [Lee *et al.*, 2010](#_ENREF_41), [Dostrovsky *et al.*, 2011](#_ENREF_18), [Sodha *et al.*, 2013](#_ENREF_64), [Eriksen *et al.*, 2014](#_ENREF_21), [Gallagher *et al.*, 2015](#_ENREF_22), [Gregori *et al.*, 2018](#_ENREF_25), [Knapik *et al.*, 2018](#_ENREF_38), [Melo *et al.*, 2018](#_ENREF_46), [Simental-Mendia *et al.*, 2018](#_ENREF_63), [Honvo *et al.*, 2019](#_ENREF_32)] (3 systematic reviews without meta-analysis, 1 network meta-analysis reporting narrative data on GS and 7 meta-analyses), for a total of 21 independent outcomes, as fully reported in **Table 1**. No systematic review or meta-analysis regarding observational studies were included, i.e. no observational studies met the inclusion/exclusion criteria.

## Descriptive findings of the articles included

**Table 1** summarizes key descriptive findings regarding the 11 articles included. Overall, 37 independent RCTs for a total of 3,949 participants (1,987 randomized to GS and 1,962 to placebo), mainly affected by knee OA with a Kellgren and Lawrence grade of 2 (definite osteophytes and possible narrowing of joint space) or 3 (moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bony ends), were included. For each article included, the mean number of RCTs included was 4 (range: 2-21) for a median of 414 participants (range: 18 to 2,228). The median follow-up period, in months, was 3 (range: 1.5 to 36). Almost all RCTs (30/37), used the dosage of 1,500 mg daily.

## Main findings of the meta-analyses

Among the 17 outcomes included in the meta-analyses, 9 were statistically significant (p<0.05). Overall, high heterogeneity (I2> 50%) was present in 8/17 outcomes, small-study effect was present in only one outcome (i.e. the use of GS on pain in people affected by OA), the largest RCT in terms of participants was statistically significant in 11/17 outcomes, as reported in **Supplementary Table 2**. Finally, no outcome included in the analysis, had a 95% PIs excluding the null value.

**Table 2** shows the findings of the statistically significant outcomes, using the GRADE approach, ranked by the level of evidence. A high certainty of evidence, as assessed by the GRADE, supported the use of GS (vs. placebo), in improving the Lequesne index (3 RCTs; 454 participants, SMD= 0.363; 95%CI: 0.202- 0.524), the joint space width change (2 RCTs; 414 participants; SMD=0.250; 95%CI: 0.120-0.380), the joint space width change after 3 years of follow-up (2 RCTs; 414 participants; SMD= 0.432; 95%CI: 0.235-0.628), joint space narrowing (2 RCTs; 414 participants; SMD= 0.410; 95%CI: 0.210-0.600), and, finally, OA progression (2 RCTs; 414 participants; OR=0.382; 95%CI: 0.216-0.677) (**Table 2**). A moderate certainty of evidence supported the use of GS in improving the WOMAC index (total score) (6 RCTs; 621 participants; MD=-3.903; 95%CI: -7.418 to -0.658), whilst a very low certainty of evidence supported the use of GS in ameliorating pain (21 RCTs; 1,772 participants; SMD=-0.646; 95%CI: -0.910 to -0.382) (including when the visual analogic scale was used; 5 RCTs; 538 participants; MD=-9.507; 95%CI: -17.128 to -1.797) and mobility (2 RCTs; 100 participants; SMD=0.501; 95%CI: 0.09-0.912).

A sensitivity analysis was carried out for the outcome pain. Ten RCTs at high risk of bias were removed, the re-calculated SMD was -0.298 (11 RCTs; n=1493; 95%CI: -0.546; -0.05); however, no differences in terms of heterogeneity (I2=87%) or prediction intervals (-0.84 to 0.28) was observed.

Of importance, as shown in **Supplementary Table 2**, no significant differences in terms of adverse events between GS and placebo was observed (5 RCTs; 632 participants; OR= 1.236; 95%CI: 0.623-2.454; p=0.54).

## Findings from the narrative systematic reviews

Of the four outcomes included in the systematic reviews without meta-analysis, GS was associated with a better glucose profile[[Dostrovsky *et al.*, 2011](#_ENREF_18)] and a better physical function performance, compared to placebo.[[Gregori *et al.*, 2018](#_ENREF_25)] On the contrary, when including people suffering on spine or temporo-mandibular joint OA, no significant effect of GS on physical function or pain was observed. [[Sodha *et al.*, 2013](#_ENREF_64), [Melo *et al.*, 2018](#_ENREF_46)]

## Quality assessment

The assessment of the risk of bias in the meta-analyses included is fully reported in **Supplementary Table 3**. Four SRs/MAs were adjudicated as having high (i.e. one non critical weakness) confidence of the results found, whilst, from the others, one was low (i.e. one critical flaw with or without non-critical weaknesses) and six critically low (i.e. having more than one critical flaw with or without non-critical weaknesses).

# DISCUSSION

In this umbrella review, including 11 systematic reviews comprising 37 RCTs, the current research regarding GS and health outcomes in humans is reported. Overall, the findings suggest that GS is a safe product and, when used as prescription drug at 1,500 mg/daily dosage, is able to positively modify the cartilage structure, reduce pain and improve function in people with knee OA, without having a greater incidence of adverse effects than placebo. The efficacy of GS was supported by different degrees of certainty of evidence, according to the GRADE evaluation, similar to that made in 2019 ESCEO updated algorithm, which is supporting the use of prescription GS as background therapy for knee OA.[[Bruyère *et al.*, 2019](#_ENREF_6)] Altogether, our findings suggest that GS might provide clinical benefits at 1500mg/daily, we should differentiate the formulation of GS that is essential for maximizing the clinical benefit, patient adherence and satisfaction with treatment.[[Bruyère *et al.*, 2018](#_ENREF_3)]

GS is widely used, particularly in older people, for the treatment of knee OA and its global use is overall increasing.[[Hopman *et al.*, 2006](#_ENREF_33), [Galvin *et al.*, 2013](#_ENREF_23)] The present umbrella review supports the assumption that, when compared to placebo, GS is able to delay the joint space narrowing, finally resulting in a minor OA progression. This analysis showed that in two RCTs [[Reginster *et al.*, 2001](#_ENREF_56), [Pavelká *et al.*, 2002](#_ENREF_50)], those randomized to GS had a 62% reduction in OA progression compared to those randomized to placebo. This evidence is supported by a high certainty of evidence, meaning that the role of potential biases is limited. These effects may be explained through several mechanisms. First, GS is able to reduce inflammatory parameters, in particular IL-1. [[Dechant *et al.*, 2005](#_ENREF_17)] In this regard, GS, if reaches appropriate doses in blood and in cartilage cells, can positively interfere with IL-1 intracellular signalling pathway and gene expression.[[Dechant *et al.*, 2005](#_ENREF_17)] However, the dose-dependent effect of GS on IL-1β-induced gene expression of MMP-3 (stromelysin-1) and ADAM-TS5 (aggrecanase 2) in human chondrocytes is optimized at clinically relevant concentrations (~10 μM) that can be obtained only at pharmacological doses of GS.[[Chiusaroli *et al.*, 2013](#_ENREF_13)] Through this mechanism, GS is able to reduce the degradation of cartilage, therefore improving the cartilage structure of the knee.

However, GS is able, according to this umbrella review, to improve clinical outcomes commonly affected in knee OA. In particular, it was found that GS is able to improve Lequesne Index[[Lequesne *et al.*, 1987](#_ENREF_42)], a tool that evaluates several aspects compromised in OA, including activities of daily living, pain, and physical function. In this sense, this umbrella review indicates that GS is able to reduce pain and disability, however, this evidence is supported by a lower certainty of evidence according to the GRADE. Traditionally, Cohen defined an effect size of 0.20 as small, of 0.50 as moderate, and of 0.80 or greater as large.[[Cohen, 2013](#_ENREF_14)] Given this, the effect of GS, compared to placebo, is ranked between small and moderate. However, as already discussed in other relevant papers[[Bruyère *et al.*, 2014](#_ENREF_4), [Bruyère *et al.*, 2018](#_ENREF_3)], these effects are almost doubled than those of paracetamol[[Towhead](#_ENREF_66)], a common medication used for knee OA pain-relief treatment. Moreover, other medications commonly used for the treatment of knee OA have a similar effect than observed for GS, as indicated in the recent network meta-analysis of Gregori et al. in which GS and celecoxib are the only long-term OA treatments associated with pain reduction (ES= 0.29 and ES= 0.18, respectively).[[Gregori *et al.*, 2018](#_ENREF_25)]

Another important aspect of this umbrella review is the potential association between GS and favourable glucose profile. Glucosamine, in fact, is an amino sugar: therefore, one might claim that this medication can lead to hyperglycemia, insulin resistance and finally to diabetes by overactivating the hexosamine pathway.[[Veronese *et al.*, 2019](#_ENREF_71)] In this sense, however, a large RCT made in 407 overweight and obese women, followed-up for 2.5 years, reported that there was no significant effect of a 2.5-year GS intervention on mean glycosilated hemoglobin level.[[Gommans *et al.*, 2017](#_ENREF_24)] Present data, although limited by the narrative nature of the review confirmed that GS is safe from a metabolic point of view, being in agreement with a large longitudinal study using the UK Biobank showing that the use of GS in OA is associated with a lower incidence of diabetes, over 8 years of follow-up.[[Ma *et al.*, 2020](#_ENREF_45)] In the same database, it is reported that GS can lead to a reduction in cardiovascular disease [[Ma *et al.*, 2019](#_ENREF_44)]and all-cause and specific-cause mortality.[[Li *et al.*, 2020](#_ENREF_43)] Further studies are encouraged in order to confirm these promising findings, since in the UK Biobank the data are reported for different glucosamine preparations and not specifically for GS. Regarding the mechanisms of action that can justify these epidemiological findings, we can argue that GS may interfere with some pro-inflammatory pathways (such as nuclear factor kappa-B [NF-κB], mitogen-activated protein kinase [MAPK] and phosphatidyl-inositol-3-kinase [PI3K]-dependent pathways) [[Largo *et al.*, 2003](#_ENREF_40), [Herrero-Beaumont *et al.*, 2020](#_ENREF_28)] that are usually involved in the pathogenesis of diabetes.[[Tsalamandris *et al.*, 2019](#_ENREF_70)]

Finally, our umbrella review is, in our opinion, important since GS use was associated with a similar incidence in adverse effects, compared to placebo, suggesting that its use is safe. One pivotal meta-analysis regarding this topic and included in this umbrella review, in fact, reports that the use of pCGS is not associated with a higher incidence of total and specific gastrointestinal, skin and subcutaneous tissue, renal and urinary adverse events when compared to placebo.[[Honvo *et al.*, 2019](#_ENREF_32)] The topic of safety for medications is clinically relevant, particularly in older people, in which knee OA is widely diffused. It is known that the median age of knee OA detection is 55 years and typically people with this condition live about 30-years with the disease.[[Charlesworth *et al.*, 2019](#_ENREF_11)] Therefore, to have medications with a good safety profile is of importance, but still debated in geriatric medicine since older people often use a high number of medications (polypharmacy) that may have unwanted interactions.

Findings from the present review should be interpreted in light of its limitations. First, the use of already established tools for quality assessment of evidence, which indirectly rely on the data reported in the selected articles can cumulatively bring some biases. In order to overcome these potential biases, we used low heterogeneity in the GRADE assessment as one of the criteria for high certainty of level. However, I2 estimates can also carry substantial uncertainty in terms of clinical parameters. Second, meta-analyses might have important limitations[[Ioannidis, 2016](#_ENREF_37)] and their results depend on the choice of the estimate from each primary study and its representation in the meta-analysis. In this regard, an umbrella review is totally dependent of the quality of SR/MAs performed and mainly the “exhaustive” character of these SR/MAs: for example, if the search strategies was not exhaustive, some important studies may have been missed. Moreover, it is also possible that some recent RCTs have not been included in this work. Third, the meta-analyses included in this umbrella review, reported data on a median of four RCTs, independently from the follow-up duration: this work should encourage further intervention research on GS, particularly in forms of OA other than knee OA. At the same time, this work has some important strengths, including the fact that, differently from previously published literature, only GS (and not other forms of glucosamine) was included and the safe profile of GS in humans is confirmed. Finally, we were not able to analyze, since no systematic review was published, the economic aspects of GS, which is indeed of great clinical importance.[[Bruyère *et al.*, 2008](#_ENREF_7), [Scholtissen *et al.*, 2010](#_ENREF_60), [Bruyère *et al.*, 2019](#_ENREF_9)]

In conclusion, the present umbrella review suggests that prescription GS, when used at 1500mg/daily dosage, can positively affect the cartilage structure, improve the pain and function in people with knee OA, without having a greater incidence of adverse effects than placebo, indicating a possible role in older people. Moreover, some promising results indicated that GS is associated with a better glucose profile than placebo. Overall, these findings, encourage further research regarding GS and other forms of OA not affecting the knee.

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**Authors’ contribution**: Conceptualization: Veronese; Data curation: Demurtas, Lee, Veronese; Formal analysis: Veronese, Honvo, Beaudart; Funding acquisition: Veronese; Methodology: Veronese, Honvo, Beaudart; Writing - original draft. Veronese, Demurtas; Writing - review & editing: Maggi. Bruyère, Reginster.

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# *Table 1. Main descriptive findings of the systematic reviews included*

| **Author, year** | **Type of review** | **Mean GS dosage**  **(number of studies)** | **Follow-up in months (median)** | **Population** | **OA grade** | **Outcomes** | **Number of RCTs** | **GS** | **Placebo** | **Total sample size** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dostrowsky 2011 | Systematic review | 1500 (n=2) | 3 | General population | - | Glucose parameters | 2 | 18 | 16 | 34 |
| Eriksen, 2014 | Meta-analysis | 1500 (n=13); lower dosages >750 mg (n=8) | 3 | OA | K-L grade  2-3 | Pain  (n=9 WOMAC;  n=3 VAS;  n=1 numeric rating scale;  n=8 not reported) | 21 | 1334 | 1303 | 2637 |
| Gallagher, 2014 | Meta-analysis | 1500 (n=2) | 36 | KOA | K-L grade  2-3 | OA progression, JSW | 2 | 207 | 207 | 414 |
| Gregori 2018 | Network meta-analysis | 1500 (n=2) | 36 | KOA | K-L grade  2-3 | Physical function | 1 | 207 | 207 | 414 |
| Honvo, 2019 | Meta-analysis | 1500 (n=5) | 3 | OA | Not reported | Adverse events  (total and specific) | 5 | 316 | 316 | 632 |
| Knapik, 2018 | Meta-analysis | 1500 (n=2) | 36 | OA | Not reported | JSW | 2 | 207 | 207 | 414 |
| Lee, 2014 | Meta-analysis | 1500 (n=2) | 36 | KOA | K-L grade  2-3 | JSW at 1 and 3 years | 2 | 207 | 207 | 414 |
| Melo 2018 | Systematic review | 1200 (n=1) | 1.5 | TMJ OA | - | Pain  (scale not reported) | 1 | 30 | 29 | 59 |
| Richy,2003 | Meta-analysis | 1500 (n=3) | 3 | OA | K-L grade  2-3 | JS narrowing, Lequesne index, VAS pain, mobility, being a responder | 7 | 511 | 509 | 1020 |
| Simental-Mendìa, 2018 | Meta-analysis | 1500 (n=5) | 3 | KOA | K-L grade  2-3 | Pain (VAS), WOMAC index (total score), WOMAC physical function, WOMAC stiffness, WOMAC pain | 5 | 267 | 271 | 538 |
| Sodha, 2013 | Systematic review | 1500 (n=1) | 6 | Spine OA | - | Pain  (n=1 numeric rating scale) | 1 | 125 | 125 | 250 |

**Abbreviations**: GS: glucose sulphate; RCT: randomized controlled trial; OA: osteoarthritis; KOA: knee osteoarthritis; TMJ OA: temporomandibular joint osteoarthritis; JSW: joint space width; JS: joint space; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; K-L: Kellgren and Lawrence

# *Table 2. Summary of the findings according to the GRADE tool for randomized controlled trials*

| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Certainty of the evidence (GRADE) |
| --- | --- | --- | --- | --- | --- |
| **Risk with placebo** | **Risk with GS** |
| Lequesne index | - | SMD **0.363 SD higher** (0.202 higher to 0.524 higher) | - | 454 (3 RCTs) | ⨁⨁⨁⨁ HIGH |
| JSW (at 3 years) | - | SMD **0.432 SD higher** (0.235 higher to 0.628 higher) | - | 414 (2 RCTs) | ⨁⨁⨁⨁ HIGH |
| JS narrowing | - | SMD **0.41 SD higher** (0.21 higher to 0.6 higher) | - | 414 (2 RCTs) | ⨁⨁⨁⨁ HIGH |
| OA progression | - | - | **OR 0.382** (0.216 to 0.677) | 414 (2 RCTs) | ⨁⨁⨁⨁ HIGH |
| JSW | - | SMD **0.25 SD higher** (0.12 higher to 0.38 higher) | - | 414 (2 RCTs) | ⨁⨁⨁⨁ HIGH |
| WOMAC index (total score) | - | MD **3.903 lower** (7.418 lower to 0.658 lower) | - | 621 (6 RCTs) | ⨁⨁⨁◯ MODERATE b |
| Pain VAS | - | MD **9.507 lower** (17.128 lower to 1.797 lower) | - | 538 (5 RCTs) | ⨁◯◯◯ VERY LOW a,b |
| Pain | - | SMD **0.646 SD** lower  (0.91 lower to 0.382 lower) | - | 1772 (21 RCTs) | ⨁◯◯◯ VERY LOW a,d,e |
| Mobility | - | SMD **0.501 SD higher** (0.091 higher to 0.912 higher) | - | 100 (2 RCTs) | ⨁◯◯◯ VERY LOW a,c |

**Explanations**

a. >30% of the RCTs included reporting high risk of bias

b. I2 between 50 and 75%

c. Sample size, in each arm, less than 100 participants

d. I2>75%

e. Egger's test (p-value)<0.05

**Abbreviations**:

RCT: randomized controlled trial; CI: confidence interval; SMD: standardized mean difference; OR: odds ratio; MD: mean difference; OA: osteoarthritis; JSW: joint space width; JS: joint space; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

# *Table 3. Main findings of the systematic reviews, without meta-analysis*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Type of review** | **Population** | **Outcome** | **Number of RCTs** | **GS** | **Placebo** | **Total sample size** | **Main findings** |
| Dostrowsky, 2011 | Systematic review | General population | Glucose parameters | 2 | 16 | 18 | 34 | Better glucose parameters in both RCTs in GS compared to placebo |
| Gregori, 2018 | Network meta-analysis | KOA | Physical function | 1 | 106 | 106 | 212 | Slight improvement in intervention group compared to placebo |
| Melo, 2018 | Systematic review | TMJ OA | Pain | 1 | 30 | 29 | 59 | No significant difference between placebo and glucosamine |
| Sodha, 2013 | Systematic review | Spine OA | Pain | 1 | 125 | 125 | 250 | No significant difference between placebo and glucosamine for pain and physical function |

**Abbreviations**: RCT: randomized controlled trial; GS: glucosamine sulphate; KOA: knee osteoarthritis; TMJ OA: temporomandibular joint osteoarthritis; OA: osteoarthritis.

Records identified through database searching in

Cinahl: 43

Embase: 128

Pubmed: 49

Additional records identified   
(n = 0)

**Identification**

Records screened  
(n =140)

Records after duplicates were removed  
(n = 140)

**Screening**

Records excluded based on title/abstract  
(n =93)

Publications excluded (n =36)

No data regarding GS (n=14)

No systematic review (n=6)

Doubled (n=6)

No GS (n=4)

No humans (n=2)

Theses (n=2)

Protocol (n=1)

Wrong design (n=1)

**Eligibility**

Full-text articles assessed for eligibility   
(n =47)



Studies included in the umbrella review

(n =11)

**Included**

# *Supplementary Table 1. Criteria evidence for the GRADE*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Downgrade** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** |
| **-1** | If one or more of the three criteria (randomization, masking, drop-out rate <30%) is not met in **10-30%** of trials included | **I2 50-74%** | The question being addressed by the guideline panel is **different** from the available evidence regarding the PICO or regarding the characteristics of those who will deliver the intervention | (a)The **overall number** of individuals included in trials is low (less than **200 individuals,** both treatment arms) **OR** (b) the 95% confidence interval includes both 1) no effect and 2) appreciable benefit (RR: ≤0.75) or appreciable harm (RR: ≥1.25) a | - |
| **-2** | If one or more of the three criteria (randomization, masking, drop-out rate>30%) is not met in **>30%** of trials included | **I2 > 75%** | The question being addressed by the guideline panel is **markedly different** from the available evidence regarding the PICO or regarding the characteristics of those who will deliver the intervention | (a) the **overall number** of individuals included in trials is **very low** (**less than 200 individuals,** both treatment arms) **AND** (b) the 95% confidence interval includes both 1) no effect and 2) appreciable benefit (RR: ≤0.75) or appreciable harm (RR: ≥1.25) a | **Egger’s test** (p-value) <0.05 |

a For **continuous outcomes** “***no effect***” means a SMD with a confidence interval that ***crosses zero***; **appreciable** benefit or appreciable harm means that the **upper or lower confidence limit crosses an effect size of 0.5** in either direction.

For **dichotomous outcomes** “***no effect***” means an estimate with a confidence interval that ***crosses one***; **appreciable** benefit or appreciable harm means that the upper or lower confidence limit **crosses a risk of 1.25 or 0.75**.

**Abbreviations: OR:** Odds ratio**; PICO:** Population, Intervention, Comparison and Outcomes; **RR**: Risk Ratio

# *Supplementary Table 2. Additional analyses for the meta-analyzable outcomes*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Population** | **Outcome** | **Type of ES** | **Number of RCTs** | **Effect size** | **Low 95%CI** | **High 95%CI** | **P-value** | **I2** | **Egger's test** | **p-value Egger** | **Largest study significant** | **Low 95% prediction intervals** | **High 95%prediction intervals** |
| OA | Lesquene index | SMD | 3 | 0.363 | 0.202 | 0.524 | 0.00001 | 0.0 | 7 | 0.126 | yes | -0.68 | 1.41 |
| KOA | JSW 3 years | SMD | 2 | 0.432 | 0.235 | 0.628 | 0.00002 | 0.0 | 29.79198 | NA | yes | NP | NP |
| OA | Pain | SMD | 21 | -0.646 | -0.910 | -0.382 | 0.00002 | 88.0 | -4.46366 | 0.003 | no | -1.84 | 0.55 |
| OA | JS narrowing | SMD | 2 | 0.410 | 0.210 | 0.600 | 0.00004 | 0.0 | -1.96 | NA | yes | NP | NP |
| KOA | OA progression | OR | 2 | 0.382 | 0.216 | 0.677 | 0.00100 | 0.0 | -1.53391 | NA | yes | NP | NP |
| OA | JSW | MD | 2 | 0.250 | 0.120 | 0.380 | 0.00242 | 0.0 | 1.367442 | NA | yes | NP | NP |
| KOA | pain VAS | WMD | 5 | -9.507 | -17.218 | -1.797 | 0.01567 | 71.5 | -5.0462 | 0.298 | no | -35.11 | 17 |
| OA | Mobility | SMD | 2 | 0.501 | 0.091 | 0.912 | 0.01664 | 0.0 | -0.39596 | NA | yes | NP | NP |
| KOA | WOMACi | WMD | 6 | -3.903 | -7.148 | -0.658 | 0.01841 | 52.4 | -0.68138 | 0.622 | yes | -12.84 | 5.04 |
| OA | JSW | SMD | 2 | -0.192 | -0.385 | 0.001 | 0.05128 | 0.0 | 15.37 | NA | yes | NP | NP |
| KOA | WOMAC pain stiffness | WMD | 4 | -0.525 | -1.055 | 0.005 | 0.05210 | 78.0 | 2.498699 | 0.134 | no | -2.74 | 1.69 |
| KOA | WOMAC physical function | WMD | 7 | -2.947 | -6.068 | 0.173 | 0.06414 | 80.4 | -0.98144 | 0.667 | no | -13.03 | 7.14 |
| OA | Being a responder | RR | 4 | 1.548 | 0.940 | 2.548 | 0.08598 | 67.5 | 1.682166 | 0.133 | yes | 0.2 | 11.95 |
| OA | VAS pain | SMD | 4 | 0.326 | -0.053 | 0.705 | 0.09183 | 61.3 | 1.429706 | 0.658 | yes | -1.18 | 1.83 |
| KOA | WOMAC pain | WMD | 7 | -1.160 | -2.839 | 0.520 | 0.17595 | 92.7 | 2.045143 | 0.676 | yes | -7.07 | 4.75 |
| KOA | JSW 1 year | SMD | 2 | 0.079 | -0.129 | 0.286 | 0.45892 | 12.6 | -277.01 | NA | no | NP | NP |
| OA | AdE | OR | 5 | 1.236 | 0.623 | 2.454 | 0.54454 | 46.0 | 0.593484 | 0.337 | no | 0.17 | 8.91 |

**The outcomes are ranked by p-value under random effect model**

**Abbreviations:** ES: effect size; RCT: randomized controlled trial; CI: confidence interval; SMD: standardized mean difference; OR: odds ratio; MD: mean difference; WMD: weighted mean difference; OA: osteoarthritis; KOA: knee osteoarthritis; JSW: joint space width; JS: joint space; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; AdE: adverse events.

# *Supplementary Table 3. AMSTAR 2 quality assessment of meta-analyses.*

| **AMSTAR 2 items a, c** | | | | | | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year**  **[Reference]** | **1** | **2** b | **3** | **4** b | **5** | **6** | **7** b | **8** | **9** b | **10** | **11** b | **12** | **13** b | **14** | **15** b | **16** | **Overall rating** (based on critical domains)**d** |
| Dostrowski 2011 | Y | N | Y | Y | Y | Y | Y | Y | Y | N | No MA conducted | No MA conducted | N | N | No MA conducted | Y | Critically Low |
| Eriksen 2014 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | High |
| Gallagher 2014 | Y | N | Y | Y | N | N | N | N | Y | N | Y | Y | Y | Y | Y | Y | Critically low |
| Gregori 2018 | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | High |
| Honvo 2019 | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | High |
| Knapik 2018 | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | High |
| Lee 2009 | Y | N | Y | Y | N | Y | N | Y | Y | N | Y | Y | Y | Y | Y | Y | Critically Low |
| Melo 2018 | Y | Y | Y | Y | Y | Y | N | PY | Y | N | No MA conducted | No MA conducted | Y | Y | No MA conducted | Y | Critically Low |
| Richy 2003 | Y | Y | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Y | Y | Low |
| Simental-Mendìa 2018 | Y | N | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | N | N | Y | Critically Low |
| Sodha 2011 | Y | N | Y | PY | Y | Y | N | Y | Y | N | No MA conducted | No MA conducted | Y | N | No MA conducted | Y | Critically Low |

a Yes, No, Other

b Critical Domains

c AMSTAR 2 items:

1. **Did the research questions and inclusion criteria for the review include the components of PICO (Population, Intervention, Comparator group, Outcome)?** YES/NO. For yes, must have all four.
2. **Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?** YES, PARTIAL YES, NO. For Partial YES: the authors state that they had a written protocol or guide that included ALL the following (review question(s), a search strategy, inclusion/exclusion criteria, a risk of bias assessment). For YES: as for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, and a plan for investigating causes of heterogeneity, justification for any deviations from the protocol.
3. **Did the review authors explain their selection of the study designs for inclusion in the review?** YES/NO. For YES, the review should satisfy one of the following: explanation for including only RCTs, or explanation for including only NRSI, or explanation for including both RCTs and NRSI.
4. **Did the review authors use a comprehensive literature search strategy?** YES, PARTIAL YES, NO. for PARTIAL YES must have all of the following: searched at least 2 databases (relevant to research question), provided key word and/or search strategy, justified publication restrictions (eg. Language). For YES should also have all of the following: searched the reference lists/biographies of included studies, searched trial/study registries, included/consulted content experts in the field, searched for grey literature where relevant, conducted search within 24 months of completion of the review.
5. **Did the review authors perform study selection in duplicate?** YES/NO. for YES, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder selected by one reviewer.
6. **Did the review authors perform data extraction in duplicate?** YES/NO. For YES, either one of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder extracted by one reviewer.
7. **Did the review authors provide a list of excluded studies to justify the exclusions?** YES, PARTIAL YES, NO. FOR partial yes must provide a list of all potentially relevant studies that were read in full text form but excluded from the review. For YES must also have justified the exclusion from the review of each potentially relevant study.
8. **Did the review authors describe the included studies in adequate detail?** YES, PARTIAL YES, NO. For PARTIAL YES, must describe all of the following: populations, interventions, comparators, outcomes, research designs. For YES should also have all of the following: described populations in detail, described intervention and comparator in detail (including doses where relevant), described study setting, timeframe or follow-up.
9. **Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For RCTs**: YES, PARTIAL YES, NO, INCLUDES ONLY NRSI. For PARTIAL YES must have assessed RoB from unconcealed allocation and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality); for YES must also have assessed RoB from allocation sequence that was not truly random and selection of the reported result from among multiple measurements or analyses of a specified outcome. **For NRSI** (Non Randomized Studies of Intervention)**:** YES, PARTIAL YES, NO, INCLUDES ONLY RCTs. For PARTIAL YES must have assessed RoB from confounding and from selection bias. For YES, must also have assessed methods used to ascertain exposures and outcomes, and selection of the reported results from among multiple measurements or analyses of a specified outcome.
10. **Did the review authors report on the sources of funding for the studies included in the review?** YES/NO. For YES: must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies
11. **If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? For RCTs:** YES, NO, NO META-ANALYSIS. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present and investigated the causes of heterogeneity. **For NRSI:** YES, NO, NO META-ANALYSIS CONDUCTED. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present, and they statistically combined effects estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available, and they reported separate summary estimates for RCTs and NRSI separately when both were included in the review.
12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** YES, NO, NO META-ANALYSIS INCLUDED. For YES: included only low risk of bias RCTs or, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analysis ton investigate possible impact of RoB on summary estimates of effect.
13. **Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?** YES/NO. for YES: included only low risk of bias RCTs or, if RCTs with moderate or high RoB, or NRSI were included, the review provided a discussion of the key impact of RoB on the results
14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** YES/NO. For Yes: there was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review
15. **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** YES, NO, NO META-ANALYSIS CONDUCTED. For YES: performed graphical statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias
16. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** YES/NO. For Yes: the authors reported no competing interests OR the authors described their funding sources and how they managed potential conflicts of interest.

**d** Rating overall confidence in the results of the review:

HIGH: *no or one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

MODERATE: *more than one non critical weakness* (multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence): the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

LOW: *one critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

CRITICALLY LOW: *more than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

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c AMSTAR items:

**1. Was an 'a priori' design provided?** The research question and inclusion criteria should be established before the conduct of the review. *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a “yes.”*

**2. Was there duplicate study selection and data extraction?** There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other’s work.*

**3. Was a comprehensive literature search performed?** At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. *Note: If at least 2 sources + one* ***Appendix*** *strategy used, select “yes” (Cochrane register/Central counts as 2 sources; a grey literature search counts as* ***Appendix****).*

**4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?** The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. *Note: If review indicates that there was a search for “grey literature” or “unpublished literature,” indicate “yes.” SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.*

**5. Was a list of studies (included and excluded) provided?** A list of included and excluded studies should be provided. *Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select “no.”*

**6. Were the characteristics of the included studies provided?** In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. *Note: Acceptable if not in table format as long as they are described as above.*

**7. Was the scientific quality of the included studies assessed and documented?** 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. *Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study (“low” or “high” is fine, as long as it is clear which studies scored “low” and which scored “high”; a summary score/range for all studies is not acceptable).*

**8. Was the scientific quality of the included studies used appropriately in formulating conclusions?** The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. *Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.*

**9. Were the methods used to combine the findings of studies appropriate?** For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., , Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., , is it sensible to combine?). *Note: Indicate “yes” if they mention or describe heterogeneity, i.e., , if they explain that they cannot pool because of heterogeneity/variability between interventions.*

**10. Was the likelihood of publication bias assessed?** An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). *Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.*

**11. Was the conflict of interest included?** Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. *Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.*