Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

Isaac Akinyemi

Turmeric or curcumin and the treatment of knee osteoarthritis:

A systematic review and meta-analysis of randomized controlled trials

Master's thesis in Public Health, specializing in Global Health
Supervisor: Abhijit Sen
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Abstract

Background: The prevalence of knee osteoarthritis (OA) is on the rise globally. This is partly due to the increase in proportion of people aged 60 years and older worldwide. Many of the current therapeutic options for the management of knee OA used in conventional medical practice have undesirable side effects which has led researchers to consider effective and safer alternatives. Curcumin, an herbal medicinal extract from the rhizome – turmeric has a favorable safety profile, and research evidence suggests that it is a viable option for the treatment of knee OA.

Objective: The objective of this systematic review and meta-analysis was to summarize and critically evaluate the published evidence from randomized controlled trials (RCTs) on the efficacy of curcumin in treating knee OA.

Methods: PubMed and Embase were searched for relevant RCTs published up until April 8, 2020. All RCTs that investigated the efficacy or effectiveness of curcumin in treating knee OA were included. Heterogeneity was assessed using I^2 statistics, and the random effects models were selected to calculate weighted mean differences (WMD) and mean change differences (MCD) for the outcome measures – visual analog scale (VAS) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores.

Results: Ten RCTs (n = 1272) were included in the meta-analysis. Curcumin significantly reduced pain (WMD for VAS (n = 3): -16.76 (-25.41, -8.11), I^2 = 87.6%, $P_{heterogeneity}$ = <0.001) and improved physical function (WMD for WOMAC physical function (n = 3): -8.63 (-10.17, -7.09), I^2 = 0.0%, $P_{heterogeneity}$ = 0.443) when compared with placebo. There was no difference in physical function (WMD for WOMAC physical function (n = 1): 0.15 (-0.30, 0.60), I^2 = 0.0%, $P_{heterogeneity}$ = .) when compared to ibuprofen or pain reduction (WMD for VAS (n=1): 0.00 (-0.24, 0.24), I^2 = 0.0%, $P_{heterogeneity}$ = .) when compared to diclofenac. Furthermore, sub-group analysis showed that difference in curcumin dosage (stronger association in doses >1000 mg/d) and type of control (RCTs with curcumin vs. active medication reported effect estimates closer to the null value) contributed significantly to the heterogeneity between the studies. Lastly, the incidence of adverse events was similar between curcumin and placebo but lower in the curcumin group when compared with active controls.

Conclusion: The findings from this review suggests that curcumin is a safe and effective option for treating the symptoms of knee OA. However, the number of RCTs included in the analysis

along with their overall quality and the total sample size was not sufficient to draw firm conclusions. Further high quality RCTs with large sample sizes should be conducted in order to provide definitive evidence that allow the adoption of curcumin as a treatment for knee OA in clinical practice.

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Abbreviations

CAM	Complementary and Alternative Medicine
CI	Confidence Interval
DALY	Disability-Adjusted Life Year
GBD	Global Burden of Diseases
HIC	High Income Country
ITT	Intention to Treat
IL-1β	Interleukin-1beta
STI	Sexually Transmitted Infection
LMIC	Low- and Middle-Income Country
MRI	Magnetic Resonance Imaging
MMP	Matrix Metalloproteinase
MCD	Mean Change Difference
NCD	Non-Communicable Disease
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NF-κB	Nuclear Factor-kappa B
OA	Osteoarthritis
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RR	Risk Ratio
SDI	Socio-Demographic Index
TKA	Total Knee Arthroplasty
TNF-α	Tumor Necrosis Factor-alpha
VAS	Visual Analogue Scale
WMD	Weighted Mean Difference
WOMAC	Western Ontario and McMaster Osteoarthritis Index
WHO	World Health Organization
YDL	Years Lived with Disability

Chapter 1: Introduction

1.1 Background

The background concepts of the intervention (curcumin) and the disease of interest (knee osteoarthritis) described in this section, provide the context that the rationale for this study is based on.

1.1.1 Knee osteoarthritis

Knee osteoarthritis (OA) is simply OA affecting the knee joint. It is a degenerative joint disease characterized by localized degradation of articular cartilage, subchondral bone remodeling, osteophyte formation, and synovitis.[1] Clinically, patients with OA present with symptoms such as pain, swelling in the joint(s), transient morning stiffness, limited range of motion, all of which lead to decrease in physical function, daily quality of life and ultimately increased morbidity and mortality.[2, 3] Obesity, age, and traumatic knee injury (especially in the younger population) are some of the risk factors associated with knee OA.[4, 5] Moreover, women are affected disproportionately and have a higher probability of experiencing a severe course of the disease.[6]

1.1.2 Global burden of Knee OA

Over 500 million people are reported to be affected by OA globally[7] with knee OA accounting for about 80%.[8] It has been estimated that 9.6% of men and 18% of women worldwide have symptomatic OA.[9] As at 2011, the prevalence of moderate and severe disability (in millions) attributable to OA in high income countries (HICs) was 1.9 among those below the age of 60 years and 8.1 in the 60 years old and above, while in lower middle income countries (LMICs) these figures stood at 14.1 and 19.4 among people below 60 years and those above 60 years, respectively.[9] The GBD 2019 study reported that OA was the 15th highest cause of years lived with disability (YLDs)[7] and was responsible for 2.2% of the total global YLDs (with 60.9% of this resulting from knee OA).[10] At present, high socio-demographic index (SDI) countries have a higher level of OA related YLDs compared to middle SDI regions.[7] However, a notable shift in trends has been observed over the years as middle SDI countries have, since 1990, experienced a steep increase in the rate of change in YLDs (89%). In comparison, high SDI countries have had an increase of 48%.[7] Furthermore, the disease burden of OA disproportionately affects LMICs due to limited access to adequate healthcare, social security systems, and flexible working conditions.[11]

Given that OA is among the leading causes of disability, it is expected that this important health condition be included in the global strategic plans for prevention and control of non-communicable diseases (NCDs). However, this is not the case despite the fact that it often coexists with diabetes, cardiovascular diseases and mental disorders, all of which are addressed in various existing action plans.[7, 12]

1.1.3 Pathogenesis

OA has traditionally been classified by etiology as either primary (idiopathic) or secondary.[13] Primary OA involves erosion of the affected joint(s) without any identifiable cause, while secondary OA is indicated in cases with a predisposing condition, such as trauma or mechanical misalignment.[13, 14]

The knee is the largest synovial joint in the human body which is responsible for weight bearing and movement, and this makes it vulnerable to injury from acute mechanical strain that can be compounded by age-related oxidative stress.[1, 15] Repeated injury to the knee joint gives rise to chronic and low-grade inflammation of the synovium influenced by elevated levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β). This sets off an enzymatic reaction that breaks down the matrix of the cartilage in the knee joint through the production of matrix metalloproteinases (MMPs).[1, 13] Additionally, the synovial cell membrane when damaged releases membrane phospholipids which initiates a cascade reaction that leads to increased levels of lipid mediators, such as prostaglandins and leukotrienes. These lipid mediators are present in significantly higher concentrations in synovial fluid samples from patients with OA when compared with identical samples obtained from unaffected participants and are responsible for the changes that occur at the local site of inflammation (increase in microvascular permeability, attraction of leucocytes, etc.).[1, 16, 17]

1.1.4 Pathophysiology

The process in which OA progresses has been described as dynamic, this is because it involves both the destruction and repair of cartilage tissue found in the affected joint.[18] At the initial stage of the disease progression, the degradation of proteoglycans and collagen in cartilage causes an increase in the water content.[18] Their combined effect in turn causes a decline in tensile stiffness and strength of the cartilage.[19] In reaction to this structural change, the hyperproliferative chondrocytes produces higher amount of cartilage matrix proteins resulting in increased thickness of the cartilage along with softening of the extracellular matrix.[20] However, as OA advances, the ability of the chondrocytes to repair the damaged cartilage

declines and the ensuing loss of structural integrity induces cartilage fibrillation that extend down to the underlying bone[18]; consequently, the subchondral bone become exposed to the articular surface which leads to the development of bone marrow edema and subchondral bone cysts, and also the formation of osteophytes along the joint margin.[20]

1.1.5 Diagnosis and conventional therapy

Although early OA changes are in most cases not visible, OA can be diagnosed on the basis of patient history and physical examination, and confirmed using plain radiography.[21, 22] X-ray imaging is commonly used to determine the severity of OA. The grading is usually done using the Kellgren-Lawrence classification system (from grade 0 indicating no presence of OA to grade 4 indicating severe OA). However, the severity of OA based on the disease progression often does not correlate with the severity of symptoms experienced by patients, in fact severe pain and disability generally occur in the early stages of OA, while at the advance stages patients experience mainly minor symptoms.[23-25] There are diverse methods of quantifying the symptoms presented by patients with OA; pain for instance can be estimated using the visual analogue scale (VAS) score while functional disability may be assessed using the Western Ontario and McMaster Osteoarthritis Index (WOMAC) and Lequesne questionnaires.[18]

Magnetic resonance imaging (MRI) and ultrasound are modern imaging modalities that have the advantage of being used to detect pre-radiographic structural changes in the synovial membrane, cartilage, peri-articular bone, etc.[26] While a number of imaging studies have been conducted to examine the validity and reliability of these modern imaging techniques in diagnosing early OA, the information accrued has so far had no influence on clinical decision making in the matter of initiating early treatment interventions which may delay the disease progression.[27-30]

In conventional medicine, non-pharmacological therapy is commonly used for patients diagnosed with minor or mild OA such as patient education, exercise, strength training, and the use of assistive devices like braces and shoe inserts, while patients with moderate OA are at first treated with over-the-counter pain-relieving medications, for example acetaminophen (used also in mild OA) and nonsteroidal anti-inflammatory drugs (NSAIDs). Moreover, prescription medications such as selective COX-2 inhibitor (celecoxib), opioids, intra-articular injections of corticosteroids and hyaluronic acid are used for the treatment when over the counter medications become ineffective.[18, 21] Surgical interventions are usually used as the last resort for patients with severe cases of OA.[21]

Current pharmacological regimens for OA do not inhibit or reverse the disease progression and their long-term use has been found to be associated with gastrointestinal complications, renal insufficiency and adverse cardiovascular events, especially in older patients.[31, 32] In advanced knee OA, the different surgical techniques in clinical use have had varying success in the management of OA symptoms over extended periods.[33] Nonetheless, with standard treatment failing to provide lasting and sustainable resolution of OA symptoms, especially during the early stages, medical practitioners risk falling into the trap of either overtreatment or undertreatment, and there is therefore a need for safer and more effective therapeutic alternatives for managing OA symptoms pending the discovery of one or more curative therapies.[7, 34, 35]

1.1.6 Complementary and alternative therapy

The term complementary and alternative medicine (CAM) refers to a diverse range of medical and health care practices that fall outside the scope of conventional medicine.[36] Many of the therapies in CAM are founded on health theories developed in alternative medical systems, including traditional Chinese medicine, Ayurveda, naturopathy and homeopathy.[36] Although CAM has gained popularity worldwide (a by-effect of globalization), there is an insufficient collection of reliable evidence on the quality, efficacy and safety of the various therapies that lie within the practice.[37] Nevertheless, the integration of conventional medicine and evidence-based CAM has been on the rise.[36] This is evident in the current management of knee OA where the supplements glucosamine and chondroitin sulfate have become widely accepted in clinical practice.[38] Treading the same path, herbal medications containing extracts from Curcuma longa, Boswellia serrata, Kaempferia galanga, etc., have demonstrated strong anti-inflammatory and anti-oxidative activities that can be beneficial in the management of symptoms experienced by patients with knee OA.[38, 39] Accordingly, the potential for the adaptation of additional complementary and alternative remedies (naturally occurring phytochemicals, mind-body therapies, etc.) lie in the exploration of evidence for their effectiveness and safety.[38, 40]

1.1.7 Curcumin

Curcumin (diferuloylmethane) is a polyphenol extracted from the rhizome of turmeric (Curcuma longa). It has been used for centuries in traditional Chinese and Ayurvedic medicine.[35] Experimental and clinical studies have shown that curcumin possesses significant

antioxidant, anti-inflammatory, anti-carcinogenic and wound healing effects with good tolerability and a favorable safety profile.[32, 41]

The exact mechanism(s) of action by which curcumin alleviates the symptoms experienced by patients with OA is not fully understood.[42] However, a plausible mechanism is by way of downregulating the activation of nuclear factor-kappa B (NF-κB). This transcription factor plays an important role in the expression of TNF-α, cell adhesion molecules, MMPs, and other inflammatory intermediates associated with OA.[38] Another proposed mechanism is through the antioxidant activity of curcumin, as it modulates the activity of glutathione, catalase, and superoxide dismutase, all of which are involved in the neutralization of free radicals (known to amplify inflammatory response).[43, 44] In the matter of safety, it has been demonstrated in several clinical trials that curcumin is safe for consumption, even with a dose as high as 8000 mg/day.[45, 46] One of the major drawbacks with the use of curcumin is its poor bioavailability (due to poor absorption, rapid metabolism, and rapid systemic elimination).[46] Consequently, various methods of enhancing the bioavailability of curcumin have been investigated, including its combination with adjuvants such as piperine, encapsulation (liposomes encapsulation, nanoemulsion encapsulation, cyclodextrin encapsulation, etc.) and the formulation of novel curcumin analogs through structural modification.[47, 48]

1.1.8 Literature on curcumin as a therapeutic agent for knee OA

Pre-clinical studies have over the last three decades proven the capability of curcumin in mitigating inflammatory response in vivo.[49-53] These studies have provided insight into the long-term use of curcumin in treating inflammatory disorders, with toxicology studies showing that large doses over long periods are safe for consumption.[54-56] In light of these findings, several clinical trials have been conducted to explore the effect of curcumin based formulations in treating the symptoms experienced by knee OA patients.[2, 32, 45, 57-61] Panahi et al.,[58] for instance, conducted a randomized controlled trial (RCT) which lasted for 6 weeks comparing the use of curcumin (1500 mg/d) with placebo among 53 participants, and concluded that curcumin was effective in alleviating symptoms caused by knee OA with no considerable adverse effects. Similarly, in an RCT conducted for 12 weeks by Wang et al.,[32] patients (n = 36) who received curcumin (1000 mg/d) experienced greater pain relief compared with patients (n = 34) given placebo; the occurrence of adverse events were similar between both groups. While Kuptniratsaikul et al.[45] conducted an RCT for 4 weeks that included 367 participants comparing curcumin (1500 mg/d) with ibuprofen (1200 mg/d). They concluded that curcumin

was as effective in relieving symptoms presented in knee OA patients with similar levels of adverse events (but fewer gastrointestinal related events in the curcumin group) when compared with ibuprofen.

Although the duration, dosage and number of participants have varied across RCTs performed to examine the efficacy and safety of curcumin as a complementary or alternative treatment option for knee OA, the findings (which favor curcumin in terms of efficacy) have been fairly consistent. However, as shown above, the findings concerning the safety of curcumin have not been entirely consistent.

1.2 Rationale

1.2.1 Rationale for the study

The global population aged 60 years and over is projected to reach 1.4 billion by 2030 and 2.1 billion by 2050 with populations in developing countries contributing more to this increase than populations in developed countries.[62] Given that age is a risk factor for the development of OA, the incidence of OA is also expected to rise. Thus, there is a need for safe and effective treatment options until disease-modifying OA drugs which halt the disease progression are fully developed and approved for treatment.[63] Numerous RCTs had been conducted to establish, in general, the efficacy and safety of curcumin in the management of pain, stiffness and functionality in patients with knee OA. However, questions remained about the dose required to optimize its effect and on whether the use of combination therapy is of greater advantage in alleviating the symptoms of OA compared with the use of curcumin alone. The aim of this project was to conduct a systematic review and meta-analysis of RCTs on the use of curcumin in the treatment of knee osteoarthritis and to critically appraise and evaluate the evidence available so as to address the knowledge gaps that were identified.

1.2.2 Research objectives

1. To assess whether curcumin is beneficial in the treatment of knee osteoarthritis and to identify the required dosage of curcumin needed to achieve optimal therapeutic effect in patients with knee OA.

2. To assess whether the use of combined therapy provides better results than the use of curcumin alone.

3. To assess the impact of moderating variables (e.g., sex, geographical location, etc.) on the relationship between the independent variable (curcumin) and the dependent variable (knee OA).

Chapter 2: Methods

2.1 Overview

This review was conducted in accordance with the Cochrane methodology, and the meta-analysis was reported as specified by the QUOROM criteria. Both the methodology and the criteria were predefined before the initiation of the screening phase. Registration of the protocol was not considered.

2.2 Data sources and search strategy

In order to access the appropriate data for this research project, an electronic literature search was conducted on both the PubMed and Embase databases in English for relevant studies published up until April, 8 2020. In June 2021, the search was updated to include any relevant studies that were published after the initial search. The following keywords were used to conduct the literature search: “curcumin”, “curcuma”, “turmeric”, “Curcuma domestica”, “Curcuma Longa”, “knee”, “arthritis”, “osteoarthritis”, “random”, “controlled”, “clinical”, and “trial” (Table 2.1).

Table 2.1 Search strategies for each database

Database	**Search strategy**
PubMed	(turmeric OR curcumin OR curcuma OR Curcuma domestica OR Curcuma Longa) [tiab] AND (knee OR arthritis* OR osteoarthritis OR “knee pain”) [tiab] AND (random* OR controlled* OR clinical* OR trial*)
Embase	(Turmeric or curcumin or curcuma or Curcuma domestica or Curcuma Longa).ab,ti. and (knee or arthritis* or knee osteoarthritis or knee pain).ab,ti. and (random* or controlled* or clinical* or trial*)

‘*’ extension of the word; ab, abstract; ti, title.

2.3 Study selection

Retrieved citations were screened manually using Reference Manager. In the first screening, the title and abstract records were coded as “included” or “excluded” on the basis of meeting the eligibility criteria which were as follows:

1. RCTs: single-blinded, double-blinded, triple-blinded and unblinded/open label;
2. participants diagnosed with knee OA;
3. intervention with curcumin or curcuma domestica extracts;
4. control with placebo or usual therapy; and
5. outcome measures including VAS or WOMAC scores.

Pre-clinical studies, non-randomized studies, observational studies and studies published as abstract alone were excluded. Additional screening was conducted to account for duplicates. And full text papers were retrieved for records coded as “included” and screened a final time to ensure that all studies included for meta-analysis met the eligibility criteria.

2.4 Data extraction

The following information were extracted from the studies selected after screening:

- study characteristics – author name, publication year, geographic location, study name, study period, sample size (experimental/control group) and type of blinding/allocation;
- demographic data – sex;
- intervention characteristics – dosage and formulation (single vs. combined therapy) of curcumin prescribed;
- comparison details – placebo or usual therapy;
- outcome measures – VAS and WOMAC scores, and their categorization as primary or secondary measures;
- number of patients assigned vs. number of patients who completed the study;
- methods of analysis such as Intention to Treat (ITT) or Per Protocol; and
- assessment of outcome – Mean and standard deviation (or error) of pain, stiffness, and other symptoms at baseline and at the end of the trial, time point for each measurement, summary measures of change provided in the studies, and reported adverse events.

The relevant data was inputted into an excel sheet with predefined columns.

2.5 Quality assessment

The quality of all included studies was assessed using Risk of Bias Tool version 2 (RoB2) from Cochrane Collaboration[64] which examines the following domains:

- Domain 1: Bias arising from the randomization process.
- Domain 2: Bias due to deviations from the intended interventions.
- Domain 3: Bias due to missing outcome data.
- Domain 4: Bias in measurement of the outcome.
- Domain 5: Bias in selection of the reported result.

A single assessment result was reported in cases where there were similar assessment results for the different outcomes of a particular study.

2.6 Outcome definition

Primary symptoms of knee OA include pain, stiffness and limitation of movement in the affected knee joint.[65] The validity and reliability of VAS and WOMAC in measuring the severity of symptoms in patients with knee OA have been scientifically established.[66] WOMAC, a self-administered questionnaire, consisted of 24 items grouped into 3 subclasses: pain - 5 items, stiffness - 2 items, and physical functioning - 17 items. Each item was scored on a scale of 0-4 and the scores were summed up to get the total score for each subclass. While VAS assessed the patient's perception of pain intensity using a straight, 10 cm line on which the severity was represented by the scores of 0-10. In both outcome measures, the scores had a positive correlation with the severity of the symptoms.

2.7 Statistical analysis

Random effects models were used to estimate weighted mean differences (WMDs) and mean changes differences (MCDs) in VAS and WOMAC, and their 95% confidence intervals (CIs) were estimated based on final scores and change in scores between baseline and final assessment, respectively.[67] Separate analyses were conducted for VAS and WOMAC and for

studies using active controls and placebo controls. The estimated effect size, i.e., WMD and MCD, was considered significant if the upper and lower bounds of the 95% CI did not contain 0. When studies reported results for two treatment groups (e.g. different dosages) vs. the control group, the results for the treatment groups were pooled using standard formula.[68] Additionally, the occurrence of adverse events were analyzed and reported as risk ratio (RR) and 95% CI.[69]

Heterogeneity between studies was analyzed using Q and I^2 statistics.[70] The Q test provided information on the presence of heterogeneity while the I^2 index described the percentage of variation across the studies attributed to heterogeneity rather than chance.[71, 72] Subgroup analysis stratified by study characteristics (type of control and dose of curcumin used) was conducted to investigate the potential sources of heterogeneity. Furthermore, small-study effects, such as publication bias, were assessed using both Egger's test and Begg's test.[73, 74] All statistical analysis were conducted using STATA version 16.1 (StataCorp, TX, USA).

2.8 Ethical consideration

Application for ethical approval is seldom required for studies analyzing secondary data. In the case of this review, it was not sought after as original research was not being carried out.

Chapter 3: Results

3.1 Study selection and characteristics

3.1.1 Overview of the search

The initial database search identified 1035 (PubMed: 365; Embase: 670) citations. After removing duplicates, 1014 records were screened based on their title and abstract. A total of 947 studies were excluded for not meeting the eligibility criteria, and after the manual removal of duplicates, full text articles for the remaining studies were retrieved for further evaluation. Of the 12 authors contacted to access the full text of their studies, 8 did not respond, hence their articles were excluded. Overall, ten studies met the pre-specified eligibility criteria and were included in this systematic review (Figure 3.1).

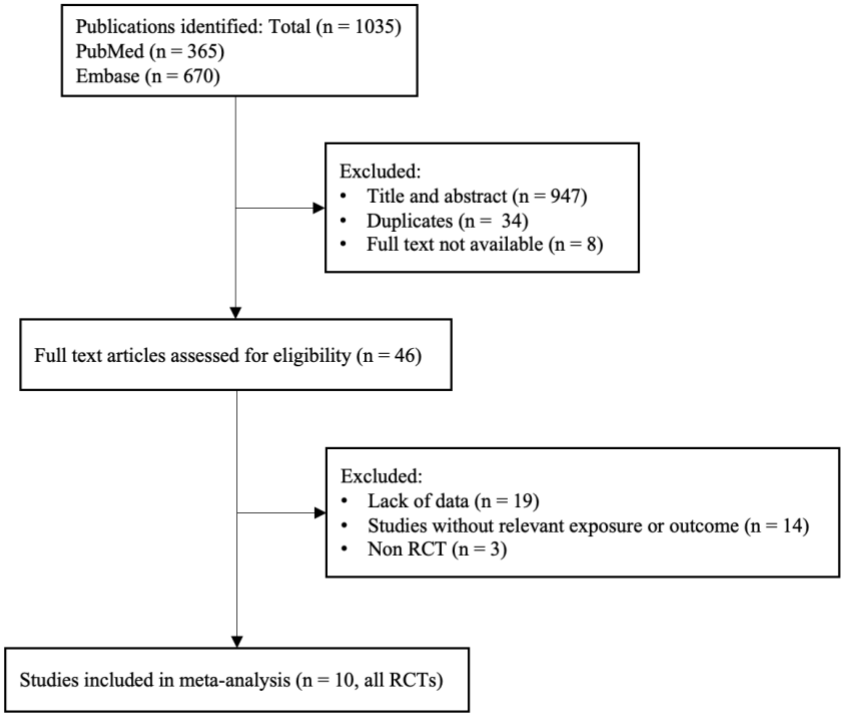

Figure 3.1 Flow-chart of screened and included studies.

3.1.2 Characteristics of the included studies

The basic characteristics of the included studies are presented in Appendix A. All ten studies were published between 2013 and 2019 in English language. They included a total of 1272 participants. The mean age ranged from 50 to 71 years (median: 55 years), and the percentage of females ranged from 33% to 93% (median: 69%). Additionally, the duration of included RCTs was between 4 and 17 weeks (median: 11 weeks).

Of the ten studies, nine were conducted in Asia (India – 6,[1, 35, 38, 43, 57, 61] Thailand – 1,[45] Armenia – 1[2] and Iran – 1[58]), and the remaining one was conducted in Italy.[75]

In seven studies,[1, 2, 43, 57, 58, 61, 75] curcumin extract formulations were compared with placebo, with three studies each using diclofenac,[61] glucosamine sulphate[57] and physical therapy[75] in both treatment and control arms of the trial. The remaining three studies were a head-to-head comparison between curcumin containing formulations and the following medications – glucosamine and chondroitin,[38] diclofenac,[35] and ibuprofen.[45] The daily dose of curcumin varied from 100 to 1500 mg. Furthermore, different techniques were used to improve the bioavailability of curcumin in some of the studies (e.g., use of bioperine to increase absorption[58]), and in other studies curcumin was used in combination with other alternative treatments.[1, 2, 38, 57, 75]

Seven studies[1, 38, 43, 57, 58, 61, 75] used both VAS and WOMAC for the assessment of OA symptoms, while the other three used either VAS – 1[35] or WOMAC – 2.[2, 45] In two studies, localized versions of WOMAC were used – Thai version[45] and Indian (Centre for Rheumatic Diseases, Pune) version[57]; they reflected the local lifestyle in the geographical areas the trials were conducted.

3.2 Risk of bias assessment

The risk of bias for the included studies was assessed in accordance with the methodology described in the Cochrane Handbook for Systematic Reviews of Interventions chapter 8 version 6.2, 2021.[76] The 5 domains of the RoB2 tool were assessed and classified as being at a 'low', or 'high' risk of bias, or showing 'some concerns' (Figure 3.2). See Appendix B for the full results for each study assessment.

3.2.1 Bias arising from the randomization process

Among the ten studies, four[2, 35, 38, 45] were classified as low risk of bias since both the methods of randomization and allocation concealment were used and described, and the baseline characteristics were similar between intervention groups. While the remaining six studies[1, 43, 57, 58, 61, 75] were classified as showing some concern because allocation concealment was not indicated.

3.2.2 Bias due to deviations from the intended interventions

All but one study[35] described some level of blinding. Six studies[2, 35, 43, 45, 57, 61] were classified as low risk of bias as they generally indicated that participants and trial personnel were not aware of the treatment allocation or ITT was used in the analysis of the results. The remaining four studies[1, 38, 58, 75] were classified as showing some concern because the trials were single-blinded or the results were analyzed per protocol.

3.2.3 Bias due to missing outcome data

Eight studies[1, 2, 35, 38, 43, 45, 57, 75] were classified as low risk of bias given that either all, or nearly all, participants were included in the final analysis, or the proportions or reasons for missing outcome data did not differ significantly between the intervention and control groups. One study[61] was classified as showing some concerns as a considerable proportion of participants did not complete the trial, but there was little difference in the proportion of missing outcome data between the intervention groups. The last study[58] left was classified as high risk of bias since the proportion of missing outcome data was significantly high, and different between the experimental and comparator intervention groups.

3.2.4 Bias in measurement of the outcome

All ten studies used the appropriate method of measuring the outcome in both the intervention and control groups and were therefore classified as low risk bias (nine studies) or high risk of bias (one study[35]) depending on whether the assessors, in this case the participants, were aware of the intervention received.

3.2.5 Bias in selection of the reported result

The pre-specified outcome measures and analyses were recorded and reported in the result section of all ten studies, and for this reason they were classified as low risk of bias.

3.2.6 Overall risk-of-bias assessment

Figure 3.3 shows the overall risk-of-bias judgement as percentages across all studies included in the assessment. Of the ten studies, two studies[2, 45] were classified as low risk of bias, six studies[1, 38, 43, 57, 61, 75] as showing some concerns and another two studies as high risk of bias.[35, 58]

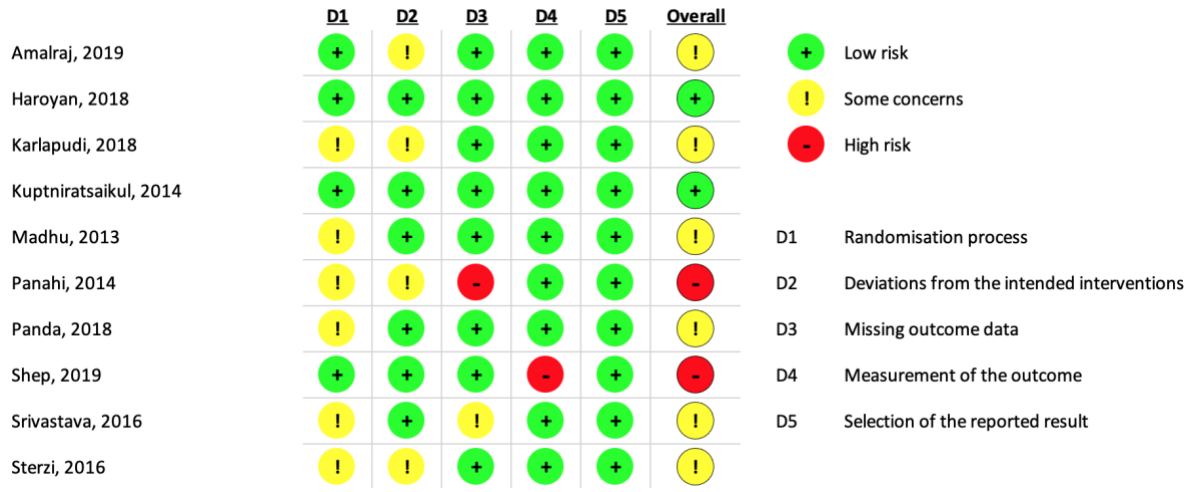

Figure 3.2 Risk of bias summary of the included studies.

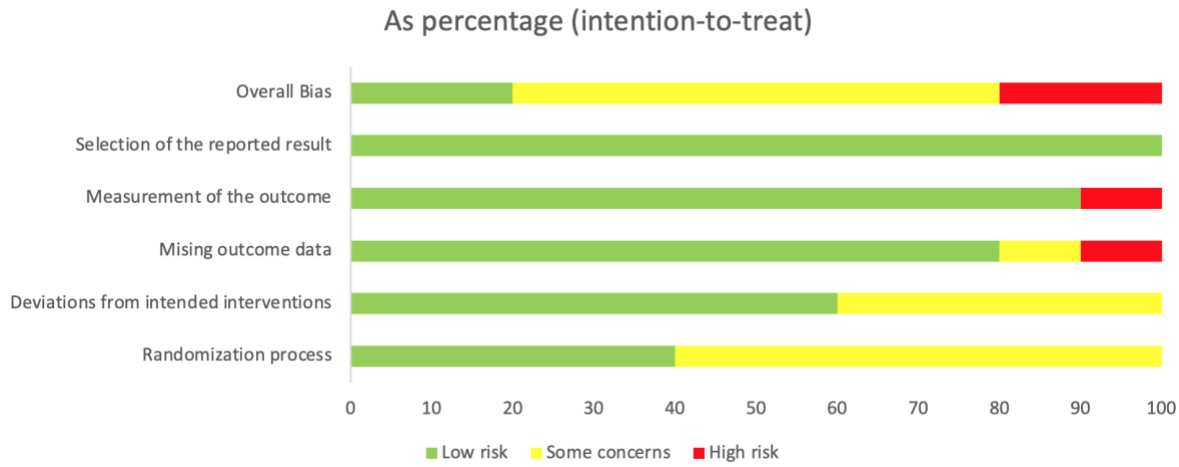

Figure 3.3 Risk of bias graph: RoB 2 domains and overall bias presented as percentages across all included studies.

3.3 Outcomes

3.3.1 Overview

Studies included in the systematic review varied in the outcome measures used in determining the effect of curcumin on the severity of knee OA. As a result, ten sets of meta-analyses were performed to estimate the WMDs, MCDs and their 95% CIs. Additionally, the studies included were stratified based on whether the control used was placebo or an active comparator. In the intervention arm of most of the trials, curcumin was used alongside other herbal or conventional medicinal products, and for this reason, the dosage of curcumin regardless of its combination was used in pooling the estimated effect size across the various meta-analyses. One study[1] had two arms for different curcumin dosages which were pooled before inclusion in the meta-analysis.

3.3.2 Effect of curcumin on VAS

Based on six studies (n = 559),[1, 35, 38, 43, 57, 61] the effect of curcumin on pain scores using VAS showed significant reduction favoring curcumin over placebo for pooled WMD: -16.76 (95% CI: -25.41, -8.11, I^2 = 87.6%, $P_{\text{heterogeneity}}$ = <0.001) and MCD: -13.80 (95% CI: -20.01, -7.59, I^2 = 85.1%, $P_{\text{heterogeneity}}$ = 0.010). Whereas with active controls, curcumin showed a weaker, but still statistically significant reduction for pooled WMD: -1.62 (95% CI: -3.03, -0.21, I^2 = 96.5%, $P_{\text{heterogeneity}}$ = <0.001), but no statistical difference for pooled MCD: -0.68 (95% CI: -1.98, 0.62, I^2 = 95.0%, $P_{\text{heterogeneity}}$ = <0.001). Results for WMD and MCD are displayed in Figures 3.4 and 3.5, respectively.

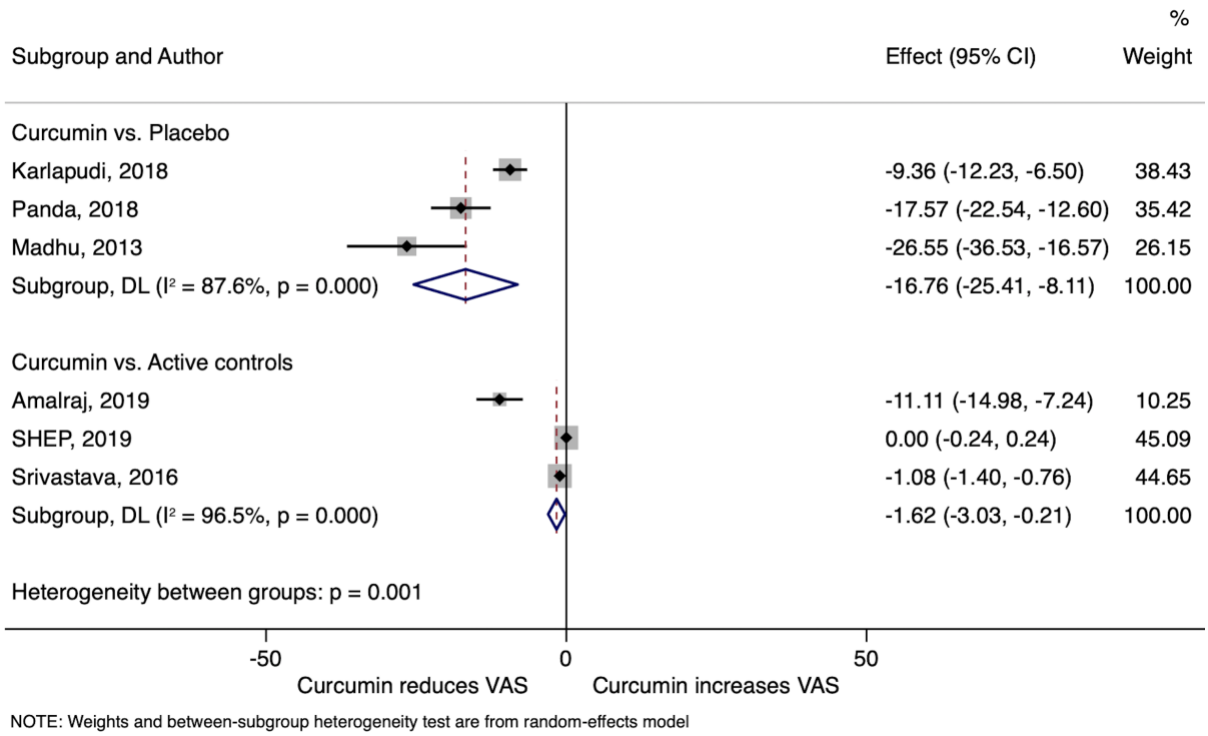

Figure 3.4 Forest plot depicting the WMD in VAS between curcumin and control groups.

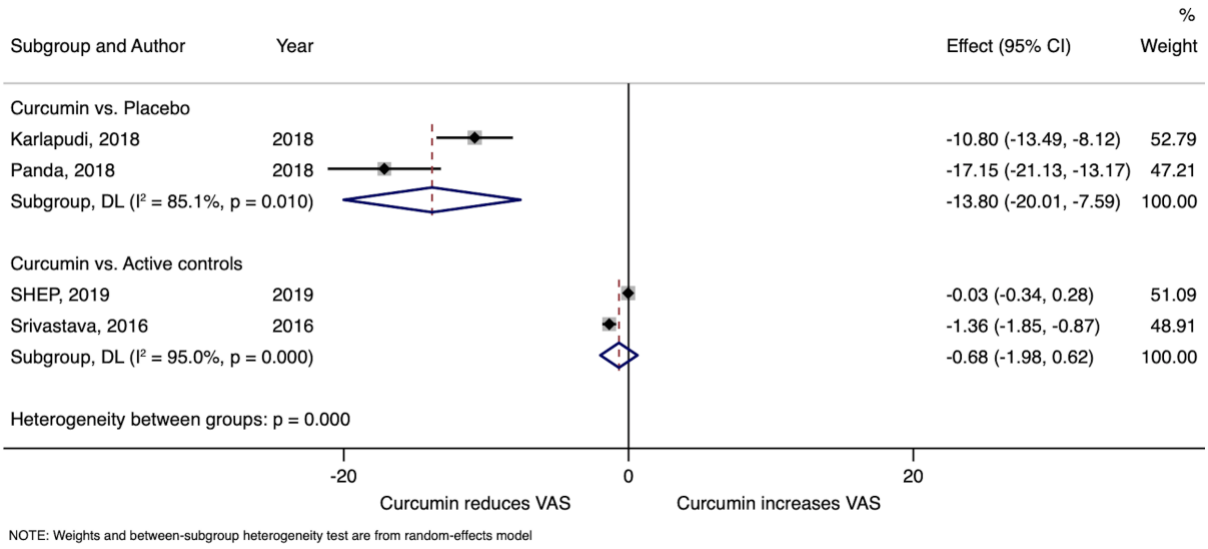

Figure 3.5 Forest plot depicting the MCD in VAS between curcumin and control groups.

3.3.3 Effect of curcumin on WOMAC pain

Seven studies[1, 2, 38, 43, 45, 58, 61] (n = 867) reported the effect of curcumin using the WOMAC subscale for pain. There was significant reduction favoring curcumin over placebo for pooled WMD: -3.76 (95% CI: -5.88, -1.65, I^2 = 88.7%, $P_{heterogeneity}$ = <0.001) and MCD: -4.60 (95% CI: -7.68, -1.52, I^2 = 95.1%, $P_{heterogeneity}$ = <0.001), but no statistical difference when compared with active controls for pooled WMD: -0.25 (95% CI: -0.56, 0.07, I^2 = 65.3%, $P_{heterogeneity}$ =

0.056) and MCD: -0.49 (95% CI: -1.42, 0.44, I^2 = 0.0%, $P_{heterogeneity}$ = .). Results for WMD and MCD are displayed in Figures 3.6 and 3.7, respectively.

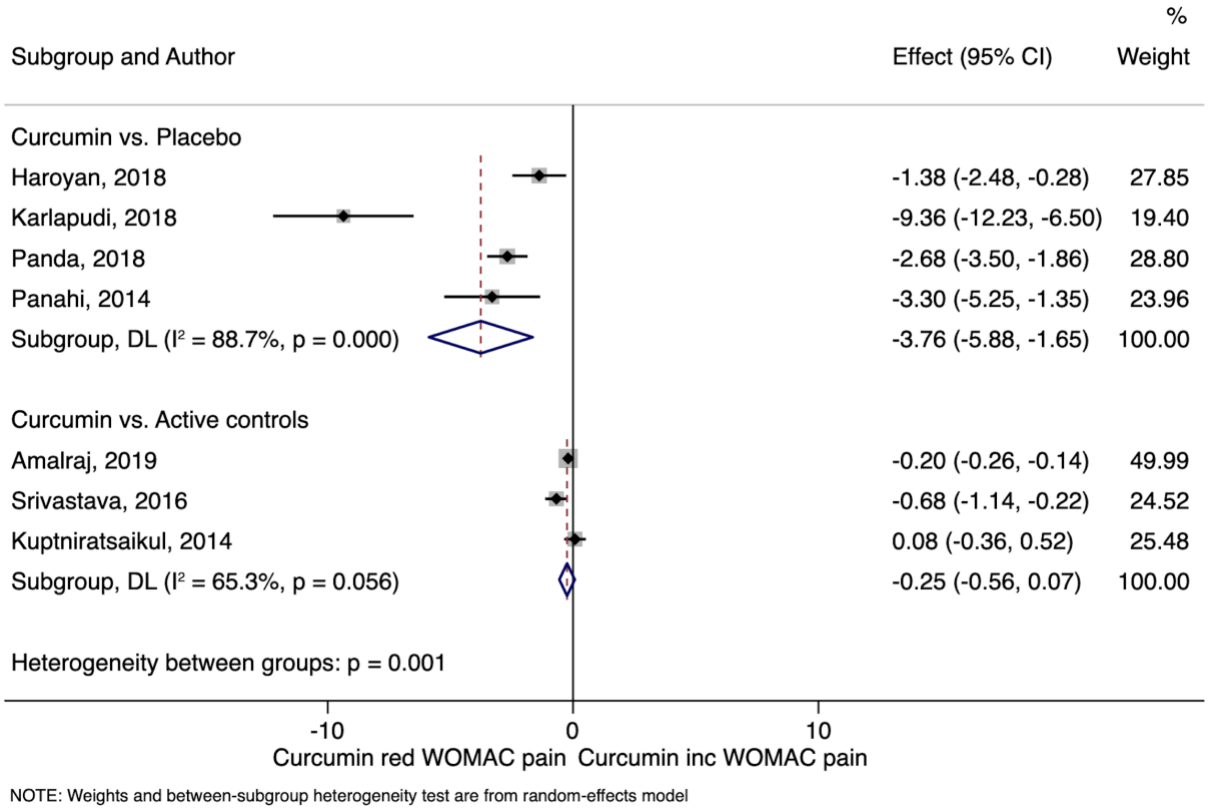

Figure 3.6 Forest plot depicting the WMD in WOMAC pain between curcumin and control groups.

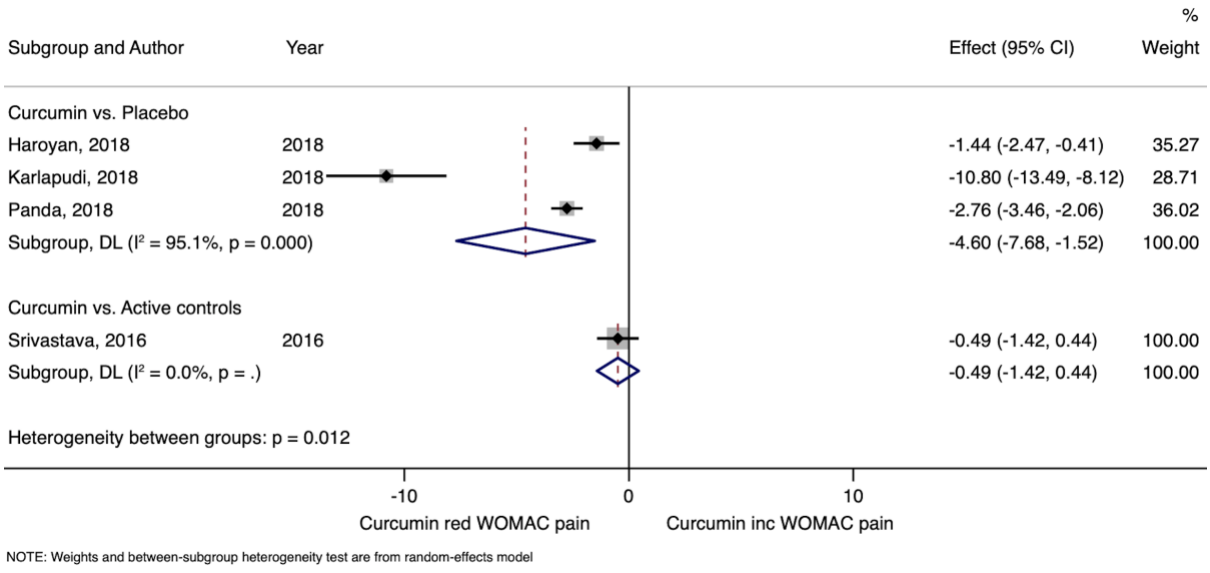

Figure 3.7 Forest plot depicting the MCD in WOMAC pain between curcumin and control groups.

3.3.4 Effect of curcumin on WOMAC stiffness

Five studies[1, 43, 45, 58, 61] (n = 709) reported the effect of curcumin using the WOMAC subscale for stiffness. There was significant improvement favoring curcumin over placebo for pooled WMD: -2.90 (95% CI: -4.86, -0.94, I^2 = 95.0%, $P_{heterogeneity}$ = <0.001) and MCD: -6.02 (95% CI: -15.20, 3.15, I^2 = 97.8%, $P_{heterogeneity}$ = <0.001), but no statistical difference when compared with active controls for pooled WMD: 0.01 (95% CI: -0.34, 0.37, I^2 = 0.0%, $P_{heterogeneity}$ = 0.578) and MCD: -0.32 (95% CI: -0.85, 0.21, I^2 = 0.0%, $P_{heterogeneity}$ = .). Results for WMD and MCD are displayed in Figures 3.8 and 3.9, respectively.

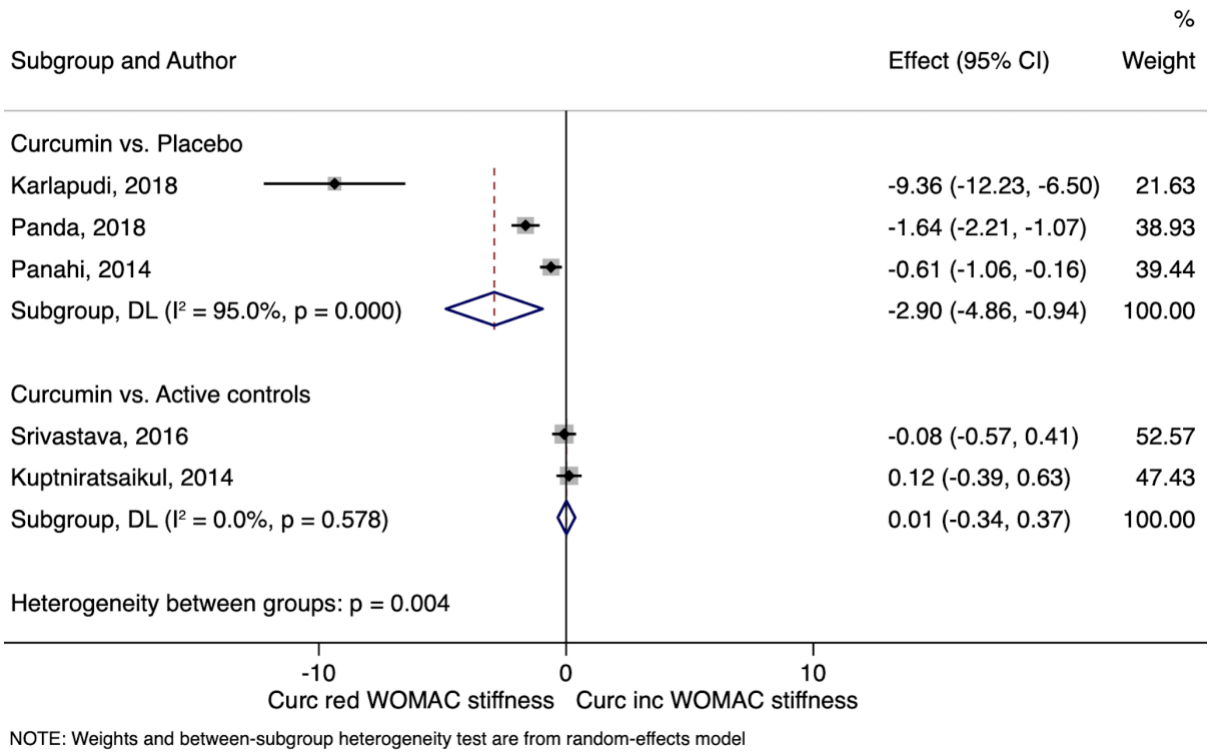

Figure 3.8 Forest plot depicting the WMD in WOMAC stiffness between curcumin and control groups.

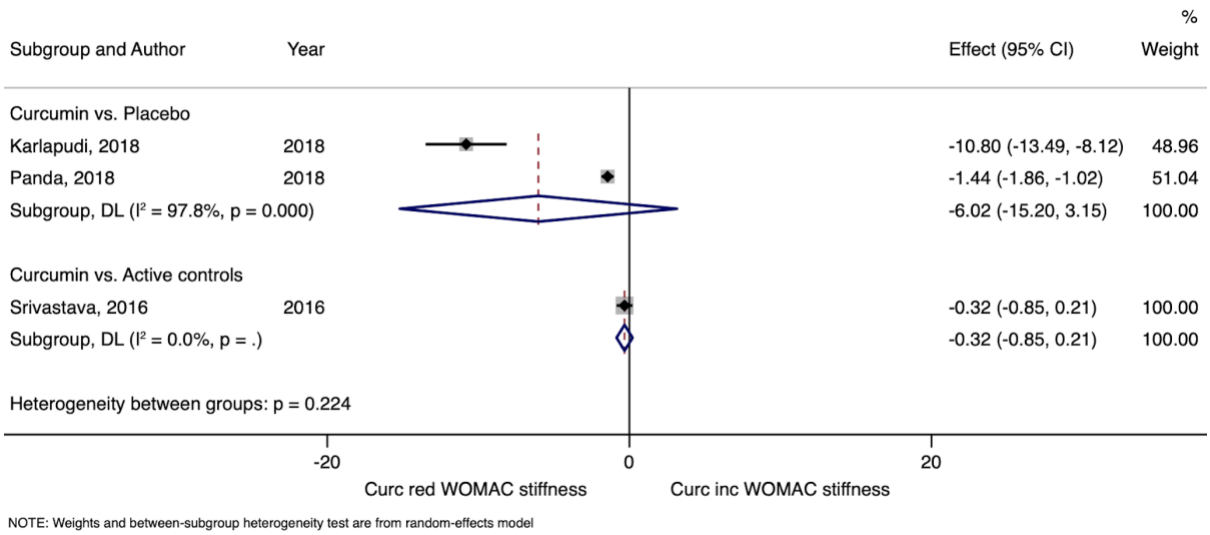

Figure 3.9 Forest plot depicting the MCD in WOMAC stiffness between curcumin and control groups.

3.3.5 Effect of curcumin on WOMAC physical function

Six studies[1, 38, 43, 45, 58, 61] (n = 733) reported the effect of curcumin using the WOMAC subscale for physical function. There was significant improvement favoring curcumin over placebo for pooled WMD: -8.63 (95% CI: -10.17, -7.09, I^2 = 0.0%, $P_{\text{heterogeneity}}$ = 0.443) and MCD: -9.43 (95% CI: -11.47, -7.39, I^2 = 47.3%, $P_{\text{heterogeneity}}$ = 0.168), and active controls for pooled MCD: -4.78 (95% CI: -7.27, -2.29, I^2 = 0.0%, $P_{\text{heterogeneity}}$ = .) but no statistical difference when compared with active controls for pooled WMD -0.27 (95% CI: -0.80, 0.25, I^2 = 75.4%, $P_{\text{heterogeneity}}$ = 0.017). Results for WMD and MCD are displayed in Figures 3.10 and 3.11, respectively.

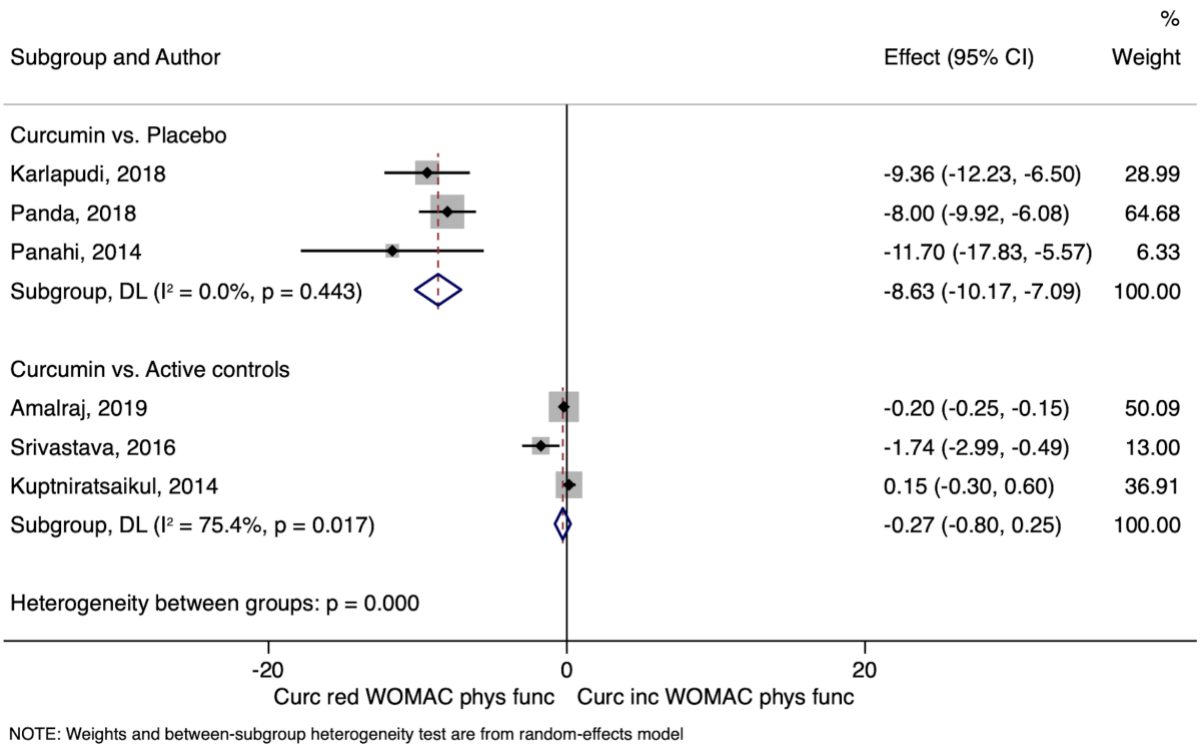

Figure 3.10 Forest plot depicting the WMD in WOMAC physical function between curcumin and control groups.

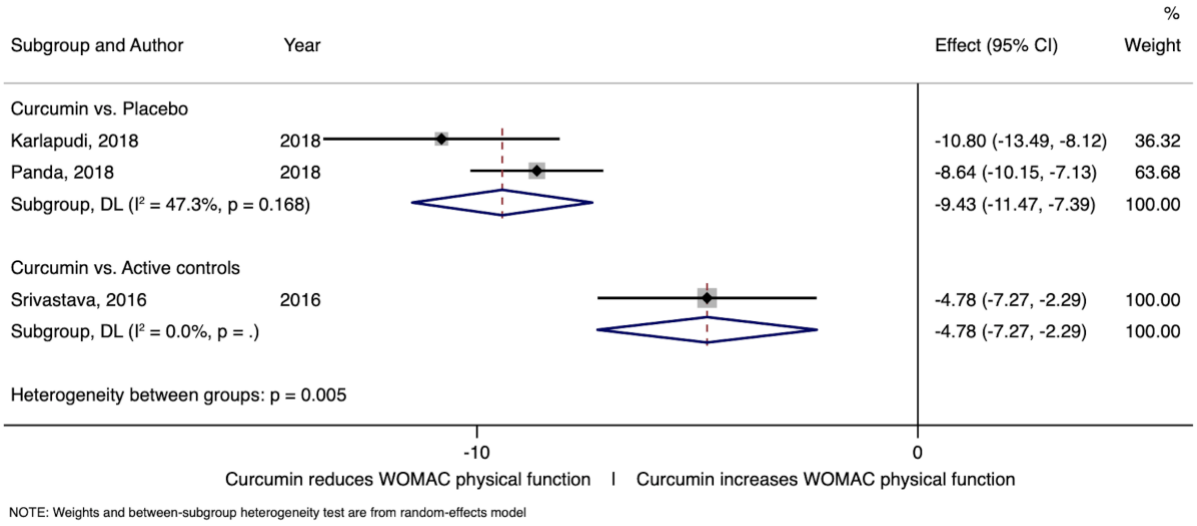

Figure 3.11 Forest plot depicting the MCD in WOMAC physical function between curcumin and control groups.

3.3.6 Effect of curcumin on WOMAC total

Eight studies[1, 2, 38, 43, 45, 57, 58, 75] (n = 815) reported the effect of curcumin using WOMAC total score (i.e., pain, stiffness, and physical function). There was significant reduction favoring curcumin over placebo for pooled WMD: -11.10 (95% CI: -14.68, -7.53, I^2 = 68.9%, $P_{\text{heterogeneity}}$

= 0.007) and MCD: -9.81 (95% CI: -13.85, -5.78, I^2 = 83.9%, $P_{heterogeneity}$ = 0.002), but no statistical difference when compared with active controls for pooled WMD: -0.11 (95% CI: -0.41, 0.19, I^2 = 57.9%, $P_{heterogeneity}$ = 0.123). Results for WMD and MCD are displayed in Figures 3.12 and 3.13, respectively.

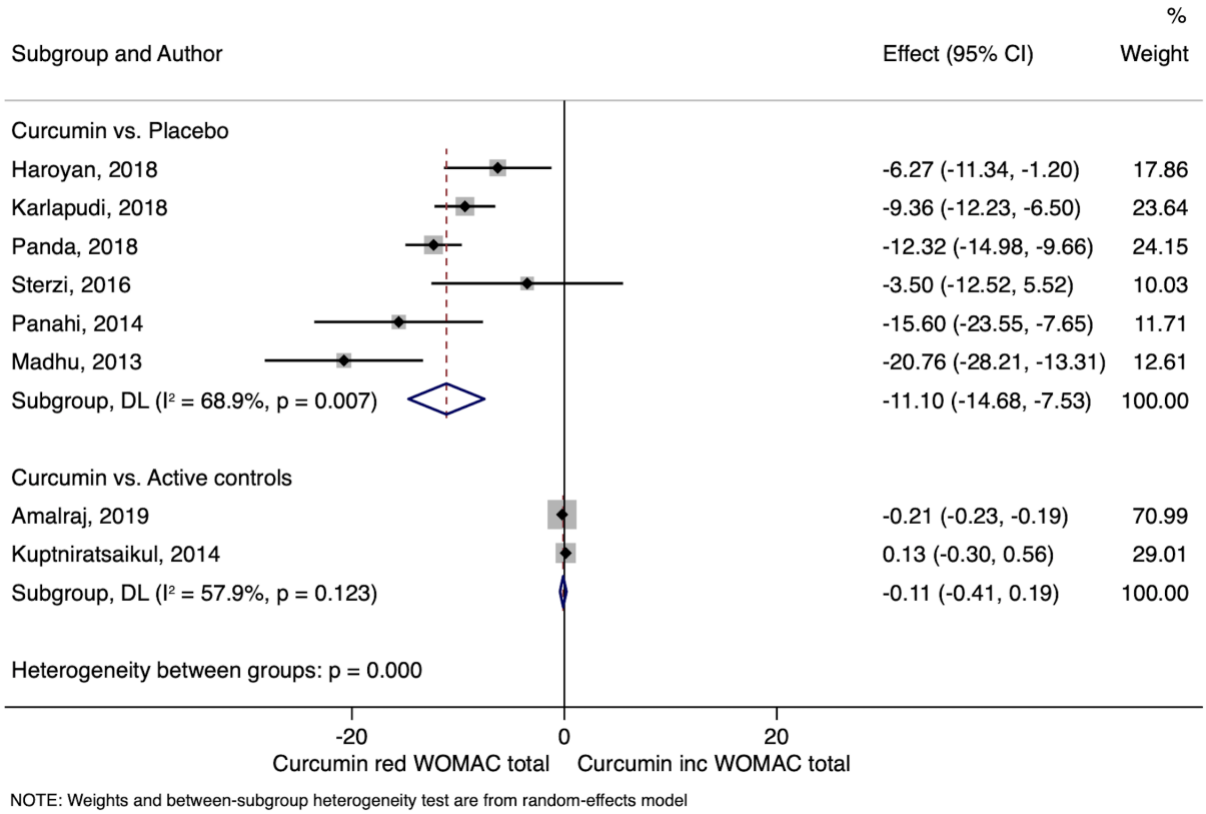

Figure 3.12 Forest plot depicting the WMD in WOMAC total between curcumin and control groups.

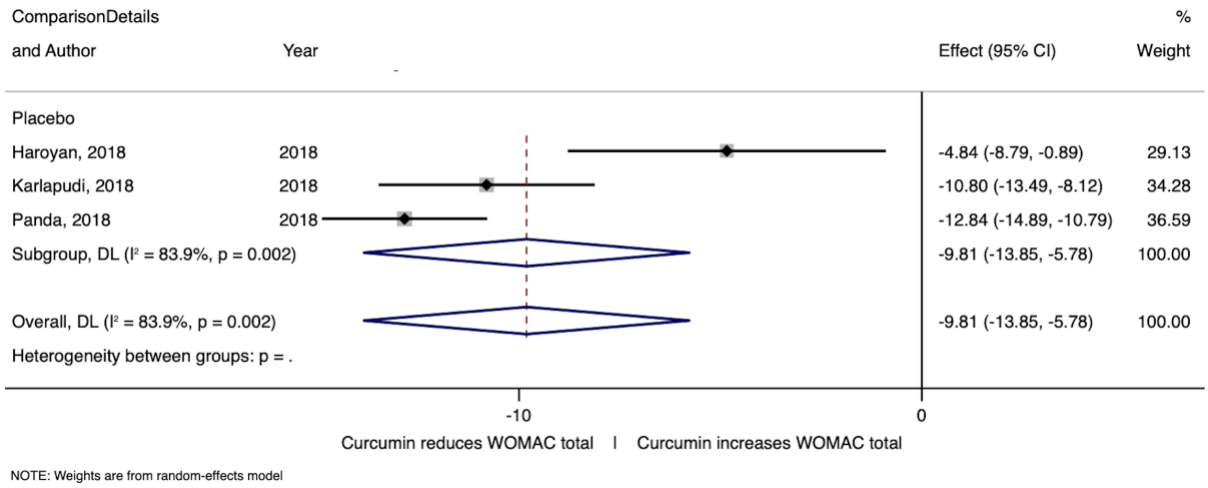

Figure 3.13 Forest plot depicting the MCD in WOMAC total between curcumin and control group.

3.4 Adverse events

Eight studies[1, 2, 35, 43, 45, 57, 58, 61] reported adverse events among participants receiving either curcumin or control (placebo and active controls). In the curcumin group, minor adverse events such as nausea, mild fever, tachycardia, and diarrhea were reported. The findings were similar in the control groups; however, participants receiving active controls, e.g., diclofenac and ibuprofen had additional complaints including melena and upper respiratory tract infection. Two studies[38, 75] did not report any adverse effects. The estimated risk ratio of all adverse events in the curcumin group vs. the control groups (stratified based on placebo and active controls) are presented in figure 3.14. Overall, the incidence of adverse events in patients receiving curcumin was statistically insignificant when compared with placebo, and lower when compared with active controls.

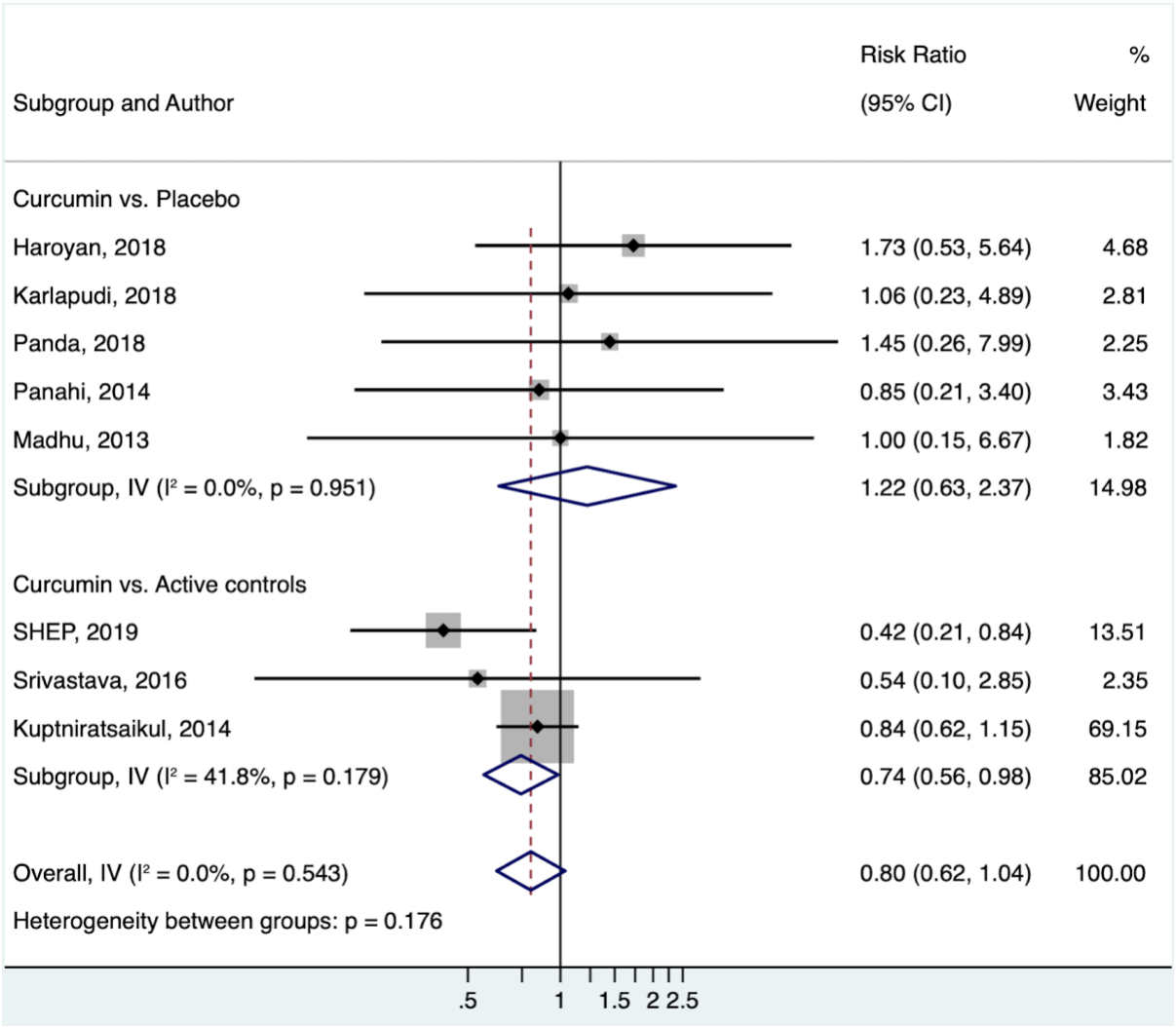

Figure 3.14 Forest plot depicting the overall estimated RR of adverse events in curcumin group compared with control groups.

3.5 Sub-group analyses

The sub-group analyses, as defined by the type of control received revealed that across all outcome measures, studies using placebo showed a much stronger association than those using ibuprofen, diclofenac, and diclofenac/placebo. While the sub-group analyses based on the dosage of curcumin (in comparison with placebo) administered to the study participants showed a stronger association for curcumin dosage above 1000 mg/d in the following outcome measures: VAS, WOMAC physical function, and WOMAC total. With the remaining outcome measures – WOMAC pain and WOMAC stiffness, curcumin dosage below 1000 mg/d had a stronger but statistically insignificant association. Heterogeneity between the sub-groups was substantial and significant in both sub-group analyses across all but one outcome measures – WOMAC physical function (in the sub-analyses by dosage of curcumin in comparison with placebo). Results from the sub-group analyses are presented in Table 3.1. See Appendix D for the graphical display of estimated results.

3.6 Publication bias

Inspection of the funnel plots indicated asymmetry with multiple outlier studies in all but one outcome measure – WOMAC stiffness (See Appendix C). However, the statistical tests showed in the individual outcome measures the following:

- VAS – There was some evidence of publication bias with Egger's test ($p = 0.005$) but no evidence with Begg's test ($p = 0.260$).
- WOMAC total – There was some evidence of publication bias with Egger's test ($p = 0.031$) but no evidence with Begg's test ($p = 0.902$).
- WOMAC pain – There was some evidence of publication bias with both Egger's test ($p = 0.036$) and Begg's test ($p = 0.016$).
- WOMAC stiffness – There was no evidence of publication bias with both Egger's test ($p = 0.085$) and Begg's test ($p = 0.462$).
- WOMAC physical function – There was no evidence of publication bias with both Egger's test ($p = 0.072$) and Begg's test ($p = 0.133$).

Table 3.1 Sub-group analyses by type of control and dosage of curcumin

Outcome measure and sub-group	***n***	***WMD (95% CI)***	***I^2 (%)***	***P_h[a]***	***P_h[b]***
VAS					
Stratification by type of control (overall)	6	-5.88 (-7.76, -4.00)	97.0	<0.001	<0.001
Placebo	3	-16.76 (- 25.41, -8.11)	87.6	<0.001	
Glucosamine & chondroitin formulation	1	- 11.11 (-14.98, -7.24)	-	-	
Diclofenac	1	0.00 (- 0.24, 0.24)	-	-	
Placebo + Diclofenac	1	-1.08 (-1.40, -0.76)	-	-	
Stratification by curcumin dosage (overall)	3	-16.76 (-25.41, -8.11)	87.6	<0.001	0.041
<1000 mg/d	2	-13.20 (-21.23, 5.17)	87.3	0.005	
>1000 mg/d	1	-26.55 (-36.53, -16.57)	-	-	
WOMAC pain					
Stratification by type of control (overall)	7	-1.61 (-2.43, -0.79)	93.6	<0.001	0.001
Placebo	4	-3.76 (- 5.88, -1.65)	88.7	<0.001	
Glucosamine & chondroitin formulation	1	- 0.20 (-0.26, -0.14)	-	-	
Placebo + Diclofenac	1	-0.68 (-1.14, -0.22)	-	-	
Ibuprofen	1	0.08 (- 0.36, 0.52)	-	-	
Stratification by curcumin dosage (overall)	4	-3.76 (-5.88, -1.65)	88.7	<0.001	0.285
<1000 mg/d	2	-5.87 (-12.41, 0.67)	94.8	<0.001	

>1000 mg/d	2	-2.16 (-4.01, -0.31)	64.5	0.093	
WOMAC stiffness					
Stratification by type of control (overall)	5	-1.32 (-2.37, -0.26)	93.4	<0.001	0.014
Placebo	3	-2.90 (- 4.86, -0.94)	95.0	<0.001	
Placebo + Diclofenac	1	-0.08 (-0.57, 0.41)	-	-	
Ibuprofen	1	0.12 (- 0.39, 0.63)	-	-	
Stratification by curcumin dosage (overall)	3	-2.90 (-4.86, -0.94)	95.0	<0.001	0.218
<1000 mg/d	2	-5.37 (-12.93, 2.19)	96.3	<0.001	
>1000 mg/d	1	-0.61 (-1.06, -0.16)	-	-	
WOMAC physical function					
Stratification by type of control (overall)	6	-3.46 (-4.97, -1.94)	96.0	<0.001	<0.001
Placebo	3	-8.63 (-10.17, -7.09)	0	0.443	
Glucosamine & chondroitin formulation	1	- 0.20 (-0.25, -0.15)	-	-	
Placebo + Diclofenac	1	-1.74 (-2.99, -0.49)	-	-	
Ibuprofen	1	0.15 (- 0.30, 0.60)	-	-	
Stratification by curcumin dosage (overall)	3	-8.63 (-10.17, -7.09)	0	0.443	0.310
<1000 mg/d	2	-8.42 (-10.01 -6.83)	0	0.439	
>1000 mg/d	1	-11.70 (-17.83, -5.57)	-	-	
WOMAC total					
Stratification by type of control (overall)	8	-5.78 (-7.63, -3.93)	95.9	<0.001	<0.001

Placebo	6	-11.10 (- 14.68, -7.53)	68.9	0.007	
Glucosamine & chondroitin formulation	1	- 0.21 (-0.23, -0.19)	-	-	
Ibuprofen	1	0.13 (- 0.30, 0.56)	-	-	
Stratification by curcumin dosage (overall)	6	-11.10 (-14.68, -7.53)	68.9	0.007	0.441
<1000 mg/d	3	-10.03 (-13.41, -6.65)	57.5	0.095	
>1000 mg/d	3	-13.87 (-23.02, -4.71)	81.8	0.004	

n denotes the number of studies

[a]*P* for heterogeneity within each sub-group

[b]*P* for heterogeneity between sub-groups

Chapter 4: Discussion

4.1 Principal findings

This systematic review and meta-analysis found a benefit of curcumin in treating knee OA when compared with placebo with improvement observed in pain as measured by VAS and WOMAC and in stiffness, physical function and total scores as measured by WOMAC. Curcumin showed similar effect to diclofenac in reducing VAS pain scores and to ibuprofen in reducing WOMAC pain scores. Furthermore, when curcumin was compared with the widely accepted nutraceutical formulation – glucosamine and chondroitin, there was significant improvement in pain scores measured with VAS but less significant difference in WOMAC scores. Supplementation of diclofenac with curcumin compared with diclofenac alone resulted in significant improvement in VAS pain scores and scores for WOMAC physical function, while in the remaining WOMAC indices, the difference was of limited significance. In terms of adverse events, the incidence in curcumin was comparable to that in placebo but lower in comparison with active controls such as diclofenac and ibuprofen. Finally, studies in which curcumin dosage above 1000 mg/d were used, showed more favorable results in the management of knee OA symptoms.

4.2 Comparison with existing reviews

The findings of this review were compared with three reviews carried out in recent times.

Onakpoya et al. examined seven RCTs (four overlapping with this review) and reported that curcumin was significantly more effective in relieving pain and improving physical function in knee OA patients when compared with placebo but less effective in comparison with ibuprofen.[77] This was consistent with findings of this review. However, their results showed that curcumin was ineffective in reducing stiffness associated with knee OA, which might be because fewer studies were included in the previous meta-analysis. Furthermore, unlike this review, they compared the frequency of adverse events in the curcumin group with the various controls and reported no significant difference; however, they stated that participants receiving ibuprofen experienced more gastrointestinal symptoms.

A total of sixteen RCTs (seven overlapping with this review) were included in the systematic review conducted by Wang et al.[78] As with this review, they concluded through their meta-analyses that the therapeutic effect of curcumin on knee pain and physical function was

clinically and statistically significant in comparison with placebo; however, the effect was similar when compared with NSAIDs. And concerning the safety profile of curcumin, they reported that the incidence of adverse events was similar when curcumin was compared with placebo, but lower when compared with active control (NSAIDs).

The findings from the review carried out by Zeng et al. were concordant with those of this review.[79] Fifteen RCTs (including six in this study) met their inclusion criteria and were used in the meta-analyses which showed the significant benefit of curcumin on pain, stiffness, and physical function in comparison with placebo. They also concluded that the supplementation of diclofenac with curcumin was more effective at relieving knee OA symptoms, although unlike this review (in which results favor only VAS and WOMAC physical function scores), significant improvement was reported in all outcome measures. Finally, they reported that the rates of adverse events were similar in the group treated with curcumin in comparison with the groups treated with placebo, and glucosamine and chondroitin but lower in comparison with the group treated with NSAIDs.

In summary, the findings of this systematic review and meta-analysis are in agreement with prior literature in terms of the efficacy and safety of curcumin in alleviating knee OA symptoms. The results from the sub-group analyses by dosage of curcumin conducted suggest that curcumin doses above 1000 mg/d may be more effective in alleviating knee OA symptoms. While this finding may be peculiar to this study, caution should be taken in the interpretation of the results due to the limited number of RCTs included and the quality of the evidence they provide.

4.3 Strengths and limitations

One of the main strengths of this review is the inclusion of RCTs that are given the highest level of evidence because they are designed to be unbiased and have less risk of systematic errors. Furthermore, it reduces the potential for confounding by balancing known and unknown confounding factors between the comparison groups. In addition, a comprehensive search strategy was employed in retrieving RCTs comparing curcumin with both placebo and conventional therapeutic options. Moreover, only two of the included studies (n = 10) were classified as high risk of bias, and their findings were consistent with those from the studies classified as low risk of bias or showing some concerns. Finally, sub-group analyses were

performed to investigate the potential sources of heterogeneity which were particularly high across the outcomes from the included trials.

Our study has several limitations. First, as outlined above, high levels of heterogeneity were observed across studies included in the meta-analyses. The results from the sub-group analyses showed that difference in curcumin dosage and type of control used in the trials contributed significantly to the highly heterogeneous outcomes, with stronger effects recorded among studies using curcumin doses above 1000 mg/d and placebo controls. Some heterogeneity remained, however, and may be due to differences in the dose of curcumin used, duration of treatment, or other methodological issues.[80, 81]

Second, the test for publication bias lacked sufficient power to distinguish chance from real asymmetry as there were fewer than ten studies in all the outcome measures assessed. Furthermore, due to the limited number of included studies, we could not perform meta-regression (as pre-specified in the study protocol) analyses across all outcome measures, which could have provided insights into the effect of study level characteristics on effect sizes.[82]

Third, the variability in the end-point measurements used in assessing knee OA symptoms along with the different formulations of curcumin included in the meta-analyses could have contributed to heterogeneity between studies. Moreover, the use of rescue medication was not taken into consideration; this may also place some restriction on the interpretation of the findings.

Lastly, the generalizability of the findings may be limited as most of the included studies (n = 9, out of 10) were conducted in Asia. In like manner, the quality, sample size (median: 113 participants) and duration (median: 11 weeks) of the trials were not sufficient to draw conclusive evidence on the efficacy of curcumin in the treatment of knee OA.

4.4 Implications for research and practice

There is a need for safer therapeutic alternatives to manage knee OA symptoms, and the increasing levels of YLDs associated with OA, particularly in LMICs, show the importance of acknowledging its contribution to the global burden of disease. While advancing the development and approval of disease-modifying OA drugs (which inhibit the structural progression of OA) remains the highest priority, clinical research into complementary and

alternative therapies for the symptomatic management of OA is becoming increasingly relevant.

The current meta-analysis suggests that curcumin may have benefits in the treatment of patients with knee OA. Given the limited geographic variation in the available studies, additional studies performed in different regions globally could provide more conclusive evidence. This can be further achieved by conducting high quality RCTs with large sample sizes and long durations of follow-up in various population groups. Moreover, researchers conducting trials in which large numbers of participants are selected could in their design phase plan to stratify the participants by sex, dosage of curcumin received, and other factors that might influence the prognosis and treatment responsiveness. In addition, the phenotypes of OA should be taken into consideration as they follow different courses in their progression, ergo the manifestation of symptoms.[83] Thus far, the outcome measures used in trials to assess OA symptoms have been subjective in nature, in future research, tools with objective methods of assessment should be considered. Finally, with investigation into new methods of enhancing the bioavailability of curcumin underway, the area of further research should cover the effect of this enhancement on its efficacy in the management of knee OA.

The potential benefits of curcumin go beyond its therapeutic usefulness. If proven with sufficient evidence to be effective in the management of knee OA, curcumin, and by extension CAM, could be a contributing factor to the reduction of inequity in global health by bridging the gap in healthcare capacity between HICs and LMICs which at present face the double burden of infectious and non-communicable diseases.[84, 85] Turmeric, the herb from which curcumin is extracted is generally inexpensive and can be cultivated in many regions of the world with warm and humid climate. This presents an opportunity for its adaptation as first, an affordable treatment option, and second, a source of agricultural income. Advocacy groups concerned with healthcare development in LMICs (with functional public institutions) could engage key stakeholders in government, agricultural firms, health agencies, etc., and prescribe a multisectoral action plan that takes advantage of the influence that upstream determinants have on the development of health care systems.[86, 87] For instance, by recommending policy revision that promotes the production and use of complementary and alternative therapies proven to be effective and affordable. In the same context, governments in LMICs that have attained significant levels of industrialization could partner with pharmaceutical firms for the research and development of bio-optimized extracts of turmeric which will be more profitable in the global market.

4.5 Conclusion

The findings of this systematic review and meta-analysis demonstrate the efficacy of curcumin in the management of pain, stiffness, and physical function in knee OA patients. Further large-scale placebo controlled randomized trials from different geographic regions could clarify the impact of different doses and formulations and may provide more conclusive evidence.

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Appendices

Appendix A: Characteristics of the included studies

Author, year, location	*No. of participants, mean age, % female*	*Intervention dose & duration*	*Comparator*	*Treatment groups (n)*	*Rescue medication*	*Author's conclusions*
Madhu et al.,[57] 2013, India	120 patients, 57.1 years, 69.2%	Turmeric polysaccharide extract 500 mg capsule Turmeric polysaccharide extract 500 mg + Glucosamine 750 mg BID 42 days	Placebo capsule Glucosamine sulphate (GS) 750 mg capsule BID	PL (n=29) TR (n = 29) GS (n = 28) TR+GS (n = 24)	Paracetamol 2000 – 4000 mg QD	Curcumin significantly effective for pain reduction in OA patients
Kuptniratsaikul et al.,[45] 2014, Thailand	367 patients, 60.6 years, 89.4%	Curcuma longa extract 1500 mg capsule QD 4 weeks	Ibuprofen 1200 mg capsule QD	CR (171) IB (160)	Tramadol	Curcumin non-inferior to Ibuprofen but with fewer adverse effects
Panahi et al.,[58] 2014, Iran	53 patients, 58.2 years, 77.5%	Curcumin 3 x 500 mg capsule + Bioperine 3 x 5 mg QD 6 weeks	Placebo capsule	CR (21) PL (19)	Naproxen	Results support efficacy of curcumin in treating OA symptoms
Srivastava et al.,[61] 2016, India	160 patients, 50.3 years, 64.4%	Curcumin longa extract 500 mg capsule + Diclofenac 50 mg tab BID 120 days	Placebo capsule + diclofenac 50 mg BID	CR + DI (78) PL + DI (82)	Diclofenac 50 mg BID Omeprazole 20 mg QD	Adjuvant therapy of curcumin longa extract along with diclofenac produces overall significant improvement in OA symptoms
Sterzi et al.,[75] 2016, Italy	53 patients, 71.2 years, 66%	Bio-curcumin 50 mg tab + Glucosamine hydrochloride 500 mg tab + Chondroitin sulfate 400 mg tab (2 tablets) QD Physical therapy three times a week	Placebo tablets Physical therapy three times a week	CR + other components (23) PL (27)	Paracetamol 500 mg tab	Preliminary results show that curcumin along with GS and CH (+ physical therapy) may improve pain in OA patients

		12 weeks				
Haroyan et al.,[2] 2018, Armenia	201 patients, 56.2 years, 93%	Curcumin 333 mg (500 mg capsule) Curcumin + Boswellia serrata 350 mg + 150 mg (500 mg capsule) TID 12 weeks	Placebo capsule	CR (66) CR + another component (67) PL (68)	None	Curcumin alone reduces pain related symptoms in OA patients. It is more effective in combination with Boswellia acid
Karlapudi et al.,[1] 2018, India	105 patients, 49.9 years, 66.7%	Curcumin longa + Boswellia serrata + Terminalia Chebula High dosage 400 mg capsule Low dosage 200 mg capsule QD 90 days	Placebo capsule	CR + other components high dosage (35) CR + other components low dosage (35) PL (35)	Ibuprofen 400 mg tab (max 1200 mg QD)	Results support efficacy and safety of the herbal formulation containing curcumin
Panda et al.,[43] 2018, India	50 patients, 54.2 years, -	Curcumin longa extracts 500 mg capsule QD 60 days	Placebo capsule	CR (25) PL (25)	Paracetamol 2000 mg QD	Curcumin provides significant improvements in clinical endpoints compared to placebo
Amalraj et al.,[38] 2019, India	24 patients, 53 years, 70.8%	Curcumin longa + Boswellia serrata + Piper nigrum + Kaempferia galanga 250mg capsule QD 90 days	Glucosamine 1500 mg + Chondroitin 1200 mg QD	CR + other components (12) GS + CN (12)	None	Health supplement containing curcumin significantly effective in relieving pain with no adverse effect
Shep et al.,[35] 2019, India	139 patients, 52.6 years, 33.1%	Curcumin 500 mg capsules TID 28 days	Diclofenac 50 mg tab BID	CR (70) DI (69)	Paracetamol 500 mg tab Ranitidine 150 mg tab	Curcumin TID has similar efficacy but better safety profile compared to diclofenac BID

BID, twice daily; CN, chondroitin; CR, curcumin; DI, diclofenac sodium; GS, glucosamine; IB, ibuprofen; OA, osteoarthritis; PL, placebo; TID, thrice daily; TR, turmeric extract; QD, once daily.

Appendix B: Risk of bias assessment – response to signaling questions

Unique ID	1	**Study ID**	Amalraj, 2019	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Reference standard (glucosamine and chondroitin formulation)	**Source**	Journal article(s)
Outcome	VAS, WOMAC total, pain and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization table used. Treatment codes were kept confidential.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Baseline characteristics were similar between intervention groups.
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	A double blinded study.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	N	Per protocol analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	PN	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	From 24 participants (12 in each group), 1 dropped out from the curcumin group.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate tools for measuring Knee OA symptoms.

	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	
	4.3 Were outcome assessors aware of the intervention received by study participants?			PN	A double blinded study.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Some concerns**	

Unique ID	2	**Study ID**	Haroyan, 2018	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	WOMAC total, pain, stiffness and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Computer generated randomization. Treatment randomization codes were concealed until the study was finalized.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Baseline characteristics were similiar between intervention groups.
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	Participants and investigators were blinded.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	10.5% of participants were lost to follow-up.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	WOMAC is an appropriate tool for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	

	4.3 Were outcome assessors aware of the intervention received by study participants?			N	Assessors were blinded.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	3	**Study ID**	Karlapudi, 2018	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		

Experimental	Curcumin	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	VAS, WOMAC total, pain, stiffness and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Participants were randomized into the various groups.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Baseline characteristics between the intervention groups were similar.
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	A double blinded study.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	N	Per protocol analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	PN	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Out of 105 participants (35 in each group), 9 dropped out (curcumin 200mg 1, curcumin 400mg 5 and placebo 3).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate tools for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	A double blinded study.

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Some concerns**	
Unique ID	4	**Study ID**	Kuptniratsaikul, 2014	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Ibuprofen	**Source**	Journal article(s)

Outcome	WOMAC total, pain, stiffness and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization by computerized method. Allocation codes were serially concealed in opaque envelops.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Baseline characteristics were similar between intervention groups.
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	Participants and investigators were blinded.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?				
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			N	Per protocol analysis.

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	PN	
	Risk of bias judgement	**Low**	Per protocol analysis was applied for non-inferioty drug design.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	367 participants were randomized to curcumin (185) and ibuprofen (182) groups. 171 completed in curcumin and 160 in ibuprofen.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	WOMAC is an appropriate tool for measure Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Assessors were blinded.

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	5	**Study ID**	Madhu, 2013	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Placebo	**Source**	Journal article(s)

Outcome	VAS, WOMAC total	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Subjects were enrolled using computer-generated simple randomization sequence.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Baseline characteristics were similar among groups.
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	Subjects and orthopedic consultants were blinded throughout the period of the trial. Study investigator was aware of treatment intervention.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	ITT analysis
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?			NA	

	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	From 120 subjects, 1 subject was lost to follow-up each from curcumin and placebo groups. The remaining 8 were from groups containing glucsoamine sulphate.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate methods for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Study investigator was aware of treatment intervention. The assessors in this case were the participants themselves.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Some concerns**	
Unique ID	6	**Study ID**	Panahi, 2014	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Placebo	**Source**	Journal article(s)

Outcome	VAS; WOMAC total, pain, stiffness and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Designed as pilot randomized placebo-controlled parellal-group trial.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Baseline characteristics between intervention groups were similar.
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	A double blinded study.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			N	Per protocol analysis.

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	PN	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Of the 53 participants (curcumin 27, placebo 26) who were present at the start of the trial, 13 (curcumin 8, placebo 5) dropped out.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	25% - high drop out rate.
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PY	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate methods for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	A double blinded study.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**High**	
Unique ID	7	**Study ID**	Panda, 2018	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Placebo	**Source**	Journal article(s)

Outcome	VAS, WOMAC total, pain, stiffness and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Computerized randomization schedule.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	No baseline differences between intervention groups.
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	A double blinded study.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	ITT analysis

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	50 participants were randomized (25 in each group). 4 dropped out (curcumin 1, placebo 3).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate tools for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	A double blinded study.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Some concerns**	
Unique ID	8	**Study ID**	Shep, 2019	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Diclofenac	**Source**	Journal article(s)
Outcome	VAS	**Results**		**Weight**	1

Domain	Signaling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization generated using Graphpad software. Allocation sequence was concealed.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	An open label study.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	149 participants were randomized (curcumin 74, placebo 75). 10 dropped out (curcumin 4, placebo 6).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS is an appropriate tool for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	An open label study.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	The study participants were the assessors in this case. There is possibility of bias.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY	
	Risk of bias judgement	**High**	

Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**High**	
Unique ID	9	**Study ID**	Srivastava, 2016	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin + diclofenac	**Comparator**	Placebo + diclofenac	**Source**	Journal article(s)
Outcome	VAS; WOMAC pain, stiffness and physical function	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the	1.1 Was the allocation sequence random?			Y	

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	A computerized randomization schedule.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics were similar between intervention groups.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	A double blinded study.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	160 participants (CL +DF 78, PC + DF 82) were randomized.

			133 completed the trial (CL + DF 66, PC + DF 67).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	16.8% of participants dropped out.
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate methods for measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	A double blinded study.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	

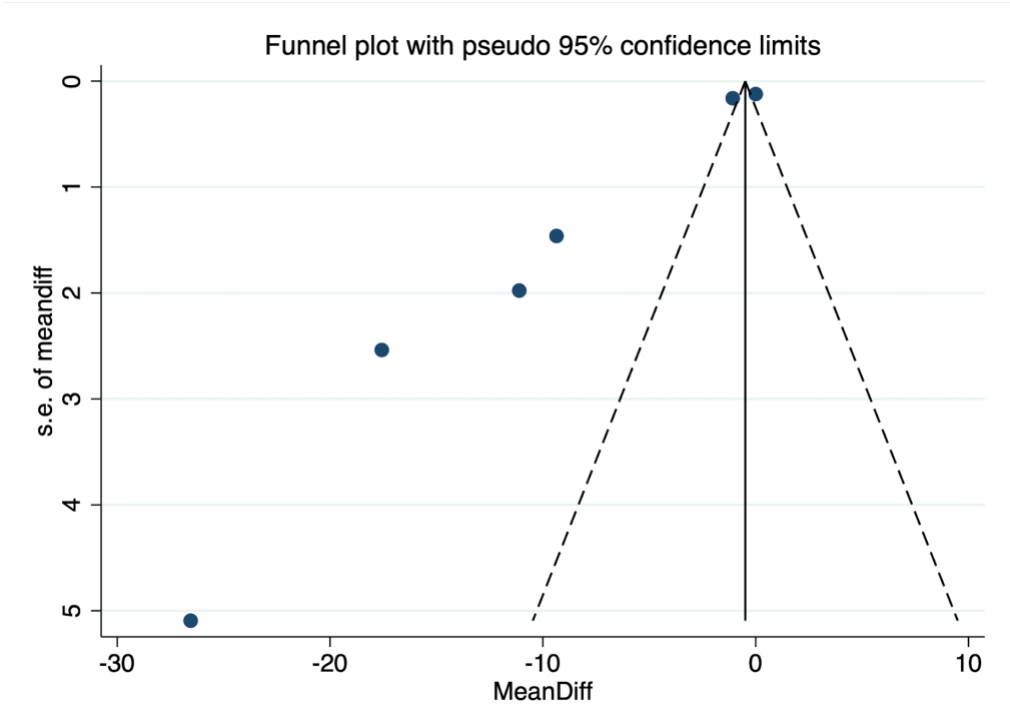
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	
	5.3 ... multiple eligible analyses of the data?			N	Analyses were performed as pre-specified.
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Some concerns**	
Unique ID	10	**Study ID**	Sterzi, 2016	**Assessor**	IA
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Curcumin	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	VAS, WOMAC total	**Results**		**Weight**	1
Domain	**Signaling question**			**Response**	**Comments**
Bias arising from the	1.1 Was the allocation sequence random?			Y	

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	Computer generated randomization.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics were similar in both intervention groups.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Both physiotherapists and participants were blinded.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	N	Per protocol analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	PN	
	Risk of bias judgement	**Some concerns**	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Of the 53 participants who were randomized (curcumin 26,

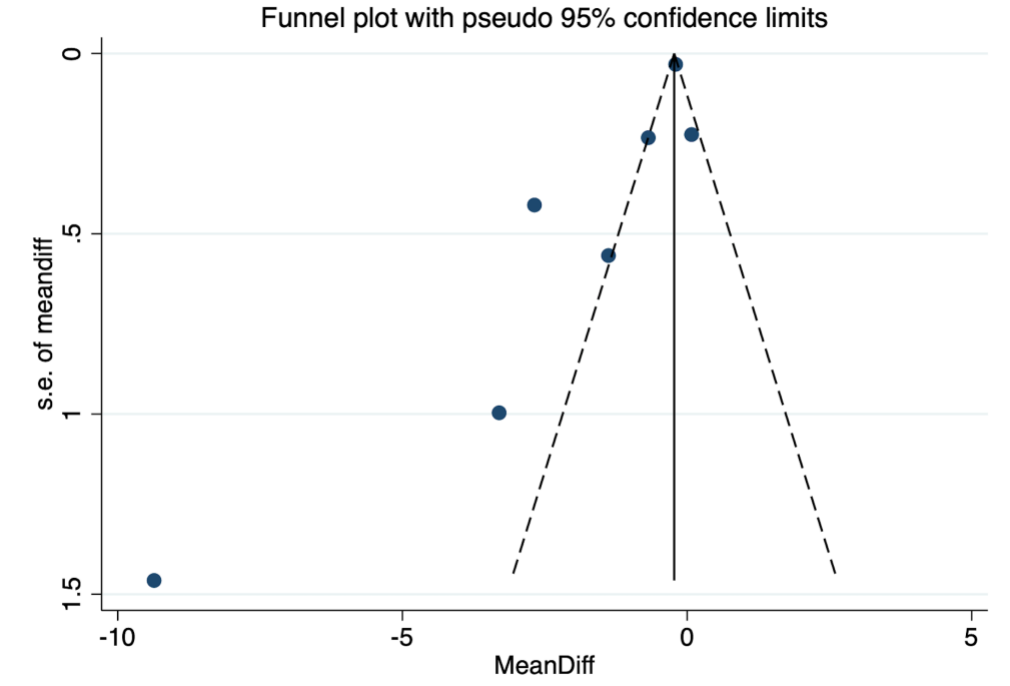
Bias due to missing outcome data			placebo 27), 50 completed the trial (curcumin 23, placebo 27).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	VAS and WOMAC are appropriate methods of measuring Knee OA symptoms.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Assessors were blinded.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	

Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	Analyses were performed as pre-specified.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

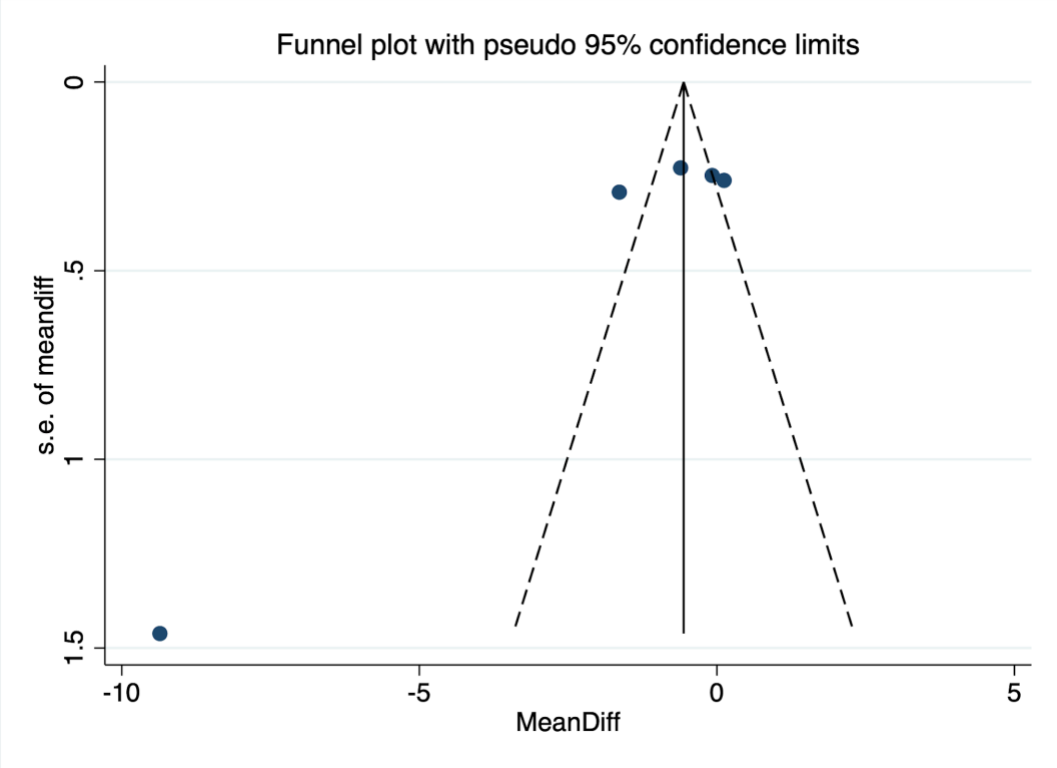
Appendix C: Funnel plot analysis to detect publication bias



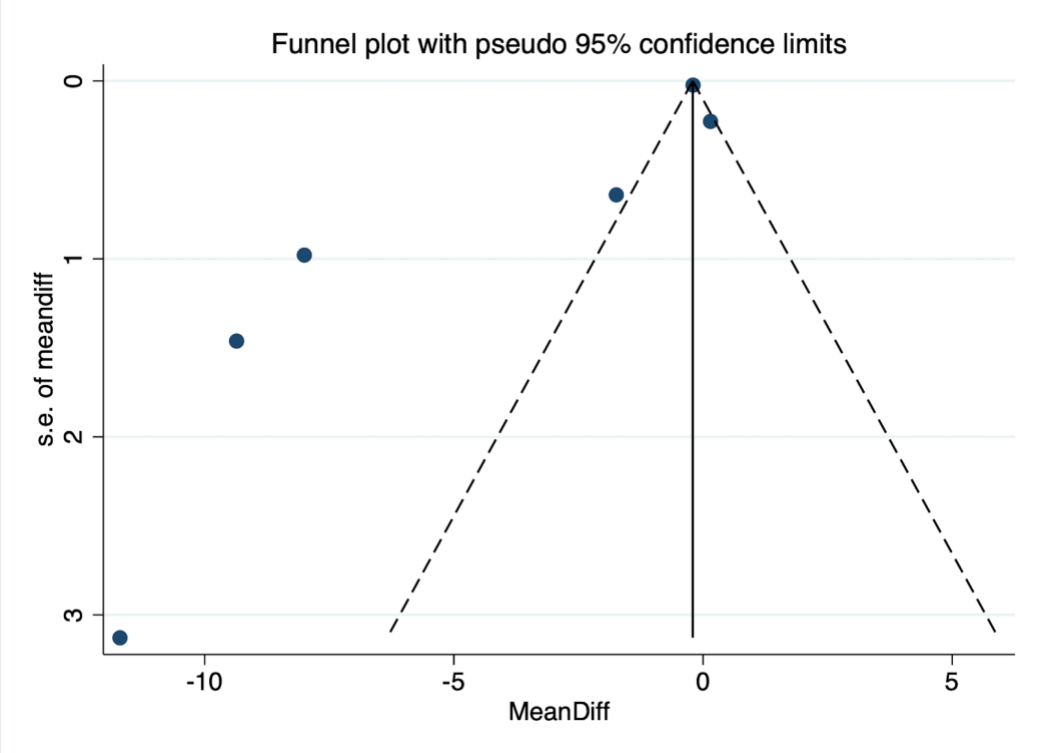
VAS



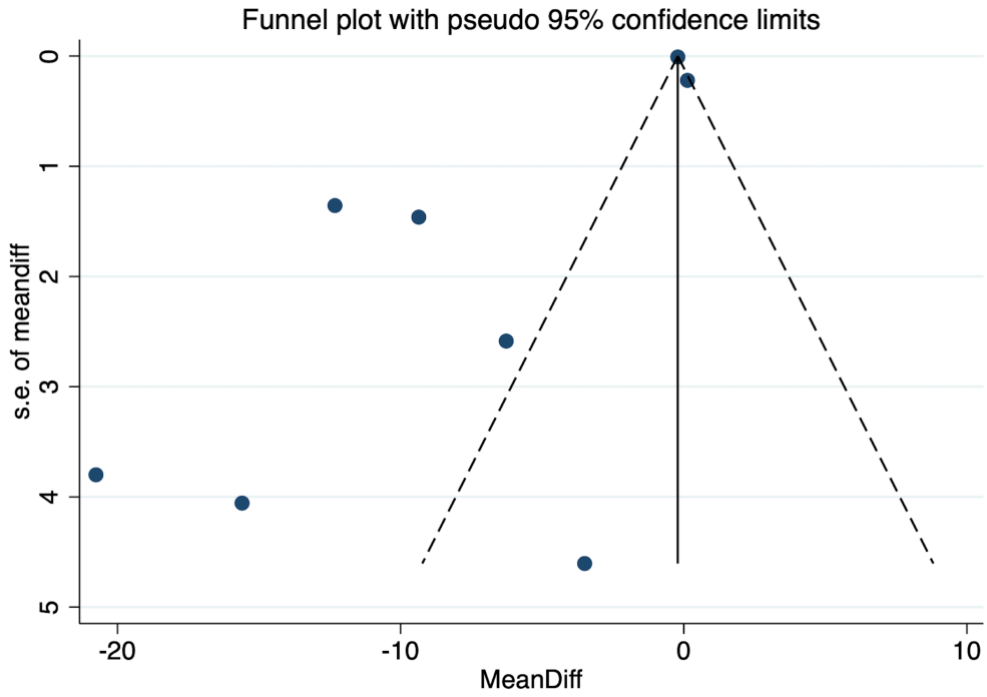
WOMAC pain



WOMAC stiffness

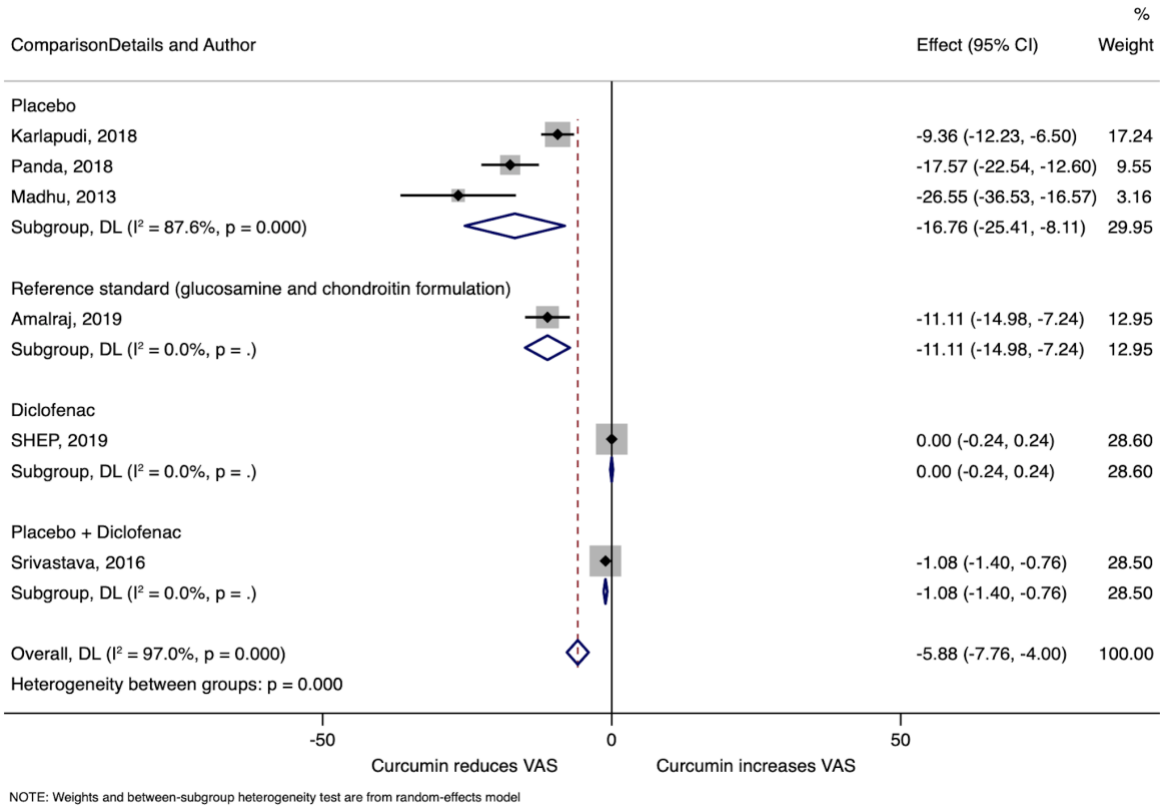


WOMAC physical function


Funnel plot with pseudo 95% confidence limits
s.e. of meandiff
0
1
2
3
4
5
-20
-10
0
10
MeanDiff

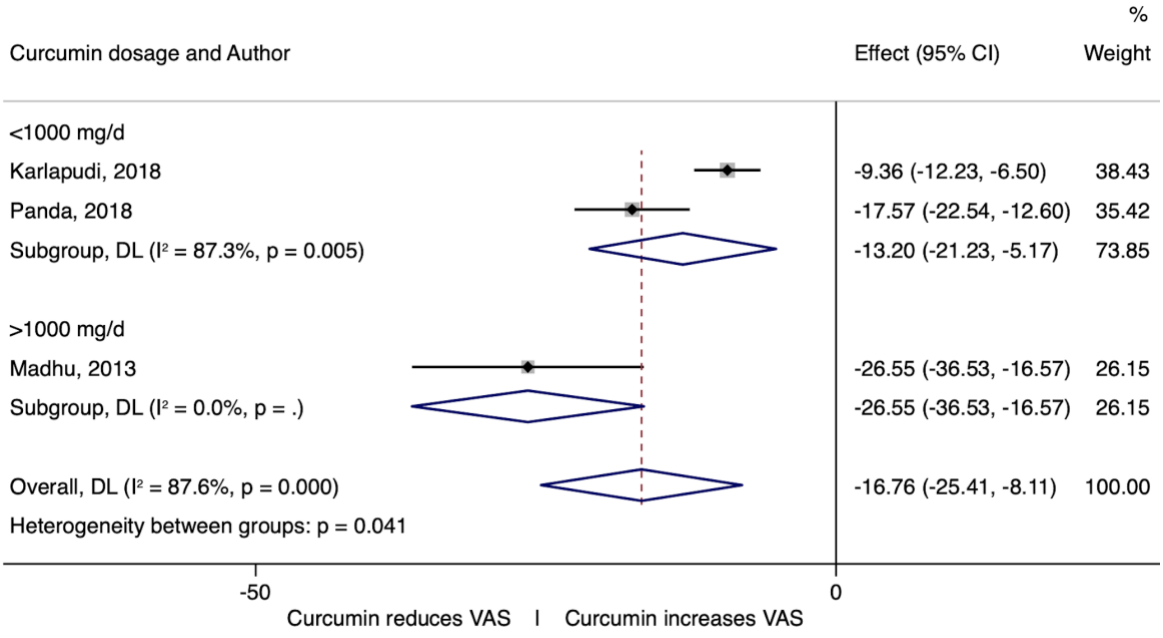
WOMAC total

Appendix D: Sub-group analyses by type of control compared with curcumin and dosage of curcumin (in comparison with placebo) administered to participants



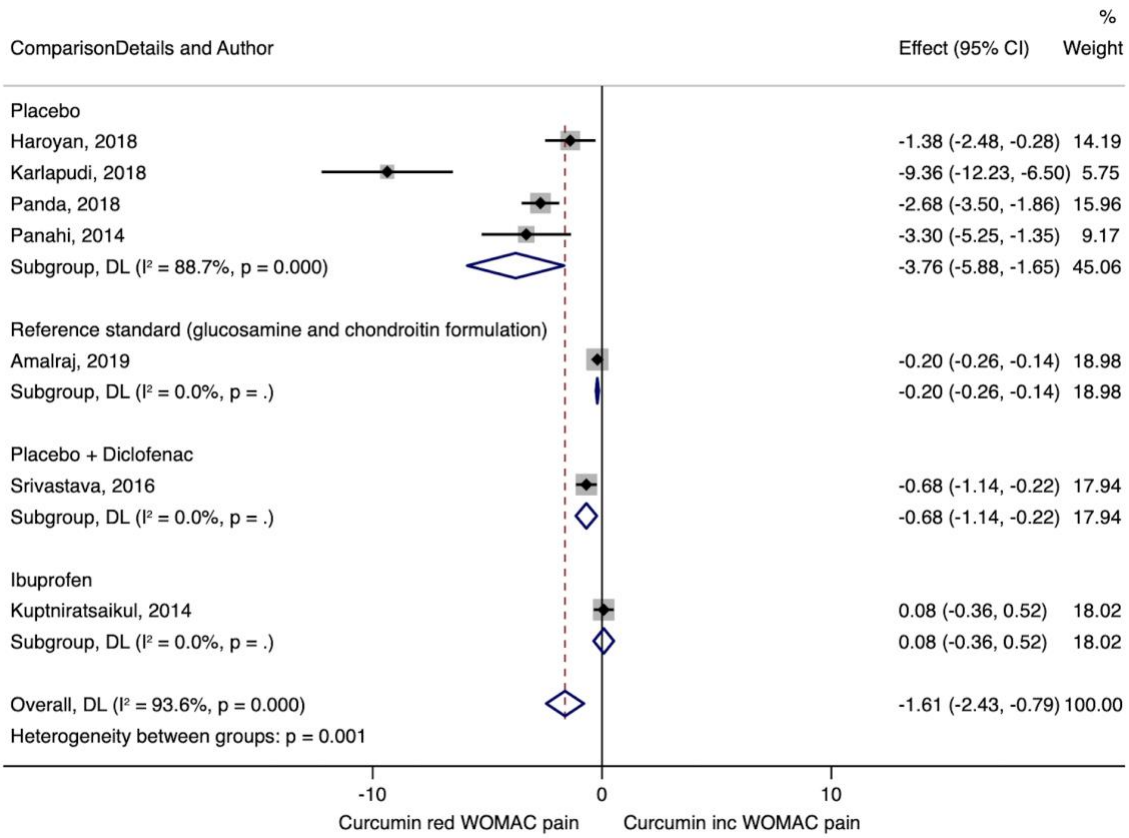
NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Stratification by type of control compared with curcumin, WMD – VAS

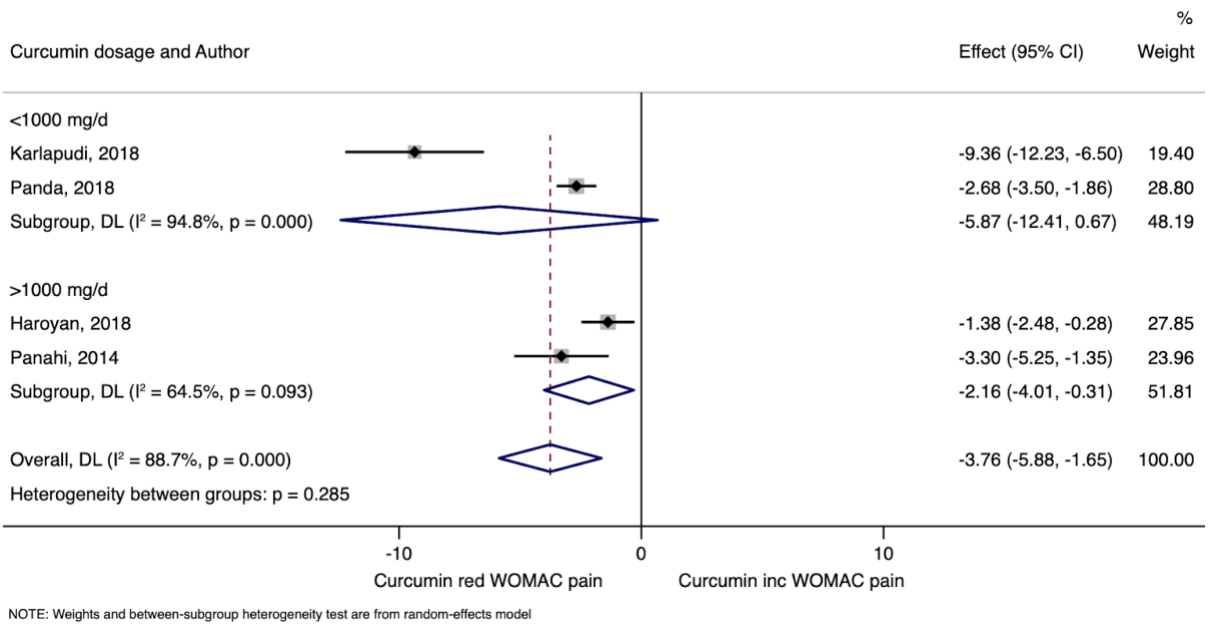


NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

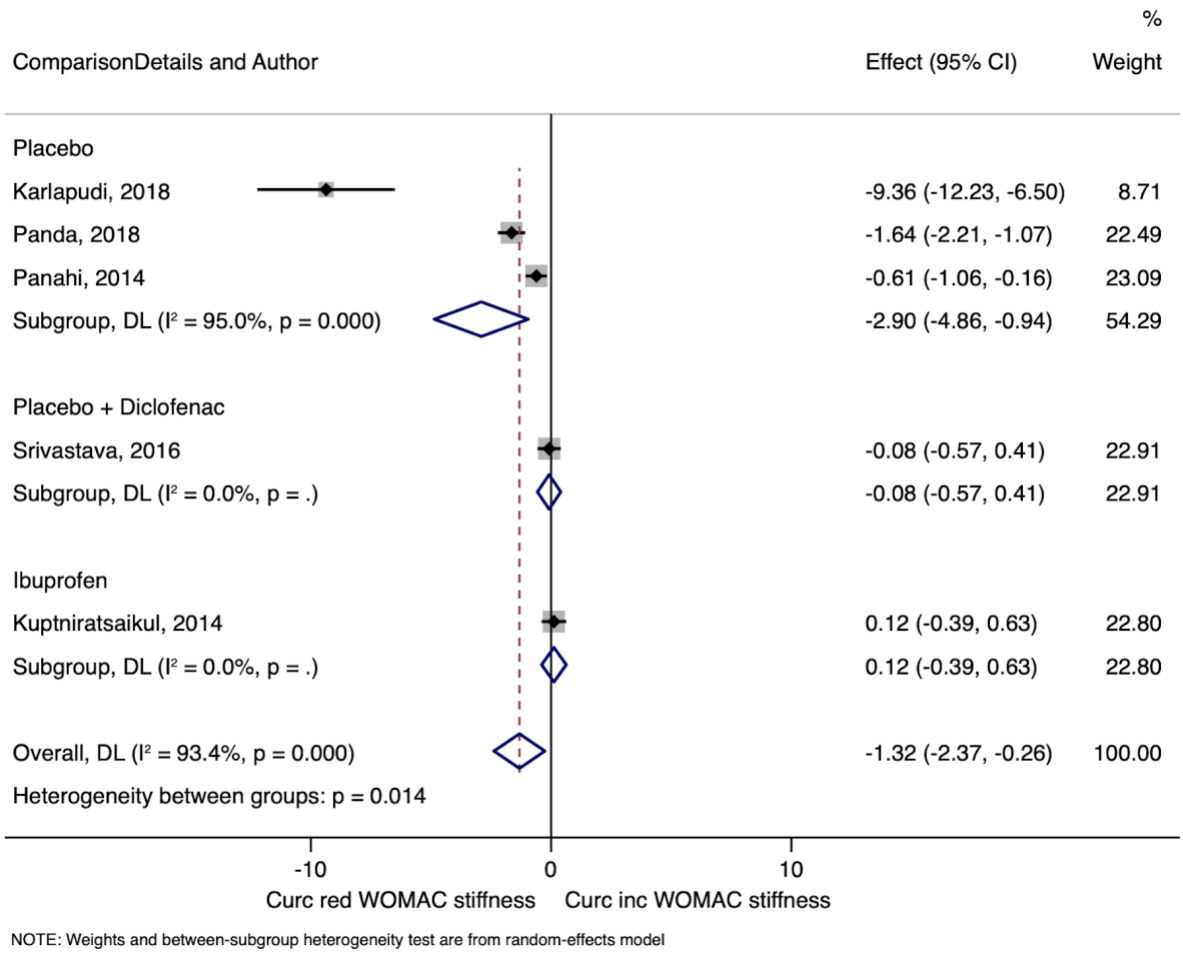
Stratification by dosage of curcumin (in comparison with placebo) administered to participants, WMD – VAS



Stratification by type of control compared with curcumin, WMD – WOMAC pain

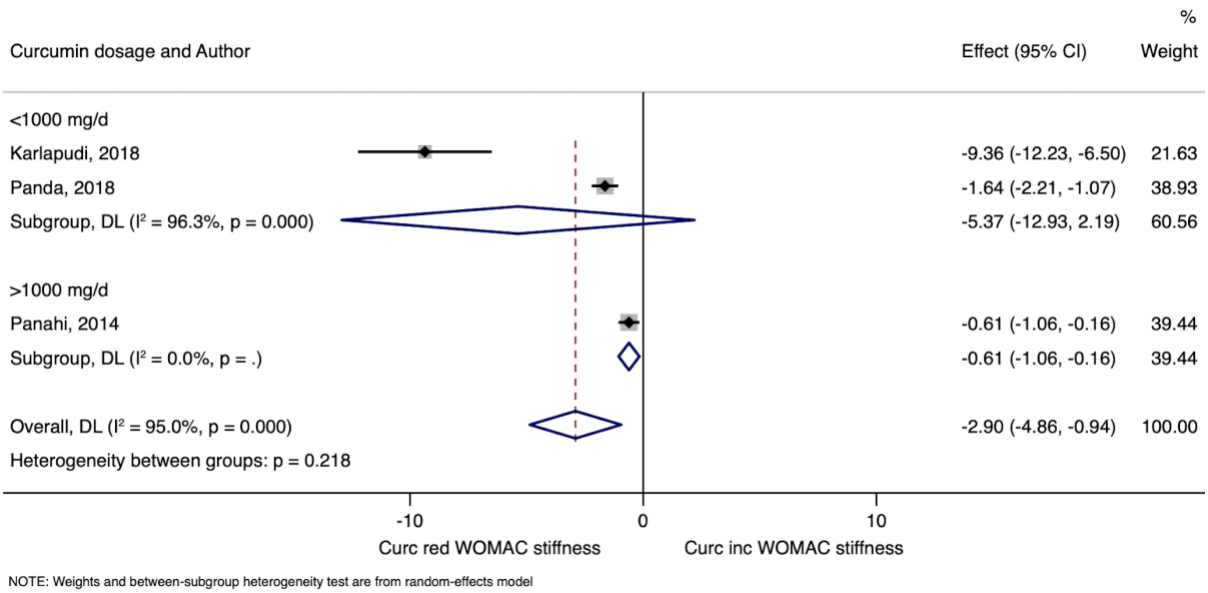


Stratification by dosage of curcumin (in comparison with placebo) administered to participants, WMD – WOMAC pain



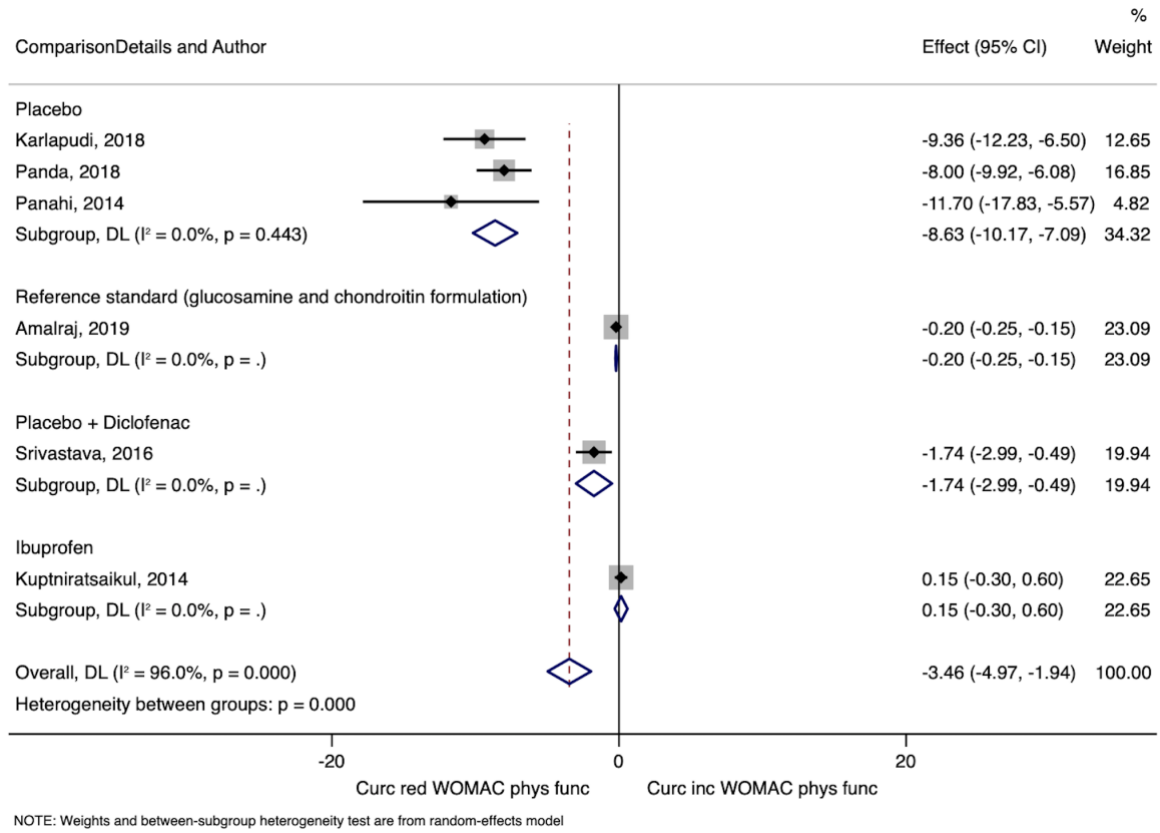
NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Stratification by type of control compared with curcumin, WMD – WOMAC stiffness

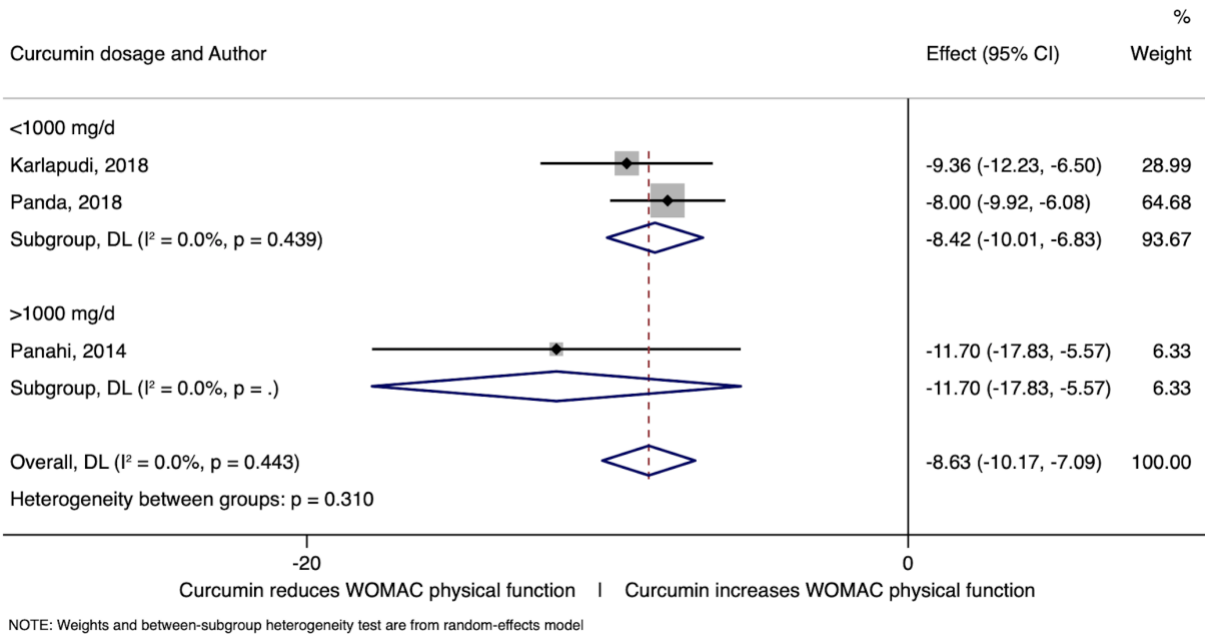


NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

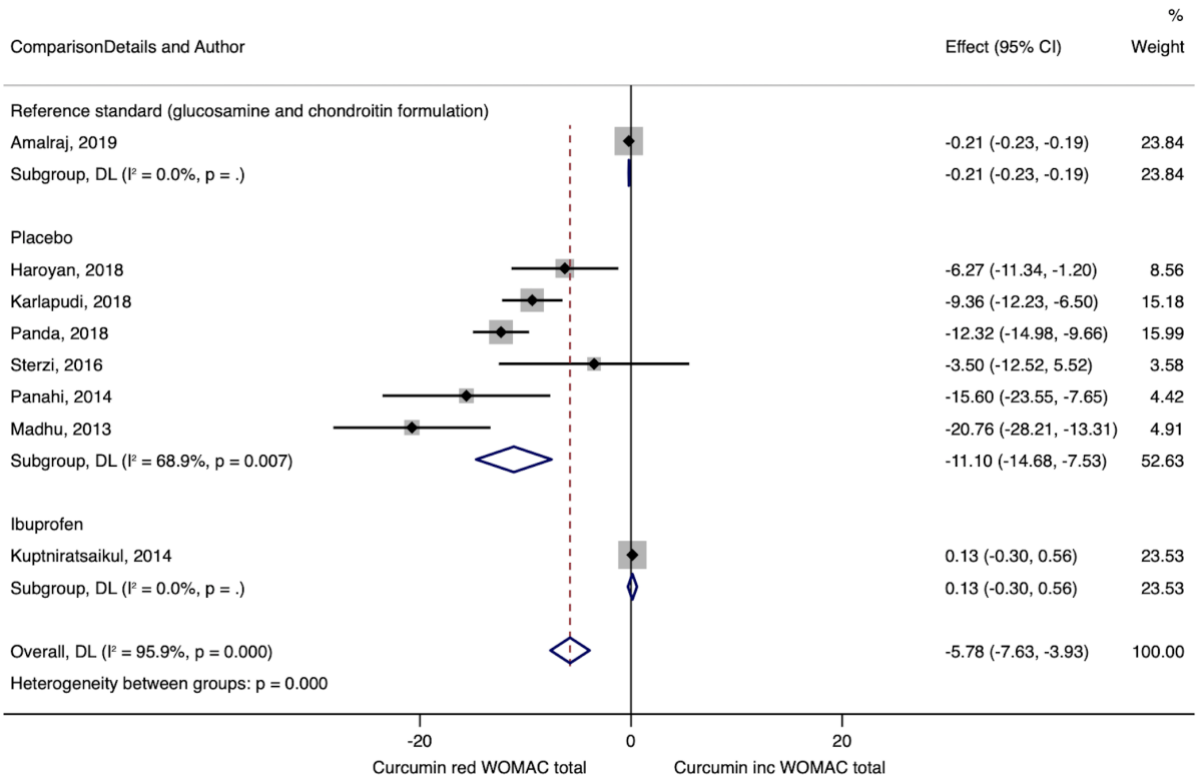
Stratification by dosage of curcumin (in comparison with placebo) administered to participants, WMD – WOMAC stiffness



Stratification by type of control compared with curcumin, WMD – WOMAC physical function

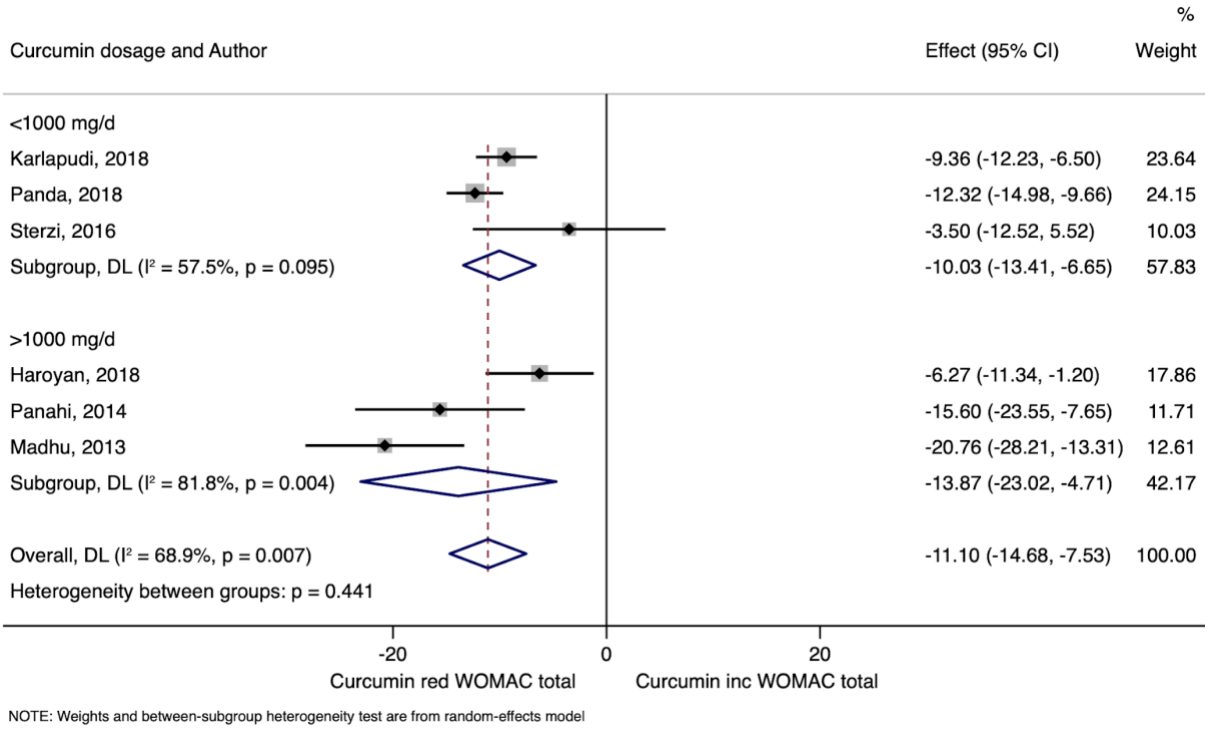


Stratification by dosage of curcumin (in comparison with placebo) administered to participants, WMD – WOMAC physical function



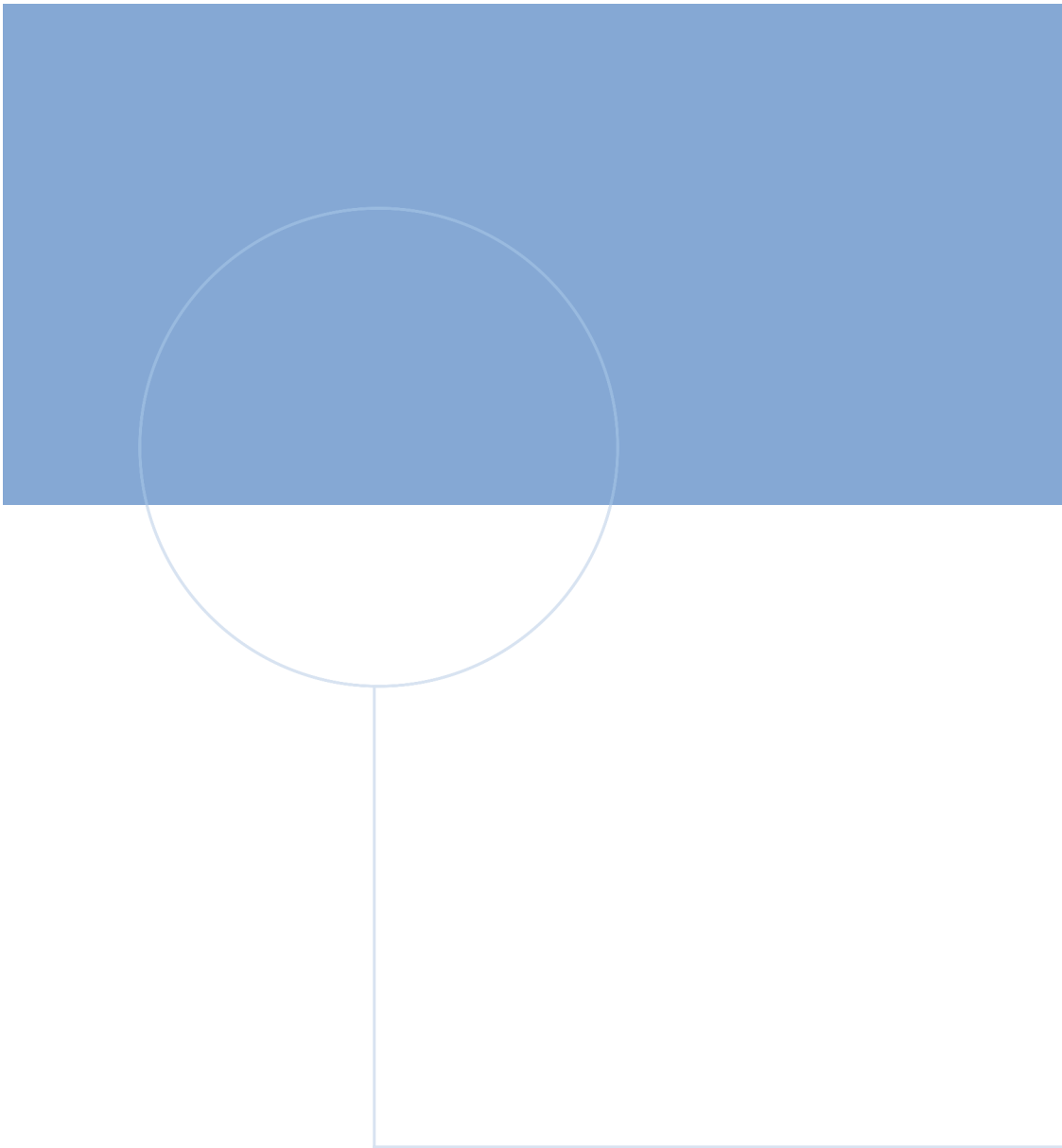
NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Stratification by type of control compared with curcumin, WMD – WOMAC total



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Stratification by dosage of curcumin (in comparison with placebo) administered to participants, WMD – WOMAC total



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