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# BMJ Open

## Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

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SCHOLARONE™  
Manuscripts

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4 **Title: Is acupuncture effective for knee osteoarthritis? A protocol for a**  
5  
6 **systematic review and meta-analysis**  
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8

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38 Number of words: 2938  
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## ABSTRACT

### **Introduction**

Knee osteoarthritis is one of the leading causes of disability. The effectiveness of acupuncture for treating KOA remains controversial. This protocol describes the method of a systematic review and meta-analysis evaluating the efficacy and safety of acupuncture for treating KOA.

### **Methods and analysis**

Four English databases (PubMed, Embase, Cochrane Library databases, and Web of Science) and four Chinese databases (China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, and Wanfang) will be searched from the database inception to September 1, 2021. All randomized controlled trials related to acupuncture for KOA will be included. Extracted data will include publication details, basic information, demographic data, intervention details and patient outcomes. The primary outcome is pain intensity. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias. Article selection, data extraction and risk of bias assessment will be performed in duplicate by two independent reviewers. If the meta-analysis is precluded, we will conduct a descriptive synthesis using a best-evidence synthesis approach. The strength of recommendations and quality of evidence will be assessed using the Grading of Recommendations Assessment Development and Evaluation working group methodology.

### **Ethics and dissemination**

1  
2  
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4 Ethics approval is not required because individual patient data are not included. This  
5  
6 protocol was registered in the international Prospective Register of Systematic  
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9 Reviews on 25 February 2021. The systematic review and meta-analysis will be  
10  
11 submitted for publication in a peer-reviewed journal. The findings will also be  
12  
13 disseminated through conference presentations.  
14  
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### 16 **Trial registration number**

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19 CRD42021232177  
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21

### 22 **Article summary**

#### 23 **Strengths and limitations of this study**

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27 1. This study will be the first of its kind to explore the difference in the efficacy  
28  
29 between manual acupuncture and electroacupuncture for KOA by synthesizing the  
30  
31 evidence from direct comparison and indirect comparison.  
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34  
35 2. We want to focus on many different factors in subgroup analysis and to explore the  
36  
37 applied law of different doses of acupuncture.  
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40  
41 3. The study design adheres to all relevant guidelines for systematic reviews and  
42  
43 meta-analyses.  
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45  
46  
47 4. We plan to search multiple Chinese and English language databases to ensure a  
48  
49 comprehensive search of the literature.  
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53 5. Transformation of pain scores will result in loss of some accuracy; however, we  
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55 believe that it is clinically irrelevant.  
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## INTRODUCTION

### Description of the condition

Osteoarthritis (OA) is a common clinical degenerative disease and is one of the leading causes of disability.<sup>1</sup> The costs of OA are considerable, estimated at between 1% and 2.5% of the gross domestic product for Western countries.<sup>2</sup> The knee is the most common location of osteoarthritis, which accounts for approximately 85% of osteoarthritis cases worldwide.<sup>3</sup> With the trends of an aging population and increasing obesity, the incidence of knee osteoarthritis (KOA) is increasing for both sexes.<sup>4 5</sup> In addition, pain symptoms associated with KOA result in physical and walking disability, which in turn have an excess risk of all-cause mortality.<sup>6 7</sup>

Exercise and weight loss, two effective nonpharmacological treatments, are strongly recommended in all people with clinical osteoarthritis.<sup>8</sup> However, for patients with KOA, it is difficult to continue exercising and losing weight. Representatives of pharmacological interventions include analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, some analgesics are not associated with long-term pain improvement and have nearly no effects at various doses.<sup>9 10</sup> Furthermore, many NSAIDs are associated with serious side effects such as cardiovascular and renal adverse effects, gastrointestinal toxicity and gastrointestinal intolerability.<sup>11 12</sup> In addition, the health care systems of Western countries are overstretched because of the increasing joint replacement requirements.<sup>13</sup> In this context, identification of the efficacy of existing treatments or development of novel therapies remains an important priority.

## Description of the intervention

Acupuncture has long been recognized as a nonpharmacologic therapy in treating various disorders by inserting fine needles into specific anatomic points (acupoints) on the skin of the patient's body. As an important component of traditional Chinese medicine (TCM), acupuncture has been used in clinical practice for more than 3000 years.

The World Health Organization (WHO) has recommended acupuncture therapies for 107 diseases. The efficacy of acupuncture for different kinds of pain diseases has been verified by a great deal of high-quality clinical trials.<sup>14-18</sup> Recently, two individual patient data meta-analyses also reported that acupuncture was effective for the treatment of chronic pain, with treatment effects persisting over time.<sup>19 20</sup> In addition, acupuncture appears to be a safe intervention that has rare adverse effects in the hands of competent practitioners.<sup>21-23</sup>

## How the intervention might work

Joint inflammation, such as low-grade inflammatory infiltrates within the synovial lining, is common in KOA.<sup>24</sup> Neurogenic inflammation produced by nociceptors is also found in KOA. Inflammatory mediators in the knee joint can sensitize nociceptors, leading to pain. Furthermore, KOA pain might be caused by other mechanisms, including activation of nociceptive pathways by nerve growth factor (NGF), direct effects of cytokines and chemokines on neurons, or infiltration of the spinal cord by immune cells.<sup>25</sup>

In recent decades, preclinical investigations of acupuncture mechanisms in KOA



1  
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4 pain have increased. These studies show that acupuncture relieves symptoms of KOA  
5  
6 by activating a variety of bioactive chemicals through peripheral, spinal, and  
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8 supraspinal mechanisms.<sup>26</sup> For example, acupuncture can desensitize peripheral  
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10 nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord.  
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<sup>26-28</sup> In addition, acupuncture dampens the transmission of noxious inputs at the spinal level with the involvement of spinal opioids, serotonin (i.e., 5-hydroxytryptamine), norepinephrine, glial cell/cytokines, and signal molecules.<sup>26 29-31</sup>

### **Why it is important to perform this review**

Research on acupuncture for KOA has been growing, but the findings have been inconsistent. Different guidelines do not reach an agreement on whether acupuncture should be recommended as an effective nonpharmacological treatment for KOA.<sup>8 32-34</sup> In 2004 and 2005, the efficacy of acupuncture for treating KOA was verified by two randomized trials.<sup>14 15</sup> In 2014, however, a clinical trial showed that acupuncture did not confer a benefit over sham treatment for pain or function.<sup>35</sup>

Most meta-analyses mainly focused on chronic pain and peripheral joint osteoarthritis and were not specific to knee osteoarthritis.<sup>19 20 36-39</sup> Although there were some systematic reviews conducted to establish the association of acupuncture with KOA, few drew a definitive conclusion.<sup>40 41</sup> One systematic review have looked at the comparative effectiveness of manual acupuncture and electroacupuncture, but considered only direct evidence.<sup>42</sup> Two previous meta-analyses have drawn opposite conclusions depending on the types of control group used for comparison in 2007.<sup>43 44</sup> However, some rigorous randomized clinical trials (RCTs) in this field published

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4 within recent years were not included in previous systematic reviews. For example, a  
5  
6 multicenter RCT published in 2020 by our team suggested that acupuncture had  
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8 potential benefits for KOA.<sup>45</sup> Thus, it is important to perform a systematic review and  
9  
10 meta-analysis to inform clinical practice.  
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### 13 14 **Objectives**

15  
16  
17 We aim to evaluate the efficacy and safety of acupuncture for treating patients with  
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19 osteoarthritis of the knee by conducting a systematic review and meta-analysis. For  
20  
21 this purpose, we put forward the following questions about this review:  
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- 24  
25 1. Is acupuncture effective for treating osteoarthritis of the knee compared with sham  
26  
27 control or no-acupuncture control?  
28  
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- 30  
31 2. Is acupuncture associated with a reduction in medication use in patients with KOA?  
32

## 33 34 **2. METHODS AND ANALYSIS**

### 35 36 **Protocol registration.**

37  
38 This protocol was registered in PROSPERO (CRD42021232177). It will be followed  
39  
40 the standard methods of systematic review and meta-analysis. It will adhere to the  
41  
42 Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA)  
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44 reporting guidelines (see appendix 1).<sup>46 47</sup>  
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### 48 49 **Criteria for including studies in this review**

#### 50 51 **Types of studies**

52  
53 RCTs (with or without blinding, including crossover design) of acupuncture therapy  
54  
55 for KOA will be included. We will consider including older RCTs that were cited in  
56  
57 previous reviews of acupuncture for osteoarthritis.  
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## **Types of participants**

Participants with a diagnosis of KOA will be included regardless of their age, sex, race, education or economic status. The diagnosis will be made on the basis of symptoms (pain, brief physical stiffness, and functional limitations) and the radiologic confirmation of osteoarthritis according to the American College of Rheumatology clinical criteria or National Institute for Health and Clinical Excellence guidelines.<sup>8 48</sup>

## **Types of Interventions**

The eligible intervention is acupuncture including manual acupuncture and electroacupuncture. There will be no restriction on the sessions of acupuncture, needling techniques or stimulation methods.

## **Types of control groups**

In this review, we plan to compare needle acupuncture with sham acupuncture, analgesic, usual care or waiting list control groups. Acupuncture plus one or more therapies with the same therapies also will be included.

## **Outcomes**

### **Primary outcome**

Pain intensity: The WOMAC Pain Subscale, Visual Analog Scale (VAS), Brief Pain Inventory (BPI), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) or other validated outcome measures.

### **Secondary outcomes**

1. Function: The WOMAC Function Subscale, Lysholm Scale or other validated scales.

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4 2. Quality of life: The 12-Item Short Form Health Survey (SF-12), 36-Item Short  
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6 Form Health Survey (SF-36), Assessment of Quality of Life Instrument (AQoL II) or  
7  
8 other validated scales.

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10  
11 3. Adverse events: Incidence and severity of adverse events

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13  
14 4. Drug use: Number of people using emergency analgesics, frequency or dosage of  
15  
16 medication for KOA.

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18  
19 5. Cost: incremental cost-effectiveness ratio of acupuncture treatment

### 20 21 22 **Criteria for excluding studies in this review**

23  
24  
25 1. Participants with knee pain but no other symptoms of KOA;

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27  
28 2. The intervention group received transcutaneous electrical nerve stimulation;

29  
30  
31 3. Follow-up periods less than 6 weeks in duration<sup>44</sup>;

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33  
34 4. Studies reported only improvement rates;

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36  
37 5. Low quality of internal validity (allocation concealment is determined to be  
38  
39 inadequate);

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41  
42 6. Study comparing one type of acupuncture with other type of acupuncture and study  
43  
44 comparing acupuncture with complementary therapies or TCM.

### 45 46 47 **Search methods for identification of studies**

#### 48 49 50 **Electronic searches**

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53 We developed search strategies for four English databases (PubMed, Embase,  
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55 Cochrane Library databases, and Web of Science) and four Chinese databases (China  
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57 National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP  
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59 Database for Chinese Technical Periodicals, and Wanfang) from database inception to  
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4 September 1, 2021. Additional trials will be identified by searching previous  
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6 systematic reviews. No language or publication status restrictions are applied. The  
7  
8 search strategy components are clinical condition (osteoarthritis, knee,  
9  
10 patellofemoral pain syndrome, knee pain, and gonarthrosis), intervention  
11  
12 (acupuncture, electroacupuncture, and acupuncture points) and study type  
13  
14 (randomized controlled trial). We will adapt the search strategies to medical subject  
15  
16 headings terms and keywords as necessary for each database (see appendix 2 for the  
17  
18 search strategy used in the PubMed database). A pilot of the systematic search was  
19  
20 conducted on 28 February 2021 (see appendix 3). We (F-TY and C-YL) will rerun the  
21  
22 searches before submission of the manuscript to identify any eligible articles  
23  
24 published since our first search.  
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### 32 **Searching other sources**

33  
34 We will search the following websites as a supplement: the WHO International  
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36 Clinical Trials Registry Platform and the National Institutes of Health clinical registry  
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38 ClinicalTrials.gov and the Chinese Clinical Registry. The search will also include a  
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40 manual search for gray literature (e.g., unpublished conference articles).  
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### 45 **Data collection and analysis**

#### 46 **Selection of studies**

47  
48 All search results will be exported to EndNote, where we will check for and exclude  
49  
50 duplicates. Two of us will screen all titles and abstracts independently to identify  
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52 potentially relevant studies. Full texts will be downloaded and printed for further  
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54 assessment. Two reviewers will screen the whole-length articles to confirm whether  
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4 the studies meet the inclusion criteria. Any disagreement will be settled by discussion.

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6 If an agreement cannot be reached, a third reviewer will be consulted. The reasons for  
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9 excluding studies will be recorded. The study selection process is shown in figure 1.

### 10 11 **Data extraction and management**

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13 All data will be extracted independently and in duplicate by two reviewers with a  
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All data will be extracted independently and in duplicate by two reviewers with a  
predesigned data extraction template. Disagreements will be settled by discussion. A  
third reviewer will be consulted if discrepancies cannot be resolved. All data will be  
cross-checked by two reviewers and transferred into Microsoft Office Excel. If  
required, we will contact the corresponding authors for more information by email.

The predefined variables for extraction are the following:

1. Publication details (study year, first author, funding source);
2. Basic information (location, study type, number of centers, sample size, study duration, and length of follow-up);
3. Participants (type and/or stage of KOA, mean age, sex, and pain intensity before treatment);
4. Interventions (type of acupuncture, choice of acupuncture points, number of sessions, treatment frequency, duration of each session, and needling techniques)
5. Control (if there is any control, details of the treatment, including the name, dosage, frequency and course);
6. Outcomes (data and time points for each measurement, type and number of adverse events in each group).

### **Risk of bias assessment in included studies**

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4 Two reviewers will assess the risk of bias in the included studies by using the  
5  
6 Cochrane Collaboration's tool for assessing risk of bias. We will assess each RCT a  
7  
8 low, high, or unclear risk of bias for 6 domains: selection bias (random sequence  
9  
10 generation and allocation concealment), performance bias (blinding of researchers and  
11  
12 participants), attrition bias (incomplete outcome data), ascertainment bias (blinding of  
13  
14 outcome assessment), reporting bias (selective outcome reporting) and other sources  
15  
16 of potential bias. Disagreements will be resolved by discussion, according to the  
17  
18 published articles and supplementary materials. We will consult the third reviewer  
19  
20 and contact the study authors when needed.  
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### 26 27 **Acupuncture adequacy assessment** 28

29  
30 We will try to use some methods to assess treatment adequacy in acupuncture RCTs.  
31  
32 We will adopt the adequacy assessment instrument, which was derived from the  
33  
34 STRICTA recommendations,<sup>49</sup> to evaluate the following 6 aspects of acupuncture  
35  
36 treatment: acupuncture rationale, needling details, treatment regimen, cointerventions,  
37  
38 practitioner background, and control intervention(s). We plan to assess adequacy  
39  
40 independently and to reach an agreement by discussion. The assessors, who will be  
41  
42 blinded to the results of the study and the publication, will conduct the assessments  
43  
44 only based on the description of the study population and the acupuncture procedure.  
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46 To test the success of the blinding, we will ask the two assessors to guess the  
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48 provenance of each study.  
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### 55 56 **Heterogeneity assessment** 57

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59 If there are sufficient data, we will conduct a meta-analysis to determine the efficacy  
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4 of acupuncture and the related factors.  $I^2$  testing will be used to quantify heterogeneity  
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6 among the included studies.<sup>50</sup> If the  $I^2$  is less than 75%, we will conduct a  
7  
8 meta-analysis. We will present summary estimates in forest plots. If the  $I^2$  is more  
9  
10 than 50%, we will explore the possible sources of heterogeneity via meta-regression  
11  
12 and subgroup analyses. If a meta-analysis is precluded, we will conduct a descriptive  
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14 synthesis using a best-evidence synthesis approach.  
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### 18 19 **Reporting bias assessment**

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21 We will also consider assessing the reporting bias and small-study effects by using  
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23 funnel plots when there are 10 or more trials. We will assess funnel plot asymmetry  
24  
25 by using Begg's and Egger's tests and will define significant publication bias as a p  
26  
27 value < 0.1. We will also use a trim-and-fill computation to estimate the effect of  
28  
29 publication bias on the interpretation of the results.<sup>51</sup>  
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### 34 35 **DATA SYNTHESIS**

36  
37 When the meta-analysis is performed, Stata 16.0 and RevMan 5.3 will be used for all  
38  
39 statistical calculations. The fixed-effects model will be used if little heterogeneity. On  
40  
41 the other hand, the random-effects model will be used if significant heterogeneity is  
42  
43 observed. For dichotomous variables, Mantel-Haenszel method will be used for  
44  
45 analyses and effect size will be reported as relative risk (RR) with 95% confidence  
46  
47 intervals (CIs). For continuous variables, inverse variance method will be used for  
48  
49 analyses and treatment effect will be reported as mean difference (MD) with 95% CIs.  
50  
51 The standardized mean difference (SMD) with 95% CIs will be used if different  
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53 scales are used to evaluate a predesigned outcome.  
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4 For pain variance, we plan to pool data from previous studies reporting VAS 100  
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6 mm, VAS 10 cm, and NRS by transforming it to a “0-100-pain measure” using an  
7  
8 appropriate multiplier. We also intend to analyze pain intensity by independently  
9  
10 reporting the aforementioned scales.  
11  
12

### 13 14 **SUBGROUP ANALYSIS**

15  
16 Subgroup analyses will be performed to explain the heterogeneity. Predefined  
17  
18 subgroups include the type of intervention, the frequency of acupuncture treatment,  
19  
20 and the stage of knee osteoarthritis.  
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### 23 24 **SENSITIVITY ANALYSIS**

25  
26 We will conduct a sensitivity analysis to verify the robustness of the review  
27  
28 conclusions. We will consider removing one study at a time to observe its effect on  
29  
30 heterogeneity and effect size. In addition, the meta-analysis will be repeated after  
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32 low-quality studies are excluded.  
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### 36 37 **Strength of recommendations and the quality of evidence**

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39 We will assess the strength of recommendations based on the Grading of  
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41 Recommendations Assessment Development and Evaluation (GRADE) working  
42  
43 group methodology. The two categories of weak/conditional evidence and strong  
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45 evidence will be used.  
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50 We will also assess the quality of evidence. The quality of evidence will be assessed  
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52 according to the domains of risk of bias, consistency, directness, precision, and  
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54 publication bias. The assessments will be adjudicated into four levels: high, moderate,  
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56 low or very low.<sup>52 53</sup>  
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## Patients and public involvement

There were no patients nor public will be directly involved in this review. Only data already existent in the literature and the aforementioned sources will be used for this study.

## DISCUSSION

This systematic review will be performed based on previous studies of acupuncture for knee osteoarthritis. Conclusions drawn from this review may be beneficial to patients with KOA, clinicians and policy makers. We will summarize and explain the characteristics and findings of the included studies by conducting a systematic narrative synthesis.

Based on the above, we want to conduct some exploratory studies. (1) Is there a difference in the efficacy between manual acupuncture and electroacupuncture? (2) Is the efficacy (if any) related to the stage of knee osteoarthritis according to the Kellgren-Lawrence score or Outbridge score,<sup>54 55</sup> some characteristics of acupuncture (e.g., choice of acupoints and treatment frequency), type of control group, measurement time points of outcomes or other variables?

Manual acupuncture and electroacupuncture are the most commonly used acupuncture therapies. Manual acupuncture maintains a moderate dose of stimulation by lifting, inserting and twisting needles to acupoints. However, it is laborious and difficult to reach an agreement on standards because of the different needle techniques. Electroacupuncture, which is widely used in clinical practice, refers to the pulse current input to acupoints on the basis of needle acupuncture. This approach can

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4 accurately control the dose of stimulation and save labor. In clinical trials for pain  
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6 conditions, better analgesia appears to be obtained when electrical stimulation is  
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8 added to manual stimulation than with manual acupuncture needle stimulation  
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10 alone.<sup>56</sup> However, the findings may not be generalizable because of the different pain  
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12 types. We will try to explore the difference in the efficacy between manual  
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14 acupuncture and electroacupuncture for KOA. Hence, we will choose sham  
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16 acupuncture as a common comparator, making an indirect comparison between  
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18 manual acupuncture and electroacupuncture. Finally, we will conduct a mixed  
19  
20 treatment comparison meta-analysis (MTC) to synthesize the evidence from direct  
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22 comparison and indirect comparison.  
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30 There are many factors affecting the efficacy of acupuncture. Our previous studies  
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32 suggested that the effect of acupuncture may be associated with the dose of  
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34 acupuncture, including needled points, Deqi response, frequency of treatment and  
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36 number of treatment sessions.<sup>57 58</sup> Hence, we want to focus on these factors in the  
37  
38 subgroup analysis and to explore the applied law of different doses of acupuncture.  
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43 We predefine that trials included have 6 weeks of observation at least. Although  
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45 this criterion has not been accepted widely, we think that RCTs with observation  
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47 periods less than 6 weeks may have methodological shortcomings that may  
48  
49 exaggerate the efficacy of acupuncture.  
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53 The proposed review has several strengths. We plan to search multiple Chinese and  
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55 English language databases to ensure a comprehensive search of the literature. Any  
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57 meta-analyses will be performed according to the Cochrane Handbook for Systematic  
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4 Reviews of Interventions. A further strength is that more stringent eligibility criteria  
5  
6 will be applied to ensure the quality of the included RCTs. In addition, pain intensity  
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8 was selected as the targeted outcome because it plays an important role in the pain  
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10 management of KOA. Transformation of pain scores measured by different pain  
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12 scales to a 0-100 pain measure will result in loss of some accuracy; however, we  
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14 believe that it is clinically irrelevant.  
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18  
19 **Contributors** C-YL is the guarantor and first author of the protocol. C-YL and L-QW  
20  
21 designed the systematic review. C-YL and L-LL drafted the manuscript. J-WY, J-FT,  
22  
23 L-QW and Myeong Soo Lee provided help to design and edited the manuscript. C-YL  
24  
25 and F-TY will independently screen the eligible studies. C-YL and X-WH will extract  
26  
27 data from included articles. J-LL and J-FT will assess the risk of bias. C-YL and  
28  
29 X-TS will assess acupuncture adequacy, Strength of recommendations and the quality  
30  
31 of evidence. C-YL, L-YQ and S-YY will finish data synthesis. L-QW will arbitrate  
32  
33 any disagreements during the review. All authors have read the manuscript and  
34  
35 approved the final publication of the protocol.  
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44  
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46  
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50  
51 **Competing interests:** None declared  
52

53 **Patient consent for publication** Not required.  
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56 **Provenance and peer review** Not commissioned; externally peer-reviewed.  
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14 **Figure legends**

15 **Figure 1** Flow diagram of the study selection process. KOA, knee osteoarthritis.  
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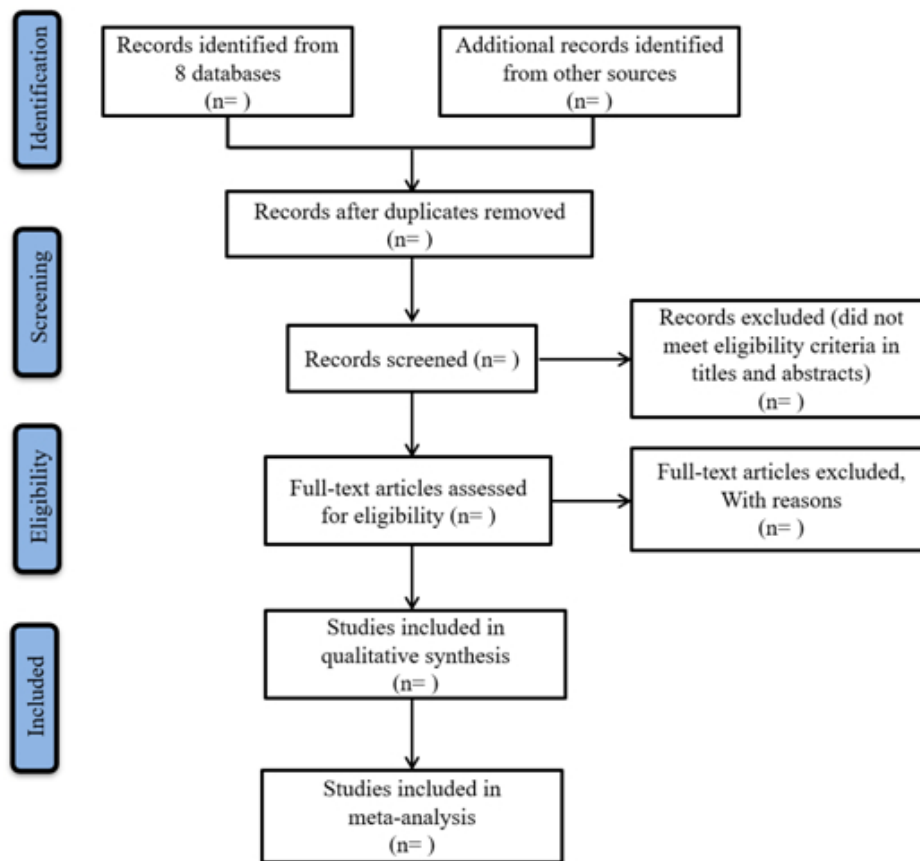


Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	18
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11 Appendix2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	N/A
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10;18
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

**Table 1 Search strategy used in the PubMed database**

#	Searches
1	Osteoarthritis, Knee[mesh]
2	Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract]
3	Patellofemoral Pain Syndrome[mesh]
4	Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract]
5	knee pain[Title/Abstract]
6	gonarthrosis[Title/Abstract]
7	OR/1-6
8	Acupuncture[mesh]
9	Pharmacopuncture[Title/Abstract]
10	Acupuncture Therapy[mesh]
11	Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract]
12	Electroacupuncture[mesh]
13	Acupuncture Points[mesh]
14	Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract]
15	OR/8-14
16	clinical[tiab]
17	trial[tiab]
18	16 AND 17
19	clinical trials as topic[mesh]
20	clinical trial[pt]
21	random*[tiab]
22	random allocation[mesh]
23	therapeutic use[sh]
24	OR/18-23
25	7 AND 15 AND 24



**Result of presearch in the PubMed database**

1. Osteoarthritis, Knee[mesh] Items found: 21,147
  2. Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract] Items found: 40,291
  3. Patellofemoral Pain Syndrome[mesh] Items found: 934
  4. Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract] Items found: 3,799
  5. knee pain[Title/Abstract] Items found: 8,083
  6. gonarthrosis[Title/Abstract] Items found: 1,095
  7. OR/1-6 Items found: 47,408
  8. Acupuncture[mesh] Items found: 1735
  9. Pharmacopuncture[Title/Abstract] Items found: 211
  10. Acupuncture Therapy[mesh] Items found: 25,321
  11. Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacopuncture Treatment OR Treatment, Pharmacopuncture OR Pharmacopuncture Therapy OR Therapy, Pharmacopuncture[Title/Abstract] Items found: 2996
  12. Electroacupuncture[mesh] Items found: 4128
  13. Acupuncture Points[mesh] Items found: 6934
  14. Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract] Items found: 6,284
  15. OR/8-14 Items found: 27,954
  16. clinical[tiab] Items found: 3,720,276
  17. trial[tiab] Items found: 638,665
  18. 16 AND 17 Items found: 294,477
  19. clinical trials as topic[mesh] Items found: 353,132
  20. clinical trial[pt] Items found: 884,322
  21. random\*[tiab] Items found: 1,202,203
  22. random allocation[mesh] Items found: 104,737
  23. therapeutic use[sh] Items found: 4,516,532
  24. OR/18-23 Items found: 5,668,908
  25. 7 AND 15 AND 24 Items found: 397
- Final Result: 397 (By 28 February 2021)

# BMJ Open

## Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

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Secondary Subject Heading:	Complementary medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, COMPLEMENTARY MEDICINE

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1 **Title: Is acupuncture effective for knee osteoarthritis? A protocol for a**  
2 **systematic review and meta-analysis**

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35 35 Key words: Acupuncture; Osteoarthritis, Knee; Meta-Analysis; Protocol  
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37 36 Number of words: 3525  
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4 45 ABSTRACT  
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6 46 **Introduction**  
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9 47 Knee osteoarthritis is one of the leading causes of disability. The effectiveness of  
10  
11 48 acupuncture for treating KOA remains controversial. This protocol describes the  
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13  
14 49 method of a systematic review and meta-analysis evaluating the efficacy and safety of  
15  
16  
17 50 acupuncture for treating KOA.  
18

19 51 **Methods and analysis**  
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21  
22 52 Four English databases (PubMed, Embase, Cochrane Library databases, and Web of  
23  
24  
25 53 Science) and four Chinese databases (China National Knowledge Infrastructure,  
26  
27  
28 54 Chinese Biomedical Literature Database, VIP Database for Chinese Technical  
29  
30  
31 55 Periodicals, and Wanfang) will be searched from the database inception to September  
32  
33 56 1, 2021. All randomized controlled trials related to acupuncture for KOA will be  
34  
35  
36 57 included. Extracted data will include publication details, basic information,  
37  
38  
39 58 demographic data, intervention details and patient outcomes. The primary outcome is  
40  
41  
42 59 pain intensity. Risk of bias will be assessed using the Cochrane Collaboration's tool  
43  
44  
45 60 for assessing risk of bias. Article selection, data extraction and risk of bias assessment  
46  
47  
48 61 will be performed in duplicate by two independent reviewers. If the meta-analysis is  
49  
50  
51 62 precluded, we will conduct a descriptive synthesis using a best-evidence synthesis  
52  
53  
54 63 approach. The strength of recommendations and quality of evidence will be assessed  
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56  
57 64 using the Grading of Recommendations Assessment Development and Evaluation  
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59  
60 65 working group methodology.

58 66 **Ethics and dissemination**  
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4 67 Ethics approval is not required because individual patient data are not included. This  
5  
6 68 protocol was registered in the international Prospective Register of Systematic  
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8  
9 69 Reviews on 25 February 2021. The systematic review and meta-analysis will be  
10  
11 70 submitted for publication in a peer-reviewed journal. The findings will also be  
12  
13  
14 71 disseminated through conference presentations.  
15  
16

17 72 **Trial registration number**

18  
19 73 CRD42021232177  
20  
21

22 74 **Article summary**

23  
24 75 **Strengths and limitations of this study**

- 25  
26  
27 76 1. This meta-analysis will evaluate the effectiveness and safety of acupuncture in  
28  
29 77 treating knee osteoarthritis by collecting comprehensive evidence.  
30  
31  
32 78 2. We want to focus on many different factors in subgroup analysis and to explore the  
33  
34 79 applied law of different doses of acupuncture.  
35  
36  
37 80 3. This study will explore the difference in the effectiveness between manual  
38  
39 81 acupuncture and electroacupuncture for knee osteoarthritis by synthesizing the  
40  
41 82 evidence from direct comparison and indirect comparison.  
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43  
44 83 4. We plan to search multiple Chinese and English language databases to ensure a  
45  
46 84 comprehensive search of the literature.  
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49 85 5. Transformation of pain scores will result in loss of some accuracy; however, we  
50  
51 86 believe that it is clinically irrelevant.  
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## 89 INTRODUCTION

### 90 Description of the condition

91 Osteoarthritis (OA) is a common clinical degenerative disease and is one of the  
92 leading causes of disability.<sup>1</sup> The excess costs of adults with OA are considerable,  
93 estimated at \$45 billion annually in United States.<sup>2</sup> Knee osteoarthritis accounts for  
94 approximately 85% of global osteoarthritis burden.<sup>3</sup> With the trends of an aging  
95 population and increasing obesity, the incidence of knee osteoarthritis (KOA) is  
96 increasing for both sexes.<sup>4 5</sup> In addition, pain symptoms associated with KOA result in  
97 physical and walking disability, which in turn have an excess risk of all-cause  
98 mortality.<sup>6 7</sup>

99 Exercise and weight loss, two effective nonpharmacological treatments, are strongly  
100 recommended in all people with clinical osteoarthritis.<sup>8</sup> However, for patients with  
101 KOA, it is difficult to continue exercising and losing weight. Representatives of  
102 pharmacological interventions include analgesics and nonsteroidal anti-inflammatory  
103 drugs (NSAIDs). However, acetaminophen (paracetamol) is not associated with  
104 long-term pain improvement.<sup>9</sup> Furthermore, many NSAIDs are associated with  
105 serious side effects such as cardiovascular, renal adverse effects and gastrointestinal  
106 bleeding.<sup>10 11</sup> In addition, the health care systems of Western countries are  
107 overstretched because of the increasing joint replacement requirements.<sup>12</sup> In this  
108 context, identification of the efficacy of existing treatments or development of novel  
109 therapies remains an important priority.

### 110 Description of the intervention



1  
2  
3  
4 111 Acupuncture has long been recognized as a nonpharmacologic therapy in treating  
5  
6 112 various disorders by inserting fine needles into specific anatomic points (acupoints)  
7  
8  
9 113 on the skin of the patient's body. As an important component of traditional Chinese  
10  
11 114 medicine (TCM), acupuncture has been used in clinical practice for more than 3000  
12  
13  
14 115 years.

16  
17 116 The World Health Organization (WHO) has recommended acupuncture therapies  
18  
19 117 for 107 diseases. The efficacy of acupuncture for different kinds of pain diseases has  
20  
21 118 been verified by a great deal of high-quality clinical trials.<sup>13-15</sup> Recently, two  
22  
23 119 individual patient data meta-analyses also reported that acupuncture was effective for  
24  
25 120 the treatment of chronic pain, with treatment effects persisting over time.<sup>16 17</sup> In  
26  
27 121 addition, acupuncture appears to be a safe intervention that has rare adverse effects in  
28  
29 122 the hands of competent practitioners.<sup>18 19</sup>

### 34 35 123 **How the intervention might work**

36  
37 124 Knee osteoarthritis (KOA) is a prevalent, chronic joint disorder, characterized by  
38  
39 125 synovitis, overgrowth of subchondral bone, development of osteophytes, erosions and  
40  
41 126 loss of the articular cartilage. Previous study found that cartilage damage is the origin  
42  
43 127 and result of KOA. With the further study of KOA, synovitis has been verified to play  
44  
45 128 a crucial part in the pathological development and the maintenance of pain in KOA.<sup>20</sup>

46  
47 129 In recent decades, preclinical investigations of acupuncture mechanisms in KOA  
48  
49 130 pain have increased. These studies show that acupuncture relieves symptoms of KOA  
50  
51 131 by activating a variety of bioactive chemicals through peripheral, spinal, and  
52  
53 132 supraspinal mechanisms.<sup>21</sup> For example, acupuncture can desensitize peripheral  
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4 133 nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord.  
5  
6 134 <sup>21-23</sup> In addition, acupuncture dampens the transmission of noxious inputs at the spinal  
7  
8  
9 135 level with the involvement of spinal opioids, serotonin (i.e., 5-hydroxytryptamine),  
10  
11 136 norepinephrine, glial cell/cytokines, and signal molecules.<sup>21 24-26</sup> In addition,  
12  
13 137 CBR1-GABA-5-HT may be a novel pathway contributed to the effect of EA on KOA  
14  
15 138 pain.<sup>27</sup> EA down-regulated IL-1 $\beta$  expression via activating the peripheral CBR2 to  
16  
17 139 inhibit the KOA pain.<sup>28</sup>

#### 140 **Why it is important to perform this review**

141 Research on acupuncture for KOA has been growing, but the findings have been  
142 inconsistent. Different guidelines do not reach an agreement on whether acupuncture  
143 should be recommended as an effective nonpharmacological treatment for KOA.<sup>8 29-31</sup>  
144 In 2014, a clinical trial showed that acupuncture did not confer a benefit over sham  
145 treatment for pain or function.<sup>32</sup> In 2019, however, a review suggested that  
146 acupuncture provided relief of pain associated with KOA.<sup>33</sup>

147 Most meta-analyses mainly focused on chronic pain and peripheral joint  
148 osteoarthritis and were not specific to knee osteoarthritis.<sup>16 17 34-37</sup> Although there were  
149 some systematic reviews conducted to establish the association of acupuncture with  
150 KOA, few drew a definitive conclusion.<sup>38 39</sup> One systematic review has looked at the  
151 comparative effectiveness of manual acupuncture (MA) and electroacupuncture (EA),  
152 but considered only direct evidence.<sup>40</sup> Two previous meta-analyses have drawn  
153 opposite conclusions depending on the types of control group used for comparison in  
154 2007.<sup>41 42</sup> However, some rigorous randomized clinical trials (RCTs) in this field

1  
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4 155 published within recent years were not included in previous systematic reviews. For  
5  
6 156 example, a multicenter RCT published in 2020 by our team suggested that  
7  
8  
9 157 acupuncture had potential benefits for KOA.<sup>43</sup> Thus, it is important to perform a  
10  
11  
12 158 systematic review and meta-analysis to inform clinical practice.

## 13 14 159 **Objectives**

15  
16  
17 160 We aim to evaluate the efficacy and safety of acupuncture for treating patients with  
18  
19  
20 161 osteoarthritis of the knee by conducting a systematic review and meta-analysis. For  
21  
22 162 this purpose, we put forward the following questions about this review:

- 23  
24  
25 163 1. Is acupuncture effective for treating osteoarthritis of the knee compared with sham  
26  
27 164 control or no-acupuncture control?  
28  
29  
30 165 2. Is there a difference in the effectiveness between manual acupuncture and  
31  
32 166 electroacupuncture?

## 33 34 35 167 **2. METHODS AND ANALYSIS**

### 36 37 38 168 **Patients and public involvement**

39  
40 169 There will be no patients or public directly involved in this review. Only data already  
41  
42  
43 170 existent in the literature and the aforementioned sources will be used for this study.

### 44 45 171 **Protocol registration.**

46  
47  
48 172 This protocol was registered in PROSPERO (CRD42021232177). It will be followed  
49  
50  
51 173 the standard methods of systematic review and meta-analysis. It will adhere to the  
52  
53 174 Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA)  
54  
55  
56 175 reporting guidelines (see appendix 1).<sup>44 45</sup>

### 57 58 176 **Criteria for including studies in this review**

59  
60

1  
2  
3  
4 177 **Types of studies**

5  
6 178 RCTs (with or without blinding, including crossover design) of acupuncture therapy  
7  
8  
9 179 for KOA will be included. We will consider including older RCTs that were cited in  
10  
11  
12 180 previous reviews of acupuncture for osteoarthritis.

13  
14 181 **Types of participants**

15  
16  
17 182 Studies enrolling participants diagnosed as KOA will be included. The diagnostic  
18  
19 183 criteria should be based on the American College of Rheumatology clinical criteria,  
20  
21  
22 184 National Institute for Health and Clinical Excellence guidelines or any other accepted  
23  
24  
25 185 guidelines.<sup>8 46</sup> There will be no restrictions on their age, sex, race, education, economic  
26  
27 186 status, Kellgren-Lawrence score or Outbridge score.<sup>47 48</sup>

28  
29  
30 187 **Types of Interventions**

31  
32 188 The eligible intervention is acupuncture including manual acupuncture and  
33  
34  
35 189 electroacupuncture. There will be no restriction on the sessions of acupuncture,  
36  
37  
38 190 needling techniques or stimulation methods.

39  
40 191 **Types of control groups**

41  
42  
43 192 In this review, we plan to compare needle acupuncture with sham acupuncture,  
44  
45 193 analgesic, usual care or waiting list control groups. Acupuncture plus one or more  
46  
47  
48 194 therapies with the same therapies also will be included.

49  
50 195 **Outcomes**

51  
52  
53 196 **Primary outcome**

54  
55  
56 197 Pain intensity: The WOMAC Pain Subscale, Visual Analog Scale (VAS), Brief Pain  
57  
58 198 Inventory (BPI), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) or other  
59  
60

1  
2  
3  
4 199 validated outcome measures.  
5

6  
7 200 **Secondary outcomes**  
8

9 201 1. Function: The WOMAC Function Subscale, Lysholm Scale or other validated  
10  
11 202 scales.

12  
13  
14 203 2. Quality of life: The 12-Item Short Form Health Survey (SF-12), 36-Item Short  
15  
16 204 Form Health Survey (SF-36), Assessment of Quality of Life Instrument (AQoL II) or  
17  
18 205 other validated scales.

19  
20  
21  
22 206 3. Adverse events: Incidence and severity of adverse events

23  
24  
25 207 4. Drug use: Number of people using emergency analgesics, frequency or dosage of  
26  
27 208 medication for KOA.

28  
29  
30 209 5. Cost: incremental cost-effectiveness ratio of acupuncture treatment

31  
32 210 **Criteria for excluding studies in this review**  
33

34  
35 211 1. Participants with knee pain but no other criteria of KOA;

36  
37 212 2. The intervention group received transcutaneous electrical nerve stimulation;

38  
39 213 3. Studies reported only improvement rates;

40  
41 214 4. Studies comparing one type of acupuncture with other type of acupuncture (except

42  
43 215 EA versus MA) and studies comparing acupuncture with complementary therapies or

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45  
46 216 TCM.  
47

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50 217 **Search methods for identification of studies**  
51

52  
53 218 **Electronic searches**  
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55  
56 219 We developed search strategies for four English databases (PubMed, Embase,

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58 220 Cochrane Library databases, and Web of Science) and four Chinese databases (China  
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4 221 National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP  
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6 222 Database for Chinese Technical Periodicals, and Wanfang) from database inception to  
7  
8  
9 223 September 1, 2021. Additional trials will be identified by searching previous  
10  
11 224 systematic reviews. No language or publication status restrictions are applied. The  
12  
13 225 search strategy components are clinical condition (osteoarthritis, chondromalacia  
14  
15 226 patellae, knee, knee pain, and gonarthrosis), intervention (acupuncture,  
16  
17 227 electroacupuncture, and acupuncture points) and study type (randomized controlled  
18  
19 228 trial). We will adapt the search strategies to medical subject headings terms and  
20  
21 229 keywords as necessary for each database (see appendix 2 for the search strategy used  
22  
23 230 in the PubMed database). A pilot of the systematic search was conducted on 28  
24  
25 231 February 2021 (see appendix 3). We (F-TY and C-YL) will rerun the searches before  
26  
27 232 submission of the manuscript to identify any eligible articles published since our first  
28  
29 233 search.

### 234 **Searching other sources**

235 We will search the following websites as a supplement: the WHO International  
236 Clinical Trials Registry Platform and the National Institutes of Health clinical registry  
237 ClinicalTrials.gov and the Chinese Clinical Registry. The search will also include a  
238 manual search for gray literature (e.g., unpublished conference articles).

### 239 **Data collection and analysis**

#### 240 **Selection of studies**

241 All search results will be exported to EndNote, where we will check for and exclude  
242 duplicates. Two of us will screen all titles and abstracts independently to identify

1  
2  
3  
4 243 potentially relevant studies. Full texts will be downloaded and printed for further  
5  
6 244 assessment. Two reviewers will screen the whole-length articles to confirm whether  
7  
8  
9 245 the studies meet the inclusion criteria. Any disagreement will be settled by discussion.  
10  
11 246 If an agreement cannot be reached, a third reviewer will be consulted. The reasons for  
12  
13  
14 247 excluding studies will be recorded. The study selection process is shown in figure 1.  
15  
16  
17 248 Besides, we will add a table of exclude studies with reasons for exclusion to the  
18  
19  
20 249 appendix of our meta-analysis.

## 21 22 250 **Data extraction and management**

23  
24  
25 251 All data will be extracted independently and in duplicate by two reviewers with a  
26  
27 252 predesigned data extraction template. Disagreements will be settled by discussion. A  
28  
29  
30 253 third reviewer will be consulted if discrepancies cannot be resolved. All data will be  
31  
32  
33 254 cross-checked by two reviewers and transferred into Microsoft Office Excel. If  
34  
35 255 required, we will contact the corresponding authors for more information by email.

36  
37  
38 256 The predefined variables for extraction are the following:

- 39  
40 257 1. Publication details (study year, first author, funding source);  
41  
42  
43 258 2. Basic information (location, study type, number of centers, sample size, study  
44  
45 259 duration, and length of follow-up);  
46  
47  
48 260 3. Participants (type and/or stage of KOA, mean age, sex, and pain intensity before  
49  
50 261 treatment);  
51  
52  
53 262 4. Interventions (type of acupuncture, choice of acupuncture points, number of  
54  
55 263 sessions, treatment frequency, duration of each session, and needling techniques)  
56  
57  
58 264 5. Control (if there is any control, details of the treatment, including the name, dosage,  
59  
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1  
2  
3  
4 265 frequency and course);

5  
6 266 6. Outcomes (data and time points for each measurement, type and number of adverse  
7  
8  
9 267 events in each group).

#### 10 11 268 **Risk of bias assessment in included studies**

12  
13  
14 269 Two reviewers will assess the risk of bias in the included studies by using the  
15  
16  
17 270 Cochrane Collaboration's tool for assessing risk of bias. We will assess each RCT a  
18  
19  
20 271 low, high, or unclear risk of bias for 6 domains: selection bias (random sequence  
21  
22  
23 272 generation and allocation concealment), performance bias (blinding of researchers and  
24  
25  
26 273 participants), attrition bias (incomplete outcome data), ascertainment bias (blinding of  
27  
28  
29 274 outcome assessment), reporting bias (selective outcome reporting) and other sources  
30  
31  
32 275 of potential bias. Disagreements will be resolved by discussion, according to the  
33  
34  
35 276 published articles and supplementary materials. We will consult the third reviewer  
36  
37  
38 277 and contact the study authors when needed.

#### 39 40 278 **Acupuncture adequacy assessment**

41  
42  
43 279 We will use the adequacy assessment instrument to assess treatment adequacy in  
44  
45  
46 280 acupuncture RCTs from the following 4 aspects of acupuncture treatment: choice of  
47  
48  
49 281 acupuncture points, number of sessions, needling technique, and experience of the  
50  
51  
52 282 acupuncturists<sup>42</sup>. Two assessors who are experienced acupuncturists will assess  
53  
54  
55 283 adequacy independently and reach an agreement by discussion. They will be blinded  
56  
57  
58 284 to the results of the study and the publication and conduct the assessments only based  
59  
60 285 on the description of the study population and the acupuncture procedure. To test the  
286 success of the blinding, we will ask the assessors to guess the provenance of each



1  
2  
3  
4 287 study.

5  
6 288 **Heterogeneity assessment**

7  
8  
9 289 If there are sufficient data, we will conduct a meta-analysis to determine the efficacy  
10  
11 290 of acupuncture and the related factors.  $I^2$  testing will be used to quantify heterogeneity  
12  
13  
14 291 among the included studies.<sup>49</sup> We will present summary estimates in forest plots. If  
15  
16  
17 292 the  $I^2$  is more than 50%, we will explore the possible sources of heterogeneity via  
18  
19  
20 293 meta-regression and subgroup analyses. If a meta-analysis is not appropriate, we will  
21  
22 294 conduct a descriptive synthesis using a best-evidence synthesis approach.

23  
24  
25 295 **Reporting bias assessment**

26  
27 296 We will also consider assessing the reporting bias and small-study effects by using  
28  
29  
30 297 funnel plots when there are 10 or more trials. We will assess funnel plot asymmetry  
31  
32  
33 298 by using Begg's and Egger's tests and will define significant publication bias as a p  
34  
35  
36 299 value  $< 0.1$ . We will also use a trim-and-fill computation to estimate the effect of  
37  
38 300 publication bias on the interpretation of the results.<sup>50</sup>

39  
40 301 **DATA SYNTHESIS**

41  
42  
43 302 When the meta-analysis is performed, Stata 16.0 and RevMan 5.3 will be used for all  
44  
45  
46 303 statistical calculations. All the analyses will be based on the random-effects model  
47  
48  
49 304 because the RCTs included by us came from different populations. For dichotomous  
50  
51  
52 305 variables, Mantel-Haenszel method will be used for analyses and effect size will be  
53  
54  
55 306 reported as relative risk (RR) with 95% confidence intervals (CIs). For continuous  
56  
57  
58 307 variables, inverse variance method will be used for analyses and treatment effect will  
59  
60 308 be reported as mean difference (MD) with 95% CIs. The standardized mean

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4 309 difference (SMD) with 95% CIs will be used if different scales are used to evaluate a  
5  
6  
7 310 predesigned outcome.

8  
9 311 For pain variance, we plan to pool data from previous studies reporting VAS 100  
10  
11 312 mm, VAS 10 cm, and NRS by transforming it to a “0-100-pain measure” using an  
12  
13  
14 313 appropriate multiplier. We also intend to analyze pain intensity by independently  
15  
16  
17 314 reporting the aforementioned scales.

### 18 19 315 **SUBGROUP ANALYSIS**

20  
21  
22 316 Subgroup analyses will be performed to explain the heterogeneity. Predefined  
23  
24  
25 317 subgroups include the location of studies, the type of intervention, the dosage of  
26  
27  
28 318 acupuncture, and the stage of knee osteoarthritis.

### 29 30 319 **SENSITIVITY ANALYSIS**

31  
32  
33 320 We will conduct a sensitivity analysis to verify the robustness of the review  
34  
35  
36 321 conclusions. We will consider removing one study at a time to observe its effect on  
37  
38  
39 322 heterogeneity and effect size. In addition, the meta-analysis will be repeated after  
40  
41  
42 323 studies with lack of allocation concealment are excluded.

### 43 44 324 **OTHER ANALYSIS**

45  
46 325 If manual acupuncture and eletroacupuncture are effective for KOA compared with  
47  
48  
49 326 sham acupuncture, we will conduct the exploratory research to compare the difference  
50  
51  
52 327 in the effectiveness between MA and EA by synthesizing the evidence from direct  
53  
54  
55 328 comparison and indirect comparison. For direct comparison results, we will use  
56  
57  
58 329 Revman to analyze. For the indirect comparison, we will choose sham acupuncture as  
59  
60 330 a common comparator and use R software to analyze. Finally, we will conduct a

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3  
4 331 mixed treatment comparison meta-analysis (MTC) to synthesize the evidence from  
5  
6 332 direct comparison and indirect comparison.  
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8

9 333 **Strength of recommendations and the quality of evidence**

10  
11 334 We will assess the strength of recommendations based on the Grading of  
12  
13 335 Recommendations Assessment Development and Evaluation (GRADE) working  
14  
15 336 group methodology. The two categories of weak/conditional evidence and strong  
16  
17 337 evidence will be used.  
18  
19

20  
21 338 We will also assess the quality of evidence. The quality of evidence will be assessed  
22  
23 339 according to the domains of risk of bias, consistency, directness, precision, and  
24  
25 340 publication bias. The assessments will be adjudicated into four levels: high, moderate,  
26  
27 341 low or very low.<sup>51 52</sup>  
28  
29

30  
31 342 **DISCUSSION**

32  
33 343 This systematic review will be performed based on previous studies of acupuncture  
34  
35 344 for knee osteoarthritis. Conclusions drawn from this review may be beneficial to  
36  
37 345 patients with KOA, clinicians and policy makers. We will summarize and explain the  
38  
39 346 characteristics and findings of the included studies by conducting a systematic  
40  
41 347 narrative synthesis.  
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47  
48 348 Based on the above, we want to conduct some exploratory studies. (1) Is there a  
49  
50 349 difference in the effectiveness between manual acupuncture and electroacupuncture?  
51  
52 350 (2) Is the efficacy (if any) related to the stage of knee osteoarthritis according to the  
53  
54 351 Kellgren-Lawrence score or Outbridge score, some characteristics of acupuncture  
55  
56 352 (e.g., treatment frequency), type of control group, measurement time points of  
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1  
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4 353 outcomes or other variables?  
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6 354 Manual acupuncture and electroacupuncture are the most commonly used  
7  
8  
9 355 acupuncture therapies. Manual acupuncture maintains a moderate dose of stimulation  
10  
11  
12 356 by lifting, inserting and twisting needles to acupoints. However, it is laborious and  
13  
14  
15 357 difficult to reach an agreement on standards because of the different needle techniques.  
16  
17 358 Electroacupuncture, which is widely used in clinical practice, refers to the pulse  
18  
19  
20 359 current input to acupoints on the basis of needle acupuncture. This approach can  
21  
22  
23 360 accurately control the dose of stimulation and save labor. In clinical trials for pain  
24  
25  
26 361 conditions, better analgesia appears to be obtained when electrical stimulation is  
27  
28  
29 362 added to manual stimulation than with manual acupuncture needle stimulation  
30  
31  
32 363 alone.<sup>53</sup> However, the findings may not be generalizable because of the different pain  
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34  
35 364 types.

36 365 There are many factors affecting the efficacy of acupuncture. One review presented  
37  
38 366 “the challenge of adequacy of dose” recently.<sup>33</sup> Our group built a scoring instrument  
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40  
41 367 to calculate the dose of acupuncture from four parameters.<sup>54</sup> Based on the sum of the  
42  
43  
44 368 scores, we defined three doses of acupuncture treatment: high dosage, medium dosage  
45  
46  
47 369 and low dosage. And we designed three subgroups according the three kinds of  
48  
49  
50 370 dosage to explore the relationship between doses of acupuncture and efficacy. Deqi  
51  
52  
53 371 response is a comprehensive sensation of soreness, numbness, heaviness, aching at  
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55  
56 372 and around acupoints produced by manipulation of the needles. It plays a role in  
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59 373 acupuncture dosage so it is only one dimension of our scoring instrument.

60 374 The proposed review has several strengths. We plan to search multiple Chinese and

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4 375 English language databases to ensure a comprehensive search of the literature. Any  
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6 376 meta-analyses will be performed according to the Cochrane Handbook for Systematic  
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9 377 Reviews of Interventions. A further strength is that stringent eligibility criteria will be  
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11 378 applied to ensure the quality of the included RCTs. In addition, pain intensity was  
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13  
14 379 selected as the targeted outcome because it plays an important role in the pain  
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16  
17 380 management of KOA. Transformation of pain scores measured by different pain  
18  
19 381 scales to a 0-100 pain measure will result in loss of some accuracy; however, we  
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21  
22 382 believe that it is clinically irrelevant.

### 23 24 25 383 **Ethics and dissemination**

26  
27 384 Ethics approval is not required because individual patient data are not included. This  
28  
29  
30 385 protocol was registered in the international Prospective Register of Systematic  
31  
32 386 Reviews on 25 February 2021. The systematic review and meta-analysis will be  
33  
34  
35 387 submitted for publication in a peer-reviewed journal. The findings will also be  
36  
37  
38 388 disseminated through conference presentations.

39  
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41  
42  
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44  
45 391 **Contributors** C-YL is the guarantor and first author of the protocol. C-YL and L-QW  
46  
47  
48 392 designed the systematic review. C-YL and L-LL drafted the manuscript. J-WY, J-FT,  
49  
50  
51 393 L-QW and Myeong Soo Lee provided help to design and edited the manuscript. C-YL  
52  
53 394 and F-TY will independently screen the eligible studies. C-YL and X-WH will extract  
54  
55  
56 395 data from included articles. J-LL and J-FT will assess the risk of bias. C-YL and  
57  
58  
59 396 X-TS will assess acupuncture adequacy, Strength of recommendations and the quality  
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3  
4 397 of evidence. C-YL, L-YQ and S-YY will finish data synthesis. L-QW will arbitrate  
5  
6 398 any disagreements during the review. All authors have read the manuscript and  
7  
8  
9 399 approved the final publication of the protocol.  
10

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12  
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16  
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18  
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21  
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23

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25

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14 556 **Figure legends**

15 557 **Figure 1** Flow diagram of the study selection process. KOA, knee osteoarthritis.

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For peer review only

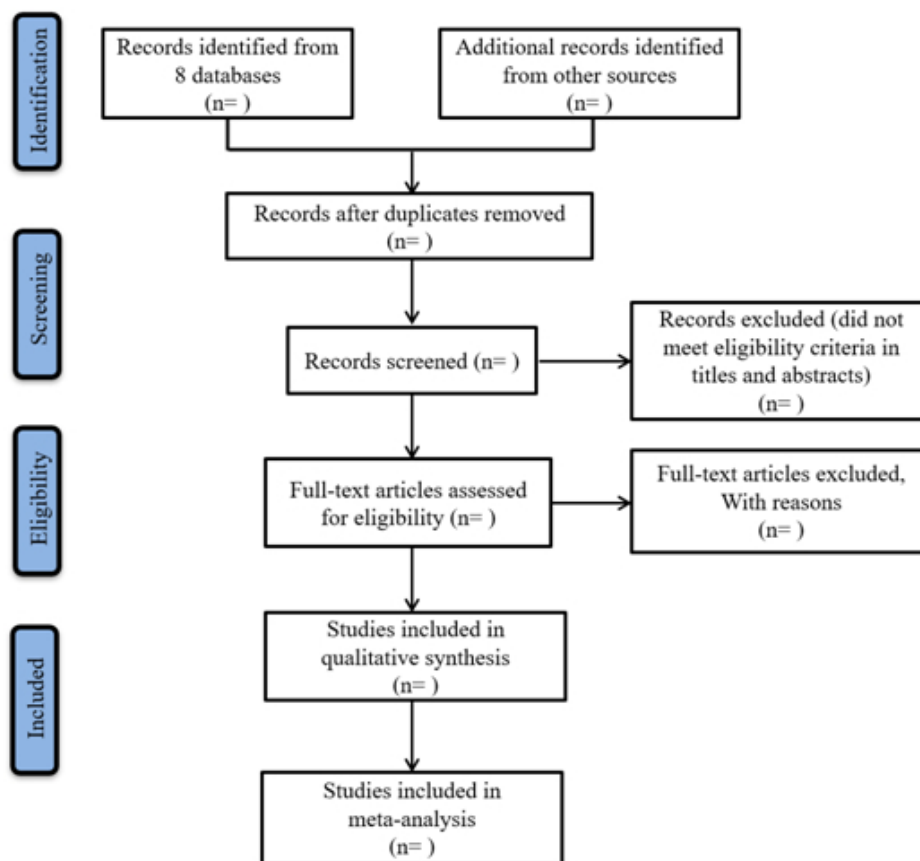


Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18-19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	19
Sponsor	5b	Provide name for the review funder and/or sponsor	19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	19
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11 Appendix2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12

1			
2			
3	Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
4			11-12
5	Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
6			12
7	Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
8			12-13
9	Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
10			9-10
11	Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
12			13
13	Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
14			14
15		15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )
16			14
17		15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
18			15
19		15d	If quantitative synthesis is not appropriate, describe the type of summary planned
20			14
21	Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
22			14
23	Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)
24			16

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*



**Table 1 Search strategy used in the PubMed database**

#	Searches
1	Osteoarthritis, Knee[mesh]
2	Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract]
3	Patellofemoral Pain Syndrome[mesh]
4	Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract]
5	knee pain[Title/Abstract]
6	gonarthrosis[Title/Abstract]
7	OR/1-6
8	Acupuncture[mesh]
9	Pharmacopuncture[Title/Abstract]
10	Acupuncture Therapy[mesh]
11	Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract]
12	Electroacupuncture[mesh]
13	Acupuncture Points[mesh]
14	Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract]
15	OR/8-14
16	clinical[tiab]
17	trial[tiab]
18	16 AND 17
19	clinical trials as topic[mesh]
20	clinical trial[pt]
21	random*[tiab]
22	random allocation[mesh]
23	therapeutic use[sh]
24	OR/18-23
25	7 AND 15 AND 24

**Result of presearch in the PubMed database**

1. Osteoarthritis, Knee[mesh] Items found: 21,147
  2. Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract] Items found: 40,291
  3. Patellofemoral Pain Syndrome[mesh] Items found: 934
  4. Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract] Items found: 3,799
  5. knee pain[Title/Abstract] Items found: 8,083
  6. gonarthrosis[Title/Abstract] Items found: 1,095
  7. OR/1-6 Items found: 47,408
  8. Acupuncture[mesh] Items found: 1735
  9. Pharmacopuncture[Title/Abstract] Items found: 211
  10. Acupuncture Therapy[mesh] Items found: 25,321
  11. Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacopuncture Treatment OR Treatment, Pharmacopuncture OR Pharmacopuncture Therapy OR Therapy, Pharmacopuncture[Title/Abstract] Items found: 2996
  12. Electroacupuncture[mesh] Items found: 4128
  13. Acupuncture Points[mesh] Items found: 6934
  14. Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract] Items found: 6,284
  15. OR/8-14 Items found: 27,954
  16. clinical[tiab] Items found: 3,720,276
  17. trial[tiab] Items found: 638,665
  18. 16 AND 17 Items found: 294,477
  19. clinical trials as topic[mesh] Items found: 353,132
  20. clinical trial[pt] Items found: 884,322
  21. random\*[tiab] Items found: 1,202,203
  22. random allocation[mesh] Items found: 104,737
  23. therapeutic use[sh] Items found: 4,516,532
  24. OR/18-23 Items found: 5,668,908
  25. 7 AND 15 AND 24 Items found: 397
- Final Result: 397 (By 28 February 2021)

# BMJ Open

## Is acupuncture effective for knee osteoarthritis? A protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052270.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Nov-2021
Complete List of Authors:	Liu, Chuanyang; Beijing University of Chinese Medicine, School of Traditional Chinese Medicine Tu, Jian Feng; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Lee, Myeong Soo; Korea Institute of Oriental Medicine, Medical Research Division Qi, Lingyu; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Yu, Fang-Ting; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina YAN, Shiyan; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Li, Jin-Ling; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Lin, Lu; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Hao, Xiao-Wan; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Su, Xin-Tong; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Yang, Jing-Wen; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina Wang, Li-Qiong; Beijing University of Chinese Medicine, School of Acupuncture-Moxibustion and Tuina
<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, COMPLEMENTARY MEDICINE

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1 **Title: Is acupuncture effective for knee osteoarthritis? A protocol for a**  
2 **systematic review and meta-analysis**

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35 35 Key words: Acupuncture; Osteoarthritis, Knee; Meta-Analysis; Protocol  
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4 45 ABSTRACT  
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6 46 **Introduction**  
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9 47 Knee osteoarthritis is one of the leading causes of disability. The effectiveness of  
10  
11 48 acupuncture for treating KOA remains controversial. This protocol describes the  
12  
13  
14 49 method of a systematic review and meta-analysis evaluating the efficacy and safety of  
15  
16  
17 50 acupuncture for treating KOA.  
18

19 51 **Methods and analysis**  
20

21  
22 52 Four English databases (PubMed, Embase, Cochrane Library databases, and Web of  
23  
24  
25 53 Science) and four Chinese databases (China National Knowledge Infrastructure,  
26  
27  
28 54 Chinese Biomedical Literature Database, VIP Database for Chinese Technical  
29  
30 55 Periodicals, and Wanfang) will be searched from the database inception to September  
31  
32  
33 56 1, 2021. All randomized controlled trials related to acupuncture for KOA will be  
34  
35  
36 57 included. Extracted data will include publication details, basic information,  
37  
38  
39 58 demographic data, intervention details and patient outcomes. The primary outcome is  
40  
41  
42 59 pain intensity. Risk of bias will be assessed using the Cochrane Collaboration's tool  
43  
44  
45 60 for assessing risk of bias. Article selection, data extraction and risk of bias assessment  
46  
47  
48 61 will be performed in duplicate by two independent reviewers. If the meta-analysis is  
49  
50  
51 62 precluded, we will conduct a descriptive synthesis using a best-evidence synthesis  
52  
53  
54 63 approach. The strength of recommendations and quality of evidence will be assessed  
55  
56  
57 64 using the Grading of Recommendations Assessment Development and Evaluation  
58  
59  
60 65 working group methodology.

58 66 **Ethics and dissemination**  
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4 67 Ethics approval is not required because individual patient data are not included. This  
5  
6 68 protocol was registered in the international Prospective Register of Systematic  
7  
8  
9 69 Reviews on 25 February 2021. The systematic review and meta-analysis will be  
10  
11 70 submitted for publication in a peer-reviewed journal. The findings will also be  
12  
13  
14 71 disseminated through conference presentations.  
15  
16

17 72 **Trial registration number**

18  
19 73 CRD42021232177  
20  
21

22 74 **Article summary**

23  
24 75 **Strengths and limitations of this study**

- 25  
26  
27 76 1. This meta-analysis will evaluate the effectiveness and safety of acupuncture in  
28  
29 77 treating knee osteoarthritis by collecting comprehensive evidence.  
30  
31  
32 78 2. We want to focus on many different factors in subgroup analysis and to explore the  
33  
34 79 applied law of different doses of acupuncture.  
35  
36  
37 80 3. This study will explore the difference in the effectiveness between manual  
38  
39 81 acupuncture and electroacupuncture for knee osteoarthritis by synthesizing the  
40  
41 82 evidence from direct comparison and indirect comparison.  
42  
43  
44 83 4. We plan to search multiple Chinese and English language databases to ensure a  
45  
46 84 comprehensive search of the literature.  
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49 85 5. Transformation of pain scores will result in loss of some accuracy; however, we  
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51 86 believe that it is clinically irrelevant.  
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## 89 INTRODUCTION

### 90 Description of the condition

91 Osteoarthritis (OA) is a common clinical degenerative disease and is one of the  
92 leading causes of disability.<sup>1</sup> The excess costs of adults with OA are considerable,  
93 estimated at \$45 billion annually in United States.<sup>2</sup> Knee osteoarthritis accounts for  
94 approximately 85% of global osteoarthritis burden.<sup>3</sup> With the trends of an aging  
95 population and increasing obesity, the incidence of knee osteoarthritis (KOA) is  
96 increasing for both sexes.<sup>4 5</sup> In addition, pain symptoms associated with KOA result in  
97 physical and walking disability, which in turn have an excess risk of all-cause  
98 mortality.<sup>6 7</sup>

99 Exercise and weight loss, two effective nonpharmacological treatments, are strongly  
100 recommended in all people with clinical osteoarthritis.<sup>8</sup> However, for patients with  
101 KOA, it is difficult to continue exercising and losing weight. Representatives of  
102 pharmacological interventions include analgesics and nonsteroidal anti-inflammatory  
103 drugs (NSAIDs). However, acetaminophen (paracetamol) is not associated with  
104 long-term pain improvement.<sup>9</sup> Furthermore, many NSAIDs are associated with  
105 serious side effects such as cardiovascular, renal adverse effects and gastrointestinal  
106 bleeding.<sup>10 11</sup> In addition, the health care systems of Western countries are  
107 overstretched because of the increasing joint replacement requirements.<sup>12</sup> In this  
108 context, identification of the efficacy of existing treatments or development of novel  
109 therapies remains an important priority.

### 110 Description of the intervention

1  
2  
3  
4 111 Acupuncture has long been recognized as a nonpharmacologic therapy in treating  
5  
6 112 various disorders by inserting fine needles into specific anatomic points (acupoints)  
7  
8  
9 113 on the skin of the patient's body. As an important component of traditional Chinese  
10  
11 114 medicine (TCM), acupuncture has been used in clinical practice for more than 3000  
12  
13  
14 115 years.

16  
17 116 The World Health Organization (WHO) has recommended acupuncture therapies  
18  
19 117 for 107 diseases. The efficacy of acupuncture for different kinds of pain diseases has  
20  
21 118 been verified by a great deal of high-quality clinical trials.<sup>13-15</sup> Recently, two  
22  
23 119 individual patient data meta-analyses also reported that acupuncture was effective for  
24  
25 120 the treatment of chronic pain, with treatment effects persisting over time.<sup>16 17</sup> In  
26  
27 121 addition, acupuncture appears to be a safe intervention that has rare adverse effects in  
28  
29 122 the hands of competent practitioners.<sup>18 19</sup>

### 34 35 123 **How the intervention might work**

36  
37 124 Knee osteoarthritis (KOA) is a prevalent, chronic joint disorder, characterized by  
38  
39 125 synovitis, overgrowth of subchondral bone, development of osteophytes, erosions and  
40  
41 126 loss of the articular cartilage. Previous study found that cartilage damage is the origin  
42  
43 127 and result of KOA. With the further study of KOA, synovitis has been verified to play  
44  
45 128 a crucial part in the pathological development and the maintenance of pain in KOA.<sup>20</sup>

46  
47 129 In recent decades, preclinical investigations of acupuncture mechanisms in KOA  
48  
49 130 pain have increased. These studies show that acupuncture relieves symptoms of KOA  
50  
51 131 by activating a variety of bioactive chemicals through peripheral, spinal, and  
52  
53 132 supraspinal mechanisms.<sup>21</sup> For example, acupuncture can desensitize peripheral  
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1  
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4 133 nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord.  
5  
6 134 <sup>21-23</sup> In addition, acupuncture dampens the transmission of noxious inputs at the spinal  
7  
8  
9 135 level with the involvement of spinal opioids, serotonin (i.e., 5-hydroxytryptamine),  
10  
11  
12 136 norepinephrine, glial cell/cytokines, and signal molecules.<sup>21 24-26</sup> In addition,  
13  
14 137 CBR1-GABA-5-HT may be a novel pathway contributed to the effect of EA on KOA  
15  
16  
17 138 pain.<sup>27</sup> EA down-regulated IL-1 $\beta$  expression via activating the peripheral CBR2 to  
18  
19  
20 139 inhibit the KOA pain.<sup>28</sup>

#### 21 22 140 **Why it is important to perform this review**

23  
24  
25 141 Research on acupuncture for KOA has been growing, but the findings have been  
26  
27  
28 142 inconsistent. Different guidelines do not reach an agreement on whether acupuncture  
29  
30  
31 143 should be recommended as an effective nonpharmacological treatment for KOA.<sup>8 29-31</sup>  
32  
33  
34 144 In 2014, a clinical trial showed that acupuncture did not confer a benefit over sham  
35  
36  
37 145 treatment for pain or function.<sup>32</sup> In 2019, however, a review suggested that  
38  
39  
40 146 acupuncture provided relief of pain associated with KOA.<sup>33</sup>

41  
42  
43 147 Most meta-analyses mainly focused on chronic pain and peripheral joint  
44  
45  
46 148 osteoarthritis and were not specific to knee osteoarthritis.<sup>16 17 34-37</sup> Although there were  
47  
48  
49 149 some systematic reviews conducted to establish the association of acupuncture with  
50  
51  
52 150 KOA, few drew a definitive conclusion.<sup>38 39</sup> One systematic review has looked at the  
53  
54  
55 151 comparative effectiveness of manual acupuncture (MA) and electroacupuncture (EA),  
56  
57  
58 152 but considered only direct evidence.<sup>40</sup> Furthermore, some rigorous randomized  
59  
60 153 clinical trials (RCTs) in this field published within recent years were not included in  
154  
155  
156 154 previous systematic reviews. For example, a multicenter RCT published in 2020 by

1  
2  
3  
4 155 our team suggested that acupuncture had potential benefits for KOA.<sup>41</sup> Thus, it is  
5  
6 156 important to perform a systematic review and meta-analysis to inform clinical  
7  
8  
9 157 practice.

## 11 158 **Objectives**

13  
14 159 We aim to evaluate the efficacy and safety of acupuncture for treating patients with  
15  
16 160 osteoarthritis of the knee by conducting a systematic review and meta-analysis. For  
17  
18  
19 161 this purpose, we put forward the following questions about this review:

- 21  
22 162 1. Is acupuncture effective for treating osteoarthritis of the knee compared with sham  
23  
24 163 control or no-acupuncture control?  
25  
26  
27 164 2. Is there a difference in the effectiveness between manual acupuncture and  
28  
29 165 electroacupuncture?

## 31 166 **2. METHODS AND ANALYSIS**

### 33 167 **Patients and public involvement**

35  
36 168 There will be no patients or public directly involved in this review. Only data already  
37  
38 169 existent in the literature and the aforementioned sources will be used for this study.

### 40 170 **Protocol registration.**

42  
43 171 This protocol was registered in PROSPERO (CRD42021232177). It will be followed  
44  
45 172 the standard methods of systematic review and meta-analysis. It will adhere to the  
46  
47 173 Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA)  
48  
49 174 reporting guidelines (see appendix 1).<sup>42 43</sup>

### 51 175 **Criteria for including studies in this review**

### 53 176 **Types of studies**

1  
2  
3  
4 177 RCTs (with or without blinding, including crossover design) of acupuncture therapy  
5  
6 178 for KOA will be included. We will consider including older RCTs that were cited in  
7  
8  
9 179 previous reviews of acupuncture for osteoarthritis.  
10

## 11 180 **Types of participants**

12  
13  
14 181 Studies enrolling participants diagnosed as KOA will be included. The diagnostic  
15  
16  
17 182 criteria should be based on the American College of Rheumatology clinical criteria,  
18  
19  
20 183 National Institute for Health and Clinical Excellence guidelines or any other accepted  
21  
22 184 guidelines.<sup>8 44</sup>There will be no restrictions on their age, sex, race, education, economic  
23  
24  
25 185 status, Kellgren-Lawrence score or Outbridge score.<sup>45 46</sup>  
26

## 27 186 **Types of Interventions**

28  
29  
30 187 The eligible intervention is acupuncture including manual acupuncture and  
31  
32  
33 188 electroacupuncture. There will be no restriction on the sessions of acupuncture,  
34  
35  
36 189 needling techniques or stimulation methods.  
37

## 38 190 **Types of control groups**

39  
40 191 In this review, we plan to compare needle acupuncture with sham acupuncture,  
41  
42  
43 192 analgesic, usual care or waiting list control groups. Acupuncture plus one or more  
44  
45  
46 193 therapies with the same therapies also will be included.  
47

## 48 194 **Outcomes**

### 49 195 **Primary outcome**

50  
51  
52  
53 196 Pain intensity: The WOMAC Pain Subscale, Visual Analog Scale (VAS), Brief Pain  
54  
55  
56 197 Inventory (BPI), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) or other  
57  
58  
59 198 validated outcome measures.  
60

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4 199 **Secondary outcomes**

5  
6 200 1. Function: The WOMAC Function Subscale, Lysholm Scale or other validated  
7  
8  
9 201 scales.

10  
11 202 2. Quality of life: The 12-Item Short Form Health Survey (SF-12), 36-Item Short  
12  
13  
14 203 Form Health Survey (SF-36), Assessment of Quality of Life Instrument (AQoL II) or  
15  
16  
17 204 other validated scales.

18  
19 205 3. Adverse events: Incidence and severity of adverse events

20  
21  
22 206 4. Drug use: Number of people using emergency analgesics, frequency or dosage of  
23  
24  
25 207 medication for KOA.

26  
27 208 5. Cost: incremental cost-effectiveness ratio of acupuncture treatment

28  
29  
30 209 **Criteria for excluding studies in this review**

31  
32 210 1. Participants with knee pain but no other criteria of KOA;

33  
34  
35 211 2. The intervention group received transcutaneous electrical nerve stimulation;

36  
37  
38 212 3. Studies reported only improvement rates;

39  
40 213 4. Studies comparing one type of acupuncture with other type of acupuncture (except

41  
42  
43 214 EA versus MA) and studies comparing acupuncture with complementary therapies or

44  
45 215 TCM.

46  
47  
48 216 **Search methods for identification of studies**

49  
50 217 **Electronic searches**

51  
52  
53 218 We developed search strategies for four English databases (PubMed, Embase,

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56 219 Cochrane Library databases, and Web of Science) and four Chinese databases (China

57  
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59 220 National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP

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4 221 Database for Chinese Technical Periodicals, and Wanfang) from database inception to  
5  
6 222 September 1, 2021. Additional trials will be identified by searching previous  
7  
8  
9 223 systematic reviews. No language or publication status restrictions are applied. The  
10  
11 224 search strategy components are clinical condition (osteoarthritis, chondromalacia  
12  
13  
14 225 patellae, knee, knee pain, and gonarthrosis), intervention (acupuncture,  
15  
16  
17 226 electroacupuncture, and acupuncture points) and study type (randomized controlled  
18  
19  
20 227 trial). We will adapt the search strategies to medical subject headings terms and  
21  
22 228 keywords as necessary for each database (see appendix 2 for the search strategy used  
23  
24  
25 229 in the PubMed database). A pilot of the systematic search was conducted on 28  
26  
27 230 February 2021 (see appendix 3). We (F-TY and C-YL) will rerun the searches before  
28  
29  
30 231 submission of the manuscript to identify any eligible articles published since our first  
31  
32  
33 232 search.

### 34 35 233 **Searching other sources**

36  
37 234 We will search the following websites as a supplement: the WHO International  
38  
39  
40 235 Clinical Trials Registry Platform and the National Institutes of Health clinical registry  
41  
42  
43 236 ClinicalTrials.gov and the Chinese Clinical Registry. The search will also include a  
44  
45  
46 237 manual search for gray literature (e.g., unpublished conference articles).

### 47 48 238 **Data collection and analysis**

#### 49 50 239 **Selection of studies**

51  
52  
53 240 All search results will be exported to EndNote, where we will check for and exclude  
54  
55  
56 241 duplicates. Two of us will screen all titles and abstracts independently to identify  
57  
58  
59 242 potentially relevant studies. Full texts will be downloaded and printed for further  
60

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4 243 assessment. Two reviewers will screen the whole-length articles to confirm whether  
5  
6 244 the studies meet the inclusion criteria. Any disagreement will be settled by discussion.  
7  
8  
9 245 If an agreement cannot be reached, a third reviewer will be consulted. The reasons for  
10  
11 246 excluding studies will be recorded. The study selection process is shown in figure 1.  
12  
13  
14 247 Besides, we will add a table of exclude studies with reasons for exclusion to the  
15  
16  
17 248 appendix of our meta-analysis.

### 19 249 **Data extraction and management**

21  
22 250 All data will be extracted independently and in duplicate by two reviewers with a  
23  
24 251 predesigned data extraction template. Disagreements will be settled by discussion. A  
25  
26  
27 252 third reviewer will be consulted if discrepancies cannot be resolved. All data will be  
28  
29  
30 253 cross-checked by two reviewers and transferred into Microsoft Office Excel. If  
31  
32 254 required, we will contact the corresponding authors for more information by email.

33  
34  
35 255 The predefined variables for extraction are the following:

- 36  
37 256 1. Publication details (study year, first author, funding source);
- 38  
39 257 2. Basic information (location, study type, number of centers, sample size, study  
40  
41 258 duration, and length of follow-up);
- 42  
43 259 3. Participants (type and/or stage of KOA, mean age, sex, and pain intensity before  
44  
45 260 treatment);
- 46  
47 261 4. Interventions (type of acupuncture, choice of acupuncture points, number of  
48  
49 262 sessions, treatment frequency, duration of each session, and needling techniques)
- 50  
51 263 5. Control (if there is any control, details of the treatment, including the name, dosage,  
52  
53 264 frequency and course);
- 54  
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4 265 6. Outcomes (data and time points for each measurement, type and number of adverse  
5  
6 266 events in each group).  
7  
8

9 267 **Risk of bias assessment in included studies**

10  
11 268 Two reviewers will assess the risk of bias in the included studies by using the  
12  
13 269 Cochrane Collaboration's tool for assessing risk of bias. We will assess each RCT a  
14  
15 270 low, high, or unclear risk of bias for 6 domains: selection bias (random sequence  
16  
17 271 generation and allocation concealment), performance bias (blinding of researchers and  
18  
19 272 participants), attrition bias (incomplete outcome data), ascertainment bias (blinding of  
20  
21 273 outcome assessment), reporting bias (selective outcome reporting) and other sources  
22  
23 274 of potential bias. Disagreements will be resolved by discussion, according to the  
24  
25 275 published articles and supplementary materials. We will consult the third reviewer  
26  
27 276 and contact the study authors when needed.  
28  
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30  
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34  
35 277 **Acupuncture adequacy assessment**

36  
37 278 We will use the adequacy assessment instrument to assess treatment adequacy in  
38  
39 279 acupuncture RCTs from the following 4 aspects of acupuncture treatment: choice of  
40  
41 280 acupuncture points, number of sessions, needling technique, and experience of the  
42  
43 281 acupuncturists<sup>47</sup>. Two assessors who are experienced acupuncturists will assess  
44  
45 282 adequacy independently and reach an agreement by discussion. They will be blinded  
46  
47 283 to the results of the study and the publication and conduct the assessments only based  
48  
49 284 on the description of the study population and the acupuncture procedure. To test the  
50  
51 285 success of the blinding, we will ask the assessors to guess the identity of each study.  
52  
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58 286 **Heterogeneity assessment**

1  
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3  
4 287 If there are sufficient data, we will conduct a meta-analysis to determine the efficacy  
5  
6 288 of acupuncture and the related factors.  $I^2$  testing will be used to quantify heterogeneity  
7  
8  
9 289 among the included studies.<sup>48</sup> We will present summary estimates in forest plots. If  
10  
11 290 the  $I^2$  is more than 50%, we will explore the possible sources of heterogeneity via  
12  
13  
14 291 meta-regression and subgroup analyses. If a meta-analysis is not appropriate, we will  
15  
16  
17 292 conduct a descriptive synthesis using a best-evidence synthesis approach.

### 19 293 **Reporting bias assessment**

21  
22 294 We will also consider assessing the reporting bias and small-study effects by using  
23  
24 295 funnel plots when there are 10 or more trials. We will assess funnel plot asymmetry  
25  
26  
27 296 by using Begg's and Egger's tests and will define significant publication bias as a p  
28  
29  
30 297 value < 0.1. We will also use a trim-and-fill computation to estimate the effect of  
31  
32  
33 298 publication bias on the interpretation of the results.<sup>49</sup>

### 35 299 **DATA SYNTHESIS**

37  
38 300 When the meta-analysis is performed, Stata 16.0 and RevMan 5.3 will be used for all  
39  
40 301 statistical calculations. All the analyses will be based on the random-effects model  
41  
42  
43 302 because the RCTs included by us came from different populations. For dichotomous  
44  
45 303 variables, Mantel-Haenszel method will be used for analyses and effect size will be  
46  
47  
48 304 reported as relative risk (RR) with 95% confidence intervals (CIs). For continuous  
49  
50  
51 305 variables, inverse variance method will be used for analyses and treatment effect will  
52  
53  
54 306 be reported as mean difference (MD) with 95% CIs. The standardized mean  
55  
56 307 difference (SMD) with 95% CIs will be used if different scales are used to evaluate a  
57  
58  
59 308 predesigned outcome.

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4 309 For pain variance, we plan to pool data from previous studies reporting VAS 100  
5  
6 310 mm, VAS 10 cm, and NRS by transforming it to a “0-100-pain measure” using an  
7  
8  
9 311 appropriate multiplier. We also intend to analyze pain intensity by independently  
10  
11  
12 312 reporting the aforementioned scales.

### 13 14 313 **SUBGROUP ANALYSIS**

15  
16  
17 314 Subgroup analyses will be performed to explain the heterogeneity. Predefined  
18  
19 315 subgroups include the location of studies, the type of intervention, the dosage of  
20  
21  
22 316 acupuncture, the stage of knee osteoarthritis, and the TCM types of KOA.

### 23 24 317 **SENSITIVITY ANALYSIS**

25  
26  
27 318 We will conduct a sensitivity analysis to verify the robustness of the review  
28  
29 319 conclusions. We will consider removing one study at a time to observe its effect on  
30  
31  
32 320 heterogeneity and effect size. In addition, the meta-analysis will be repeated after  
33  
34  
35 321 studies with lack of allocation concealment are excluded.

### 36 37 322 **OTHER ANALYSIS**

38  
39  
40 323 If manual acupuncture and eletroacupuncture are effective for KOA compared with  
41  
42 324 sham acupuncture, we will conduct the exploratory research to compare the difference  
43  
44 325 in the effectiveness between MA and EA by synthesizing the evidence from direct  
45  
46  
47 326 comparison and indirect comparison. For direct comparison results, we will use  
48  
49 327 Revman to analyze. For the indirect comparison, we will choose sham acupuncture as  
50  
51  
52 328 a common comparator and use R software to analyze. Finally, we will conduct a  
53  
54  
55 329 mixed treatment comparison meta-analysis (MTC) to synthesize the evidence from  
56  
57  
58 330 direct comparison and indirect comparison.  
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4 **331 Strength of recommendations and the quality of evidence**

5  
6  
7 332 We will assess the strength of recommendations based on the Grading of  
8  
9 333 Recommendations Assessment Development and Evaluation (GRADE) working  
10  
11 334 group methodology. The two categories of weak/conditional evidence and strong  
12  
13  
14 335 evidence will be used.

15  
16  
17 336 We will also assess the quality of evidence. The quality of evidence will be assessed  
18  
19 337 according to the domains of risk of bias, consistency, directness, precision, and  
20  
21  
22 338 publication bias. The assessments will be adjudicated into four levels: high, moderate,  
23  
24  
25 339 low or very low.<sup>50 51</sup>

26  
27 **340 DISCUSSION**

28  
29  
30 341 This systematic review will be performed based on previous studies of acupuncture  
31  
32 342 for knee osteoarthritis. Conclusions drawn from this review may be beneficial to  
33  
34  
35 343 patients with KOA, clinicians and policy makers. We will summarize and explain the  
36  
37  
38 344 characteristics and findings of the included studies by conducting a systematic  
39  
40  
41 345 narrative synthesis.

42  
43 346 Based on the above, we want to conduct some exploratory studies. (1) Is there a  
44  
45 347 difference in the effectiveness between manual acupuncture and electroacupuncture?  
46  
47  
48 348 (2) Is the efficacy (if any) related to the stage of knee osteoarthritis according to the  
49  
50  
51 349 Kellgren-Lawrence score or Outbridge score, some characteristics of acupuncture  
52  
53  
54 350 (e.g., treatment frequency), type of control group, measurement time points of  
55  
56  
57 351 outcomes or other variables?

58  
59 352 Manual acupuncture and electroacupuncture are the most commonly used  
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4 353 acupuncture therapies. Manual acupuncture maintains a moderate dose of stimulation  
5  
6 354 by lifting, inserting and twisting needles to acupoints. However, it is laborious and  
7  
8  
9 355 difficult to reach an agreement on standards because of the different needle techniques.  
10  
11 356 Electroacupuncture, which is widely used in clinical practice, refers to the pulse  
12  
13  
14 357 current input to acupoints on the basis of needle acupuncture. This approach can  
15  
16  
17 358 accurately control the dose of stimulation and save labor. In clinical trials for pain  
18  
19  
20 359 conditions, better analgesia appears to be obtained when electrical stimulation is  
21  
22 360 added to manual stimulation than with manual acupuncture needle stimulation  
23  
24  
25 361 alone.<sup>52</sup> However, the findings may not be generalizable because of the different pain  
26  
27 362 types.

28  
29  
30 363 There are many factors affecting the efficacy of acupuncture. One review presented  
31  
32 364 “the challenge of adequacy of dose” recently.<sup>33</sup> Our group built a scoring instrument  
33  
34  
35 365 to calculate the dose of acupuncture from four parameters.<sup>53</sup> Based on the sum of the  
36  
37  
38 366 scores, we defined three doses of acupuncture treatment: high dosage, medium dosage  
39  
40  
41 367 and low dosage. And we designed three subgroups according the three kinds of  
42  
43  
44 368 dosage to explore the relationship between doses of acupuncture and efficacy. Deqi  
45  
46 369 response is a comprehensive sensation of soreness, numbness, heaviness, aching at  
47  
48  
49 370 and around acupoints produced by manipulation of the needles. It plays a role in  
50  
51  
52 371 acupuncture dosage so it is only one dimension of our scoring instrument. On the one  
53  
54  
55 372 hand, not all types of acupuncture need a Deqi response during sessions. For example,  
56  
57  
58 373 manual acupuncture and electroacupuncture are required to cause a Deqi response  
59  
60 374 while wrist-ankle acupuncture is not. Furthermore, electrical stimulation can enhance

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4 375 Deqi response elicited by manipulation of needles. Based on the different duration of  
5  
6 376 active stimulation, it is necessary to compare the effectiveness of manual acupuncture  
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8  
9 377 and electroacupuncture.<sup>54</sup> On the other hand, Deqi response is more emphasized in  
10  
11 378 China than Western.<sup>55</sup>

12  
13  
14 379 Acupuncture has both specific effects caused by intervention itself and non-specific  
15  
16 380 effects including patient-acupuncturist relationship, patient expectations, etc. Sham  
17  
18 381 acupuncture group has usually been set in order to eliminate non-specific effects. The  
19  
20 382 sham acupuncture can be divided into superficial insertion and non-penetrating  
21  
22 383 insertion at traditional acupuncture points or not.<sup>56</sup> Superficial insertion is not a  
23  
24 384 physiologically inert procedure and thus decreases the difference between groups.<sup>57</sup>  
25  
26 385 Therefore, more and more trials choose non-penetrating sham acupuncture at  
27  
28 386 non-acupoints as control to minimize the physiological effects of sham acupuncture.  
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34  
35 387 The proposed review has several strengths. We plan to search multiple Chinese and  
36  
37 388 English language databases to ensure a comprehensive search of the literature. Any  
38  
39 389 meta-analyses will be performed according to the Cochrane Handbook for Systematic  
40  
41 390 Reviews of Interventions. A further strength is that stringent eligibility criteria will be  
42  
43 391 applied to ensure the quality of the included RCTs. In addition, pain intensity was  
44  
45 392 selected as the targeted outcome because it plays an important role in the pain  
46  
47 393 management of KOA. Transformation of pain scores measured by different pain  
48  
49 394 scales to a 0-100 pain measure will result in loss of some accuracy; however, we  
50  
51 395 believe that it is clinically irrelevant.  
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## 58 396 **Ethics and dissemination**

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4 397 Ethics approval is not required because individual patient data are not included. This  
5  
6 398 protocol was registered in the international Prospective Register of Systematic  
7  
8  
9 399 Reviews on 25 February 2021. The systematic review and meta-analysis will be  
10  
11 400 submitted for publication in a peer-reviewed journal. The findings will also be  
12  
13  
14 401 disseminated through conference presentations.

15  
16  
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18  
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20  
21  
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23  
24 405 designed the systematic review. C-YL and L-LL drafted the manuscript. J-WY, J-FT,  
25  
26  
27 406 L-QW and Myeong Soo Lee provided help to design and edited the manuscript. C-YL  
28  
29 407 and F-TY will independently screen the eligible studies. C-YL and X-WH will extract  
30  
31 408 data from included articles. J-LL and J-FT will assess the risk of bias. C-YL and  
32  
33  
34 409 X-TS will assess acupuncture adequacy, Strength of recommendations and the quality  
35  
36  
37 410 of evidence. C-YL, L-YQ and S-YY will finish data synthesis. L-QW will arbitrate  
38  
39 411 any disagreements during the review. All authors have read the manuscript and  
40  
41 412 approved the final publication of the protocol.

42  
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45  
46  
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48  
49 415 **Competing interests:** None declared

50  
51 416 **Patient consent for publication** Not required.

52  
53 417 **Provenance and peer review** Not commissioned; externally peer-reviewed.

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6 575 **Figure legends**

7 576 **Figure 1** Flow diagram of the study selection process. KOA, knee osteoarthritis.

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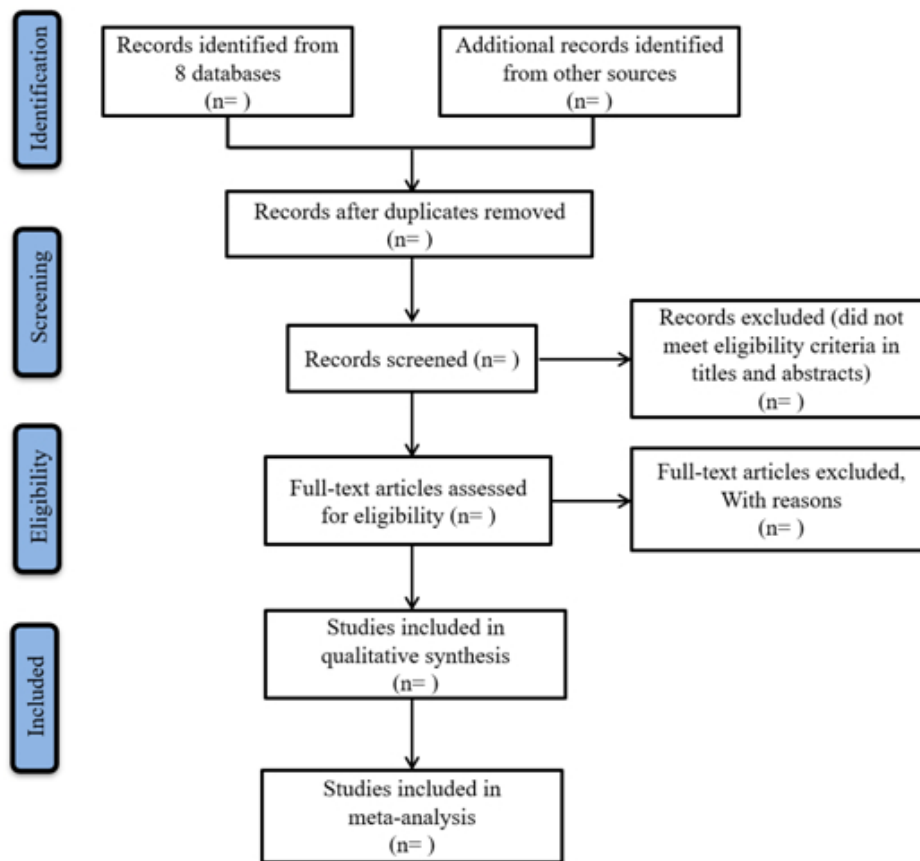


Figure 1 Flow diagram of the study selection process. KOA, knee osteoarthritis.



**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	19
Sponsor	5b	Provide name for the review funder and/or sponsor	19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	19
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11 Appendix2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12

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3	Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
4			11-12
5	Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
6			12
7	Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
8			12-13
9	Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
10			9-10
11	Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
12			13
13	Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
14			14
15		15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )
16			14
17		15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
18			15
19		15d	If quantitative synthesis is not appropriate, describe the type of summary planned
20			14
21	Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
22			14
23	Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)
24			16

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

**Table 1 Search strategy used in the PubMed database**

#	Searches
1	Osteoarthritis, Knee[mesh]
2	Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract]
3	Patellofemoral Pain Syndrome[mesh]
4	Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract]
5	knee pain[Title/Abstract]
6	gonarthrosis[Title/Abstract]
7	OR/1-6
8	Acupuncture[mesh]
9	Pharmacopuncture[Title/Abstract]
10	Acupuncture Therapy[mesh]
11	Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract]
12	Electroacupuncture[mesh]
13	Acupuncture Points[mesh]
14	Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract]
15	OR/8-14
16	clinical[tiab]
17	trial[tiab]
18	16 AND 17
19	clinical trials as topic[mesh]
20	clinical trial[pt]
21	random*[tiab]
22	random allocation[mesh]
23	therapeutic use[sh]
24	OR/18-23
25	7 AND 15 AND 24

**Result of presearch in the PubMed database**

1. Osteoarthritis, Knee[mesh] Items found: 21,147
  2. Knee Osteoarthritides OR Knee Osteoarthritis OR Osteoarthritis of Knee OR Osteoarthritis of the Knee OR Osteoarthritis, Knee OR KOA[Title/Abstract] Items found: 40,291
  3. Patellofemoral Pain Syndrome[mesh] Items found: 934
  4. Pain Syndrome, Patellofemoral OR Anterior Knee Pain Syndrome OR Patellofemoral Syndrome OR Patellofemoral Pain OR Pain, Patellofemoral OR Patellofemoral Pains[Title/Abstract] Items found: 3,799
  5. knee pain[Title/Abstract] Items found: 8,083
  6. gonarthrosis[Title/Abstract] Items found: 1,095
  7. OR/1-6 Items found: 47,408
  8. Acupuncture[mesh] Items found: 1735
  9. Pharmacopuncture[Title/Abstract] Items found: 211
  10. Acupuncture Therapy[mesh] Items found: 25,321
  11. Acupuncture Treatment OR Acupuncture Treatments OR Treatment, Acupuncture OR Therapy, Acupuncture OR Pharmacoacupuncture Treatment OR Treatment, Pharmacoacupuncture OR Pharmacoacupuncture Therapy OR Therapy, Pharmacoacupuncture[Title/Abstract] Items found: 2996
  12. Electroacupuncture[mesh] Items found: 4128
  13. Acupuncture Points[mesh] Items found: 6934
  14. Acupuncture Point OR Point, Acupuncture OR Points, Acupuncture OR Acupoints OR Acupoint[Title/Abstract] Items found: 6,284
  15. OR/8-14 Items found: 27,954
  16. clinical[tiab] Items found: 3,720,276
  17. trial[tiab] Items found: 638,665
  18. 16 AND 17 Items found: 294,477
  19. clinical trials as topic[mesh] Items found: 353,132
  20. clinical trial[pt] Items found: 884,322
  21. random\*[tiab] Items found: 1,202,203
  22. random allocation[mesh] Items found: 104,737
  23. therapeutic use[sh] Items found: 4,516,532
  24. OR/18-23 Items found: 5,668,908
  25. 7 AND 15 AND 24 Items found: 397
- Final Result: 397 (By 28 February 2021)