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[Intervention Protocol]

Cupping therapy for chronic non-specific low back pain

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of cupping therapy for people with chronic non-specific LBP.

BACKGROUND

Description of the condition

Low back pain (LBP) is a highly prevalent health condition worldwide, and the main cause of years lived with disability, absenteeism, and high medical expenses (Balague 2016; Wu 2020). It is a symptom rather than a disorder and can be defined as pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without pain referred to the leg(s) (Hartvigsen 2018). The majority of people with LBP are classified as having non-specific LBP, of which there is no identifiable cause of the symptoms, and only a small portion of these individuals may have a serious underlying disease, or suffer from radicular pain or spinal canal stenosis (Hartvigsen 2018; Maher 2017). It is projected that more than 800 million people will have LBP globally in 2050 (GBD 2023). LBP also places an economic burden on society, which spends up to USD 28.2 billion annually on patient management in the United States (Dagenais 2008).

The management of non-specific LBP typically involves a multimodal approach aimed at reducing pain, improving function, and preventing recurrences or flare-ups (de Oliveira 2019). Advice to remain active, reassurance on the favourable prognosis, and pain education should be provided to all patients presenting with non-specific LBP in primary care (Almeida 2018; NICE Guideline 2020). Best evidence recommends exercise therapy, manual therapies, and psychological interventions (Almeida 2018; Hayden 2021; NICE Guideline 2020; Saragiotto 2016; Yamato 2015). Pharmacological therapies are often recommended if conservative management does not produce the expected results, and most guidelines do not recommend passive therapies (e.g. electrophysical agents), surgery, or other invasive therapies for managing LBP (Almeida 2018).

Description of the intervention

Cupping therapy (also known as vacuum cupping or hijama) is used as part of non-pharmacological and complementary therapies for non-specific LBP (Al-Bedah 2019). The technique includes the use of glass, plastic, or bamboo cups to achieve suction of the skin and hypodermis through a mechanical or thermal negative pressure and causing a vacuum in subcutaneous tissues (Al-Bedah 2019; Qureshi 2017). Cupping therapy consists of various treatment techniques (Aboushanab 2018). The most common form is dry cupping, where cups are placed on the skin to create suction without additional procedures (Moura 2018). This is theorised to promote blood flow and decrease muscle tension (Choi 2021). Wet cupping involves creating suction, making small incisions on the skin, and then reapplying the cups to draw out a small amount of blood, a technique believed to aid in detoxification and improve circulation (Mardani-Kivi 2019). Pulsatile cupping involves a mechanical device with flexible silicone or plastic cups that generate a pulsating negative pressure, believed to provide a more controlled and dynamic stimulation of the skin and underlying tissues (Teut 2018). Massage cupping is performed by applying massage oil to the skin and moving suction cups across the body, which is theorised to enhance circulation and create a deep tissue massage-like effect (Aboushanab 2018; Al-Bedah 2016). The suction power of the cups can vary from light to medium, strong, and pulsatile, while the suction methods can involve the use of fire, manual manipulation, or automatic devices (Al-Bedah 2019; Mehta 2015; Qureshi 2017; Zhang 2021). Cupping therapy can also be used with additional therapies (i.e. herbs, water, ozone, moxa, needle, laser, electrical, magnetic) and for a range of different conditions and purposes, such as cosmetic, sports-related, facial, and musculoskeletal conditions (Al-Bedah 2019; Qureshi 2017). After the application, the appearance of bruises (so-called cupping marks) may occur, which vary from light pink to dark red and disappear within a period of up to 10 days (Qureshi 2017).

How the intervention might work

The mechanism of action of cupping therapy is not well understood (Al-Bedah 2019). Clinicians trained in Western medical sciences primarily approach the biomedical causes of disease to understand the therapeutic effects, while traditional medicine practitioners embrace a holistic approach that encompasses various aspects of an individual's well-being. These views conflict with the understanding of the mechanism of action of this therapy. That being said, numerous theories have been proposed to explain the effects and mechanisms of action of cupping therapy.

In the context of pain reduction, some authors have suggested the pain-gate theory by Melzack & Wall (Melzack 1965), the diffuse noxious inhibitory controls (i.e. cupping triggers the release of chemicals in the body that can reduce the perception of pain) (Le Bars 1991), and reflex zone theory (i.e. stimulating specific areas can have therapeutic effects on various parts of the body) (Lett 2000). However, there is no validation of such theories by clinical studies testing cupping therapy (Al-Bedah 2019). Other authors hypothesise that cupping therapy increases circulation in the area around its placement and promotes muscle relaxation, explained by a release of nitric oxide theory (Al-Bedah 2019; Wang 2017; Zeng 2016). Cupping therapy has also been linked with the activation and strengthening of the immune system through the induction of local inflammation, activating the complementary system, and increasing the production of immune products (i.e. interferon and tumour necrotising factor) (Al-Bedah 2019; Zeng 2016). Recent findings using computer simulation found a significant decrease in the abundance of haemoglobin β subunit in cupping-induced blister fluid, proposing a hemorphin-based analgesia as a probable explanation (Song 2023). It is also important to acknowledge the existence of the placebo effect, which could contribute to the observed analgesic effects of cupping therapy in clinical trials. Finally, more extensive research is required to comprehend these mechanisms and confirm their role in the therapeutic effects of cupping therapy.

Why it is important to do this review

The existing literature summarising the effects of cupping therapy for non-specific LBP is limited, making any clinical recommendation difficult. Previous systematic reviews lack methodological rigour and suffer from biases (e.g. no interpretation of certainty of the evidence, no proper risk of bias assessment in included studies, no meta-analysis), or limited the outcomes investigated (Huang 2013; Shen 2022; Wang 2017; Wood 2020; Yuan 2015; Zhang 2024). Additionally, with the emergence of new clinical trials (Almeida 2021; Salemi 2021), a comprehensive and systematic review is needed to synthesise the latest evidence, identify any gaps or inconsistencies, and provide a reliable assessment of the therapy's potential benefits and safety. This review will focus specifically on chronic non-specific LBP, as it represents the most common and persistent form of LBP encountered in clinical practice, is associated with higher healthcare utilisation

and disability burden, and is typically the target population for complementary and alternative interventions such as cupping therapy (Hoy 2010; van Tulder 2005. A well-conducted Cochrane review with meta-analysis is thus important to better inform clinicians, patients, and policymakers about the effectiveness of cupping therapy in people with chronic non-specific LBP.

OBJECTIVES

To assess the benefits and harms of cupping therapy for people with chronic non-specific LBP.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs (qRCTs) (trials that use quasi-random methods of allocation, such as alternation and date of birth), and cross-over RCTs. Although RCTs are the gold standard to assess the effectiveness of health-related interventions, quasi-RCTs will be considered as the overall literature on cupping therapy is expected to be scarce.

Types of participants

We will include adult participants (≥ 18 years) of both sexes, with non-specific chronic LBP. We will define chronic LBP as pain lasting longer than 12 weeks with or without leg pain or numbness in the legs. We will consider general populations, mixed conditions (e.g. subacute and chronic pain) and symptom characteristics (e.g. signs and symptoms of radiculopathy) if most participants have chronic LBP (≥ 80% total sample). We will consider participants recruited from any healthcare setting.

We will exclude studies that enrolled individuals with LBP caused by specific pathologies (i.e. disc herniation, spinal stenosis, fracture, axial spondyloarthritis, infection, and malignancy). We will also exclude studies occurring during pregnancy and after surgery.

Types of interventions

We will consider studies that use any specific technique and form of delivery of cupping therapy. There is no consensus on the ideal application time or suction force, but a treatment period of between 5 and 10 minutes with a negative pressure of 300 millibars (two manual suction pump suction) has been recommended for LBP (Al-Bedah 2016; Markowski 2014; Moura 2018). Cupping therapy could be delivered individually or combined with other interventions (e.g. cupping therapy plus physical rehabilitation). We will consider combined interventions where cupping therapy is the main component during the sessions or the total study intervention. Cupping therapy could be delivered by any certified healthcare professional or a therapist with previous training. We will include all types of cupping therapy in this review (e.g. wet, dry, massage, pulsatile).

We will compare cupping therapy against the following.

- Sham cupping: a simulated procedure using specially modified cups that prevent real suction. This method mimics the experience of cupping without delivering the therapeutic effect, allowing participant blinding.
- Minimal intervention: this includes no treatment, waiting list, or usual care.
- Combination therapy controls: studies in which both the cupping and comparison groups receive an additional co-intervention (e.g. all participants receive exercise or medication).

Usual care refers to the standard management that patients would typically receive outside a trial context. It is not standardised or delivered under controlled conditions by the study investigators. It may include medication, advice or education, self-management strategies, or general practitioner care, depending on local clinical practices. When usual care involves no structured or active therapeutic component, it will be grouped under minimal intervention for the purpose of analysis. Otherwise, it will be considered a distinct comparator.

We will not include studies comparing cupping therapy to other active interventions (e.g. exercise, manual therapy, pharmacological therapy).

To maintain interpretability, we will categorise and analyse comparisons separately based on the nature of the control condition, as follows.

- Cupping therapy versus sham (main comparison)
- Cupping therapy versus minimal intervention
- Cupping therapy plus co-intervention versus co-intervention alone

Types of outcome measures

Major outcomes

- Pain: measured by reliable and valid self-report continuous outcome in the following order of preference: visual analogue scale (VAS), numerical rating scale (NRS), a scale within a composite pain measure (e.g. McGill Pain Questionnaire (Melzack 1975), other algofunctional scales).
- Disability: analysed by continuous validated scales in the following order of preference: Roland-Morris Disability Questionnaire (RMDQ) (Roland 2000; Yamato 2017), Oswestry Disability Index (ODI) (Fairbank 1980), or other algofunctional scales.
- Health-related quality of life: we will synthesise health-related quality of life outcomes using one of a prioritised list of measures, as available: SF-36 or SF-12 (Ware 1992), PROMIS-GH-10 (Hays 2009), EQ-5D (EuroQol Group 1996), CDC HRQOL-14 (or other versions) (Moriarty 2003) (Health-Related Quality of Life) (Guyatt 1993), WHOQOL-BREF (World Health Organization Quality of Life Scale) (THE WHOQOL GROUP 1998), NHP (Nottingham Health Profile) (Wiklund 1990), QOLS (Quality of Life Scale) (Burckhardt 2003), or SIP (Sickness Impact Profile) (Bergner 1976). For the SF-36, SF-12, or PROMIS-GH-10, we will separately synthesise the physical and mental component scores, as recommended.
- Psychological functioning (anxiety and depression): measured as a continuous outcome in the following order of preference: Hospital Anxiety and Depression Scale (Zigmond 1983), Spielberger State-Trait Anxiety Inventory (Skapinakis 2014), Center for Epidemiological Studies Depression Scale (Lewinsohn 1997), Beck Depression Inventory (Dozois 1998), or other scales.

- Adverse events: we will document all reported adverse events, including mild adverse events, such as transient and self-resolving events (e.g. minor pain, mild bruising, or temporary skin marks) that do not require medical intervention, and treatment-specific adverse events which are more severe than mild adverse events (e.g. significant skin infections or severe burns) and may require medical intervention, but that do not necessitate hospitalisation or result in long-term disability.
- Withdrawals due to adverse events: situations where adverse effects are significant enough for participants to decide not to continue with the intervention. We will also record withdrawals due to other reasons, such as inefficacy or other.
- Global improvement or perceived recovery: measured by the Global Perceived Effect Scale (Kamper 2010) or other algofunctional scale, preferentially; or by dichotomous measures such as proportion reporting participant-reported global impression of clinical change (much or very much improved), or similar measure (e.g. proportion achieving 30% reduction in pain), or proportion reporting a good or excellent outcome, or any other definition of 'success' as reported in the trials, extracted as a dichotomous measure.

Timing of outcome assessments

We will extract and report outcome data across the following time periods.

- Immediate (end of treatment): follow-up measured within one week before or after the final cupping session. This will be the primary time point for analysis, as cupping therapy is hypothesised to have immediate effects similar to other passive physical interventions (e.g. needling, manual therapy).
- Short term: follow-up measured more than 1 week and up to 12 weeks after the end of treatment.
- Medium term: follow-up measured more than 12 weeks and up to 24 weeks post-treatment.
- Long term: follow-up measured more than 24 weeks (i.e. > 6 months) after the end of treatment. When multiple long-term time points are reported, we will prioritise those closest to 12 months.

If more than one time point is reported within the same time frame, we will extract the one closest to the defined cutoff (i.e. closest to the end of treatment for immediate, 12 weeks for short term, 24 weeks for medium term, and 12 months for long term).

Search methods for identification of studies

Electronic searches

We will search the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE via OvidSP (1946 to current);
- Embase via OvidSP (1980 to current);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL EBSCO; 1982 to current);
- Physiotherapy Evidence Database (PEDro; 1999 to current);
- Latin American and Caribbean Health Science Information database (LILACS; 1982 to current);
- Wanfang Data (1950 to current);
- China National Knowledge Infrastructure database (CNKI; 1996 to current).

We will base search strategies on the methods described by Cochrane Musculoskeletal and the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022). The search strategy is available in Appendix 1. We will adapt the electronic search for all databases. There will be no restrictions on search date, language, or publication status.

We will conduct searches in Chinese language databases (e.g. Wanfang, CNKI) by adapting our search strategy from MEDLINE, with the assistance of a native Chinese-speaking colleague. They will review the selected search terms and translate them appropriately to ensure they align with the terminology used in Chinese databases.

We will search trial register websites, including ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/), to identify ongoing clinical trials.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search for errata or retractions from included studies published in full text on PubMed (pubmed.ncbi.nlm.nih.gov/) and report the date this was done within the review.

Data collection and analysis

Selection of studies

One review author (HJ) will conduct the electronic database searches and import the search results into EndNote reference management software for de-duplication (EndNote), and then import them into Covidence for the screening process (Covidence). Two review authors (HJ and LJ) will independently screen the titles and abstracts of records identified by the search for potential relevance. We will retrieve the full-text study reports/publications of all potentially eligible studies, and two review authors (HJ and LJ) will independently screen the full texts and identify studies for inclusion, and record the reasons for exclusion of ineligible studies. We will resolve any disagreements through discussion or in consultation with a third review author (BS) if required. We will identify and exclude duplicates and collate multiple reports of the same study under a single reference ID so that each study, rather than each report, is the unit of interest in the review. We will contact study authors to request additional information, such as missing details on methods or results, as needed to determine eligibility. We will report the study selection process in sufficient detail to complete a PRISMA flow diagram (PRISMA Group 2020). We anticipate that some articles from Chinese language databases may not have a translated title, abstract, or full text; in such cases, we will collaborate with native Chinese-speaking colleagues to assist with translation and data extraction.

Data extraction and management

We will use a data collection form for study characteristics and outcome data that has been piloted on at least one study in the review. One review author (LJ) will extract study characteristics from the included studies. A second review author (HJ) will spot-

check the study characteristics for accuracy against the trial report. We will extract the following study characteristics.

- Bibliometric data (i.e. author, year of publication, and language).
- Methods (i.e. study design, settings, sample size, and country).
- Participants (i.e. sex, age, race/ethnicity, socioeconomic status of participants, time of symptoms, inclusion and exclusion criteria, and severity of the condition).
- Interventions (i.e. type of suction cup, technique, form of delivery, adherence, session frequency, session duration, total study time, co-intervention and medicines).
- Outcomes (i.e. name of the measurement instrument used, its measurement properties (e.g. scale from 0 to 10), and interpretation of values (e.g. 0 = no pain, 10 = worst possible pain). For dichotomous outcomes, we will extract the number of events and number of participants per group. For continuous outcomes, we will extract means and standard deviations per group).
- Time periods for outcome assessment (i.e. immediate (≤ 2 weeks), short (greater than 2 weeks and < 6 months), long (≥ 6 months) after randomisation).
- Notes (i.e. trial registration (prospective/retrospective registered), sources of funding, and conflicts of interest).

Two review authors (LJ and HJ) will independently extract outcome data from the included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way and when data were transformed or estimated from a graph. We will resolve disagreements by consensus or by involving a third review author (BS). One review author (LJ) will transfer data into the RevMan file (RevMan 2024). We will double-check that data have been entered correctly by comparing the data presented in the systematic review with the study reports.

We will use WebPlotDigitizer to extract data from graphs or figures (WebPlotDigitizer). These data will also be extracted in duplicate.

We will use the following decision rules to select which data to extract in the event of multiple outcome reporting, including:

- if both final values and change-from-baseline values are reported for the same outcome, we will use change scores;
- if both unadjusted and adjusted values for the same outcome are reported, we will use unadjusted values;
- if data are analysed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we will use ITT data.

Assessment of risk of bias in included studies

Two review authors (WR and HJ) will independently conduct the risk of bias assessment for randomised trials using the Cochrane RoB 1 tool (Appendix 2) (Higgins 2017). We will resolve any disagreements by discussion or by involving another review author (BS). We will assess risk of bias according to the following domains.

- Selection bias (method of randomisation, treatment allocation concealment).
- Performance bias (blinding of participants and care provider).
- Detection bias (blinding of outcome assessors).
- Attrition bias (missing outcome data/dropouts).
- Reporting bias (selective outcome reporting).
- Other bias: unequal application of co-interventions across treatment groups, unit of analysis issues, unplanned interim analysis; unequal cross-over of participants from one treatment group to another (e.g. from usual care control to cupping); and design-specific issues such as inadequate wash-out period in a cross-over trial (i.e. at least one month).

We will classify each potential source of bias as low, high, or unclear risk and report judgements for each domain in a risk of bias table.

We will summarise the risk of bias judgements across different studies for each of the domains listed.

We will present the graphs generated by the RoB 1 tool to provide a summary assessment of the risk of bias.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse continuous data using mean difference (MD) or standardised mean difference (SMD), depending on whether the same scale is used across studies, and 95% confidence intervals (CIs). We will analyse dichotomous data using risk ratios (RR) and 95% CIs. Pain and disability outcomes will be adjusted to a 0-to-100 scale and analysed using MDs and 95% CIs. Previous evidence indicates that standard measures of disability, such as the RMDQ and the ODI, are correlated and similarly responsive to the pool in the meta-analysis (Chiarotto 2016). When using SMDs, we will back-translate the estimates to a typical scale by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial) to improve interoperability (Higgins 2023a).

We will categorise effect sizes as small (MD 10% to 20% of the scale; SMD 0.2 to 0.5), moderate (MD 20% to 30% of the scale; SMD 0.5 to 0.8), and large (MD > 30% of the scale; SMD > 0.8). For continuous outcomes, we will consider a 15-point change on a 0-to-100 scale, or 15% of the scale (SMD 0.4), the minimum clinically important difference (MCID) (Ostelo 2008); for dichotomous outcomes, we will define clinical relevance based on absolute risk differences (ARDs) and relative risk reductions (RRRs). We will consider an absolute risk reduction (ARR) of ≥ 10% or an RRR of ≥ 25% (RR ≤ 0.75 or ≥ 1.25) as clinically meaningful. For rare but serious outcomes (e.g. severe adverse events), we will consider a smaller ARR of 5% clinically important.

Unit of analysis issues

We will consider the participant as the main unit of analysis for all trials. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting. If we identify cross-over trials, we will extract data from the first phase of the trial to avoid potential carry-over effects; if no data are available for the first phase, we will attempt

to approximate a paired analysis by imputing missing standard deviations, according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023).

Dealing with missing data

We will contact the trial investigators or sponsors to verify key features of the trial and to obtain missing numerical outcome data where possible (for example, when a trial is identified as abstract only, or when data are not available for all participants). Where this is not possible, and missing data are considered to introduce severe bias, we will explore the impact of including such studies on the overall assessment of outcomes through a sensitivity analysis. Any assumptions and imputations to deal with missing data will be clearly described, and the effect of imputation explored by sensitivity analyses. Where possible, missing standard deviations will be computed from other statistics such as standard errors, CIs, or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). If standard deviations cannot be calculated, they will be imputed (e.g. from other studies in the review).

Assessment of heterogeneity

We will assess clinical and methodological diversity in terms of participants, interventions, outcomes, and study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will be conducted by observing the data from the data extraction tables. We will assess statistical heterogeneity by visual inspection of the forest plot to look for obvious differences in results between the studies, and using the I^2 and Chi^2 statistical tests.

We will interpret the I^2 statistic as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022), where an I^2 value of:

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity; and
- 75% to 100% represents considerable heterogeneity.

As noted in the *Cochrane Handbook* (Deeks 2022), we will keep in mind that the importance of I^2 depends on: (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity.

We will consider a Chi^2 test where a P value ≤ 0.10 as indicating statistical heterogeneity.

If we identify substantial heterogeneity, we will report it and investigate possible causes according to the recommendations in Section 10.10 of the *Cochrane Handbook* (Deeks 2022).

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small-study biases. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry as outlined in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, following the recommendations in Section 13.3 of the *Cochrane Handbook* (Page 2020).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the WHO ICTRP (trialsearch.who.int/) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will group and analyse studies based on the following planned comparisons.

- Cupping therapy versus placebo/sham cupping (main comparison).
- Cupping therapy versus minimal interventions (no treatment, waitlist control, or usual care). When usual care includes a structured or active therapeutic component, it will be grouped as a separate comparator (i.e. cupping therapy versus usual care).
- Cupping therapy plus co-intervention versus co-intervention alone.

We will assess the clinical and methodological diversity of the included studies, in terms of participants, interventions, outcomes, and study characteristics, to determine whether meta-analysis is appropriate. We plan to pool outcomes from trials with similar characteristics (participants, interventions, and common comparators, outcome measures, and timing of outcome measurement) to provide estimates of benefit and harm. We will present the results for each outcome by grouping studies with the intervention and a common comparator, as listed above. Within a comparison, we will pool data for each outcome in a meta-analysis and display the results in forest plots.

We plan to synthesise effect estimates using a random-effects meta-analysis model, based on the assumption that clinical diversity is likely to exist, and that different studies are estimating different intervention effects. For continuous outcomes, we will use generic inverse variance. For dichotomous outcomes, we will use the Mantel-Haenszel method. For both continuous and dichotomous outcomes, we will use the DerSimonian and Laird method for estimating heterogeneity and the Wald-type method for calculating 95% CIs for the summary effect (DerSimonian 1986).

We will perform random-effects meta-analyses using RevMan software (RevMan 2024). The primary analysis will include all trials regardless of their risk of bias.

If interventions and outcomes are too dissimilar to be included in a meta-analysis, we will present effect estimates and 95% CIs of each trial in tables, and summarise the results in the text (McKenzie 2022).

We will categorise and analyse data based on the timing of outcomes postrandomisation, specifically into immediate (≤ 2 weeks), short-term (greater than 2 weeks and less than 6 months), and long-term (≥ 6 months) periods, to assess the temporal effects of the intervention.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses for the main comparison of cupping versus placebo/sham for pain and disability at post-treatment.

- Cupping mode (i.e. dry, wet and massage), since different types of cupping therapy may produce varying physiological effects.
- Country where the study was performed. This exploratory subgroup analysis aims to assess whether contextual factors, such as cultural familiarity with cupping therapy, integration into routine health systems, practitioner expertise, or differences in health beliefs and expectations, may influence treatment outcomes. In countries where cupping is more widely practised and culturally accepted, these factors may affect both how the intervention is delivered and how outcomes are reported (China versus non-China). While this analysis is not based on direct evidence of differential response by country, it acknowledges the potential role of cultural and healthcare system influences on trial results. We will interpret the findings with appropriate caution.

We will employ the formal test for subgroup interactions in RevMan (RevMan 2024) and use caution in the interpretation of subgroup analyses as advised in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). We will compare the magnitude of the effects between the subgroups by means of assessing the overlap of the CIs of the summary estimate. Non-overlap of the CIs indicates statistical significance.

Sensitivity analysis

We plan to carry out the following sensitivity analyses to investigate the robustness of the treatment effect for pain intensity and disability for the main comparison of cupping versus placebo/sham at short term.

- Excluding studies with unclear or high risk of selection bias.
- Excluding studies with unclear or high risk of detection bias.
- Excluding studies where data were imputed (e.g. standard deviations) or where median values were presented.

Summary of findings and assessment of the certainty of the evidence

We will follow the guidelines in Chapters 14 and 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* for interpreting results (Schunemann 2020; Schunemann 2020a) and will be aware of distinguishing a lack of evidence of effect from a lack of effect. We will base our conclusions only on the findings from this review's quantitative or narrative synthesis of included studies. We will avoid making recommendations for practice, and our implications for research will suggest future research priorities and outline the remaining uncertainties in the area.

We will create a summary of findings table for the primary comparison (cupping therapy versus sham) and for cupping therapy versus minimal intervention using the following outcomes at immediate follow-up.

- Pain
- Disability
- Health-related quality of life
- Psychological functioning (anxiety and depression)
- Total adverse events
- Treatment-specific adverse events
- Withdrawals due to adverse events

Two review authors (WR and HJ) will independently assess the certainty of the evidence. We will use the five GRADE considerations (study limitations, consistency of results, indirectness, imprecision, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Appendix 3). We will report the certainty of evidence as high, moderate, low, or very low. We will use GRADEpro GDT software to prepare the summary of findings tables (GRADEpro GDT). We will use version 3 of the GRADEpro view to display our summary of findings tables. We will justify all decisions to downgrade the certainty of evidence using footnotes and will make comments to aid the reader's understanding of the review where necessary.

ACKNOWLEDGEMENTS

We involved two consumers with lived experience of chronic low back pain to help ensure our review focuses on outcomes that matter to consumers. Through a discussion with two consumers, we explored which outcomes they considered most relevant and how acceptable they found cupping therapy as a treatment option. We are grateful to Luana Isabeli and João Nunes for generously sharing their time and insights.

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APPENDICES

Appendix 1. Search strategy for MEDLINE

1 exp Low Back Pain/

2 low back pain.tw

3 exp Back Pain/

4 ((lumb* or back) adj3 pain).tw

5 dorsalgia.tw

6 lumbago.tw

7 coccydynia.tw

8 sciatica.tw

9 exp sciatic neuropathy/

10 (backache or back ache).tw

11 radiculopathy/

12 (radiculopath$ or radicular pain).tw

13 or/1-12

14 Cupping Therapy/ or cupping.mp or hijama.mp or Ba Guan.mp or Baguan.mp or Schropfen.mp or bloodletting or cup$.mp

15 exp randomized controlled trial/

16 controlled clinical trial.pt.

17 randomized.ab.

18 placebo.ab.

19 drug therapy.fs.

20 randomly.ab.

21 trial.ab.

22 groups.ab.

23 or/15- 22

24 exp animals/ not humans.sh.

25 23 not 24

26 13 AND 14 AND 25

Appendix 2. RoB 1 tool

Domain	Description	Judgement for low risk of bias*
1. Selection bias	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with two groups), rolling a dice (for studies with two or more groups), drawing of balls of different colours, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are: alternation, birth date, social insurance/security number, date invited to participate in the study, and hospital registration number.
2. Performance bias	Describe all measures used, if any, to blind study participants from knowledge of which intervention a participant received. Provide any information relating to whether the in-	Index and comparison groups are indistinguishable for the participants; or the success of blinding was tested among the participants, and it was successful (i.e. participants in both the index and comparison groups felt that they received 'the best' treatment); or any lack of blinding did not lead to deviations from the intended intervention.

(Continued)

	tended blinding was effective.	
3. Detection bias	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective. Describe the intention-to-treat analysis.	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored low risk if the success of blinding was tested among the outcome assessors, and it was successful, or: • for self-reported outcomes in which the participant is the outcome assessor (e.g. pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored low risk; • for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g. clinical examination): the blinding procedure is adequate if participants are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination; • for outcome criteria that do not suppose contact with participants (e.g. radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome; • for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between participants and care providers (e.g. co-interventions, hospitalisation length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if blinding of care providers is scored low risk; • for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data; • all randomised participants are reported/analysed in the group to which they were allocated by randomisation for the most important outcome follow-up time points (minus missing values) irrespective of non-compliance and co-interventions.
4. Attrition bias	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	The number of participants who were included in the study but did not complete the observation period, or who were not included in the analysis, must be described and reasons given. If the percentage of withdrawals and dropouts does not exceed 20% for short-term follow-up and 30% for long-term follow-up, and does not lead to substantial bias, a score of low risk is made. (N.B. these percentages are arbitrary, not supported by literature)
5. Reporting bias	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	All results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is obtained either by comparing the protocol and the report, or in the absence of the protocol, a determination that the published report includes enough information to permit a judgement.
6. Other bias	Describe if co-interventions were avoided or were comparable and compliance rates across	If there were no co-interventions, or they were similar between the index and control groups. The review author determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention and con-

(Continued)

	groups. Cross-over trials: specific biases including carry-over effects, wash-out periods, and treatment order	trol intervention(s). For example, physiotherapy treatment is usually administered for several sessions, therefore it is necessary to assess how many sessions each participant attended. For single-session interventions (e.g. surgery), this item is irrelevant (i.e. low risk).

Appendix 3. GRADE approach to evidence synthesis

We will use the following criteria to downgrade the certainty of evidence based on the five GRADE considerations and will interpret according to GRADE recommendations (Santesso 2020).

Study design and risk of bias

We will assess the risk of bias in comparisons based on the proportion of participants from studies at high overall risk of bias (i.e. one or more bias domains judged as high risk). As a general guideline, we will consider downgrading the certainty of evidence by one level if more than 25% of participants in the comparison are from studies at high risk of bias and by two levels if this proportion reaches 50% or over. However, we will also take into account whether the risk of bias appears to influence the direction or magnitude of the effect. Where possible, we will use sensitivity analyses to explore this impact, that is by assessing whether removing studies at high risk of bias alters the effect estimate. If the effect remains stable despite excluding studies at high risk of bias, we may decide not to downgrade. In cases where sensitivity analysis is not possible (e.g. small comparisons with limited studies, or when all studies are at high risk of bias), we will make a judgement based on the potential for bias to influence the findings and the overall certainty of the included evidence.

Inconsistency

We will assess inconsistency based on the visual assessment of the forest plot and statistical heterogeneity based on I^2 statistics. We will assess each direct comparison for consistency in the direction and magnitude of the effect sizes from individual trials, considering the width of the prediction interval and the magnitude of the heterogeneity parameter. We will downgrade the certainty of evidence by one level if we identify important and unexplained heterogeneity through visual inspection or considerable heterogeneity in the I^2 statistic (> 50%). When there is evidence of severe unexplained inconsistency (heterogeneity in test I^2 greater than 75%), we will downgrade the certainty of evidence by two levels. For meta-analyses with fewer than 10 studies, we will rely primarily on visual inspection and the range of effect sizes to assess inconsistency, rather than I^2, which may be unreliable with a small number of studies.

Indirectness

We will downgrade the certainty of evidence by one level if more than 50% of the population, interventions, comparators, or outcomes are not fully or outside the target group.

Imprecision

We will assess imprecision primarily using the confidence interval (CI) approach (Zeng 2022). If the 95% CI includes both a negligible effect and a clinically meaningful benefit or harm, we will downgrade by one level. If the CI spans both an important benefit and an important harm, we will downgrade by two levels. If the CI is extremely wide, making the certainty of the effect highly uncertain, we will downgrade by three levels.

If the CI does not cross a threshold, we will consider the optimal information size (OIS) approach. For continuous outcomes, we will downgrade by two levels if the total sample size is less than 30% to 50% of the estimated OIS. For dichotomous outcomes, if the upper-to-lower boundary ratio of the CI exceeds 2.5 for odds ratios or 3 for risk ratios, we will downgrade by two levels. The OIS will be calculated after study inclusion based on the actual data from included studies (e.g. standard deviations).

Publication bias

We will evaluate publication bias through funnel plots if at least 10 trials examine the same intervention comparison in the review. If the funnel plot suggests asymmetry, indicating potential missing data, we will consider downgrading the certainty of evidence by one level. Additionally, we will assess the number of completed but unpublished trials by reviewing the trial registries. If there is evidence of missing results that could meaningfully impact our conclusions, we will also consider downgrading.

CONTRIBUTIONS OF AUTHORS

Dr Saragiotto conceived the idea for the review, contributed to the design and development of the protocol, and drafted the final version of the manuscript.

Mr Almeida Silva provided clinical expertise and contributed to the study design and development of the protocol.

Mr Fandim provided guidance and expertise in the methodology and statistical analysis plan for the protocol and critically reviewed and revised the protocol for intellectual content.

Mr Rios assisted with the development of the review question and study objectives and methods, and drafted the initial version of the manuscript.

Dr Medeiros provided clinical and methodological expertise, contributed to the study design, participated in the development of the review protocol, and reviewed and revised the manuscript for important intellectual content.

Dr Silva provided clinical and methodological expertise, contributed to the study design and development of the protocol, and reviewed and revised the manuscript for important intellectual content.

Dr Jenkins provided clinical and methodological expertise, contributed to the study design and development of the protocol, and reviewed and revised the protocol for intellectual content.

Dr Souza provided methodological expertise, contributed to the study design, participated in the development of the review protocol, and reviewed and revised the manuscript for important intellectual content.

All authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

Bruno T Saragiotto: no relevant conflicts of interest

Hugo Jario Almeida Silva: no relevant conflicts of interest

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Germanna Medeiros Barbosa: no relevant conflicts of interest

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Luke Jenkins: no relevant conflicts of interest

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SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

NOTES

This protocol is based on a template developed by the Cochrane Musculoskeletal Group editorial base.