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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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ABSTRACT

Introduction

Although the effectiveness of acupuncture for episodic migraine has been confirmed by series of clinical trials and Cochrane systematic reviews, the mechanisms underlying the specific effect of acupuncture for migraine remain controversial. We aim to evaluate the effectiveness and safety of acupuncture for both episodic migraine and chronic migraine by meta-analysis and explore the possible factors influencing the specific effect of acupuncture for migraine by meta-regression.

Methods and analysis

We will search for randomized control trials (RCTs) of acupuncture for migraine in the following eight databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED (via OVID), and four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. We will also search OpenSIGLE (opensigle.inist.fr) for conference abstracts. No language restriction will be applied. The selection of studies, data extraction and coding, and assessment of risk of bias of the include studies will be conducted independently by two reviewers. Standard meta-analysis and, if appropriate, meta-regression will be performed using the R packages Meta and Metafor.

Discussion

The possible findings of this meta-analysis will not only sharpen the understanding of the effectiveness and specific effect of acupuncture for treating migraine, but will also explore how acupuncture treatment can be optimized for migraine in a pragmatic clinical setting.

Ethics and dissemination The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data which will be used do not contain individual patient data, therefore ethical approval is not required.

Trial registration number: PROSPERO CRD42018087270.

Keywords: Acupuncture; migraine; meta-regression; meta-analysis

Strengths and Limitations:

Meta-analysis and the possible meta-regression will be performed by R packages Meta and Metafor, which allow us to detect multiple factors influencing the clinical effect of acupuncture for preventing migraine in the same model.

Searching database for Korean and Japanese will not be used in electronic searches, therefore language bias may exist.

Introduction

Description of the condition

Migraine is one of the most common headache disorders and is characterized by recurrent unilateral, throbbing, moderate-to-severe attacks of headache lasting from 4–72 h, with or without aura [1]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia, and phonophobia, and is aggravated by physical exertion. According to the 2010 Global Burden of Disease Survey, migraine ranked as the third most predominant disorder, as well as the seventh-highest specific cause of disability worldwide. In the US, an estimated 36 million experience migraine attacks, with approximately 16%–18% of women and 6%–8% of men suffering recurrent migraine attacks during their professional lives [2–3]. Migraine usually can be categorized as episodic migraine (migraine attacks happening fewer than 15 days each month) and chronic migraine (migraine attacks happening more than 15 days per month) [1]. Two large population-based studies documented a strong tendency for episodic migraine to evolve into chronic migraine, often associated with overuse of analgesics [4]. Further, a systematic review focusing on the global prevalence of migraine reported that the prevalence of chronic migraine is 0–5.1%, with estimates typically among 1.4–2.2% [5]. Recently, many studies also demonstrated a correlation between migraine and cardiovascular and cerebrovascular diseases [6–7]. A systematic review investigating migraine and cardiovascular disease found that the risk of ischemic stroke was doubled in people who had migraine with aura [8]. It is well accepted that migraine without aura is associated with ischemic stroke in younger women (age ≤ 45 years) [9].

Description of the intervention

Effective treatments for migraine are required to reduce the occurrence of migraine attacks and relieve symptoms in order to improve patients' quality of life and decrease related healthcare utilization. Pharmacological agents for migraine are widely used to reduce migraine attack frequency and pain intensity, including propranolol, metoprolol, flunarizine, valproic acid and topiramate [10]. Unlike acute migraine that can often be managed with drugs, chronic migraine is difficult to control due to the frequency of attacks and overuse of drugs among migraine patients [5]. Furthermore, pharmacological treatment for migraine with oral nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans has a modest effect and often leads to several side effects, such as gastrointestinal and cardiovascular disorders [11]. Thus, there is a strong need installing additional long-term effective, low-risk treatments for migraine.

Acupuncture is a procedure whereby fine needles are inserted into and manipulated within the skin at acupoints at certain depths to reduce symptoms and achieve curing of diseases [12]. Acupuncture originate in China and Chinese civilization, and has become one of the most widely used forms of Traditional Chinese Medicine (TCM). The essence of acupuncture lies in the unique meridians and acupoints theory from ancient China, as well as the spirit of holism and personalized treatment. The treatment effect of acupuncture is regarded as balancing the disorder of the human body, to treat diseases by activating accurate meridians and acupoints of the body using diverse needling techniques, according to disease and personal status. Following ancient acupuncture theory, choosing accurate acupoints, applying adequate needling manipulation in sufficient treatment sessions, as well as targeting the corresponding disease and personal status are pivotal aspects for the effect of acupuncture in the clinical setting.

Currently, even without a clear understanding of the mechanism responsible for the effect of acupuncture in Western studies, acupuncture has been used for migraine prophylaxis and chronic pain treatment worldwide. According to a survey in the US, 9.9% of patients who received acupuncture treatment did so in search of relief from

migraine and other headaches [13]. A 2016 Cochrane Review from Germany concluded that acupuncture is safe and effective for episodic migraine prophylaxis compared to prophylactic drug treatment [14].

How the intervention might work

While enhanced calcitonin gene-related peptide (CGRP) and spontaneous cortical spreading depression (CSD) are regarded as causative in triggering migraine [15], the pathophysiology of migraine is attributed to multiple factors, and many of these aspects still remain unclear. Recently, an increasing number of studies has confirmed that acupuncture activates the release of opioid peptides in the central nervous system (CNS), corresponding to long-lasting activation of ascending sensory tracks, thereby relieving an array of pain conditions [16-19]. Furthermore, Zhao LP et al. confirmed in a migraine rat model that electro-acupuncture treatment can depress CGRP expression in the trigeminal ganglion, which plays a key role in inducing migraine attack [20]. Li Z et al. also found that acupuncture restores the impaired descending pain modulatory system (DPMS) in migraine patients by decreasing the resting state functional connectivity (rs-fc) between the periaqueductal gray (PAG) and rostral anterior cingulate cortex/medial prefrontal cortex (rACC/mPFC), which directly correlated with the intensity of pain during the migraine attack [21].

In contrast to the current evidence concerning the mechanism by which acupuncture relieves migraine, evidence of the effectiveness of acupuncture for migraine was provided by a series of Cochrane systematic reviews and a large individual patient meta-analysis [14, 22]. However, the concept of a “placebo effect” and “specific effect” regarding the clinical effect of acupuncture for migraine is still controversial [22]. An updated Cochrane review of acupuncture for episodic migraine concluded that acupuncture is an effective treatment for the prevention of migraine, but on the other hand, the difference in the effect size between acupuncture and sham acupuncture was relatively small [14]. Linde K et al. argued that understanding the specific effect of acupuncture is essential for the acceptance of acupuncture as a legal treatment in Western countries. Therefore, evidence confirming the specific effect of acupuncture is still in high demand for biomedicine [23]. Nevertheless, key

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3 components of the effect of acupuncture remain to be fully uncovered. Accordingly,
4 designing appropriate sham acupuncture as a placebo control is still a difficulty for
5 clinical acupuncture trials. Thus, this debated issue may be an obstacle for both
6 Western scientific researchers and policy makers to accept acupuncture as a valid
7 therapy in pain management.
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10 11 12 **Why it is important to do this review**

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14 To investigate the effect and specificity of acupuncture, a newly update
15 Individual Patient Data Meta-Analysis of acupuncture for chronic pain [24] concluded
16 that true acupuncture has a long-term effect compared with sham acupuncture, but it
17 also pinpointed that characteristics of acupuncture treatment sessions contribute to the
18 effect of acupuncture, in addition to the specific effects of needling. However, this
19 meta-analysis mainly focuses on chronic pain and chronic headache, not specific to
20 migraine. There is still insufficient evidence to elucidate the specific mechanism of
21 the effect of acupuncture for migraine. Furthermore, a recent German Cochrane
22 Review [14] already demonstrated the effectiveness of acupuncture for the prevention
23 of episodic migraine. However, there has been no systematic review of the effect of
24 acupuncture for prevention of chronic migraine. Therefore, three pivotal question
25 arise from the former meta-analysis and clinical studies of acupuncture for migraine: i)
26 Is acupuncture an effective therapy for both episodic migraine and chronic migraine
27 in the clinical setting? ii) Are there any important factors that influence the effect of
28 acupuncture? and iii) Are there any features that alter the specific effect of
29 acupuncture compared with sham acupuncture or other controls in clinical
30 acupuncture treatment for migraine? To address these important questions, we will
31 conduct a meta-analysis of RCTs of acupuncture for migraine.
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49 **Objective**

50 This meta-analysis in adults with episodic or chronic migraine aims to assess:

- 51 1. the effectiveness and safety of acupuncture compared to sham acupuncture and
52 drug treatment or waiting list controls in the prevention of migraine;
- 53 2. features that may contribute to: i) different effect sizes between acupuncture and
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controls, ii) the specific effect of acupuncture, iii) non-specific effects of sham acupuncture or other controls, and iv) which factors among all those studied most strongly influence the effect of acupuncture.

Methods

Criteria for considering studies for this review

Types of studies

We will only include RCTs investigating the effect of acupuncture on episodic and chronic migraine in adults [4]. We will only include RCTs (parallel groups as well as cross-over) using well-described randomization and allocation concealment methods.

We will exclude quasi-randomized clinical trials and trials with follow-up less than 8 weeks after randomization. The Cochrane Collaboration's risk of bias tool [25] will be used to assess study quality.

Types of participants

We will include patients of either sex with an age ranging from 18–65 years, who have been diagnosed either with episodic or chronic migraine. Migraine diagnoses must be based on the International Headache Society (ICHD-III beta 2013 and its previous editions ICHD-II 2004; IHS1988) and the Ad Hoc Committee on the Classification of Headache (Ad Hoc 1962) [26-29]. If no specified criteria were documented in the studies, the migraine diagnosis must be based on discriminable and important characteristics of migraine attacks (e.g., recurrent headache, unilateral pain, pulsating quality, moderate or severe intensity, in association with nausea and/or photophobia and phonophobia), as confirmed by patients' doctors or general practitioners. In general, episodic migraine occurs in two to eight episodes but with less than 15 days of migraine attacks per month, whereas chronic migraine patients usually suffer at least 15 days of migraine attacks per month (180 days per year) for at least 3 months [1].

The duration of migraine history must be longer than 1 year in the majority of patients. This criterion will be considered met if:

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3 1) An explicit description of the duration of migraine history longer than 1 year
4 is noted in the inclusion criteria; or
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6 2) The mean duration minus one standard deviation is longer than 1 year as
7 shown in the table of baseline characteristics; or
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10 3) Other information confirms that the criterion was met (e.g., proportions with
11 duration ranges are presented in the studies).
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14 We will include studies in which patients were defined as having ‘combination’
15 or ‘mixed’ migraine only if we can extract the data on participants affected with
16 migraine.
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19 We will exclude trials including patients with secondary headache. Studies
20 including chronic migraine patients with medication-overuse history (according to the
21 International Classification of Headache Disorders, 3rd beta edition (ICHD-IIIβ)
22 criteria) will also be excluded.
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27 **Types of intervention**

28 **Experimental intervention**

29 We define acupuncture (both manual and electrical stimulation) as the
30 experimental intervention. Acupuncture is defined as insertion of specific needles into
31 the skin of the body at selected acupoints (defined as ‘meridian acupoints’, which
32 belong to 14 meridians in the body according to traditional acupuncture theory) or
33 pain points (defined as ‘a-shi points’ in the location of pain condition according to
34 traditional acupuncture theory), or extraordinary points (defined as ‘extra points’,
35 which do not belong to the 14 meridians but have a therapeutic effect in the body
36 according to traditional acupuncture theory) up to definite therapeutic depths. To
37 ensure acupuncture treatment could be clinically effective, the dosage of acupuncture
38 treatment must have at least six treatment sessions, with a duration of at least 20
39 minutes per session and at least one session per week in the majority of patients.
40 Acupuncturists in the included studies should be confirmed to have a relevant
41 acupuncture qualification or professional affiliation, or years in acupuncture practice.
42 In addition, trials that define acupuncture in combination with other pharmacological
43 treatment or physical treatment as the experimental intervention but mainly
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investigate the effectiveness of acupuncture will also be included.

As this meta-analysis will mainly focus on the effectiveness of acupuncture on the basis of traditional acupuncture theory and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [30], we will exclude trials in which:

- 1) Acupuncture was performed at one of specific body area but not acupoints among the body, such as scalp acupuncture, ear acupuncture, and wrist-ankle acupuncture.
- 2) Acupoints were stimulated by other techniques without traditional acupuncture needling, including acupressure, laser stimulation, injection acupuncture, dry needling, and trigger point therapy.

Control interventions

We will include three types of control interventions:

- 1) No treatment or waiting list-control during trial period.
- 2) Sham acupuncture (intervention resembling verum acupuncture treatment but using superficial needle insertion, needle insertion at non-acupuncture points or at points not indicated for the condition under study, and 'placebo' needles that seem to be inserted into skin but actually are not [31-34], etc). Trials with intervention groups that compared either acupuncture alone with sham intervention alone or acupuncture plus one or more therapies with sham intervention plus the same therapies also will be included.
- 3) Pharmacological treatment that is given as a control during a comparable time as application of acupuncture treatment.

Because our objective is to evaluate the effectiveness of acupuncture treatment compared to sham acupuncture treatment, no treatment, or western medicine treatment, we will exclude trials with herbal medicine, moxibustion, bleeding therapy, and other different forms of acupuncture as control interventions.

Types of outcome measures

To be considered for inclusion, trials must have evaluated at least one of the following primary efficacy outcome measures [35] for at least 4 weeks from the

beginning of acupuncture treatment:

- 1) Number of migraine attacks per evaluation interval;
- 2) Number of migraine days per evaluation interval;

Before the review process, a review board consisting of an epidemiologist, acupuncturist, migraine patient, social policymakers, and statistician will be established to determine all the key outcomes, with respect of migraine patients' opinions and values.

We will exclude studies that:

- 1) Included outcome measurements of any "effectiveness rate";
- 2) Exclusively used objective or surrogate outcome measures;
- 3) Evaluated treatment or measurement of acute migraine attack;
- 4) Had outcome evaluation periods shorter than 4 weeks (after randomization to end of treatment).

According to the guidelines for controlled trials of drugs in migraine published by the IHS [35], the main outcomes will be:

Primary outcome:

Migraine frequency:

We will consider the following outcomes measuring headache frequency:

- 1) Numbers of migraine attacks per evaluation interval;
- 2) Number of migraine days per evaluation interval.

Secondary outcomes:

1) Migraine intensity: outcomes recording pain intensity using numerical/verbal scale, such as average headache severity per evaluation interval.

2) Responders rate (patients with $\geq 50\%$ reduction in headache frequency) per evaluation interval.

3) Medication intake used for migraine per evaluation interval.

4) Adverse events, including the number of patients who dropped out and the number of patients who reported adverse events.

In contrast to previous meta-analysis of acupuncture for prevention of migraine, we define responder rate as a secondary outcome. According to the IHS guideline [35],

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3 the responder rate is comparatively insensitive to the treatment effect and particularly
4 vulnerable to selection bias. The responder rate can be evaluated as an important
5 secondary outcome in placebo-controlled RCTs of migraine.
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8 Outcome measurement may be performed at specific time points; the choice will
9 depend on the time when outcomes are reported in the reviewed studies. Specific
10 decisions will be made by the review board.
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13 The following outcome measures will be presented in the 'Summary of findings'
14 table:
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- 16 1) Migraine frequency.
 - 17 2) Migraine intensity.
 - 18 3) Responder rate.
 - 19 4) Medication use for migraine attacks.
 - 20 5) Adverse events.
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27 **Search methods for identification of studies**

28 We will conduct our systematic review in accordance with the PRISMA
29 (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.
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32 **Electronic searches**

33 We will search the Cochrane Central Register of Controlled Trials, MEDLINE,
34 EMBASE, and AMED (via OVID) databases as well as four Chinese databases
35 (Chinese Biomedical Literature Database, China National Knowledge Infrastructure,
36 Chinese Science and Technology Periodical Database, and Wanfang Database) from
37 inception to December 31, 2017. No language restriction will be applied. The
38 reference lists of retrieved trials and previous systematic reviews will be searched for
39 citation of potentially eligible trials. We will contact the corresponding author of
40 articles, if any questions about trials arise.
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49 The search strategy for MEDLINE is shown in Table 1.
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Table 1 Search strategy to be used in MEDLINE (OVID) database

Number	Search terms
1	Headache Disorders [MeSH]
2	Headache[MeSH]
3	(headache or migraine or cephalgia or cephalalgia or chronic migraine):ti,ab (Word variations have been searched)
4	1 or 2 or 3
5	Acupuncture Therapy [MeSH]
6	(acupuncture or electroacupuncture or electro-acupuncture) :ti,ab
7	5 or 6
8	randomised :ti, ab.
9	randomized :ti,ab.
10	randomly :ti,ab.
11	placebo :ti,ab
12	clinical trials [MeSH]
13	trial ti,ab.
14	randomized controlled trial [MeSH]:ti,ab.
15	randomised controlled trial [MeSH]:ti,ab.
16	controlled clinical trial :ti,ab
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	humans
19	17 and 18
20	4 and 7 and 19

Searching other resources

We will search the US National Institutes of Health Ongoing Trials Register (<http://www.clinicaltrials.gov>), the WHO International Clinical Trials Registry Platform (<http://www.who.int/trialsearch>), and the metaRegister of Controlled Trials (<http://www.controlledtrials.com>) for any relevant ongoing or unpublished trials. OpenSIGLE (opensigle.inist.fr) will be searched for conference abstracts. We will also search Google Scholar (scholar.google.com/advancedscholarsearch?hl=en&lr=) using the search string “acupuncture AND (headache OR migraine OR chronic migraine)” for potential relevant trials from inception to December 31, 2017.

Data collection and analysis

Selection of studies

Two independent reviewers will examine titles and abstracts of the identified studies and will exclude irrelevant trials. When the first selection is made, full articles will be obtained and checked again in more detail. Following this assessment, a second selection will be performed. The criteria for both selections will be extracted and documented. Possible conflicts will be resolved by discussion, which will also include a third reviewer. Selection process will be presented in the PRISMA flow diagram(Figure.1)

Data extraction and coding

Two independent reviewers will extract data from the selected studies using pilot-tested data forms. They include the following study information: author, year of publication, study populations (European ancestry or not), study design, numbers of patients randomized and treated, number of patients analyzed, baseline analysis, random sequence generation, allocation concealment method, blinding method, imputation method, withdrawals of data, interventions, controls, and primary and secondary outcomes at all reported time points. For investigating the characteristics of acupuncture effect, we will extract data on age, sex, populations, headache classifications, number and duration of treatment sessions, features of acupuncture treatment (such as type of acupuncture, needle depths, selection of points, achievement of de-chi, manipulation between acupuncture treatment or not), features of control interventions (sham methods, drug use, or standard treatment details), patients' expectations, and experience of acupuncturists in accordance with Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [30].

We also will document to each outcome of interest the percentage of missing values reported in the study.

For the purpose of analyzing the influence of characteristics of acupuncture on its effect size, a coding sheet will be developed to transform all the described data into categorical data. A pilot testing on this coding sheet will be performed on a separate subset of studies. A coding book will be subsequently established to guide the coding

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3 process when the code sheet is completed. Two independent reviewers and
4 statisticians will check the coding sheet when coding process has been finished [36].
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7 **Assessing risk of bias in included studies**

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9 Two reviewers will independently assess the risk of bias for each included RCTs
10 using the Cochrane Collaboration's risk of bias tool [25]. The critical assessment for
11 the risk of bias will be evaluated in seven domains: random sequence generation,
12 allocation concealment, blinding of participants and personnel, blinding of outcome
13 assessment, incomplete outcome data, selective reporting, and other sources of bias.
14 This assessment will be achieved by assigning a judgement of 'low risk' of bias, 'high
15 risk' of bias, or 'unclear risk' of bias. Any disagreement will be resolved by
16 discussion or consensus with a third reviewer. The graphical presentation of
17 assessment of risk of bias will be generated by RevMan V.5.3.5.
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25 **Measures of treatment effect**

26 To address the clinical effect difference between the intervention and control
27 groups, headache frequency at the completion of treatment and at the end of follow-up
28 will be used as a primary outcome. Pain intensity, responder rate and medication intake
29 at the completion of treatment and at the end of follow-up also will be extracted as
30 secondary outcomes. For these continuous outcomes, the mean difference (MD) and
31 standard deviations (SDs) will be extracted and calculated as an effect estimate.
32 Negative values will indicate better outcomes in the acupuncture group.
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39 If the MD or SDs were not reported and not available after contacting the authors,
40 we will use the data that is available, such as the median or P values and confidence
41 intervals, and try to re-calculate MD and SD values from the information recorded in
42 the study.
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46 The safety or adverse outcome will be the number of participants who dropped
47 out due to adverse effects and the number of participants who reported at least one
48 adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will be
49 calculated as the effect estimate. An odds ratio greater than 1 will indicate more
50 events (e.g., dropouts) in the acupuncture group.
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55 For the time window analysis, we will extract outcomes with all the time points
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3 using pilot-tested data forms. Subsequently, we will document the quantitative
4 outcomes at the end of treatment together with the length of the treatment period. In a
5 meta-regression, we will adjust treatment effects for time. Using the R package
6 *metafor* will allow us to give for each outcome a meta-analytic result at different
7 treatment periods. Standard meta-analyses, especially for subgroups, will be
8 performed using the R-package *meta* [37-38].
9

14 **Unit of analysis issues**

15 The unit of analysis will be based on aggregated outcome data due to the lack of
16 individual patient data.
17

18 **Dealing with missing data**

19 We will perform a sensitivity analysis to elucidate the amount of missing data on
20 the effect estimates. This can be performed by a meta-regression adjusting for the
21 amount of missing data.
22

23 **Assessment of heterogeneity**

24 We will evaluate heterogeneity of included studies with I^2 statistic and the τ^2
25 test. A cutoff point of at least 50% in I^2 statistic will be considered as substantial
26 heterogeneity.
27

28 Our second aim is to investigate which clinical setting and which acupuncture
29 features do influence the size and the heterogeneity of the intervention. First, we will
30 define characteristics that may modify the intervention effect according to
31 experienced acupuncturists and STRICTA [30]. Second, we will examine the
32 correlation between these covariates to exclude possible masking and to establish a
33 core-set of covariates. A random-effect meta-regression analysis will be conducted
34 using *metafor* [37] to elucidate the impact of core set covariates on treatment effects.
35

36 Before the meta-analysis can be conducted, the relevant results from each study
37 must be quantified in such a way that the resulting values can be further aggregated
38 and compared. Depending on different aspects (goals of the meta-analysis, the design
39 and types of studies included, and the information provided therein), we will calculate
40 the effect size of interest using the *escalc* function.
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42 Subsequently, random/mix-effects of the meta-regression model will be fitted by
43 *rma()* function [37]. The **restricted maximum-likelihood estimator**, which is an
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3 approximately unbiased and efficient estimator, will be used to address the amount of
4 residual heterogeneity τ^2 . The pre-defined covariates will be first fitted
5 independently to examine the possible independent factors contributing to variation in
6 the intervention effect. Subsequently, interaction between covariates can be added and
7 detected in the model using the **mods** argument. For the limit of included studies, we
8 will put covariates ≤ 3 into the same model for each model. For the result
9 interpretation, the **estimate** represents the average effect estimates of covariates, and a
10 P value ≤ 0.05 represents a significant difference that indicates the corresponding
11 covariate plays an important role for the intervention effect and heterogeneity. In
12 addition, the amount of heterogeneity in the effect estimate will be estimated by **tau**².
13 The **I**² statistic estimates (in percent) how much of the total variability in the effect
14 size estimate (which is composed of heterogeneity and sampling variability) can be
15 attributed to heterogeneity among the true effects.

26 **Assessment of reporting biases**

27 Reporting bias will be explored using funnel plot and Egger's test, if there are at
28 least 10 trials included in meta-analysis.

31 **Data synthesis**

32 The synthesis will be done by a forest plot for meta-regression. This plot does
33 not contain a summary measure given by a prism below the single studies, but by a
34 prism which is shown for each single study and which shows the aggregated effect for
35 the type of study which is represented by the specific study (depending on the
36 covariates of the meta-regression). If the heterogeneity test indicates there is no
37 substantial heterogeneity between studies, the Mantel-Haenszel method implemented
38 by the **rma.mh()** function will be fitted for calculating pooled estimates, 95%
39 confidence intervals, and combined P values. If substantial heterogeneity is indicated
40 by $I^2 \geq 50\%$, the random effect model will be performed by the DerSimonian and Laird
41 method (DerSimonian 1986) and the **rma** function. The significance of the P value
42 represents the strength of evidence against the null hypothesis of no intervention
43 effect.

54 **Subgroup analysis**

55 Subgroup analysis will be performed according to the primary and secondary

objectives. To detect possible heterogeneity of the results, subgroup analysis will be conducted for both the primary outcome and secondary outcomes, at the end of the treatment session and the end of the follow-up period. We will investigate the effects for four subgroup analyses:

- 1) episodic migraine VS chronic migraine
- 2) acupuncture VS different type of sham acupuncture and controls
- 3) Western studies VS Chinese studies
- 4) early time-point of outcomes VS later time-point of outcomes

In addition, if we detect any important and significant covariates contributing to the variation of the intervention effect by meta-regression, subgroup analyses will also be conducted according to these covariates.

Sensitivity analysis

To confirm the robustness of our findings, a sensitivity analysis will be conducted based on the different levels of bias of the included studies. To evaluate the internal validity of studies or treatment adequacy, we will subsequently remove studies of ‘high risk’ of bias, studies of ‘unclear risk’ of bias, and studies of ‘low risk’ of bias using the **metafor** package and **leave1out()** function.

Summary of evidence

We will summarize the quality of evidence using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) [39] and present ‘Summary of findings’ tables. The ‘Summary of findings’ tables will be generated by the GRADE working group software (GRADEpro or GRADEpro GDT [www.gradepr.org]). The content of the ‘Summary of findings’ tables (main outcomes that are important to patients and decision makers) will be determined by the review group described above. Where possible, both relative and absolute measures of effect will be provided. To assess the quality of evidence, the GRADE approach evaluates the quality of evidence as ‘high’, ‘moderate’, ‘low’, or ‘very low’ by outcome. Evidence can be downgraded in category by concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias, and also can be upgraded by a large effect size, plausible confounding that could change the effect size, and

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3 dose-response relation. Reviewers will downgrade or upgrade the evidence according
4 to the GRADE guideline in the Cochrane handbook, Chapter 11 [25] and also take
5 into account the differences in anticipated effects in the group of primary interest. The
6 total quality of evidence will be decided by not only the reviewers but also based on the
7 opinion of patients, decision makers, and acupuncturists. The whole summarization of
8 the evidence process will be succinct and transparent.
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15 **Discussion**

16 This meta-analysis will not only evaluate evidence from published RCTs for the
17 effectiveness of acupuncture in treating both episodic migraine and chronic migraine,
18 but also will detect possible characteristics that influence the main effect and the
19 specific effect of acupuncture for migraine. This will be achieved by using
20 meta-regression. We hope that using meta-regression techniques in this meta-analysis
21 will not only provide a deeper understanding of the effect of acupuncture in patients
22 with migraine, but also create evidence for factors that modify the effect, which will
23 support the optimization of acupuncture treatment for migraine in the pragmatic
24 clinical setting. If this protocol must be amended, we will present the date of each
25 amendment with a description of the change and the corresponding rationale.
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Author Contributions

UM is the guarantor. ZG, UM, CG and ZX contributed to the conception of the study. The manuscript presenting the protocol was drafted by ZG and revised by UM. The search strategy was developed by all authors and will be run by ZG and LQ, who will also independently screen the potential studies, extract data from included studies, assess the risk of bias, and finish the data synthesis. CH will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors have approved the publication of the protocol.

Competing interests

None declared

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Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement: Technical appendix, statistical code and data set are available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the data set.

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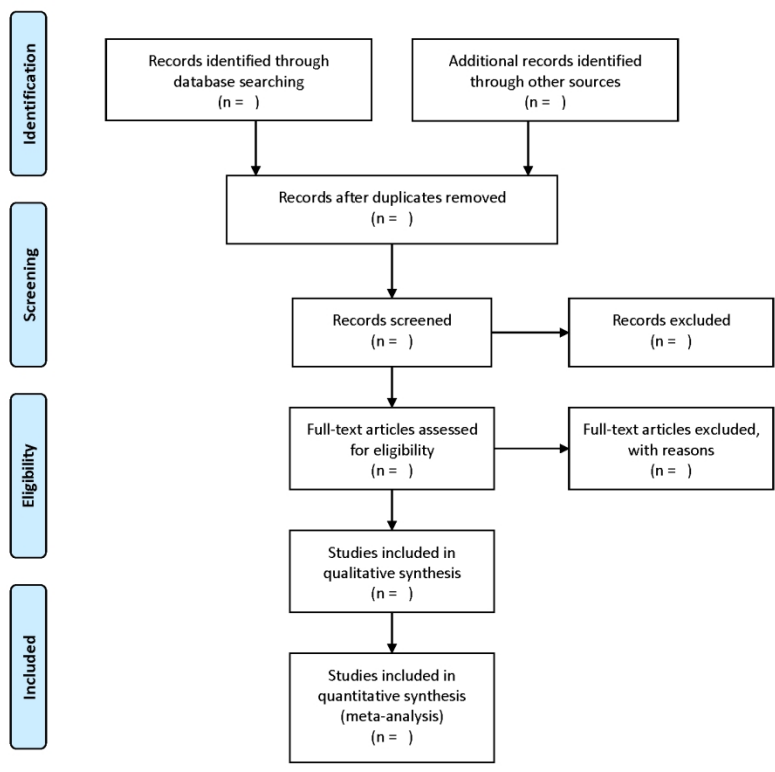
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Based on the PRISMA-P guidelines.

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Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

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		Reporting Item	Page Number
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	18
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19
	#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	18

		protocol amendments	
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2	Sources	#5a Indicate sources of financial or other support for the review	19
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4	Sponsor	#5b Provide name for the review funder and / or sponsor	19
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7	Role of sponsor or	#5c Describe roles of funder(s), sponsor(s), and / or institution(s),	19
8	funder	if any, in developing the protocol	
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11	Rationale	#6 Describe the rationale for the review in the context of what is	3
12		already known	
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14	Objectives	#7 Provide an explicit statement of the question(s) the review will	6
15		address with reference to participants, interventions,	
16		comparators, and outcomes (PICO)	
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20	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design,	7-10
21		setting, time frame) and report characteristics (such as years	
22		considered, language, publication status) to be used as	
23		criteria for eligibility for the review	
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27	Information	#9 Describe all intended information sources (such as electronic	11
28	sources	databases, contact with study authors, trial registers or other	
29		grey literature sources) with planned dates of coverage	
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32	Search strategy	#10 Present draft of search strategy to be used for at least one	12
33		electronic database, including planned limits, such that it	
34		could be repeated	
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37	Study records -	#11a Describe the mechanism(s) that will be used to manage	13
38	data management	records and data throughout the review	
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41	Study records -	#11b State the process that will be used for selecting studies (such	13
42	selection process	as two independent reviewers) through each phase of the	
43		review (that is, screening, eligibility and inclusion in meta-	
44		analysis)	
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48	Study records -	#11c Describe planned method of extracting data from reports	13
49	data collection	(such as piloting forms, done independently, in duplicate), any	
50	process	processes for obtaining and confirming data from investigators	
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53	Data items	#12 List and define all variables for which data will be sought	13
54		(such as PICO items, funding sources), any pre-planned data	
55		assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be sought,	10
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
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6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	13
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
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13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	14
14			synthesised	
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17		#15b	If data are appropriate for quantitative synthesis, describe	14-15
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
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24		#15c	Describe any proposed additional analyses (such as	16-17
25			sensitivity or subgroup analyses, meta-regression)	
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28		#15d	If quantitative synthesis is not appropriate, describe the type	16
29			of summary planned	
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31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	16
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	17
38	cumulative		assessed (such as GRADE)	
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 44 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Acupuncture, Meta analysis protocol, Meta regression, Migraine < NEUROLOGY

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Manuscripts

Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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ABSTRACT

Introduction

Although the effectiveness of acupuncture for episodic migraine has been confirmed by multiple clinical trials and Cochrane systematic reviews, the mechanisms underlying the specific effect of acupuncture for migraine remain controversial. We aim to evaluate the effectiveness and safety of acupuncture for both episodic migraine and chronic migraine by meta-analysis and explore the possible factors influencing the specific effect of acupuncture for migraine by meta-regression.

Methods and analysis

We will search for randomized control trials (RCTs) of acupuncture for migraine in the following eight databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED (via OVID), and four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. We will also search OpenSIGLE (opensigle.inist.fr) for conference abstracts. No language restriction will be applied. The selection of studies, data extraction and coding, and assessment of risk of bias of the included studies will be conducted independently by two reviewers. Standard meta-analysis and, if appropriate, meta-regression will be performed using the R packages Meta and Metafor.

Ethics and dissemination: The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data that will be used will not contain individual patient data; therefore, ethical approval is not required.

Trial registration number: PROSPERO CRD42018087270.

Keywords: Acupuncture; Migraine; Meta-regression; Meta-analysis

Strengths and Limitations:

1. This meta-analysis will not only evaluate the effectiveness of acupuncture in treating both episodic migraine and chronic migraine but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine.

2. Equipped with advanced machine learning techniques and R packages Meta and Metafor, this meta-analysis could uniquely explore the interaction and combinatory effects of different clinical factors that may affect the main effect and specific effect of acupuncture for migraine.

3. The results of this meta-analysis may reveal pivotal factors that impact the clinical effect of acupuncture, and thus, will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting.

4. Electronic databases for Korean and Japanese studies will not be searched; therefore, language bias may exist.

Introduction

Description of the condition

Migraine is one of the most common headache disorders and is characterized by recurrent unilateral, throbbing, moderate-to-severe attacks of headache lasting from 4–72 h, with or without aura [1]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia, and phonophobia and is aggravated by physical exertion. According to the 2010 Global Burden of Disease Survey, migraine ranked as the third most predominant disorder, as well as the seventh highest specific cause of disability worldwide. In the US, an estimated 36 million individuals experience migraine attacks, with approximately 16%–18% of women and 6%–8% of men suffering recurrent migraine attacks during their professional lives [2–3]. Migraine usually can be categorized as episodic migraine (migraine attacks happening fewer than 15 days each month) and chronic migraine (migraine attacks happening more than 15 days per month) [1]. Two large population-based studies documented a strong tendency for episodic migraine to evolve into chronic migraine, often associated with

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overuse of analgesics [4]. Further, a systematic review focusing on the global prevalence of migraine reported that the prevalence of chronic migraine is 0–5.1%, with estimates typically among 1.4–2.2% [5]. Recently, many studies also demonstrated a correlation between migraine and cardiovascular and cerebrovascular diseases [6-7]. A systematic review investigating migraine and cardiovascular disease found that the risk of ischemic stroke was doubled in people who had migraine with aura [8]. It is well accepted that migraine without aura is associated with ischemic stroke in younger women (age ≤ 45 years) [9].

Description of the intervention

Effective treatments for migraine are required to reduce the occurrence of migraine attacks and relieve symptoms in order to improve patients' quality of life and decrease related healthcare utilization. Pharmacological agents for migraine are widely used to reduce migraine attack frequency and pain intensity, including propranolol, metoprolol, flunarizine, valproic acid, and topiramate [10]. Unlike acute migraine that can often be managed with drugs, chronic migraine is difficult to control due to the frequency of attacks and overuse of drugs among migraine patients [5]. Furthermore, pharmacological treatment for migraine with oral nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans has a modest effect and often leads to several side effects, such as gastrointestinal and cardiovascular disorders [11]. Thus, there is a strong need for the development and implementation of additional long-term effective, low-risk treatments for migraine.

Acupuncture is a procedure whereby fine needles are inserted into and manipulated within the skin at acupoints at certain depths to reduce symptoms and achieve curing of diseases [12]. Acupuncture originated in China within the Chinese civilization and has become one of the most widely used forms of Traditional Chinese Medicine (TCM). The treatment effect of acupuncture is regarded as balancing the disorder within the human body in order to treat diseases by activating accurate meridians and acupoints of the body using diverse needling techniques, according to disease and personal status. Currently, even without a clear understanding of the

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3 mechanism responsible for the effect of acupuncture in Western studies, acupuncture
4 has been widely used for migraine prophylaxis and chronic pain treatment worldwide.
5 According to a survey in the US, 9.9% of patients who received acupuncture
6 treatment did so in search of relief from migraine and other headaches [13]. A 2016
7 Cochrane Review from Germany concluded that acupuncture is safe and effective for
8 episodic migraine prophylaxis compared to prophylactic drug treatment [14].
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16 **How the intervention might work**

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18 While enhanced calcitonin gene-related peptide (CGRP) and spontaneous
19 cortical spreading depression (CSD) are regarded as causative in triggering migraine
20 [15], the pathophysiology of migraine is attributed to multiple factors, and many of
21 these aspects remain unclear. Recently, an increasing number of studies has confirmed
22 that acupuncture activates the release of opioid peptides in the central nervous system
23 (CNS), corresponding to long-lasting activation of ascending sensory tracks, thereby
24 relieving an array of pain conditions [16-19]. Furthermore, Zhao et al. confirmed in a
25 migraine rat model that electro-acupuncture treatment can depress CGRP expression
26 in the trigeminal ganglion, which plays a key role in inducing migraine attack [20]. Li
27 et al. also found that acupuncture restores the impaired descending pain modulatory
28 system (DPMS) in migraine patients by decreasing the resting state functional
29 connectivity (rs-fc) between the periaqueductal gray (PAG) and rostral anterior
30 cingulate cortex/medial prefrontal cortex (rACC/mPFC), which directly correlated
31 with the intensity of pain during the migraine attack [21].
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44 In contrast to the conflicting evidence concerning the mechanism by which
45 acupuncture relieves migraine, evidence of the effectiveness of acupuncture for
46 migraine was provided by a series of Cochrane systematic reviews and a large
47 individual patient meta-analysis [14, 22]. However, the concept of a “placebo effect”
48 and “specific effect” regarding the clinical effect of acupuncture for migraine is still
49 controversial [22]. An updated Cochrane review of acupuncture for episodic migraine
50 concluded that acupuncture is an effective treatment for the prevention of migraine,
51 but on the other hand, the difference in the effect size between acupuncture and sham
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3 acupuncture was relatively small [14]. Linde et al. argued that understanding the
4 specific effect of acupuncture is essential for the acceptance of acupuncture as a
5 legitimate treatment in Western countries. Therefore, evidence confirming the specific
6 effect of acupuncture is still in high demand for biomedicine [23]. Nevertheless, key
7 components of the effect of acupuncture remain to be fully uncovered. Accordingly,
8 designing appropriate sham acupuncture as a placebo control is still a difficulty for
9 clinical acupuncture trials. Thus, this debated issue may be an obstacle for the
10 acceptance of acupuncture as a valid therapy in pain management by both Western
11 scientific researchers and policy makers.
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22 **Why is this review important?**

23 To investigate the effect and specificity of acupuncture, a newly updated
24 Individual Patient Data Meta-Analysis of acupuncture for chronic pain [24] concluded
25 that true acupuncture has a long-term effect compared with sham acupuncture, but it
26 also pinpointed that characteristics of acupuncture treatment sessions contribute to the
27 effect of acupuncture, in addition to the specific effects of needling. However, this
28 meta-analysis mainly focused on chronic pain and chronic headache and was not
29 specific to migraine. There is still insufficient evidence to elucidate the specific
30 mechanism of the effect of acupuncture for migraine. Furthermore, a recent German
31 Cochrane Review [14] demonstrated the effectiveness of acupuncture for the
32 prevention of episodic migraine. However, there has been no systematic review of the
33 effect of acupuncture for the prevention of chronic migraine. Therefore, three pivotal
34 questions arise from the former meta-analysis and clinical studies of acupuncture for
35 migraine: i) is acupuncture an effective therapy for both episodic migraine and
36 chronic migraine in the clinical setting? ii) are there any important factors that
37 influence the effect of acupuncture? and iii) are there any features that alter the
38 specific effect of acupuncture compared with sham acupuncture or other controls in
39 clinical acupuncture treatment for migraine? To address these important questions, we
40 will conduct a meta-analysis of RCTs of acupuncture for migraine.
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Objective

This meta-analysis in adults with episodic or chronic migraine aims to assess:

1. the effectiveness and safety of acupuncture compared to sham acupuncture and drug treatment or waiting list controls in the prevention of migraine;
2. features that may contribute to: i) different effect sizes between acupuncture and controls, ii) the specific effect of acupuncture, iii) non-specific effects of sham acupuncture or other controls, and iv) which factors among all those studied most strongly influence the effect of acupuncture.

Methods

Criteria for considering studies for this review

Types of studies

We will only include RCTs investigating the effect of acupuncture on episodic and chronic migraine in adults [4]. We will only include RCTs (parallel groups as well as cross-over) using well-described randomization and allocation concealment methods.

We will exclude quasi-randomized clinical trials and trials with follow-up less than 8 weeks after randomization.

Types of participants

We will include patients of either sex with an age ranging from 18–65 years who have been diagnosed either with episodic or chronic migraine. Migraine diagnoses must be based on the International Headache Society (ICHD-III beta 2013 and its previous editions ICHD-II 2004; IHS1988) and the Ad Hoc Committee on the Classification of Headache (Ad Hoc 1962) [25-28]. If no specified criteria were documented in the studies, the migraine diagnosis must be based on discriminable and important characteristics of migraine attacks (e.g., recurrent headache, unilateral pain, pulsating quality, moderate or severe intensity, in association with nausea and/or photophobia and phonophobia), as confirmed by patients' doctors or general practitioners. In general, episodic migraine occurs in two to eight episodes but with migraine attacks on less than 15 days per month, whereas chronic migraine patients

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3 usually suffer migraine attacks on at least 15 days per month (180 days per year) for
4 at least 3 months [1].
5

6 The duration of migraine history must be longer than 1 year in the majority of
7 patients. This criterion will be considered met if:
8

9
10 1) An explicit description of the duration of migraine history longer than 1 year
11 is noted in the inclusion criteria;
12

13 2) The mean duration minus one standard deviation is longer than 1 year as
14 shown in the table of baseline characteristics; or
15

16 3) Other information confirms that the criterion was met (e.g., proportions with
17 duration ranges are presented in the studies).
18

19 We will include studies in which patients were defined as having ‘combination’
20 or ‘mixed’ migraine only if we can extract the data on participants affected with
21 migraine.
22

23 We will exclude trials including patients with secondary headache. Studies
24 including chronic migraine patients with medication-overuse history (according to the
25 International Classification of Headache Disorders, 3rd beta edition (ICHD-IIIβ)
26 criteria) will also be excluded.
27

28 **Types of intervention**

29 **Experimental intervention**

30 We define acupuncture (both manual and electrical stimulation) as the
31 experimental intervention. Acupuncture is defined as insertion of specific needles into
32 the skin of the body at selected acupoints (defined as ‘meridian acupoints’, which
33 belong to 14 meridians in the body according to traditional acupuncture theory), pain
34 points (defined as ‘a-shi points’ in the location of pain condition according to
35 traditional acupuncture theory), or extraordinary points (defined as ‘extra points’,
36 which do not belong to the 14 meridians but have a therapeutic effect in the body
37 according to traditional acupuncture theory) up to definite therapeutic depths. In
38 accordance with a previous Cochrane systematic review of acupuncture for migraine
39 [14], the dosage of acupuncture treatment must be at least six treatment sessions, with
40 a duration of at least 20 minutes per session and at least one session per week in the
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majority of patients. Also, for the purpose of ensuring the clinical effectiveness of acupuncture treatment, the acupuncturists who administered treatment in the included studies should be confirmed to have a relevant acupuncture qualification or professional affiliation, or a certain number of years in acupuncture practice. In addition, trials that define acupuncture in combination with other pharmacological treatment or physical treatment as the experimental intervention but mainly investigate the effectiveness of acupuncture will be included.

As this meta-analysis will mainly focus on the effectiveness of acupuncture on the basis of traditional acupuncture theory and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [29], we will exclude trials in which:

- 1) Acupuncture was performed at one specific body area but not at acupoints of the body, such as scalp acupuncture, ear acupuncture, and wrist-ankle acupuncture.
- 2) Acupoints were stimulated by other techniques without traditional acupuncture needling, including acupressure, laser stimulation, injection acupuncture, dry needling, and trigger point therapy.

Control interventions

We will include three types of control interventions:

- 1) No treatment or waiting list-control during trial period.
- 2) Sham acupuncture (intervention resembling verum acupuncture treatment but using superficial needle insertion, needle insertion at non-acupuncture points or at points not indicated for the condition under study, and 'placebo' needles that seem to be inserted into skin but actually are not [30-33], etc). Trials with intervention groups that compared either acupuncture alone with sham intervention alone or acupuncture plus one or more therapies with sham intervention plus the same therapies also will be included.
- 3) Pharmacological treatment that is given as a control during a comparable time as application of acupuncture treatment.

Because our objective is to evaluate the effectiveness of acupuncture treatment compared to sham acupuncture treatment, no treatment, or western medicine

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3 treatment, we will exclude trials with herbal medicine, moxibustion, bloodletting,
4 and other different forms of acupuncture as control interventions.
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7 **Types of outcome measures**

8 To be considered for inclusion, trials must have evaluated at least one of the
9 following primary efficacy outcome measures [34] for at least 4 weeks from the
10 beginning of acupuncture treatment:
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- 13 1) Number of migraine attacks per evaluation interval;
- 14 2) Number of migraine days per evaluation interval;
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- 16

17 Before the review process, a review board consisting of an epidemiologist,
18 acupuncturist, migraine patient, social policymakers, and statistician will be
19 established to determine all the key outcomes, with respect of migraine patients'
20 opinions and values.
21
22

23 We will exclude studies that:

- 24 1) Included outcome measurements of any “effectiveness rate”;
- 25 2) Exclusively used objective or surrogate outcome measures;
- 26 3) Evaluated treatment or measurement of acute migraine attack;
- 27 4) Had outcome evaluation periods shorter than 4 weeks (after randomization to
28 end of treatment).
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35 According to the guidelines for controlled trials of drugs in migraine published
36 by the IHS [34], the main outcomes will be:
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39 **Primary outcome:**

40 Migraine frequency:

41 We will consider the following outcomes measuring headache frequency:

- 42 1) Numbers of migraine attacks per evaluation interval;
- 43 2) Number of migraine days per evaluation interval.
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48 **Secondary outcomes:**

49 1) Migraine intensity: outcomes recording pain intensity using numerical/verbal
50 scale, such as average headache severity per evaluation interval.
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53 2) Responder rate (patients with $\geq 50\%$ reduction in headache frequency) per
54 evaluation interval.
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3 3) Medication intake used for migraine per evaluation interval.

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5 4) Adverse events, including the number of patients who dropped out due to an
6
7 adverse event and the number of patients who reported adverse events.

8
9 In contrast to a previous meta-analysis of acupuncture for migraine prophylaxis, we
10 define responder rate as a secondary outcome. According to the IHS guideline [34],
11 the responder rate is comparatively insensitive to the treatment effect and particularly
12 vulnerable to selection bias. The responder rate can be evaluated as an important
13 secondary outcome in placebo-controlled RCTs of migraine.

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16 Outcome measurement may be performed at specific time points; the choice will
17 depend on the time when outcomes are reported in the reviewed studies. Specific
18 decisions will be made by the review board.

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21 The following outcome measures will be presented in the 'Summary of findings'
22 table:

- 23
24
25 1) Migraine frequency.
26
27 2) Migraine intensity.
28
29 3) Responder rate.
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31 4) Medication use for migraine attacks.
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33 5) Adverse events.
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37 **Patient and public involvement**

38
39 Patient and public involvement will be considered during the whole meta-analysis.
40 We collected the patient's suggestions and comments at both China and Italy for
41 selection of primary, secondary outcome, and conceiving the design of this
42 meta-analysis. As we also have collaborated with Italian Federation of Acupuncture
43 Societies (FISA) to create novel evidence of acupuncture for migraine and established
44 long-term medical collaboration through the European Union's Seventh Framework
45 Programme FP7/2007-2013/ under REA grant agreement number
46 PIRSES-GA-2013-612 589: CHETCH (China and Europe Taking Care of Healthcare
47 solutions), our findings will regularly disseminated to both Chinese and European
48 residents by the local medical institutions.
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Search methods for identification of studies

We will conduct our meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [35] and will report this meta-analysis based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and AMED (via OVID) databases as well as four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. No language restriction will be applied. The reference lists of retrieved trials and previous systematic reviews will be searched for citation of potentially eligible trials. We will contact the corresponding author of articles, if any questions about trials arise.

The search strategy for MEDLINE is shown in Table 1.

Table 1 Search strategy to be used in MEDLINE (OVID) database

Number	Search terms
1	Headache Disorders [MeSH]
2	Headache[MeSH]
3	(headache or migraine or cephalgia or cephalalgia or chronic migraine):ti,ab (Word variations have been searched)
4	1 or 2 or 3
5	Acupuncture Therapy [MeSH]
6	(acupuncture or electroacupuncture or electro-acupuncture) :ti,ab
7	5 or 6
8	randomised:ti, ab.
9	randomized:ti,ab.
10	randomly:ti,ab.
11	placebo:ti,ab
12	clinical trials [MeSH]
13	trial ti,ab.
14	randomized controlled trial [MeSH]:ti,ab.
15	randomised controlled trial [MeSH]:ti,ab.
16	controlled clinical trial:ti,ab
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	humans
19	17 and 18

20 4 and 7 and 19

Searching other resources

We will search the US National Institutes of Health Ongoing Trials Register (<http://www.clinicaltrials.gov>), the WHO International Clinical Trials Registry Platform (<http://www.who.int/trialsearch>), and the metaRegister of Controlled Trials (<http://www.controlledtrials.com>) for any relevant ongoing trials. OpenSIGLE (<http://www.opensigle.inist.fr>) will be searched for conference abstracts. We will also search Google Scholar (scholar.google.com/advancedscholarsearch?hl=en&lr=) using the search string “acupuncture AND (headache OR migraine OR chronic migraine)” for potential relevant trials from inception to December 31, 2017.

Data collection and analysis

Selection of studies

Two independent reviewers will examine titles and abstracts of the identified studies and will exclude irrelevant trials. When the first selection is made, full articles will be obtained and checked again in more detail. Following this assessment, a second selection will be performed. The criteria for both selections will be extracted and documented. Possible conflicts will be resolved by discussion, which will also include a third reviewer. The selection process will be presented in a PRISMA flow diagram (Figure 1).

Data extraction and coding

Two independent reviewers will extract data from the selected studies using pilot-tested data forms. They include the following study information: author, year of publication, study populations (European ancestry or not), study design, numbers of patients randomized and treated, number of patients analyzed, baseline analysis, random sequence generation, allocation concealment method, blinding method, imputation method, withdrawals of data, interventions, controls, medication records, and primary and secondary outcomes at all reported time points. For investigating the

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3 characteristics of acupuncture effect, we will extract data on age, sex, populations,
4 headache classifications, number and duration of treatment sessions, features of
5 acupuncture treatment (such as type of acupuncture, needle depths, selection of points,
6 achievement of de-chi, manipulation between acupuncture treatment or not), features
7 of control interventions (sham methods, drug use, or standard treatment details),
8 patients' expectations, and experience of acupuncturists in accordance with STRICTA
9 [29].

10
11 We also will document for each outcome of interest the percentage of missing
12 values reported in the study.
13

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15 For the purpose of analyzing the influence of characteristics of acupuncture on
16 its effect size, a coding sheet will be developed to transform all the described data into
17 categorical data. A pilot testing on this coding sheet will be performed on a separate
18 subset of studies. A coding book will be subsequently established to guide the coding
19 process when the code sheet is completed. Two independent reviewers and
20 statisticians will check the coding sheet when coding process has been finished [36].
21
22

23 **Assessing risk of bias in included studies**

24
25 Two reviewers will independently assess the risk of bias for each included RCTs
26 using the Cochrane Collaboration's risk of bias tool [35]. The critical assessment for
27 the risk of bias will be evaluated in seven domains: random sequence generation,
28 allocation concealment, blinding of participants and personnel, blinding of outcome
29 assessment, incomplete outcome data, selective reporting, and other sources of bias.
30 This assessment will be achieved by assigning a judgement of 'low risk' of bias, 'high
31 risk' of bias, or 'unclear risk' of bias. Because we will only include RCTs using
32 well-described randomization and allocation concealment methods, only those RCTs
33 evaluated as having a low risk of bias for both random sequence generation and
34 allocation concealment will be included. Any disagreement will be resolved by
35 discussion or consensus with a third reviewer. The graphical presentation of
36 assessment of risk of bias will be generated by RevMan V.5.3.5.
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39 **Measures of treatment effect**

40 To address the clinical effect difference between the intervention and control
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3 groups, headache frequency at the completion of treatment and at the end of follow-up
4 will be used as a primary outcome. Pain intensity, responder rate, and mediation
5 intake at the completion of treatment and at the end of follow-up also will be
6 extracted as secondary outcomes. For these continuous outcomes, the mean difference
7 (MD) and standard deviations (SDs) will be extracted and calculated as an effect
8 estimate. Negative values will indicate better outcomes in the acupuncture group.
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14 If the MD or SDs were not reported and not available after contacting the authors,
15 we will use the data that are available, such as the median or P values and confidence
16 intervals, and try to re-calculate MD and SD values from the information recorded in
17 the study.
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23 The safety or adverse outcome will be the number of participants who dropped
24 out due to adverse effects and the number of participants who reported at least one
25 adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will be
26 calculated as the effect estimate. An odds ratio greater than 1 will indicate more
27 events (e.g., dropouts) in the acupuncture group.
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33 For the time window analysis, we will extract outcomes with all the time points
34 using pilot-tested data forms. Subsequently, we will document the quantitative
35 outcomes at the end of treatment together with the length of the treatment period. In a
36 meta-regression, we will adjust treatment effects for time. The R package metafor will
37 allow us to give each outcome a meta-analytic result at different treatment periods.
38 Standard meta-analyses, especially for subgroups, will be performed using the
39 R-package meta [37-38].
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41 42 43 **Unit of analysis issues**

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47 The unit of analysis will be based on aggregated outcome data due to the lack of
48 individual patient data.

48 49 50 **Dealing with missing data**

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60 If there are insufficient details or missing data related to the characteristics of the
studies included for the meta-analysis, we will attempt to contact the study authors for
further information at first. For missing participant data due to dropout or loss to
follow-up, we will apply the following strategies to address missing data assumed to

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3 be not missing at random:

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5 1) If intention to-treat (ITT) analyses were performed in the included studies,
6 we will use the ITT data instead of missing data as the first option.

7
8 2) For continuous missing outcome data, we will try to re-calculate MD and SD
9 values as the first option when the medians, P values or confidence intervals were
10 reported in the included studies.

11
12 3) If there are no ITT data or possible data for re-calculation, we will perform a
13 sensitivity analysis to elucidate the influence of missing data on the effect estimates as
14 a second option. This can be performed by a meta-regression adjusting for the amount
15 of missing data.

16 **Assessment of heterogeneity**

17
18 We will evaluate the heterogeneity of the included studies with I^2 statistic and the
19 τ^2 test. A cutoff point of at least 50% for the I^2 statistic will indicate substantial
20 heterogeneity.

21
22 Our second aim is to investigate which clinical setting and which acupuncture
23 features do influence the effect size and the heterogeneity of the intervention. First,
24 we will define characteristics that may modify the intervention effect according to
25 experienced acupuncturists whose have a qualified acupuncture license and at least 10
26 years of clinical acupuncture experience in accordance with STRICTA [29]. Second,
27 we will examine the correlation between these covariates to exclude possible masking
28 and to establish a core set of covariates. A random-effects meta-regression analysis
29 will be conducted using **metafor** [37] to elucidate the impact of core set covariates on
30 treatment effects.

31
32 Before the meta-analysis can be conducted, the relevant results from each study
33 must be quantified in such a way that the resulting values can be further aggregated
34 and compared. Depending on different aspects (goals of the meta-analysis, the design
35 and types of studies included, and the information provided therein), we will calculate
36 the effect size of interest using the **escalc** function.

37
38 Subsequently, random/mix-effects of the meta-regression model will be fitted by
39 the **rma()** function [37]. The **restricted maximum-likelihood estimator**, which is an

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3 approximately unbiased and efficient estimator, will be used to address the amount of
4 residual heterogeneity τ^2 . The pre-defined covariates (e.g., characteristics of the
5 acupuncturists) will be first fitted independently to examine the possible independent
6 factors contributing to variation in the intervention effect. Subsequently, interaction
7 between covariates (e.g., characteristics of the acupuncturists and session of
8 acupuncture treatment) can be added and detected in the model using the **mods**
9 argument. For the limit of included studies, we will put covariates ≤ 3 into the same
10 model for each model. For the result interpretation, the **estimate** represents the
11 average effect estimates of covariates, and a P value ≤ 0.05 represents a significant
12 difference that indicates the corresponding covariate plays an important role for the
13 intervention effect and heterogeneity. In addition, the amount of heterogeneity in the
14 effect estimate will be estimated by τ^2 . The **I²** statistic estimates (in percent) how
15 much of the total variability in the effect size estimate (which is composed of
16 heterogeneity and sampling variability) can be attributed to heterogeneity among the
17 true effects. The results of the meta-regression outlined above will be presented in a
18 series of summary tables in the meta-analysis.

32 **Assessment of reporting biases**

33 Reporting bias will be explored by constructing funnel plots and performing
34 Egger's test, if there are at least 10 trials included in meta-analysis.

37 **Data synthesis**

38 The synthesis will be done by generating a forest plot for meta-regression. This
39 plot does not contain a summary measure given by a prism below the single studies,
40 but by a prism shown for each single study that shows the aggregated effect for the
41 specific type of study (depending on the covariates of the meta-regression). If the
42 heterogeneity test indicates there is no substantial heterogeneity between studies, the
43 Mantel-Haenszel method implemented by the **rma.mh()** function will be fitted for
44 calculating pooled estimates, 95% confidence intervals, and combined P values. If
45 substantial heterogeneity is indicated by $I^2 \geq 50\%$, the random-effects model will be
46 performed by the DerSimonian and Laird method (DerSimonian 1986) and the **rma**
47 function. The significance of the P value represents the strength of evidence against
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3 the null hypothesis of no intervention effect.

4 **Subgroup analysis**

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6 Subgroup analysis will be performed according to the primary and secondary
7 objectives. To detect possible heterogeneity of the results, subgroup analysis will be
8 conducted for both the primary outcome and secondary outcomes at the end of the
9 treatment session and the end of the follow-up period. We will investigate the effects
10 for four subgroup analyses:
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- 15 1) episodic migraine vs. chronic migraine
- 16 2) acupuncture vs. different type of sham acupuncture and controls
- 17 3) Western studies vs. Chinese studies
- 18 4) early time-point of outcomes vs. later time-point of outcomes

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21 In addition, if we detect any important and significant covariates contributing to
22 the variation of the intervention effect by meta-regression, subgroup analyses will also
23 be conducted according to these covariates.
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27 **Sensitivity analysis**

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29 To confirm the robustness of our findings, a sensitivity analysis will be
30 conducted based on the different levels of bias of the included studies. To evaluate the
31 internal validity of studies or treatment adequacy, we will subsequently remove
32 studies of ‘high risk’ of bias, studies of ‘unclear risk’ of bias, and studies of ‘low risk’
33 of bias using the **metafor** package and **leave1out()** function.
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38 **Summary of evidence**

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40 We will summarize the quality of evidence using the GRADE (Grading of
41 Recommendations Assessment, Development and Evaluation) approach [39] and
42 present ‘Summary of findings’ tables. The ‘Summary of findings’ tables will be
43 generated by the GRADE working group software (GRADEpro or GRADEpro GDT
44 [www.gradepr.org]). The content of the ‘Summary of findings’ tables (main
45 outcomes that are important to patients and decision makers) will be determined by
46 the review group described above. Where possible, both relative and absolute
47 measures of effect will be provided. To assess the quality of evidence, the GRADE
48 approach evaluates the quality of evidence as ‘high’, ‘moderate’, ‘low’, or ‘very low’
49 by outcome. Evidence can be downgraded in category by concerns about risk of bias,
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3 imprecision, inconsistency, indirectness, or publication bias, and also can be upgraded
4 by a large effect size, plausible confounding that could change the effect size, and
5 dose-response relation. Reviewers will downgrade or upgrade the evidence according
6 to the GRADE guideline in the Cochrane handbook, Chapter 11 [35] and also take
7 into account the differences in anticipated effects in the group of primary interest. The
8 total quality of evidence will be decided by not only the reviewers but also based on the
9 opinion of patients, decision makers, and acupuncturists. The whole summarization of
10 the evidence process will be succinct and transparent.
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18 **Ethics and dissemination**

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20 The results of this meta-analysis and meta-regression will be disseminated through
21 publication in a peer-reviewed journal and presented at a relevant conference. The
22 data that will be used will not contain individual patient data; therefore, ethical
23 approval is not required, and there is no concerns about patient's privacy.
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27 **Discussion**

28 This meta-analysis will not only evaluate evidence from published RCTs for the
29 effectiveness of acupuncture in treating both episodic migraine and chronic migraine,
30 but also will detect possible characteristics that influence the main effect and the
31 specific effect of acupuncture for migraine. This will be achieved by using
32 meta-regression. We hope that using meta-regression techniques in this meta-analysis
33 will not only provide a deeper understanding of the effect of acupuncture in patients
34 with migraine but also generate evidence for factors that modify the effect, which will
35 support the optimization of acupuncture treatment for migraine in the pragmatic
36 clinical setting. If this protocol must be amended, we will present the date of each
37 amendment with a description of the change and the corresponding rationale.
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Author Contributions

UM is the guarantor. ZG, UM, CG and ZX contributed to the conception of the study. The manuscript presenting the protocol was drafted by ZG and revised by UM. The search strategy was developed by all authors and will be run by ZG and HL, who will also independently screen the potential studies, extract data from included studies, assess the risk of bias. ZG and UM will conduct and finish the data synthesis. LQ and CH will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors have approved the publication of the protocol.

Competing interests

None declared

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Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement: Technical appendix, statistical code and data set are available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the data set.

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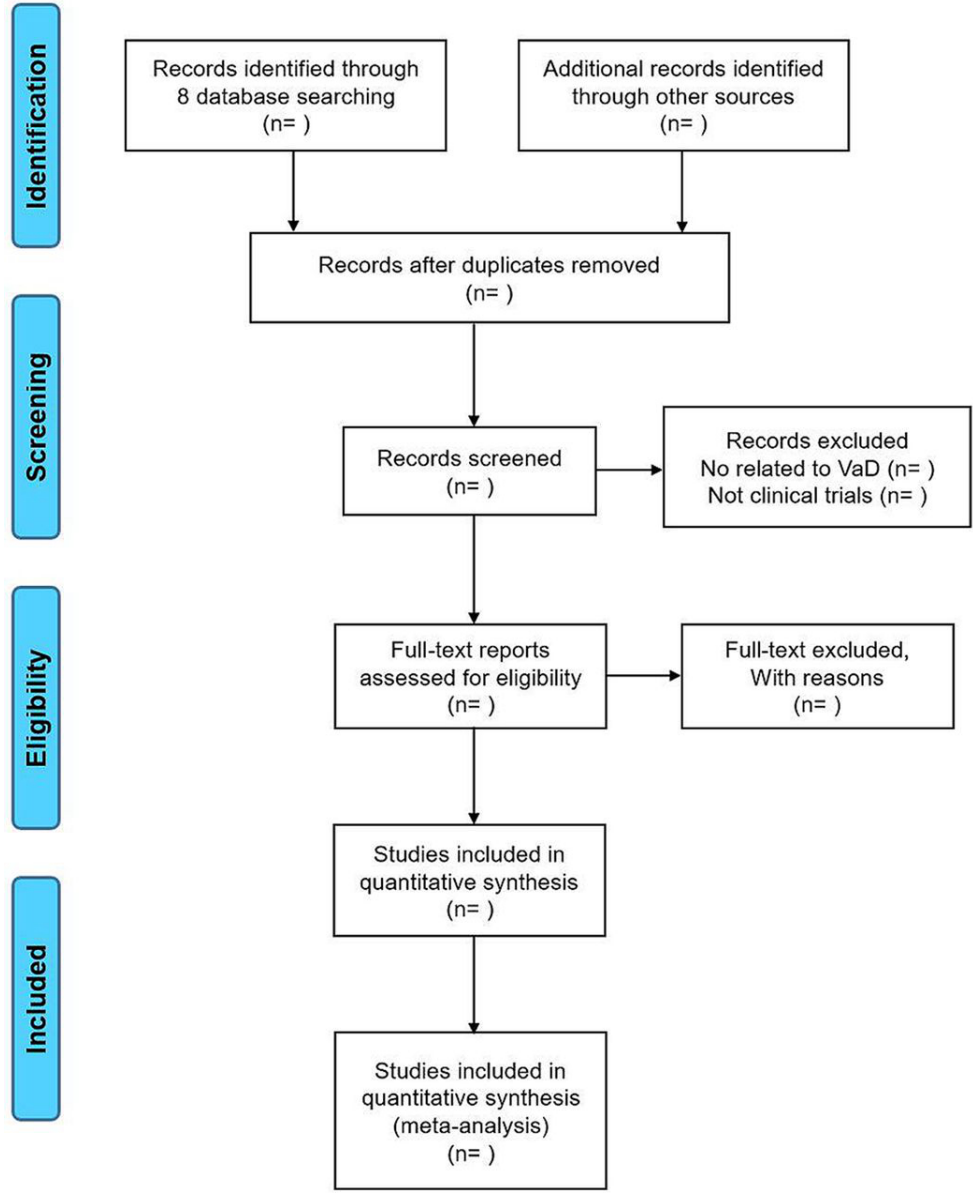
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FIGURES**FIGURE 1. Prisma 2009 flow diagram**

For peer review only

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Prisma_2009_flow_diagram
88x108mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
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	18
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19
	#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	18

1			protocol amendments	
2	Sources	#5a	Indicate sources of financial or other support for the review	19
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4	Sponsor	#5b	Provide name for the review funder and / or sponsor	19
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7	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s),	19
8	funder		if any, in developing the protocol	
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11	Rationale	#6	Describe the rationale for the review in the context of what is	3
12			already known	
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15	Objectives	#7	Provide an explicit statement of the question(s) the review will	6
16			address with reference to participants, interventions,	
17			comparators, and outcomes (PICO)	
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20	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design,	7-10
21			setting, time frame) and report characteristics (such as years	
22			considered, language, publication status) to be used as	
23			criteria for eligibility for the review	
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27	Information	#9	Describe all intended information sources (such as electronic	11
28	sources		databases, contact with study authors, trial registers or other	
29			grey literature sources) with planned dates of coverage	
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32	Search strategy	#10	Present draft of search strategy to be used for at least one	12
33			electronic database, including planned limits, such that it	
34			could be repeated	
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37	Study records -	#11a	Describe the mechanism(s) that will be used to manage	13
38	data management		records and data throughout the review	
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41	Study records -	#11b	State the process that will be used for selecting studies (such	13
42	selection process		as two independent reviewers) through each phase of the	
43			review (that is, screening, eligibility and inclusion in meta-	
44			analysis)	
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48	Study records -	#11c	Describe planned method of extracting data from reports	13
49	data collection		(such as piloting forms, done independently, in duplicate), any	
50	process		processes for obtaining and confirming data from investigators	
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53	Data items	#12	List and define all variables for which data will be sought	13
54			(such as PICO items, funding sources), any pre-planned data	
55			assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be sought,	10
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
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6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	13
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
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13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	14
14			synthesised	
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17		#15b	If data are appropriate for quantitative synthesis, describe	14-15
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
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24		#15c	Describe any proposed additional analyses (such as	16-17
25			sensitivity or subgroup analyses, meta-regression)	
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28		#15d	If quantitative synthesis is not appropriate, describe the type	16
29			of summary planned	
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31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	16
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	17
38	cumulative		assessed (such as GRADE)	
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 44 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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Acupuncture for Migraine: A Protocol for a Meta-Analysis and Meta-regression of Randomized Controlled Trials

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ABSTRACT

Introduction

Although the effectiveness of acupuncture for episodic migraine has been confirmed by multiple clinical trials and Cochrane systematic reviews, the mechanisms underlying the specific effect of acupuncture for migraine remain controversial. We aim to evaluate the effectiveness and safety of acupuncture for both episodic migraine and chronic migraine by meta-analysis and explore the possible factors influencing the specific effect of acupuncture for migraine by meta-regression.

Methods and analysis

We will search for randomized control trials (RCTs) of acupuncture for migraine in the following eight databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED (via OVID), and four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. We will also search OpenSIGLE (opensigle.inist.fr) for conference abstracts. No language restriction will be applied. The selection of studies, data extraction and coding, and assessment of risk of bias of the included studies will be conducted independently by two reviewers. Standard meta-analysis and, if appropriate, meta-regression will be performed using the R packages Meta and Metafor.

Ethics and dissemination

The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data used in this meta-analysis will not contain individual patient data; therefore, ethical approval is not required.

Trial registration number: PROSPERO CRD42018087270.

Keywords: acupuncture; migraine; meta-regression; meta-analysis

Strengths and limitations of this study

1. This meta-analysis will not only evaluate the effectiveness of acupuncture in treating both episodic migraine and chronic migraine but also will detect possible characteristics that influence the main effect and the specific effect of acupuncture for migraine.

2. Equipped with advanced machine learning techniques and R packages Meta and Metafor, this meta-analysis could uniquely explore the interaction and combinatory effects of different clinical factors that may affect the main effect and specific effect of acupuncture for migraine.

3. The results of this meta-analysis may reveal pivotal factors that impact the clinical effect of acupuncture, and thus, will support the optimization of acupuncture treatment for migraine in the pragmatic clinical setting.

4. Electronic databases for Korean and Japanese studies will not be searched. Therefore, language bias may exist.

Introduction

Description of the condition

Migraine is one of the most common headache disorders and is characterized by recurrent unilateral, throbbing, moderate-to-severe attacks of headache lasting from 4–72 h, with or without aura [1]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia and phonophobia, and is aggravated by physical exertion. According to the 2010 Global Burden of Disease Survey, migraine ranked as the third most predominant disorder, as well as the seventh highest specific cause of disability worldwide. In the US, an estimated 36 million individuals experience migraine attacks, with approximately 16%–18% of women and 6%–8% of men suffering recurrent migraine attacks during their professional lives [2–3]. Migraine usually can be categorized as episodic migraine (migraine attacks happening fewer than 15 days each month) and chronic migraine (migraine attacks happening more than 15 days per month) [1]. Two large population-based studies documented a strong tendency for episodic migraine to evolve into chronic migraine, often associated with overuse of

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4 analgesics [4]. Further, a systematic review focusing on the global prevalence of
5 migraine reported that the prevalence of chronic migraine is 0–5.1%, with estimates
6 typically among 1.4–2.2% [5]. Recently, many studies also demonstrated a correlation
7 between migraine and cardiovascular and cerebrovascular diseases [6-7]. A systematic
8 review investigating migraine and cardiovascular disease found that the risk of ischemic
9 stroke was doubled in people who had migraine with aura [8]. It is well accepted that
10 migraine with aura is associated with ischemic stroke in younger women (age \leq 45 years)
11 [9].
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21 **Description of the intervention**

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23 To be considered effective, treatments for migraine should reduce the occurrence
24 of migraine attacks and relieve symptoms in order to improve patients' quality of life
25 and decrease related healthcare utilization. Pharmacological agents for migraine are
26 widely used to reduce migraine attack frequency and pain intensity, including
27 propranolol, metoprolol, flunarizine, valproic acid, and topiramate [10]. Unlike acute
28 migraine that can often be managed with drugs, chronic migraine is difficult to control
29 due to the frequency of attacks and overuse of drugs among migraine patients [5].
30 Furthermore, pharmacological treatment for migraine with oral nonsteroidal anti-
31 inflammatory drugs (NSAIDs) and triptans has a modest effect and often leads to
32 several side effects, such as gastrointestinal and cardiovascular disorders [11]. Thus,
33 there is a strong need for the development and implementation of additional long-term
34 effective, low-risk treatments for migraine.
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46 Acupuncture is a procedure whereby fine needles are inserted into and
47 manipulated within the skin of acupoints at certain depths to reduce symptoms and
48 achieve curing of diseases [12]. Acupuncture originated in China within the Chinese
49 civilization and has become one of the most widely used forms of Traditional Chinese
50 Medicine (TCM). The treatment effect of acupuncture is regarded as balancing the
51 disorder within the human body in order to treat diseases. Such balancing is achieved
52 by activating accurate meridians and acupoints of the body using diverse needling
53 techniques, according to disease and personal status. Currently, even without a clear
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4 understanding of underlying mechanisms, acupuncture has been extensively used for
5 migraine prophylaxis and chronic pain treatment worldwide. According to a survey in
6 the US, 9.9% of patients who received acupuncture treatment did so in search of relief
7 from migraine and other headaches [13]. A 2016 Cochrane Review from Germany
8 concluded that acupuncture is safe and effective for episodic migraine prophylaxis
9 compared to prophylactic drug treatment [14].
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17 **How the intervention might work**

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19 While enhanced calcitonin gene-related peptide (CGRP) and spontaneous cortical
20 spreading depression (CSD) are regarded as causative in triggering migraine [15], the
21 pathophysiology of migraine is attributed to multiple factors, and many of which remain
22 unclear. Recently, an increasing number of studies have confirmed that acupuncture
23 activates the release of opioid peptides in the central nervous system (CNS). Release of
24 these peptides corresponds to long-lasting activation of ascending sensory tracks,
25 thereby relieving an array of pain conditions [16-19]. Furthermore, Zhao et al.
26 confirmed in a migraine rat model that electro-acupuncture treatment can depress
27 CGRP expression in the trigeminal ganglion, which plays a key role in inducing
28 migraine attack [20]. Li et al. also found that acupuncture restores the impaired
29 descending pain modulatory system (DPMS) in migraine patients by decreasing the
30 resting state functional connectivity (rs-fc) between the periaqueductal gray (PAG) and
31 rostral anterior cingulate cortex/medial prefrontal cortex (rACC/mPFC), which directly
32 correlated with the intensity of pain during the migraine attack [21].
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47 In contrast to the conflicting evidence concerning the mechanism by which
48 acupuncture relieves migraine, evidence of the effectiveness of acupuncture for
49 migraine was provided by a series of Cochrane systematic reviews and a large
50 individual patient meta-analysis [14, 22]. However, the concept of a “placebo effect”
51 and “specific effect” regarding the clinical effect of acupuncture for migraine is still
52 controversial [22]. An updated Cochrane review of acupuncture for episodic migraine
53 concluded that acupuncture is an effective treatment for the prevention of migraine, but
54 on the other hand, the difference in the effect size between acupuncture and sham
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4 acupuncture was relatively small [14]. Linde et al. argued that understanding the
5 specific effect of acupuncture is essential for the acceptance of acupuncture as a
6 legitimate treatment in Western countries. Therefore, evidence confirming the specific
7 effect of acupuncture is still in high demand for biomedicine [23]. Nevertheless, key
8 components of the effect of acupuncture remain to be fully uncovered. Accordingly,
9 designing appropriate sham acupuncture as a placebo control is still a difficulty for
10 clinical acupuncture trials. Thus, this debated issue may be an obstacle to the acceptance
11 of acupuncture as a valid therapy in pain management by both Western scientific
12 researchers and policy makers.
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23 **Why it is important to do this review**

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25 To investigate the effect and specificity of acupuncture, a newly updated
26 Individual Patient Data Meta-Analysis of acupuncture for chronic pain [24] concluded
27 that true acupuncture has a long-term effect compared with sham acupuncture.
28 Nevertheless, it also pinpointed that characteristics of acupuncture treatment sessions
29 contribute to the effect of acupuncture, in addition to the specific effects of needling.
30 However, this meta-analysis mainly focused on chronic pain and chronic headache and
31 was not specific to migraine. There is still insufficient evidence to elucidate the specific
32 mechanism of the effect of acupuncture for migraine. Furthermore, a recent German
33 Cochrane Review [14] demonstrated the effectiveness of acupuncture in the prevention
34 of episodic migraine. Whereas, there has been no systematic review of the effect of
35 acupuncture in the prevention of chronic migraine. Therefore, three pivotal questions
36 arise from the former meta-analysis and clinical studies of acupuncture for migraine: i)
37 is acupuncture an effective therapy for both episodic migraine and chronic migraine in
38 the clinical setting? ii) are there any important factors that influence the effect of
39 acupuncture? and iii) are there any features that alter the specific effect of acupuncture
40 compared with sham acupuncture or other controls in clinical acupuncture treatment
41 for migraine? To address these critical questions, we will conduct a meta-analysis of
42 RCTs of acupuncture for migraine.
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Objective

This meta-analysis in adults with episodic or chronic migraine aims to assess:

1. The effectiveness and safety of acupuncture compared to sham acupuncture and drug treatment or waiting list controls in the prevention of migraine;
2. The features that may contribute to: i) different effect sizes between acupuncture and controls, ii) the specific effect of acupuncture, iii) the non-specific effects of sham acupuncture or other controls, and to identify iv) which factors among all those studied most strongly influence the effect of acupuncture.

Methods

Criteria for considering studies for this review

Types of studies

We will only include RCTs investigating the effect of acupuncture on episodic and chronic migraine in adults [4]. We will only include RCTs (parallel groups as well as cross-over) using well-described randomization methods.

We will exclude quasi-randomized clinical trials.

Types of participants

We will include patients of either sex with an age aged 18 and older, who have been diagnosed either with episodic or chronic migraine. Migraine diagnoses must be based on the International Headache Society (ICHD-III beta 2013 and its previous editions ICHD-II 2004; IHS1988) and the Ad Hoc Committee on the Classification of Headache (Ad Hoc 1962) [25-28]. If no specified criteria were documented in the studies, the migraine diagnosis must be based on discriminable and important characteristics of migraine attacks (e.g., recurrent headache, unilateral pain, pulsating quality, moderate or severe intensity, in association with nausea and/or photophobia and phonophobia), as confirmed by patients' doctors or general practitioners. In general, episodic migraine occurs in two to eight episodes but with migraine attacks less than 15 days per month, whereas chronic migraine patients usually suffer migraine attacks at least 15 days per month (180 days per year) for at least 3 months [1].

The duration of migraine history must be longer than 1 year in the majority of

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4 patients. This criterion will be considered met if:

5 1) An explicit description of the duration of migraine history longer than 1 year is
6 noted in the inclusion criteria;

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8 2) The mean duration minus one standard deviation is longer than 1 year as shown
9 in the table of baseline characteristics; or

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11 3) Other information confirms that the criterion was met (e.g., proportions with
12 duration ranges are presented in the studies).

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14 We will include studies in which patients were defined as having ‘combination’ or
15 ‘mixed’ migraine only if we can extract the data on participants affected with migraine.

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17 We will exclude trials including patients with secondary headache. Studies
18 including chronic migraine patients with medication-overuse history (according to the
19 International Classification of Headache Disorders, 3rd beta edition (ICHD-IIIβ)
20 criteria [25]) will also be excluded.

21 22 **Types of intervention**

23 24 **Experimental intervention**

25
26 We define acupuncture (both manual and electrical stimulation) as the
27 experimental intervention. Acupuncture is defined as insertion of specific needles into
28 the skin of the body at selected acupoints (defined as ‘meridian acupoints’, which
29 belong to 14 meridians in the body according to traditional acupuncture theory), pain
30 points (defined as ‘a-shi points’ in the location of pain condition according to traditional
31 acupuncture theory), or extraordinary points (defined as ‘extra points’, which do not
32 belong to the 14 meridians but have a therapeutic effect in the body according to
33 traditional acupuncture theory) up to definite therapeutic depths. In accordance with a
34 previous Cochrane systematic review of acupuncture for migraine [14], the dosage of
35 acupuncture treatment must be at least six treatment sessions, with a duration of at least
36 20 minutes per session and at least one session per week in the majority of patients.
37 Also, for the purpose of ensuring the clinical effectiveness of acupuncture treatment,
38 the acupuncturists who administered treatment in the included studies should be
39 confirmed to have a relevant acupuncture qualification or professional affiliation, or a
40 certain number of years in acupuncture practice. In addition, trials that define
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4 acupuncture in combination with other pharmacological treatment or physical treatment
5 as the experimental intervention but mainly investigate the effectiveness of acupuncture
6 will also be included.
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9 As this meta-analysis will mainly focus on the effectiveness of acupuncture on the
10 basis of traditional acupuncture theory and the Standards for Reporting Interventions in
11 Clinical Trials of Acupuncture (STRICTA) [29], we will exclude trials in which:
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15 1) Acupuncture was performed at one specific body area but not at acupoints of
16 the body, such as scalp acupuncture, ear acupuncture, and wrist-ankle acupuncture.
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19 2) Acupoints were stimulated by other techniques without traditional acupuncture
20 needling, including acupressure, laser stimulation, injection acupuncture, dry needling,
21 and trigger point therapy.
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24 **Control interventions**

25 We will include three types of control interventions:
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28 1) No treatment or waiting list-control during the trial period.
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31 2) Sham acupuncture (intervention resembling verum acupuncture treatment but
32 using superficial needle insertion, needle insertion at non-acupuncture points or at
33 points not indicated for the condition under study, and 'placebo' needles that seem to be
34 inserted into skin but actually are not [30-33], etc). Trials which have intervention
35 groups that compared either acupuncture alone with sham intervention alone or
36 acupuncture plus one or more therapies with sham intervention plus the same therapies
37 also will be included.
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44 3) Pharmacological treatment that is given as a control during a comparable time
45 as application of acupuncture treatment.
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48 Because our objective is to evaluate the effectiveness of acupuncture treatment
49 compared to sham acupuncture treatment, no treatment, or western medicine treatment,
50 we will exclude trials with herbal medicine, moxibustion, bloodletting, and other
51 different forms of acupuncture as control interventions.
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55 **Types of outcome measures**

56 To be considered for inclusion, trials must have evaluated at least one of the
57 following primary efficacy outcome measures [34] for at least 4 weeks from the
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beginning of acupuncture treatment:

- 1) Number of migraine attacks per evaluation interval;
- 2) Number of migraine days per evaluation interval;

Before the review process, a review board consisting of an epidemiologist, acupuncturist, migraine patient, social policymakers, and statistician will be established to determine all the key outcomes, with respect of migraine patients' opinions and values.

We will exclude studies that:

- 1) Included primary outcome measurements only using "effectiveness rate";
- 2) Exclusively used objective or surrogate outcome measures;
- 3) Evaluated treatment or measurement of acute migraine attack;
- 4) Had outcome evaluation periods shorter than 4 weeks (after randomization to end of treatment).

According to the guidelines for controlled trials of drugs in migraine published by the IHS [34], the main outcomes will be:

Primary outcome:

Migraine frequency:

We will consider the following outcomes measuring headache frequency:

- 1) Numbers of migraine attacks per evaluation interval;
- 2) Number of migraine days per evaluation interval.

Secondary outcomes:

1) Migraine intensity: outcomes recording pain intensity using numerical/verbal scale, such as average headache severity per evaluation interval.

2) Responder rate (patients with $\geq 50\%$ reduction in headache frequency) per evaluation interval.

3) Medication intake for migraine per evaluation interval.

4) Adverse events, including the number of patients who dropped out due to an adverse event and the number of patients who reported adverse events.

In contrast to a previous meta-analysis of acupuncture for migraine prophylaxis, we define responder rate as a secondary outcome. According to the IHS guideline [34], the

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4 responder rate is comparatively insensitive to the treatment effect and particularly
5 vulnerable to selection bias. The responder rate can be evaluated as an important
6 secondary outcome in placebo-controlled RCTs of migraine.
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9 Outcome measurement may be performed at specific time points; the choice will
10 depend on the time when the outcomes are reported in the reviewed studies. Specific
11 decisions will be made by the review board.
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14 The following outcome measures will be presented in the 'Summary of findings'
15 table:
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- 17 1) Migraine frequency.
- 18 2) Migraine intensity.
- 19 3) Responder rate.
- 20 4) Medication use for migraine attacks.
- 21 5) Adverse events.

22 **Patient and public involvement**

23 Patient and public involvement will be considered during the entire meta-analysis.
24 We collected patients' suggestions and comments from both China and Italy for the
25 selection of outcomes and design of this meta-analysis. In addition, we will collaborate
26 with the Italian Federation of Acupuncture Societies (FISA) to collect novel evidence
27 for the application of acupuncture for migraine and establish a long-term medical
28 collaboration through the European Union's Seventh Framework Programme
29 (FP7/2007-2013) under REA grant agreement number PIRSES-GA-2013-612 589:
30 CHETCH (China and Europe Taking Care of Healthcare solutions). Thus, our findings
31 will be regularly disseminated to both Chinese and European residents by the local
32 medical institutions.
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49 **Search methods for identification of studies**

50 We will conduct our meta-analysis in accordance with the Cochrane Handbook
51 for Systematic Reviews of Interventions [35] and will report this meta-analysis based
52 on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)
53 guideline.
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59 **Electronic searches**

We will search the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and AMED (via OVID) databases as well as four Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Science and Technology Periodical Database, and Wanfang Database) from inception to December 31, 2017. No language restriction will be applied. The reference lists of retrieved trials and previous systematic reviews will be searched for citation of potentially eligible trials. We will contact the corresponding author of articles, if any questions about trials arise.

The search strategy for MEDLINE is shown in Table 1.

Table 1 Search strategy to be used in MEDLINE (OVID) database

Number	Search terms
1	Headache Disorders [MeSH]
2	Headache[MeSH]
3	(headache or migraine or cephalgia or cephalalgia or chronic migraine):ti,ab (Word variations have been searched)
4	1 or 2 or 3
5	Acupuncture Therapy [MeSH]
6	(acupuncture or electroacupuncture or electro-acupuncture) :ti,ab
7	5 or 6
8	randomised:ti, ab.
9	randomized:ti,ab.
10	randomly:ti,ab.
11	placebo:ti,ab
12	clinical trials [MeSH]
13	trial ti,ab.
14	randomized controlled trial [MeSH]:ti,ab.
15	randomised controlled trial [MeSH]:ti,ab.
16	controlled clinical trial:ti,ab
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	humans
19	17 and 18
20	4 and 7 and 19

Searching other resources

We will search the US National Institutes of Health Ongoing Trials Register (<http://www.clinicaltrials.gov>), the WHO International Clinical Trials Registry Platform (<http://www.who.int/trialsearch>), and the metaRegister of Controlled Trials (<http://www.controlledtrials.com>) for any relevant ongoing or unpublished trials.

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4 OpenSIGLE (opensigle.inist.fr) will be searched for conference abstracts. We will also
5 search Google Scholar (scholar.google.com/advanced scholar search?hl=en&lr=) using
6 the search string “acupuncture AND (headache OR migraine OR chronic migraine)”
7
8 for potentially relevant trials from inception to December 31, 2017.
9

11 **Data collection and analysis**

13 **Selection of studies**

15 Two independent reviewers will examine titles and abstracts of the identified
16 studies and will exclude irrelevant trials. When the first selection is made, full articles
17 will be obtained and checked again in more detail. Following this assessment, a second
18 selection will be performed. The criteria for both selections will be extracted and
19 documented. Possible conflicts will be resolved by discussion, which will also include
20 a third reviewer. The selection process will be presented in a PRISMA flow diagram
21 (Figure 1).
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29 **Data extraction and coding**

31 Two independent reviewers will extract data from the selected studies using pilot-
32 tested data forms. They will include the following study information: author, year of
33 publication, study populations (European ancestry or not), study design, numbers of
34 patients randomized and treated, number of patients analyzed, baseline analysis,
35 random sequence generation, allocation concealment method, blinding method,
36 imputation method, withdrawals of data, interventions, controls, medication records,
37 and primary and secondary outcomes at all reported time points. For investigating the
38 characteristics of acupuncture effect, we will extract data on age, sex, populations,
39 headache classifications, number and duration of treatment sessions, features of
40 acupuncture treatment (such as type of acupuncture, needle depths, selection of points,
41 achievement of de-chi, manipulation between acupuncture treatment or not), features
42 of control interventions (sham methods, drug use, or standard treatment details),
43 patients' expectations, and experience of acupuncturists in accordance with STRICTA
44 [29].
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58 We also will document for each outcome of the percentage of missing values
59 reported in the study.
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4 For the purpose of analyzing the influence of characteristics of acupuncture on its
5 effect size, a coding sheet will be developed to transform all the described data into
6 categorical data. Pilot testing on this coding sheet will be performed on a separate subset
7 of studies. A coding book will be subsequently established to guide the coding process
8 when the code sheet is completed. Two independent reviewers and statisticians will
9 check the coding sheet when coding process has been finished [36].
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15 **Assessing risk of bias in included studies**

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17 Two reviewers will independently assess the risk of bias for each included RCTs
18 using the Cochrane Collaboration's risk of bias tool [35]. The critical assessment for
19 the risk of bias will be evaluated in seven domains: random sequence generation,
20 allocation concealment, blinding of participants and personnel, blinding of outcome
21 assessment, incomplete outcome data, selective reporting, and other sources of bias.
22 This assessment will be achieved by assigning a judgement of 'low risk' of bias, 'high
23 risk' of bias, or 'unclear risk' of bias. Because we will only include RCTs using well-
24 described randomization and allocation concealment methods, only those RCTs
25 considered to have a low risk of bias for both random sequence generation and
26 allocation concealment will be included. Any disagreement will be resolved by
27 discussion or consensus with a third reviewer. The graphical presentation of
28 assessment of risk of bias will be generated by RevMan V.5.3.5.
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40 **Measures of treatment effect**

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42 To address the clinical effect difference between the intervention and control
43 groups, headache frequency at the completion of treatment and at the end of follow-up
44 will be used as a primary outcome. Pain intensity, responder rate, and medication intake
45 at the completion of treatment and at the end of follow-up also will be extracted as
46 secondary outcomes. For these continuous outcomes, the mean difference (MD) and
47 standard deviations (SDs) will be extracted and calculated as an effect estimate.
48 Negative values will indicate better outcomes in the acupuncture group.
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56 If the MD or SDs were not reported and not available after contacting the authors,
57 we will use the data that are available, such as the median or P values and confidence
58 intervals, and try to re-calculate MD and SD values from the information recorded in
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4 the study.

5 The safety or adverse outcome will be the number of participants who dropped out
6 due to adverse effects and the number of participants who reported at least one adverse
7 event or effect. For these dichotomous outcomes, the odds ratio (OR) will be calculated
8 as the effect estimate. An odds ratio greater than 1 will indicate more events (e.g.,
9 dropouts) in the acupuncture group.
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15 For the time window analysis, we will extract outcomes with all the time points
16 using pilot-tested data forms. Subsequently, we will document the quantitative
17 outcomes at the end of treatment together with the length of the treatment period. In a
18 meta-regression, we will adjust treatment effects for the time. The R package metafor
19 will allow us to give each outcome a meta-analytic result at different treatment periods.
20 Standard meta-analyses, especially for subgroups, will be performed using the R-
21 package meta [37-38].
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29 **Unit of analysis issues**

30 The unit of analysis will be based on aggregated outcome data due to the lack of
31 individual patient data.
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34 **Dealing with missing data**

35 If there are insufficient details or missing data in relation to the characteristics of
36 the studies included in the meta-analysis, we will attempt to contact the study authors
37 for further information first. For missing participant data due to dropout or loss to
38 follow-up, we will apply the following strategies to address missing data assumed to be
39 not missing at random:
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45 1) If intention to-treat (ITT) analyses were performed in the included studies, we
46 will use the ITT data instead of missing data as the first option.
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49 2) For continuous missing outcome data, we will try to re-calculate MD and SD
50 values as the first option when the medians, P values or confidence intervals are
51 reported in the included studies.
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55 3) If there are no ITT data or possible data for re-calculation, we will perform a
56 sensitivity analysis to elucidate the influence of missing data on the effect estimates as
57 a second option. This can be performed by a meta-regression adjusting for the amount
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4 of missing data.

5 **Assessment of heterogeneity**

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7 We will evaluate the heterogeneity of the included studies with I^2 statistic and the
8 tau² test. A cutoff point of at least 50% for the I^2 statistic will indicate substantial
9 heterogeneity.
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12 Our second aim is to investigate which clinical setting and which acupuncture
13 features do influence the effect size and the heterogeneity of the intervention. First, we
14 will define characteristics that may modify the intervention effect according to
15 experienced acupuncturists. These acupuncturists are required to have a qualified
16 acupuncture license and at least 10 years of clinical acupuncture experience in
17 accordance with STRICTA [29]. Second, we will examine the correlation between
18 these covariates to exclude possible masking and to establish a core set of covariates.
19 A random-effects meta-regression analysis will be conducted using **metafor** [37] to
20 elucidate the impact of core set covariates on treatment effects.
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24 Before the meta-analysis can be conducted, the relevant results from each study
25 must be quantified in such a way that the resulting values can be further aggregated and
26 compared. Depending on different aspects (goals of the meta-analysis, the design and
27 types of studies included, and the information provided therein), we will calculate the
28 effect size of interest using the **escalc** function.
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31 Subsequently, random/mix-effects of the meta-regression model will be fitted by
32 the **rma()** function [37]. The **restricted maximum-likelihood estimator**, which is an
33 approximately unbiased and efficient estimator, will be used to address the amount of
34 residual heterogeneity tau². The pre-defined covariates (e.g., characteristics of the
35 acupuncturists) will be first fitted independently to examine the possible independent
36 factors contributing to variation in the intervention effect. Subsequently, interaction
37 between covariates (e.g., characteristics of the acupuncturists and session of
38 acupuncture treatment) can be added and detected in the model using the **mods**
39 argument. For the limit of included studies, we will put covariates_{≤3} into the same
40 model for each model. For the result interpretation, the **estimate** represents the average
41 effect estimates of covariates, and a P value_{≤0.05} represents a significant difference
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4 that indicates the corresponding covariate plays an important role for the intervention
5 effect and heterogeneity. In addition, the amount of heterogeneity in the effect estimates
6 will be estimated by τ^2 . The I^2 statistic estimates (in percent) how much of the total
7 variability in the effect size estimate (which is composed of heterogeneity and sampling
8 variability) can be attributed to heterogeneity among the true effects. The results of the
9 meta-regression outlined above will be presented in a series of summary tables in the
10 meta-analysis.
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17 **Assessment of reporting biases**

18 Reporting bias will be explored by constructing funnel plots and performing
19 Egger's test, if there are at least 10 trials included in meta-analysis.
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22 **Data synthesis**

23 The synthesis will be done by generating a forest plot for meta-regression. This
24 plot does not contain a summary measure given by a prism below the single studies,
25 but by a prism shown for each single study that shows the aggregated effect for the
26 specific type of study (depending on the covariates of the meta-regression). If the
27 heterogeneity test indicates there is no substantial heterogeneity between studies, the
28 Mantel-Haenszel method implemented by the `rma.mh()` function will be fitted for
29 calculating pooled estimates, 95% confidence intervals, and combined P values. If
30 substantial heterogeneity is indicated by $I^2 \geq 50\%$, the random-effects model will be
31 performed by the DerSimonian and Laird method (DerSimonian 1986) and the `rma`
32 function. The significance of the P value represents the strength of evidence against the
33 null hypothesis of no intervention effect.
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45 **Subgroup analysis**

46 Subgroup analysis will be performed according to the primary and secondary
47 objectives. To detect possible heterogeneity of the results, subgroup analysis will be
48 conducted for both the primary outcome and secondary outcomes at the end of the
49 treatment session and the end of the follow-up period. We will investigate the effects
50 in four subgroup analyses:
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- 55 1) Episodic migraine vs. chronic migraine
- 56 2) Acupuncture vs. different type of sham acupuncture and controls
- 57 3) Western studies vs. Chinese studies

4) Early time-point of outcomes vs. later time-point of outcomes

In addition, if we detect any important and significant covariates contributing to the variation of the intervention effect by meta-regression, subgroup analyses will also be conducted according to these covariates.

Sensitivity analysis

To confirm the robustness of our findings, a sensitivity analysis will be conducted based on the different levels of bias of the included studies. To evaluate the internal validity of studies or treatment adequacy, we will subsequently remove studies of ‘high risk’ of bias, studies of ‘unclear risk’ of bias, and studies of ‘low risk’ of bias using the **metafor** package and **leave1out** function.

Summary of evidence

We will summarize the quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [39] and present ‘Summary of findings’ tables. The ‘Summary of findings’ tables will be generated by the GRADE working group software (GRADEpro or GRADEpro GDT [www.gradepr.org]). The content of the ‘Summary of findings’ tables (main outcomes that are important to patients and decision makers) will be determined by the review group described above. Where possible, both relative and absolute measures of effect will be provided. To assess the quality of evidence, the GRADE approach evaluates the quality of evidence as ‘high’, ‘moderate’, ‘low’, or ‘very low’ by the outcome. Evidence can be downgraded in category by concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias, and also can be upgraded by a large effect size, plausible confounding that could change the effect size, and dose-response relation. Reviewers will downgrade or upgrade the evidence according to the GRADE guideline in the Cochrane handbook, Chapter 11 [35] and also take into account the differences in anticipated effects in the group of primary interest. The total quality of the evidence will be on the basis of both reviewers and all the members of the review board.

Ethics and dissemination

The results of this meta-analysis and meta-regression will be disseminated through

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4 publication in a peer-reviewed journal and be presented at a relevant conference. The
5 data that will be used will not contain individual patient data; therefore, ethical approval
6 is not required, and there are no concerns about patients' privacy.
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10 **Discussion**

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12 This meta-analysis will not only evaluate the evidence from published RCTs for
13 the effectiveness of acupuncture in treating both episodic migraine and chronic
14 migraine, but also will detect possible characteristics that influence the main effect and
15 the specific effect of acupuncture for migraine. This will be achieved by using meta-
16 regression. We hope that using meta-regression techniques in this meta-analysis will
17 not only provide a deeper understanding of the effect of acupuncture in patients with
18 migraine, but also generate evidence for factors that modify the effect, which will
19 support the optimization of acupuncture treatment for migraine in the pragmatic clinical
20 setting. If this protocol must be amended, we will present the date of each amendment
21 with a description of the change and the corresponding rationale.
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Author Contributions

UM is the guarantor. ZG, UM, CG and ZX contributed to the conception of the study. The manuscript presenting the protocol was drafted by ZG and revised by UM. The search strategy was developed by all authors and will be run by ZG and HL, who will also independently screen the potential studies, extract data from included studies, and assess the risk of bias. ZG and UM will conduct and finish the data synthesis. LQ and CH will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors have approved the publication of the protocol.

Competing interests

None declared

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Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement A technical appendix, the statistical code, and the data set are available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the data set.

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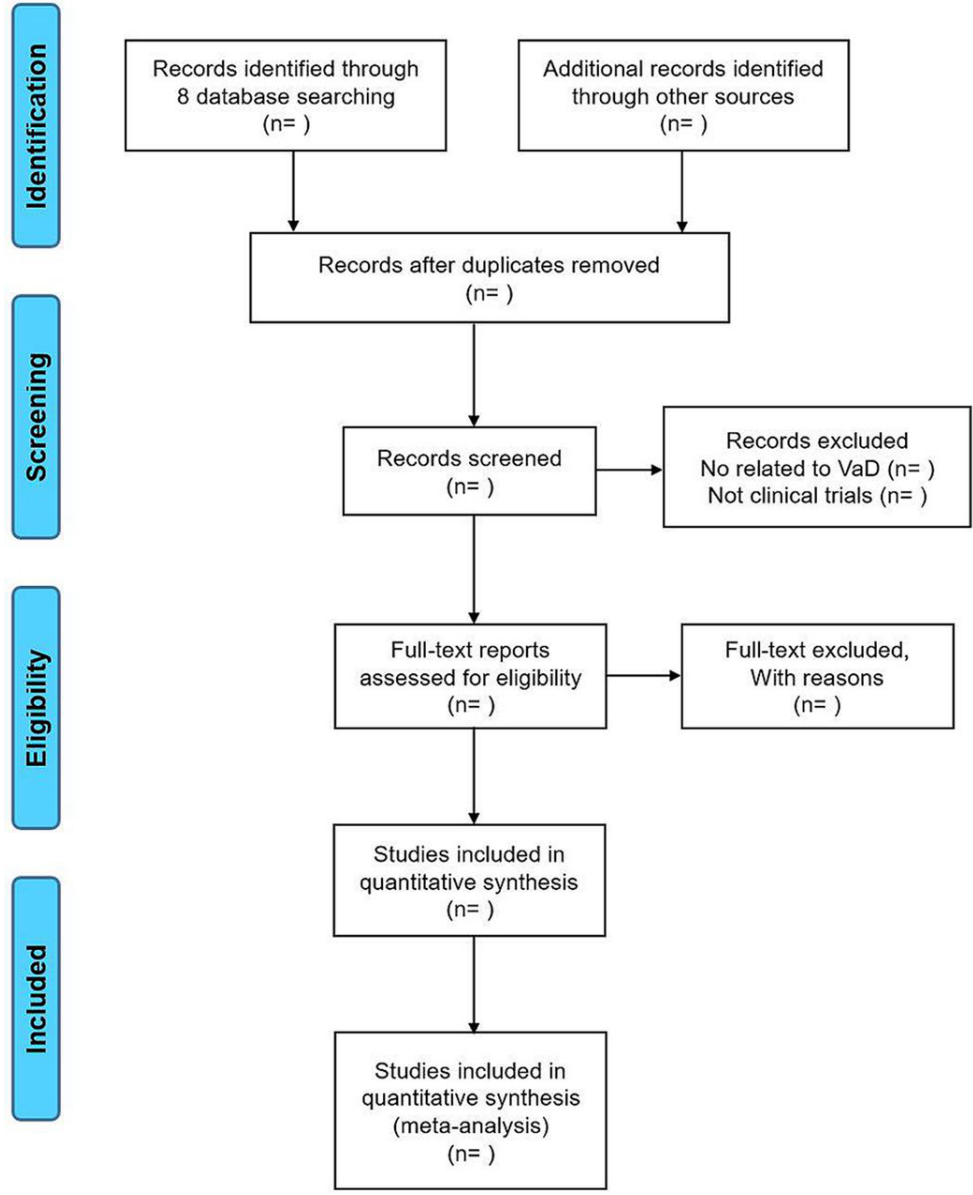
FIGURES

FIGURE 1. Prisma 2009 flow diagram

For peer review only

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Prisma_2009_flow_diagram
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
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	18
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19
	#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	18

		protocol amendments	
1			
2	Sources	#5a Indicate sources of financial or other support for the review	19
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4	Sponsor	#5b Provide name for the review funder and / or sponsor	19
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6			
7	Role of sponsor or	#5c Describe roles of funder(s), sponsor(s), and / or institution(s),	19
8	funder	if any, in developing the protocol	
9			
10			
11	Rationale	#6 Describe the rationale for the review in the context of what is	3
12		already known	
13			
14	Objectives	#7 Provide an explicit statement of the question(s) the review will	6
15		address with reference to participants, interventions,	
16		comparators, and outcomes (PICO)	
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20	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design,	7-10
21		setting, time frame) and report characteristics (such as years	
22		considered, language, publication status) to be used as	
23		criteria for eligibility for the review	
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27	Information	#9 Describe all intended information sources (such as electronic	11
28	sources	databases, contact with study authors, trial registers or other	
29		grey literature sources) with planned dates of coverage	
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32	Search strategy	#10 Present draft of search strategy to be used for at least one	12
33		electronic database, including planned limits, such that it	
34		could be repeated	
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37	Study records -	#11a Describe the mechanism(s) that will be used to manage	13
38	data management	records and data throughout the review	
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41	Study records -	#11b State the process that will be used for selecting studies (such	13
42	selection process	as two independent reviewers) through each phase of the	
43		review (that is, screening, eligibility and inclusion in meta-	
44		analysis)	
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48	Study records -	#11c Describe planned method of extracting data from reports	13
49	data collection	(such as piloting forms, done independently, in duplicate), any	
50	process	processes for obtaining and confirming data from investigators	
51			
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53	Data items	#12 List and define all variables for which data will be sought	13
54		(such as PICO items, funding sources), any pre-planned data	
55		assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be sought,	10
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
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6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	13
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
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13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	14
14			synthesised	
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17		#15b	If data are appropriate for quantitative synthesis, describe	14-15
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
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24		#15c	Describe any proposed additional analyses (such as	16-17
25			sensitivity or subgroup analyses, meta-regression)	
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28		#15d	If quantitative synthesis is not appropriate, describe the type	16
29			of summary planned	
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31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	16
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	17
38	cumulative		assessed (such as GRADE)	
39	evidence			
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 44 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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