BMJ Open

Factors Associated with the Magnitude Of acUpuncture treatment effectS (FAMOUS): a meta-epidemiological study of acupuncture randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060237
Article Type:	Original research
Date Submitted by the Author:	16-Dec-2021
Complete List of Authors:	Gang, Weijuan; China Academy of Chinese Medical Sciences, Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Centre for Evidence-Based Traditional Chinese Medicine Xiu, Wencui; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Shi, Lanjun; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Zhou, Qi; McMaster University Jiao, Ruimin; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Yang, Jiwei; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Shi, Xiaoshuang; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Sun, Xiaoyue; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Zeng, Zhao; Guangzhou University of Chinese Medicine Witt, Claudia; University of Zurich, Institute for Complementary and Integrative Medicine, University Hospital Zurich Thabane, Lehana; McMaster University, Song, Ping; China Academy of Chinese Medical Sciences Yang, Longhui; China Academy of Chinese Medical Sciences Guyatt, Gordon; McMaster University, Jing, Xianghong; China Academy of Chinese Medical Sciences, Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Centre for Evidence Based Traditional Chinese Medicine Zhang, Yuqing; McMaster University, Department of Health Research Methods, Evidence, and Impact; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion
Keywords:	COMPLEMENTARY MEDICINE, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Original Investigation

Factors Associated with the Magnitude Of acUpuncture treatment effectS (FAMOUS): a meta-epidemiological study of acupuncture randomized controlled trials

Wei-Juan Gang[1,2], MD, PhD; Wen-Cui Xiu[1,2], MD Candidate; Lan-Jun Shi[1,2], MD Candidate; Qi Zhou[3], PhD; Rui-Min Jiao[1,2], MD; Ji-Wei Yang[1,2], MD; Xiao-Shuang Shi[1,2], MD, PhD; Xiao-Yue Sun[1,2], MD Candidate; Zhao Zeng[4], MD; Claudia M. Witt[5], MD, MBA; Lehana Thabane[3], PhD; Ping Song[6], MD; Long-Hui Yang[6], MD; Gordon Guyatt[3,7], MD. MSc; Xiang-Hong Jing[1,2†], MD, PhD; and Yu-Qing Zhang[1,3,8†], MD, MSc, PhD, on behalf of FAMOUS Group

Affiliations

1 Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China

2 China Center for Evidence-Based Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, China

3 Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

4 Guangzhou University of Chinese Medicine, Guangzhou, China

5 Institute for Complementary and Integrative Medicine, University Hospital Zurich and University of Zurich, Zurich, Switzerland

6 China Academy of Chinese Medical Sciences, Beijing, China

7 Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

8 Ningbo Nottingham Grade center, University of Nottingham, Ningbo, China

† Authors equally contributed to this work.

†Correspondence to:

Xiang-Hong Jing, Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China.

Email: xhjingt66@163.com

Phone: +86 13671120972

Yu-Qing Zhang, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada

Email: madisonz1220@gmail.com

TEL: +19059205829

Manuscript word count: 3193

ABSTRACT

OBJECTIVE

To identify factors and assess to what extent they impact the magnitude of the treatment effect of acupuncture therapies across therapeutic areas.

DATA SOURCE

Medline, Embase, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Wanfang Database, VIP Database, and China Biology Medicine disc, between 2015 and 2019.

STUDY SELECTION

The inclusion criteria were trials with a total number of randomized patients larger than 100, at least one patient-important outcome and one of two sets of comparisons.

DATA ANALYSIS

The potential independent variables were identified by reviewing relevant literature and consulting with experts. We conducted meta-regression analyses with standardized mean difference (SMD) as effect estimate for the dependent variable. The analyses included univariable meta-regression and multivariable meta-regression using a three-level robust mixed model.

RESULTS

1304 effect estimates from 584 acupuncture RCTs were analysed. The multivariable analyses contained 15 independent variables due to missing factor data and collinearity. In the multivariable analysis, the following produced larger treatment effects of large magnitude (>0.4): quality of life (difference of adjusted SMDs 0.51, 95% confidence interval 0.24 to 0.77), or pain (0.48, 0.27 to 0.69), or function (0.41, 0.21 to 0.61) versus major events. The following produced larger treatment effects of moderate magnitude (0.2-0.4): single-centered versus multicentered RCTs (0.38, 0.10 to 0.66); penetration acupuncture versus non-penetration types of acupuncture (0.34, 0.15 to 0.53); non-pain symptoms versus major events (0.32, 0.12 to 0.52). The following produced larger treatment effects of small (<0.2)

magnitude: high versus low frequency treatment sessions (0.19, 0.03 to 0.35); pain versus non-pain symptoms (0.16, 0.04 to 0.27); unreported versus reported funding (0.12, 0 to 0.25).

CONCLUSION

Patients, clinicians, and policymakers should consider penetrating over non-penetrating acupuncture and more frequent treatment sessions when feasible and acceptable. When designing future acupuncture RCTs, trialists should consider factors that impact acupuncture treatment effects.

Keywords:

Acupuncture; randomised controlled trial (RCT); influential factor; treatment effect; meta-regression; meta-epidemiology; multivariable analysis

STRENGTHS AND LIMITATIONS OF THE STUDY

- Our study is highly patient-centered and clinically relevant. To ensure the conclusion from our study is the most pertinent for healthcare decision-making, we included only patient-important outcomes. We consulted a group of international clinicians, researchers, and patients when choosing the independent variables.
- We constructed a robust three-level mixed model multivariable analysis to adjust for multiple variables to reduce the potential bias raised from the univariable analysis. To deal with the collinearity and substantial amount of outlier and influential values in our datasets, we used Cramer's V and the weighting approach of robust regression.
- Our study has a high methodological rigor. We worked with an experienced medical librarian to develop a systematic and exhaustive search strategy. Teams of reviewers then screened and extracted data independently and in duplicate, with third-party adjudication of disagreement.
- Acupuncture RCTs poorly reported the risk of bias and acupuncture techniques related factors. Thus, we could not include some important independent variables such as practitioners' experience in the multivariable analyses.

- Some factors (e.g., country, trial registered) distributed extremely imbalanced, limiting the results' generalisability.

INTRODUCTION

Acupuncture is one of the most used and researched interventions under the integrative medicine umbrella.[1-4] By 2014, the total number of acupuncture randomized controlled trial (RCT) has increased dramatically and accounted for 20.3% of all acupuncture studies[5]. Since 2010, over 1,000 acupuncture RCTs were published annually, with the total number exceeding 10,000 to date.[6]

Acupuncture's treatment effect varies largely across trials.[7] [8] Efforts to determine factors associated with effect size in acupuncture RCTs have reported conflicting findings. For example, Vickers et al. reported that, in studies of chronic pain, penetrating sham versus non-penetrating and non-needle sham control showed larger treatment effects.[9] However, other studies reported that the effect of acupuncture in pain studies was unrelated to the type of sham acupuncture [10] [11]. Some found the total number of acupuncture treatments[11-13], frequency of treatment sessions[14] , and acupuncture type (manual acupuncture versus electroacupuncture) [14] were significant factors of the treatment effect whereas others did not.[9] [15] The reason may be related to little data variation[15], small number of included studies[12] [14], and variation of the clinical areas and settings investigated[10] [11] [16].

To improve acupuncture RCTs' design, and optimize acupuncture interventions' clinical effectiveness, we conducted this meta-epidemiological study, including acupuncture RCTs published between 2015 to 2019 across therapeutic areas and outcomes, and explored the factors of acupuncture's treatment effects. We aim to a) identify factors regarding patient, acupuncture, comparator, outcome, and methodology that impact the magnitude of the treatment effect of acupuncture therapies and b) explore to what extent the factors impact the treatment effect across therapeutic areas.

METHODS

Definitions

We define acupuncture therapies based on the World Health Organization definition:

Acupuncture literally means to puncture with a needle. However, there may also involve the

application of other kinds of stimulation to certain points[17]. The study addressed commonly used acupuncture modalities, including manual acupuncture, electroacupuncture (electro-acupuncture), laser acupuncture, transcutaneous electrical acupoint stimulation (TEAS), acupressure, traditional body needling, ear (auricular) acupuncture, and scalp acupuncture.

We define sham acupuncture as an intervention with a minimal treatment effect designed to blind patients as they received real acupuncture [18]. Often sham acupuncture includes 'placebo' needles with a blunt collapsing tip that does not penetrate the skin, real acupuncture but inserted at non-acupuncture points, or true acupuncture points but not targeting the intended disease. Non-needle sham can be detuned lasers, deactivated transcutaneous electric nerve stimulation devices, or less pressure on acupuncture points.

We define a patient-important outcome as one in which the patient would be interested, despite the risk, burden or cost, were it the only outcome to improve with an intervention[19]. To differentiate from individual outcomes (e.g., dysphagia), we define a construct as a category of patient-important outcomes (e.g., functional status).

We define a therapeutic area as a class of related diseases or conditions based on modified ICD-11 criteria (e.g., Neurology). In this study, the classification of the therapeutic areas targeted disease or conditions for which patients seek acupuncture treatment. For example, if an acupuncture RCT investigated post-stroke depression, we would classify the RCT into "Mental health" rather than "Neurology".

Literature Search

In collaboration with clinical and methodological experts, a medical information specialist developed a search strategy that included PubMed, Embase, the Cochrane Central Register of Controlled Trials, and 4 Chinese databases, including China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database for Chinese Technical Periodicals (VIP) and China Biology Medicine disc (CBM). We searched acupuncture RCTs published from 2015 January to 2019 December with no language restrictions. The detailed search strategy is presented in eAppendix 1 in the supplement.

Eligibility criteria

Eligible studies fulfilled the following inclusion criteria:

- RCT defined by authors
- Reported at least one of two sets of comparisons: acupuncture versus no intervention, sham acupuncture or waiting list; or acupuncture plus other interventions versus other interventions with or without sham acupuncture. The other interventions must be conventional medical treatment and identical in both intervention and control groups.
- Reported at least one patient-important outcome
- Randomized over 100 individuals
- Appeared in a peer-reviewed journal publication in any language

We excluded conference abstracts, letters, commentaries, editorials, protocols, non-human trials, cluster RCTs, n-of-1 trials, cost-utility studies, secondary analyses of RCTs, reviews, and meta-analyses, RCTs in which control groups received any traditional Chinese medicine (TCM) related therapies (e.g., acupuncture, moxibustion, scraping, cupping, bloodletting, acupoint catgut embedding, massage, Chinese herbal medicine) and studies in which tables and text reported contradictory results on the selected outcomes.

Study selection

We exported Chinese citations to Endnote X9.0 and English citations to a web-based software (https://collaboratron.epistelab.com/) for eligibility screening. To conduct, independently and in duplicate, title and abstract and full-text screening, a team of 16 Chinese and 22 English reviewers worked in pairs using standardized forms with detailed instructions. To ensure screening quality, reviewers participated in a calibration exercise prior. If needed, reviewers resolved disagreements through discussion or arbitrated by a third party.

Generation and ranking of the factors that impact treatment effect

We first, through the literature review and consultation with acupuncturists, generated a list of potential factors that might be associated with the magnitude of effect resulting in 13 methodological factors and 26 clinical factors. To ensure our list was comprehensive, and to

rank the importance of the factors, we conducted an online survey using Wenjuanxing (www.wjx.cn) among a global panel (n=27) composed of acupuncture trialists, acupuncturists, surgeons, trial methodologists, patients, and statisticians. The survey results added 7 factors, and we finally included 46 factors (eAppendix 2 in the supplement) in the meta-regression analyses.

Data extraction

We classified patient-important outcomes into six constructs (box1).

Box 1

I. Mortality

II. Major events (e.g., live birth rate)

Ⅲ. Pain (e.g., low back pain)

Ⅳ. Non-pain symptoms (e.g., nausea and vomiting)

Ⅴ.Quality of life (e.g., health-related quality of life)

Ⅵ. Functional status (e.g., dysphagia)

To select outcomes, we first extracted all patient-important outcomes, classified them into the six constructs (box 1), and then, within constructs, classified each outcome into therapeutic areas (we will refer to these as subconstructs). For example, for the non-pain symptoms construct, reviewers classified nausea and vomiting into "gastroenterology". We retained the subconstructs, including 30 studies or more.

Within each construct /subconstruct, for each outcome, we calculated the number of studies reporting the outcome. If one study reported multiple outcomes within the same subconstruct, we extracted the more frequently reported outcome across all studies. When studies reported the same outcome measured by different instruments, we selected the most frequently reported instrument for that outcome across all studies.

If the above process excluded either the primary outcome or the first patient-important outcome in the result, in addition to the outcomes selected through that process, we also included the first patient-important or primary outcome reported in the result section.

For multiple-arm RCTs, we considered only those comparisons that met eligibility criteria. For RCTs with multiple follow-up times, we selected the outcome both at the end of treatment and at the longest follow-up time in which the loss to follow-up rate was 20% or less. Following a calibration exercise, a team of 10 reviewers, working in pairs, independently extracted data and resolved discrepancies through discussion. If they could not reach a consensus, an arbiter resolved the conflict.

For outcome selection, three pairs of reviewers reviewed all included studies selecting outcomes. After completing the outcome selection and discussing as necessary to come to an agreement, reviewers extracted data on the pre-selected outcomes.

For each trial, reviewers extracted the number of randomized and analyzed participants, data on all factors, and recorded the selected outcomes' effect estimates. For dichotomous outcomes, we collected the number of events and for continuous outcomes, point and associated variabilities, ranges, and directions. To extract data from figures in which the data were unavailable in the text or tables, we used GetData Graph Digitizer 2.25 (by Mark Mitchell) software.

Statistical analysis

Depending on the data distribution, we summarized data using means and standard deviations, or medians and interquartile ranges. For statistical tests, we used a threshold p-value of 0.05 to indicate a statistical significance. To combine the outcomes from different measurement scales, we applied the standardized mean difference (SMD). A positive SMD indicated a beneficial effect. The variance of SMD[20] was given by

$$V_d = \frac{n_1 + n_2}{n_1 n_2} + \frac{SMD^2}{2(n_1 + n_2)}.$$

where n_1 and n_2 were the sample sizes of the acupuncture therapies group and the control group, respectively. For the dichotomous outcome, by the method of Hasselblad and Hedges[20,21], we converted the calculated log odds ratio to SMD using

$$d = LogOddsRatio \times \frac{\sqrt{3}}{\pi}$$

where π is the mathematical constant (approximately 3.14159). The variance of SMD was obtained by

$$V_d = V_{LogOddsRatio} \times \frac{3}{\pi^2}$$

We initially considered 46 variables (eAppendix 2 in the supplement) to investigate factors that might influence the SMD among the RCTs. However, 26 variables were excluded from the multivariate analysis because they were missing in more than 90% of the studies (eAppendix 3 in the supplement). To detect possible multicollinearity, we calculated the Cramer's V statistics [22 23] (ranges 0 to 1) between every pair of the variables using a threshold of 0.70. When excessive collinearity existed, we excluded those variables from the regression analysis (eAppendix 3 in the supplement).

To account for the heterogeneity between the studies and the dependency of the multiple outcomes within a study, we used a meta-regression in three-level random-effects mixed model [24-26] to simulate the sampling variation for each effect size (level one), variation over outcomes within a study (level two), and variation over studies (level three). The dependent variable was the SMD of the acupuncture therapies. The independent variables were the study level factors treated as fixed effects.

We had three different specifications in conducting the analyses. The first specification was an empty model with no independent variables to test heterogeneity of effect sizes at the study and outcome levels. The second specification (primary analysis) was a multivariable analysis that estimated the effects of the multiple independent variables associated with the SMD. To ensure sufficient power for the estimation, we determined the number of independent variables included in the model by applying the rule of 10 observations per variable. If no enough sample would contain all independent variables, a hierarchical list of variables was used to determine the priority of entry into the model. The third specification was a univariable analysis with a single factor each time.

To limit the influence of outliers and provide the resistant (stable) results, we incorporated the robust regression approach [27] to the three-level random-effects mixed model for the analysis

and used the difference of the least-squares means of the SMDs (or the difference of adjusted SMDs) to indicate the effect of a factor. We used 0.2 and 0.4 as the thresholds to name small, moderate, and large (<0.2 as small, 0.2-0.4 as moderate, >0.4 as large) for the effect.

We conducted all the analyses in SAS, version 9.4.

Patient and Public Involvement

The online survey on potential factors involved empirical data and input from a global panel that included patients.

RESULTS

The search yielded 169,406 studies, of which 6530 proved eligible. We retrieved and screened the full texts, excluded 5946 ineligible studies, and finally included 584 studies. (Figure 1)

Characteristics of included studies

The 584 eligible studies published between 2015 and 2019 reported 1304 effect estimates that met our relevance criteria. eTables 1.1, 1.2 and 1.3 in the supplement show the basic and clinical characteristics, and risk of bias of included studies, respectively. Over 90% of the trials (n=540, 92.5%) were conducted in China. Of the 584 studies, 444 (76%) tested traditional Chinese acupuncture, and 313 (53.6%) used manual acupuncture. Acupuncture was the add-on intervention in 564 studies (96.8%), and 542 studies (92.8%) used other interventions as control. Some variables were important but poorly reported and thus excluded from the multivariable analysis.

Included RCTs had a high risk of bias. For example, over 90% of the RCTs were labeled as inadequate or probably inadequate allocation concealment (n=536, 91.8%); close to 90% of the trials did not report any allocation concealment approaches (524, 89.7%).

The extent of the heterogeneity of the acupuncture's treatment effect when compared to sham or no acupuncture control (unconditional model-specification 1)

We applied a robust mixed model without exploratory variables to examine the effect sizes' variations at study and outcome levels and observed significant heterogeneity ($p < 0.0001$).

This finding provided a basis for the multivariable analysis to further explore the influencing factors of heterogeneity.

Assessment on factors influencing acupuncture treatment effect (multivariable analysis - specification 2)

Of the 46 factors, 20 met our criterion of <10% of missing (retained at least 526 studies or 1174 outcomes) factor data. The Cramer's V assessments for multicollinearity assessment further excluded publication language, journal impact factors, trial registration, therapeutic areas and blinding of participants due to the high association with other independent variables (Cramer's V statistic > 0.7, eAppendix 3 in the supplement); thus resulted in 15 variables that were eventually included in the analysis (eAppendix 4 in the supplement).

The multivariable analysis, including 1133 effect estimates from 508 studies, identified 5 significant factors: type of outcome, acupuncture type, frequency of treatment sessions, number of centers, and funding availability (Table 1).

Compared to major events outcomes, effects proved larger in quality of life (large magnitude, difference of adjusted SMDs 0.51, 0.24 to 0.77; P<0.001), pain (large magnitude, 0.48, 0.27 to 0.69; P<0.001), function (large magnitude, 0.41, 0.21 to 0.61; P<0.001), and non-pain symptoms (moderate magnitude, 0.32, 0.12 to 0.52; P<0.001). Compared to non-pain symptoms, effects proved larger in pain (small magnitude, 0.16, 0.04 to 0.27; P=0.01). Single center, compared to multicenter, was associated with moderately larger effects (0.38, 0.10 to 0.66; p=0.01). Penetration acupuncture (i.e., manual acupuncture and electroacupuncture), compared to non-penetration type of acupuncture (i.e., laser acupuncture, TEAS and acupressure), was associated with moderately larger effects (0.34, 0.15 to 0.53; P<0.001). High frequency acupuncture treatment sessions, compared to low frequency, was associated with larger effects of small magnitude (0.19, 0.03 to 0.35; P=0.02). Compared to reported funding, effects proved larger of small magnitude in studies that did not report funding (0.12, 0 to 0.25; P=0.03). (Figure 2, eTable 2 in the supplement)

Assessment on factors influencing acupuncture treatment effect (univariable analysis - specification 3)

Univariable analysis for independent variables excluded from the multivariable analysis

In univariable analysis, of 31 independent variables excluded from the multivariable analyses, 17 were statistically significant factors (Table 2). However, these significances may be attributed to extremely large sample sizes and/or the absence of the other strong predictors in the model.

eTable 3 in the supplement presents the effect sizes of significant factors impacting acupuncture's effect in univariable analysis (excluded from multivariable analysis).

Significant factors in multivariable versus univariable analyses

Of the 15 independent variables, multivariable analysis proved five significant factors associated with the magnitude of effect; in contrast, univariable analysis proved 14 (Table 2).

DISCUSSION

Principal findings

We conducted a meta-epidemiological study including 1304 effect estimates from 584 RCTs. Our robust three-level mixed multivariable analyses identified five significant factors that impacted the magnitude of the acupuncture effect. Acupuncture produced the largest treatment effect on quality-of-life, followed by function, pain, non-pain symptoms, and major events. Penetration acupuncture induced a larger effect than non-penetration acupuncture. High-frequency acupuncture sessions, single-centered acupuncture RCTs, and acupuncture RCTs that did not report funding are associated with larger effects.

Strengths and limitations of the study

This study is the first three-level multivariable meta-epidemiological analysis and the largest in RCTs across all therapeutic areas, exploring factors associated with acupuncture's treatment effect. Our study has several strengths. Firstly, our study is highly patient-centered and clinically relevant. To ensure the conclusion from our study is the most pertinent for healthcare decision-making, we included only patient-important outcomes. We consulted a

group of international clinicians, researchers, and patients when choosing the independent variables.

Secondly, we constructed a robust three-level mixed model multivariable analysis to adjust for multiple variables to reduce the potential bias raised from the univariable analysis. To deal with the collinearity and substantial amount of outlier and influential values in our datasets, we used Cramer's V and the weighting approach of robust regression.

Thirdly, our study has a high methodological rigor. We worked with an experienced medical librarian to develop a systematic and exhaustive search strategy. Teams of reviewers then screened and extracted data independently and in duplicate, with third-party adjudication of disagreement.

Our study has several limitations. Firstly, we used a cut-off value of 0.7 in Cramer's V statistics to identify collinearity, and when applicable, dropped the less important independent variable. Others might find a cut-off of 0.7 being too stringent and therefore left out too many independent variables from the multivariable model. Secondly, acupuncture RCTs poorly reported the risk of bias and acupuncture techniques related factors. Thus, we could not include some important independent variables such as practitioners' experience in the multivariable analyses. Finally, some factors (e.g., country, trial registered) distributed extremely imbalanced, limiting the results' generalisability.

Comparison with other studies

Previous studies[9-11 12-15] typically performed univariable analyses in a small number of studies (5 to 39 trials) and identified 15 significant factors, including ten clinical, one methodological, and four other factors. Although our univariable analyses confirmed all these factors, the multivariable analyses identified only five significant factors.

An individual patient data meta-analysis (IPDMA) on chronic pain trials found the total number of acupuncture treatments was a significant factor [9 15] and more treatment sessions were associated with better effects when comparing acupuncture to no acupuncture controls. Meta-regression studies also revealed the same results.[11-13] However, due to a considerable

amount of studies that didn't report the number of treatment sessions, we could not include total number of acupuncture treatment sessions in our multivariable analysis.

One study suggested treatment frequency as a significant predictor for tension-type headaches (more frequent treatment, larger effects)[14] while others did not.[9 15] In our multivariable analyses, the frequency of treatment sessions proved a significant factor. Some studies included homogeneous treatment frequency [9 15] whereas others included varied frequency, leading to different findings.

For the type of sham acupuncture, the IPDMA[9 15] reported that compared to non-penetrating and non-needle sham, penetrating needle sham associated with a larger effect. In contrast, a systematic review[10] found no association between the type of sham and acupuncture's treatment effect. Similarly, our multivariable analyses did not identify the type of sham as a significant factor.

Implications for practice and research

When feasible and acceptable, patients, clinicians, and policymakers should consider using penetrating over non-penetrating types of acupuncture with more frequent treatment sessions. Identifying significant factors for acupuncture's treatment effect in trials has important implications for future trials design and conducting secondary analyses. When trialist collaboration designs an acupuncture trial: 1) they should follow Consolidated Standards of Reporting Trials (CONSORT)[28] and STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [29] reporting guidelines, especially for those that might impact the treatment effect (random sequence generation and allocation concealment, acupuncture technique related information, and practitioners related information); 2) consider the quality of life outcome more often; 3) carefully choose the type of acupuncture, frequency of treatment sessions, choice of single or multicenter as those impact the treatment effect. When exploring factors associated with acupuncture's treatment effect, researchers should use multivariable analyses over univariable analyses to avoid confounding variables caused biases.

Researchers can further investigate factors excluded from multivariable analyses (e.g., practitioners' expertise).

The following are members of FAMOUS group: Wei-Juan Gang, Wen-Cui Xiu, Lan-Jun Shi, Qi zhou, Rui-Min Jiao, Ji-Wei Yang, Xiao-Shuang Shi, Xiao-Yue Sun, Zhao Zeng, Claudia M. Witt, Lehana Thabane, Ping Song, Long-Hui Yang, Gordon Guyatt, Xiang-Hong Jing, Yu-Qing Zhang, Zhi-Yun Zhang, Heng-Cong Li, Jing-Tao Shi, An-Li Chen, Zheng-Yang Qu, Ling Zou, Dong-Xiao Mou, Xiao-Yu Wang, Qing-Quan Yu, Li-Zhen Chen, Yu-Ting Huang, Tiago V. Pereira, Jason Chambers, Cameron Ho, Layla Bakaa, Kevin Loniewski, Kyle Tong, Jaryd Tong, Jared E. Dookie, Jenny Zhu, Malini Hu, Yujin Suk, Kay Wu, Luciane Cruz Lopes, Julia White, Tayler A Buchan, Lauren Giustti Mazzei, Maíra Ramos Alves, Mariana Del Grossi, Cristiane De Cassia Bergamaschi Motta, Jing Meng, Cynthia Chan, Flávia Blaseck.

ACKNOWLEDGMENTS

We thank the global panel, including Zhisun Liu, Baoyan Liu, Hui Zheng, Lee Myeong Soo, Tae-Hun Kim, Caroline Smith, Kim L Bennell, Jun Mao, Lixing Lao, Michael E Wechsler, Karen J Sherman, Andrew J Vickers, Emily Vertosick, Benno Brinkhaus, Klaus Linde, Cummings Mike, Anna Kim, Jiani Wu, Yan Liu, Mohit Bhandari, Philip J Devereaux, and Jianping Liu for ranking the importance of a list of factors, and Jun Mao, Lixing Lao, Klaus Linde and Dawn Richards for discussing the paper's content at the Society of Acupuncture Research 2021 International Research Conference, and Daniel Pérez Rada for supporting the online screening system.

CONTRIBUTORS

XHJ, YQZ, and WJG had the idea and designed the study. GG was involved in designing the study. YQZ, WJG, ZZ, PS and LHY designed the search strategy. WJG, WCX, LJS, RMJ, JWY, XSS, XYS, Zhi-yun Zhang, Heng-cong Li, Jing-tao Shi, An-li Chen, Zheng-yang Qu, Ling Zou, Dong-xiao Mou, Xiao-yu Wang, Qing-quan Yu,

Li-zhen Chen, Yu-ting Huang, Tiago V. Pereira, Jason Chambers, Cameron Ho, Layla Bakaa, Kevin Loniewski, Kyle Tong, Jaryd Tong, Jared E. Dookie, Jenny Zhu, Malini Hu, Yujin Suk, Kay Wu, Luciane Cruz Lopes, Julia White, Tayler A Buchan, Lauren Giustti Mazzei, Maíra Ramos Alves, Mariana Del Grossi, Cristiane De Cassia Bergamaschi Motta, Jing Meng, Cynthia Chan and Flávia Blaseck screened abstracts. WJG, WCX, LJS, RMJ, JWY, XSS, XYS, Zhi-yun Zhang, Heng-cong Li, Jing-tao Shi, An-li Chen, Zheng-yang Qu, Ling Zou, Dong-xiao Mou, Xiao-yu Wang, Qing-quan Yu, Li-zhen Chen and Yu-ting Huang screened full texts.WJG, WCX, LJS, RMJ, JWY, XSS, and XYS extracted data. WCX coordinated the reviewers' tasks. QZ proposed the analysis plan and analyzed the data. LT reviewed and confirmed the statistical analysis plan. WJG, YQZ and QZ drafted the manuscript, with revision from all authors. YQZ and GG substantially revised the manuscript. XHJ is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others have been omitted.

FUNDING

This work was supported by the China Academy of Chinese Medical Sciences (No. CI2021A03503, GH201901, 2020YJSZX-1) and the National Natural Science Foundation of China (No. 81973968). The funders had no role in considering the study design, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

COMPETING INTERESTS

None declared

Patient and public involvement

The online survey on potential factors involved empirical data and input from a global panel that included patients.

Ethics Approval

This study does not involve human participants.

Data availability statement

Data are available on reasonable request. The data that support the findings of this study are available from the corresponding author, on reasonable request.

REFERENCES

1 World Health Organization. WHO traditional medicine strategy:2014-2023. Geneva: WHO Press, 2013.

2 Cui J, Wang SB, Ren JH, Zhang J, Jing J. Use of acupuncture in the USA: changes over a decade (2002-2012). Acupunct Med. 2017; 35(3): 200-7. doi: 10.1136/acupmed-2016-011106. Epub 2017 Jan 13

3 Yang L, Adams J, Sibbritt D. Prevalence and factors associated with the use of acupuncture and Chinese medicine: results of a nationally representative survey of 17161 Australian women. Acupunct Med. 2017; 35(3): 189-99. doi: 10.1136/acupmed-2016-011179. Epub 2017 Mar 9

4 Fu JY, Zhang X, Zhao YH, Tong HF, Chen DZ, Huang MH. Bibliometric analysis of acupuncture research fronts and their worldwide distribution over three decades. Afr J Tradit Complement Altern Med. 2017; 14(3): 257-73. doi:10.21010/ajtcam.v14i3.27. eCollection 2017

5 Ma Y, Dong M, Zhou KH, Mita C, Liu JP, Wayne PM. Publication trends in acupuncture research: a 20-year bibliometric analysis based on PubMed. PLoS One. 2016; 11(12): e0168123. doi: 10.1371/journal.pone.0168123. eCollection 2016

6 Wang Yy, Wang LQ, Chai QY, Liang N, Liu JP. [Literature review on control interventions in randomized clinical trials on acupuncture published in mainland Chinese biomedical journals]. World Chinese Medicine. 2014; 9(10),1264-8. Chinese. doi:10.3969/j.issn.1673-7202.2014.10.003

7 Xue CC, Dong L, Polus B, et al. Electroacupuncture for tension-type headache on distal acupoints only: a randomized, controlled, crossover trial. Headache. 2004; 44(4): 333-41. doi: 10.1111/j.1526-4610.2004.04077.x

8 Melchart D, Streng A, Hoppe A, et al. Acupuncture in patients with tension-type headache: randomised controlled trial. BMJ. 2005; 331(7513): 376-82. doi: 10.1136/bmj.38512.405440.8F. Epub 2005 Jul 29

9 Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for chronic pain: update of an individual patient data meta-analysis. J Pain. 2018; 19(5): 455-74. doi: 10.1016/j.jpain.2017.11.005. Epub 2017 Dec 2

10 Madsen MV, Gøtzsche PC, Hróbjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009; 338: a3115. doi: 10.1136/bmj.a3115

11 Yuan QL, Wang P, Liu L, et al. Acupuncture for musculoskeletal pain: a meta-analysis and meta-regression of sham-controlled randomized clinical trials. Sci Rep. 2016; 6: 30675. doi: 10.1038/srep30675

12 Qin Z, Wu J, Xu C, Liu Z. Using meta-regression approach to explore the dose-response association between acupuncture sessions and acupuncture effects on chronic prostatitis/chronic pelvic pain syndrome. Ann Transl Med. 2019; 7(6): 116. doi: 10.21037/atm.2018.11.45

13 Deng YZ , Xu LG , Chen L , Zhou D, Liu Y. Effectiveness of acupuncture in the management of cervical spondylosis: a meta-analysis. J Biol Regul Homeost Agents. 2017; 31(4):1017-22.

14 Hao XA, Xue CC, Dong L, Zheng Z. Factors associated with conflicting findings on acupuncture for tension-type headache: qualitative and quantitative analyses. J Altern Complement Med. 2013; 19(4): 285-97. doi: 10.1089/acm.2011.0914. Epub 2012 Oct 17

15 MacPherson H, Maschino AC, Lewith G, et al. Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomised controlled trials. PLoS One. 2013; 8(10): e77438. doi: 10.1371/journal.pone.0077438. eCollection 2013

16 Manheimer E, van der Windt D, Cheng K, et al. The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2013; 19(6): 696-713. doi: 10.1093/humupd/dmt026. Epub 2013 Jun 27

17 World Health Organization. Acupuncture: Review and analysis of reports on controlled clinical trials. Geneva: World Health Organization, 2003.

18 Vickers AJ, Cronin AM, Maschino AC, et al. Individual patient data meta-analysis of acupuncture for chronic pain: protocol of the Acupuncture Trialists' Collaboration. Trials. 2010; 11: 90. doi: 10.1186/1745-6215-11-90

19 Akl EA, Briel M, You JJ, Lamontagne F, et al. LOST to follow-up Information in Trials (LOST-IT): a protocol on the potential impact. Trials. 2009; 10: 40. doi: 10.1186/1745-6215-10-40

20 Michael Borenstein LVH, Rothstein JPTHaHR. Introduction to Meta-Analysis. John Wiley & Sons, Ltd, 2009.

21 Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. Psychol Bull. 1995; 117(1): 167-78. doi: 10.1037/0033-2909.117.1.167

22 Harald C. Mathematical methods of statistics (PMS-9). Princeton university press, 2016.

23 Sadiq M, Mehmood T, Aslam M. Identifying the factors associated with cesarean section modeled with categorical correlation coefficients in partial least squares. PLoS One. 2019; 14(7): e0219427. doi: 10.1371/journal.pone.0219427. eCollection 2019

24 Mariola Moeyaerta MU, S. Natasha Beretvasc JF, Van den Noortgateb RBaW. Methods for dealing with multiple outcomes in meta-analysis: a comparison between averaging effect sizes, robust variance estimation and multilevel meta-analysis. Int J Soc Res Methodol. 2017; 20(6): 559-72. doi: 10.1080/13645579.2016.1252189

25 Konstantopoulos S. Fixed effects and variance components estimation in three-level meta-analysis. Res Synth Methods. 2011; 2(1): 61-76. doi: 10.1002/jrsm.35. Epub 2011 Jun 10

26 Van den Noortgate W, López-López JA, Marín-Martínez F, Sánchez-Meca J. Meta-analysis of multiple outcomes: a multilevel approach. Behav Res Methods. 2015; 47(4): 1274-94. doi: 10.3758/s13428-014-0527-2

27 Chen C. Robust Regression and Outlier Detection with the ROBUSTREG Procedure. In Proceedings of the Twenty-Seventh Annual SAS Users Group International Conference. Cary, NC: SAS Institute Inc, 2002.

28 Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340:c332. doi: 10.4103/0976-500X.72352

29 MacPherson H, Altman DG, Hammerschlag R, et al; STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med. 2010; 7(6): e1000261. doi: 10.1136/aim.2009.001370. Epub 2010 Jun 8

Table 1 Multivariable meta-regression analysis

Table 2 Univariable meta-regression analysis

Figure 1 Study selection flow diagram

Figure 2 Forest plots of significant factors in the multivariable analysis

Table 1 Multivariable meta-regression analysis

Factors	Significance
Acupuncture type	√
Acupuncture regimen	
Frequency of treatment sessions	√
Style of acupuncture	
Type of outcome	√
Type of control group	
The course of disease (chronic or acute)	
Random sequence generation	
Allocation concealment	
Blinding of outcome assessors	
Sample size	
Number of centers	√
Funding available	√
Country	
Type of journal	

Notes：

√ The factor is a significant predictor ($p<0.05$).

Blank: The factor is not a significant predictor.

Table 2 Univariable meta-regression analysis

Factors	Significance
Total number of acupuncture treatments	√
Type of acupuncture stimulation	√
Source of acupuncture regimen	√
Duration of treatment_chronic	√
Duration of treatment_acute	
Education or training of practitioners	√
Acupuncturist experience	
Type of comparisons	√
Therapeutic area	√
Blinding of participants	√
Longest follow-up time	√
Missing data reported	√
The proportion of missing data	√
Trial registration	√
Language of publication	√
Type of funding	√
Journal Impact factor	√
Stratification or block randomization	√
Needle retention time(20min)	
Needling angle	
Depth of insertion	
Number of needles used	
De qi	
Patient expectation	√
Acupuncture-specific patient-practitioner interactions	
Ever received acupuncture	

Location of needles	
The clinical specialty of practitioners	
Acupuncture manipulation after needles inserted	
Needling direction	
Intensity of stimulation	
Acupuncture type*	√
Acupuncture regimen*	
Frequency of treatment sessions*	√
Style of acupuncture*	√
Type of outcome*	√
Type of control group*	√
The course of disease (Chronic or acute)*	√
Random sequence generation*	√
Allocation concealment*	√
Blinding of outcome assessors*	√
Sample size*	√
Number of centers*	√
Funding available*	√
Country*	√
Type of Journal*	√

Notes:

√ The factor is a significant predictor ($p<0.05$).

* Included in the multivariable analysis.

Blank: The factor is not a significant predictor.

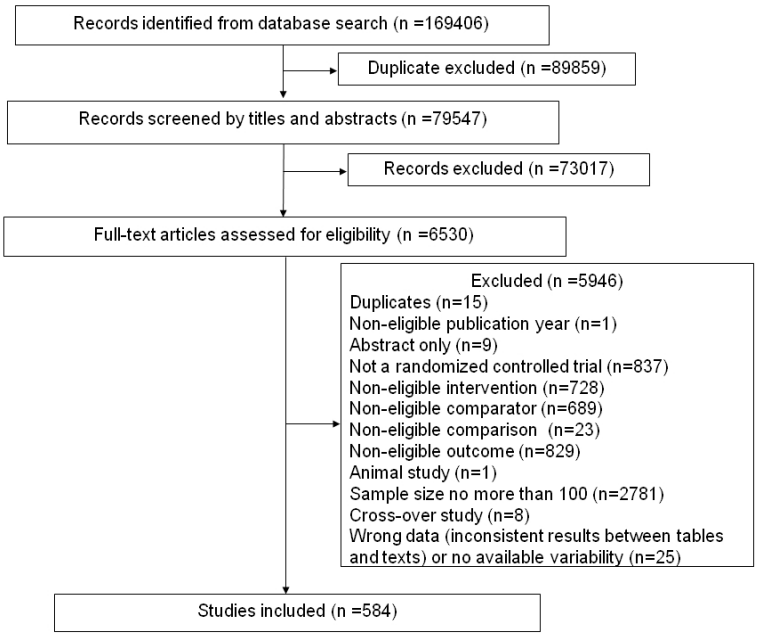

Fig 1 Study selection flow diagram

296x209mm (96 x 96 DPI)

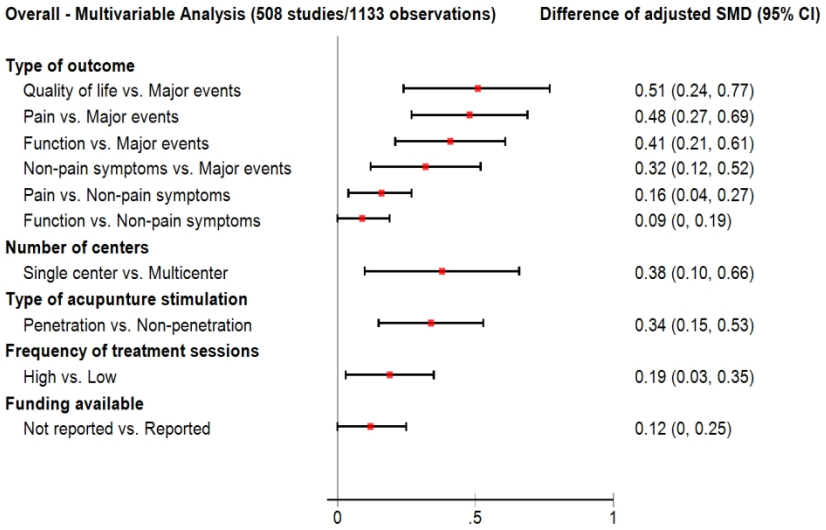

Fig 2 Forest plots of significant factors in the overall multivariable analyses

296x209mm (144 x 144 DPI)

Supplement

eAppendix 1 Search strategy

eAppendix 2 Independent variables ranked by importance

eAppendix 3 Excluded independent variables from multivariable analysis

eAppendix 4 Independent variables included in multivariable analysis

eAppendix 5 Classification of acupuncture treatment frequency, duration, and the total number of treatments

eTable 1.1 Basic characteristics of included studies

eTable 1.2 Clinical characteristics of included studies

eTable 1.3 Risk of bias of included studies

eTable 2 Magnitude of significant factors impacting treatment effect in multivariable analysis

eTable3 Magnitude of significant factors in univariable analysis (excluded from multivariable analysis)

eAppendix 1 Search strategy

1. **MEDLINE via PubMed Strategy**

   ((electroacupuncture or "acupuncture"[mesh terms] or "acupuncture"[all fields] or "acupuncture therapy"[mesh terms] or "acupuncture therapy"[all fields] or auricular acupuncture or auricular needle or ear acupuncture or auricular plaster therapy or transcutaneous electric nerve stimulation or tens or electric stimulation therapy or laser acupuncture or auricular point sticking or acupressure or dry needle or scalp acupuncture or scalp sensory or scalp stimulation or filliform needle or filiform needle) and (randomized controlled trial or Controlled Clinical Trial or placebo[Title/Abstract] or sham[Title/Abstract] or randomized[Title/Abstract] or randomly[Title/Abstract] or trial[Title/Abstract] or groups[Title/Abstract])) not (animals NOT humans) and ("2015/01/01"[date - publication] : "2019/12/31"[date - publication])

2. **EMBASE Search strategy**

   ('electroacupuncture'/exp OR electroacupuncture OR 'acupuncture therapy'/exp OR 'acupuncture therapy' OR (('acupuncture'/exp OR acupuncture) AND ('therapy'/exp OR therapy)) OR 'acupuncture moxibustion' OR 'acupuncture moxibustion'/exp OR (('acupuncture'/exp OR acupuncture) AND moxibustion) OR 'auricular acupuncture'/exp OR 'auricular acupuncture' OR (auricular AND ('acupuncture'/exp OR acupuncture)) OR 'auricular needle'/exp OR 'auricular needle' OR (auricular AND ('needle'/exp OR needle)) OR 'ear acupuncture'/exp OR 'ear acupuncture' OR (('ear'/exp OR ear) AND ('acupuncture'/exp OR acupuncture)) OR 'auricular plaster therapy' OR (auricular AND ('plaster'/exp OR plaster) AND ('therapy'/exp OR therapy)) OR 'transcutaneous electric nerve stimulation'/exp OR 'transcutaneous electric nerve stimulation' OR (transcutaneous AND electric AND ('nerve'/exp OR nerve) AND ('stimulation'/exp OR stimulation)) OR tens OR 'electric stimulation therapy'/exp OR 'electric stimulation therapy' OR (electric AND ('stimulation'/exp OR stimulation) AND ('therapy'/exp OR therapy)) OR 'laser acupuncture'/exp OR 'laser acupuncture' OR (('laser'/exp OR laser) AND ('acupuncture'/exp OR acupuncture)) OR 'auricular point sticking' OR (auricular AND point AND sticking) OR 'acupressure'/exp OR acupressure OR 'dry needle' OR (dry AND ('needle'/exp OR needle)) OR 'scalp acupuncture'/exp OR 'scalp acupuncture' OR (('scalp'/exp OR scalp) AND ('acupuncture'/exp OR acupuncture)) OR 'scalp sensory' OR (('scalp'/exp OR scalp) AND ('sensory'/exp OR sensory)) OR 'scalp stimulation' OR (('scalp'/exp OR scalp) AND ('stimulation'/exp OR stimulation)) OR 'filliform needle' OR (filliform AND ('needle'/exp OR needle)) OR 'filiform needle' OR (filiform AND ('needle'/exp OR needle))) AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR (randomized AND controlled AND ('trial'/exp OR trial)) OR 'controlled clinical trial'/exp OR 'controlled clinical trial' OR (controlled AND ('clinical'/exp OR clinical) AND ('trial'/exp OR trial)) OR 'placebo'/exp OR placebo OR sham OR randomized OR randomly OR 'trial'/exp OR trial OR groups) AND 'human'/exp NOT 'animal'/de NOT 'rat'/exp NOT 'mouse'/exp AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py)

3. **CENTRAL**

- **Title Abstract Keyword**

(electroacupuncture OR acupuncture OR auricular needle OR auricular plaster therapy OR transcutaneous electric nerve stimulation OR electric stimulation therapy OR auricular point sticking OR acupressure OR dry needle OR scalp sensory OR scalp stimulation OR filiform needle OR tens) AND (randomized controlled trial OR controlled clinical trial OR placebo OR sham OR randomized OR randomly OR trial OR groups) NOT (animal or rat or mouse)

- Publication year: from 2015 to 2019

4. CNKI search strategy [Chinese database]

English translation from Chinese version

- Professional retrieval：

(SU=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point sticking'+'acupressure'+'laser acupoint irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse') OR
TI=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point sticking'+'acupressure'+'laser acupoint irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse') OR
KY=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point sticking'+'acupressure'+'laser acupoint irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse') OR
AB=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point

sticking'+'acupressure'+'laser point irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse')) AND (SU='random' or TI='random' or KY='random' or AB='random')

Note：SU=subject，TI=title，KY=keyword，AB=abstract

- Publication date：from 2015-01-01to 2019-12-31.

Chinese version

- 专业检索：

(SU=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠') OR TI=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠') OR KY=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠') OR AB=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠')) AND (SU='随机' or TI='随机' or KY='随机' or AB='随机')

注：SU=主题，TI=题名，KY=关键词，AB=摘要

- 发表时间（Publication date）：2015-01-01 至 2019-12-31.

5. Wanfang search strategy [Chinese database]

English translation from Chinese version

- Professional retrieval：

(Title OR Keyword:(“electroacupuncture” OR “laser acupuncture” OR “transcutaneous electric” OR “transcutaneous nerve” OR “electric stimulation” OR “electroanalgesia” OR “body acupuncture” OR “auricular acupuncture” OR “scalp acupuncture” OR “filiform needle” OR “dry needle” OR “auricular point sticking” OR “acupressure” OR “laser acupoint irradiation” OR “tens” OR “analgesic skin electrical stimulation” OR “acupuncture treatment” OR “acupuncture and moxibustion therapy”) OR Abstract:(“electroacupuncture” OR “laser acupuncture” OR “transcutaneous electric” OR “transcutaneous nerve” OR “electric stimulation” OR “electroanalgesia” OR “body acupuncture” OR “auricular acupuncture” OR “scalp acupuncture” OR “filiform needle” OR “dry needle” OR “auricular point sticking” OR “acupressure” OR “laser acupoint irradiation” OR “tens” OR “analgesic skin electrical stimulation” OR “acupuncture treatment” OR “acupuncture and

moxibustion therapy") OR Title OR Keyword:("acupuncture and moxibustion" OR "acupuncture") OR Abstract:("acupuncture and moxibustion" OR "acupuncture")) AND (Title OR Keyword:"random" OR Abstract:"random") NOT (Title OR Keyword:("animal" OR "rat" OR "mouse") OR Abstract:("animal" OR "rat" OR "mouse"))

- Publication type：Journal articles.
- Publication date：from 2015to 2019.

Chinese version

- 专业检索：
  (题名或关键词:("电针" OR "激光针" OR "经皮电" OR "经皮神经" OR "电刺激" OR "电止痛" OR "体针" OR "耳针" OR "头针" OR "毫针" OR "干针" OR "耳穴贴压" OR "穴位按压" OR "激光穴位照射" OR "tens" OR "镇痛皮肤电刺激" OR "针刺治疗" OR "针灸疗法") OR 摘要:("电针" OR "激光针" OR "经皮电" OR "经皮神经" OR "电刺激" OR "电止痛" OR "体针" OR "耳针" OR "头针" OR "毫针" OR "干针" OR "耳穴贴压" OR "穴位按压" OR "激光穴位照射" OR "tens" OR "镇痛皮肤电刺激" OR "针刺治疗" OR "针灸疗法") OR 题名或关键词:("针灸" OR "针刺") OR 摘要:("针灸" OR "针刺")) AND (题名或关键词:"随机" OR 摘要:"随机") NOT (题名或关键词:("动物" OR "鼠") OR 摘要:("动物" OR "鼠"))
- 文献类型(Publication type)：期刊论文(Journal articles).
- 发表时间（Publication date）：2015 至 2019.

6. VIP search strategy [Chinese database]

English translation from Chinese version

- Retrieval type search：
  (U=(electroacupuncture OR laser acupuncture OR transcutaneous electric OR transcutaneous electric stimulation treatment OR transcutaneous electric stimulation nerve OR transcutaneous electric stimulation OR transcutaneous nerve OR electric stimulation OR electroanalgesia OR body acupuncture OR auricular acupuncture OR scalp acupuncture OR filiform needle OR dry needle OR auricular point sticking OR acupressure OR laser acupoint irradiation OR "tens" OR analgesic skin electrical stimulation OR acupuncture treatment OR acupuncture and moxibustion therapy OR transcutaneous nerve electric stimulation OR laser acupoint) OR M=(acupuncture and moxibustion OR acupuncture) OR R=(acupuncture and moxibustion OR acupuncture)) AND (M=random OR R=random) NOT (M=(animal OR rat OR mouse) OR R=(animal OR rat OR mouse))
  Note: U=all fields, M=title/keyword, R=abstract
- publication date：from 2015 to 2019.

Chinese version

- 检索式检索：
  (U=(电针 OR 激光针 OR 经皮电 OR 经皮电刺激治疗 OR 经皮电刺激神经 OR 经皮电刺激 OR 经皮神经 OR 电刺激 OR 电止痛 OR 体针 OR 耳针 OR 头针 OR

毫针 OR 干针 OR 耳穴贴压 OR 穴位按压 OR 激光穴位照射 OR “tens” OR 镇痛皮肤电刺激 OR 针刺治疗 OR 针灸疗法 OR 经皮神经电刺激 OR 激光穴位) OR M=(针灸 OR 针刺) OR R=(针灸 OR 针刺)) AND (M=随机 OR R=随机) NOT (M=(动物 OR 鼠) OR R=(动物 OR 鼠))

注：字段标识符 U=任意字段、M=题名或关键词、R=文摘

- 时间限定（publication date）：2015 至 2019.

7. CBM search strategy [Chinese database]

English translation from Chinese version:

#1【Rapid retrieal】acupuncture OR electroacupuncture OR auricular acupuncture OR scalp acupuncture OR body acupuncture OR filiform needle OR acupuncture and moxibustion OR acupuncture and moxibustion therapy OR transcutaneous nerve electric stimulation OR transcutaneous nerve OR electric stimulation OR laser acupuncture OR auricular point sticking OR dry needle OR acupressure OR laser acupoint irradiation OR acupuncture therapy OR electric stimulation therapy (publication date: 2015-2019)

#2【Subject retrieval】acupoint, auricular acupuncture (publication date: 2015-2019)

#3【Rapid retrieal】randomized controlled trial OR randomized controlled study OR randomized controlled clinical OR multicenter study OR multicenter clinical OR multicenter (publication date: 2015-2019)

#4【Rapid retrieal】animal OR rat OR mouse (publication date: 2015-2019)

#5 (#1 or #2) and #3

#6 (#1 or #2) and publication type（randomized controlled trial OR multicenter study）

#7 (#5 or #6) not #4

Chinese version:

#1【快速检索状态】: 针刺 OR 电针 OR 耳针 OR 头针 OR 体针 OR 毫针 OR 针灸 OR 针灸疗法 OR 经皮神经电刺激 OR 经皮神经 OR 电刺激 OR 激光针 OR 耳穴贴压 OR 干针 OR 穴位按压 OR 激光穴位照射 OR 针刺疗法 OR 电刺激疗法 （时间：2015-2019）

#2【主题检索状态】: 穴位, 耳针 （时间：2015-2019）

#3【快速检索状态】: 随机对照试验 OR 随机对照研究 OR 随机对照临床 OR 多中心研究 OR 多中心临床 OR 多中心（时间：2015-2019）

#4【快速检索状态】: 动物 OR 大鼠 OR 小鼠 OR 鼠（时间：2015-2019）

#5 (#1 or #2) and #3

#6 (#1 or #2) and 文献类型限定（随机对照试验、多中心研究）

#7 (#5 or #6) not #4

eAppendix 2

eAppendix 2 Independent variables ranked by importance

Order	Independent variable	Category
1	Allocation concealment	1=Probably yes 2=Probably no
2	Control group*	1=Penetrating needle sham 2=Non-penetrating needling sham 3=Non-needle sham 4=High-intensity control (No sham) 5=Usual care (No sham) 6=Low-intensity control (No sham)
3	Total number of acupuncture treatments	1=Low 2=High
4	Randomization sequence generation	1=Probably yes 2=Probably no
5	Acupuncture stimulation	1=Manual acupuncture 2=Electro-acupuncture 3=Laser acupuncture 4=TEAS 5=Acupressure
6	Acupuncture type	1=Penetrating acupuncture 2=Non-penetrating acupuncture
7	Blinding of outcome assessors	1=Probably yes 2=Probably no
8	Trial registration	1=Reported 2=Not reported
9	Sample size	1=101-149 2=150-499 3=>=500

10	Therapeutic areas	1=Musculoskeletal system 2=Neurology 3=Gastroenterology 4=Urology 5=Mental health 6=Obstetrics and gynecology 7=Dermatology 8=Respirology 9=Sleep-wake disorders 10=Cardiovascular disorders 11=Ophthalmology 12=Endocrinology and nutrition 13=Oncology 14=Trauma and injuries 15=Otorhinolaryngology 16=Acupuncture anesthesia 17=Pediatrics
11	Blinding of participants	1=Probably yes 2=Probably no
12	Frequency of treatment sessions	1=Low 2=High
13	Type of outcome	1=Pain 2=Quality of life (e.g., general quality of life, disease specific quality of life) 3=Function 4=Non-pain Symptoms (such as anxiety, depression, etc.) 5=Major events
14	Country	1=Western countries (countries in Europe, America, Australia and Africa) 2=Eastern countries (Asian countries) 3= both Western and Eastern countries
15	Acupuncture regimen	1=Fixed formula 2=Flexible formula 3=Individualized formula
16	Location of needles	1=Local points only 2=Distal points only 3=Both local and distal points (only for body acupuncture)

17	Education or training of practitioner	1=Systematic acupuncture or TCM education (undergraduate, graduate, diploma training) 2=Short term training (none of the training mention in 1)
18	Number of centers	1=Single center 2=Multicenter
19	Number of needles	1=1-4 2=5-9 3=10-14 4=15-20 5=>20
20	Depth of insertion	1=Deep needling (> 10mm) 2=Superficial needling (< 10mm)
21	Acupuncture manipulation after needles insertion	1=Yes 2=No 3=Not reported 4=Not applicable
22	Needle retention time	1=≥20min 2=＜20min
23	Intensity of stimulation	1=Strong stimulation 2=Moderate stimulation 3=Mild stimulation 4=Not reported
24	Acupuncturist experience	1=＜5y 2=5-10y 3=＞10y
25	Acupuncture-specific patient-practitioner interactions	1=Yes (trialists allowed or encouraged the interactions) 2=No (the interactions were prohibited) 3=Not reported
26	Clinical specialty of practitioner	1=Acupuncturist 2=Others 3=Not reported
27	Publication language	1=English 2=Chinese 3=Other language
28	Source of acupuncture regimen	1=Expert consensus 2=Textbook or literature 3=Clinical experience 4=Mix of some 5=Unclear

29	Needling angle	1=Reported 2=Not reported
30	Needling direction	1=Reported 2=Not reported
31	De qi	1=Yes 2=No 3=Not reported 4=Not applicable
32	Patient expectations	1=Reported 2=Not reported
33	Funding availability	1=Reported 2=Not reported
34	Style of acupuncture	1=TCM acupuncture (TCMA) 2=Japanese acupuncture (JA) 3=Korean acupuncture (KA) 4=Western medical acupuncture (WMA) 5=Five Element acupuncture (FEA) 6=Scalp stimulation 7=Auricular acupuncture 8=Dry needling
35	Type of funding	1=National funding 2=Foundation funding 3=Provincial funding 4=Institutional funding 5=For-profit funding 6=Not reported
36	Type of Journal	1= CAM (Complementary and Alternative Medicine) journals 2=Non- CAM journals
37	Journal Impact factor	1=0 2=Between 0 and1.99 3=Between 2 and 4.99 4=No less than 5
38	Course of diseases	1=Acute or perioperative issue 2=Chronic disease

39	Type of comparison	1=Acupuncture vs no intervention or waiting list 2=Acupuncture vs sham acupuncture 3=Acupuncture +other intervention vs other intervention 4=Acupuncture +other intervention vs sham acupuncture +other intervention
40	Missing data reported	1=Yes, stating missing data occur 2=No, stating missing data do not occur 3=No explicit statement
41	Proportion of missing data	1=>20% 2=<=20% 3=Not reported
42	Stratification or block of randomization	1=Only stratification randomization used 2=Only block randomization used 3=Both stratification and block randomization used 4=Not reported
43	Ever received acupuncture	1=Yes 2=No 3=Not reported
44	Duration of treatment for chronic diseases	1=1-4 weeks 2=5-8 weeks 3=9-12 weeks 4=>12 weeks
45	Duration of treatment for acute disease	1=1 day 2=>1 day
46	Longest follow-up time	1=1-3 months 2=3-6 months 3=>6 months

*When one study included both sham and other interventions as comparators, we classified the category based on the sham type.

We classified sham acupuncture into three types: penetrating needle sham, non-penetrating needle sham and non-needle sham.

eAppendix 3

eAppendix 3 Excluded independent variables from multivariable analysis	
Due to missing factor data	
1	Total number of acupuncture treatments
2	Acupuncture stimulation (manual acupuncture, electroacupuncture, laser acupuncture, TEAS, acupressure)
3	Source of acupuncture regimen
4	Duration of treatment_chronic
5	Duration of treatment_acute
6	Education or training of practitioners
7	Acupuncturist experience
8	Type of comparisons
9	Longest follow-up time
10	Missing data reported
11	The proportion of missing data
12	Type of funding
13	Stratification or block randomization
14	Needle retention time
15	Needling angle
16	Depth of insertion
17	Number of needles used
18	Acupuncture-specific patient-practitioner interactions
19	Ever received acupuncture
20	Location of needles
21	The clinical specialty of practitioners
22	Acupuncture manipulation after needles inserted
23	Needling direction
24	Intensity of stimulation
25	De qi
26	Patient expectations
Due to collinearity	
27	Language of publication
28	Journal impact factors
29	Trial registration
30	Therapeutic areas
31	Blinding of participants

eAppendix 4

eAppendix 4 Independent variables included in multivariable analysis

1	Random sequence generation
2	Allocation concealment
3	Course of diseases (chronic or acute)
4	Acupuncture stimulation
5	Acupuncture regimen
6	Frequency of treatment sessions
7	Sample size
8	Number of centers
9	Type of control
10	Style of acupuncture
11	Country
12	Type of journal
13	Funding availability
14	Blinding of outcome assessors
15	Type of outcome

eAppendix 5

eAppendix 5 Classification of acupuncture treatment frequency, duration and total number of treatments

Category	Low	High
Frequency of treatment sessions		
Acupressure	<=3/day	>3/day
Non-acupressure + Acute	1/day	>1/day
Non-acupressure + Chronic	<=3/week	>3/w
Duration of treatments		
Acute diseases	1day	>1day
Chronic diseases	<=4 weeks	>4 weeks
Total number of acupuncture treatments		
Acute + Acupressure	<=3	>3
Acute + non-acupressure	1	>1
Chronic + Acupressure	<=12	>12
Chronic + non-acupressure	<=12	>12

eTables

eTable 1.1 Basic characteristics of included studies（n=584）

Characteristic	No. (%)
Year of publication	
2015	67 (11.5)
2016	96 (16.4)
2017	133 (22.8)
2018	127 (21.8)
2019	161 (27.6)
Regions	
Eastern regions (Asian countries) [a]	554 (94.9)
Western regions (countries in Europe, America, Australia, and Africa) [b]	29 (5.0)
Both eastern and western regions[c]	1 (0.2)
Language	
Chinese	506 (86.6)
English	76 (13.0)
Persian	2 (0.3)
Type of Journal	
Complementary and Alternative Medicine	297 (50.9)
Non-Complementary and Alternative Medicine	287 (49.1)
Journal impact factor	
0	517 (88.5)
0.1-1.99	17 (2.9)
2-4.99	37 (6.3)
>5	13 (2.2)
Funding	
Non for profit	
National	57 (9.8)
Provincial	146 (25.0)
Institutional	20 (3.4)
Foundational	5 (0.9)
For-profit	0
Not reported	356 (60.9)
Randomized sample size	
101-150	418 (71.6)
151-499	156 (26.7)
>=500	10 (1.7)
Trial registration	
Reported	57 (9.8)
Not reported	527 (90.2)
Informed consent with patients	
Reported	254 (43.5)
Not reported	330 (56.5)
Compensation for participants	
Reported	2 (0.3)
Not reported	582 (99.7)
Number of centers	
Multicenter	36 (6.2)

Single-center	546 (93.5)
Not reported	2 (0.3)
Primary analysis	
Intention to treat analysis (Modified intention to treat)	37 (6.3)
Per protocol analysis	1 (0.2)
No explicit statement	546 (93.5)
Methods dealing with missing participant data (MPD)	
Data deletion	3 (0.5)
Single imputation	9(1.5)
• Mean imputation	1 (0.2)
• Last Observation Caring Forward	5 (0.9)
• Regression for MPD	1 (0.2)
worst-case scenarios	1 (0.2)
best- and worst-case scenarios	1 (0.2)
Multiple imputation	9 (1.5)
Mixed effect model for missing data	2 (0.3)
No missing data	27 (4.6)
No explicit statement	534 (91.4)

* Each study can contribute more than one estimate.

[a] Eastern regions include China(n=540), Iran(n=11), South Korea(n=1), India(n=1) and Malaysia(n=1).

b Western regions include USA (n=9), Spain(n=4), Australia(n=4), Brazil(n=3), German(n=2), Turkey(n=2), Denmark, France, Sweden, UK, Australia and Zealand.

c Both eastern and western regions include one multicenter study conducted in China and the USA.

eTable 1.2 Clinical characteristics of included studies（n=584）

Characteristic	No. (%)
Therapeutic area *	
Neurology	203 (34.8)
Gastroenterology	77 (13.2)
Musculoskeletal system	58 (9.9)
Obstetrics and gynecology	54 (9.2)
Mental health	53 (9.1)
Trauma and injuries	34 (5.8)
Urology	27 (4.6)
Respirology	18 (3.1)
Sleep-wake disorders	15 (2.6)
Cardiovascular disorders	12 (2.1)
Acupuncture anesthesia	10 (1.7)
Endocrinology and nutrition	8 (1.4)
Oncology	8 (1.4)
Dermatology	4 (0.7)
Otorhinolaryngology	2 (0.3)
Ophthalmology	1 (0.2)
Pediatrics	1 (0.3)
Course of disease	
Acute (related to procedure such as surgery)	172 (29.4)
Chronic	412 (70.6)
Patient expectation	
Reported	8 (1.4)
Not reported	576 (98.6)
Ever received acupuncture	
Yes	3 (0.5)
No	5 (0.9)
Not reported	576 (98.6)
Style of acupuncture*	
Traditional Chinese acupuncture	444 (76)
Auricular acupuncture	78 (13.4)
Western medical acupuncture	24 (4.1)
Scalp acupuncture	12 (2.1)
Dry needling	2 (0.3)
Not reported	24 (4.1)
Acupuncture stimulation*	
Manual acupuncture	313 (53.6)
Acupressure	131 (22.4)
Electro-acupuncture	99 (17.0)
Transcutaneous Electrical Acupoint Stimulation (TEAS)	44 (7.5)
Laser acupuncture	1 (0.2)
Source of acupuncture regimen	
Textbook or literature	61 (10.4)
Expert consensus	9 (1.5)
Clinical experience	4 (0.7)
Mix of some	12 (2.1)
Not reported	498 (85.3)
Acupuncture regimen*	
Fixed regimen	461 (78.9)
Flexible regimen	93 (15.9)
Individualized regimen	29 (5.0)
Not reported	1 (0.2)
Location of acupuncture points*	
Local	76 (13.0)
Distal	64 (11.0)
Both local and distal	292 (50.0)
Not reported	1 (0.2)
Not applicable	154 (26.4)

Number of needles used*	
1 to 4	54 (9.2)
5 to 9	116 (19.9)
10 to 14	117 (20.0)
15 to 20	70 (12.0)
>20	38 (6.5)
Not reported	18 (3.1)
Not applicable	175 (30.0)
De qi	
Yes	265 (45.4)
No	2 (0.3)
Not reported	80 (13.7)
Not applicable	237 (40.6)
Depth of insertion*	
Deep needling (> 10mm)	153 (26.2)
Superficial needling (< 10mm)	14 (2.4)
Not reported	244 (41.8)
Not applicable	175 (30.0)
Acupuncture manipulation after needles inserted*	
Yes	267 (45.7)
No	9 (1.5)
Not reported	134 (22.9)
Not applicable	175 (30.0)
The intensity of stimulation*	
Strong stimulation	15 (2.6)
Moderate stimulation	4 (0.7)
Mild stimulation	2 (0.3)
Not reported	566 (96.9)
Needling angle*	
Reported	146 (25.0)
Not reported	264 (45.2)
Not applicable	175 (30.0)
Needling direction*	
Reported	87 (14.9)
Not reported	323 (55.3)
Not applicable	175 (30.0)
Needle retention time*	
<=20 min	116 (19.9)
> 20 min	296 (50.7)
Not reported	174 (29.8)
Not applicable	114 (19.5)
Frequency of treatment sessions*[a]	
Low	180 (30.8)
High	356 (61.0)
Not applicable	8 (1.4)
Not reported	43 (7.4)
Duration of treatment for chronic diseases [a] (n=412)	
1-4 weeks	227 (55.1)
5-8 weeks	79 (19.2)
9-12 weeks	53 (12.9)
> 12 weeks	22 (5.3)
Not reported	31 (7.5)
Duration of treatment for acute or perioperative issues*[a] (n=172)	
One day	85 (49.4)
> 1day	53 (30.8)
Not reported	34 (19.8)
Total number of treatments*[a]	
High	356 (61.0)
Low	128 (21.9)
Not applicable	7 (1.2)
Not reported	103 (17.6)

Acupuncturist experience (years)	
<=5	22 (3.8)
5-10y	1 (0.2)
>=10y	6 (1.0)
Not reported	555 (95.0)
Education or training of the practitioner	
Systematic acupuncture or Traditional Chinese Medicine Education	37 (6.3)
Short term training	55 (9.4)
Not reported	492 (84.3)
The clinical specialty of the practitioner	
Acupuncturist	45 (7.7)
Others	65 (11.1)
Not reported	474 (81.2)
Acupuncture-specific patient-practitioner interactions	
Yes (trialists allowed or encouraged the interactions)	73 (12.5)
No (the interactions were prohibited)	43 (7.4)
Not reported	468 (80.1)
Type of control group*	
Penetrating needle sham	25 (4.3)
Non-penetrating needle sham	13 (2.2)
Non-needle sham	41 (7.0)
High-intensity control (No sham) [b]	395 (67.6)
Usual care control (No sham)	145 (24.8)
Low-intensity control (No sham) [c]	2 (0.3)
Type of comparisons*	
Acupuncture vs. waitlist or no intervention	3 (0.5)
Acupuncture vs. sham acupuncture	43 (7.4)
Acupuncture + other interventions .vs. other interventions	528 (90.4)
Acupuncture + other interventions vs. sham acupuncture + other interventions	36 (6.2)
Type of outcome*	
Pain	177 (30.3)
Non-pain symptoms	267 (45.7)
Function	314 (53.8)
Quality of life	46 (7.9)
Major events	54 (9.2)
Longest follow-up time	
1-3 months	52 (8.9)
3-6 months	18 (3.1)
>6 months	7 (1.2)
End of treatment	507 (86.8)

* Each study can contribute more than one estimate.

[a] We classified the frequency of treatment sessions, duration of treatments, and the total number of treatments into high and low according to the categories of type of acupuncture stimulation and course of diseases. Details of criteria were provided in eAppendix 5.

[b] In the high-intensity control group, patients received the specific protocol-guided treatment with identical aims to acupuncture treatment.

[c] In the low-intensity control, some active treatments are not permitted. For example, in an RCT where acupuncture was the intervention for low back pain, patients in the waitlist control group could take oral nonsteroidal anti-inflammatory drugs but prohibitted to take analgestics for central nervous systems.

eTable 1.3 Risk of bias of included studies（n=584）

Characteristic	No. (%)
Random sequence generation	
Inadequate or unclear	246 (42.1)
Adequate	338 (57.9)
Allocation concealment	
Inadequate or unclear	536 (91.8)
Adequate	48 (8.2)
Blinding of outcome assessors	
No and probably no	521 (89.2)
Yes and probably yes	63 (10.8)
Blinding of participants*	
No and probably no	536 (91.8)
Yes and probably yes	63 (10.8)
Stratification or block randomization	
Only used Stratification	4 (0.7)
Only used Block randomization	14 (2.4)
Stratification and block randomization	17 (2.9)
Not reported	549 (94.0)
Missing data reported	
Yes, state MPD occurs (in the main text or CONSORT flow diagram)	100 (17.1)
Yes, state MPD did not occur (in the main text or the CONSORT flow diagram)	27 (4.6)
Not reported	457 (78.3)
The proportion of missing data	
0%	27 (4.6)
< 20%	94 (16.1)
>20%	6 (1.0)
Not reported	457 (78.3)

* Each study can contribute more than one estimate.

eTable 2 Magnitude of significant factors impacting treatment effect in multivariable analysis

Significant predictors	Differences of adjusted SMD	95% CI	P-value
Type of outcome			
Quality of life vs major events	0.51	0.24 to 0.77	<0. 001
Pain vs major events	0.48	0.27 to 0.69	<0.001
Function vs major events	0.41	0.21 to 0.61	<0.001
Non-pain symptoms vs major events	0.32	0.12 to 0.52	<0.001
Pain vs non-pain symptoms	0.16	0.04 to 0.27	0.01
Function vs non-pain symptoms	0.09	0 to 0.19	0.06
Quality of life vs non-pain symptoms	0.19	-0.01 to 0.39	0.06
Pain vs function	0.06	-0.05 to 0.18	0.27
Quality of life vs pain	0.03	-0.18 to 0.24	0.77
Quality of life vs function	0.10	-0.10 to 0.29	0.35
Number of centers			
Single center vs multicenter	0.38	0.10 to 0.66	0.01
Acupuncture type			
Penetration vs non-penetration	0.34	0.15 to 0.53	<0.001
Frequency of treatment sessions			
High vs low	0.19	0.03 to 0.35	0.02
Funding availability			
Not reported vs reported	0.12	0 to 0.25	0.04

SMD=standardized mean difference; CI=confidence interval; Vs=versus

eTable 3 Magnitude of **significant factors in univariable analyses (excluded from multivariable analysis)**

Predictors	Differences of adjusted SMD (95% CI), *P* value
Total number of acupuncture treatments	
High vs low	0.48 (0.33 to 0.62), <0.001
Type of acupuncture stimulation	
Manual acupuncture vs electro-acupuncture	0.21 (0.06 to 0.37), 0.008
Manual acupuncture vs Laser acupuncture	-0.37(-1.73 to 0.99), 0.60
Manual acupuncture vs TEAS	0.64(0.41to 0.86), <0.001
Manual acupuncture vs acupressure	0.41(0.26 to 0.56), <0.001
Electro-acupuncture vs Laser acupuncture	-0.58 (-1.95 to 0.78), 0.40
Electro-acupuncture vs TEAS	0.42(0.17 to 0.68), 0.001
Electro-acupuncture vs acupressure	0.19(0.01 to 0.38), 0.04
Laser acupuncture vs TEAS	1.01(-0.37 to 2.38), 0.15
Laser acupuncture vs acupressure	0.78(-0.59 to 2.14), 0.26
TEAS vs acupressure	-0.23(-0.47 to 0.01), 0.06
Source of acupuncture regimen	
Expert consensus vs textbook or literature	-0.56(-0.87 to -0.26), 0.001
Expert consensus vs clinical experience	-0.21(-0.73 to 0.31), 0.42
Expert consensus vs mix of some	-0.10(-0.48 to 0.28), 0.60
Textbook or literature vs clinical experience	0.35(-0.10 to 0.80), 0.12
Textbook or literature vs mix of some	0.46(0.19 to 0.74), 0.001
Clinical experience vs mix of some	0.11(-0.39 to 0.61), 0.66
Duration of treatment_chronic	
1-4 weeks vs 5-8 weeks	0.28(0.09 to 0.48), 0.005
1-4 weeks vs 9-12 weeks	0.28(0.06 to 0.51), 0.01
1-4 weeks vs > 12 weeks	0.39(0.05 to 0.73), 0.03
5-8 weeks vs 9-12 weeks	-0.002(-0.27 to 0.26), 0.99
5-8 weeks vs > 12 weeks	0.11(-0.26 to 0.47), 0.57
9-12 weeks vs > 12 weeks	0.11(-0.28 to 0.49), 0.58
Patient expectation	
Not reported vs reported	0.79(0.33 to 1.25), <0.001

Education or training of practitioner	
Systematic acupuncture or TCM education (undergraduate, graduate, diploma training) vs short term training (none of the training mention in 1)	-0.22(-0.44 to -0.01), 0.04
Type of comparisons	
Acupuncture vs waitlist or no intervention vs Acupuncture vs sham acupuncture	0.04(-0.52 to 0.59), 0.90
Acupuncture vs waitlist or no intervention vs Acupuncture + other interventions vs other interventions	-0.40(-1.00 to 0.17), 0.17
Acupuncture vs waitlist or no intervention vs Acupuncture + other interventions vs sham acupuncture + other interventions	0.09(-0.51 to 0.70), 0.77
Acupuncture vs sham acupuncture vs Acupuncture + other interventions vs other interventions	-0.44(-0.63 to -0.24), <0.001
Acupuncture vs sham acupuncture vs Acupuncture + other interventions vs sham acupuncture + other interventions	0.05(-0.23 to 0.34), 0.70
Acupuncture + other interventions vs other interventions vs Acupuncture + other interventions vs sham acupuncture + other interventions	0.49(0.28 to 0.70), <0.001
Blinding of participants	
Probably no vs probably yes	0.49(0.33 to 0.65), <0.001
Therapeutic areas	
Gastroenterology vs Musculoskeletal system	-0.34(-0.59 to -0.09), 0.01
Gastroenterology vs Neurology	-0.52(-0.71 to -0.34), <0.001
Gastroenterology vs Respirology	-0.42(-0.82 to -0.01), 0.04
Dermatology vs Endocrinology and nutrition	0.95(0.01 to 1.89), 0.05
Endocrinology and nutrition vs Musculoskeletal system	-0.63(-1.11 to -0.16), 0.01
Endocrinology and nutrition vs Neurology	-0.82(-1.23 to -0.37), <0.001
Endocrinology and nutrition vs Respirology	-0.71(-1.28 to -0.14), 0.02
Obstetrics and gynecology vs Musculoskeletal system	-0.38(-0.73 to -0.04), 0.03
Obstetrics and gynecology vs Neurology	-0.57(-0.87 to -0.27), <0.001
Mental health vs Neurology	-0.42(-0.63 to -0.21), <0.001
Musculoskeletal system vs Oncology	0.69(0.14 to 1.23), 0.01
Musculoskeletal system vs Obstetrics and gynecology	0.40(0.13 to 0.67), 0.003

Musculoskeletal system vs Trauma and injuries	0.39(0.09 to 0.70), 0.01
Oncology vs Neurology	-0.87(-1.39 to -0.35), 0.001
Oncology vs Respirology	-0.76(-1.39 to -0.13), 0.02
Neurology vs Obstetrics and gynecology	0.59(0.38 to 0.80), <0.001
Neurology vs Sleep-wake disorders	0.52(0.14 to 0.89), 0.007
Neurology vs Respirology	0.58(0.33 to 0.84), <0.001
Respirology vs Trauma and injuries	0.47(0.03 to 0.91), 0.04
Longest follow-up time	
1-3months vs 3-6months	0.14(-0.25 to 0.53), 0.48
1-3months vs >6months	0.02(-0.51to 0.55), 0.94
1-3months vs end of treatment	-0.41(-0.61 to -0.21), <0.001
3-6months vs >6months	-0.12(-0.71 to 0.48), 0.70
3-6months vs end of treatment	-0.55(-0.89 to -0.20), 0.002
>6months vs end of treatment	-0.43(-0.92 to 0.07), 0.09
Missing data reported	
Yes, state MPD occur (in the main text or in CONSORT flow diagram) vs Yes, state MPD did not occur (in the main text or in CONSORT flow diagram)	-0.40(-0.61 to -0.18), 0.001
Proportion of missing data	
0% vs < 20%	0.37(0.16 to 0.59), 0.001
0% vs ≥20%	0.68(0.28 to 1.08), 0.001
< 20% vs ≥20%	0.30(-0.06 to 0.67), 0.10
Trial registration	
Not reported vs reported	0.76(0.59 to 0.94), <0.001
Type of funding	
National vs foundation	0.21(-0.28 to 0.69), 0.40
National vs provincial	-0.54(-0.75 to -0.33), <0.001
National vs institution	-0.05(-0.39 to 0.28), 0.75
Foundation vs provincial	-0.75(-1.21 to -0.28), 0.002
Foundation vs institution	-0.26(-0.76 to 0.24), 0.30
Provincial vs institution	0.49(0.18 to 0.79), 0.002
Publication language	
Chinese vs English	0.72(0.57 to 0.88), <0.001
Chinese vs Persian	0.76(-0.41 to 1.92), 0.20
English vs Persian	0.03(-1.14 to 1.20), 0.96
Journal Impact factor	
0 vs. 0.1-1.99	0.6(0.29 to 0.92), 0.001
0 vs 2-4.99	0.7(0.49 to 0.91), <0.001
0 vs ≥5	1.02(0.67 to 1.37)，<0.001
0.1-1.99 vs 2-4.99	0.1(-0.27 to 0.47), 0.60

0.1-1.99 vs ≥5	0.42(-0.04 to 0.88), 0.07
2-4.99 vs ≥5	0.32(-0.08 to 0.72), 0.12
Stratification or block randomization	
Only stratification randomization used vs. only block randomization used	-0.56(-1.36 to 0.25), 0.18
Only stratification randomization used vs. both stratification and block randomization	-0.02(-0.81 to 0.77), 0.96
Only block randomization used vs. both stratification and block randomization	0.53(0.04 to 1.02), 0.03

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P6, eAppendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Not applicable
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P9-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P9-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P11, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not applicable
Study characteristics	17	Cite each included study and present its characteristics.	P11, eTable 1.1-1.3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P12-13, Fig 2, Table1,2 eTable 2,3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P13
	23b	Discuss any limitations of the evidence included in the review.	P13
	23c	Discuss any limitations of the review processes used.	P14
	23d	Discuss implications of the results for practice, policy, and future research.	P15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	no
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	no
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	no
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P16
Competing interests	26	Declare any competing interests of review authors.	P17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	no

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

BMJ Open

Factors Associated with the Magnitude Of acUpuncture treatment effectS (FAMOUS): a meta-epidemiological study of acupuncture randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060237.R1
Article Type:	Original research
Date Submitted by the Author:	01-Jun-2022
Complete List of Authors:	Gang, Weijuan; China Academy of Chinese Medical Sciences, Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Centre for Evidence-Based Traditional Chinese Medicine Xiu, Wencui; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Shi, Lanjun; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Zhou, Qi; McMaster University Jiao, Ruimin; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Yang, Jiwei; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Shi, Xiaoshuang; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Sun, Xiaoyue; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Center for Evidence-Based Traditional Chinese Medicine Zeng, Zhao; Guangzhou University of Chinese Medicine Witt, Claudia; University of Zurich, Institute for Complementary and Integrative Medicine, University Hospital Zurich Thabane, Lehana; McMaster University, Song, Ping; China Academy of Chinese Medical Sciences Yang, Longhui; China Academy of Chinese Medical Sciences Guyatt, Gordon; McMaster University, Jing, Xianghong; China Academy of Chinese Medical Sciences, Institute of Acupuncture and Moxibustion; China Academy of Chinese Medical Sciences, China Centre for Evidence Based Traditional Chinese Medicine Zhang, Yuqing; McMaster University, Department of Health Research Methods, Evidence, and Impact; China Academy of Chinese Medical Sciences Institute of Acupuncture and Moxibustion
Primary Subject Heading:	Complementary medicine

Secondary Subject Heading:	Evidence based practice
Keywords:	COMPLEMENTARY MEDICINE, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Original Investigation

Factors Associated with the Magnitude Of acUpuncture treatment effectS (FAMOUS): a meta-epidemiological study of acupuncture randomized controlled trials

Wei-Juan Gang[1,2], MD, PhD; Wen-Cui Xiu[1,2], MD Candidate; Lan-Jun Shi[1,2], MD Candidate; Qi Zhou[3], PhD; Rui-Min Jiao[1,2], MD; Ji-Wei Yang[1,2], MD; Xiao-Shuang Shi[1,2], MD, PhD; Xiao-Yue Sun[1,2], MD Candidate; Zhao Zeng[4], MD; Claudia M. Witt[5], MD, MBA; Lehana Thabane[3], PhD; Ping Song[6], MD; Long-Hui Yang[6], MD; Gordon Guyatt[3,7], MD. MSc; Xiang-Hong Jing[1,2†], MD, PhD; and Yu-Qing Zhang[1,3,8,9†], MD, MSc, PhD, on behalf of FAMOUS Group

Affiliations

1 Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China

2 China Center for Evidence-Based Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, China

3 Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

4 Guangzhou University of Chinese Medicine, Guangzhou, China

5 Institute for Complementary and Integrative Medicine, University Hospital Zurich and University of Zurich, Zurich, Switzerland

6 China Academy of Chinese Medical Sciences, Beijing, China

7 Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

8 Nottingham Ningbo GRADE center, University of Nottingham Ningbo China, Ningbo, China

9 CEBIM (Center for Evidence Based Integrative Medicine)-Clarity Collaboration, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

† Authors equally contributed to this work.

†Correspondence to:

Xiang-Hong Jing, Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China.

Email: xhjingt66@163.com

Phone: +86 13671120972

Yu-Qing Zhang, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada

Email: madisonz1220@gmail.com

TEL: +19059205829

Manuscript word count: 3254

ABSTRACT

OBJECTIVE

To identify factors and assess to what extent they impact the magnitude of the treatment effect of acupuncture therapies across therapeutic areas.

DATA SOURCE

Medline, Embase, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Wanfang Database, VIP Database, and China Biology Medicine disc, between 2015 and 2019.

STUDY SELECTION

The inclusion criteria were trials with a total number of randomized patients larger than 100, at least one patient-important outcome and one of two sets of comparisons.

DATA ANALYSIS

The potential independent variables were identified by reviewing relevant literature and consulting with experts. We conducted meta-regression analyses with standardized mean difference (SMD) as effect estimate for the dependent variable. The analyses included univariable meta-regression and multivariable meta-regression using a three-level robust mixed model.

RESULTS

1304 effect estimates from 584 acupuncture RCTs were analysed. The multivariable analyses contained 15 independent variables due to missing factor data and collinearity. In the multivariable analysis, the following produced larger treatment effects of large magnitude (>0.4): quality of life (difference of adjusted SMDs 0.51, 95% confidence interval 0.24 to 0.77), or pain (0.48, 0.27 to 0.69), or function (0.41, 0.21 to 0.61) versus major events. The following produced larger treatment effects of moderate magnitude (0.2-0.4): single-centered versus multicentered RCTs (0.38, 0.10 to 0.66); penetration acupuncture versus non-penetration types of acupuncture (0.34, 0.15 to 0.53); non-pain symptoms versus major events (0.32, 0.12 to 0.52). The following produced larger treatment effects of small (<0.2)

magnitude: high versus low frequency treatment sessions (0.19, 0.03 to 0.35); pain versus non-pain symptoms (0.16, 0.04 to 0.27); unreported versus reported funding (0.12, 0 to 0.25).

CONCLUSION

Patients, clinicians, and policymakers should consider penetrating over non-penetrating acupuncture and more frequent treatment sessions when feasible and acceptable. When designing future acupuncture RCTs, trialists should consider factors that impact acupuncture treatment effects.

Keywords:

Acupuncture; randomised controlled trial (RCT); influential factor; treatment effect; meta-regression; meta-epidemiology; multivariable analysis

STRENGTHS AND LIMITATIONS OF THE STUDY

- This study included a comprehensive search, independent and duplicated screening and data extraction, rigorous data analysis, and interpretation by multidisciplinary researchers.
- This study focused on patient-important outcomes and chose the independent variables considering literature, clinicians, and patients' perspectives.
- This study constructed a robust three-level mixed model multivariable analysis to adjust for multiple variables to reduce the potential bias and used Cramer's V and the weighting approach of robust regression to deal with the collinearity and substantial amount of outlier and influential values.
- The multivariable analyses excluded important independent variables such as practitioners' experience due to poor reporting.
- Including extremely imbalanced variables (e.g., country, trial registered) limits the generalizability of the study results.

INTRODUCTION

Acupuncture is one of the most used and researched interventions under the integrative medicine umbrella.[1-4] By 2014, the total number of acupuncture randomized controlled trial (RCT) has increased dramatically and accounted for 20.3% of all acupuncture studies[5]. Since 2010, over 1,000 acupuncture RCTs were published annually, with the total number exceeding 10,000 to date.[6]

Acupuncture's treatment effect varies largely across trials.[7, 8] Efforts to determine factors associated with effect size in acupuncture RCTs have reported conflicting findings. For example, Vickers et al. reported that, in studies of chronic pain, penetrating sham versus non-penetrating and non-needle sham control showed larger treatment effects.[9] However, other studies reported that the effect of acupuncture in pain studies was unrelated to the type of sham acupuncture [10, 11]. Some found the total number of acupuncture treatments[11-13], frequency of treatment sessions[14], and acupuncture type (manual acupuncture versus electroacupuncture) [14] were significant factors of the treatment effect whereas others did not.[9, 15] The reason may be related to little data variation[15], small number of included studies[12 14], and variation of the clinical areas and settings investigated[10, 11, 16].

To improve acupuncture RCTs' design, and optimize acupuncture interventions' clinical effectiveness, we conducted this meta-epidemiological study, including acupuncture RCTs published between 2015 to 2019 across therapeutic areas and outcomes, and explored the factors of acupuncture's treatment effects. We aim to a) identify factors regarding patient, acupuncture, comparator, outcome, and methodology that impact the magnitude of the treatment effect of acupuncture therapies and b) explore to what extent the factors impact the treatment effect across therapeutic areas.

METHODS

Definitions

We define acupuncture therapies based on the World Health Organization definition:

Acupuncture literally means to puncture with a needle. However, there may also involve the

application of other kinds of stimulation to certain points[17]. The study addressed commonly used acupuncture modalities, including manual acupuncture, electroacupuncture (electro-acupuncture), laser acupuncture, transcutaneous electrical acupoint stimulation (TEAS), acupressure, traditional body needling, ear (auricular) acupuncture, and scalp acupuncture.

We define sham acupuncture as an intervention with a minimal treatment effect designed to blind patients as they received real acupuncture [18]. Often sham acupuncture includes 'placebo' needles with a blunt collapsing tip that does not penetrate the skin, real acupuncture but inserted at non-acupuncture points, or true acupuncture points but not targeting the intended disease. Non-needle sham can be detuned lasers, deactivated transcutaneous electric nerve stimulation devices, or less pressure on acupuncture points.

We define a patient-important outcome as one in which the patient would be interested, despite the risk, burden or cost, were it the only outcome to improve with an intervention[19]. To differentiate from individual outcomes (e.g., dysphagia), we define a construct as a category of patient-important outcomes (e.g., functional status).

We define a therapeutic area as a class of related diseases or conditions based on modified ICD-11 criteria (e.g., Neurology). In this study, the classification of the therapeutic areas targeted disease or conditions for which patients seek acupuncture treatment. For example, if an acupuncture RCT investigated post-stroke depression, we would classify the RCT into "Mental health" rather than "Neurology".

Literature Search

In collaboration with clinical and methodological experts, a medical information specialist developed a search strategy that included PubMed, Embase, the Cochrane Central Register of Controlled Trials, and 4 Chinese databases, including China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database for Chinese Technical Periodicals (VIP) and China Biology Medicine disc (CBM). We searched acupuncture RCTs published from 2015 January to 2019 December with no language restrictions. The detailed search strategy is presented in eAppendix 1 in the supplement.

Eligibility criteria

Eligible studies fulfilled the following inclusion criteria:

- RCT defined by authors
- Reported at least one of two sets of comparisons: acupuncture versus no intervention, sham acupuncture or waiting list; or acupuncture plus other interventions versus other interventions with or without sham acupuncture. The other interventions must be conventional medical treatment and identical in both intervention and control groups.
- Reported at least one patient-important outcome
- Randomized over 100 individuals
- Appeared in a peer-reviewed journal publication in any language

We excluded conference abstracts, letters, commentaries, editorials, protocols, non-human trials, cluster RCTs, n-of-1 trials, cost-utility studies, secondary analyses of RCTs, reviews, and meta-analyses, RCTs in which control groups received any traditional Chinese medicine (TCM) related therapies (e.g., acupuncture, moxibustion, scraping, cupping, bloodletting, acupoint catgut embedding, massage, Chinese herbal medicine) and studies in which tables and text reported contradictory results on the selected outcomes.

Study selection

We exported Chinese citations to Endnote X9.0 and English citations to a web-based software (https://collaboratron.epistelab.com/) for eligibility screening. To conduct, independently and in duplicate, title and abstract and full-text screening, a team of 16 Chinese and 22 English reviewers worked in pairs using standardized forms with detailed instructions. To ensure screening quality, reviewers participated in a calibration exercise prior. If needed, reviewers resolved disagreements through discussion or arbitrated by a third party.

Generation and ranking of the factors that impact treatment effect

We first, through the literature review and consultation with acupuncturists, generated a list of potential factors that might be associated with the magnitude of effect resulting in 13 methodological factors and 26 clinical factors. To ensure our list was comprehensive, and to

rank the importance of the factors, we conducted an online survey using Wenjuanxing (www.wjx.cn) among a global panel (n=27) composed of acupuncture trialists, acupuncturists, surgeons, trial methodologists, patients, and statisticians. The survey results added 7 factors, and we finally included 46 factors (eAppendix 2 in the supplement) in the meta-regression analyses.

Data extraction

We classified patient-important outcomes into six constructs (box1).

Box 1

I. Mortality

II. Major events include morbid events (e.g., incidence of myocardial infarction,fracture, stroke) , recurrence (e.g., the recurrence of facial spasm) or or fertilization-related events (e.g., live birth rate).

Ⅲ. Pain (e.g., low back pain)

Ⅳ. Non-pain symptoms (e.g., nausea and vomiting)

Ⅴ.Quality of life (e.g., health-related quality of life)

Ⅵ. Functional status (e.g., dysphagia)

To select outcomes, we first extracted all patient-important outcomes, classified them into the six constructs (box 1), and then, within constructs, classified each outcome into therapeutic areas (we will refer to these as subconstructs). For example, for the non-pain symptoms construct, reviewers classified nausea and vomiting into "gastroenterology". We retained the subconstructs, including 30 studies or more.

Within each construct /subconstruct, for each outcome, we calculated the number of studies reporting the outcome. If one study reported multiple outcomes within the same subconstruct, we extracted the more frequently reported outcome across all studies. When studies reported the same outcome measured by different instruments, we selected the most frequently reported instrument for that outcome across all studies.

If the above process excluded either the primary outcome or the first patient-important outcome in the result, in addition to the outcomes selected through that process, we also included the first patient-important or primary outcome reported in the result section.

For multiple-arm RCTs, we considered only those comparisons that met eligibility criteria.

For RCTs with multiple follow-up times, we selected the outcome both at the end of treatment and at the longest follow-up time in which the loss to follow-up rate was 20% or less.

Following a calibration exercise, a team of 10 reviewers, working in pairs, independently extracted data and resolved discrepancies through discussion. If they could not reach a consensus, an arbiter resolved the conflict.

For outcome selection, three pairs of reviewers reviewed all included studies selecting outcomes. After completing the outcome selection and discussing as necessary to come to an agreement, reviewers extracted data on the pre-selected outcomes.

For each trial, reviewers extracted the number of randomized and analyzed participants, data on all factors, and recorded the selected outcomes' effect estimates. Risk of bias was assessed using the Cochrane Collaboration tool.[20] For dichotomous outcomes, we collected the number of events and for continuous outcomes, point and associated variabilities, ranges, and directions. To extract data from figures in which the data were unavailable in the text or tables, we used GetData Graph Digitizer 2.25 (by Mark Mitchell) software.

Statistical analysis

Depending on the data distribution, we summarized data using means and standard deviations, or medians and interquartile ranges. For statistical tests, we used a threshold p-value of 0.05 to indicate a statistical significance. To combine the outcomes from different measurement scales, we applied the standardized mean difference (SMD). A positive SMD indicated a beneficial effect. The variance of SMD[21] was given by

$$V_d = \frac{n_1 + n_2}{n_1 n_2} + \frac{SMD^2}{2(n_1 + n_2)}.$$

where n_1 and n_2 were the sample sizes of the acupuncture therapies group and the control group, respectively. For the dichotomous outcome, by the method of Hasselblad and Hedges[21, 22], we converted the calculated log odds ratio to SMD using

$$d = LogOddsRatio \times \frac{\sqrt{3}}{\pi}$$

where π is the mathematical constant (approximately 3.14159). The variance of SMD was obtained by

$$V_d = V_{LogOddsRatio} \times \frac{3}{\pi^2}$$

We initially considered 46 variables (eAppendix 2 in the supplement) to investigate factors that might influence the SMD among the RCTs. However, 26 variables were excluded from the multivariate analysis because they were missing in more than 90% of the studies (eAppendix 3 in the supplement). To detect possible multicollinearity, we calculated the Cramer's V statistics [23, 24] (ranges 0 to 1) between every pair of the variables using a threshold of 0.70. When excessive collinearity existed, we excluded those variables from the regression analysis (eAppendix 3 in the supplement).

To account for the heterogeneity between the studies and the dependency of the multiple outcomes within a study, we used a meta-regression in three-level random-effects mixed model [25-27] to simulate the sampling variation for each effect size (level one), variation over outcomes within a study (level two), and variation over studies (level three). The dependent variable was the SMD of the acupuncture therapies. The independent variables were the study level factors treated as fixed effects.

We had three different specifications in conducting the analyses. The first specification was an empty model with no independent variables to test heterogeneity of effect sizes at the study and outcome levels. The second specification (primary analysis) was a multivariable analysis that estimated the effects of the multiple independent variables associated with the SMD. To ensure sufficient power for the estimation, we determined the number of independent variables included in the model by applying the rule of 10 observations per variable. If no

enough sample would contain all independent variables, a hierarchical list of variables was used to determine the priority of entry into the model. The third specification was a univariable analysis with a single factor each time.

To limit the influence of outliers and provide the resistant (stable) results, we incorporated the robust regression approach [28] to the three-level random-effects mixed model for the analysis and used the difference of the least-squares means of the SMDs (or the difference of adjusted SMDs) to indicate the effect of a factor. We used 0.2 and 0.4 as the thresholds to name small, moderate, and large (<0.2 as small, 0.2-0.4 as moderate, >0.4 as large) for the effect.

We conducted all the analyses in SAS, version 9.4.

Patient and Public Involvement

The online survey on potential factors involved empirical data and input from a global panel that included patients.

RESULTS

The search yielded 169,406 studies, of which 6530 proved eligible. We retrieved and screened the full texts, excluded 5946 ineligible studies, and finally included 584 studies. (Figure 1)

Characteristics of included studies

The 584 eligible studies published between 2015 and 2019 reported 1304 effect estimates that met our relevance criteria. eTables 1.1, 1.2 and 1.3 in the supplement show the basic and clinical characteristics (classification of acupuncture treatment frequency, duration, and the total number of treatments provided in eAppendix 4), and risk of bias of included studies, respectively. Over 90% of the trials (n=540, 92.5%) were conducted in China. Of the 584 studies, 444 (76%) tested traditional Chinese acupuncture, and 313 (53.6%) used manual acupuncture. Acupuncture was the add-on intervention in 564 studies (96.8%), and 542 studies (92.8%) used other interventions as control. Some variables were important but poorly reported and thus excluded from the multivariable analysis.

Included RCTs had a high risk of bias. For example, over 90% of the RCTs were labeled as inadequate or probably inadequate allocation concealment (n=536, 91.8%); close to 90% of the trials did not report any allocation concealment approaches (524, 89.7%).

The extent of the heterogeneity of the acupuncture's treatment effect when compared to sham or no acupuncture control (unconditional model-specification 1)

We applied a robust mixed model without exploratory variables to examine the effect sizes' variations at study and outcome levels and observed significant heterogeneity ($p < 0.0001$). This finding provided a basis for the multivariable analysis to further explore the influencing factors of heterogeneity.

Assessment on factors influencing acupuncture treatment effect (multivariable analysis - specification 2)

Of the 46 factors, 20 met our criterion of <10% of missing (retained at least 526 studies or 1174 outcomes) factor data. The Cramer's V assessments for multicollinearity assessment further excluded publication language, journal impact factors, trial registration, therapeutic areas and blinding of participants due to the high association with other independent variables (Cramer's V statistic > 0.7, eAppendix 3 in the supplement); thus resulted in 15 variables that were eventually included in the analysis (eAppendix 5 in the supplement).

The multivariable analysis, including 1133 effect estimates from 508 studies, identified 5 significant factors: type of outcome, acupuncture type, frequency of treatment sessions, number of centers, and funding availability (Table 1).

Compared to major events outcomes, effects proved larger in quality of life (large magnitude, difference of adjusted SMDs 0.51, 0.24 to 0.77; P<0.001), pain (large magnitude, 0.48, 0.27 to 0.69; P<0.001), function (large magnitude, 0.41, 0.21 to 0.61; P<0.001), and non-pain symptoms (moderate magnitude, 0.32, 0.12 to 0.52; P<0.001). Compared to non-pain symptoms, effects proved larger in pain (small magnitude, 0.16, 0.04 to 0.27; P=0.01). Single center, compared to multicenter, was associated with moderately larger effects (0.38, 0.10 to 0.66; p=0.01). Penetration acupuncture (i.e., manual acupuncture and electroacupuncture),

compared to non-penetration type of acupuncture (i.e., laser acupuncture, TEAS and acupressure), was associated with moderately larger effects (0.34, 0.15 to 0.53; P<0.001). High frequency acupuncture treatment sessions, compared to low frequency, was associated with larger effects of small magnitude (0.19, 0.03 to 0.35; P=0.02). Compared to reported funding, effects proved larger of small magnitude in studies that did not report funding (0.12, 0 to 0.25; P=0.03). (Figure 2, eTable 2 in the supplement)

Assessment on factors influencing acupuncture treatment effect (univariable analysis - specification 3)

Univariable analysis for independent variables excluded from the multivariable analysis

In univariable analysis, of 31 independent variables excluded from the multivariable analyses, 17 were statistically significant factors (Table 2). However, these significances may be attributed to extremely large sample sizes and/or the absence of the other strong predictors in the model.

eTable 3 in the supplement presents the effect sizes of significant factors impacting acupuncture's effect in univariable analysis (excluded from multivariable analysis).

Significant factors in multivariable versus univariable analyses

Of the 15 independent variables, multivariable analysis proved five significant factors associated with the magnitude of effect; in contrast, univariable analysis proved 14 (Table 2).

DISCUSSION

Principal findings

We conducted a meta-epidemiological study including 1304 effect estimates from 584 RCTs. Our robust three-level mixed multivariable analyses identified five significant factors that impacted the magnitude of the acupuncture effect. Acupuncture produced the largest treatment effect on quality-of-life, followed by function, pain, non-pain symptoms, and major events. Penetration acupuncture induced a larger effect than non-penetration acupuncture. High-frequency acupuncture sessions, single-centered acupuncture RCTs, and acupuncture RCTs that did not report funding are associated with larger effects.

Strengths and limitations of the study

This study is the first three-level multivariable meta-epidemiological analysis that included the largest number of RCTs across all therapeutic areas, exploring factors associated with acupuncture's treatment effect. Hence, the rigorous study provided robust results on critical design factors for acupuncture trialists to consider when designing future RCTs. This study provided a favorable type of acupuncture and treatment regimen for patients, clinicians, and policymakers to achieve acupuncture's maximum treatment effect for clinical and health system decisions. Our study has several strengths. Firstly, our study is highly patient-centered and clinically relevant. To ensure the conclusion from our study is the most pertinent for healthcare decision-making, we included only patient-important outcomes. We consulted a group of international clinicians, researchers, and patients when choosing the independent variables.

Secondly, we constructed a robust three-level mixed model multivariable analysis to adjust for multiple variables to reduce the potential bias raised from the univariable analysis. To deal with the collinearity and substantial amount of outlier and influential values in our datasets, we used Cramer's V and the weighting approach of robust regression.

Thirdly, our study has a high methodological rigor. We worked with an experienced medical librarian to develop a systematic and exhaustive search strategy. Teams of reviewers then screened and extracted data independently and in duplicate, with third-party adjudication of disagreement.

Our study has several limitations. Firstly, we used a cut-off value of 0.7 in Cramer's V statistics to identify collinearity, and when applicable, dropped the less important independent variable. Others might find a cut-off of 0.7 being too stringent and therefore left out too many independent variables from the multivariable model. Secondly, acupuncture RCTs poorly reported the risk of bias and acupuncture techniques related factors. Thus, we could not include some important independent variables such as practitioners' experience in the

multivariable analyses. Finally, some factors (e.g., country, trial registered) distributed extremely imbalanced, limiting the results' generalisability.

Comparison with other studies

Previous studies[9-11, 12-15] typically performed univariable analyses in a small number of studies (5 to 39 trials) and identified 15 significant factors, including ten clinical, one methodological, and four other factors. Although our univariable analyses confirmed all these factors, the multivariable analyses identified only five significant factors.

An individual patient data meta-analysis (IPDMA) on chronic pain trials found the total number of acupuncture treatments was a significant factor [9, 15] and more treatment sessions were associated with better effects when comparing acupuncture to no acupuncture controls. Meta-regression studies also revealed the same results.[11-13] However, due to a considerable amount of studies that didn't report the number of treatment sessions, we could not include total number of acupuncture treatment sessions in our multivariable analysis.

One study suggested treatment frequency as a significant predictor for tension-type headaches (more frequent treatment, larger effects)[14] while others did not.[9, 15] In our multivariable analyses, the frequency of treatment sessions proved a significant factor. Some studies included homogeneous treatment frequency [9, 15] whereas others included varied frequency, leading to different findings.

For the type of sham acupuncture, the IPDMA[9, 15] reported that compared to non-penetrating and non-needle sham, penetrating needle sham associated with a larger effect. In contrast, a systematic review[10] found no association between the type of sham and acupuncture's treatment effect. Similarly, our multivariable analyses did not identify the type of sham as a significant factor.

Implications for practice and research

When feasible and acceptable, patients, clinicians, and policymakers should consider using penetrating over non-penetrating types of acupuncture with more frequent treatment sessions.

Identifying significant factors for acupuncture's treatment effect in trials has important implications for future trials design and conducting secondary analyses. When trialist collaboration designs an acupuncture trial: 1) they should follow Consolidated Standards of Reporting Trials (CONSORT)[29] and STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [30] reporting guidelines, especially for those that might impact the treatment effect (random sequence generation and allocation concealment, acupuncture technique related information, practitioners related information, and the source of funding); 2) consider the quality of life outcome more often; 3) carefully choose the type of acupuncture, frequency of treatment sessions, choice of single or multicenter as those impact the treatment effect. When exploring factors associated with acupuncture's treatment effect, researchers should use multivariable analyses over univariable analyses to avoid confounding variables caused biases. Researchers can further investigate factors excluded from multivariable analyses (e.g., practitioners' expertise).

The following are members of FAMOUS group: Wei-Juan Gang, Wen-Cui Xiu, Lan-Jun Shi, Qi zhou, Rui-Min Jiao, Ji-Wei Yang, Xiao-Shuang Shi, Xiao-Yue Sun, Zhao Zeng, Claudia M. Witt, Lehana Thabane, Ping Song, Long-Hui Yang, Gordon Guyatt, Xiang-Hong Jing, Yu-Qing Zhang, Zhi-Yun Zhang, Heng-Cong Li, Jing-Tao Shi, An-Li Chen, Zheng-Yang Qu, Ling Zou, Dong-Xiao Mou, Xiao-Yu Wang, Qing-Quan Yu, Li-Zhen Chen, Yu-Ting Huang, Tiago V. Pereira, Jason Chambers, Cameron Ho, Layla Bakaa, Kevin Loniewski, Kyle Tong, Jaryd Tong, Jared E. Dookie, Jenny Zhu, Malini Hu, Yujin Suk, Kay Wu, Luciane Cruz Lopes, Julia White, Tayler A Buchan, Lauren Giustti Mazzei, Maíra Ramos Alves, Mariana Del Grossi, Cristiane De Cassia Bergamaschi Motta, Jing Meng, Cynthia Chan, Flávia Blaseck.

Acknowledgments

We thank the global panel, including Zhisun Liu, Baoyan Liu, Hui Zheng, Lee Myeong Soo, Tae-Hun Kim, Caroline Smith, Kim L Bennell, Jun Mao, Lixing Lao, Michael E Wechsler,

Karen J Sherman, Andrew J Vickers, Emily Vertosick, Benno Brinkhaus, Klaus Linde, Cummings Mike, Anna Kim, Jiani Wu, Yan Liu, Mohit Bhandari, Philip J Devereaux, and Jianping Liu for ranking the importance of a list of factors, and Jun Mao, Lixing Lao, Klaus Linde and Dawn Richards for discussing the paper's content at the Society of Acupuncture Research 2021 International Research Conference, and Daniel Pérez Rada for supporting the online screening system.

Funding Statement

This research was supported by the China Academy of Chinese Medical Sciences (No. CI2021A03503, GH201901, 2020YJSZX-1) and the National Natural Science Foundation of China (No. 81973968). The funders had no role in considering the study design, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Contributorship

XHJ, YQZ, and WJG had the idea and designed the study. GG was involved in designing the study. YQZ, WJG, and ZZ designed the search strategy. WJG, WCX, LJS, RMJ, JWY, XSS, XYS, Zhi-yun Zhang, Heng-cong Li, Jing-tao Shi, An-li Chen, Zheng-yang Qu, Ling Zou, Dong-xiao Mou, Xiao-yu Wang, Qing-quan Yu, Li-zhen Chen, Yu-ting Huang, Tiago V. Pereira, Jason Chambers, Cameron Ho, Layla Bakaa, Kevin Loniewski, Kyle Tong, Jaryd Tong, Jared E. Dookie, Jenny Zhu, Malini Hu, Yujin Suk, Kay Wu, Luciane Cruz Lopes, Julia White, Tayler A Buchan, Lauren Giustti Mazzei, Maíra Ramos Alves, Mariana Del Grossi, Cristiane De Cassia Bergamaschi Motta, Jing Meng, Cynthia Chan and Flávia Blaseck screened abstracts. WJG, WCX, LJS, RMJ, JWY, XSS, XYS, Zhi-yun Zhang, Heng-cong Li, Jing-tao Shi, An-li Chen, Zheng-yang Qu, Ling Zou, Dong-xiao Mou, Xiao-yu Wang, Qing-quan Yu, Li-zhen Chen and Yu-ting Huang screened full texts.WJG, WCX, LJS, RMJ, JWY, XSS, and XYS extracted data. WCX coordinated the reviewers' tasks. QZ proposed the analysis plan and analyzed the data. LT reviewed and confirmed the statistical analysis plan.

WJG, YQZ and QZ drafted the manuscript, with revision from all authors. YQZ and GG substantially revised the manuscript. XHJ is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others have been omitted.

Competing of Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare support from supported by China Academy of Chinese Medical Sciences (CACMS) Innovation Fund, the National Natural Science Foundation of China, the Fundamental Research Funds for the Central public welfare research institutes, and China Center for Evidence Based Traditional Chinese Medicine for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval

This study does not involve human participants.

Data sharing

All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

[1] World Health Organization. WHO traditional medicine strategy:2014-2023. Geneva: World Health Organization, 2013.

[2] Cui J, Wang SB, Ren JH, Zhang J, Jing J. Use of acupuncture in the USA: changes over a decade (2002-2012). Acupunct Med. 2017; 35(3): 200-7. doi: 10.1136/acupmed-2016-011106. Epub 2017 Jan 13

[3] Yang L, Adams J, Sibbritt D. Prevalence and factors associated with the use of acupuncture and Chinese medicine: results of a nationally representative survey of 17161 Australian women. Acupunct Med. 2017; 35(3): 189-99. doi: 10.1136/acupmed-2016-011179. Epub 2017 Mar 9

[4] Fu JY, Zhang X, Zhao YH, Tong HF, Chen DZ, Huang MH. Bibliometric analysis of acupuncture research fronts and their worldwide distribution over three decades. Afr J Tradit Complement Altern Med. 2017; 14(3): 257-73. doi:10.21010/ajtcam.v14i3.27. eCollection 2017

[5] Ma Y, Dong M, Zhou KH, Mita C, Liu JP, Wayne PM. Publication trends in acupuncture research: a 20-year bibliometric analysis based on PubMed. PLoS One. 2016; 11(12): e0168123. doi: 10.1371/journal.pone.0168123. eCollection 2016

[6] Wang YY, Wang LQ, Chai QY, Liang N, Liu JP. [Literature review on control interventions in randomized clinical trials on acupuncture published in mainland Chinese biomedical journals]. World Chinese Medicine. 2014; 9(10),1264-8. Chinese. doi:10.3969/j.issn.1673-7202.2014.10.003

[7] Wang Y, Xue CC, Helme R, Costa CD, Zheng Z. Acupuncture for frequent migraine: a randomized, patient/assessor blinded, controlled trial with one-year follow-up. Evid Based Complement Alternat Med. 2015;2015:920353. doi: 10.1155/2015/920353 26060503

[8] Xu S, Yu L, Luo X, et al. Manual acupuncture versus sham acupuncture and usual care for prophylaxis of episodic migraine without aura: multicentre, randomised clinical trial. BMJ. 2020;368:m697. doi: 10.1136/bmj.m697.

[9] Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for chronic pain: update of an individual patient data meta-analysis. J Pain. 2018; 19(5): 455-74. doi: 10.1016/j.jpain.2017.11.005. Epub 2017 Dec 2

[10] Madsen MV, Gøtzsche PC, Hróbjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009; 338: a3115. doi: 10.1136/bmj.a3115

[11] Yuan QL, Wang P, Liu L, et al. Acupuncture for musculoskeletal pain: a meta-analysis and meta-regression of sham-controlled randomized clinical trials. Sci Rep. 2016; 6: 30675. doi: 10.1038/srep30675

[12] Qin Z, Wu J, Xu C, Liu Z. Using meta-regression approach to explore the dose-response association between acupuncture sessions and acupuncture effects on chronic prostatitis/chronic pelvic pain syndrome. Ann Transl Med. 2019; 7(6): 116. doi: 10.21037/atm.2018.11.45

[13] Deng YZ , Xu LG , Chen L , Zhou D, Liu Y. Effectiveness of acupuncture in the management of cervical spondylosis: a meta-analysis. J Biol Regul Homeost Agents. 2017; 31(4):1017-22.

[14] Hao XA, Xue CC, Dong L, Zheng Z. Factors associated with conflicting findings on acupuncture for tension-type headache: qualitative and quantitative analyses. J Altern Complement Med. 2013; 19(4): 285-97. doi: 10.1089/acm.2011.0914. Epub 2012 Oct 17

[15] MacPherson H, Maschino AC, Lewith G, et al. Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomised controlled trials. PLoS One. 2013; 8(10): e77438. doi: 10.1371/journal.pone.0077438. eCollection 2013

[16] Manheimer E, van der Windt D, Cheng K, et al. The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2013; 19(6): 696-713. doi: 10.1093/humupd/dmt026. Epub 2013 Jun 27

[17] World Health Organization. Acupuncture: Review and analysis of reports on controlled clinical trials. Geneva: World Health Organization, 2003.

[18] Vickers AJ, Cronin AM, Maschino AC, et al. Individual patient data meta-analysis of acupuncture for chronic pain: protocol of the Acupuncture Trialists' Collaboration. Trials. 2010; 11: 90. doi: 10.1186/1745-6215-11-90

[19] Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. BMJ. 2012;344:e2809. doi: 10.1136/bmj.e2809.

[20] Higgins JPT, Altman DG, Gøtzsche PC, et al. Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi:10.1136/bmj.d5928

[21] Borenstein Michael, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. John Wiley & Sons, Ltd, 2021.

[22] Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. Psychol Bull. 1995; 117(1): 167-78. doi: 10.1037/0033-2909.117.1.167

[23] Harald C. Mathematical methods of statistics (PMS-9). Princeton university press, 2016.

[24] Sadiq M, Mehmood T, Aslam M. Identifying the factors associated with cesarean section modeled with categorical correlation coefficients in partial least squares. PLoS One. 2019; 14(7): e0219427. doi: 10.1371/journal.pone.0219427. eCollection 2019

[25] Moeyaert M, Ugille M, Beretvas SN, Ferron J, Bunuan R, Van den Noortgate W. Methods for dealing with multiple outcomes in meta-analysis: a comparison between averaging effect sizes, robust variance estimation and multilevel meta-analysis. Int J Soc Res Methodol. 2017; 20(6): 559-72. doi: 10.1080/13645579.2016.1252189

[26] Konstantopoulos S. Fixed effects and variance components estimation in three-level meta-analysis. Res Synth Methods. 2011; 2(1): 61-76. doi: 10.1002/jrsm.35. Epub 2011 Jun 10

[27] Van den Noortgate W, López-López JA, Marín-Martínez F, Sánchez-Meca J. Meta-analysis of multiple outcomes: a multilevel approach. Behav Res Methods. 2015; 47(4): 1274-94. doi: 10.3758/s13428-014-0527-2

[28] Chen C. Robust Regression and Outlier Detection with the ROBUSTREG Procedure. In Proceedings of the Twenty-Seventh Annual SAS Users Group International Conference. Cary, NC: SAS Institute Inc, 2002.

[29] Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340:c332. doi: 10.4103/0976-500X.72352

[30] MacPherson H, Altman DG, Hammerschlag R, et al; STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med. 2010; 7(6): e1000261. doi: 10.1136/aim.2009.001370. Epub 2010 Jun 8

Table 1 Multivariable meta-regression analysis

Table 2 Univariable meta-regression analysis

Figure 1 Study selection flow diagram

Figure 2 Forest plots of significant factors in the multivariable analysis

Table 1 Multivariable meta-regression analysis

Factors	Significance
Acupuncture type	√
Acupuncture regimen	
Frequency of treatment sessions	√
Style of acupuncture	
Type of outcome	√
Type of control group	
The course of disease (chronic or acute)	
Random sequence generation	
Allocation concealment	
Blinding of outcome assessors	
Sample size	
Number of centers	√
Funding available	√
Country	
Type of journal	

Notes：

√ The factor is a significant predictor ($p<0.05$).

Blank: The factor is not a significant predictor.

Table 2 Univariable meta-regression analysis

Factors	Significance
Total number of acupuncture treatments	√
Type of acupuncture stimulation	√
Source of acupuncture regimen	√
Duration of treatment_chronic	√
Duration of treatment_acute	
Education or training of practitioners	√
Acupuncturist experience	
Type of comparisons	√
Therapeutic area	√
Blinding of participants	√
Longest follow-up time	√
Missing data reported	√
The proportion of missing data	√
Trial registration	√
Language of publication	√
Type of funding	√
Journal Impact factor	√
Stratification or block randomization	√
Needle retention time(20min)	
Needling angle	
Depth of insertion	
Number of needles used	
De qi	
Patient expectation	√
Acupuncture-specific patient-practitioner interactions	
Ever received acupuncture	

Location of needles	
The clinical specialty of practitioners	
Acupuncture manipulation after needles inserted	
Needling direction	
Intensity of stimulation	
Acupuncture type*	√
Acupuncture regimen*	
Frequency of treatment sessions*	√
Style of acupuncture*	√
Type of outcome*	√
Type of control group*	√
The course of disease (Chronic or acute)*	√
Random sequence generation*	√
Allocation concealment*	√
Blinding of outcome assessors*	√
Sample size*	√
Number of centers*	√
Funding available*	√
Country*	√
Type of Journal*	√

Notes：

√ The factor is a significant predictor ($p<0.05$).

* Included in the multivariable analysis.

Blank: The factor is not a significant predictor.

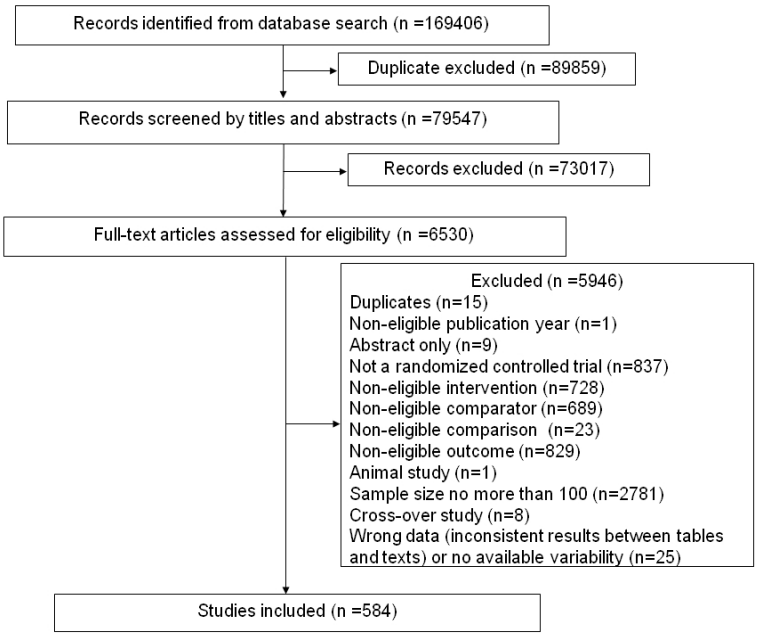

Fig 1 Study selection flow diagram

296x209mm (96 x 96 DPI)

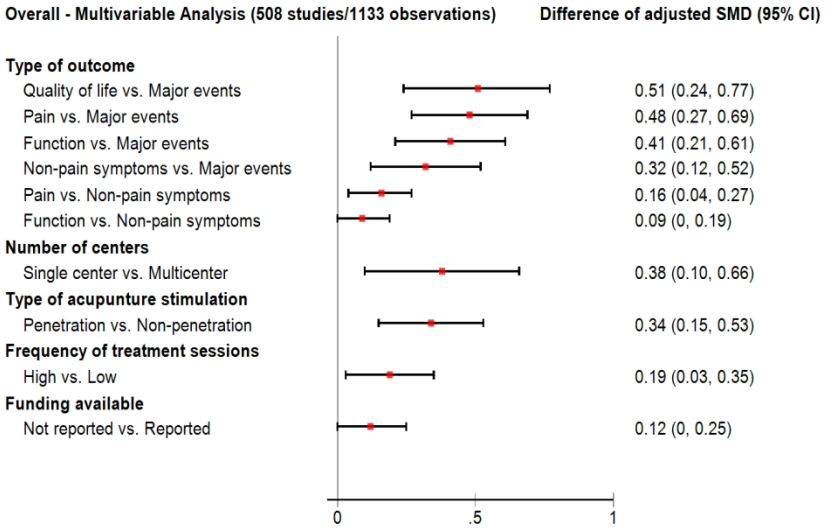

Fig 2 Forest plots of significant factors in the overall multivariable analyses

296x209mm (144 x 144 DPI)

Supplement

eAppendix 1 Search strategy

eAppendix 2 Independent variables ranked by importance

eAppendix 3 Excluded independent variables from multivariable analysis

eAppendix4 Classification of acupuncture treatment frequency, duration, and the total number of treatments

eAppendix 5 Independent variables included in multivariable analysis

eTable 1.1 Basic characteristics of included studies

eTable 1.2 Clinical characteristics of included studies

eTable 1.3 Risk of bias of included studies

eTable 2 Magnitude of significant factors impacting treatment effect in multivariable analysis

eTable3 Magnitude of significant factors in univariable analysis (excluded from multivariable analysis)

eAppendix 1 Search strategy

1. **MEDLINE via PubMed Strategy**

   ((electroacupuncture or "acupuncture"[mesh terms] or "acupuncture"[all fields] or "acupuncture therapy"[mesh terms] or "acupuncture therapy"[all fields] or auricular acupuncture or auricular needle or ear acupuncture or auricular plaster therapy or transcutaneous electric nerve stimulation or tens or electric stimulation therapy or laser acupuncture or auricular point sticking or acupressure or dry needle or scalp acupuncture or scalp sensory or scalp stimulation or filliform needle or filiform needle) and (randomized controlled trial or Controlled Clinical Trial or placebo[Title/Abstract] or sham[Title/Abstract] or randomized[Title/Abstract] or randomly[Title/Abstract] or trial[Title/Abstract] or groups[Title/Abstract])) not (animals NOT humans) and ("2015/01/01"[date - publication] : "2019/12/31"[date - publication])

2. **EMBASE Search strategy**

   ('electroacupuncture'/exp OR electroacupuncture OR 'acupuncture therapy'/exp OR 'acupuncture therapy' OR (('acupuncture'/exp OR acupuncture) AND ('therapy'/exp OR therapy)) OR 'acupuncture moxibustion' OR 'acupuncture moxibustion'/exp OR (('acupuncture'/exp OR acupuncture) AND moxibustion) OR 'auricular acupuncture'/exp OR 'auricular acupuncture' OR (auricular AND ('acupuncture'/exp OR acupuncture)) OR 'auricular needle'/exp OR 'auricular needle' OR (auricular AND ('needle'/exp OR needle)) OR 'ear acupuncture'/exp OR 'ear acupuncture' OR (('ear'/exp OR ear) AND ('acupuncture'/exp OR acupuncture)) OR 'auricular plaster therapy' OR (auricular AND ('plaster'/exp OR plaster) AND ('therapy'/exp OR therapy)) OR 'transcutaneous electric nerve stimulation'/exp OR 'transcutaneous electric nerve stimulation' OR (transcutaneous AND electric AND ('nerve'/exp OR nerve) AND ('stimulation'/exp OR stimulation)) OR tens OR 'electric stimulation therapy'/exp OR 'electric stimulation therapy' OR (electric AND ('stimulation'/exp OR stimulation) AND ('therapy'/exp OR therapy)) OR 'laser acupuncture'/exp OR 'laser acupuncture' OR (('laser'/exp OR laser) AND ('acupuncture'/exp OR acupuncture)) OR 'auricular point sticking' OR (auricular AND point AND sticking) OR 'acupressure'/exp OR acupressure OR 'dry needle' OR (dry AND ('needle'/exp OR needle)) OR 'scalp acupuncture'/exp OR 'scalp acupuncture' OR (('scalp'/exp OR scalp) AND ('acupuncture'/exp OR acupuncture)) OR 'scalp sensory' OR (('scalp'/exp OR scalp) AND ('sensory'/exp OR sensory)) OR 'scalp stimulation' OR (('scalp'/exp OR scalp) AND ('stimulation'/exp OR stimulation)) OR 'filliform needle' OR (filliform AND ('needle'/exp OR needle)) OR 'filiform needle' OR (filiform AND ('needle'/exp OR needle))) AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR (randomized AND controlled AND ('trial'/exp OR trial)) OR 'controlled clinical trial'/exp OR 'controlled clinical trial' OR (controlled AND ('clinical'/exp OR clinical) AND ('trial'/exp OR trial)) OR 'placebo'/exp OR placebo OR sham OR randomized OR randomly OR 'trial'/exp OR trial OR groups) AND 'human'/exp NOT 'animal'/de NOT 'rat'/exp NOT 'mouse'/exp AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py)

3. **CENTRAL**

- **Title Abstract Keyword**

(electroacupuncture OR acupuncture OR auricular needle OR auricular plaster therapy OR transcutaneous electric nerve stimulation OR electric stimulation therapy OR auricular point sticking OR acupressure OR dry needle OR scalp sensory OR scalp stimulation OR filiform needle OR tens) AND (randomized controlled trial OR controlled clinical trial OR placebo OR sham OR randomized OR randomly OR trial OR groups) NOT (animal or rat or mouse)

- Publication year: from 2015 to 2019

4. CNKI search strategy [Chinese database]

English translation from Chinese version

- Professional retrieval：

(SU=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point sticking'+'acupressure'+'laser acupoint irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse') OR
TI=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point sticking'+'acupressure'+'laser acupoint irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse') OR
KY=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point sticking'+'acupressure'+'laser acupoint irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse') OR
AB=('acupuncture'+'electroacupuncture'+'acupuncture and moxibustion'+'laser acupuncture'+'transcutaneous electric'+'transcutaneous nerve'+'electric stimulation'+'electroanalgesia'+'body acupuncture'+'auricular acupuncture'+'scalp acupuncture'+'filiform needle'+'dry needle'+'auricular point

sticking'+'acupressure'+'laser point irradiation'+'transcutaneous electric stimulation treatment'+'transcutaneous electric stimulation nerve'+'transcutaneous electric stimulation'+'acupuncture treatment'+'acupuncture and moxibustion therapy'+'transcutaneous nerve electric stimulation'+'laser acupoint'-'animal'-'rat'-'mouse')) AND (SU='random' or TI='random' or KY='random' or AB='random')

Note：SU=subject，TI=title，KY=keyword，AB=abstract

- Publication date：from 2015-01-01to 2019-12-31.

Chinese version

- 专业检索：

(SU=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠') OR TI=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠') OR KY=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠') OR AB=('针刺'+'电针'+'针灸'+'激光针'+'经皮电'+'经皮神经'+'电刺激'+'电止痛'+'体针'+'耳针'+'头针'+'毫针'+'干针'+'耳穴贴压'+'穴位按压'+'激光穴位照射'+'经皮电刺激治疗'+'经皮电刺激神经'+'经皮电刺激'+'针刺治疗'+'针灸疗法'+'经皮神经电刺激'+'激光穴位'-'动物'-'鼠')) AND (SU='随机' or TI='随机' or KY='随机' or AB='随机')

注：SU=主题，TI=题名，KY=关键词，AB=摘要

- 发表时间（Publication date）：2015-01-01 至 2019-12-31.

5. Wanfang search strategy [Chinese database]

English translation from Chinese version

- Professional retrieval：

(Title OR Keyword:(“electroacupuncture” OR “laser acupuncture” OR “transcutaneous electric” OR “transcutaneous nerve” OR “electric stimulation” OR “electroanalgesia” OR “body acupuncture” OR “auricular acupuncture” OR “scalp acupuncture” OR “filiform needle” OR “dry needle” OR “auricular point sticking” OR “acupressure” OR “laser acupoint irradiation” OR “tens” OR “analgesic skin electrical stimulation” OR “acupuncture treatment” OR “acupuncture and moxibustion therapy”) OR Abstract:(“electroacupuncture” OR “laser acupuncture” OR “transcutaneous electric” OR “transcutaneous nerve” OR “electric stimulation” OR “electroanalgesia” OR “body acupuncture” OR “auricular acupuncture” OR “scalp acupuncture” OR “filiform needle” OR “dry needle” OR “auricular point sticking” OR “acupressure” OR “laser acupoint irradiation” OR “tens” OR “analgesic skin electrical stimulation” OR “acupuncture treatment” OR “acupuncture and

moxibustion therapy") OR Title OR Keyword:("acupuncture and moxibustion" OR "acupuncture") OR Abstract:("acupuncture and moxibustion" OR "acupuncture")) AND (Title OR Keyword:"random" OR Abstract:"random") NOT (Title OR Keyword:("animal" OR "rat" OR "mouse") OR Abstract:("animal" OR "rat" OR "mouse"))

- Publication type：Journal articles.
- Publication date：from 2015to 2019.

Chinese version

- 专业检索：
  (题名或关键词:("电针" OR "激光针" OR "经皮电" OR "经皮神经" OR "电刺激" OR "电止痛" OR "体针" OR "耳针" OR "头针" OR "毫针" OR "干针" OR "耳穴贴压" OR "穴位按压" OR "激光穴位照射" OR "tens" OR "镇痛皮肤电刺激" OR "针刺治疗" OR "针灸疗法") OR 摘要:("电针" OR "激光针" OR "经皮电" OR "经皮神经" OR "电刺激" OR "电止痛" OR "体针" OR "耳针" OR "头针" OR "毫针" OR "干针" OR "耳穴贴压" OR "穴位按压" OR "激光穴位照射" OR "tens" OR "镇痛皮肤电刺激" OR "针刺治疗" OR "针灸疗法") OR 题名或关键词:("针灸" OR "针刺") OR 摘要:("针灸" OR "针刺")) AND (题名或关键词:"随机" OR 摘要:"随机") NOT (题名或关键词:("动物" OR "鼠") OR 摘要:("动物" OR "鼠"))
- 文献类型(Publication type)：期刊论文(Journal articles).
- 发表时间（Publication date）：2015 至 2019.

6. VIP search strategy [Chinese database]

English translation from Chinese version

- Retrieval type search：
  (U=(electroacupuncture OR laser acupuncture OR transcutaneous electric OR transcutaneous electric stimulation treatment OR transcutaneous electric stimulation nerve OR transcutaneous electric stimulation OR transcutaneous nerve OR electric stimulation OR electroanalgesia OR body acupuncture OR auricular acupuncture OR scalp acupuncture OR filiform needle OR dry needle OR auricular point sticking OR acupressure OR laser acupoint irradiation OR "tens" OR analgesic skin electrical stimulation OR acupuncture treatment OR acupuncture and moxibustion therapy OR transcutaneous nerve electric stimulation OR laser acupoint) OR M=(acupuncture and moxibustion OR acupuncture) OR R=(acupuncture and moxibustion OR acupuncture)) AND (M=random OR R=random) NOT (M=(animal OR rat OR mouse) OR R=(animal OR rat OR mouse))
  Note: U=all fields, M=title/keyword, R=abstract
- publication date：from 2015 to 2019.

Chinese version

- 检索式检索：
  (U=(电针 OR 激光针 OR 经皮电 OR 经皮电刺激治疗 OR 经皮电刺激神经 OR 经皮电刺激 OR 经皮神经 OR 电刺激 OR 电止痛 OR 体针 OR 耳针 OR 头针 OR

毫针 OR 干针 OR 耳穴贴压 OR 穴位按压 OR 激光穴位照射 OR “tens” OR 镇痛皮肤电刺激 OR 针刺治疗 OR 针灸疗法 OR 经皮神经电刺激 OR 激光穴位) OR M=(针灸 OR 针刺) OR R=(针灸 OR 针刺)) AND (M=随机 OR R=随机) NOT (M=(动物 OR 鼠) OR R=(动物 OR 鼠))

注：字段标识符 U=任意字段、M=题名或关键词、R=文摘

- 时间限定（publication date）：2015 至 2019.

7. CBM search strategy [Chinese database]

English translation from Chinese version:

#1【Rapid retrieal】acupuncture OR electroacupuncture OR auricular acupuncture OR scalp acupuncture OR body acupuncture OR filiform needle OR acupuncture and moxibustion OR acupuncture and moxibustion therapy OR transcutaneous nerve electric stimulation OR transcutaneous nerve OR electric stimulation OR laser acupuncture OR auricular point sticking OR dry needle OR acupressure OR laser acupoint irradiation OR acupuncture therapy OR electric stimulation therapy (publication date: 2015-2019)

#2【Subject retrieval】acupoint, auricular acupuncture (publication date: 2015-2019)

#3【Rapid retrieal】randomized controlled trial OR randomized controlled study OR randomized controlled clinical OR multicenter study OR multicenter clinical OR multicenter (publication date: 2015-2019)

#4【Rapid retrieal】animal OR rat OR mouse (publication date: 2015-2019)

#5 (#1 or #2) and #3

#6 (#1 or #2) and publication type（randomized controlled trial OR multicenter study）

#7 (#5 or #6) not #4

Chinese version:

#1【快速检索状态】: 针刺 OR 电针 OR 耳针 OR 头针 OR 体针 OR 毫针 OR 针灸 OR 针灸疗法 OR 经皮神经电刺激 OR 经皮神经 OR 电刺激 OR 激光针 OR 耳穴贴压 OR 干针 OR 穴位按压 OR 激光穴位照射 OR 针刺疗法 OR 电刺激疗法 （时间：2015-2019）

#2【主题检索状态】: 穴位, 耳针 （时间：2015-2019）

#3【快速检索状态】: 随机对照试验 OR 随机对照研究 OR 随机对照临床 OR 多中心研究 OR 多中心临床 OR 多中心（时间：2015-2019）

#4【快速检索状态】: 动物 OR 大鼠 OR 小鼠 OR 鼠（时间：2015-2019）

#5 (#1 or #2) and #3

#6 (#1 or #2) and 文献类型限定（随机对照试验、多中心研究）

#7 (#5 or #6) not #4

eAppendix 2

eAppendix 2 Independent variables ranked by importance

Order	Independent variable	Category
1	Allocation concealment	1=Probably yes 2=Probably no
2	Control group*	1=Penetrating needle sham 2=Non-penetrating needling sham 3=Non-needle sham 4=High-intensity control (No sham) 5=Usual care (No sham) 6=Low-intensity control (No sham)
3	Total number of acupuncture treatments	1=Low 2=High
4	Randomization sequence generation	1=Probably yes 2=Probably no
5	Acupuncture stimulation	1=Manual acupuncture 2=Electro-acupuncture 3=Laser acupuncture 4=TEAS 5=Acupressure
6	Acupuncture type	1=Penetrating acupuncture 2=Non-penetrating acupuncture
7	Blinding of outcome assessors	1=Probably yes 2=Probably no
8	Trial registration	1=Reported 2=Not reported
9	Sample size	1=101-149 2=150-499 3=>=500

10	Therapeutic areas	1=Musculoskeletal system 2=Neurology 3=Gastroenterology 4=Urology 5=Mental health 6=Obstetrics and gynecology 7=Dermatology 8=Respirology 9=Sleep-wake disorders 10=Cardiovascular disorders 11=Ophthalmology 12=Endocrinology and nutrition 13=Oncology 14=Trauma and injuries 15=Otorhinolaryngology 16=Acupuncture anesthesia 17=Pediatrics
11	Blinding of participants	1=Probably yes 2=Probably no
12	Frequency of treatment sessions	1=Low 2=High
13	Type of outcome	1=Pain 2=Quality of life (e.g., general quality of life, disease specific quality of life) 3=Function 4=Non-pain Symptoms (such as anxiety, depression, etc.) 5=Major events
14	Country	1=Western countries (countries in Europe, America, Australia and Africa) 2=Eastern countries (Asian countries) 3= both Western and Eastern countries
15	Acupuncture regimen	1=Fixed formula 2=Flexible formula 3=Individualized formula
16	Location of needles	1=Local points only 2=Distal points only 3=Both local and distal points (only for body acupuncture)

17	Education or training of practitioner	1=Systematic acupuncture or TCM education (undergraduate, graduate, diploma training) 2=Short term training (none of the training mention in 1)
18	Number of centers	1=Single center 2=Multicenter
19	Number of needles	1=1-4 2=5-9 3=10-14 4=15-20 5=>20
20	Depth of insertion	1=Deep needling (> 10mm) 2=Superficial needling (< 10mm)
21	Acupuncture manipulation after needles insertion	1=Yes 2=No 3=Not reported 4=Not applicable
22	Needle retention time	1=≥20min 2=＜20min
23	Intensity of stimulation	1=Strong stimulation 2=Moderate stimulation 3=Mild stimulation 4=Not reported
24	Acupuncturist experience	1=＜5y 2=5-10y 3=＞10y
25	Acupuncture-specific patient-practitioner interactions	1=Yes (trialists allowed or encouraged the interactions) 2=No (the interactions were prohibited) 3=Not reported
26	Clinical specialty of practitioner	1=Acupuncturist 2=Others 3=Not reported
27	Publication language	1=English 2=Chinese 3=Other language
28	Source of acupuncture regimen	1=Expert consensus 2=Textbook or literature 3=Clinical experience 4=Mix of some

		5=Unclear
29	Needling angle	1=Reported 2=Not reported
30	Needling direction	1=Reported 2=Not reported
31	De qi	1=Yes 2=No 3=Not reported 4=Not applicable
32	Patient expectations	1=Reported 2=Not reported
33	Funding availability	1=Reported 2=Not reported
34	Style of acupuncture	1=TCM acupuncture (TCMA) 2=Japanese acupuncture (JA) 3=Korean acupuncture (KA) 4=Western medical acupuncture (WMA) 5=Five Element acupuncture (FEA) 6=Scalp stimulation 7=Auricular acupuncture 8=Dry needling
35	Type of funding	1=National funding 2=Foundation funding 3=Provincial funding 4=Institutional funding 5=For-profit funding 6=Not reported
36	Type of Journal	1= CAM (Complementary and Alternative Medicine) journals 2=Non- CAM journals
37	Journal Impact factor	1=0 2=Between 0 and1.99 3=Between 2 and 4.99 4=No less than 5
38	Course of diseases	1=Acute or perioperative issue 2=Chronic disease

39	Type of comparison	1=Acupuncture vs no intervention or waiting list 2=Acupuncture vs sham acupuncture 3=Acupuncture +other intervention vs other intervention 4=Acupuncture +other intervention vs sham acupuncture +other intervention
40	Missing data reported	1=Yes, stating missing data occur 2=No, stating missing data do not occur 3=No explicit statement
41	Proportion of missing data	1=>20% 2=<=20% 3=Not reported
42	Stratification or block of randomization	1=Only stratification randomization used 2=Only block randomization used 3=Both stratification and block randomization used 4=Not reported
43	Ever received acupuncture	1=Yes 2=No 3=Not reported
44	Duration of treatment for chronic diseases	1=1-4 weeks 2=5-8 weeks 3=9-12 weeks 4=>12 weeks
45	Duration of treatment for acute disease	1=1 day 2=>1 day
46	Longest follow-up time	1=1-3 months 2=3-6 months 3=>6 months

*When one study included both sham and other interventions as comparators, we classified the category based on the sham type.

We classified sham acupuncture into three types: penetrating needle sham, non-penetrating needle sham and non-needle sham.

eAppendix 3

eAppendix 3 Excluded independent variables from multivariable analysis	
Due to missing factor data	
1	Total number of acupuncture treatments
2	Acupuncture stimulation (manual acupuncture, electroacupuncture, laser acupuncture, TEAS, acupressure)
3	Source of acupuncture regimen
4	Duration of treatment_chronic
5	Duration of treatment_acute
6	Education or training of practitioners
7	Acupuncturist experience
8	Type of comparisons
9	Longest follow-up time
10	Missing data reported
11	The proportion of missing data
12	Type of funding
13	Stratification or block randomization
14	Needle retention time
15	Needling angle
16	Depth of insertion
17	Number of needles used
18	Acupuncture-specific patient-practitioner interactions
19	Ever received acupuncture
20	Location of needles
21	The clinical specialty of practitioners
22	Acupuncture manipulation after needles inserted
23	Needling direction
24	Intensity of stimulation
25	De qi
26	Patient expectations
Due to collinearity	
27	Language of publication
28	Journal impact factors
29	Trial registration
30	Therapeutic areas
31	Blinding of participants

eAppendix 4

eAppendix 4 Classification of acupuncture treatment frequency, duration and total number of treatments

Category	Low	High
Frequency of treatment sessions		
Acupressure	<=3/day	>3/day
Non-acupressure + Acute	1/day	>1/day
Non-acupressure + Chronic	<=3/week	>3/w
Duration of treatments		
Acute diseases	1day	>1day
Chronic diseases	<=4 weeks	>4 weeks
Total number of acupuncture treatments		
Acute + Acupressure	<=3	>3
Acute + non-acupressure	1	>1
Chronic + Acupressure	<=12	>12
Chronic + non-acupressure	<=12	>12

eAppendix 5

eAppendix 5 Independent variables included in multivariable analysis

1	Random sequence generation
2	Allocation concealment
3	Course of diseases (chronic or acute)
4	Acupuncture stimulation
5	Acupuncture regimen
6	Frequency of treatment sessions
7	Sample size
8	Number of centers
9	Type of control
10	Style of acupuncture
11	Country
12	Type of journal
13	Funding availability
14	Blinding of outcome assessors
15	Type of outcome

eTables

eTable 1.1 Basic characteristics of included studies（n=584 ）

Characteristic	No. (%)
Year of publication	
2015	67 (11.5)
2016	96 (16.4)
2017	133 (22.8)
2018	127 (21.8)
2019	161 (27.6)
Regions	
Eastern regions (Asian countries) [a]	554 (94.9)
Western regions (countries in Europe, America, Australia, and Africa) [b]	29 (5.0)
Both eastern and western regions[c]	1 (0.2)
Language	
Chinese	506 (86.6)
English	76 (13.0)
Persian	2 (0.3)
Type of Journal	
Complementary and Alternative Medicine	297 (50.9)
Non-Complementary and Alternative Medicine	287 (49.1)
Journal impact factor	
0	517 (88.5)
0.1-1.99	17 (2.9)
2-4.99	37 (6.3)
>5	13 (2.2)
Funding	
Non for profit	
National	57 (9.8)
Provincial	146 (25.0)
Institutional	20 (3.4)
Foundational	5 (0.9)
For-profit	0
Not reported	356 (60.9)
Randomized sample size	
101-150	418 (71.6)
151-499	156 (26.7)
>=500	10 (1.7)
Trial registration	
Reported	57 (9.8)
Not reported	527 (90.2)
Informed consent with patients	
Reported	254 (43.5)
Not reported	330 (56.5)
Compensation for participants	
Reported	2 (0.3)
Not reported	582 (99.7)
Number of centers	

Multicenter	36 (6.2)
Single-center	546 (93.5)
Not reported	2 (0.3)
Primary analysis	
Intention to treat analysis (Modified intention to treat)	37 (6.3)
Per protocol analysis	1 (0.2)
No explicit statement	546 (93.5)
Methods dealing with missing participant data (MPD)	
Data deletion	3 (0.5)
Single imputation	9(1.5)
• Mean imputation	1 (0.2)
• Last Observation Caring Forward	5 (0.9)
• Regression for MPD	1 (0.2)
worst-case scenarios	1 (0.2)
best- and worst-case scenarios	1 (0.2)
Multiple imputation	9 (1.5)
Mixed effect model for missing data	2 (0.3)
No missing data	27 (4.6)
No explicit statement	534 (91.4)

* Each study can contribute more than one estimate.

[a] Eastern regions include China(n=540), Iran(n=11), South Korea(n=1), India(n=1) and Malaysia(n=1).

b Western regions include USA (n=9), Spain(n=4), Australia(n=4), Brazil(n=3), German(n=2), Turkey(n=2), Denmark, France, Sweden, UK, Australia and Zealand.

c Both eastern and western regions include one multicenter study conducted in China and the USA.

eTable 1.2 Clinical characteristics of included studies（n=584 ）

Characteristic	No. (%)
Therapeutic area *	
Neurology	203 (34.8)
Gastroenterology	77 (13.2)
Musculoskeletal system	58 (9.9)
Obstetrics and gynecology	54 (9.2)
Mental health	53 (9.1)
Trauma and injuries	34 (5.8)
Urology	27 (4.6)
Respirology	18 (3.1)
Sleep-wake disorders	15 (2.6)
Cardiovascular disorders	12 (2.1)
Acupuncture anesthesia	10 (1.7)
Endocrinology and nutrition	8 (1.4)
Oncology	8 (1.4)
Dermatology	4 (0.7)
Otorhinolaryngology	2 (0.3)
Ophthalmology	1 (0.2)
Pediatrics	1 (0.3)
Course of disease	
Acute (related to procedure such as surgery)	172 (29.4)
Chronic	412 (70.6)
Patient expectation	
Reported	8 (1.4)
Not reported	576 (98.6)
Ever received acupuncture	
Yes	3 (0.5)
No	5 (0.9)
Not reported	576 (98.6)
Style of acupuncture*	
Traditional Chinese acupuncture	444 (76)
Auricular acupuncture	78 (13.4)
Western medical acupuncture	24 (4.1)
Scalp acupuncture	12 (2.1)
Dry needling	2 (0.3)
Not reported	24 (4.1)
Acupuncture stimulation*	
Manual acupuncture	313 (53.6)
Acupressure	131 (22.4)
Electro-acupuncture	99 (17.0)
Transcutaneous Electrical Acupoint Stimulation (TEAS)	44 (7.5)
Laser acupuncture	1 (0.2)
Source of acupuncture regimen	
Textbook or literature	61 (10.4)
Expert consensus	9 (1.5)
Clinical experience	4 (0.7)
Mix of some	12 (2.1)
Not reported	498 (85.3)
Acupuncture regimen*	
Fixed regimen	461 (78.9)
Flexible regimen	93 (15.9)
Individualized regimen	29 (5.0)
Not reported	1 (0.2)
Location of acupuncture points*	
Local	76 (13.0)
Distal	64 (11.0)
Both local and distal	292 (50.0)
Not reported	1 (0.2)

Not applicable	154 (26.4)
Number of needles used*	
1 to 4	54 (9.2)
5 to 9	116 (19.9)
10 to 14	117 (20.0)
15 to 20	70 (12.0)
>20	38 (6.5)
Not reported	18 (3.1)
Not applicable	175 (30.0)
De qi	
Yes	265 (45.4)
No	2 (0.3)
Not reported	80 (13.7)
Not applicable	237 (40.6)
Depth of insertion*	
Deep needling (> 10mm)	153 (26.2)
Superficial needling (< 10mm)	14 (2.4)
Not reported	244 (41.8)
Not applicable	175 (30.0)
Acupuncture manipulation after needles inserted*	
Yes	267 (45.7)
No	9 (1.5)
Not reported	134 (22.9)
Not applicable	175 (30.0)
The intensity of stimulation*	
Strong stimulation	15 (2.6)
Moderate stimulation	4 (0.7)
Mild stimulation	2 (0.3)
Not reported	566 (96.9)
Needling angle*	
Reported	146 (25.0)
Not reported	264 (45.2)
Not applicable	175 (30.0)
Needling direction*	
Reported	87 (14.9)
Not reported	323 (55.3)
Not applicable	175 (30.0)
Needle retention time*	
<=20 min	116 (19.9)
> 20 min	296 (50.7)
Not reported	174 (29.8)
Not applicable	114 (19.5)
Frequency of treatment sessions*[a]	
Low	180 (30.8)
High	356 (61.0)
Not applicable	8 (1.4)
Not reported	43 (7.4)
Duration of treatment for chronic diseases [a] (n=412)	
1-4 weeks	227 (55.1)
5-8 weeks	79 (19.2)
9-12 weeks	53 (12.9)
> 12 weeks	22 (5.3)
Not reported	31 (7.5)
Duration of treatment for acute or perioperative issues*[a] (n=172)	
One day	85 (49.4)
> 1day	53 (30.8)
Not reported	34 (19.8)
Total number of treatments*[a]	
High	356 (61.0)
Low	128 (21.9)

Not applicable	7 (1.2)
Not reported	103 (17.6)
Acupuncturist experience (years)	
<=5	22 (3.8)
5-10y	1 (0.2)
>=10y	6 (1.0)
Not reported	555 (95.0)
Education or training of the practitioner	
Systematic acupuncture or Traditional Chinese Medicine Education	37 (6.3)
Short term training	55 (9.4)
Not reported	492 (84.3)
The clinical specialty of the practitioner	
Acupuncturist	45 (7.7)
Others	65 (11.1)
Not reported	474 (81.2)
Acupuncture-specific patient-practitioner interactions	
Yes (trialists allowed or encouraged the interactions)	73 (12.5)
No (the interactions were prohibited)	43 (7.4)
Not reported	468 (80.1)
Type of control group*	
Penetrating needle sham	25 (4.3)
Non-penetrating needle sham	13 (2.2)
Non-needle sham	41 (7.0)
High-intensity control (No sham) [b]	395 (67.6)
Usual care control (No sham)	145 (24.8)
Low-intensity control (No sham) [c]	2 (0.3)
Type of comparisons*	
Acupuncture vs. waitlist or no intervention	3 (0.5)
Acupuncture vs. sham acupuncture	43 (7.4)
Acupuncture + other interventions .vs. other interventions	528 (90.4)
Acupuncture + other interventions vs. sham acupuncture + other	36 (6.2)
Type of outcome*	
Pain	177 (30.3)
Non-pain symptoms	267 (45.7)
Function	314 (53.8)
Quality of life	46 (7.9)
Major events	54 (9.2)
Longest follow-up time	
1-3 months	52 (8.9)
3-6 months	18 (3.1)
>6 months	7 (1.2)
End of treatment	507 (86.8)

* Each study can contribute more than one estimate.

[a] We classified the frequency of treatment sessions, duration of treatments, and the total number of treatments into high and low according to the categories of type of acupuncture stimulation and course of diseases. Details of criteria were provided in eAppendix 4.

[b] In the high-intensity control group, patients received the specific protocol-guided treatment with identical aims to acupuncture treatment.

[c] In the low-intensity control, some active treatments are not permitted. For example, in an RCT where acupuncture was the intervention for low back pain, patients in the waitlist control group could take oral nonsteroidal anti-inflammatory drugs but prohibitted to take analgestics for central nervous systems.

eTable 1.3 Risk of bias of included studies（n=584)

Characteristic	No. (%)
Random sequence generation	
Inadequate or unclear	246 (42.1)
Adequate	338 (57.9)
Allocation concealment	
Inadequate or unclear	536 (91.8)
Adequate	48 (8.2)
Blinding of outcome assessors	
No and probably no	521 (89.2)
Yes and probably yes	63 (10.8)
Blinding of participants*	
No and probably no	536 (91.8)
Yes and probably yes	63 (10.8)
Success of participants' blinding**	
Yes	7 (70.0)
No	3 (30.0)
Stratification or block randomization	
Only used Stratification	4 (0.7)
Only used Block randomization	14 (2.4)
Stratification and block randomization	17 (2.9)
Not reported	549 (94.0)
Missing data reported	
Yes, state MPD occurs (in the main text or CONSORT flow diagram)	100 (17.1)
Yes, state MPD did not occur (in the main text or the CONSORT flow	27 (4.6)
Not reported	457 (78.3)
The proportion of missing data	
0%	27 (4.6)
< 20%	94 (16.1)
>20%	6 (1.0)
Not reported	457 (78.3)

* Each study can contribute more than one estimate.

** Only ten studies counducted test the success of participants' blingding

eTable 2 Magnitude of significant factors impacting treatment effect in multivariable analysis

Significant predictors	Differences of adjusted SMD	95% CI	P-value
Type of outcome			
Quality of life vs major events	0.51	0.24 to 0.77	<0. 001
Pain vs major events	0.48	0.27 to 0.69	<0.001
Function vs major events	0.41	0.21 to 0.61	<0.001
Non-pain symptoms vs major events	0.32	0.12 to 0.52	<0.001
Pain vs non-pain symptoms	0.16	0.04 to 0.27	0.01
Function vs non-pain symptoms	0.09	0 to 0.19	0.06
Quality of life vs non-pain symptoms	0.19	-0.01 to 0.39	0.06
Pain vs function	0.06	-0.05 to 0.18	0.27
Quality of life vs pain	0.03	-0.18 to 0.24	0.77
Quality of life vs function	0.10	-0.10 to 0.29	0.35
Number of centers			
Single center vs multicenter	0.38	0.10 to 0.66	0.01
Acupuncture type			
Penetration vs non-penetration	0.34	0.15 to 0.53	<0.001
Frequency of treatment sessions			
High vs low	0.19	0.03 to 0.35	0.02
Funding availability			
Not reported vs reported	0.12	0 to 0.25	0.04

SMD=standardized mean difference; CI=confidence interval; Vs=versus

eTable 3 Magnitude of significant factors in univariable analyses (excluded from multivariable analysis)

Predictors	Differences of adjusted SMD (95% CI), *P* value
Total number of acupuncture treatments	
High vs low	0.48 (0.33 to 0.62), <0.001
Type of acupuncture stimulation	
Manual acupuncture vs electro-acupuncture	0.21 (0.06 to 0.37), 0.008
Manual acupuncture vs Laser acupuncture	-0.37(-1.73 to 0.99), 0.60
Manual acupuncture vs TEAS	0.64(0.41to 0.86), <0.001
Manual acupuncture vs acupressure	0.41(0.26 to 0.56), <0.001
Electro-acupuncture vs Laser acupuncture	-0.58 (-1.95 to 0.78), 0.40
Electro-acupuncture vs TEAS	0.42(0.17 to 0.68), 0.001
Electro-acupuncture vs acupressure	0.19(0.01 to 0.38), 0.04
Laser acupuncture vs TEAS	1.01(-0.37 to 2.38), 0.15
Laser acupuncture vs acupressure	0.78(-0.59 to 2.14), 0.26
TEAS vs acupressure	-0.23(-0.47 to 0.01), 0.06
Source of acupuncture regimen	
Expert consensus vs textbook or literature	-0.56(-0.87 to -0.26), 0.001
Expert consensus vs clinical experience	-0.21(-0.73 to 0.31), 0.42
Expert consensus vs mix of some	-0.10(-0.48 to 0.28), 0.60
Textbook or literature vs clinical experience	0.35(-0.10 to 0.80), 0.12
Textbook or literature vs mix of some	0.46(0.19 to 0.74), 0.001
Clinical experience vs mix of some	0.11(-0.39 to 0.61), 0.66
Duration of treatment_chronic	
1-4 weeks vs 5-8 weeks	0.28(0.09 to 0.48), 0.005
1-4 weeks vs 9-12 weeks	0.28(0.06 to 0.51), 0.01
1-4 weeks vs > 12 weeks	0.39(0.05 to 0.73), 0.03
5-8 weeks vs 9-12 weeks	-0.002(-0.27 to 0.26), 0.99
5-8 weeks vs > 12 weeks	0.11(-0.26 to 0.47), 0.57
9-12 weeks vs > 12 weeks	0.11(-0.28 to 0.49), 0.58
Patient expectation	
Not reported vs reported	0.79(0.33 to 1.25), <0.001

Education or training of practitioner	
Systematic acupuncture or TCM education (undergraduate, graduate, diploma training) vs short term training (none of the training mention in 1)	-0.22(-0.44 to -0.01), 0.04
Type of comparisons	
Acupuncture vs waitlist or no intervention vs Acupuncture vs sham acupuncture	0.04(-0.52 to 0.59), 0.90
Acupuncture vs waitlist or no intervention vs Acupuncture + other interventions vs other interventions	-0.40(-1.00 to 0.17), 0.17
Acupuncture vs waitlist or no intervention vs Acupuncture + other interventions vs sham acupuncture + other interventions	0.09(-0.51 to 0.70), 0.77
Acupuncture vs sham acupuncture vs Acupuncture + other interventions vs other interventions	-0.44(-0.63 to -0.24), <0.001
Acupuncture vs sham acupuncture vs Acupuncture + other interventions vs sham acupuncture + other interventions	0.05(-0.23 to 0.34), 0.70
Acupuncture + other interventions vs other interventions vs Acupuncture + other interventions vs sham acupuncture + other interventions	0.49(0.28 to 0.70), <0.001
Blinding of participants	
Probably no vs probably yes	0.49(0.33 to 0.65), <0.001
Therapeutic areas	
Gastroenterology vs Musculoskeletal system	-0.34(-0.59 to -0.09), 0.01
Gastroenterology vs Neurology	-0.52(-0.71 to -0.34), <0.001
Gastroenterology vs Respirology	-0.42(-0.82 to -0.01), 0.04
Dermatology vs Endocrinology and nutrition	0.95(0.01 to 1.89), 0.05
Endocrinology and nutrition vs Musculoskeletal system	-0.63(-1.11 to -0.16), 0.01
Endocrinology and nutrition vs Neurology	-0.82(-1.23 to -0.37), <0.001
Endocrinology and nutrition vs Respirology	-0.71(-1.28 to -0.14), 0.02
Obstetrics and gynecology vs Musculoskeletal system	-0.38(-0.73 to -0.04), 0.03
Obstetrics and gynecology vs Neurology	-0.57(-0.87 to -0.27), <0.001
Mental health vs Neurology	-0.42(-0.63 to -0.21), <0.001
Musculoskeletal system vs Oncology	0.69(0.14 to 1.23), 0.01
Musculoskeletal system vs Obstetrics and	0.40(0.13 to 0.67), 0.003

gynecology	
Musculoskeletal system vs Trauma and injuries	0.39(0.09 to 0.70), 0.01
Oncology vs Neurology	-0.87(-1.39 to -0.35), 0.001
Oncology vs Respirology	-0.76(-1.39 to -0.13), 0.02
Neurology vs Obstetrics and gynecology	0.59(0.38 to 0.80), <0.001
Neurology vs Sleep-wake disorders	0.52(0.14 to 0.89), 0.007
Neurology vs Respirology	0.58(0.33 to 0.84), <0.001
Respirology vs Trauma and injuries	0.47(0.03 to 0.91), 0.04
Longest follow-up time	
1-3months vs 3-6months	0.14(-0.25 to 0.53), 0.48
1-3months vs >6months	0.02(-0.51to 0.55), 0.94
1-3months vs end of treatment	-0.41(-0.61 to -0.21), <0.001
3-6months vs >6months	-0.12(-0.71 to 0.48), 0.70
3-6months vs end of treatment	-0.55(-0.89 to -0.20), 0.002
>6months vs end of treatment	-0.43(-0.92 to 0.07), 0.09
Missing data reported	
Yes, state MPD occur (in the main text or in CONSORT flow diagram) vs Yes, state MPD did not occur (in the main text or in CONSORT flow diagram)	-0.40(-0.61 to -0.18), 0.001
Proportion of missing data	
0% vs < 20%	0.37(0.16 to 0.59), 0.001
0% vs ≥20%	0.68(0.28 to 1.08), 0.001
< 20% vs ≥20%	0.30(-0.06 to 0.67), 0.10
Trial registration	
Not reported vs reported	0.76(0.59 to 0.94), <0.001
Type of funding	
National vs foundation	0.21(-0.28 to 0.69), 0.40
National vs provincial	-0.54(-0.75 to -0.33), <0.001
National vs institution	-0.05(-0.39 to 0.28), 0.75
Foundation vs provincial	-0.75(-1.21 to -0.28), 0.002
Foundation vs institution	-0.26(-0.76 to 0.24), 0.30
Provincial vs institution	0.49(0.18 to 0.79), 0.002
Publication language	
Chinese vs English	0.72(0.57 to 0.88), <0.001
Chinese vs Persian	0.76(-0.41 to 1.92), 0.20
English vs Persian	0.03(-1.14 to 1.20), 0.96
Journal Impact factor	
0 vs. 0.1-1.99	0.6(0.29 to 0.92), 0.001
0 vs 2-4.99	0.7(0.49 to 0.91), <0.001

0 vs ≥5	1.02(0.67 to 1.37)，<0.001
0.1-1.99 vs 2-4.99	0.1(-0.27 to 0.47), 0.60
0.1-1.99 vs ≥5	0.42(-0.04 to 0.88), 0.07
2-4.99 vs ≥5	0.32(-0.08 to 0.72), 0.12
Stratification or block randomization	
Only stratification randomization used vs. only block randomization used	-0.56(-1.36 to 0.25), 0.18
Only stratification randomization used vs. both stratification and block randomization	-0.02(-0.81 to 0.77), 0.96
Only block randomization used vs. both stratification and block randomization	0.53(0.04 to 1.02), 0.03

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P6, eAppendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Not applicable
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P9-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P9-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P11, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not applicable
Study characteristics	17	Cite each included study and present its characteristics.	P11, eTable 1.1-1.3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P12-13, Fig 2, Table1,2 eTable 2,3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P13
	23b	Discuss any limitations of the evidence included in the review.	P13
	23c	Discuss any limitations of the review processes used.	P14
	23d	Discuss implications of the results for practice, policy, and future research.	P15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	no
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	no
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	no
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P16
Competing interests	26	Declare any competing interests of review authors.	P17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	no

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Correction: *Factors Associated with the Magnitude Of acUpuncture treatment effectS (FAMOUS): a meta-epidemiological study of acupuncture randomised controlled trials*

Gang W, Xiu W, Shi L On behalf of FAMOUS Group, *et al*. Factors Associated with the Magnitude Of acUpuncture treatment effectS (FAMOUS): a meta-epidemiological study of acupuncture randomised controlled trials. *BMJ Open* 2022;12:e060237. doi: 10.1136/bmjopen-2021-060237

The authors want to alert the readers that collaborators have been added to the article as authors.

BMJ Open 2023;**13**:e060237Corr1. doi:10.1136/bmjopen-2021-060237Corr1