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### 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 |
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| Keywords: | COMPLEMENTARY MEDICINE, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY |
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Factors Associated with the Magnitude Of Acupuncture treatment effects (FAMOUS):
a meta-epidemiological study of acupuncture randomized controlled trials

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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) 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\textsuperscript{17}. The study addressed commonly used acupuncture modalities, including manual acupuncture, electroacupuncture (electroacupuncture), 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\textsuperscript{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\textsuperscript{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 (box 1).

| 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\(^2\) was given by

\[
V_d = \frac{n_1 + n_2}{n_1n_2} + \frac{SMD^2}{2(n_1 + n_2)}
\]

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

\[
d = \log\text{OddsRatio} \times \frac{\sqrt{3}}{\pi}
\]
where $\pi$ is the mathematical constant (approximately 3.14159). The variance of SMD was obtained by

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

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 (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 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 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 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 and more treatment sessions
were associated with better effects when comparing acupuncture to no acupuncture controls.
Meta-regression studies also revealed the same results. 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, Maira 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 I Bennell, Jun Mao, Lixing Lao, Michael E Wechsler, Karen J Sherman, Andrew J Vickers, Emily Vertosick, Benno Brinkhaus, Klaus Linde, Cummings Mike, Anna Kim, Jianli 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,
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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.
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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.
Records identified from database search (n = 169406)

Duplicate excluded (n = 89856)

Records screened by titles and abstracts (n = 79547)

Records excluded (n = 73017)

Full-text articles assessed for eligibility (n = 6530)

Excluded (n = 5946)
- Duplicates (n = 15)
- Non-eligible publication year (n = 1)
- Abstract only (n = 9)
- Not a randomized controlled trial (n = 837)
- Non-eligible intervention (n = 728)
- Non-eligible comparator (n = 689)
- Non-eligible comparison (n = 23)
- Non-eligible outcome (n = 820)
- Animal study (n = 1)
- Sample size no more than 100 (n = 2781)
- Cross-over study (n = 8)
- Wrong data (inconsistent results between tables and texts) or no available variability (n = 25)

Studies included (n = 584)

Fig 1 Study selection flow diagram

296x209mm (96 x 96 DPI)
Overall - Multivariable Analysis (608 studies/1133 observations)

| Type of outcome                                      | Difference of adjusted SMD (95% CI) |
|------------------------------------------------------|-------------------------------------|
| Quality of life vs. Major events                     | 0.51 (0.24, 0.77)                   |
| Pain vs. Major events                                | 0.48 (0.27, 0.69)                   |
| Function vs. Major events                            | 0.41 (0.21, 0.61)                   |
| Non-pain symptoms vs. Major events                  | 0.32 (0.12, 0.52)                   |
| Pain vs. Non-pain symptoms                           | 0.16 (0.04, 0.27)                   |
| Function vs. Non-pain symptoms                       | 0.09 (0.0, 0.19)                    |
| Number of centers                                    |                                     |
| Single center vs. Multicenter                        | 0.38 (0.10, 0.66)                   |
| Type of acupuncture stimulation                      |                                     |
| Penetration vs. Non-penetration                      | 0.34 (0.15, 0.53)                   |
| Frequency of treatment sessions                      |                                     |
| High vs. Low                                         | 0.19 (0.03, 0.35)                   |
| Funding available                                    |                                     |
| Not reported vs. Reported                            | 0.12 (0, 0.25)                      |

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

eTable 3 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'/exp 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 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')
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 2015-01-01 to 2019-12-31.

5. Wanfang search strategy [Chinese database]

- 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 “dry needle”) AND (SU=('random' or TI=('random' or KY=('random' or AB='random')))

Note: SU=subject, TI=title, KY=keyword, AB=abstract
- Publication date: from 2015-01-01 to 2019-12-31.

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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 2015 to 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 "针刺疗法" 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 "针刺疗法" 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))

- **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...
7. CBM search strategy [Chinese database]

English translation from Chinese version:

#1 【Rapid retrieval】 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 retrieval】 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 retrieval】 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 耳穴 OR 推拿 OR 针灸 OR 针炎疗法 OR 经皮电刺激 OR 经皮神经电刺激 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，耳穴 （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 Independent variables ranked by importance**

| Order | Independent variable                  | Category                                                                 |
|-------|---------------------------------------|--------------------------------------------------------------------------|
| 1     | Allocation concealment                | 1=Probably yes<br>2=Probably no                                          |
| 2     | Control group                         | 1=Penetrating needle sham<br>2=Non-penetrating needling sham<br>3=Non-needle sham<br>4=High-intensity control (No sham)<br>5=Usual care (No sham)<br>6=Low-intensity control (No sham) |
| 3     | Total number of acupuncture treatments| 1=Low<br>2=High                                                          |
| 4     | Randomization sequence generation     | 1=Probably yes<br>2=Probably no                                          |
| 5     | Acupuncture stimulation               | 1=Manual acupuncture<br>2=Electro-acupuncture<br>3=Laser acupuncture<br>4=TEAS<br>5=Acupressure |
| 6     | Acupuncture type                      | 1=Penetrating acupuncture<br>2=Non-penetrating acupuncture               |
| 7     | Blinding of outcome assessors         | 1=Probably yes<br>2=Probably no                                          |
| 8     | Trial registration                    | 1=Reported<br>2=Not reported                                              |
| 9     | Sample size                           | 1=101-149<br>2=150-499<br>3=>=500                                       |
|   | Therapeutic areas                                      |   |
|---|-------------------------------------------------------|---|
| 1 | Musculoskeletal system                               | 1 |
| 2 | Neurology                                             | 2 |
| 3 | Gastroenterology                                     | 3 |
| 4 | Urology                                               | 4 |
| 5 | Mental health                                         | 5 |
| 6 | Obstetrics and gynecology                            | 6 |
| 7 | Dermatology                                           | 7 |
| 8 | Respirology                                           | 8 |
| 9 | Sleep-wake disorders                                 | 9 |
| 10| Cardiovascular disorders                             | 10|
| 11| Ophthalmology                                         | 11|
| 12| Endocrinology and nutrition                          | 12|
| 13| Oncology                                              | 13|
| 14| Trauma and injuries                                  | 14|
| 15| Otorhinolaryngology                                  | 15|
| 16| Acupuncture anesthesia                               | 16|
| 17| Pediatrics                                            | 17|

|   | Blinding of participants                            |   |
|---|-----------------------------------------------------|---|
| 1 | Probably yes                                        | 1 |
| 2 | Probably no                                         | 2 |

|   | Frequency of treatment sessions                     |   |
|---|-----------------------------------------------------|---|
| 1 | Low                                                 | 1 |
| 2 | High                                                | 2 |

|   | Type of outcome                                     |   |
|---|-----------------------------------------------------|---|
| 1 | Pain                                                | 1 |
| 2 | Quality of life (e.g., general quality of life,    | 2 |
|    | disease specific quality of life)                   |   |
| 3 | Function                                            | 3 |
| 4 | Non-pain Symptoms (such as anxiety, depression, etc.) | 4 |
| 5 | Major events                                        | 5 |

|   | Country                                             |   |
|---|-----------------------------------------------------|---|
| 1 | Western countries (countries in Europe, America,   | 1 |
|    | Australia and Africa)                               |   |
| 2 | Eastern countries (Asian countries)                 | 2 |
| 3 | both Western and Eastern countries                  | 3 |

|   | Acupuncture regimen                                 |   |
|---|-----------------------------------------------------|---|
| 1 | Fixed formula                                       | 1 |
| 2 | Flexible formula                                     | 2 |
| 3 | Individualized formula                              | 3 |

|   | Location of needles                                 |   |
|---|-----------------------------------------------------|---|
| 1 | Local points only                                   | 1 |
| 2 | Distal points only                                  | 2 |
| 3 | Both local and distal points                        | 3 |
| (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 = ≤ 5y                                                                                  |
|   |                                                                                           | 2 = 5-10y                                                                                 |
|   |                                                                                           | 3 = > 10y                                                                                 |
| 24| **Acupuncturist experience**                                                              | 1 = Yes (trialists allowed or encouraged the interactions)                                |
|   |                                                                                           | 2 = No (the interactions were prohibited)                                                  |
|   |                                                                                           | 3 = Not reported                                                                          |
| 25| **Acupuncture-specific patient-practitioner interactions**                                | 1 = Acupuncturist                                                                          |
|   |                                                                                           | 2 = Others                                                                                |
|   |                                                                                           | 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 and 1.99  
|    |                    | 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**

|   | Description |
|---|-------------|
| 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**

|   | Description |
|---|-------------|
| 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**

|   | Variable                                      |
|---|----------------------------------------------|
| 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 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                        | 1 day             | >1 day            |
| 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) *          | 554 (94.9)       |
| Western regions (countries in Europe, America, Australia, and Africa) * | 29 (5.0)         |
| Both eastern and western regions              | 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)         |
| Methods dealing with missing participant data (MPD) |   |
|---------------------------------------------------|---|
| Data deletion                                      | 3 (0.5) |
| Single imputation                                  | 9 (1.5) |
|   - Mean imputation                                | 1 (0.2) |
|   - Last Observation Carrying 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), Germany (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) |
| Parameter                                      | Value   |
|-----------------------------------------------|---------|
| 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*              |         |
| Low                                           | 180 (30.8)|
| High                                          | 356 (61.0)|
| Not applicable                                | 8 (1.4)|
| Not reported                                  | 43 (7.4)|
| Duration of treatment for chronic diseases *   |         |
| (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* | (n=172) |
| One day                                       | 85 (49.4)|
| > 1 day                                       | 53 (30.8)|
| Not reported                                  | 34 (19.8)|
| Total number of treatments*                   |         |
| 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) a | 395 (67.6) |   |
| Usual care control (No sham)         | 145 (24.8) |   |
| Low-intensity control (No sham) b     | 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 prohibited to take analgesics for central nervous systems.
| 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 (0.41 to 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**

| Comparison                                                                 | OR     | 95% CI       | p-value |
|---------------------------------------------------------------------------|--------|--------------|---------|
| 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**

| Blinding                                                                 | OR     | 95% CI       | p-value |
|-------------------------------------------------------------------------|--------|--------------|---------|
| Probably no vs probably yes                                              | 0.49   | (0.33 to 0.65), <0.001 |         |

**Therapeutic areas**

| Therapeutic area                          | OR     | 95% CI       | p-value |
|-------------------------------------------|--------|--------------|---------|
| 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 Respiriology          | -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 Respiriology | -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 |         |
| Study Comparison | Effect Size (95% CI) | p-value |
|------------------|----------------------|---------|
| 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 Respiratory | -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 Respiratory | 0.58 (0.33 to 0.84) | <0.001 |
| Respiratory vs Trauma and injuries | 0.47 (0.03 to 0.91) | 0.04 |

**Longest follow-up time**

| Time Comparison | Effect Size (95% CI) | p-value |
|-----------------|----------------------|---------|
| 1-3 months vs 3-6 months | 0.14 (-0.25 to 0.53) | 0.48 |
| 1-3 months vs >6 months | 0.02 (-0.51 to 0.55) | 0.94 |
| 1-3 months vs end of treatment | -0.41 (-0.61 to -0.21) | <0.001 |
| 3-6 months vs >6 months | -0.12 (-0.71 to 0.48) | 0.70 |
| 3-6 months vs end of treatment | -0.55 (-0.89 to -0.20) | 0.002 |
| >6 months vs end of treatment | -0.43 (-0.92 to 0.07) | 0.09 |

**Missing data reported**

| Data Type | Effect Size (95% CI) | p-value |
|-----------|----------------------|---------|
| Yes, state MPD occurred 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**

| Proportion | Effect Size (95% CI) | p-value |
|------------|----------------------|---------|
| 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**

| Registration Reported | Effect Size (95% CI) | p-value |
|-----------------------|----------------------|---------|
| Not reported vs reported | 0.76 (0.59 to 0.94) | <0.001 |

**Type of funding**

| Funding Type | Effect Size (95% CI) | p-value |
|--------------|----------------------|---------|
| 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**

| Language | Effect Size (95% CI) | p-value |
|----------|----------------------|---------|
| 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**

| Impact Factor Range | Effect Size (95% CI) | p-value |
|---------------------|----------------------|---------|
| 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 |
| Range   | Stratification or block randomization                                      |
|---------|--------------------------------------------------------------------------|
| 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  |
|          | -0.02(-0.81 to 0.77), 0.96                                               |
|          | Only block randomization used vs. both stratification and block          |
|          | 0.53(0.04 to 1.02), 0.03                                                 |
## PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item                                                                 | Location where item is reported |
|-------------------|--------|---------------------------------------------------------------------------------|---------------------------------|
| **Title**         | 1      | Identify the report as a systematic review.                                     | P1                              |
| **Abstract**      | 2      | See the PRISMA 2020 for Abstracts checklist.                                    | P3                              |
| **Introduction**  | 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**       | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | P7                              |
|                   | 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, eAppendix 1                  |
|                   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | P6                              |
|                   | 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                              |
|                   | 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                  |
| Section and Topic | Item # | Checklist item                                                                                                                                                                                                 | Location where item is reported |
|-------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| 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/
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 |
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Original Investigation

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

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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. By 2014, the total number of acupuncture randomized controlled trial (RCT) has increased dramatically and accounted for 20.3% of all acupuncture studies. Since 2010, over 1,000 acupuncture RCTs were published annually, with the total number exceeding 10,000 to date.

Acupuncture's treatment effect varies largely across trials. 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. However, other studies reported that the effect of acupuncture in pain studies was unrelated to the type of sham acupuncture. Some found the total number of acupuncture treatments, frequency of treatment sessions, and acupuncture type (manual acupuncture versus electroacupuncture) were significant factors of the treatment effect whereas others did not. The reason may be related to little data variation, small number of included studies, and variation of the clinical areas and settings investigated.

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\textsuperscript{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 \textsuperscript{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\textsuperscript{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, acupuncture 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 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. 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 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

\[
d = \log\text{OddsRatio} \times \frac{\sqrt{3}}{\pi}
\]

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

\[
V_d = V_{\log\text{OddsRatio}} \times \frac{3}{\pi^2}
\]

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)\(^2\) and STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)\(^3\) 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, Maira 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, Taylor A Buchan, Lauren Giustti Mazzei, Maira 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.
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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
| 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.

Records identified from database search (n=169406)
- Duplicate excluded (n=89856)

Records screened by titles and abstracts (n=79547)
- Records excluded (n=73017)

Full-text articles assessed for eligibility (n=6530)
- Excluded (n=5946)
  - Duplicates (n=15)
  - Non-eligible publication year (n=1)
  - Abstract only (n=0)
  - Not a randomized controlled trial (n=837)
  - Non-eligible intervention (n=728)
  - Non-eligible comparator (n=689)
  - Non-eligible comparison (n=23)
  - Non-eligible outcome (n=629)
  - Animal study (n=1)
  - Sample size no more than 100 (n=2781)
  - Cross-over study (n=8)
  - Wrong data (inconsistent results between tables and texts) or no available variability (n=25)

Studies included (n=584)

296x209mm (96 x 96 DPI)
Overall - Multivariable Analysis (608 studies/1133 observations)  

| Type of outcome                          | Difference of adjusted SMD (95% CI) |
|------------------------------------------|-------------------------------------|
| Quality of life vs. Major events         | 0.51 (0.24, 0.77)                  |
| Pain vs. Major events                    | 0.48 (0.27, 0.69)                  |
| Function vs. Major events                | 0.41 (0.21, 0.61)                  |
| Non-pain symptoms vs. Major events       | 0.32 (0.12, 0.52)                  |
| Pain vs. Non-pain symptoms               | 0.16 (0.04, 0.27)                  |
| Function vs. Non-pain symptoms           | 0.09 (0.0, 0.19)                   |
| Number of centers                        |                                     |
| Single center vs. Multicenter            | 0.38 (0.10, 0.66)                  |
| Type of acupuncture stimulation          |                                     |
| Penetration vs. Non-penetration          | 0.34 (0.15, 0.53)                  |
| Frequency of treatment sessions          |                                     |
| High vs. Low                             | 0.19 (0.03, 0.35)                  |
| Funding available                        |                                     |
| Not reported vs. Reported                | 0.12 (0, 0.25)                     |

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 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

eTable 3 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 'filiform needle' OR (filiform 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 treatment'+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 treatment'+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 treatment'+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 acupoint irradiation'+transcutaneous electric stimulation treatment'+transcutaneous electric stimulation nerve'+transcutaneous electric stimulation treatment'+acupuncture treatment'+acupuncture and moxibustion therapy'+transcutaneous nerve electric stimulation'+laser acupoint'+animal'-rat'-mouse') OR
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 2015-01-01 to 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 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 2015 to 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
7. CBM search strategy [Chinese database]

English translation from Chinese version:

#1【Rapid retrieval】: 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 retrieval】: 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 retrieval】: 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 经皮神经电刺激 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 needle 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) |
|   | Description                                                                 | Options                                                                 |
|---|-----------------------------------------------------------------------------|------------------------------------------------------------------------|
| 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=< .5y                                                                |
                                           | 2=5-10y                                                                |
                                           | 3=>10y                                                                 |
| 24| Acupuncturist experience                                                    | 1=Yes (trialists allowed or encouraged the interactions)              |
                                           | 2=No (the interactions were prohibited)                                 |
                                           | 3=Not reported                                                          |
| 25| Acupuncture-specific patient-practitioner interactions                       | 1=Acupuncturist                                                        |
                                           | 2=Others                                                               |
                                           | 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                                                           |
|   |   |   |
|---|---|---|
| 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 and 1.99  
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                  | 1 day          | >1 day         |
| 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

**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**                               |         |

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| Multicenter | 36 (6.2) |
|-------------|---------|
| Single-center | 546 (93.5) |
| Not reported | 2 (0.3) |

**Primary analysis**

| Analysis | Count |
|----------|-------|
| 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)**

| Method | Count |
|--------|-------|
| Data deletion | 3 (0.5) |
| Single imputation | 9 (1.5) |
| - Mean imputation | 1 (0.2) |
| - Last Observation Carrying 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), Germany (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.
| 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) |
| Respiratory | 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) |
|                          |       |
|--------------------------|-------|
| **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** |       |
| Low                      | 180 (30.8) |
| High                     | 356 (61.0) |
| Not applicable           | 8 (1.4) |
| Not reported             | 43 (7.4) |
| **Duration of treatment for chronic diseases** |       |
| (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** |       |
| (n=172)                  |       |
| One day                  | 85 (49.4) |
| > 1 day                  | 53 (30.8) |
| Not reported             | 34 (19.8) |
| **Total number of treatments** |       |
| High                     | 356 (61.0) |
| Low                      | 128 (21.9) |
| Category                                                                 | Count (Percentage) |
|-------------------------------------------------------------------------|--------------------|
| 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 Appendix 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 prohibited to take analgesics for central nervous systems.
### Table 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 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.

** Only ten studies conducted test the success of participants' blinding.
**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
### Table 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 (0.41 to 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** | |
| 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

| Type of comparisons                          | Effect Size | CI        | p-value  |
|----------------------------------------------|-------------|-----------|----------|
| 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

| Blinding of participants | Effect Size | CI        | p-value  |
|--------------------------|-------------|-----------|----------|
| Probably no vs probably yes | 0.49       | (0.33 to 0.65) | <0.001   |

## Therapeutic areas

| Therapeutic areas                          | Effect Size | CI        | p-value  |
|--------------------------------------------|-------------|-----------|----------|
| 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 Respiriology           | -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 Respiriology | -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    |

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| Comparison                                      | Effect Size (95% CI)   | p Value |
|------------------------------------------------|------------------------|---------|
| 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 (-0.51 to 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  |
| Comparison                | Odds Ratio (95% CI) |
|--------------------------|--------------------|
| 0 vs \( \geq 5 \)         | 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 \( \geq 5 \)  | 0.42 (-0.04 to 0.88), 0.07 |
| 2-4.99 vs \( \geq 5 \)    | 0.32 (-0.08 to 0.72), 0.12 |

**Stratification or block randomization**

| Comparison                                      | Odds Ratio (95% CI) |
|------------------------------------------------|--------------------|
| 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 |
|-------------------|--------|----------------|
| **TITLE**         | 1      | Identify the report as a systematic review. |
| **ABSTRACT**      | 2      | See the PRISMA 2020 for Abstracts checklist. |
| **INTRODUCTION**  | 3      | Describe the rationale for the review in the context of existing knowledge. |
|                   | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. |
| **METHODS**       | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. |
|                   | 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. |
|                   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. |
|                   | 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. |
|                   | 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. |
|                   | 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. |
|                   | 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. |
| **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. |
| **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. |
| **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)). |
|                   | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. |
|                   | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses. |
|                   | 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. |
|                   | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). |
|                   | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. |
| **Reporting bias assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). |
| **Certainty**     | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. |
| Section and Topic                  | Item # | Checklist item                                                                 | Location where item is reported |
|-----------------------------------|--------|---------------------------------------------------------------------------------|---------------------------------|
| **RESULTS**                       |        |                                                                                 |                                 |
| Study selection                   | 16a    | Describe the results of the search and selection process, from the number of    | P11, Fig 1                      |
|                                  |        | records identified in the search to the number of studies included in the       |                                 |
|                                  |        | review, ideally using a flow diagram.                                          |                                 |
|                                  | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were   | Not applicable                  |
|                                  |        | excluded, and explain why they were excluded.                                   |                                 |
| 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     | Not applicable                  |
|                                  |        | group (where appropriate) and (b) an effect estimate and its precision (e.g.    |                                 |
|                                  |        | confidence/credible interval), ideally using structured tables or plots.        |                                 |
| Results of syntheses              | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias      | Not applicable                  |
|                                  |        | among contributing studies.                                                     |                                 |
|                                  | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was    | Not applicable                  |
|                                  |        | 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.                                   |                                 |
|                                  | 20c    | Present results of all investigations of possible causes of heterogeneity      | P12-13, Fig 2, Table1,2         |
|                                  |        | among study results.                                                            | eTable 2,3                      |
|                                  | 20d    | Present results of all sensitivity analyses conducted to assess the robustness  | Not applicable                  |
|                                  |        | of the synthesized results.                                                     |                                 |
| Reporting biases                  | 21     | Present assessments of risk of bias due to missing results (arising from       | Not applicable                  |
|                                  |        | reporting biases) for each synthesis assessed.                                 |                                 |
| Certainty of evidence             | 22     | Present assessments of certainty (or confidence) in the body of evidence for    | Not applicable                  |
|                                  |        | each outcome assessed.                                                          |                                 |
| **DISCUSSION**                    |        |                                                                                 |                                 |
| Discussion                        | 23a    | Provide a general interpretation of the results in the context of other        | P13                             |
|                                  |        | evidence.                                                                       |                                 |
|                                  | 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    | no                              |
|                                  |        | registration number, or state that the review was not registered.               |                                 |
|                                  | 24b    | Indicate where the review protocol can be accessed, or state that a protocol    | no                              |
|                                  |        | was not prepared.                                                               |                                 |
|                                  | 24c    | Describe and explain any amendments to information provided at registration or  | no                              |
|                                  |        | in the protocol.                                                               |                                 |
| Support                           | 25     | Describe sources of financial or non-financial support for the review, and the  | P16                             |
|                                  |        | role of the funders or sponsors in the review.                                 |                                 |
| Competing interests               | 26     | Declare any competing interests of review authors.                              | P17                             |
| Availability of data, code and    | 27     | Report which of the following are publicly available and where they can be      | no                              |
| other materials                   |        | found: template data collection forms; data extracted from included studies;    |                                 |
|                                  |        | data used for all analyses; analytic code; any other materials used in the     |                                 |
|                                  |        | review.                                                                        |                                 |
PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Houfmann 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

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