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

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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 randomised 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 standardised 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 randomised controlled trials (RCTs) were analysed. The multivariable analyses contained 15 independent variables . 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% CI 0.24 to 0.77), or pain (0.48, 95% CI 0.27 to 0.69), or function (0.41, 95% CI 0.21 to 0.61) vs major events. The following produced larger treatment effects of moderate magnitude (0.2–0.4): single-centred vs multicentred RCTs (0.38, 95% CI 0.10 to 0.66); penetration acupuncture vs non-penetration types of acupuncture (0.34, 95% CI 0.15 to 0.53); non-pain symptoms vs major events (0.32, 95% CI 0.12 to 0.52). The following produced larger treatment effects of small magnitude (<0.2): high vs low frequency treatment sessions (0.19, 95% CI 0.03 to 0.35); pain vs non-pain symptoms (0.16, 95% CI 0.04 to 0.27); unreported vs reported funding (0.12, 95% CI 0 to 0.25).

Conclusion Patients, clinicians and policy-makers 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.

STRENGTHS AND LIMITATIONS OF THIS 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 (eg, country, trial registered) limits the generalisability of the study results.

INTRODUCTION

Acupuncture is one of the most used and researched interventions under the integrative medicine umbrella.[1–4] By 2014, the total number of acupuncture randomised controlled trial (RCT) has increased dramatically and accounted for 20.3% of all acupuncture studies.[5] Since 2010, over 1000 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 vs 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 vs electroacupuncture)[14] were significant factors of the treatment effect whereas others did not.[9 15] The reason may be related to little data variation,[15] small number of included studies,[12 14] and variation of the clinical areas and settings investigated.[10 11 16]

To improve acupuncture RCTs' design, and optimise acupuncture interventions' clinical effectiveness, we conducted this meta-epidemiological study, including acupuncture RCTs published between 2015 and 2019 across therapeutic areas and outcomes, and explored the factors of acupuncture's treatment effects. We aim to (1) identify factors regarding patient, acupuncture, comparator, outcome and methodology that impact the magnitude of the treatment effect of acupuncture therapies and (2) explore to what extent the factors impact the treatment effect across therapeutic areas.

METHODS

Definitions

We define acupuncture therapies based on the WHO definition: Acupuncture literally means to puncture with a needle. However, there may also involve the application of other kinds of stimulation to certain points.[17] The study addressed commonly used acupuncture modalities, including manual acupuncture, electroacupuncture (electro-acupuncture), laser acupuncture, transcutaneous electrical acupoint stimulation (TEAS), acupressure, traditional body needling, ear (auricular) acupuncture and scalp acupuncture.

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

We define a patient-important outcome as one in which the patient would be interested, despite the risk, burden or cost, were it the only outcome to improve with an intervention.[19]

To differentiate from individual outcomes (eg, dysphagia), we define a construct as a category of patient-important outcomes (eg, functional status).

We define a therapeutic area as a class of related diseases or conditions based on modified International Classification of Diseases 11th Revision (ICD-11) criteria (eg, Neurology). In this study, the classification of the therapeutic areas targeted diseases 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 online supplemental eAppendix 1.

Eligibility criteria

Eligible studies fulfilled the following inclusion criteria:

- RCT defined by authors.
- Reported at least one of two sets of comparisons: acupuncture vs no intervention, sham acupuncture or waiting list; or acupuncture plus other interventions vs 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.
- Randomised 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 related therapies (eg, 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 V.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 standardised forms with detailed instructions. To ensure screening quality, reviewers participated in a calibration

Box 1 Classification of constructs

1. Mortality.
2. Major events include morbid events (eg, incidence of myocardial infarction,fracture, stroke), recurrence (eg, the recurrence of facial spasm) or fertilisation-related events (eg, live birth rate).
3. Pain (eg, low back pain).
4. Non-pain symptoms (eg, nausea and vomiting).
5. Quality of life (eg, health-related quality of life).
6. Functional status (eg, dysphagia).

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 seven factors, and we finally included 46 factors (online supplemental eAppendix 2) in the meta-regression analyses.

Data extraction

We classified patient-important outcomes into six constructs box 1.

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 preselected outcomes.

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

Statistical analysis

Depending on the data distribution, we summarised data using means and SD, or medians and IQRs. 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 standardised mean difference (SMD). A positive SMD indicated a beneficial effect. The variance of SMD[21] was given by

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

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

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

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

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

We initially considered 46 variables (online supplemental eAppendix 2) 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 (online supplemental eAppendix 3). To detect possible multicollinearity, we calculated the Cramer's V statistics[23 24] (ranges 0–1) between every pair of the variables using a threshold of 0.70. When excessive collinearity existed, we excluded those variables from the regression analysis (online supplemental eAppendix 3).

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 3). 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, V.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. Online supplemental eTables 1.1, 1.2 and 1.3 show the basic and clinical characteristics (classification of acupuncture treatment frequency, duration and the total number of treatments provided in online supplemental 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.

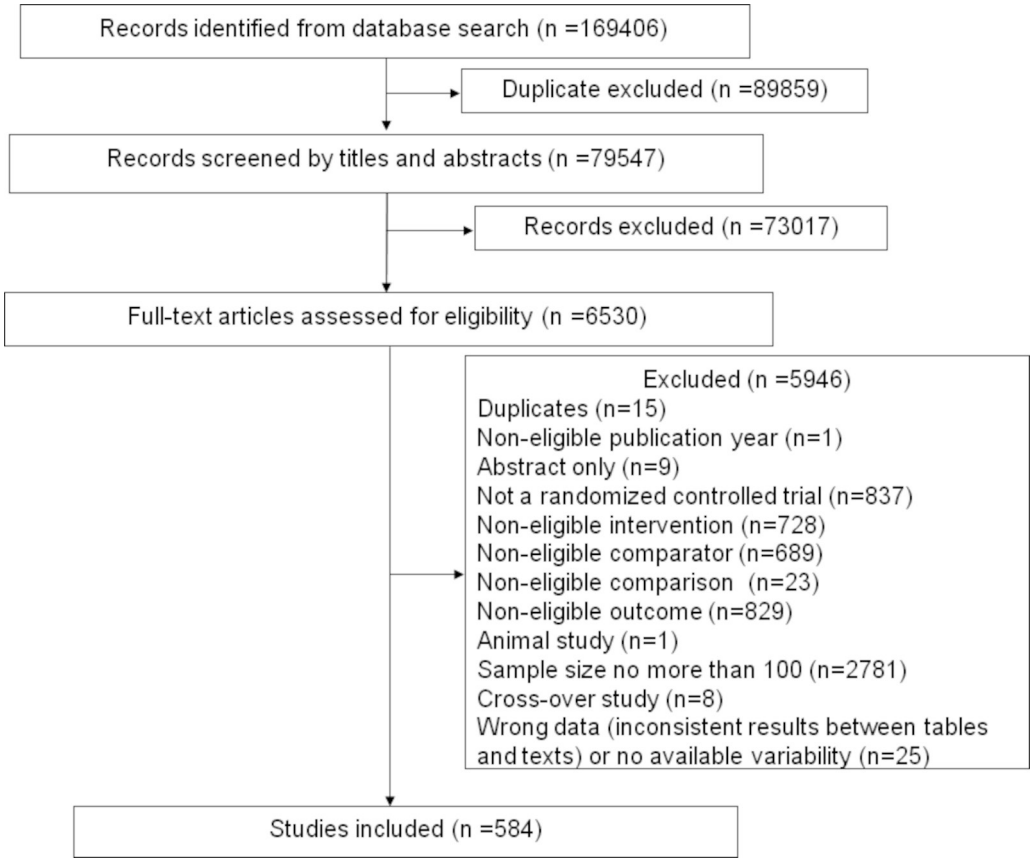

Figure 1 Study selection flow diagram.

Included RCTs had a high risk of bias. For example, over 90% of the RCTs were labelled 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 with 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, online supplemental eAppendix 3); thus resulted in 15 variables that were eventually included in the analysis (online supplemental eAppendix 5).

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 centres and funding availability (table 1).

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 centres	√
Funding available	√
Country	
Type of journal	

√The factor is a significant predictor (p<0.05).
Blank: The factor is not a significant predictor.

Compared with major events outcomes, effects proved larger in quality of life (large magnitude, difference of adjusted SMDs 0.51, 95% CI 0.24 to 0.77; p<0.001), pain (large magnitude, 0.48, 95% CI 0.27 to 0.69; p<0.001), function (large magnitude, 0.41, 95% CI 0.21 to 0.61; p<0.001) and non-pain symptoms (moderate magnitude, 0.32, 95% CI 0.12 to 0.52; p<0.001). Compared with non-pain symptoms, effects proved larger in pain (small magnitude, 0.16, 95% CI 0.04 to 0.27; p=0.01). Single centre, compared with multicentre, was associated with moderately larger effects (0.38, 95% CI 0.10 to 0.66; p=0.01). Penetration acupuncture (ie, manual acupuncture and electroacupuncture), compared with non-penetration type of acupuncture (ie, laser acupuncture, TEAS and acupressure), was associated with moderately larger effects (0.34, 95% CI 0.15 to 0.53; p<0.001). High frequency acupuncture treatment sessions, compared with low frequency, was associated with larger effects of small magnitude (0.19, 95% CI 0.03 to 0.35; p=0.02). Compared with reported funding, effects proved larger of small magnitude in studies that did not report funding (0.12, 95% CI 0 to 0.25; p=0.03) (figure 2, online supplemental eTable 2)

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.

Online supplemental eTable 3 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-centred acupuncture RCTs and acupuncture RCTs

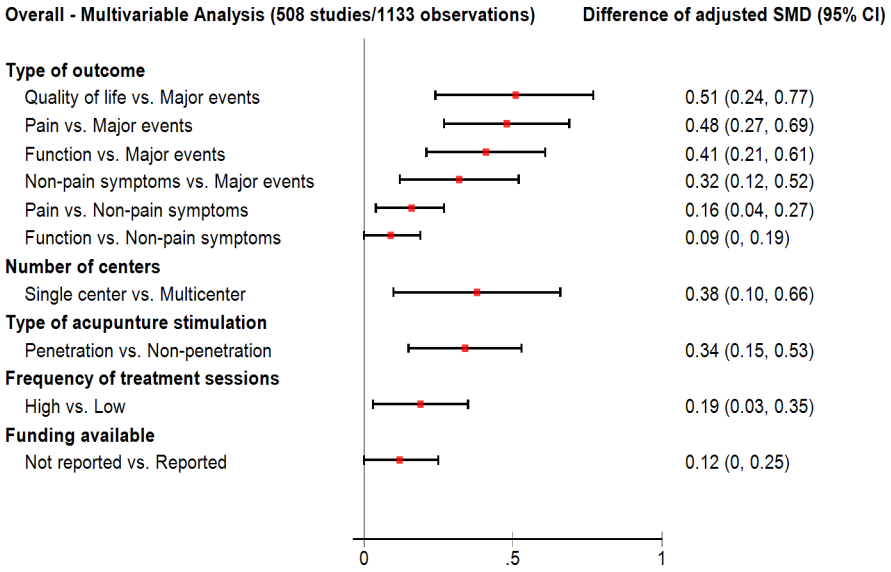

Figure 2 Forest plots of significant factors in the multivariable analysis. SMD, standardised mean difference.

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 favourable type of acupuncture and treatment regimen for patients, clinicians and policy-makers to achieve acupuncture's maximum treatment effect for clinical and health system decisions. Our study has several strengths. First, our study is highly patient-centred 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.

Second, 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.

Third, our study has a high methodological rigour. 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. First, 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. Second, 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 (eg, country, trial registered) distributed extremely imbalanced, limiting the results' generalisability.

Comparison with other studies

Previous studies[9–15] typically performed univariable analyses in a small number of studies (5 to 39 trials) and identified 15 significant factors, including 10 clinical, 1 methodological and 4 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 with non-penetrating and non-needle sham, penetrating needle sham associated with a

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 randomisation	√
Needle retention time(20 min)	
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 centres*	√
Funding available*	√
Country*	√
Type of Journal*	√

√The factor is a significant predictor (p<0.05).
Blank: The factor is not a significant predictor.
*Included in the multivariable analysis.

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 policy-makers 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[29] and STandards for Reporting Interventions in Clinical Trials of Acupuncture[30] reporting guidelines, especially for those that might impact the treatment effect (random sequence generation and allocation concealment, acupuncture technique related information, practitioners related information, and the source of funding); (2) consider the quality of life outcome more often; (3) carefully choose the type of acupuncture, frequency of treatment sessions, choice of single or multicentre 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 (eg, practitioners' expertise).

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Contributors 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, ZYZ, HCL, JTS, ALC, ZYQ, LZ, DXM, XYW, QQY, LZC, YTH, TVP, JC, CH, LB, KL, KT, JT, JED, JZ, MH, YS, KW, LCL, JW, TAB, LGM, MRA, MDG, CDCBM, JM, CC and FB screened abstracts. WJG, WCX, LJS, RMJ, JWY, XSS, XYS, ZhYZ, HCL, JTS, ALC, ZYQ, LZ, DXM, XYW, QQY, LZC and YTH screened full texts. WJG, WCX, LJS, RMJ, JYW, 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.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Supplement

eAppendix 1 Search strategy

eAppendix 2 Independent variables ranked by importance

eAppendix 3 Excluded independent variables from multivariable analysis

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

eAppendix 5 Independent variables included in multivariable analysis

eTable 1.1 Basic characteristics of included studies

eTable 1.2 Clinical characteristics of included studies

eTable 1.3 Risk of bias of included studies

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

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

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eAppendix 1 Search strategy

1. **MEDLINE via PubMed Strategy**

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

2. **EMBASE Search strategy**

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

3. **CENTRAL**

- **Title Abstract Keyword**

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

- Publication year: from 2015 to 2019

4. CNKI search strategy [Chinese database]

English translation from Chinese version

- Professional retrieval：

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

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

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

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

Chinese version

- 专业检索：

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

注：SU=主题，TI=题名，KY=关键词，AB=摘要

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

5. Wanfang search strategy [Chinese database]

English translation from Chinese version

- Professional retrieval：

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

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

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

Chinese version

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

6. VIP search strategy [Chinese database]

English translation from Chinese version

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

Chinese version

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

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

注：字段标识符 U=任意字段、M=题名或关键词、R=文摘

- 时间限定（publication date）：2015 至 2019.

7. CBM search strategy [Chinese database]

English translation from Chinese version:

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

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

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

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

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

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

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

Chinese version:

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

#2【主题检索状态】：穴位, 耳针 （时间：2015-2019）

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

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

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

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

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

eAppendix 2

eAppendix 2 Independent variables ranked by importance

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

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

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

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

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

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

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

eAppendix 3

eAppendix 3 Excluded independent variables from multivariable analysis

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

eAppendix 4

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

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

eAppendix 5

eAppendix 5 Independent variables included in multivariable analysis

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

eTables

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

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

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

* Each study can contribute more than one estimate.

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

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

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

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

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

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

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

* Each study can contribute more than one estimate.

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

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

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

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

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

* Each study can contribute more than one estimate.

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

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

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

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

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

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

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

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

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