BMJ Open

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

Wei-Juan Gang ,[1,2] Wen-Cui Xiu,[1,2] Lan-Jun Shi,[1,2] Qi Zhou,[3] Rui-Min Jiao,[1,2] Ji-Wei Yang,[1,2] Xiao-Shuang Shi ,[1,2] Xiao-Yue Sun,[1,2] Zhao Zeng,[4] Claudia M Witt,[5] Lehana Thabane ,[6] Ping Song,[7] Long-Hui Yang,[7] Gordon Guyatt,[3,6] Zhi-Yun Zhang,[1] Heng-Cong Li,[1] Jing-Tao Shi,[1] An-Li Chen,[1] Zheng-Yang Qu,[1] Ling Zou,[1] Dong-Xiao Mou,[1] Xiao-Yu Wang,[1] Qing-Quan Yu,[1] Li-Zhen Chen,[1] Yu-Ting Huang,[1] Tiago V Pereira,[8] Jason Chambers,[9] Cameron Ho,[10] Layla Bakaa,[11] Kevin Loniewski,[12] Kyle Tong,[6] Jaryd Tong,[13] Jared E Dookie,[14] Jie-wei Zhu,[13] Malini Hu,[15] Yujin Suk,[16,17,18] Kay Wu,[19] Luciane Cruz Lopes,[20] Julia White,[10] Tayler A Buchan,[3] Lauren Giustti Mazzei,[21] Maíra Ramos Alves,[22] Mariana Del Grossi Moura,[23] Cristiane De Cássia Bergamaschi,[20] Jing Meng,[24] Cynthia Chan,[25] Flávia Blaseck Sorrilha,[23] Xiang-Hong Jing,[1,2] Yu-Qing Zhang [1,3,26]

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

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-060237).

X-HJ and Y-QZ contributed equally.

Received 16 December 2021
Accepted 10 June 2022

Check for updates

For numbered affiliations see end of article.

Correspondence to
Dr Xiang-Hong Jing; xhjingt66@163.com

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,

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.

trialists should consider factors that impact acupuncture treatment effects.

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 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

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).

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

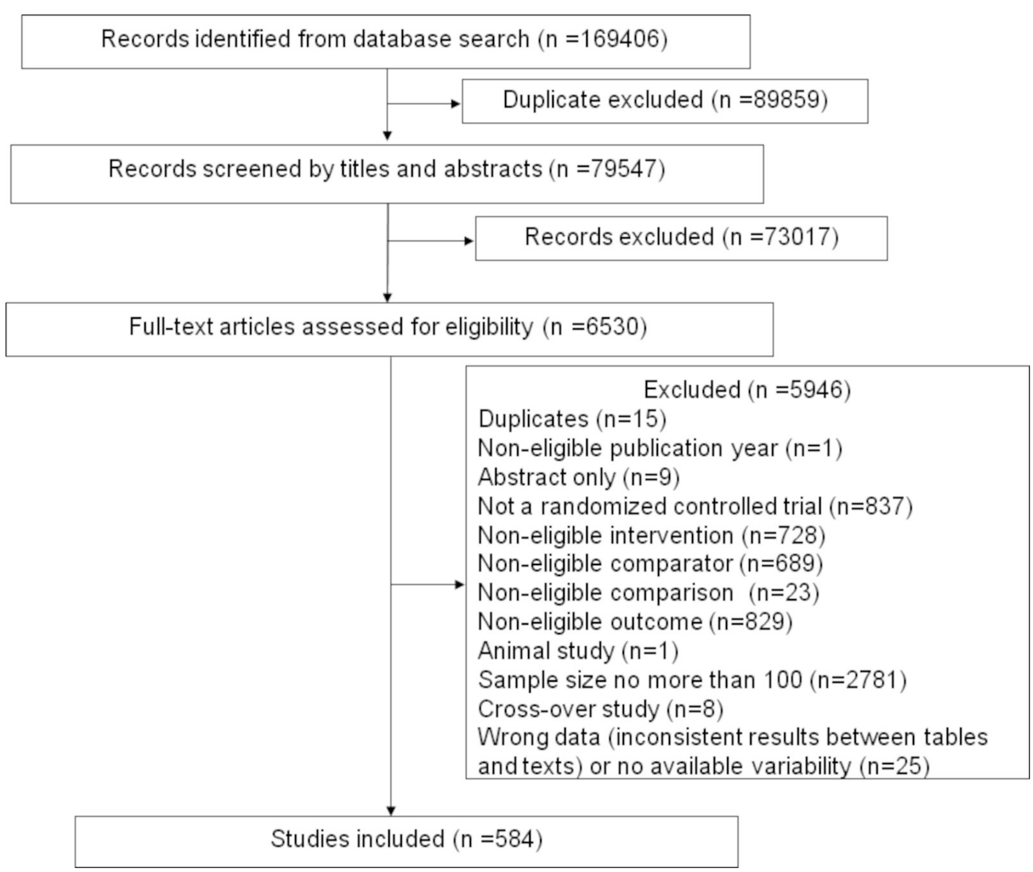

Figure 1 Study selection flow diagram.

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.

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).

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)

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.

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).

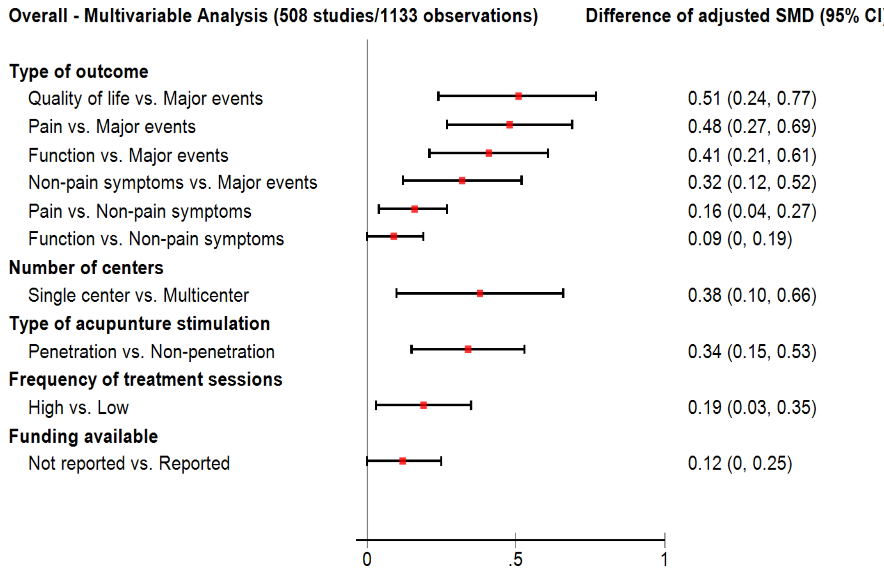

Figure 2 Forest plots of significant factors in the multivariable analysis. SMD, standardised mean difference.

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 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

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.

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 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).

Author affiliations
[1]Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China

[2]China Centre for Evidence-Based Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, China
[3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
[4]Library of Guangzhou University of Chinese Medicine, Guangzhou, China
[5]Institute for Complementary and Integrative Medicine, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[6]Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[7]China Academy of Chinese Medical Sciences, Beijing, China
[8]Department of Health Sciences, University of Leicester, Leicester, UK
[9]Schulich School of Medicine, Western University, London, Ontario, Canada
[10]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
[11]Department of Psychology, McMaster University, Hamilton, Ontario, Canada
[12]Faculty of Health, York University, Toronto, Ontario, Canada
[13]University of Toronto, Toronto, Ontario, Canada
[14]Schulich School of Medicine and Dentistry,Western University, Ontario, Canada, Western University, London, Ontario, Canada
[15]Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[16]Centre for Discovery in Cancer Research (CDCR), McMaster University, Hamilton, Ontario, Canada
[17]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada
[18]Michael G DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[19]Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada
[20]Pharmaceutical Sciences Graduate Course, University of Sorocaba, São Paulo, Brazil
[21]Physical Therapy Course, University of Sorocaba, São Paulo, Brazil
[22]Psychology Course, University of Sorocaba, São Paulo, Brazil
[23]University of Sorocaba, São Paulo, Brazil
[24]Obstetric & Gynaecology department, Dunedin Hospital, Health, Dunedin, New Zealand
[25]Department of Family Medicine, Faculty of Medicine, University of Ottawa, Canada, Canada
[26]Nottingham Ningbo GRADE Centre, University of Nottingham Ningbo China, Ningbo, China

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

Contributors XHJ, YQZ and WJG had the idea and designed the study. GG was involved in designing the study. YQZ, WJG, 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.

Funding 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).

Disclaimer 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 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 organisations 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.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Wei-Juan Gang http://orcid.org/0000-0003-2073-3167
Xiao-Shuang Shi http://orcid.org/0000-0003-1515-4072
Lehana Thabane http://orcid.org/0000-0003-0355-9734
Yu-Qing Zhang http://orcid.org/0000-0002-6318-3575

REFERENCES

1 World Health Organization. WHO traditional medicine strategy:2014-2023. Geneva: World Health Organization; 2013.
2 Cui J, Wang S, Ren J, *et al*. Use of acupuncture in the USA: changes over a decade (2002-2012). *Acupunct Med* 2017;35:200–7.
3 Yang L, Adams J, Sibbritt D. Prevalence and factors associated with the use of acupuncture and Chinese medicine: results of a nationally representative survey of 17161 Australian women. *Acupunct Med* 2017;35:189–99.
4 Fu J-Y, Zhang X, Zhao Y-H, *et al*. Bibliometric analysis of acupuncture research fronts and their worldwide distribution over three decades. *Afr J Tradit Complement Altern Med* 2017;14:257–73.
5 Ma Y, Dong M, Zhou K, *et al*. Publication trends in acupuncture research: a 20-year bibliometric analysis based on PubMed. *PLoS One* 2016;11:e0168123.
6 Wang YY, Wang LQ, Chai QY. [Literature review on control interventions in randomized clinical trials on acupuncture published in mainland Chinese biomedical journals]. *World Chinese Medicine* 2014;9:1264–8.
7 Wang Y, Xue CC, Helme R, *et al*. Acupuncture for frequent migraine: a randomized, patient/assessor blinded, controlled trial with one-year follow-up. *Evid Based Complement Alternat Med* 2015;2015:1–14.
8 Xu S, Yu L, Luo X, *et al*. Manual acupuncture versus sham acupuncture and usual care for prophylaxis of episodic migraine without aura: multicentre, randomised clinical trial. *BMJ* 2020;368:m697.
9 Vickers AJ, Vertosick EA, Lewith G, *et al*. Acupuncture for chronic pain: update of an individual patient data meta-analysis. *J Pain* 2018;19:455–74.
10 Madsen MV, Gøtzsche PC, Hróbjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *BMJ* 2009;338:a3115.
11 Yuan Q-L, Wang P, Liu L, *et al*. Acupuncture for musculoskeletal pain: a meta-analysis and meta-regression of sham-controlled randomized clinical trials. *Sci Rep* 2016;6:30675.
12 Qin Z, Wu J, Xu C, *et al*. Using meta-regression approach to explore the dose-response association between acupuncture sessions

and acupuncture effects on chronic prostatitis/chronic pelvic pain syndrome. *Ann Transl Med* 2019;7:116.
13 Deng YZ, Xu LG, Chen L, *et al*. Effectiveness of acupuncture in the management of cervical spondylosis: a meta-analysis. *J Biol Regul Homeost Agents* 2017;31:1017–22.
14 Hao XA, Xue CC, Dong L, *et al*. Factors associated with conflicting findings on acupuncture for tension-type headache: qualitative and quantitative analyses. *J Altern Complement Med* 2013;19:285–97.
15 MacPherson H, Maschino AC, Lewith G, *et al*. Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomised controlled trials. *PLoS One* 2013;8:e77438.
16 Manheimer E, van der Windt D, Cheng K, *et al*. The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. *Hum Reprod Update* 2013;19:696–713.
17 World Health Organization. Acupuncture: review and analysis of reports on controlled clinical trials. Geneva: World Health Organization; 2003.
18 Vickers AJ, Cronin AM, Maschino AC, *et al*. Individual patient data meta-analysis of acupuncture for chronic pain: protocol of the acupuncture Trialists' collaboration. *Trials* 2010;11:90.
19 Akl EA, Briel M, You JJ, *et al*. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. *BMJ* 2012;344:e2809.
20 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
21 Michael B, Hedges LV, Higgins JPT, *et al*. *Introduction to meta-analysis*. John Wiley & Sons, Ltd, 2021.
22 Hasselblad V, Hedges LV. Meta-Analysis of screening and diagnostic tests. *Psychol Bull* 1995;117:167–78.
23 Harald C. *Mathematical methods of statistics (PMS-9)*. Princeton university press, 2016.
24 Sadiq M, Mehmood T, Aslam M. Identifying the factors associated with cesarean section modeled with categorical correlation coefficients in partial least squares. *PLoS One* 2019;14:e0219427.
25 Moeyaert M, Ugille M, Natasha Beretvas S, *et al*. Methods for dealing with multiple outcomes in meta-analysis : a comparison between averaging effect sizes, robust variance estimation and multilevel meta-analysis. *Int J Soc Res Methodol* 2017;20:559–72.
26 Konstantopoulos S. Fixed effects and variance components estimation in three-level meta-analysis. *Res Synth Methods* 2011;2:61–76.
27 Van den Noortgate W, López-López JA, Marín-Martínez F, *et al*. Meta-Analysis of multiple outcomes: a multilevel approach. *Behav Res Methods* 2015;47:1274–94.
28 Chen C. Robust regression and outlier detection with the ROBUSTREG procedure. *Proceedings of the Twenty-Seventh Annual SAS Users Group International Conference*, Cary, NC: SAS Institute Inc, 2002.
29 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
30 MacPherson H, Altman DG, Hammerschlag R, *et al*. Revised standards for reporting interventions in clinical trials of acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med* 2010;7:e1000261.

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

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

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

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