Electroacupuncture for Hypertension in Adults: Study Protocol of a Systematic Review and Meta-Analysis

Furong Zhang (zxfxrx1014@163.com)
Chengdu University of Traditional Chinese Medicine https://orcid.org/0000-0002-4671-2295
Pan Zhang
Chengdu University of TCM
Yalan Chen
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
Hong Pei
The Fifth Hospital of Sichuan Province
Yuzhu Qu
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
Jiyao Chen
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
Xiaoguo He
The Fifth People's Hospital of Sichuan Province
Fanrong Liang
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
Rongjiang Jin
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
Mingxiao Yang
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Protocol

Keywords: electroacupuncture, hypertension, systematic review, meta-analysis

Posted Date: October 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1008098/v1

Abstract

Introduction: Hypertension is a common, prevalent cardiovascular disease that requires multidisciplinary treatments. In Asian countries, electroacupuncture (EA) is often used as an adjunct to antihypertensive drugs for lowering blood pressure and relieving related symptoms. However, till now the effects of EA for hypertension are not fully evaluated. This study aims to assess the efficacy and safety of EA in patients with hypertension through a systematic review and meta-analysis of randomized controlled trials.

Methods and analysis: Seven electronic databases including Medline, EMBASE, CENTRAL, CNKI, CBM, Wanfang, and VIP Database will be searched from inception to May 30, 2021, to identify clinical trials of EA treating hypertension in adults. Eligible comparisons will be limited to 1) EA versus valid comparators including placebo, antihypertensives, waiting list and 2) EA as an adjunct to antihypertensives versus antihypertensives. Clinical outcomes include blood pressure, response rate, somatic symptom relief, quality of life, and safety from baseline to post-treatment. The Cochrane Risk of Bias assessment tool will be used to evaluate the quality of the included studies and the GRADE system will be employed to summarize the overall quality of evidence. Random-effects model will be performed, where efficacy data will be reported with mean difference (continuous data) or risk ratio (dichotomous data). In addition, heterogeneity and publication bias will be tested with the I^2 statistic and the Egger's test/funnel plot.

Ethics and dissemination: As a secondary literature study, this systematic review doesn't require ethical approval. The study results will be disseminated via peer-review publication or conference presentation.

Registration: PROSPERO registration ID CRD42019133937.

1 Introduction

Hypertension, featured by persistently elevated arterial blood pressure, is the leading cause of major cardiovascular diseases and premature death worldwide [1]. Chronic increase in blood pressure might be asymptomatic yet can cause hypertension-mediated target organ damage which can be life-threatening. Epidemiology study showed that 31.1% of adults (1.39 billion) worldwide had hypertension in 2010 [1]. Under the 2017 American College of Cardiology(ACC)/ American Heart Association (AHA) guidelines[2], the prevalence of hypertension increased from 32–45.4% in the U.S. and from 23.2–46.4% in China[3 4], highlighting the urgent need for early diagnosis and intervention of hypertension. Currently, antihypertensive drugs remain the mainstream for hypertension treatment, yet limited somehow in patients' compliance, medical cost, and drug-related side effects [5]. Non-pharmacological therapies recommended by the ACC/AHA are gaining increased popularity in clinical practice, especially for early-staged hypertension intervention, relief of related somatic symptoms, and prevention of target organ damages [2].

Acupuncture is an important non-pharmacological intervention widely used in China for angina pectoris, hypertension, cardiac arrhythmia and other cardiovascular diseases. In clinical practice,

electroacupuncture (EA), integrating electric stimulation with classic acupuncture, is well recognized and applied in hypertension management [6]. EA, by using unified apparatus and prameters, brings a more standerized and less biased treatment, when compared to manual acupuncture that mostly influenced by the experience of acupuncturists. Besides, Clinical studies showed that EA helps not only with blood pressure reduction, but also the improvement in its circadian rhythm and daily variations in the hypertensives[7 8]. Researches demonstrated that hypertension is highly associated with immune inflammation[9 10], and newly released report in *Nature* has just verified low-intensity EA stimulation at ST36 can induce anti-inflammatory effects through vagal-adrenal axis, which provides the potential neuroanatomical bais of EA for hypertension[11]. Other basic science studies supported that EA may trigger the neuroendocrine system and modulate metabolic function to activate neurotransmitter release and exert sympathoinhibitory actions [12 13]. Those mentioned above have provided potential neuroanatomical baises of EA in treating hypertension.

High-quality systematic reviews serve clinicians, policy makers with best reliable evidence, which enables evidence-based decision making and clinical practice for patient care [14]. Yet, to our knowledge, a critical appraisal of clinical studies with a focus on EA for hypertension is lacking till now. Previous systematic reviews on acupuncture for hypertension failed to differentiate the antihypertensive effect of EA from that of manual acupuncture and provided no specific evidence for EA treating hypertension [15]. Given many studies are statistically underpowered, a pooled analysis is needed [16]. Therefore, the present study is deigned to summarize the results of current trials available and assess the efficacy and safety of EA for adults with hypertension. The study is designed in line with the PRISMA and the Cochrane guidelines[17 18].

2 Objectives

The objective of this review is to systematically evaluate the efficacy and safety of EA for adult patients with hypertension compared with sham acupuncture, antihypertensives, and waiting list .

3 Methods

3.1 Protocol register

This protocol has been composed under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines, and we used the PRISMA-P checklist when writing our report. This protocol has been previously registered on PROSPERO platform (https://www.crd.york.ac.uk/PROSPERO/) with an assigned registration number CRD42019133937.

3.2 Eligibility criteria

The PICOS (participant, intervention, comparison, outcome and study design) principle will be employed in this study protocol.

3.2.1 Types of study design

Only paralleled randomized controlled trials(RCTs) will be included. Studies with other designs, unobtainable data, duplicate publications, animal experiments and reviews or case reports will be excluded.

3.2.2 Types of Participants

Adult patients (≥18 years old) clinically diagnosed with essential hypertension, with a systolic blood pressure (SBP) no less than 130 mmHg or a diastolic blood pressure (DBP) no less than 80 mmHg, or both or used antihypertensive drugs will be included.

3.2.3 Types of Interventions

(1) Experimental interventions

EA with needle insertion will be considered eligible intervention in this study. EA is defined as a form of acupuncture which delivers electric stimulation to treat disease through needles inserted at acupoints. EA can be used alone or as an add-on to anti-hypertensive agents. We excluded other methods of stimulating acupoints without needle insertion (such as laser stimulation or transcutaneous electrical stimulation).

(2) Comparator interventions

Comparators are as previously reported[19], including 1) no treatment or waiting list, 2) sham acupuncture, defined as intervention mimicking 'true' acupuncture, but deviating from at least one perspective regarded essential based on TCM acupuncture theory, such as skin penetration or non-acupoint location, and 3) positive controls like anti-hypertensive agents recommended by officially released guidelines. Studies comparing different styles of acupuncture therapies (such as EA VS manual acupuncture) or EA of different sessions will be excluded.

3.2.4 Types of Outcomes

(1) Primary outcomes

Change in SBP and DBP from baseline from baseline to post-treatment.

(2) Secondary outcomes

1) Response rate: responder is defined as a patient demonstrating an SBP reduction > 3mmHg from baseline to post-treatment[20 21].

2) The relief of somatic symptoms such as dizziness, headache, insomnia, etc.

3) Common health-related quality of life measured by validated tools like 36-Item Short Form Health Survey etc.

4) Adverse events.

3.3 Information sources and search strategy

Electronic databases including Medline via Ovid, and EMBASE via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), the Chinese Biomedical Literature Database (CBM), Wanfang Database and VIP Database will be searched for related randomized controlled trials (RCTs) from their inception to May 31, 2021, without language restrictions. A comprehensive search will be implemented by using combination of medical subject headings (MeSH) and keywords. The search strategies applied in Medline (via Ovid) are listed in Table 1, which will be appropriately adapted according to syntax-related or lingual requirements of other electronic databases. To acquire potential unpublished data of ongoing RCTs, clinical trials registries like the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), clinicaltrials.gov and the Chinese Clinical Trial Register (ChiCTR) will also be searched. References of relevant systematic reviews will be screened, and a manual search of related journals and conference abstracts will be conducted as supplements. Study authors will be contacted via email if needed. All literature citations retrieved will be stored and managed in EndNote X9 software.

Table 1
search strategy of MEDLINE via Ovid

No.	Searching items
1	exp acupuncture therapy/
2	(acupunctur$ or electroacupunctur$ or electro-acupunctur$ or acupoint$ or acu-point$ or acupress$).mp.
3	((meridian$ or non-meridian or trigger) adj10 point$).tw.
4	(zhenjiu or zhen jiu or zhenci or zhen ci or cizhen or dianzhen or dian zhen or zhen ya or er zhen or ti zhen or she zhen or tou pi zhen or zue wei).tw.
5	((ching adj2 lo) or (jing adj2 luo) or jinglo).tw.
6	or/1-5
7	hypertension/
8	hypertens$.tw.
9	exp blood pressure/
10	(blood pressure or bloodpressure).tw.
11	or/7-10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	randomized.ab.
15	placebo.ab.
16	drug therapy.fs.
17	randomly.ab.
18	trial.ab.
19	groups.ab.
20	or/12-19
21	animals/not (humans/ and animals/)
22	20 not 21
23	6 and 11 and 22
24	remove duplicates from 23

3.4 Selection of studies and data extraction process

Study selection and data extraction process will be independently conducted and cross-checked by two authors, respectively (Pan Zhang & Yalan Chen). A piloting form will be designed for date extraction, including general information like first author, publication year, founding source, as well as details of participants, methods, interventions, outcomes, and results. Unreported data will be acquired as possible through contacting authors of included RCTs if necessary. Any discrepancies between the two reviewers will be settled by discussion or the introduction of a third reviewer (Furong Zhang). The flow chart based on PRISMA statement[22] is displayed in Figure 1.

3.5 Risk of bias assessment in included studies

The risk of bias (RoB) of each study included will be independently evaluated by two investigators (Yuzhu Qu and JiyaoChen) according to the Cochrane RoB 2[23] assessment tool. According to RoB 2, bias will be evaluated per clinical outcome in five distinct domains. Within each domain, signaling questions will be answered for further rating “low risk of bias,” “some concerns,” or “high risk of bias”. All these five rates contribute to an overall risk-of-bias judgment for the result assessed, which helps to stratify meta-analyses. Disagreements between the two authors will be resolved by discussion. If the consensus fails to be reached after discussion, a third reviewer (Furong Zhang) will be consulted for final decision.

3.6 Data mining: characterization of EA for hypertension

Data mining enables to uncover associations between diseases and acupoints[24]. To figure out potential relationship between points selected and essential hypertension, we plan to implement a data mining by collecting and analyzing acupoints selected for treatment from included RCT.

3.7 Data synthesis

Continuous and categorical data will be expressed as standard mean differences (SMDs) and risk ratios (RRs) respectively, with 95% confidence intervals (95% CIs). Pair-wise meta-analysis will be performed for direct comparisons with 95%CIs. Chi^2 and I^2 test will be applied to assess for heterogeneity among included studies. I^2 values serves as signs for the degree of statistical heterogeneity. I^2 lower than 50% is considered as homogeneous and a fixed model will be used; while I^2 over 50% implies a significant heterogeneity. Otherwise, a narrative review will be conducted. Meta-regression will be conducted for screening the influencing factors of heterogeneity, then sensitivity analysis including leave-one-out and subgroup analysis will be implemented to figure out potential clinical heterogeneity. Besides, subgroup analysis based on hypertension subtypes will be conducted to differentiate benefit degrees of EA when appropriate. Publication bias will be checked with a funnel plot if with over 10 studies included, and the Egger’s test will be carried out if it needs to be quantified. Statistical analysis will be conducted with Review Manager 5.3 software.

3.8 GRADE framework-based quality of the evidence

The GRADE framework will be employed for rating the overall quality of the evidence. In GRADE, high-quality evidence is considered as RCTs without important limitations and some observational studies.

Five limitations including study limitations, inconsistent results, indirectness of evidence, imprecision, and publication bias will downgrade evidence quality While three factors can upgrade the quality of evidence like large magnitude of effect; plausible confounding, which would reduce a demonstrated effect; and dose-response gradient. The quality of evidence will be evaluated as high, low or very low quality based on integrative assessment of results.

3.9 Patient and public involvement

The protocol is based on a review of relevant studies and does not include original patient data. No patient involved in this protocol.

4 Discussion

Given that systematic reviews topped of the evidence pyramid, high-quality SRs can help provide best evidence in clinical practice. Till now, no consensus reached on efficacy and safety of EA for hypertension, partially owing to the heterogeneity in the types of interventions which mixed EA with other forms of acupuncture. As is known that EA can bring a more standerized and less biased treatment, by using unified apparatus and prameters, yet manual acupuncture might vary from individual acupuncturist's experience. Therefore, in this proposed study, we will focus on the efficacy and safety of EA for hypertension only.

Recent clinical studies demonstrated inconsistent conclusions. Despite the discrepancies in previous studies, a recent randomized controlled trial showed that compared with sham acupuncture, 6-week EA treatment led to a statistically significant systolic blood pressure reduction at week 9 but not week 6 [25] [26] [27]. The inconsistency requires a further pooled analysis of current evidence to address the benefits of EA for patients with hypertension. To our knowledge, a critical appraisal of clinical studies focusing on EA for hypertension is still lacking till now. More importantly, our study highlights the effects of EA for the relief of hypertension-associated somatic symptoms, which distinguishes our study from previous ones.

By conducting this study, we will also identify possible methodological limitations of current clinical studies. Such findings may contribute to improving the design of sham-controlled RCTs in a more rigorous way, thus minimizing bias, to provide evidence of better confidence on acupuncture treatment for hypertension. The findings will provide evidence on the effects of EA for hypertension to inform evidence-based practice of nonpharmacologic hypertension management; and also identify possible methodological limitations of current studies to facilitate the design of more rigorous trials on acupuncture treatment for hypertension.

Abbreviations

EA: electroacupuncture

EMBASE: Excerpta Medica Database

CENTRAL: The Cochrane Central Register of Controlled Trials

CNKI: China National Knowledge Infrastructure

CBM: Chinese Biomedical Literature Database

VIP: Chinese Science and Technology Periodical Database

GRADE: Grading of Recommendations Assessment, Development and Evaluation

PROSPERO: Prospective Register of Systematic Reviews

ACC: American College of Cardiology

AHA: American Heart Association

PRISMA: Preferred Reporting Item for Systematic Review and Meta-analysis

PRISMA-P: Preferred Reporting Item for Systematic Review and Meta-analysis Protocol

PICOS: participant, intervention, comparison, outcome, and study design

RCTs: randomized controlled trials

SBP: systolic blood pressure

DBP: diastolic blood pressure

TCM: Traditional Chinese Medicine

WHO ICTRP: World Health Organization International Clinical Trials Registry Platform

ChiCTR: Chinese Clinical Trial Register

RoB: the risk of bias

SMDs: standard mean differences

95% CIs: 95% confidence intervals

SRs: systematic reviews

Declarations

Author Contributions

Conceptualization: Mingxiao Yang; Data curation: Pan Zhang, Yalan Chen, Hong Pei; Analysis planning: Mingxiao Yang, Furong Zhang, Yuzhu Qu, Xiaoguo He; Investigation: Pan Zhang, Yalan Chen, Yuzhu Qu, Jiyao Chen; Methodology: Rongjiang Jin, Mingxiao Yang; Draft manuscript: Furong Zhang, Pan Zhang; Manuscript revision: Mingxiao Yang, Rongjiang Jin, Fanrong Liang

Acknowledgements

We thank Drs. Fanrong Liang, Fang Zeng, and Lixing Lao for their professional guidance and insightful instructions for our project. And thank the library of Chengdu University of TCM for providing literature resources.

Funding

This work will be supported by the National Natural Science Foundation of China (grant number 81904304) and the Young Elite Scientists Sponsorship Program by the CAST (YESS) (No. CACM-2019-QNRC1-04). The funders had no role in study design, data collection and analysis, report writing, or decision-making for publication.

Competing interests

None declared.

References

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nature Reviews Nephrology* 2020;16(4):223–37. doi: 10.1038/s41581-019-0244-2
2. Whelton P, Carey R, Aronow W, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018;138(17):e426-e83. doi: 10.1161/cir.0000000000000597
3. Bundy J, Mills K, Chen J, et al. Estimating the Association of the 2017 and 2014 Hypertension Guidelines With Cardiovascular Events and Deaths in US Adults: An Analysis of National Data. *JAMA cardiology* 2018;3(7):572–81. doi: 10.1001/jamacardio.2018.1240
4. Wang JG. Unique approaches to hypertension control in China. *Ann Transl Med* 2018;6(15):296. doi: 10.21037/atm.2018.07.27 [published Online First: 2018/09/14]
5. Chobanian A, Bakris G, Black H, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension (Dallas, Tex: 1979)* 2003;42(6):1206–52. doi: 10.1161/01.HYP.0000107251.49515.c2

6. Liu A, Li J, Li H, et al. Electroacupuncture for Acute Ischemic Stroke: A Meta-Analysis of Randomized Controlled Trials. *The American journal of Chinese medicine* 2015;43(8):1541–66. doi: 10.1142/s0192415x15500883
7. Tan X, Pan Y, Su W, et al. Acupuncture therapy for essential hypertension: a network meta-analysis. *Annals of translational medicine* 2019;7(12):266. doi: 10.21037/atm.2019.05.59
8. Yang M, Yu Z, Deng S, et al. A Targeted Metabolomics MRM-MS Study on Identifying Potential Hypertension Biomarkers in Human Plasma and Evaluating Acupuncture Effects. *Sci Rep* 2016;6:25871. doi: 10.1038/srep25871 [published Online First: 2016/05/18]
9. Wenzel UO, Ehmke H, Bode M. Immune mechanisms in arterial hypertension. Recent advances. *Cell Tissue Res* 2021;385(2):393–404. doi: 10.1007/s00441-020-03409-0 [published Online First: 2021/01/05]
10. Drummond GR, Vinh A, Guzik TJ, et al. Immune mechanisms of hypertension. *Nat Rev Immunol* 2019;19(8):517–32. doi: 10.1038/s41577-019-0160-5 [published Online First: 2019/04/18]
11. Liu S, Wang Z, Su Y, et al. A neuroanatomical basis for electroacupuncture to drive the vagal–adrenal axis. *Nature* 2021 doi: 10.1038/s41586-021-04001-4
12. Longhurst JC, Tjen-A-Looi SC. Evidence-based blood pressure reducing actions of electroacupuncture: mechanisms and clinical application. *Sheng Li Xue Bao* 2017;69(5):587–97.
13. Yang M, Lao L. Emerging Applications of Metabolomics in Traditional Chinese Medicine Treating Hypertension: Biomarkers, Pathways and More. *Front Pharmacol* 2019;10:158. doi: 10.3389/fphar.2019.00158 [published Online First: 2019/03/25]
14. Young D. Policymakers, experts review evidence-based medicine. *Am J Health Syst Pharm* 2005;62(4):342–3. doi: 10.1093/ajhp/62.4.0342 [published Online First: 2005/03/05]
15. Yang J, Chen J, Yang M, et al. Acupuncture for hypertension. *Cochrane Database of Systematic Reviews* 2018(11)
16. Zhao H, Li D, Li Y, et al. Efficacy and safety of acupuncture for hypertension: An overview of systematic reviews. *Complement Ther Clin Pract* 2019;34:185–94. doi: 10.1016/j.ctcp.2018.12.003 [published Online First: 2019/02/05]
17. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]
18. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). *Cochrane* 2020
19. Yang J, Chen J, Yang M, et al. Acupuncture for hypertension. *The Cochrane database of systematic reviews* 2018;11:CD008821. doi: 10.1002/14651858.CD008821.pub2
20. Hess NC, Carlson DJ, Inder JD, et al. Clinically meaningful blood pressure reductions with low intensity isometric handgrip exercise. A randomized trial. *Physiol Res* 2016;65(3):461–8. doi: 10.33549/physiolres.933120 [published Online First: 2016/04/14]

21. Wong GW, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *Cochrane Database Syst Rev* 2014(2):CD007452. doi: 10.1002/14651858.CD007452.pub2 [published Online First: 2014/03/04]
22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62(10):1006–12. doi: 10.1016/j.jclinepi.2009.06.005 [published Online First: 2009/07/28]
23. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898 [published Online First: 2019/08/30]
24. Hwang YC, Lee IS, Ryu Y, et al. Exploring traditional acupuncture point selection patterns for pain control: data mining of randomised controlled clinical trials. *Acupunct Med* 2020:964528420926173. doi: 10.1177/0964528420926173 [published Online First: 2020/06/23]
25. Silva M, Lustosa T, Arai V, et al. Effects of acupuncture on obstructive sleep apnea severity, blood pressure control and quality of life in patients with hypertension: A randomized controlled trial. *Journal of sleep research* 2020;29(2):e12954. doi: 10.1111/jsr.12954
26. Zheng H, Li J, Li Y, et al. Acupuncture for patients with mild hypertension: A randomized controlled trial. *Journal of clinical hypertension (Greenwich, Conn)* 2019;21(3):412–20. doi: 10.1111/jch.13490
27. Flachskampf F, Gallasch J, Gefeller O, et al. Randomized trial of acupuncture to lower blood pressure. *Circulation* 2007;115(24):3121–9. doi: 10.1161/circulationaha.106.661140

Figures

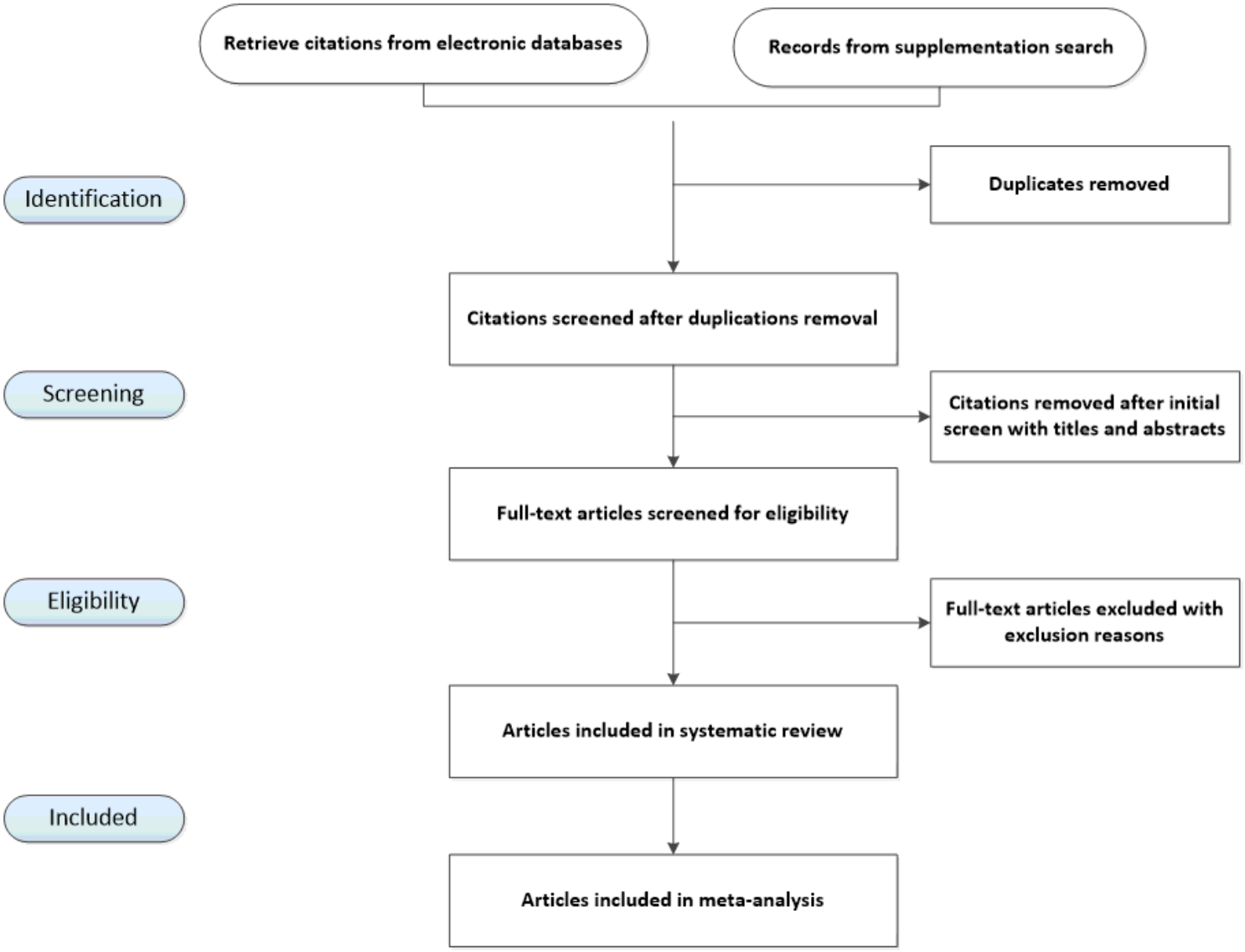

Figure 1

Flowchart of study selection.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAPchecklist.docx