Electroacupuncture/Transcutaneous Electrical Acupoint Stimulation for perioperative neurocognitive disorder in elderly patients undergoing cardiac surgery: a protocol for systematic review and meta-analysis

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Abstract

Background: Perioperative neurocognitive disorder (PND) is a critical concern for elderly cardiac surgery patients, impacting cognitive function and quality of life. Electroacupuncture (EA) and Transcutaneous Electrical Acupoint Stimulation (TEAS) hold promise for mitigating PND. This protocol outlines a systematic review and meta-analysis to thoroughly assess EA/TEAS efficacy in elderly cardiac surgery patients with PND, informing up-to-date evidence for PND prevention and treatment.

Objective: To thoroughly assess the efficacy of electroacupuncture and transcutaneous electrical acupoint stimulation on elderly cardiac surgery patients with perioperative neurocognitive disorder, informing up-to-date evidence for perioperative neurocognitive disorder prevention and treatment.

Methods: A comprehensive and systematic approach will be employed to identify eligible studies from a diverse range of electronic databases, including nine major sources such as PubMed and Cochrane, as well as two clinical trial registration websites. These studies will focus on investigating the effects of EA/TEAS on PND in elderly patients undergoing cardiac surgery. The study selection will adhere to the criteria outlined in the PICOS format. Data extraction will be carried out by two independent researchers, utilizing established tools to evaluate the risk of bias. The primary outcome will be PND incidence, with secondary outcomes including Mini-Mental State Examination scores, neuron-specific enolase, S100?, interleukin-1?, interleukin-6, tumor necrosis factor-?, time to first flatus, first defecation, bowel sound recovery, and hospitalization duration to be selectively reported. Adverse events linked to acupuncture, such as bleeding, needle site pain, and local reactions, rather than serious adverse events, will also be considered. Meta-analysis will be performed using appropriate statistical methods to assess the overall effect of EA/TEAS on PND prevention, treatment, or other relevant outcomes. the Cochrane Collaboration Risk of Bias (ROB) tool will be utilized for assessment, and data synthesis will be executed using the RevMan 5.4 software.

Results: We plan to summarize the eligible studies through the utilization of a PRISMA flowchart. The findings will be showcased in the form of a summary table of evidence. Figures and forest plots will be employed to illustrate the outcomes of the meta-analysis.

Conclusions: The impact of electroacupuncture and transcutaneous acupoint electrical stimulation interventions on Perioperative neurocognitive disorder in elderly cardiac surgery patients has not yet been established. This protocol addresses a critical gap by thoroughly assessing EA and TEAS for PND in elderly cardiac surgery patients, enhancing understanding of non-pharmacological interventions and guiding future research and clinical practices in this field. Its strength lies in rigorous methodology, including comprehensive search strategies, independent review processes, and thorough assessments of the risk of bias. Clinical Trial: PROSPERO registration number: CRD42023411927.

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ABSTRACT

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PROSPERO registration number: CRD42023411927.

KEYWORDS: Perioperative neurocognitive disorder; cardiac surgery; elderly patients; systematic review; meta-analysis

INTRODUCTION

Perioperative neurocognitive disorder

PND remains a significant concern in the context of cardiac surgery[1]. PND encompasses a spectrum of cognitive deficits that manifest during the perioperative period, ranging from mild cognitive impairment to delirium and overt dementia[2]. These deficits impact a range of cognitive

areas, encompassing memory, concentration, executive skills, and language abilities[3,4]. The manifestation of these impairments becomes evident in the aftermath of surgery[5], typically peaking within the initial postoperative week and occasionally enduring for an extended duration[3,6]. These cognitive changes carry substantial implications for patients' quality of life, functional independence, healthcare expenditure, and postoperative outcomes[7-9].

PND in elderly patients undergoing cardiac surgery

The relationship between PND and elderly patients undergoing cardiac surgery is of particular interest, given the vulnerability of this population to cognitive decline[10,11]. As the worldwide population ages and surgical methods and anesthetic practices advance, the volume of individuals undergoing cardiac surgery is on the rise, prompting a greater focus on enhancing their perioperative management. The exact pathophysiological mechanisms of PND are multifactorial and complex, remaining elusive. Factors such as age-related physiological changes, surgical anesthesia stress, increased susceptibility to inflammation, and potential preexisting cognitive deficits may render elderly patients more susceptible to PND[12-19]. Furthermore, cardiac surgery introduces potential risks of neurocognitive complications due to cardiopulmonary bypass and associated factors[20,21]. Epidemiological studies have indicated that the occurrence rates of PND in elderly individuals undergoing cardiac surgery vary between 25% and 50%[22-25]. This wide variability underscores the complexity of PND's etiology and the need for comprehensive investigation and intervention strategies[26].

Related management methods of PND

Current conventional approaches for managing PND primarily focus on mitigating risk factors through neuroprotective agents, refined anesthesia management, and inflammation minimization[27,28]. Nevertheless, these strategies have limitations in preventing PND occurrence or

effectively treating established cases, and many medications exhibit side effects, falling short of addressing the disorder's multifaceted nature and potential adverse effects[26,29]. To bridge these gaps in the treatment landscape, exploring alternative or supplementary therapeutic interventions targeting PND's multifaceted nature is compelling to attenuate cognitive decline. Among emerging alternative approaches, acupuncture has garnered attention as a potentially promising intervention for PND. Rooted in traditional Chinese medicine, acupuncture is suggested to offer advantages such as modulating neuroinflammation, enhancing cerebral perfusion, and promoting neural plasticity[30-36]. Furthermore, acupuncture's favorable safety profile aligns with the elderly population's increased susceptibility to pharmacological agents' adverse effects[37]. Particularly, EA and TEAS, involving non-invasive application of electrical currents to modulate neural activity, hold promise as non-pharmacological interventions that may prevent or ameliorate cognitive decline. The results of a randomized controlled trial (RCT) revealed that the acupuncture group exhibited a shorter time to first remission of delirium and a significantly higher number of delirium-free days compared to the standard treatment group in the treatment of elderly patients with delirium, with no observed adverse safety events[38].

Limitations of previous studies

While previous studies have explored various interventions for PND, prior meta-analyses have primarily focused on the overall population without distinguishing between surgical types, resulting in considerable heterogeneity[39,40]. Currently, there is a recognized gap in the literature regarding the impact of EA and TEAS specifically on PND in elderly patients undergoing cardiac surgery, with no systematic reviews or meta-analyses available. A previous meta-analysis included 18 RCTs to evaluate the impact of TEAS on cognitive function in elderly individuals after general anesthesia. Despite this effort, it was not possible to analyze the incidence of postoperative delirium due to the limited number of original studies and poor methodology[41]. In 2021, a review of 16 RCTs

involving 1241 patients suggested that acupuncture appears to be a promising adjunct intervention for the treatment/prevention of postoperative cognitive dysfunction. However, the evidence is insufficient and has limitations[42]. Another systematic review and meta-analysis in 2023 included 12 studies with a total of 1058 patients to explore the use of acupuncture-related techniques in treating postoperative cognitive complications. Nonetheless, the enrolled studies varied in surgical types, and no definitive conclusions could be drawn[43]. Consequently, the acupuncture research landscape for PND remains intricate, with varied study methodologies, inconsistent intervention protocols, and divergent outcome measures contributing to fragmented evidence lacking a comprehensive synthesis. The curative effect of acupuncture on PND remains controversial, and the optimal acupuncture regimen for preventing or treating PND is unclear.

Aims

Given the gaps in knowledge and potential implications for clinical practice, this systematic review and meta-analysis protocol aims to consolidate current research findings on EA/TEAS interventions' potential effectiveness in preventing or ameliorating PND in elderly cardiac surgery patients. By synthesizing available evidence, we endeavor to provide a comprehensive overview of the existing literature, identify key research gaps, and offer insights into potential mechanisms. Specifically, our objective is to offer a comprehensive perspective by comparing treatment outcomes and phenomena associated with acupuncture, addressing the following questions: (a) What is the impact of EA and TEAS on the incidence and severity of PND in elderly patients undergoing cardiac surgery? (b) what are the effects of EA and TEAS on serum biomarkers in elderly patients undergoing cardiac surgery? Through addressing current knowledge gaps, these insights have the potential to inform clinical practice, clarify controversies, and shape future research endeavors. Additionally, they contribute to the development of evidence-based strategies aiming to optimize perioperative care for elderly patients undergoing cardiac surgery, ultimately leading to improvements in postoperative cognitive

outcomes.

METHODS

Study registration

The meta-analysis protocol has been registered with the International Prospective Register of Systematic Reviews under Prospero registration number CRD42023411927. In addition, the preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocols guidelines has been used to report this protocol **(online supplemental appendix 1)**[44]. Our systematic review will be conducted following the guidelines outlined in the Cochrane Collaboration Handbook[45], and we will ensure transparency in reporting by adhering to the PRISMA 2020 guidelines[46].

Study design

We intend to incorporate a range of study designs, such as RCTs, quasi-experimental approaches, and prospective cohort studies, as well as controlled clinical trials (CCTs) that assess the effectiveness and safety of EA/TEAS in PND in elderly patients undergoing cardiac surgery[47].

Type of participants/populations

Incorporating patients who are sixty years of age or older, this study endeavors to investigate the inclusion of individuals scheduled for elective cardiac surgery, ensuring that they do not exhibit any pre-existing neurocognitive disorders. It is worth noting that participants' eligibility will not be restricted by factors such as gender, race, surgical history, or underlying medical conditions.

Type of intervention/exposure

The treatment groups will undergo EA/TEAS therapies. The study will not impose any limitations on the sample size, intervention duration, perioperative care, or the underlying treatment modalities employed. This inclusivity will facilitate a comprehensive exploration of the treatment's efficacy.

Type of control/comparator(s) groups

To provide a comparative framework, the control/comparator groups may encompass a range of approaches. These include the application of general anesthesia as part of conventional care, sham acupuncture, as well as pharmacotherapy involving Western medicine. It is crucial to note that interventions deviating from these specified approaches will be excluded from the comparator groups, ensuring a coherent and consistent comparison.

Types of outcome measures

To assess the impact of the chosen interventions, a comprehensive set of outcomes has been strategically determined. Primary outcomes will focus on evaluating the incidence of PND. Emphasizing the significance of a comprehensive evaluation, a host of secondary outcomes will be collected and subjected to meticulous analysis. These encompass evaluating neurocognitive function through the use of Mini-mental state examination (MMSE) scores, alongside measuring serum levels of neuron-specific enolase (NSE), S100β, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Additionally, vital secondary outcomes include evaluating the time to first flatus, first defecation, bowel sound recovery, and the duration of hospitalization. It is crucial to highlight that adverse events associated with acupuncture, such as bleeding, needle site pain, and other localized reactions, will be documented and analyzed, while serious adverse events will be addressed separately[48].

Search strategy

To perform a thorough review of the literature, we have formulated an expansive search approach, encompassing the exploration of 9 distinct databases, specifically PubMed, Embase, Cochrane Library, Web of Science, Scopus, China National Knowledge Infrastructure, Chinese BioMedical Database, WanFang Database, and VIP Database. Additionally, two registered websites[49, 50], will

also be explored. To maximize the scope of the review, reference lists from relevant articles will be manually examined. Importantly, there will be no limitations placed on the publication status, source country, or publication year. To ensure a comprehensive search, a predefined list of search terms, including EA, TEAS, PND, cardiac surgery, elderly, and RCTs, will be utilized in combination with the subject words unique to each database[51]. Notably, the comprehensive search approach utilized within PubMed can be found in **Table 1**, with specific search strategies tailored for individual databases accessible in the **online supplemental appendix 2**. To further supplement this comprehensive approach, additional sources, such as dissertations, conference papers, grey literature, and unpublished research from relevant entities, will be assessed. And seek advice from experts in acupuncture and cardiac surgery. To streamline this process, Endnote 20 will be employed to manage the literature and eliminate any duplicate studies. In order to uphold research integrity, the eligibility of studies will be independently screened and evaluated by two researchers, PY and SL. Any disagreements will be resolved through deliberation with other members of the research team. Both Chinese and English language studies will be retrieved and considered in this study. The manuscripts screening process is shown in **Figure 1**.

Table 1 The search strategy for Pubmed.

Order	Strategy
#1	"Postoperative Cognitive Complications"[Mesh]
#2	"postoperative delirium"[Mesh]
#3	"perioperative neurocognitive disorder"[Title/Abstract]
#4	"cognit*"[Title/Abstract] OR "cognition disorder"[Title/Abstract] OR "cognition impairment"[Title/Abstract] OR "cognition decline"[Title/Abstract] OR "cognitive dysfunction"[Title/Abstract] OR "cognitive function"[Title/Abstract] OR "delirium"[Title/Abstract] OR "neurocognitive disorder"[Title/Abstract]
#5	"postop*"[Title/Abstract] OR "postoperative*"[Title/Abstract] OR "postoperative"[Title/Abstract] OR "postoperative period"[Title/Abstract]
#6	#4 AND #5
#7	#1 OR #2 OR #3 OR #6
#8	"acupuncture"[MeSH Terms] OR "acupuncture therapy"[MeSH Terms] OR "acupuncture therapy"[MeSH Terms] OR "electroacupuncture"[MeSH Terms]
#9	"Acupuncture"[Title/Abstract] OR "Electroacupuncture"[Title/Abstract] OR "EA"[Title/Abstract] OR "transcutaneous electrical acupoint

	stimulation"[Title/Abstract] OR "TEAS"[Title/Abstract]
#10	#8 OR #9
#11	((((((((((Thoracic Surgery[MeSH Terms]) OR (Cardiac Surgical Procedures[MeSH Terms])) OR (Surgery, Thoracic)) OR (Surgery, Cardiac)) OR (Surgery, Heart)) OR (Heart Surgery)) OR (Cardiac Surgery)) OR (Procedure*, Cardiac Surgical)) OR (Surgical Procedure*, Cardiac)) OR (Surgical Procedure*, Heart)) OR (Cardiac Surgical Procedure*)) OR (Heart Surgical Procedure*)) OR (Procedure*, Heart Surgical)
#12	elderly OR older OR geriatric
#13	#7 AND #10 AND #11 AND #12

Inclusion criteria

The criteria for inclusion in this review were established following the patient, intervention, comparison, outcome, and studies (PICOS) framework:

(1) The study's target population comprises elderly individuals (aged 65 years or older) undergoing cardiac surgery. These patients may exhibit a range of cardiac conditions necessitating surgical procedures, including coronary artery bypass grafting, valve replacement, or a combination of interventions.

(2) The primary intervention of interest is EA or TEAS. Studies utilizing either of these interventions as a therapeutic modality in the perioperative period will be considered. The interventions may involve varying frequencies, intensity, waveform, durations, and acupoint selections. Research that involves other forms of acupuncture or non-acupuncture interventions will be excluded unless they are employed within the context of a comparative group.

(3) Eligible studies will encompass those incorporating an appropriate comparative group. This may involve sham/placebo interventions, standard care lacking any EA/TEAS application, or alternative interventions designed to mitigate perioperative neurocognitive disorder. Studies comparing different forms of EA/TEAS protocols will also be considered, including studies comparing different frequencies, intensities, waveforms, acupoints, or durations of EA/TEAS interventions.

(4) Primary Outcome: Incidence of PND. Secondary Outcomes: the MMSE scores, NSE, S100β, IL-1β, IL-6, and TNF-α, time to first flatus, first defecation, bowel sound recovery, and duration of

hospitalization will be selectively reported. Adverse incidents linked to acupuncture, such as bleeding, discomfort at needle insertion sites, and local reactions, will be considered, with a focus on non-serious adverse events.

(5) The eligible studies will encompass RCTs, quasi-experimental designs, prospective cohort studies, as well as CCTs.

Language and Publication Date

No language restrictions.

Publication date up to June 15, 2024.

Exclusion criteria

The exclusion criteria are as follows:

(1) Research focusing on patients who are not elderly (aged < 65 years) or those undergoing surgeries unrelated to cardiac procedures.

(2) Studies lacking proper cognitive assessment as an outcome measure.

(3) Studies involving animals, retrospective investigations, case reports, commentaries, literature reviews, duplicate publications, and articles with unavailable full text.

(4) Studies where EA/TEAS is combined with other interventions that cannot be adequately isolated for analysis.

Data extraction and risk of bias assessment

The extraction of data will be carried out independently by two researchers (PY and SL). Throughout the process, any differences will be resolved through discussion or by involving another researcher (WK). The essential data extracted from the manuscripts include the author's name, publication year, country, sample size, gender distribution, age distribution, disease duration, treatment duration, intervention details, and study outcomes. The inclusion or exclusion of EA/TEAS interventions in

each article will be itemized meticulously in accordance with the Standards for Reporting Interventions in Clinical Trials of Acupuncture checklist[52,53]. A pre-designed data collection form will be employed to conduct data extraction for each study, with a prime focus on extracting the following PICOS components and funding details.

Two evaluators (PY and SL) will individually evaluate potential biases in each study by applying the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions. Any discrepancies will be resolved through constructive dialogue or by enlisting the participation of another author (WK). We will assess the literature's quality using the "bias risk assessment tool" recommended by the Cochrane Collaboration. The bias risk will be documented in a table, where high risk will be indicated in red, low risk in green, and uncertain risk in yellow. We will add annotations to the tables to supplement information about the risk of bias and unpublished data sources obtained by contacting trial authors. Each item in the risk of bias assessment will be considered independently without assigning an overall score. We will consider the potential impact of bias in each study when assessing the effectiveness of the treatment, as it could have affected the results.

Data synthesis and analysis

We will utilize RevMan 5.4 software to conduct the meta-analysis and generate the risk of bias graph. For binary data, we will employ risk ratios and Mantel-Haenszel tests, along with a 95% confidence interval (CI) analysis. Continuous variables will be represented as the mean difference, effect value, and 95% CI. In cases where outcome measures vary across studies, the standard mean difference will be employed. To assess statistical heterogeneity, we will perform tests including the I^2 statistic, which ranges from 0% to 100%. Statistical heterogeneity will be evaluated using the standard χ^2 test (α=0.1) and the I^2 test[54]. If $I^2 \leq 50\%$, the fixed effects model will be used. If $I^2 > 50\%$, the random-effects model will be applied[55]. In instances of conspicuous clinical heterogeneity, the random-effects

model will be employed. The forest plots will display the results of the meta-analysis, where a *P* less than 0.05 indicates statistical significance. If a study is not amenable to quantitative synthesis, a descriptive analysis will be conducted and presented using a summary table.

Management of missing data

Efforts will be made to reach out to the primary author or corresponding author of the initial publication for the acquisition of any absent or inadequate data. In cases where such data cannot be obtained, an examination of the available data will be performed.

Subgroup and sensitivity analyses

If excessive heterogeneity is observed, we will conduct grouping and sensitivity analyses to investigate the potential sources of major inconsistencies or heterogeneity. Subgroup analysis will be performed based on different types of acupuncture and PND. The type of acupuncture, surgical methods, anesthesia, and other complicating factors will be analyzed if there are a sufficient number of studies and a variety of regimens are used[48]. During the sensitivity analysis, certain trials will be omitted to pinpoint potential origins of bias and evaluate the uniformity of the meta-analysis findings. Specifically, studies that did not report an intention-to-treat analysis, experienced high rates of participant dropout, or had other missing data will be excluded[56]. Additionally, sensitivity analysis will be performed to evaluate the potential influence of any missing data on the outcomes.

Evaluation of publication bias

In cases where there are more than 10 studies included for each outcome, we will employ funnel plots generated in RevMan to visually assess the presence of publication bias and assess the quality of evidence.

Grade quality of evidence

Moreover, we will employ the Grading of recommendations, assessment, development, and evaluation (GRADE) criteria to rank the quality of evidence. We will then evaluate the level of evidence and strength of recommendations for the outcomes under consideration. The levels of evidence certainty encompass four categories: "high," "moderate," "low," or "very low." These categories signify the degree of confidence in the effect estimate, with "high certainty" denoting a robust level of confidence and "very low certainty" indicating minimal confidence[57]. Confidence levels may be adjusted based on considerations such as risk of bias, imprecision, inconsistency, indirectness, or publication bias. Since only RCTs will be included in the review, reasons for updating the study (such as large effects, dose-response relationships, and confounders) do not apply[58].

Sample size evaluation

Trial sequential analysis (TSA) will be used for sample size estimation in systematic reviews or meta-analyses. TSA overcomes the limitations of classical systematic reviews or meta-analyses[59]. It reduces the occurrence of incorrect positive outcomes resulting from random errors in situations where the number of cases included in a meta-analysis is insufficient. TSA refers to the required information size, which denotes the minimum number of cases necessary to achieve statistically significant distinctions in a meta-analysis. Generally, the sample size requisite for meta-analysis is regarded as no smaller than what is needed for a properly designed and statistically robust individual RCT. In this study, the TSA program version 0.9.5.10 Beta will be used to control the risks of type I and type II errors by estimating RIS and monitoring testing sequences[60].

Patient and public involvement

The design, execution, reporting, and dissemination plans of this research will not involve the participation of patients and the public, given the systematic review and meta-analysis nature. Nevertheless, upon completion of the research, our findings will be disseminated and shared through peer-reviewed journals, conferences, and seminars focusing on the care and treatment of elderly surgical patients.

Ethical considerations

Ethical clearance is not required for this systematic review, as it relies on previously published data.

Validity, reliability, and rigour

Our systematic review will present findings in accordance with the best practice PRISMA guidelines, and meta-analyses will be carried out utilizing a random-effects meta-analytic approach, as recommended for synthesizing study outcomes[61].

Amendments

The protocol for this systematic review will be amended when necessary.

RESULTS

The results of this study will be presented at conferences and published in journals with peer review. We will maintain regular updates to our searches across all databases every two months to incorporate any newly available data into the systematic review.

DISCUSSION

Hypothesized

Due to increasing cardiovascular issues, there is a growing demand for cardiac surgeries[62]. In accordance with traditional Chinese medical principles, which emphasize the interconnectedness of the heart and the brain, it is suggested that the "Heart and Brain Co-govern Spirit," wherein the spirit encompasses both the nervous system and mental faculties. Consequently, cardiac surgery patients are more susceptible to cognitive impairment[63,64]. Research has indicated that reduced cardiac ejection fraction can activate the autonomic nervous system, elevate catecholamine and endothelin levels, disrupt cerebral autoregulation, and subsequently cause insufficient cerebral perfusion, diminished cerebral blood flow, damage to nerve cells, and the onset of cognitive deficiencies and changes in mental conditions. These factors align with some of the underlying factors associated with acupuncture[65]. Our study hypothesizes that EA and TEAS can significantly reduce the incidence of PND in elderly patients undergoing cardiac surgery.

Potential effect of acupuncture on PND

To date, no interventions are offering a complete cure for PND, and common pharmacotherapies may pose challenges due to patient compliance and potential adverse reactions[66,67]. Measures aimed at enhancing patient understanding and acceptance of the disease and its treatment, such as EA and TEAS, have gained prominence. These simple, convenient, cost-effective, and safe modalities empower patients to proactively monitor and manage PND. The empirical use of acupuncture in treating cognitive impairments spans millennia[68]. Previous research suggests that acupuncture may serve as an effective adjunctive therapy for neurological conditions such as depressive symptoms[69], Mild cognitive impairment[70], post-stroke cognitive impairment[71,72], vascular

dementia[73], schizophrenia[74] and Alzheimer's disease[75]. EA and TEAS represent novel acupuncture therapies that combine electrical stimulation with acupuncture point stimulation. As non-pharmacological interventions, they offer advantages such as no drug-related side effects and minimal invasiveness, making them widely used in clinical practice, especially in perioperative management[76-78]. Numerous emerging trials presently demonstrate the clinical efficacy of EA/TEAS in managing PND[79-82]. Currently, theories related to the pathogenesis of PND include central inflammatory responses, reduced central cholinergic system function, synaptic dysfunction, abnormal protein function, and disturbances in gut microbiota[83,84]. Among these, the central inflammatory response mechanism is of particular concern[85-87]. Early studies have suggested that EA/TEAS can alleviate both central and peripheral inflammatory responses, inhibit microglial cell activation, suppress neuronal apoptosis, and provide significant neuroprotection through various pathways, thereby delaying the pathological progression of PND[88,89]. Furthermore, numerous emerging trials have also demonstrated that adjunctive use of EA/TEAS in the perioperative period has regulatory effects on the gastrointestinal system, improves circulation, reduces anesthesia requirements, enhances immunity, decreases inflammation, and alleviates stress. This leads to shorter patient recovery and hospitalization times, ultimately improving patient quality of life, and indicating the potential efficacy of EA/TEAS in treating PND[90,91]. Regrettably, despite certain systematic reviews having assessed the effectiveness of EA/TEAS-related approaches in PND management, these reviews invariably manifest limitations encompassing diversities in terms of race, age, gender, intervention methodologies, and acupuncture treatment protocols. Such diversification might engender heightened clinical and statistical heterogeneity[92]. Additionally, some of the earlier studies lacked standardized protocols for assessing PND, leading to inconsistencies in the definition and diagnosis of the condition. These constraints have posed challenges in developing a comprehensive comprehension of the efficacy of approaches like EA/TEAS in preventing or mitigating PND. Therefore, as of the present, no compelling evidence has materialized, thereby

limiting the applicability of acupuncture.

Outcome indicator selection reasons

In light of the limitations in previous research, our meta-analysis concentrates on a specific aspect: the impact of EA/TEAS on PND in elderly patients undergoing cardiac surgery. By narrowing our scope to this particular intervention and patient population, we aimed to provide a more comprehensive and normative approach to evaluating the evidence for EA/TEAS in preventing or treating PND. This approach allows for a more homogeneous pool of studies, which enhances the comparability and generalizability of our findings. The primary outcome measure, the incidence of PND, was chosen as it represents the most direct and fundamental outcome of cognitive dysfunction post-cardiac surgery. It facilitates an assessment of whether EA/TEAS has the potential to reduce the risk of cognitive impairment. The inclusion of the MMSE as a secondary outcome measurement is motivated by its widespread use as a highly sensitive, standardized, and reliable tool for assessing cognitive function. MMSE scores will enable a detailed examination of specific cognitive domains, allowing for a more nuanced analysis of the impact of EA/TEAS on cognitive performance. Neurobiological markers such as NSE, S100β, and pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α are selected as secondary outcomes to explore the potential mechanisms underlying observed cognitive effects. Monitoring these biomarkers will provide insights into the neuroinflammatory response and neuronal damage associated with PND, helping to elucidate the pathways through which EA/TEAS may exert its influence. In addition to cognitive outcomes, we are also attentive to impacts on certain clinical manifestations, with gastrointestinal function being a crucial aspect of overall recovery after cardiac surgery. This study will assess postoperative parameters of gastrointestinal recovery, including the first flatus time, the first defecation time, and the recovery of bowel sounds. EA/TEAS is considered to potentially accelerate intestinal function recovery through its effects on the neuroendocrine and autonomic nervous systems, thereby

influencing these indicators. These measures offer a comprehensive perspective on the impact of acupuncture-based interventions on postoperative physiological recovery, potentially influencing patient comfort and overall surgical outcomes. Furthermore, prolonged hospitalization is associated with increased medical costs and potential complications. Evaluating the impact of EA/TEAS on the length of hospital stay provides valuable insights into the overall recovery trajectory and cost-effectiveness of the intervention. In summary, the selection of these primary and secondary outcome measures was driven by the need to capture a holistic picture of the intervention's multifaceted impact on cognitive function, neuroprotection, inflammatory response, and overall postoperative recovery in elderly patients undergoing cardiac surgery. These outcomes collectively aim to contribute to the existing knowledge base, provide scientific information for clinical practice, and potentially improve patient outcomes in this vulnerable population.

Implications and conclusions

If our meta-analysis can demonstrate the effectiveness of EA/TEAS in preventing or ameliorating PND in elderly cardiac surgery patients, its significance will be profound. Firstly, patients undergoing cardiac surgery might experience better cognitive results and an improved quality of life postoperatively. This finding offers significant hope for elderly patients who are particularly prone to PND. Frontline healthcare providers, including cardiac surgeons and anesthesiologists, can benefit from our research results by considering the inclusion of EA/TEAS in their perioperative care protocols. This may result in enhanced patient results, diminished healthcare expenses linked to the treatment of complications related to PND, and increased patient contentment. Additionally, our research may inspire additional exploration in the realm of safeguarding cognitive function during the perioperative period. It may encourage researchers to explore other complementary interventions, refine protocols, and conduct randomized controlled trials to establish causality and optimize clinical practices. In conclusion, our meta-analysis represents a critical step toward addressing the limitations

of previous research on PND in elderly cardiac surgery patients.

Limitations

It is essential to acknowledge the limitations of the proposed systematic review and meta-analysis. Variability in acupoint selection and the heterogeneity of cardiac surgical procedures may introduce challenges in synthesizing the evidence. Additionally, publication bias and the quality of included studies may impact the robustness of the conclusions drawn. Building upon the results of this protocol, future research avenues could explore the optimal timing, duration, and frequency of EA and TEAS interventions. Moreover, investigating the mechanisms underlying the observed effects may provide valuable insights into the neurobiological processes influenced by acupuncture-based therapies. To conclude, by focusing on EA/TEAS and adopting a more standardized approach, we hope to contribute valuable insights for clinicians and researchers, positioning acupuncture as a viable treatment option for PND. This, in turn, can provide better choices for patient management and guide future research efforts to improve perioperative cognitive outcomes.

Abbreviations

CCTs, controlled clinical trials; CI, confidence interval; EA, Electroacupuncture; GRADE, Grading of recommendations, assessment, development and evaluation; IL-1β, interleukin-1β; IL-6, interleukin-6; MMSE, Mini-mental state examination; NSE, neuron-specific enolase; PICOS, patient, intervention, comparison, outcome, and studies; PND, perioperative neurocognitive disorder; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; RCT, randomized controlled trial; TEAS, Transcutaneous electrical acupoint stimulation; TNF-α, tumor necrosis factor-α; TSA, Trial sequential analysis.

Author Contributions

All authors directly participated in this study. Conceptualization, WK and ZJ; methodology, WX; systematic review registration, PY and SL; quality assessment, PY and WX; manuscript writing, PY, WX and SL; All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Availability of data and materials

The authors will provide the raw data supporting the conclusions of this study to any qualified researcher without reservation.

Ethics and dissemination

Because no original data will be collected, this study does not require ethical approval. The results will be presented at conferences and published in journals with peer review.

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REFERENCES

1. Selnes OA, Gottesman RF, Grega MA, et al. Cognitive and neurologic outcomes after coronary-artery bypass surgery. N Engl J Med. 2012;366(3):250-257. doi:10.1056/NEJMra1100109
2. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. Br J Anaesth. 2018;121(5):1005-1012. doi:10.1016/j.bja.2017.11.087
3. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998;351(9106):857-861. doi:10.1016/s0140-6736(97)07382-0
4. Evered LA, Silbert BS, Scott DA, et al. Preexisting cognitive impairment and mild cognitive impairment in subjects presenting for total hip joint replacement. Anesthesiology. 2011;114(6):1297-1304. doi:10.1097/ALN.0b013e31821b1aab
5. Rundshagen I. Postoperative cognitive dysfunction. Dtsch Arztebl Int. 2014;111(8):119-125. doi:10.3238/arztebl.2014.0119

6. BEDFORD PD. Adverse cerebral effects of anaesthesia on old people. Lancet. 1955;269(6884):259-263. doi:10.1016/s0140-6736(55)92689-1
7. Li T, Li J, Yuan L, et al. Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. JAMA. 2022;327(1):50-58. doi:10.1001/jama.2021.22647
8. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg. 2011;112(5):1202-1211. doi:10.1213/ANE.0b013e3182147f6d
9. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108(1):18-30. doi:10.1097/01.anes.0000296071.19434.1e
10. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery [published correction appears in N Engl J Med 2001 Jun 14;344(24):1876]. N Engl J Med. 2001;344(6):395-402. doi:10.1056/NEJM200102083440601
11. Canet J, Raeder J, Rasmussen LS, et al. Cognitive dysfunction after minor surgery in the elderly. Acta Anaesthesiol Scand. 2003;47(10):1204-1210. doi:10.1046/j.1399-6576.2003.00238.x
12. Houx PJ, Vreeling FW, Jolles J. Rigorous health screening reduces age effect on memory scanning task. Brain Cogn. 1991;15(2):246-260. doi:10.1016/0278-2626(91)90029-8
13. Patel N, Minhas JS, Chung EM. Intraoperative Embolization and Cognitive Decline After Cardiac Surgery: A Systematic Review. Semin Cardiothorac Vasc Anesth. 2016;20(3):225-231. doi:10.1177/1089253215626728
14. Evered L, Silbert B, Scott DA, et al. Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction. Anesthesiology. 2016;124(2):353-361. doi:10.1097/ALN.0000000000000953
15. Hudetz AG. General anesthesia and human brain connectivity. Brain Connect. 2012;2(6):291-302. doi:10.1089/brain.2012.0107
16. Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand. 2001;45(3):275-289. doi:10.1034/j.1399-6576.2001.045003275.x
17. Terrando N, Brzezinski M, Degos V, et al. Perioperative cognitive decline in the aging population. Mayo Clin Proc. 2011;86(9):885-893. doi:10.4065/mcp.2011.0332
18. Rudolph JL, Schreiber KA, Culley DJ, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. Acta Anaesthesiol Scand. 2010;54(6):663-677. doi:10.1111/j.1399-6576.2010.02236.x
19. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367(1):30-39. doi:10.1056/NEJMoa1112923
20. Savageau JA, Stanton BA, Jenkins CD, et al. Neuropsychological dysfunction following elective cardiac operation. II. A six-month reassessment. J Thorac Cardiovasc Surg. 1982;84(4):595-600. PMID: 6981735.
21. Shaw PJ, Bates D, Cartlidge NE, et al. Long-term intellectual dysfunction following coronary artery bypass graft surgery: a six month follow-up study. Q J Med. 1987;62(239):259-268. PMID: 3498965.
22. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. JAMA. 2012;308(1):73-81. doi:10.1001/jama.2012.6857
23. Igwe EO, Nealon J, O'Shaughnessy P, et al. Incidence of postoperative delirium in older adults undergoing surgical procedures: A systematic literature review and meta-analysis. Worldviews Evid Based Nurs. 2023;20(3):220-237. doi:10.1111/wvn.12649
24. Nemeth E, Vig K, Racz K, et al. Influence of the postoperative inflammatory response on cognitive decline in elderly patients undergoing on-pump cardiac surgery: a controlled, prospective observational study. BMC Anesthesiol. 2017;17(1):113. Published 2017 Aug 29. doi:10.1186/s12871-017-0408-1
25. Smulter N, Lingehall HC, Gustafson Y, et al. Delirium after cardiac surgery: incidence and risk

factors. Interact Cardiovasc Thorac Surg. 2013;17(5):790-796. doi:10.1093/icvts/ivt323
26. Kong H, Xu LM, Wang DX. Perioperative neurocognitive disorders: A narrative review focusing on diagnosis, prevention, and treatment. CNS Neurosci Ther. 2022 Aug;28(8):1147-1167. doi: 10.1111/cns.13873
27. Fink HA, Hemmy LS, MacDonald R, et al. Cognitive Outcomes After Cardiovascular Procedures in Older Adults: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Nov 17. PMID: 25905147.
28. Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand. 2001;45(3):275-289. doi:10.1034/j.1399-6576.2001.045003275.x
29. Méndez-Martínez C, Fernández-Martínez MN, García-Suárez M, et al. Related Factors and Treatment of Postoperative Delirium in Old Adult Patients: An Integrative Review. Healthcare (Basel). 2021;9(9):1103. Published 2021 Aug 26. doi:10.3390/healthcare9091103
30. Shao S, Tang Y, Guo Y, et al. Effects of acupuncture on patients with Alzheimer's disease: Protocol for a systematic review and meta-analysis. Medicine (Baltimore). 2019;98(4):e14242. doi:10.1097/MD.0000000000014242
31. Wen J, Chen X, Yang Y, et al. Acupuncture Medical Therapy and its Underlying Mechanisms: A Systematic Review. Am J Chin Med. 2021;49(1):1-23. doi:10.1142/S0192415X21500014
32. Leung AW, Lam LC, Kwan AK, et al. Electroacupuncture for older adults with mild cognitive impairment: study protocol for a randomized controlled trial. Trials. 2015;16:232. Published 2015 May 27. doi:10.1186/s13063-015-0740-z
33. Liu CZ, Yu JC, Zhang XZ, et al. Acupuncture prevents cognitive deficits and oxidative stress in cerebral multi-infarction rats. Neurosci Lett. 2006;393(1):45-50. doi:10.1016/j.neulet.2005.09.049
34. Wang Z, Nie B, Li D, et al. Effect of acupuncture in mild cognitive impairment and Alzheimer disease: a functional MRI study. PLoS One. 2012;7(8):e42730. doi:10.1371/journal.pone.0042730
35. Cao L, Li X, Li M, et al. The effectiveness of acupuncture for Parkinson's disease: An overview of systematic reviews. Complement Ther Med. 2020;50:102383. doi:10.1016/j.ctim.2020.102383
36. Yuan S, Zhang X, Bo Y, et al. The effects of electroacupuncture treatment on the postoperative cognitive function in aged rats with acute myocardial ischemia-reperfusion. Brain Res. 2014 Dec 17;1593:19-29. doi: 10.1016/j.brainres.2014.10.005
37. Wildiers H, Highley MS, de Bruijn EA, et al. Pharmacology of anticancer drugs in the elderly population. Clin Pharmacokinet. 2003;42(14):1213-1242. doi:10.2165/00003088-200342140-00003
38. Levy I, Gavrieli S, Hefer T, et al. Acupuncture Treatment of Delirium in Older Adults Hospitalized in Internal Medicine Departments: An Open-Label Pragmatic Randomized-Controlled Trial. J Geriatr Psychiatry Neurol. 2022 May;35(3):333-343. doi: 10.1177/0891988721996804
39. Li S, Jiang H, Liu W, et al. Transcutaneous electrical acupoint stimulation for the prevention of perioperative neurocognitive disorders in geriatric patients: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2022 Dec 16;101(50):e32329
40. Huang KY, Liang S, Chen L, et al. Transcutaneous electrical acupoint stimulation for the prevention of postoperative delirium in elderly surgical patients: A systematic review and meta-analysis. Front Aging Neurosci. 2023 Jan 31;15:1046754. doi: 10.3389/fnagi.2023.1046754
41. Chen X, Kong D, Du J, et al. Transcutaneous electrical acupoint stimulation affects older adults' cognition after general anesthesia: A meta-analysis. Geriatr Nurs. 2022 Jul-Aug;46:144-156. doi: 10.1016/j.gerinurse.2022.05.010
42. Tang Y, Wang T, Yang L, et al. Acupuncture for post-operative cognitive dysfunction: a systematic review and meta-analysis of randomized controlled trials. Acupunct Med. 2021 Oct;39(5):423-431. doi: 10.1177/0964528420961393
43. Zhang J, Cairen Z, Shi L, et al. Acupuncture-related techniques for postoperative cognitive complications: a systemic review and meta-analysis. Perioper Med (Lond). 2023 May 3;12(1):14. doi: 10.1186/s13741-023-00303-5

44. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. Published 2015 Jan 1. doi:10.1186/2046-4053-4-1
45. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Available from www.training.cochrane.org/handbook: Cochrane 2022.
46. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. Published 2021 Mar 29. doi:10.1136/bmj.n160
47. Xiong FJ, Zhao W, Jia SJ, et al. Effect of oral pre-emptive analgesia on pain management after total knee arthroplasty: a protocol for systematic review and meta-analysis. BMJ Open. 2023;13(3):e070998. Published 2023 Mar 16. doi:10.1136/bmjopen-2022-070998
48. Bäumler P, Zhang W, Stübinger T, et al. Acupuncture-related adverse events: systematic review and meta-analyses of prospective clinical studies. BMJ Open. 2021;11(9):e045961. Published 2021 Sep 6. doi:10.1136/bmjopen-2020-045961
49. https://clinicaltrials.gov/
50. http://www.chictr.org.cn/
51. Mi X, Wang X, Yang N, et al. Hundred most cited articles in perioperative neurocognitive disorder: a bibliometric analysis. BMC Anesthesiol. 2021;21(1):186. Published 2021 Jul 2. doi:10.1186/s12871-021-01408-4
52. 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(6):e1000261. Published 2010 Jun 8. doi:10.1371/journal.pmed.1000261
53. Liu J, Song G, Huang Y, et al. Placebo Response Rates in Acupuncture Therapy Trials for Functional Dyspepsia: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2022;56(4):299-310. doi:10.1097/MCG.0000000000001679
54. Rücker G, Schwarzer G, Carpenter JR, et al. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol. 2008;8:79. Published 2008 Nov 27. doi:10.1186/1471-2288-8-79
55. Zheng J, Du L, Du B, et al. Airway nerve blocks for awake tracheal intubation: A meta-analysis of randomized control trials and trial sequential analysis. J Clin Anesth. 2023;88:111122. doi:10.1016/j.jclinane.2023.111122
56. Xu L, Zhou C, Pan X, et al. Effect of ASA on the risk of cerebrovascular ischemic events in patients with PFO. Ann Clin Transl Neurol. 2022;9(9):1384-1391. doi:10.1002/acn3.51638
57. Limketkai BN, Akobeng AK, Gordon M, et al. Probiotics for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2020;7(7):CD006634. Published 2020 Jul 17. doi:10.1002/14651858.CD006634.pub3
58. Cui S, Chen N, Yang M, et al. Cerebrolysin for vascular dementia. Cochrane Database Syst Rev. 2019;2019(11):CD008900. Published 2019 Nov 11. doi:10.1002/14651858.CD008900.pub3
59. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. BMC Med Res Methodol. 2017;17(1):39. Published 2017 Mar 6. doi:10.1186/s12874-017-0315-7
60. Brok J, Thorlund K, Gluud C, et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol. 2008;61(8):763-769. doi:10.1016/j.jclinepi.2007.10.007
61. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
62. Bellinger DC, Wypij D, duPlessis AJ, et al. Neurodevelopmental status at eight years in children

with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg. 2003;126(5):1385-1396. doi:10.1016/s0022-5223(03)00711-6
63. Bhushan S, Li Y, Huang X, et al. Progress of research in postoperative cognitive dysfunction in cardiac surgery patients: A review article. Int J Surg. 2021;95:106163. doi:10.1016/j.ijsu.2021.106163
64. van Nieuwkerk AC, Delewi R, Wolters FJ, et al. Cognitive Impairment in Patients With Cardiac Disease: Implications for Clinical Practice. Stroke. 2023;54(8):2181-2191. doi:10.1161/STROKEAHA.123.040499
65. Zhang Z, Zheng L, Liu X, et al. Prevalence of heart failure in Chinese cognitive impairment patients:a meta-analysis. Shanghai Journal of Preventive Medicine. 2021;33(04):327-334. doi:10.19428/j.cnki.sjpm.2021.20375
66. Duning T, Ilting-Reuke K, Beckhuis M, et al. Postoperative delirium - treatment and prevention. Curr Opin Anaesthesiol. 2021;34(1):27-32. doi:10.1097/ACO.0000000000000939
67. Avidan MS, Maybrier HR, Abdallah AB, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet. 2017;390(10091):267-275. doi:10.1016/S0140-6736(17)31467-8
68. Méndez-Martínez C, Fernández-Martínez MN, García-Suárez M, et al. Related Factors and Treatment of Postoperative Delirium in Old Adult Patients: An Integrative Review. Healthcare (Basel). 2021;9(9):1103. Published 2021 Aug 26. doi:10.3390/healthcare9091103
69. Guo T, Guo Z, Zhang W, et al. Electroacupuncture and cognitive behavioural therapy for sub-syndromal depression among undergraduates: a controlled clinical trial. Acupunct Med. 2016;34(5):356-363. doi:10.1136/acupmed-2015-010981
70. Kim H, Kim HK, Kim SY, et al. Cognitive improvement effects of electro-acupuncture for the treatment of MCI compared with Western medications: a systematic review and Meta-analysis. BMC Complement Altern Med. 2019;19(1):13. Published 2019 Jan 8. doi:10.1186/s12906-018-2407-2
71. Chou P, Chu H, Lin JG. Effects of electroacupuncture treatment on impaired cognition and quality of life in Taiwanese stroke patients. J Altern Complement Med. 2009;15(10):1067-1073. PMID: 20050300.
72. Kuang X, Fan W, Hu J, et al. Acupuncture for post-stroke cognitive impairment: a systematic review and meta-analysis. Acupunct Med. 2021;39(6):577-588. doi:10.1177/09645284211009542
73. Chen Y, Wang H, Sun Z, et al. Effectiveness of acupuncture for patients with vascular dementia: A systematic review and meta-analysis. Complement Ther Med. 2022;70:102857. doi:10.1016/j.ctim.2022.102857
74. Sun ZL, Liu J, Guo W, et al. Serum brain-derived neurotrophic factor levels associate with cognitive improvement in patients with schizophrenia treated with electroacupuncture. Psychiatry Res. 2016;244:370-375. doi:10.1016/j.psychres.2016.07.040
75. Kosenko EA, Tikhonova LA, Montoliu C, et al. Metabolic Abnormalities of Erythrocytes as a Risk Factor for Alzheimer's Disease. Front Neurosci. 2018;11:728. Published 2018 Jan 5. doi:10.3389/fnins.2017.00728
76. Francis RP, Johnson MI. The characteristics of acupuncture-like transcutaneous electrical nerve stimulation (acupuncture-like TENS): a literature review. Acupunct Electrother Res. 2011;36(3-4):231-258. doi:10.3727/036012911803634139
77. Chiou YF, Yeh ML, Wang YJ. Transcutaneous Electrical Nerve Stimulation on Acupuncture Points Improves Myofascial Pain, Moods, and Sleep Quality. Rehabil Nurs. 2020;45(4):225-233. doi:10.1097/RNJ.0000000000000198
78. Zhang T, Ou L, Chen Z, et al. Transcutaneous Electrical Acupoint Stimulation for the Prevention of Postoperative Cognitive Dysfunction: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;8:756366. Published 2021 Dec 6. doi:10.3389/fmed.2021.756366

79. He W, Li M, Han X, Zhang W. Acupuncture for Mild Cognitive Impairment and Dementia: An Overview of Systematic Reviews. Front Aging Neurosci. 2021;13:647629. Published 2021 May 14. doi:10.3389/fnagi.2021.647629
80. Huang KY, Liang S, Chen L, et al. Transcutaneous electrical acupoint stimulation for the prevention of postoperative delirium in elderly surgical patients: A systematic review and meta-analysis. Front Aging Neurosci. 2023;15:1046754. Published 2023 Jan 31. doi:10.3389/fnagi.2023.1046754
81. Kim H, Kim HK, Kim SY, et al. Cognitive improvement effects of electro-acupuncture for the treatment of MCI compared with Western medications: a systematic review and Meta-analysis. BMC Complement Altern Med. 2019;19(1):13. Published 2019 Jan 8. doi:10.1186/s12906-018-2407-2
82. Li S, Jiang H, Liu W, et al. Transcutaneous electrical acupoint stimulation for the prevention of perioperative neurocognitive disorders in geriatric patients: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2022;101(50):e32329. doi:10.1097/MD.0000000000032329
83. Xu X, Hu Y, Yan E, et al. Perioperative neurocognitive dysfunction: thinking from the gut?. Aging (Albany NY). 2020;12(15):15797-15817. doi:10.18632/aging.103738
84. Wang Y, Shen X. Postoperative delirium in the elderly: the potential neuropathogenesis. Aging Clin Exp Res. 2018;30(11):1287-1295. doi:10.1007/s40520-018-1008-8
85. Selnes OA, Grega MA, Bailey MM, et al. Cognition 6 years after surgical or medical therapy for coronary artery disease. Ann Neurol. 2008;63(5):581-590. doi:10.1002/ana.21382
86. McDonagh DL, Berger M, Mathew JP, et al. Neurological complications of cardiac surgery. Lancet Neurol. 2014;13(5):490-502. doi:10.1016/S1474-4422(14)70004-3
87. Hovens IB, Schoemaker RG, van der Zee EA, et al. Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning. Brain Behav Immun. 2014;38:202-210. doi:10.1016/j.bbi.2014.02.002
88. Ding L, Ning J, Guo Y, et al. The Preventive Effect of Transcutaneous Electrical Acupoint Stimulation on Postoperative Delirium in Elderly Patients with Time Factors: A Randomized Trial. J Integr Complement Med. 2022;28(8):689-696. doi:10.1089/jicm.2021.0141
89. Lin JG, Hsieh CL, Lin YW. Analgesic Effect of Electroacupuncture in a Mouse Fibromyalgia Model: Roles of TRPV1, TRPV4, and pERK. PLoS One. 2015;10(6):e0128037. Published 2015 Jun 4. doi:10.1371/journal.pone.0128037
90. Ho YS, Zhao FY, Yeung WF, et al. Application of Acupuncture to Attenuate Immune Responses and Oxidative Stress in Postoperative Cognitive Dysfunction: What Do We Know So Far?. Oxid Med Cell Longev. 2020;2020:9641904. Published 2020 Feb 13. doi:10.1155/2020/9641904
91. Zhang W, Zhang H, Wang SM, et al. Perioperative Acupuncture Optimizes Surgical Outcomes: Theory, Clinical Practice and Future Perspectives. Am J Chin Med. 2022;50(4):961-978. doi:10.1142/S0192415X22500392
92. Li F, Yan CQ, Lin LT, et al. Acupuncture attenuates cognitive deficits and increases pyramidal neuron number in hippocampal CA1 area of vascular dementia rats. BMC Complement Altern Med. 2015;15:133. Published 2015 Apr 28. doi:10.1186/s12906-015-0656-x

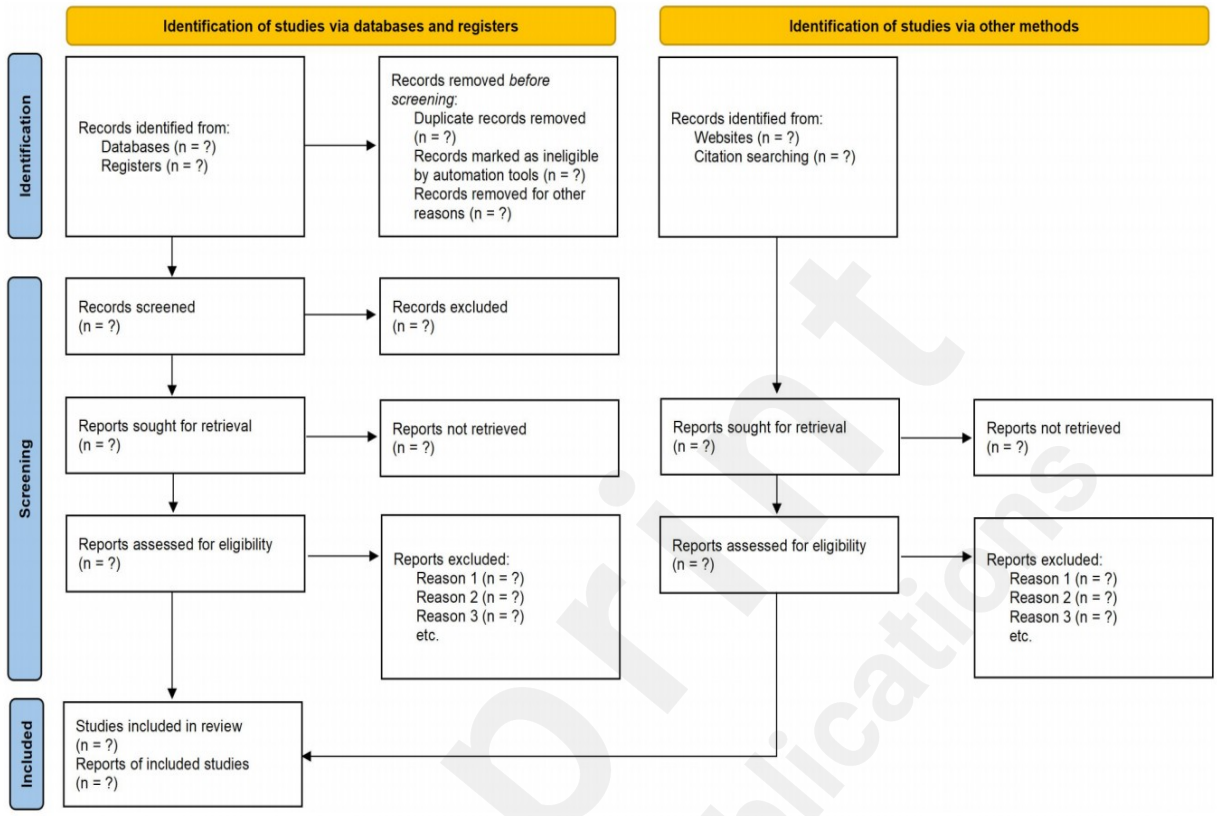

FIGURE 1 PRISMA flow diagram of study identification and selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses[36].

Supplementary Files

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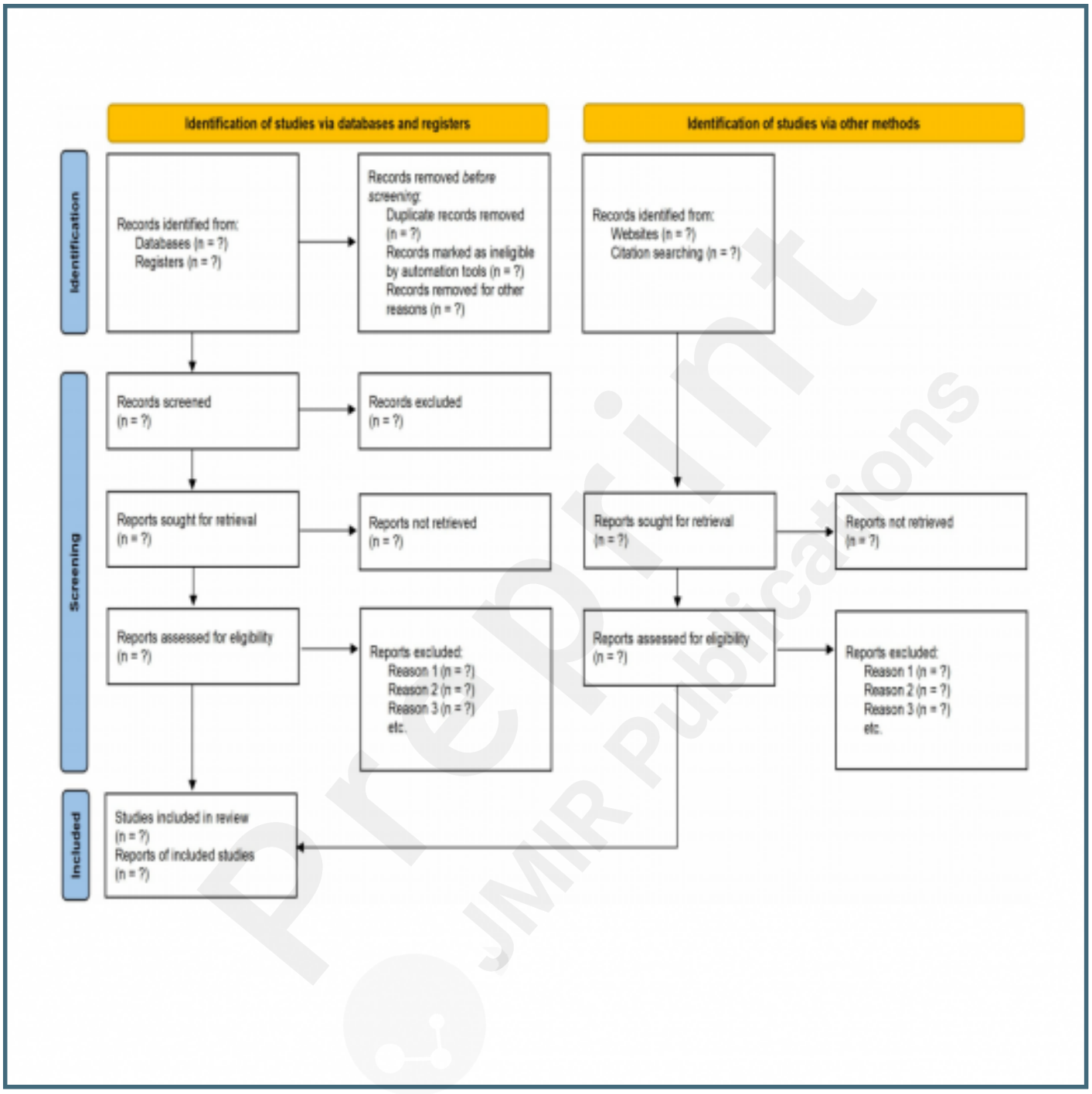
Figures

PRISMA flow diagram of study identification and selection.



Multimedia Appendixes

Funding 1.
URL: http://asset.jmir.pub/assets/6b201b4ab28bf25fd74dc235a1cc093f.pdf

Funding 2.
URL: http://asset.jmir.pub/assets/0f8bd74fdc7badeb0c02acc32d382d8c.pdf

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Funding 4.
URL: http://asset.jmir.pub/assets/a83275b3c81a37c07b1d966eb33befb4.pdf

Funding 5.
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CONSORT (or other) checklists

PRISMA-P 2015 checklist.
URL: http://asset.jmir.pub/assets/6180de317b513029a13a91d8350443a2.pdf