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Meta-analysis with trial sequential analysis investigating the impact of adjunctive electroacupuncture therapy on vascular mild cognitive impairment

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BACKGROUND: To systematically collect, evaluate, and synthesize evidence from randomized controlled trials (RCTs) supporting the use of electroacupuncture (EA) as an additional treatment option for Vascular mild cognitive impairment (VaMCI), a meta-analysis was carried out.
METHODS: Electronic searches of eight databases were used to locate RCTs that evaluated EA as a VaMCI adjuvant therapy. The Cochrane Risk of bias was used to assess the included trials' methodological quality. Review Manager 5.4 was used to analyze the data. Trial sequential analysis (TSA) was conducted with the trial sequential analysis program.
RESULTS: There were 15 RCTs with 1033 subjects in them. Compared to conventional therapy (CT) alone, the Montreal Cognitive Assessment (SMD 0.72, 95 percent CI [0.55, 0.88]), Mini-mental State Examination (SMD 0.73, 95 percent CI [0.60, 0.87]), and activities of daily living (SMD 0.83, 95 percent CI [0.54, 1.12]) were significantly improved while EA was used in conjunction with CT. The current studies exceeded the required information size, according to trial sequential analysis (TSA), demonstrating the reliability of EA adjuvant therapy VaMCI.
CONCLUSIONS: According to the pooled data, EA as an adjunct therapy for the treatment of VaMCI increases clinical efficacy. Although the TSA confirms a stable conclusion, it is encouraged to conduct studies of the highest quality standards.

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INTRODUCTION

Vascular mild cognitive impairment (VaMCI) is a clinical syndrome characterized by cognitive decline due to cerebrovascular disorders, and it is a major risk factor for dementia and functional impairment [1, 2]. VaMCI imposes a substantial socioeconomic burden on the aging population worldwide [3]. In the United States, dementia affects 11% of people over 65 years old, and vascular dementia (VD) is the second most common type [4]. Approximately 10%, 19%, and 46% of VaMCI patients progress to VD within one, two, and five years, respectively [5]. Therefore, VaMCI is regarded as a prodromal stage of VD [5]. Citicoline is the most frequently used pharmacological agent for vascular cognitive decline [6]. However, its efficacy is limited, as shown by randomized, placebo-controlled trials [7]. Consequently, there is a growing interest in non-pharmacological interventions that can preserve cognitive function and improve quality of life in VaMCI patients [8, 9].

Acupuncture is a traditional Chinese medicine technique that involves inserting fine needles into specific points on the body to modulate the flow of energy. Electroacupuncture (EA), a modified form of traditional acupuncture, is one such non-pharmacological intervention that has shown promise. EA involves inserting fine needles into specific points on the body and applying small electrical currents to stimulate the acupoints, integrating modern electrotherapy with traditional principles [10, 11]. The Ottawa Panel clinical practice guidelines endorse acupuncture as an alternative therapy to enhance post-stroke rehabilitation [12]. Acupuncture has been shown to have beneficial effects on VaMCI in several systematic reviews and meta-analyses based on evidence-based medicine [13–15]. Furthermore, acupuncture may be effective for mild amnestic cognitive impairment when used as a standalone or adjunctive treatment [14].

The potential advantages of electroacupuncture for treating VaMCI are significant. EA not only leverages the benefits of traditional acupuncture but also enhances the stimulation of acupoints through electrical currents, which may lead to improved therapeutic outcomes. This dual approach could offer a more robust and sustained improvement in cognitive functions for VaMCI patients compared to traditional methods [16].

Non-pharmacological interventions aimed at preserving cognitive function and improving the quality of life of VaMCI patients have garnered increased attention. In various patient populations suffering from chronic diseases, EA has been applied successfully. For instance, EA has shown benefits in managing chronic pain [17], improving neurological function in stroke patients [18], and alleviating symptoms in those with Parkinson's disease [19]. These applications highlight the versatility and potential of EA as a therapeutic intervention in chronic conditions, further supporting its use in managing VaMCI.

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Table 1. Search strategy for the Pubmed database.

Query	Search term
#1	"Cognitive Dysfunction"[Mesh]
#2	Cognitive Dysfunctions*[Title/Abstract] OR Cognitive Impairment*[Title/Abstract] OR Brain Infarction*[Title/Abstract] OR Cognitive Disorder*[Title/Abstract] OR Mild Cognitive Impairment*[Title/Abstract] OR Cognitive Decline*[Title/Abstract] OR Mental Deterioration*[Title/Abstract]
#3	#1 OR #2
#4	"Acupuncture"[Mesh]
#5	Acupuncture[Title/Abstract] OR acupuncture therapy[Title/Abstract] OR electroacupuncture[Title/Abstract] OR electroaucpuncture therapy[Title/Abstract] OR electric acupuncture[Title/Abstract] OR electrical acupuncture[Title/Abstract] OR electrical stimulation therapy[Title/Abstract]
#6	#4 OR #5
#7	"Randomized Controlled Trials as Topic"[Mesh]
#8	Randomized Controlled Trials[Title/Abstract] OR random*[Title/Abstract] OR controlled clinical trial[Title/Abstract] OR rct[Title/Abstract]
#9	#7 OR #8
#10	#3 AND #6 AND #9

A preliminary literature review indicates that an increasing number of randomized controlled trials (RCTs) are investigating the impact of EA on VaMCI. However, no systematic assessments of EA for VaMCI have been conducted to date. Therefore, the aim of this study was to systematically retrieve, appraise, and synthesize the available evidence.

METHODS

This meta-analysis followed the Cochrane Handbook [20] and revised PRISMA criteria [21]. The protocol of this review has been registered in the PROSPERO database (no. CRD42021269595).

Literature search and selection

We have conducted a systematic search of the CNKI, Wanfang, VIP, CBM, PubMed, the Cochrane Library, Web of Science, and Embase databases from their inception to 31 August 2023. We used a combination of keywords and MeSH terms related to our research topic, including 'Electroacupuncture', 'Randomized Controlled Trials as Topic', and 'Cognitive Dysfunction'. To ensure a comprehensive search, we used various keyword variations and Boolean operators. For instance, for the term 'Electroacupuncture', we also included variations such as 'electrical acupuncture' and 'electrical acupuncture'. Similarly, for 'mild cognitive impairment', we included 'Cognitive Impairment' and 'Cognitive Dysfunctions'. Table 1 in the manuscript displays the detailed PubMed search strategy employed in this study. A comprehensive search strategy for each of the other databases is provided in the Supplementary File.

Inclusion and exclusion criteria

The inclusion criteria were: (I) study type: only RCTs; (II) participants: diagnosed with VaMCI; (III) interventions: EA and conventional therapy (CT); (IV) the comparison was conventional therapy; (V) types of outcomes: Minimum Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) or similar recognized cognitive assessment tools.

Data extraction and outcome measures

After reading the titles and abstracts during the initial test step and the full texts during the final filter, two independent reviewers assessed the articles in conformity with the inclusion and exclusion criteria. Data on the first author, year of publication, sample size, patient characteristics, interventions, and outcomes were gathered from the included trials.

Quality assessment

Two independent reviewers used the Cochrane risk of bias tool to independently assess the bias across seven domains: (I) randomization process; (II) allocation concealment; (III) blind method; (IV) outcome assessors; (V) missing outcome data processing; (VI) selection of the reported result; (VII) other bias.

Statistical analysis

The data were analyzed using Review Manager 5.4 software, with standard mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and relative risk (RR) for dichotomous outcomes. Standard mean differences were calculated using the following formula:

$$\mathrm{SMD} = \frac{\mathrm{mean}_1 - \mathrm{mean}_2}{\text{pooled standard deviation}}$$

where mean_1 and mean_2 are the means of the two groups being compared, and the pooled standard deviation is calculated as:

$$\text{pooled standard deviation} = \sqrt{\frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1+n_2-2}}$$

Following Cohen's guidelines [22], we classified SMDs of 0.2, 0.5, and 0.8 as representing small, medium, and large effect sizes, respectively. Results were considered statistically significant when the p-value was less than 0.05. To assess heterogeneity, we employed the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. The I^2 statistic is calculated as follows:

$$I^2 = 100\% \times \left(\frac{Q-df}{Q}\right)$$

Where Q is the Cochran's heterogeneity statistic and df is the degrees of freedom (number of studies minus one). Negative I^2 values are set to 0, resulting in a range from 0% (indicating no observed heterogeneity) to 100% (indicating maximal heterogeneity). An I^2 value exceeding 50% is indicative of substantial heterogeneity. In cases of significant heterogeneity, a random-effects model was applied to the analysis; otherwise, a fixed-effects model was used. Subgroup analyses were based on treatment duration, and sensitivity analyses were performed to assess the robustness and consistency of the results. Publication bias was assessed using a funnel plot. Trial sequential analysis (TSA) was conducted using a fixed-effects model for MMSE and MoCA outcomes, with a statistical significance level of 5%, a power of 80%, and a relative risk reduction of 10% [23]. The TSA was performed using Trial Sequential Analysis v.0.9.5.10 beta, which corrects for model variance-based heterogeneity (Copenhagen

Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, https://www.ctu.dk/tsa).

RESULTS

Literature search

From the eight databases, 1181 records were retrieved, and 259 duplicates were ruled out. After screening the titles and abstracts, 854 records were removed. Fifteen trials [24–38] were eligible for full-text analysis after 68 records were eventually identified (Fig. 1).

Characteristics of included studies

Between 2012 and 2021, 19 to 120 trials with sample sizes ranging from 16 to 120 were included. They included 1033 participants, 518 in the control group and 515 in the EA group. Each treatment lasted between 30 and 45 min, and the cycle lasted from 4 to 12 weeks. Additional information is provided in Table 2.

Quality of included studies

A summary of the bias risk is provided in Figs. 2 and 3. Three studies [28, 32, 33] were at high risk for random assignment, and only one study [38] was at low risk for blinded and concealed assignment.

Meta-analysis

MoCA. The MoCA was used in nine studies comprising 493 participants to evaluate its efficacy. The outcome assessment endpoints were weeks 4, 6, 8, and 12 after treatment (Fig. 4). Five studies [24, 26, 31–33] recorded the MoCA before and after treatment at week 4. The meta-analysis showed that EA enhanced the MoCA score compared to the control group ($p = 0.25$; SMD 0.71, 95% CI: 0.49–0.92). One study [37] recorded the MoCA before and after treatment at week 6. The MoCA improved in the EA group compared to the control group (SMD 0.64, 95% CI: 012–1.15). Two studies [25, 28] recorded the MoCA before and after treatment at week 8. The meta-analysis showed an improvement in MoCA scores in the EA group compared to the control group ($p = 0.74$; SMD 0.94, 95% CI: 0.56–1.32). One study [33] recorded the MoCA before and after treatment at week 12. Compared to the control group, the meta-analysis showed that the MoCA scores improved in the EA group (SMD 0.51, 95% CI: 0.06–0.97). Overall, the meta-analysis showed that the MoCA score changed in the EA group compared to the control group ($p = 0.54$; SMD 0.72, 95% CI: 0.55–0.88). The TSA for MoCA scores demonstrated that the meta-analysis exceeded the required information size (n = 314) and the conventional boundary, as well as the trial sequential monitoring boundary (TSA; Fig. 5). Therefore, the conclusion is trustworthy and confirmatory, and no additional trials are required.

MMSE. Thirteen studies, with 893 participants, used the MMSE to evaluate the efficacy. The outcome assessment endpoints were weeks 4, 6, 8, and 12 after treatment (Fig. 6). Eight studies [24, 25, 27, 29, 30, 32, 34, 36] recorded the MMSE before and after week 4. The meta-analysis showed that the MMSE scores increased in the EA group compared to the control group ($p = 0.09$; SMD 0.76, 95% CI: 0.58–0.93). One study [37] recorded the MMSE before and after treatment at week 6, and the meta-analysis showed that MMSE scores were promoted in the EA group compared to the control group (SMD 0.60, 95% CI: 0.08–1.12). Four studies [25, 27, 29, 38] recorded the MMSE before and after treatment at week 8. The meta-analysis showed a higher MMSE score in the EA group compared to the control group ($p = 0.83$; SMD 0.72, 95% CI: 0.44–0.99). One study [35] recorded the MMSE before and after treatment at week 12, and the meta-analysis showed improvement in MMSE scores in the EA group compared to the control group (SMD 0.75, 95% CI: 0.29–1.21). Overall, the meta-analysis showed that the

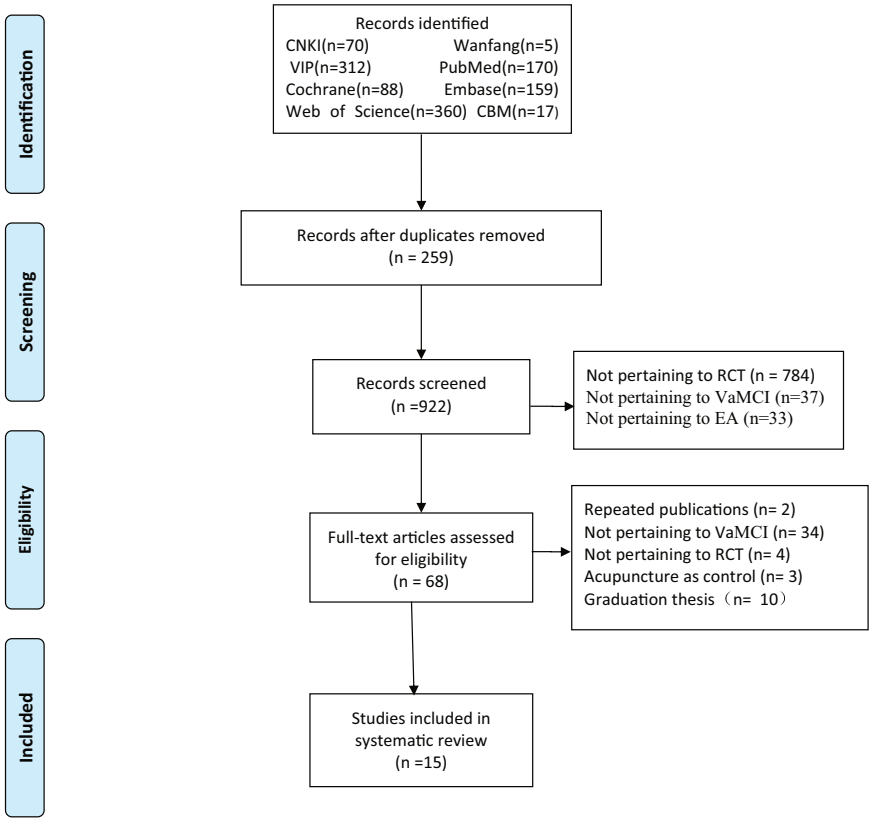

Fig. 1 PRISMA flowchart for literature selection.

Table 2. Descriptive analysis of the characteristics.

First author. year	Sample		Age		Time post onset		Acupoints	Duration & frequency of trials period	Main outcomes
	I	C	I	C	I	C			
Li et al. [24]	30	30	60.3 ± 6.2	59.1 ± 7.1	36.1 ± 11.9d	36.1 ± 11.9d	DU20, DU24, EX-HN1, C6, KI3, B39, SP6	30 min.times/d, 5 days/ week, 4 weeks	MMSE, MoCA
Jiang et al. [25]	30	30	58 ± 4.2	58 ± 4.2	Unclear	Unclear	DU20, DU24	45 min.times/d, 5 days/ week, 8 weeks	MMSE, MoCA, MBI, P300
Zhou et al. [26]	60	60	61.44 ± 8. 77	62.04 ± 8. 69	5.42 ± 1.87m	5.37 ± 1.98m	DU20, DU24	30 min.times/d, 6 days/ week, 4 weeks	MoCA, MMSE
Ma et al. [27]	30	30	60.12 ± 6. 56	62.32 ± 8 .84	29.67 ± 23.74d	29.67 ± 23.74d	LI4, LR3	times/d, 15 days	MMSE
Sun et al. [28]	30	30	65.07 ± 7.06	64.07 ± 6.58	Unclear	Unclear	DU20, DU24, EX-HN1, HT7, PC6	30 min.times/d, 6 days/ week, 8 weeks	MoCA, MMSE, ADL
Wang et al. [29]	30	30	53.27 ± 11.62	56.73 ± 9.32	3m-1y	3m-1y	DU20, ST36	30 min.times/d, 6 days/ week, 8 weeks	MMSE, ADL
Liao et al. [30]	40	40	30-85	30-85	Unclear	Unclear	DU20, GB13	30 min.times/d, 4 weeks	MMSE
Liao et al. [31]	40	40	30-85	30-85	Unclear	Unclear	DU24, GB13	30 min.times/d, 4 weeks	MoCA
Liu et al. [32]	19	16	52.42 ± 7.62	51.06 ± 11.62	11.26 ± 4.01d	13.81 ± 8.16d	EX-HN1, DU24, GB13	30 min.times/d, 5 days/ week, 4 weeks	MoCA, MMSE
Zhang [33]	30	30	70.90 ± 5.62	71.27 ± 5.91	Unclear	Unclear	DU20, DU24, EX-HN1, PC6, KI3, GB39, SP6	30 min.times/d, 5 days/ week, 4 weeks	MMSE, MoCA
Song et al. [34]	60	60	62.50 ± 4.52	63.01 ± 4.67	11.42 ± 4.26d	11.71 ± 4.32d	BL23, KI3	30 min.times/d, 6 days/ week, 4 weeks	MMSE
Li et al. [35]	39	39	62.8 ± 5.9	61.9 ± 6.8	Unclear	Unclear	GV16, DU23, BL62, PC7	qod, 12 weeks	MMSE, MoCA, ADL
Zhang et al. [36]	30	30	68.80 ± 7.25	67.93 ± 10.63	11.00 ± 7.05d	12.13 ± 6.16d	DU20, EX-HN1, DU24, GB13, PC6, HT7, SP6, KI3	30 min.times/d, 6 days/ week, 4 weeks	MMSE
Shao [37]	30	30	63.37 ± 3.886	66.13 ± 8.85	12.57 ± 1.165d	12.53 ± 1.252d	DU20, DU24, KI3, HT7	30 min.times/d, 5 days/ week, 6 weeks	MMSE, MoCA
Jiang [38]	20	20	62.85 ± 5.67	61.75 ± 6.35	93.61 ± 41.85d	81.1 ± 41.15d	DU20, DU24	30 min.times/d, 7 days/ week, 8 weeks	MMSE, P300

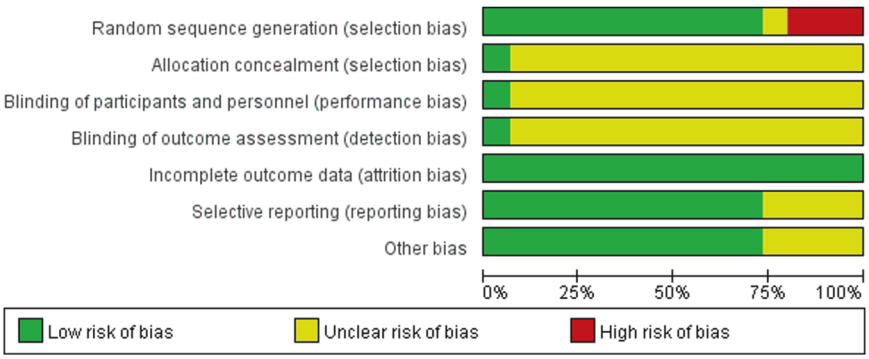

Fig. 2 Risk of bias percentage chart.

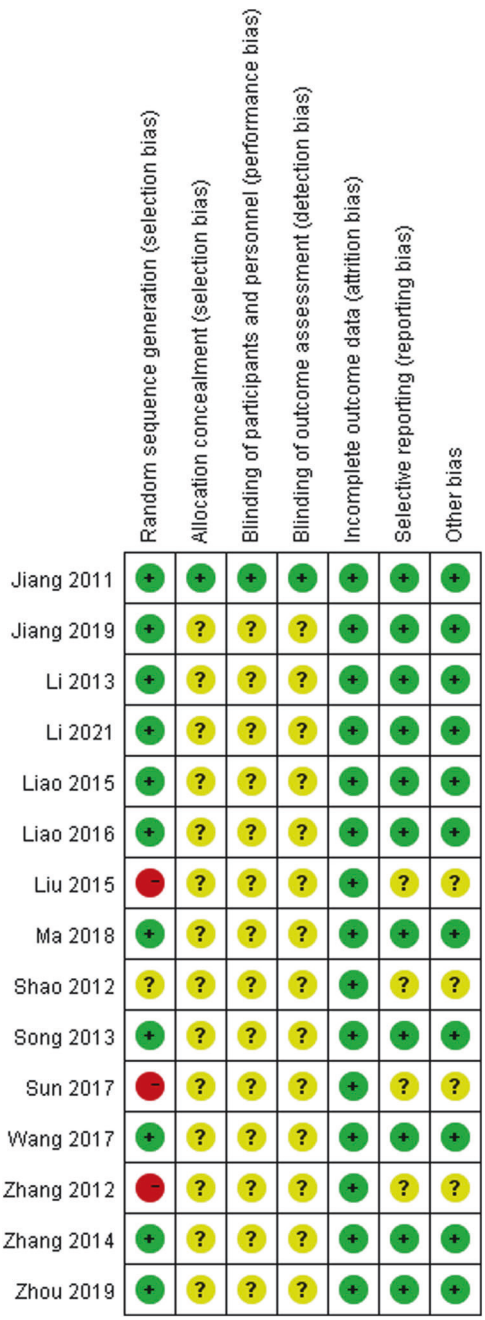

Fig. 3 Risk of bias distribution diagram.

EA group had higher MMSE scores than the control group ($p = 0.41$; SMD 0.73, 95% CI: 0.60–0.87). The TSA for MMSE demonstrated that the cumulative Z curves exceeded not only the required information size ($n = 281$) but also the conventional and trial sequential monitoring boundaries (Fig. 7). Therefore, there is no need for additional tests, and the conclusion is dependable and confirmatory.

Activities of daily living (ADL). Three studies [28, 29, 35] with 198 participants evaluated the efficacy using the ADL. Pooled analysis using a fixed effects model showed that the EA group had higher ADL scores than the control group (SMD 0.83, 95% CI: 0.54–1.12). In the subgroup analysis based on treatment duration, both subgroups showed improvement in ADL scores compared to controls (8 weeks of treatment: SMD 0.75, 95% CI: 0.37–1.12; 12 weeks of treatment: SMD 0.96, 95% CI: 0.49–1.43). Additional information is provided in Fig. 8.

DISCUSSION

Over 65% stroke survivors experience cognitive impairment, impacting motor function and quality of life over 12 months post-onset [39]. Acupuncture has been long used to treat VaMCI in China, and evidence-based medical evidence supports its efficacy [40]. EA is a complementary therapy for post-stroke rehabilitation, playing a role in traditional and extended acupuncture techniques. In China, it's used as an adjunctive treatment for cognitive impairment. A meta-analysis and TSA of RCTs are conducted to compare available evidence.

Summary of main findings

The meta-analysis found that EA as an adjuvant treatment for VaMCI improved MoCA, MMSE, and ADL scores. However, the study's conclusions need careful consideration due to potential bias, lack of clarity in trial randomization, and the limited duration of treatment. Additionally, the study's implementation protocols, including acupoint selection, stimulation technique, needle retention time, and treatment duration, varied widely, making it difficult to promote EA for VaMCI.

Agreements and disagreements with other published reviews

The positive effects of acupuncture on MCI have been described in almost all previous systematic reviews and meta-analyses [7–13]. Regarding EA as an alternative treatment for VaMCI, our review concurs with other studies. A systematic review in Korea in 2019 showed that EA was an effective treatment for improving cognitive function in MCI patients [34]. Another systematic review showed that acupuncture combined with other therapies significantly improved the MMSE scores of VaMCI patients [41]. This study suggested that acupuncture as a monotherapy or adjunctive therapy might improve the cognitive function and daily performance of VaMCI patients with few side effects [42].

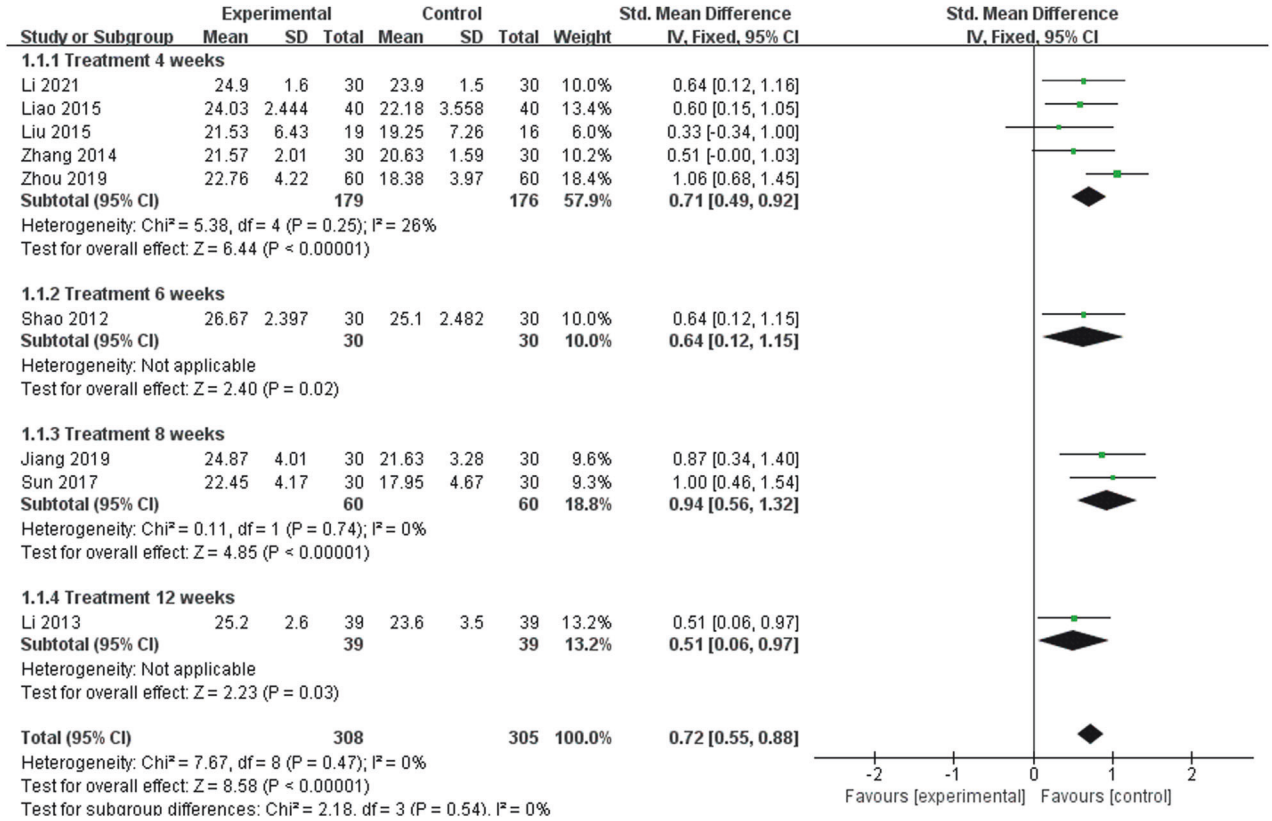

Fig. 4 Meta-analysis in MoCA.

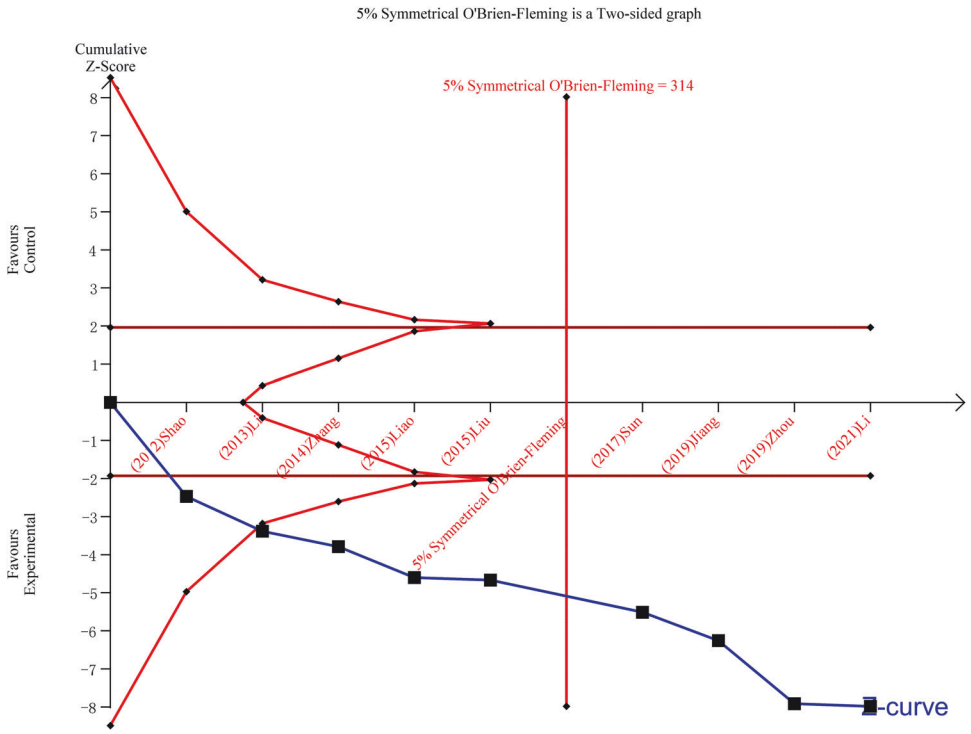

Fig. 5 TSA for MoCA.

EA is an important component of acupuncture and is often used as an adjuvant treatment for VaMCI in clinical practice. However, there is no systematic review of EA as an adjunctive therapy for VaMCI.

Implications for research

The 15 trials included in this study had varying sample sizes, with 12 having low bias during randomization and one reporting allocation concealment. To evaluate the efficacy of EA in treating VaMCI,

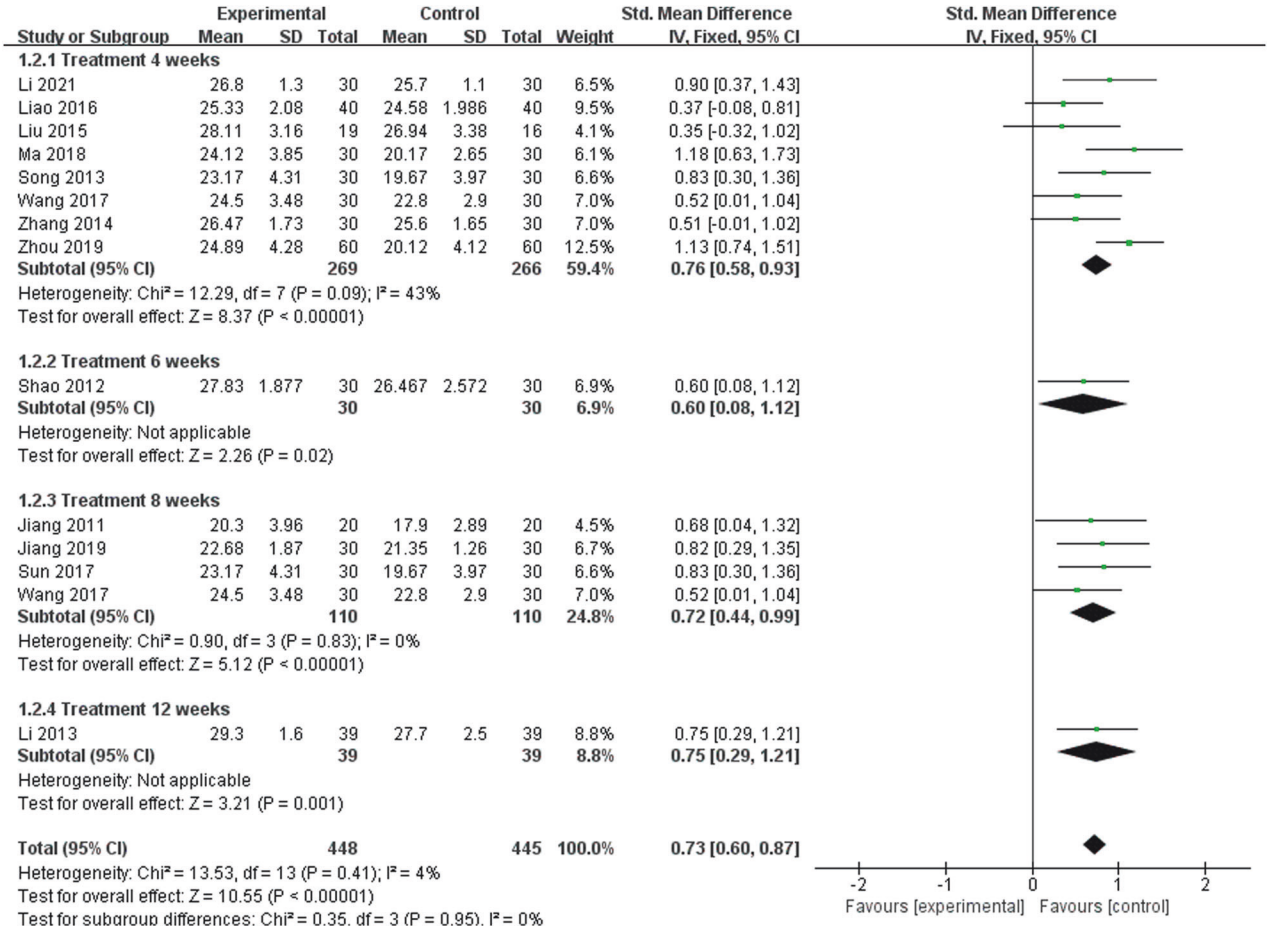

Fig. 6 Meta-analysis in MMSE.

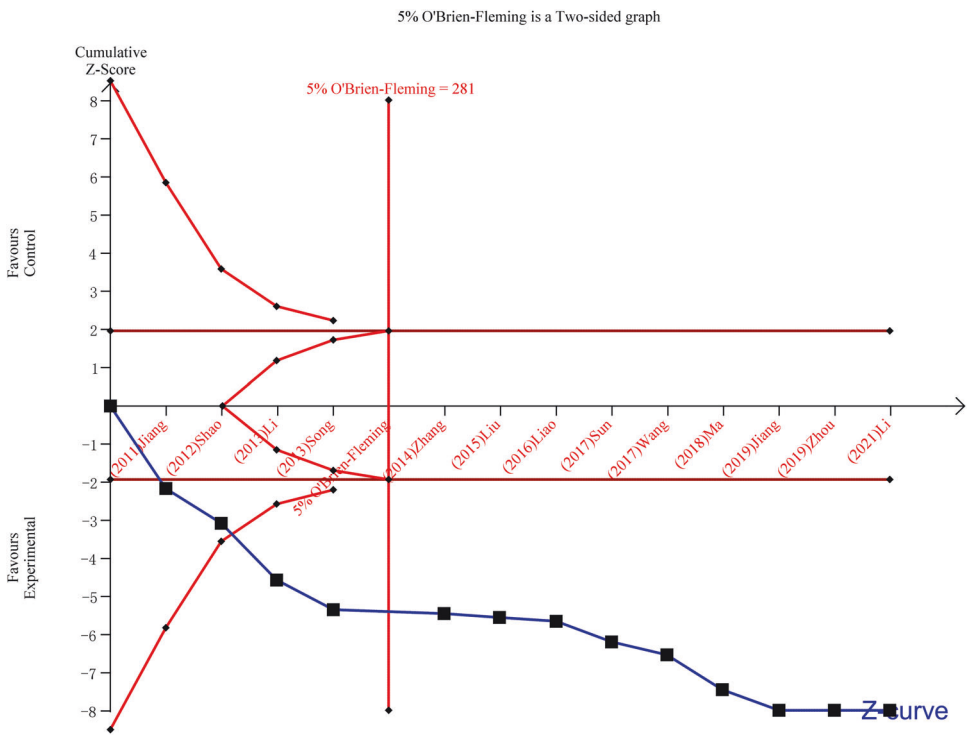

Fig. 7 TSA for MMSE.

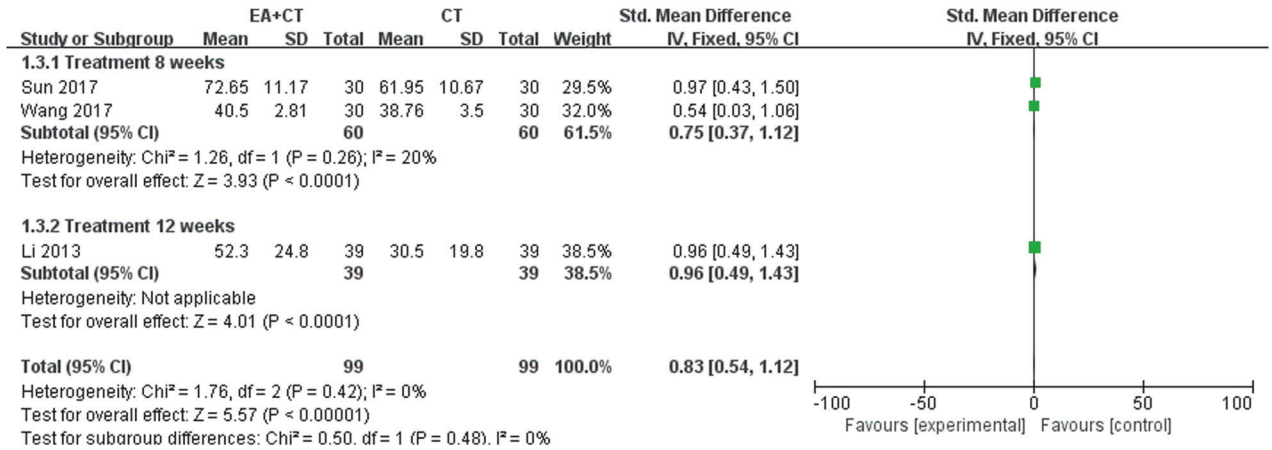

Fig. 8 Meta-analysis in ADL.

future research should prioritize multicenter, high-quality trials. These trials must include detailed information on randomization methods and allocation concealment to ensure rigor. Additionally, future studies should investigate EA's impact on long-term functional outcomes and aim to develop a standardized treatment protocol. Given that most studies are conducted in China, it is essential to perform reliable studies across diverse ethnic groups to assess potential differences in treatment response.

Potential mechanisms of action

Although there is currently limited evidence supporting EA for VaMCI, research is elucidating the mechanisms by which EA alleviates its symptoms. A study using functional magnetic resonance imaging (fMRI) [43] demonstrated that acupuncture at Tai Chong (LR3) and He Gu (LI4) activates specific cognitive-related regions in Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients. A recent study from 2022 [44] showed that acupuncture therapy modulates brain regions in MCI patients. The expression of p70S6 kinase and ribosomal protein S6 plays a significant role in the pathogenesis of vascular dementia (VD). EA was found to increase the expression of these proteins, thereby improving learning and spatial memory in VD rats [45]. Another study revealed that EA enhances spatial learning and memory while suppressing inflammation via the Sirt1/STAT3 pathway in VD rats [46]. Inhibition of miR-219a ameliorates vascular cognitive impairment (VCI) by regulating NMDAR-mediated synaptic plasticity in animal models of cerebral ischemia [47]. Furthermore, EA treatment alleviates cognitive impairment by inhibiting synaptic degeneration and neuroinflammation in a mouse model of AD [48]. Stimulation at GV 20 and GV 24 acupoints may serve as a potential alternative therapy for preventing cognitive deficits in AD by suppressing NLRP3 inflammasome activation [49]. The inhibition of NF-κB-mediated neuronal apoptosis could be one mechanism through which EA at Baihui and Shenting acupoints exerts its therapeutic effects on post-stroke cognitive impairment [50]. EA also increases the expression of BDNF, its high-affinity receptor TrkB, and PSD-95 in the hippocampus of rats with brain ischemia/reperfusion injury [51]. EA stimulation at DU20 and DU14 acupoints has been shown to improve memory deficits and suppress the expression of inhibitory synaptic proteins [52]. Therefore, based on these potential mechanisms of action, EA might be a promising treatment option for VaMCI.

Limitations

The meta-analysis has limitations, including inability to evaluate long-term effects of EA on VaMCI and not evaluating acupoint combinations, limiting its foundation for specific acupoint selection techniques.

CONCLUSION

In conclusion, EA could potentially improve clinical outcomes for people with VaMCI when used as an adjunctive treatment, providing a new therapeutic option. However, the quality of the evidence is limited due to methodological shortcomings and varied treatment protocols. While the TSA supports our findings, more high-quality, diverse RCTs are needed to validate EA's efficacy and safety for VaMCI.

DATA AVAILABILITY

The datasets used in the present review are available from the corresponding author upon reasonable request.

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COMPETING INTERESTS

The authors declare no competing interests.

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