

Acupuncture for amnesic mild cognitive impairment: a meta-analysis of randomised controlled trials

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ABSTRACT

Objective Mild cognitive impairment (MCI) is a pre-dementia state; 5–10% of cases per year will evolve into dementia. MCI can be amnesic (AMCI) or non-amnesic. AMCI is associated with a higher risk of progression. In recent years, interest in acupuncture as a potential treatment for AMCI has grown. The aim of this meta-analysis was to estimate the clinical effectiveness and safety of acupuncture for AMCI.

Methods Randomised controlled trials (RCTs) of acupuncture versus medical treatment for AMCI were identified using the following databases from inception to July 2015: PubMed; Medline; CENTRAL; Chinese Scientific Journal Database; The Chinese Acupuncture Trials Register; China National Knowledge Infrastructure (CNKI); and Wanfang database. Data were extracted from RCTs meeting the inclusive criteria according to Cochrane methods. Meta-analyses were conducted using Rev Man V.5.3 software.

Results Five trials involving 568 subjects were included. Meta-analysis showed that participants receiving acupuncture had better outcomes than those receiving nimodipine with greater clinical efficacy rates (odds ratio (OR) 1.78, 95% CI 1.19 to 2.65; $p < 0.01$), minimal state examination (MMSE) scores (mean difference (MD) 0.99, 95% CI 0.71 to 1.28; $p < 0.01$), and picture recognition score (MD 2.12, 95% CI 1.48 to 2.75; $p < 0.01$). Meta-analysis also showed acupuncture in conjunction with nimodipine significantly improved MMSE scores (MD 1.09, 95% CI 0.29 to 1.89; $p < 0.01$) compared to nimodipine alone. Three trials reported adverse events. Methodological quality of the included studies was judged to be generally poor.

Conclusions Acupuncture appears effective for AMCI when used as an alternative or adjunctive treatment; however, caution must be exercised given the low methodological quality of included trials. Further, more rigorously designed studies are needed.

INTRODUCTION

Dementia is characterised by progressive cognitive decline and is an increasingly common phenomenon within our ageing population.¹ The most common type of dementia is Alzheimer's disease (AD), which accounts for at least half of cases and is a permanent and irreversible disease.² Mild cognitive impairment (MCI) refers to a transitional state between normal ageing and dementia. Around 5–10% of cases of MCI will evolve into dementia per year.^{3–5} As a pre-dementia stage, MCI is defined by a subtle, clinical deterioration in memory performance to a level below that of normal ageing but which does not constitute a clinical diagnosis of dementia.⁵ A Canadian study demonstrated that almost half of patients with MCI will progress to fulfill the diagnostic criteria of dementia after 5 years.⁶ MCI based on memory deficits can be categorised as amnesic (AMCI) and non-amnesic. AMCI is characterised by a decline in memory capacity with retention of largely intact executive functions.⁷ It has been confirmed that AMCI patients have a higher chance of proceeding to AD than those with no such cognitive alterations.⁸ Cognitive impairments and psychological symptoms form an integral part of MCI. To date, no intervention has been proven to prevent conversion to dementia. However, several studies have suggested that acupuncture might be beneficial in MCI.⁹

Traditional Chinese acupuncture has been practised for more than 3000 years. Recent research has reported that acupuncture may be an effective adjunctive therapy for neurological diseases, including stroke,¹⁰ Parkinson's disease,¹¹ vascular dementia,¹² and AD.¹³ In recent years, a number of basic and clinical

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studies have provided evidence that acupuncture is beneficial for the treatment of dementia or MCI.^{14 15} The potential mechanisms of action underlying its putative effects in cognitively impaired patients include enhanced release of neurotrophic factors, reduced oxidative stress and expression of apoptosis-related genes, improved synaptic plasticity, and proliferation and survival of neuronal precursor cells in the hippocampal CA1 and dentate gyrus area.^{16–18}

Although the use of acupuncture for AMCI has attracted growing interest, a comprehensive evaluation of the effect of the acupuncture intervention on behavioural and psychological symptoms of AMCI compared with other treatments is lacking. Therefore, the aim of the present study was to perform a systematic review and meta-analysis of clinical trials of acupuncture for the treatment of patients with AMCI.

METHODS

Inclusion criteria

Randomised controlled trials (RCTs) or quasi-randomised clinical trials evaluating the comparative effectiveness of acupuncture for AMCI were included. Diagnostic criteria were adopted in accordance with the 2006 Chinese expert consensus on cognitive dysfunction¹⁹ and other clinical guidelines.⁵ For a study to be included, patients in the experimental group needed to have received acupuncture (either alone or in conjunction with other treatment modalities) and patients in the control group needed to have been receiving another active treatment. The outcome measurements needed to include at least one authority scale of cognitive assessment such as the Montreal cognitive assessment (MoCA), mini-mental state examination (MMSE), clock drawing task (CDT) or Wechsler memory scale (WMS). There was no limitation placed on language of publication or publication type.

Literature search and study selection

We performed a medical literature search of the following databases from their inception until July 2015: PubMed; Medline; Cochrane Central Register of Controlled Trials (CENTRAL); Chinese Scientific Journal Database; The Chinese Acupuncture Trials Register; China National Knowledge Infrastructure (CNKI); and the Wanfang Database. The key search terms in these databases were as follows: ['mild cognitive impairment' OR 'amnesic mild cognitive impairment' OR 'cognitive impairment' OR 'MCI' OR 'AMCI'] AND ['acupuncture' OR 'meridian' OR 'acupuncture treatment' OR 'acupuncture therapy']. Animal experiments, reviews and duplicate articles were excluded.

Data extraction and quality assessment

Two reviewers (X-FW and MD) independently evaluated the search results, identified studies meeting our

inclusion criteria, and collected the relevant information using a standardised data extraction form, which included the name of the author, year of publication, number of participants, average age of the participants, details of acupuncture treatment, type of control, treatment course, cognitive outcome measurements, adverse effects, and quality of trial design. Risk of bias of the included RCTs was evaluated using the Cochrane criteria.²⁰ Any disagreements regarding methodological quality were resolved by discussion until consensus was reached.

Data synthesis and statistical analysis

The statistical analysis was performed using RevMan V.5.3 (Cochrane Collaboration). Effect estimates for dichotomous data were presented as odds ratios (ORs) with their 95% confidence intervals (CIs) and continuous data were presented as mean differences (MDs) and their 95% CIs. The standard χ^2 test and I^2 test were used to assess the heterogeneity of the data. A random effects model was employed when there was significant heterogeneity, otherwise a fixed effects model was used.

RESULTS

Literature search

Our initial electronic database search identified 215 potential literature citations, from which 34 duplicated articles, 108 animal studies, and six reviews were excluded. Following the initial screening of titles and abstracts, 57 studies were excluded because they were either case reports (two studies), lacked a comparison group (25 studies) or because the trials did not focus on acupuncture therapy for AMCI (30 studies). Ten randomised trials were obtained for full-text assessment. After applying the inclusion criteria, five studies^{14 21–24} were ultimately included in the qualitative synthesis and meta-analysis. A flow diagram of the search strategy is shown in figure 1.

Characteristics of included trials

The five included RCTs were published between 2012 and 2013. The total number of AMCI participants was 568, with 288 patients allocated to the acupuncture group (experimental group) and 280 patients allocated to receive conventional medication, namely nimodipine (control group). Three trials directly compared acupuncture with nimodipine (comparative effectiveness) and two trials examined the role of acupuncture as an adjunct to nimodipine, wherein patients in both groups received medical therapy and were randomised to receiving additional acupuncture or not. The number of participants in each study varied from 26 to 94 and acupuncture treatment was provided three to five times per week for 8 weeks in all but one trial, in which treatment lasted 3 months. All trials used electroacupuncture (EA) (frequency 3–

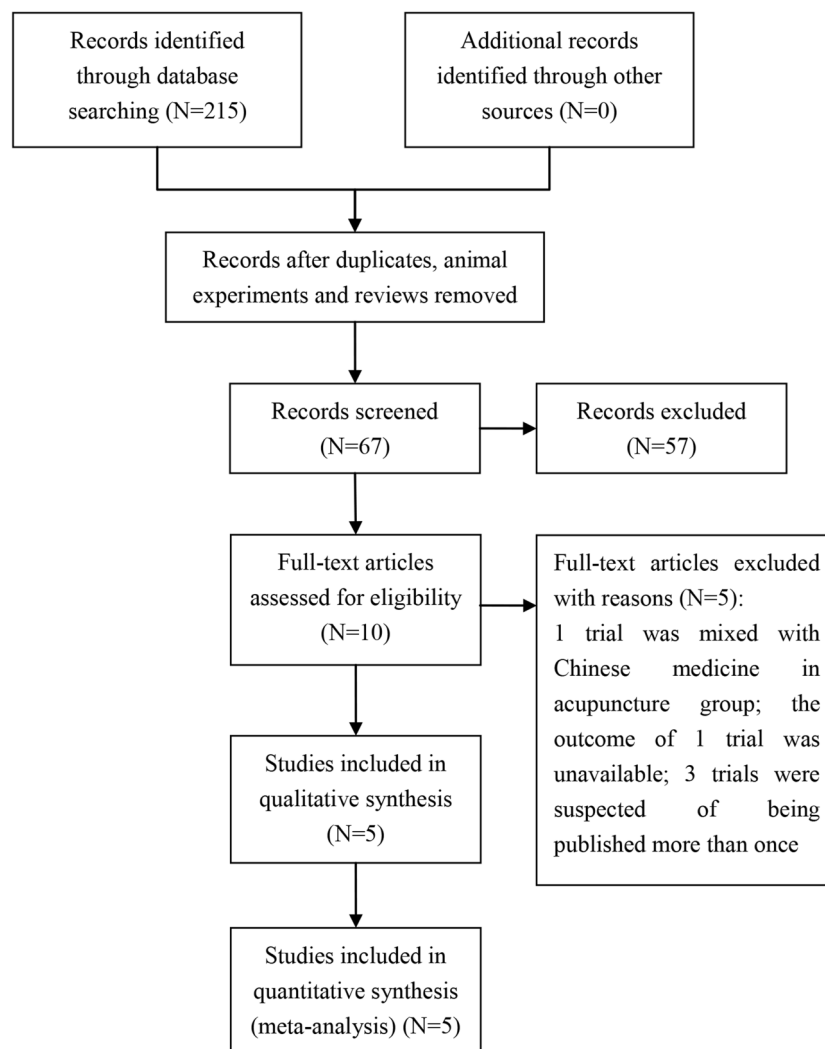


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

15 Hz, intensity 2–4 mA) and each treatment session lasted 30 min. The most frequently used acupuncture points were GV20 (*Baihui*), GB20 (*Fengchi*), GV24 (*Shenting*) and Sishencong. Outcome measures included clinical efficacy rate, MMSE, picture recognition, CDT, MBI (modified Barthel index), and HDS-R (revised Hasegawa dementia scale). Other characteristics of the studies are summarised in [table 1](#).

Methodological quality

All five included studies reported the baseline data of the participants and mentioned random sequence generation. One trial²¹ used a random number table to allocate participants to treatment groups. The sequence generation of another trial²⁴ was based on visiting time point and was therefore considered to only be quasi-randomised. The remaining three trials^{14 22 23} did not describe the method of random sequence generation. No trial mentioned allocation concealment and none used a sham intervention,

therefore blinding of participants or practitioners was not applicable to this review. The methodological quality of each trial is summarised in [figure 2](#).

Acupuncture versus conventional therapy

Three trials^{14 21 22} randomising a total of 403 patients compared acupuncture with nimodipine. Clinical efficacy rate at the end of the treatment was reported in all three trials with no significant heterogeneity ($I^2=0\%$, $p=0.73$, [figure 3A](#)). Meta-analysis demonstrated that the clinical efficacy rate was significantly higher in the acupuncture group compared with the control group (OR 1.78, 95% CI 1.19 to 2.65; $p<0.01$). MMSE at the end of the treatment was also measured in all three trials with minimal heterogeneity ($I^2=5\%$, $p=0.35$, [figure 3B](#)).^{14 21 22} Meta-analysis showed that acupuncture significantly improved MMSE scores relative to the control group (MD 0.99, 95% CI 0.71 to 1.28; $p<0.01$). Picture

Table 1 Characteristics of included studies

Study (first author/year)	Participants, male/female		Mean age (years)		Intervention		Course of treatment		Outcome measures
	E	C	E	C	E	C	E	C	
Zhang 2013 ¹⁴	80 (39/41)	75 (37/38)	71	72	Scalp EA	Nimodipine	30 min, once a day, 3 days for a week, 8 weeks	30 mg/pill, 3 times a day, 8 weeks	MMSE, picture recognition, CDT
Zhao Y 2012 ²¹	26 (12/4)	26 (9/4)	73.35	72.96	Scalp EA	Nimodipine	30 min, once a day, 3 days for a week, 8 weeks	30 mg/pill, 3 times a day, 8 weeks	MMSE, CDT
Zhao L 2012 ²²	94 (46/48)	93 (44/49)	69	67	Scalp EA	Nimodipine	30 min, once a day, 3 days for a week, 8 weeks	30 mg/pill, 3 times a day, 8 weeks	MMSE, picture recognition
Luo 2013 ²³	40	40	Unavailable		Scalp EA plus nimodipine	Nimodipine	30 min, once a day, 3 days for a week, 8 weeks	30 mg/pill, 3 times a day, 8 weeks	MMSE, picture recognition
Li 2012 ²⁴	48 (30/18)	46 (24/22)	68.29	69.22	EA plus nimodipine	Nimodipine	30 min, once a day, 5 days for a week, 3 months	30 mg/pill, 3 times a day, 3 months	MMSE, MBI, HDS-R

C, control group; CDT, clock drawing task; E, experimental group; EA, electroacupuncture; HDS-R, revised Hasegawa dementia scale; MBI, modified Barthel index; MMSE, mini-mental state examination.

recognition at the end of the treatment was measured in two of the trials^{14 22} with 342 patients in total and no significant heterogeneity ($I^2=0\%$, $p=0.56$, figure 3B). Meta-analysis demonstrated that acupuncture improved picture recognition scores compared to the control group (MD 2.12, 95% CI 1.48 to 2.75; $p<0.01$). Finally, two trials^{14 21} included CDT scores; however, one of these¹⁴ did not report CDT results after treatment. The other²¹ reported that patients treated with acupuncture did not significantly increase their CDT scores compared with those of the control group.

Acupuncture as an adjunct to conventional therapy

Two trials^{23 24} evaluated acupuncture as an adjunct to nimodipine. One trial²⁴ reported that patients treated with acupuncture and nimodipine exhibited increased clinical efficacy rate compared to treatment with nimodipine alone (figure 4A). The other²³ showed that patients treated with acupuncture and nimodipine had increased picture recognition scores compared to nimodipine therapy alone (figure 4B). MMSE at the end of the treatment was measured in two trials^{23 24} with 174 patients and moderate heterogeneity ($I^2=49\%$, $p=0.16$, figure 4B). Meta-analysis found that acupuncture combined with nimodipine significantly improved MMSE scores compared to nimodipine therapy alone (MD 1.09, 95% CI 0.29 to 1.89; $p<0.01$).

Adverse events

Three studies^{22–24} reported adverse events in detail. The adverse events associated with acupuncture included errhysis at the needle sites^{23 24} and fainting during treatment.²² Adverse events associated with nimodipine therapy predominantly consisted of gastrointestinal reactions and mild headache.²² Two

studies^{14 21} did not report whether any adverse events or side effects had occurred in the experimental or control groups.

DISCUSSION

Although acupuncture has been used clinically in the management of AMCI in recent years,¹⁴ no systematic review or meta-analysis has been performed to evaluate the effectiveness of acupuncture specifically for this condition. The present study analysed data from five RCTs involving 568 individuals to summarise and evaluate the available evidence on the efficacy and safety of acupuncture therapy for AMCI. All trials used EA in the treatment group. Moreover, the treatment was generally consistent in several other respects, including the number, frequency and duration of the acupuncture sessions, the acupuncture points selected and the comparator groups, all of which might have helped decrease clinical heterogeneity to some extent. Our meta-analysis suggested that acupuncture treatment had a significant effect on clinical efficacy rate compared to a nimodipine control group. Similarly, acupuncture therapy significantly improved MMSE and picture recognition scores compared with nimodipine therapy. Overall, our meta-analysis suggests that acupuncture was a useful therapy in improving cognitive function for patients with AMCI. It also suggested that acupuncture was effective when used as an adjunctive treatment to nimodipine for AMCI. However, these seemingly positive findings must be interpreted cautiously due to the low methodological quality of the included RCTs. Furthermore, in this review, only three of five studies mentioned adverse events. The side effects of the treatment group were acupuncture point errhysis and fainting during acupuncture treatment, while those of the nimodipine control group

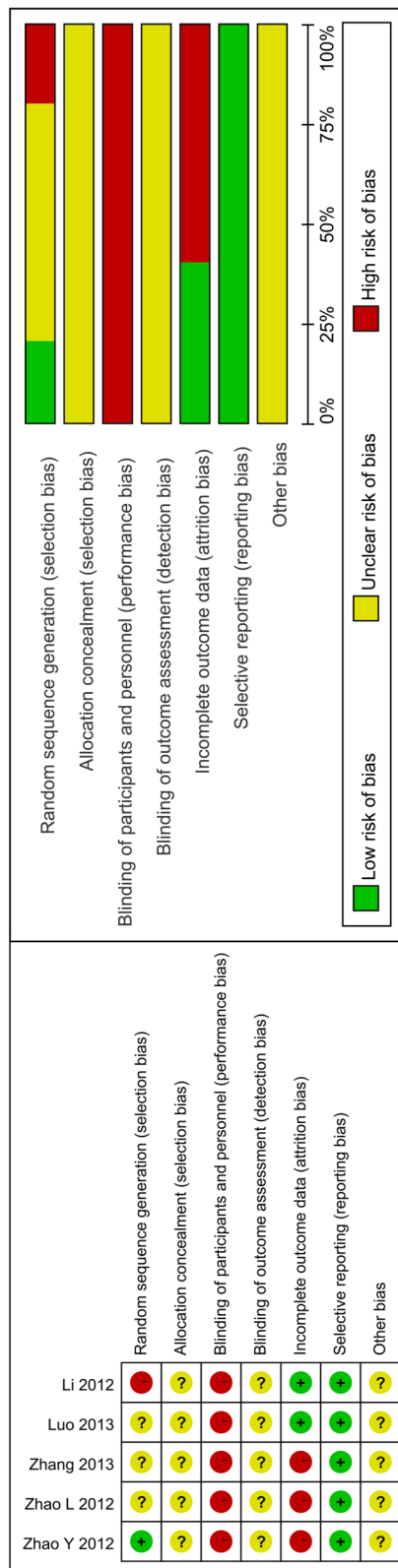


Figure 2 Risk of bias summary of included studies.

included gastrointestinal reaction and mild headache. The two other RCTs did not report on adverse events or side effects at all. Thus, although the existing literature on acupuncture suggests that it is a relatively safe

treatment modality, conclusions regarding the safety of acupuncture therapy specifically for AMCI cannot be reached.

The methodological quality of the included studies was judged to be generally poor because there was high or unclear risk of bias. Three of the five RCTs included in this meta-analysis mentioned random sequence generation, but failed to describe concretely the way in which it was achieved. The random sequence generation of one trial was performed according to visiting time points, which is not considered true randomisation. No study reported allocation concealment or blinding assessment. The suboptimal methodological quality of the primary data (poor internal validity) unavoidably inhibits a robust evaluation of the effectiveness of acupuncture for AMCI.

There were several potential limitations of this review. Although one trial was published in English, all included RCTs were conducted in China, which might implicate publication bias.²⁵ Chinese patients may have a preference for acupuncture treatment over medical intervention, and the design of the included studies did not control for potential placebo effects. Therefore, rigorous clinical studies in Western settings should be considered before extrapolating the results to other populations. Future trials should also take placebo effects into consideration in order to provide evidence of a specific effect of acupuncture.^{26, 27} The sample populations of included studies in this meta-analysis were small, with >100 patients recruited in only two of the five trials. Additionally, differences in acupuncture practitioners might introduce deviations in the effect size attributable to acupuncture therapy.

Given the methodological limitations of the current evidence base, we would recommend that future clinical trials should be conducted more rigorously and be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement²⁸ for RCTs and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines²⁹ for acupuncture studies. Allocation concealment and blinding of outcome assessors should be applied, and the type of randomisation and acupuncture procedures should be described in detail. Although acupuncture therapy is generally well tolerated, a condition-specific safety evaluation should also be rigorously carried out and reported in future trials.

In conclusion, the results of this meta-analysis suggest that acupuncture therapy has a significant positive effective on cognitive and memory function in patients with AMCI compared with nimodipine alone. The results also show that acupuncture is effective as an adjunctive treatment to nimodipine for AMCI. Due to the small number of available RCTs and the relatively poor methodological quality of the available evidence, further rigorously-designed studies

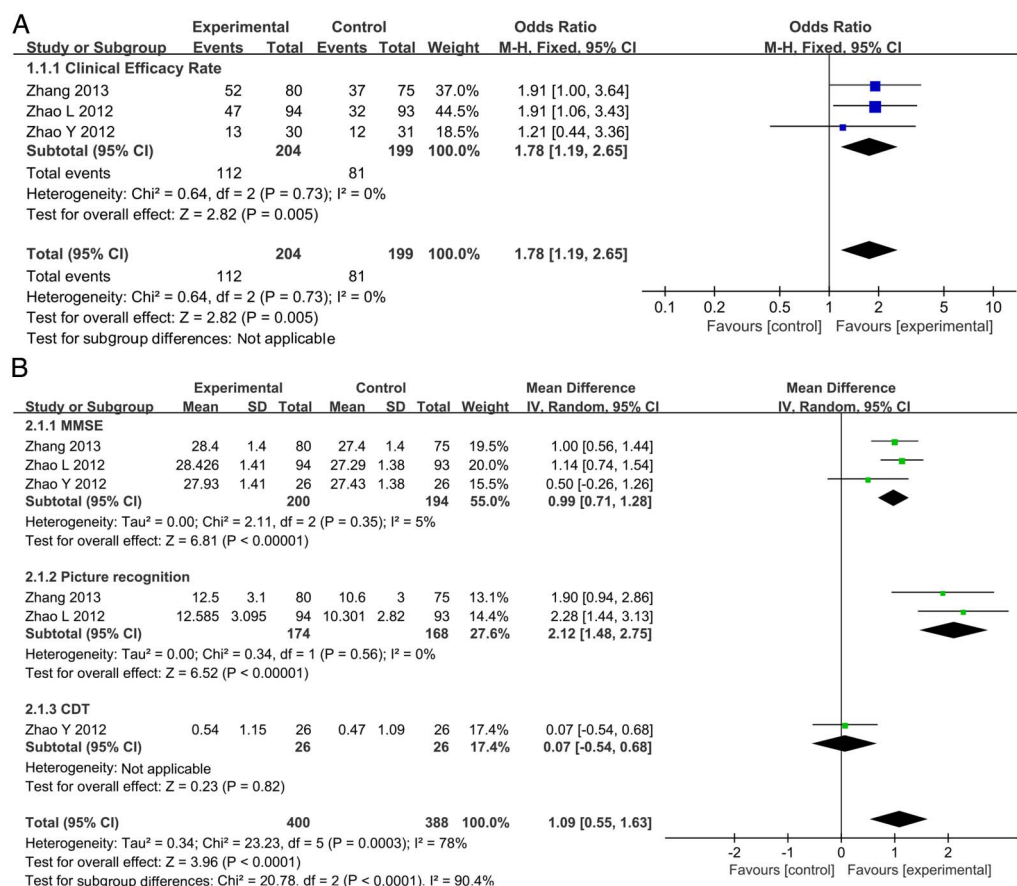


Figure 3 Forest plot of acupuncture (experimental group) versus nimodipine (control group) for treatment of amnesic mild cognitive impairment. MMSE, mini-mental state examination; CDT, clock drawing task.

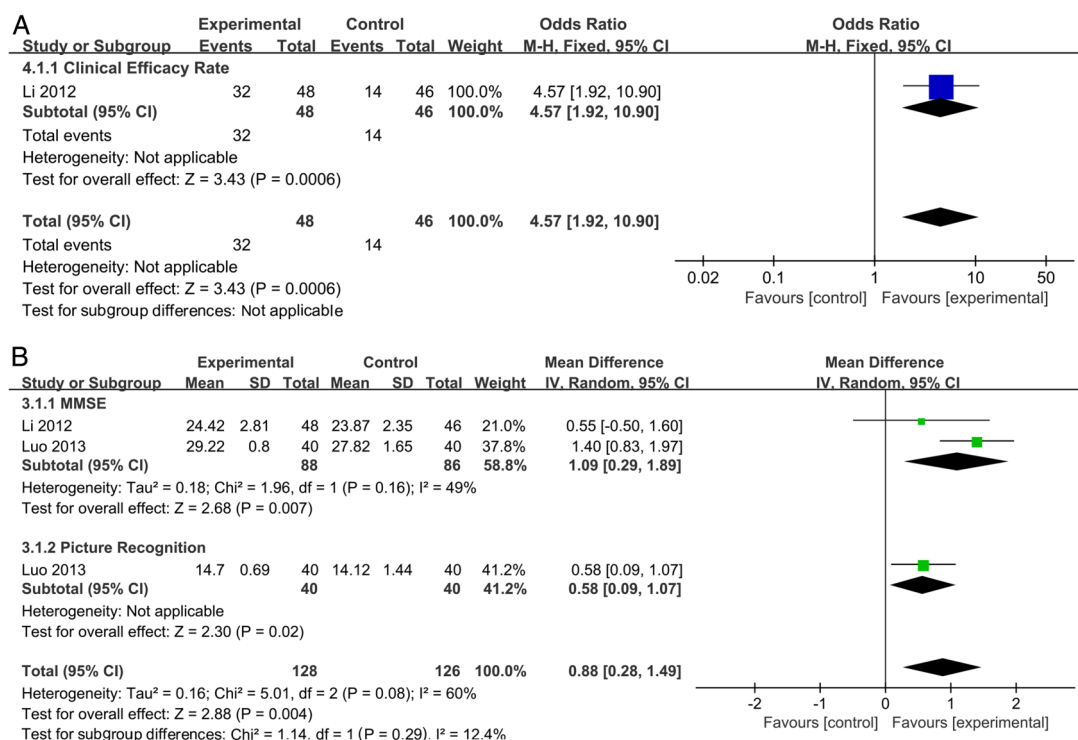


Figure 4 Forest plot of acupuncture plus nimodipine (experimental group) versus nimodipine alone (control group) for treatment of amnesic mild cognitive impairment. MMSE, mini-mental state examination.

with large samples are needed to evaluate systematically the effectiveness and safety of acupuncture therapy for AMCI patients.

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Competing interests None declared.

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REFERENCES

- Cunningham EL, McGuinness B, Herron B, *et al.* Dementia. *Ulster Med J* 2015;84:79–87.
- Alzheimer's Association. 2015 Alzheimer's disease facts and figures. *Alzheimers Dement* 2015;11:332–84.
- Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009;119:252–65.
- Petersen RC, Doody R, Kurz A, *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985–92.
- Gauthier S, Reisberg B, Zaudig M, *et al.* Mild cognitive impairment. *Lancet* 2006;367:1262–70.
- Wentzel C, Rockwood K, MacKnight C, *et al.* Progression of impairment in patients with vascular cognitive impairment without dementia. *Neurology* 2001;57:714–6.
- McKhann GM, Knopman DS, Chertkow H, *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from The National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
- Han Y, Wang J, Zhao Z, *et al.* Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnesic mild cognitive impairment: a resting-state fMRI study. *Neuroimage* 2011;55:287–95.
- Cao H, Wang Y, Chang D, *et al.* Acupuncture for vascular mild cognitive impairment: a systematic review of randomised controlled trials. *Acupunct Med* 2013;31:368–74.
- Ernst E, Lee MS. Acupuncture during stroke rehabilitation. *Stroke* 2010;41:e549; author reply e50.
- Joh TH, Park HJ, Kim SN, *et al.* Recent development of acupuncture on Parkinson's disease. *Neurol Res* 2010;32 (Suppl 1):5–9.
- Zhang X, Wu B, Nie K, *et al.* Effects of acupuncture on declined cerebral blood flow, impaired mitochondrial respiratory function and oxidative stress in multi-infarct dementia rats. *Neurochem Int* 2014;65:23–9.
- Rong P, Liu A, Zhang J, *et al.* An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. *Chin Med J* 2014;127:300–4.
- Zhang H, Zhao L, Yang S, *et al.* Clinical observation on effect of scalp electroacupuncture for mild cognitive impairment. *J Tradit Chin Med* 2013;33:46–50.
- Gu W, Jin XX, Zhang YJ, *et al.* Clinical observation of Alzheimer's disease treated with acupuncture. *Zhongguo Zhen Jiu* 2014;34:1156–60.
- Hwang IK, Chung JY, Yoo DY, *et al.* Effects of electroacupuncture at Zusanli and Baihui on brain-derived neurotrophic factor and cyclic AMP response element-binding protein in the hippocampal dentate gyrus. *J Vet Med Sci* 2010;72:1431–6.
- Zeng BY, Salvage S, Jenner P. Effect and mechanism of acupuncture on Alzheimer's disease. *Int Rev Neurobiol* 2013;111:181–95.
- Liu F, Jiang YJ, Zhao HJ, *et al.* Electroacupuncture ameliorates cognitive impairment and regulates the expression of apoptosis-related genes Bcl-2 and Bax in rats with cerebral ischaemia-reperfusion injury. *Acupunct Med* 2015;33:478–84.
- Group CDP. A consensus of cognitive dysfunction prevention from the experts in China. *J Intern Med* 2006;45:171–3.
- Higgins J, Altman D, Sterne J. Assessing risk of bias in included studies. In: Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. Chichester, DC: The Cochrane Collaboration and John Wiley & Sons Ltd 2011:187–235.
- Zhao Y, Zhang H, Zhao L. Observations on the efficacy of electric scalp acupuncture in treating mild cognitive impairment. *J Sichuan Tradit Chin Med* 2012;30:112–14.
- Zhao L, Zhang FW, Zhang H, *et al.* Mild cognitive impairment disease treated with electroacupuncture: a multi-center randomized controlled trial. *Zhongguo Zhen Jiu* 2012;32:779–84.
- Luo Z, Zheng LQ, Li H, *et al.* Efficacy of combined treatment of drugs and electric acupuncture on cognitive function of patients with mild cognitive impairment. *Chin Med Herald* 2013;10:118–20.
- Li W, Cheng YH, Yu XG. Observation on therapeutic effect of acupuncture combined with medicine on mild cognition disorders in patients with post-stroke. *Zhongguo Zhen Jiu* 2012;32:3–7.
- Vickers A, Goyal N, Harland R, *et al.* Do certain countries produce only positive results? A systematic review of controlled trials. *Controlled clinical trials* 1998;19:159–66.
- Williams N, Lawler D, Dilworth P. It's all in the mind! Or is it? Positive acupuncture responses in patients with dementia: a series of case reports. *Acupunct Med* 2014;32:186–9.
- Benedetti F. Can low placebo responsiveness in dementia be exploited in clinical trials? *Acupunct Med* 2014;32:98–9.
- Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
- MacPherson H, Altman DG, Hammerschlag R, *et al.* Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med* 2010;7:e1000261.