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Effectiveness of Acupuncture for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis*

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Summary: Acupuncture has reportedly improved memory and cognitive impairment in both animal and clinical studies. It may be an effective treatment for Alzheimer's disease (AD). The purpose of this meta-analysis was to review the effectiveness of acupuncture for the treatment of AD. Eight databases were searched for articles published up to and including July 2017, and 13 studies fulfilling the inclusion criteria were identified. The main outcomes assessed were clinical efficacy rate, Mini-Mental State Examination score, Ability of Daily Living Scale score, Alzheimer's Disease Assessment Scale-Cognition score, Hasegawa's Dementia Scale (HDS) score, and adverse events. The methodological quality of the articles was assessed using Cochrane's risk of bias. All the studies compared the efficacy of acupuncture with that of medication, and were published in Chinese journals. Meta-analysis revealed that acupuncture yielded positive results as determined via all the indexes scored except the HDS (95% CI –0.26 to 0.90, Z=0.35, P=0.73). Only one of the studies reported adverse events associated with acupuncture and medication. The rate of adverse events in the medication group was 13%. In most of the studies assessed in the current meta-analysis, acupuncture alone was better than conventional western medicines for the treatment of AD.
Key words: acupuncture; medication; meta-analysis; systematic review

Dementia is a syndrome involving deterioration in cognitive function, memory, comprehension, thinking, calculation, orientation, language, and judgment[1]. It has become one of the most prevalent conditions influencing daily function of contemporary populations[1], affecting approximately 46 million people in 2015[2] and accounting for 1.7 million deaths in 2013, twice more than that in 1990[3]. The most common cause of dementia is Alzheimer's disease (AD), which accounts for up to 70% of the cases, followed by cases of mixed AD and vascular dementia (approximately 25%)[1, 4].

Studies investigating the pathogenesis of AD are abundant. The most commonly proposed neurobiological mechanisms involve cholinergic activity, glutamatergic neurotransmission, amyloid peptide, tau protein, oxidative stress, and calcium[5]. Of these, the function of cholinergic neurons has demonstrated a close relationship with cortical structures involved in memory and execution[6]. Deficiency of cholinergic neurons in the basal forebrain, prefrontal cortex, and hippocampus reportedly plays a unique role in the severity of dementia[6–8]. N-methyl-D-aspartate receptors mediate neuronal signaling, affect neural transmission, and are involved in neuronal plasticity, survival, and memory processes[9]. Excessive stimulation of these receptors leads to neuronal damage or death, and results in many neurological diseases[10]. Therefore, most evidence-based guidelines for the treatment of AD have generally recommended the use of acetylcholinesterase inhibitor and the N-methyl-D-aspartate receptor antagonist[11–13]. However, the benefit of these medications may be minor[14–16] and the need for special care increases the family burden[17]. Hence, some patients choose complementary and alternative medicine to treat AD in an effort to improve quality of life and limit cognitive decline[18, 19].

Acupuncture, which has been demonstrated to be effective for improving memory and cognition in animal experiments[18, 20], has been commonly used clinically in China for years. Two systematic reviews

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on the treatment of AD with acupuncture were reported several years ago[21, 22]. However, the interventions investigated in these two reviews were complex and the sample sizes were small. They do not conclusively clarify the effectiveness of acupuncture in this context. In the past 2 years, some new studies investigating the use of acupuncture alone to treat AD have been published. In order to better assess the effectiveness of acupuncture for the treatment of AD, we conducted a meta-analysis assessing the current evidence available pertaining to the utilization of acupuncture for the treatment of AD.

1 MATERIALS AND METHODS

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

1.1 Data Sources and Search Strategy

Reports that described randomized controlled trials of acupuncture for the treatment of AD were obtained. We used Medical Subject Headings (MeSH) and the keywords AD, RCTs (an abbreviation for "randomized controlled trials"), and different spellings of acupuncture, including electroacupuncture, scalp needle, and acupuncture treatment. The following electronic databases were searched from inception up to July 2017: PubMed, Medline, Embase, the Cochrane Library, Clinical trials and Chinese Biomedicine Literature, China National Knowledge Infrastructure, Chinese Scientific Journals Database, and Wan Fang Med Online. Relevant references from published studies were also searched manually. No language restrictions were imposed. To locate appropriate studies in the Pubmed data-base, we used the following search constructs: ("Random*" OR "Randomized Controlled Trial" OR "RCT") AND ("electroacupuncture" OR "scalp needle" OR "Acupuncture Therapy" OR "Acupuncture Treatment" OR "acupuncture" OR "acupunct*") AND ("Alzheimer Disease" OR "senile dementia of Alzheimer type" OR "Alzheimer Dementia" OR "Presenile Dementia" OR "AD" OR "Alzheim*"). This search strategy was modified as appropriate for other databases.

1.2 Inclusion and Exclusion Criteria

The following criteria were applied when research reports were selected to be included in the analysis: Research subjects were patients with a definite diagnosis of AD as determined via the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association[23], the Clinical Dementia Rating[24], the Diagnostic and Statistical Manual of Mental Disorders, 4th text version[25], or the International Classification of Diseases[26]. In terms of interventions, intervention group received acupuncture only; control group received sham acupuncture treatment, western medicine, placebo, no treatment, physical therapy, or any interventions except for the treatments listed below in the exclusion criteria.

Exclusion criteria were as follows: (1) Studies that only compared two different forms of acupuncture, or compared the effectiveness of different acupoints or different amounts of stimulation; (2) studies that compared acupuncture to Chinese herbs, because the effects of Chinese herbs are individualized and their efficacy is unclear; (3) studies that did not report sufficient clinical data to enable meaningful comparisons; (4) studies in which the participants were receiving any treatment for AD other than the acupuncture intervention or the specified control treatment; (5) studies with inadequate randomization; (6) animal studies.

1.3 Outcomes

1.3.1 Efficacy Rate Clinical efficacy was categorized as cured, markedly effective, effective, or ineffective. The ability of acupuncture to improve the score of clinical symptoms and signs of AD compared to the score before treatment in a patient without other interventions was deemed to indicate effectiveness. In cases where clinical symptoms and signs were not ameliorated or got worse, acupuncture was deemed ineffective. We merged "cure", "markedly effective", and "effective" to calculate effectiveness rate.

1.3.2 Mini-Mental State Examination (MMSE) Score The MMSE is a brief neuropsychological test for evaluating cognitive impairment[27]. It consists of 20 questions including 30 items. The highest score is 30 points. Less than 27 points is considered to indicate dementia.

1.3.3 Activities of Daily Living (ADL) Scale The ADL scale[28] includes 10 items, and the highest possible score is 100 points. Zero point indicates that daily living is completely dependent on others, and 100 points means "normal". Below 40 points indicates severely compromised ADL function, 41–60 points moderately compromised ADL function, and ≥61 points mildly compromised ADL.

1.3.4 Alzheimer's Disease Assessment Scale-Cognition (ADAS-cog) The ADAS-cog is the most widely used general cognitive measure in clinical trials of AD[29, 30]. It consists of 12 items, and the score range is 0–75 points where higher scores indicate greater cognitive impairment.

1.3.5 Hasegawa's Dementia Scale (HDS) HDS[31] consists of 11 items, and it has become one of the most widely used tools for evaluating AD. A total of 32.5 points was divided into four thresholds in the current study: dementia ≤10.0 points, suspicious dementia 10.5–21.5 points, borderline AD state 22.0–30.5 points,

and normal ≥31.0 points.

1.4 Data Extraction and Assessment of Quality

Citations were merged together in Endnote X7 (Clarivate Analytics, USA) to facilitate management. Eligible trials identified from search results were screened by two reviewers (Qi HUANG and Li CHEN) independently and verified by another reviewer (Feng-xia LIANG). Two reviewers (Qi HUANG and Li CHEN) compiled a table listing the general study characteristics (*e.g.,* study name, diagnosis, participant number, intervention method, randomization method, main outcome measures, and adverse events). Missing data were obtained from the authors via emails or phone calls. In cases of multiple reports of the same study, data were extracted from a full journal article if the majority of information could be obtained from that report. In cases of duplicate publication, the earliest publication was chosen.

Each study's risk of bias was evaluated via the Cochrane Risk of Bias scale, which considers blinding, sequence generation, allocation concealment, and other aspects pertaining to bias[32]. Those assessments were conducted independently by two reviewers (Qi HUANG and Li CHEN). Any discrepancies between reviewers during the above processes were resolved via discussion, or the opinion of a third reviewer (Rui CHEN). The search did not include unpublished reports or conference abstracts because detailed methods were needed to assess study quality.

1.5 Statistical Analysis

All statistical analyses were conducted using the STATA 12.0 package (Statacorp, College Station, USA). For trials comparing two different forms of acupuncture to other interventions, the two different forms of acupuncture were grouped together via a formula for combining groups described in the Cochrane Handbook[33]. Data were reported using relative risk (RR) and corresponding 95% confidence interval (CI) for binary outcomes or mean difference (MD) with 95% CI for continuous outcomes. Studies were evaluated for statistical heterogeneity by estimating the variance with Cochran's Q test and the I^2 statistic[34]. We considered I^2 <30% low statistical heterogeneity, ≥30% to <50% moderate heterogeneity, ≥ 50% to <75% substantial heterogeneity, and ≥75% considerable heterogeneity[33]. A fixed-effect model was used when I^2 was < 50%. Otherwise, a randomized effect model was used. Subgroup analysis was performed by different interventions in control groups in order to investigate heterogeneity. Sensitivity analysis was conducted via the leave-one-out method. If there were enough studies, potential publication bias was to be explored by using funnel plotting or meta-regression analysis. Binary outcomes were detected via Harbord's test, and for continuous outcomes Egger's tests were used. P<0.05 was considered statistically significant.

2 RESULTS

2.1 Study Selection and Study Characteristics

We found 18 studies that satisfied our inclusion criteria, but 2 were deemed to contain insufficient data[35, 36]. We attempted to contact the corresponding authors to request data that were missing from their publication, but one was unable to be contacted[35] and the other did not respond[36]. We also found 3 studies that were part of clinical trials, but no results were reported. Ultimately, 13 studies were identified that provided all the data needed for the analysis. A PRISMA flowchart is shown in fig. 1, and details of the studies included are shown in table 1.

All studies (100%) were published in Chinese Journals and compared acupuncture to medication. Nine studies (69%) were two-arm trials, 1 (8%) was a three-arm trial involving a group in which acupuncture plus western medicine was given, and 3 (23%) were analyzed as multi-arm trials with four different comparisons. Of the multiple comparisons of interventions, we extracted the data from groups that were appropriate for the review objective and excluded unrelated groups. Seven (54%) of these studies compared acupuncture to donepezil, 3 (23%) compared it with nimodipine, 2 (15%) compared it with piracetam, and 1 (8%) compared it with almitrine. As main outcomes, 12 (92%) studies assessed efficacy rate, 11 (85%) MMSE results, 8 (62%) ADL, 4 (31%) HDS scores, and 3 (23%) ADAS-cog scores.

A total of 750 cases were included in the 13 studies. Ten of these studies reported the average age of the subjects, while the other three[37–39] reported the age range of the subjects. However, the three studies described that there was no significant difference in the average age between the intervention groups (P>0.05), but they did not adequately descript their statistical analyses. The overall mean age of the subjects in the remaining 10 studies was 69.5 years. The duration of treatment ranged from 4 weeks to 16 weeks, and in 6 trials (46%) the subjects were treated for 12 weeks. Only 1 (8%)[40] of the 13 studies reported adverse events.

2.2 Assessment of Risk of Bias in the Included Studies

Table 2 shows the overall quality of the studies included in the final analysis based on Cochrane's risk of bias. All the studies reported randomization. Eight[38, 40–46] reported the use of a random number table. None of the 13 studies mentioned allocation concealment. One[39] reported blinding but did not describe the procedure in detail. Only one[40] indicated that there were dropouts in both intervention groups, but intention-to-treat analysis was not used. One[47] reported follow-up outcomes after 12 weeks of the treatment, but dropout data were not mentioned. Two

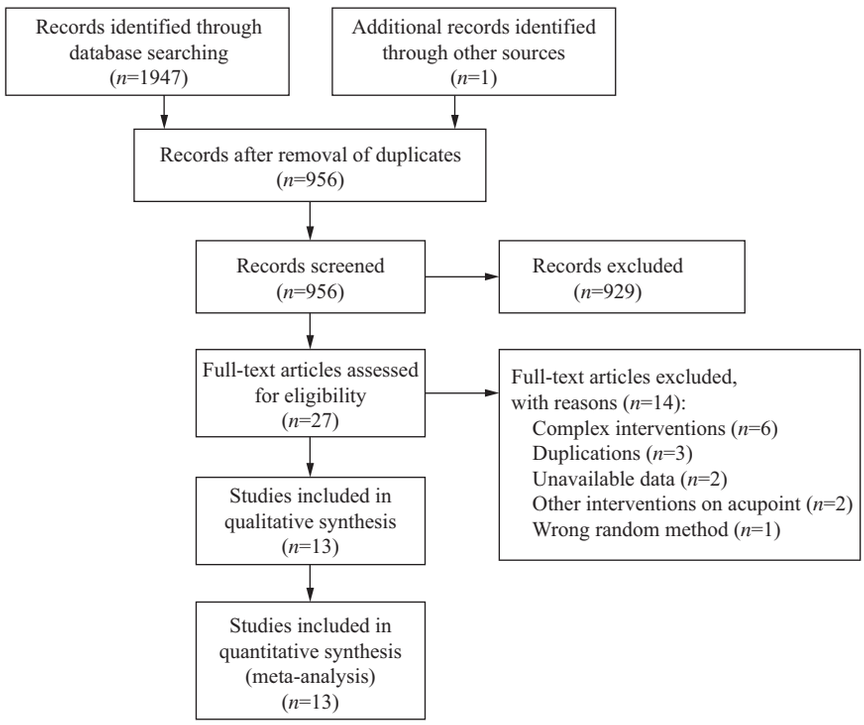


Fig. 1 PRISMA flow diagram of the study selection process

Table 1 Main characteristics of included studies

Studies	Participants EG/CG	Course of intervention	Intervention			Main Outcomes
			EG	CG	OG	
Zhao *et al* (2007)[37]	16/16	8 weeks	Acupuncture (40 min, once daily)	Nimodipine (20 mg, three times a day)	N	MMSE, ADL, FAQ, HDS, efficacy rate
Zhu *et al* (2010)[38]	20/20	12 weeks	Acupuncture (30 min, once daily)	Donepezil (5 mg once daily)	Chinese herbs; acupuncture plus Chinese herbs	MMAE, efficacy rate
Jia *et al* (2010)[39]	25/26	16 weeks	Acupuncture (once daily)	Piracetam (1.2 g, three times a day)	N	MMSE, ADL, efficacy rate
Gu *et al* (2014)[40]	72/69	12 weeks	Acupuncture (30 min, once daily, 6 times/week)	Donepezil (5 mg, 4 weeks later changed to 10 mg once daily)	N	MMSE, ADL, DS, ADAS-cog
Wang *et al* (2015)[41]	36/36	10 weeks	Electroacupuncture (30 min, once daily, 6 times/week)	Donepezil (5 mg, 4 weeks later changed to 10 mg once daily)	N	MMSE, MBI, efficacy rate
Liu *et al* (2008)[42]	40/40	4 weeks	Acupuncture (60 min, once daily, 5 times/ week)	Duxil (40 mg, twice a day, 5 times/once week)	N	MMSE, HDS, efficacy rate
Ke *et al* (2014)[43]	32/32	12 weeks	Acupunncture (40 min, once daily, 6 times/week)	Donepezil (5 mg once daily)	N	MMSE, ADL, SDSD, efficacy rate
Lin *et al* (2016)[44]	30/30	12 weeks	Acupunture (30 min, once daily, 5 times/week)	Donepezil (5 mg once daily)	Acupunture plus donepezil	MMSE, ADAS-cog, ADL, efficacy rate
Liu *et al* (2015)[45]	20/20	12 weeks	Acupuncture (40 min, once daily)	Donepezil (5 mg once daily)	Chinese herbs; acupuncture plus Chinese herbs	Efficacy rate
Zhu *et al* (2014)[46]	40/40	12 weeks	Acupuncture (30 min, once daily)	Piracetam (1.4 g, three times a day)	N	CDR, efficacy rate
Lin *et al* (2014)[47]	18/18	8 weeks	Electroacupuncture (30 min, once daily, 6 times/week)	Donepezil (5 mg once daily)	N	MMSE, ADAS-cog, ADL, efficacy rate
Ou *et al* (1999)[48]	16/14	8 weeks	Acupuncture (30 min, once daily, 6 times/week)	Nimodipine (20-40 mg, three times a day)	N	HDS, ADL,WMS, efficacy rate
Li *et al* (2002)[49]	37/14	8 weeks	Acupuncture (30 min, once daily, 6 times/week)	Nimodipine (20-40 mg, three times a day)	Chinese herbs; acupuncture plus Chinese herbs	HDS, MMSE, ADL, efficacy rate

EG: experiment group; CG: control group; OG: other intervention group; N: No; MMSE: Mini Mental State Examination; ADL: ability of daily living; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognition; HDS: Hasegawa's Dementia Scale; FAQ: Functional Activities Questionnaire; MBI: Modified Barthel Index; SDSD: Sydrome Differentiation Scale for Dementia; DS: Digit Span; CDR: Clinical Dementia Rating

studies[43, 44] described expected outcomes in their study design and included the relevant results in their report. One[48] indicated that the outcomes of Wechsler Memory Scale testing were not reported due to poor patient compliance and insufficient data. In general, for the majority of the studies the risk of bias was deemed to be unclear (table 2).

2.3 Outcome of Interventions

2.3.1 Efficacy Rate Twelve studies[37–39, 41–49] evaluated efficacy, involving acupuncture *vs*. donepezil (6 trials)[38, 41, 43–45, 47], acupuncture *vs*. nimodipine (3 trials)[37, 48, 49] acupuncture *vs*. piracetam (2 trials)[39, 46] and acupuncture *vs*. almitrine (1 trial)[42]. Based on collective results from all the relevant studies, there was a significant difference in MMSE scores between the acupuncture groups and the other treatment groups (RR=1.17, 95% CI 1.06–1.29, Z=3.2, P=0.001). The I^2 value was 0% (P=0.496). However, the differences in efficacy for acupuncture *vs*. nimodipine (RR=0.97, 95% CI 0.73–1.3) and acupuncture *vs*. almitrine (RR= 1.03, 95% CI 0.8–1.34) were not statistically significant (fig. 2A).

2.3.2 MMSE Ten trials[37–44, 47, 49] reported cognitive assessment using MMSE scores, and a statistically significant difference was found between acupuncture and medication (MD=1.96, 95% CI 0.66–3.26, Z=2.96, P=0.003). Forest plotting suggested that acupuncture was associated with better cognitive performance. Significant heterogeneity existed between studies (I^2=98.9%, P<0.01). Comparisons of acupuncture *vs*. nimodipine (MD=–0.58, 95% CI –1.4–2.56) and acupuncture *vs*. almitrine (MD=–0.16, 95% CI –0.74 to 0.42) did not yield statistically significant differences (fig. 2B).

2.3.3 ADL Eight trials[37, 39, 40, 43, 44, 47–49] reported changes in ADL scores after treatment. Meta-analysis suggested that acupuncture improved ADL scores compared to medication (MD=1.99, 95% CI 0.65–3.34, Z=2.9, P=0.004). However, there was no significant difference between acupuncture and nimodipine (MD=0.41, 95% CI –1.22–2.04). As for MMSE, high heterogeneity existed between the studies with regard to ADL (I^2=97.8%, P<0.01) (fig. 3A).

2.3.4 ADAS-cog Three trials[40, 44, 47] compared acupuncture with donepezil and reported superior effects of acupuncture with regard to ADAS-cog scores (MD=3.56, 95% CI 1.1–6.03, Z=2.84, P=0.005). The I^2 value was 97.9% (P<0.001) (fig. 3B).

2.3.5 HDS Four studies[37, 42, 48, 49] reported that there was no significant difference in HDS score between acupuncture and medication, including nimodipine and almitrine (MD=–0.17, 95% CI –0.26–0.90, Z=0.35, P=0.728). The I^2 value was 90.1% (P<0.001) (fig. 3C).

2.4 Adverse Events

The reporting of adverse events was inadequate in almost all of the studies included in the analysis. Only one[40] described them. That study reported spot-bleeding and pain in the acupuncture group, and varying degrees of reduced appetite, nausea, diarrhea, and insomnia in the medication group. The incidence of adverse events in the medication group was 13% (9 cases).

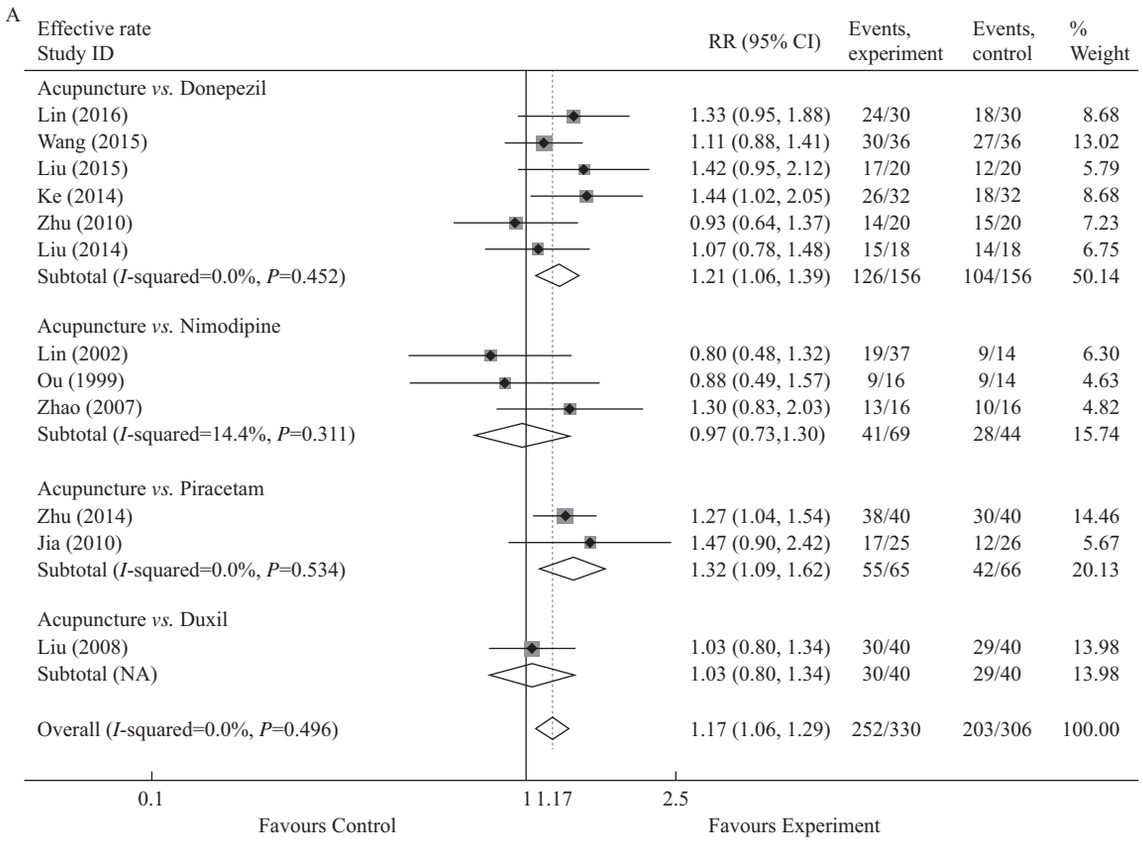
2.5 Sensitivity and Heterogeneity Analysis

Apart from the efficacy rate, significant heterogeneity between the studies in the analysis was found (fig. 2A and 2B, fig. 3A–3C). Subgroup analyses in terms of year of publication, intervention duration, sample size, different gender and intervention (data not shown), and excluding experiments with more than 2 controls (data not shown) revealed no significant effect of these parameters on between-study heterogeneity (table 3). Electroacupuncture and acupuncture did not show significant differences in efficacy rate, MMSE scores and ADL scores. Sensitivity analysis indicated that the observed results could not be attributed to a single study (fig. 4A), with the exception of ADAS-cog scores. The leave-one-out analysis showed that a key factor in the heterogeneity was one study conducted by Lin *et al*[47] (MD=2.28, 95% CI 1.58–2.98) (fig. 4B). After excluding that study, the heterogeneity was

Table 2 Bias assessment of RCTs by Cochrane Risk of Bias

Study	RM	AC	Blinding	Follow-up	Selective reporting	Other bias
Zhao *et al* (2007)[37]	U	U	U	U	U	U
Zhu *et al* (2010)[38]	Y	U	U	U	U	U
Jia *et al* (2010)[39]	U	U	U	U	U	U
Gu *et al* (2014)[40]	Y	U	U	U	U	U
Wang *et al* (2015)[41]	Y	U	U	U	U	U
Liu *et al* (2008)[42]	Y	U	U	U	U	U
Ke *et al* (2014)[43]	Y	U	U	U	Y	U
Lin *et al* (2016)[44]	Y	U	U	U	Y	U
Liu *et al* (2015)[45]	Y	U	U	U	U	U
Zhu *et al* (2014)[46]	Y	U	U	U	U	U
Lin *et al* (2014)[47]	U	U	U	N	U	U
Ou *et al* (1999)[48]	U	U	U	U	N	U
Li *et al* (2002)[49]	U	U	U	U	U	U

RM: randomization method; AC: allocation concealment; Y: yes (Low risk of bias); U: unclear; N: no (high risk of bias)



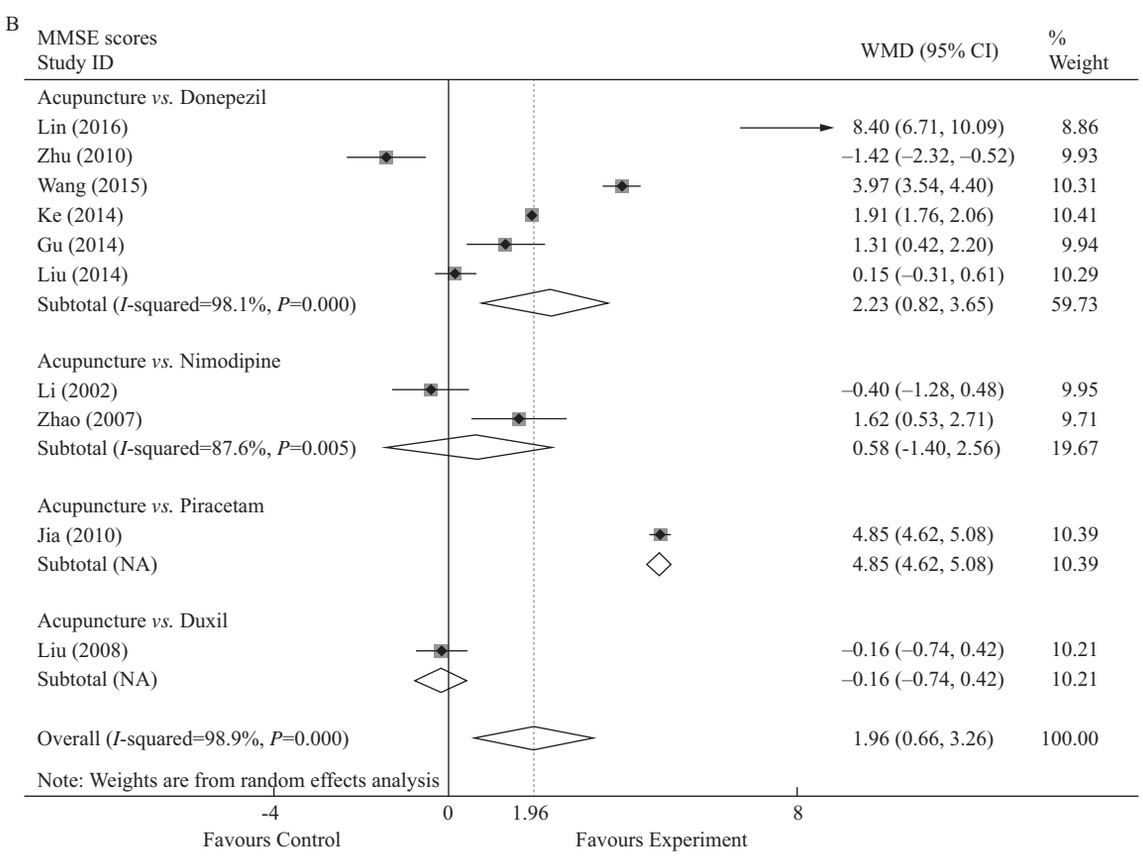


Fig. 2 A: meta-analysis of the efficacy rate of acupuncture *versus* that of medication for Alzheimer's disease; B: meta-analysis of Mini-Mental State Examination scores in trials assessing acupuncture *versus* medication for Alzheimer's disease

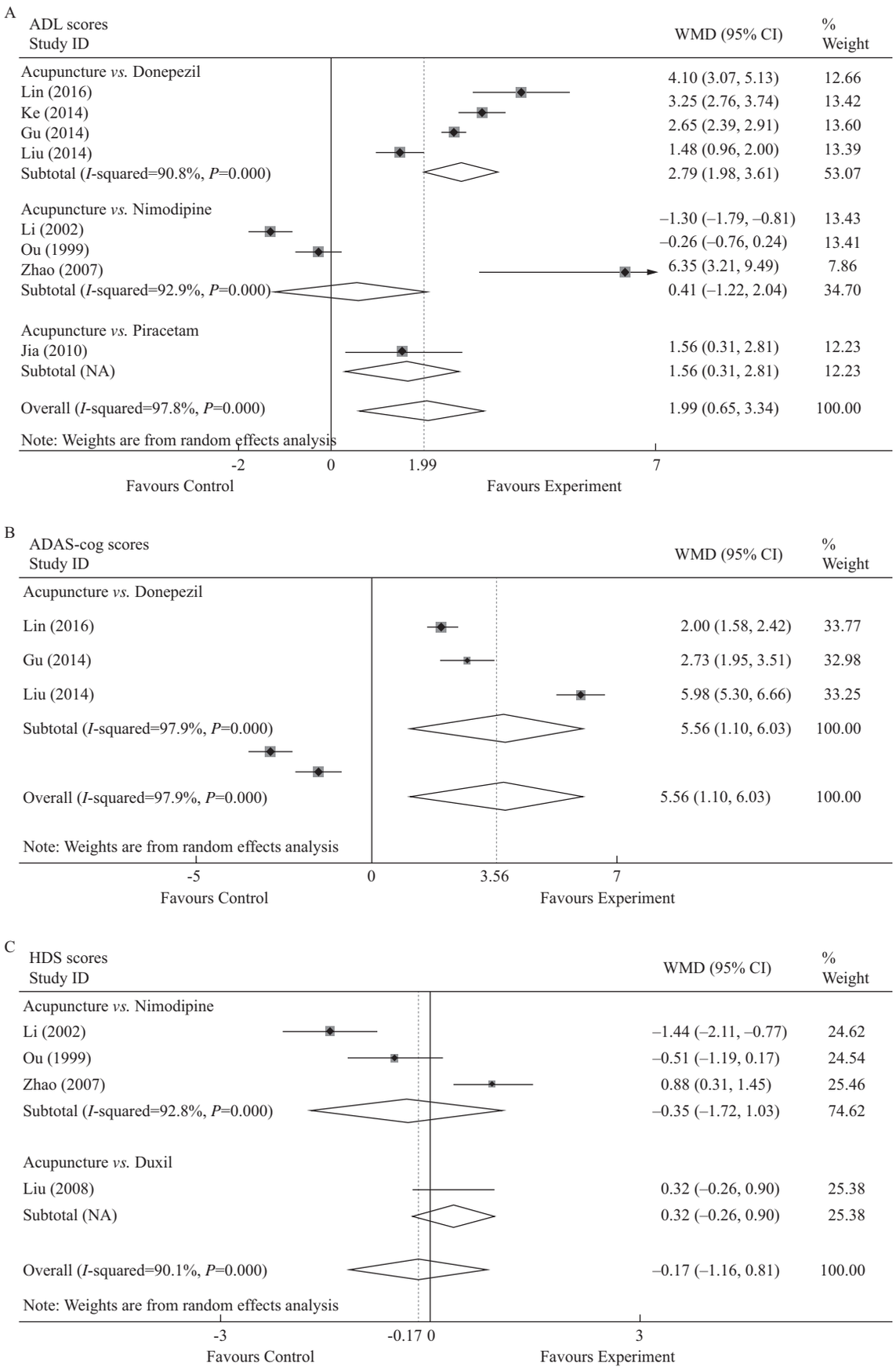


Fig. 3 A: meta-analysis of Activities of Daily Living scores in trials assessing acupuncture *versus* medication for Alzheimer's disease; B: meta-analysis of Alzheimer's Disease Assessment Scale-Cognition scores in trials assessing acupuncture *versus* donepezil for Alzheimer's disease; C: meta-analysis of Hasegawa's Dementia Scale scores in trials assessing acupuncture *versus* medication for Alzheimer's disease

Table 3 Subgroup analysis and investigation of heterogeneity

Subgroup	Outcome	Factors	Number of Studies	Effective size MD(95% CI)	Test for effect *P*-value	Heterogeneity I^2
Publish year	MMSE	Before 2010	5[37–39, 42, 49]	0.91 (–2.13, 3.94)	0.558	98.0%
		After 2010	5[40,41, 43, 44, 47]	2.93 (1.48, 4.38)	0.000	99.2%
	ADL	Before 2010	4[40, 43, 44, 47]	0.77 (–0.73, 2.28)	0.314	92.5%
		After 2010	4[37, 39, 48, 49]	2.79 (1.98, 3.61)	0.000	90.8%
	HDS	Before 2005	2[48, 49]	–0.98 (–1.89, –0.07)	0.036	72.5%
		After 2005	2[37, 42]	0.60 (0.05, 1.15)	0.031	45.7%
	ADAS-cog	2014	2[40, 47]	4.36 (1.18, 7.55)	0.007	97.4%
		2016	1[44]	2.0 (1.58, 2.42)	0.000	NA
Duration of intervention	MMSE	4 week	1[43]	1.91 (1.76, 2.06)	0.000	NA
		8-12 week	4[37, 38, 42, 49]	–0.13 (–1.15, 0.90)	0.809	83.3%
		≥12 week	5[39–41, 44, 47]	3.65 (1.52, 5.77)	0.001	99.0%
	ADL	4 week	1[43]	3.25 (2.76, 3.74)	0.000	NA
		8-12 week	3[37, 48, 49]	0.41 (–1.22, 2.04)	0.623	92.9%
		≥12 week	4[39, 40, 44, 47]	2.43 (1.49, 3.37)	0.000	89.1%
Sample size	MMSE	≥50	7[39–44, 49]	2.75 (1.24, 4.27)	0.000	99.1%
		<50	3[37, 38, 47]	0.09 (–1.31, 1.48)	0.900	89.1%
	ADL	≥50	5[39, 40, 43, 44, 49]	2.04 (0.20, 3.88)	0.030	98.3%
		<50	3[37, 47, 48]	1.71 (–0.16, 3.57)	0.073	94.3%
	HDS	≥50	2[42, 49]	–0.55 (–2.28, 1.17)	0.531	93.4%
		<50	2[37, 48]	0.20 (–1.16, 1.56)	0.775	89.4%
	ADAS-cog	≥50	2[40, 44]	2.29 (1.59, 2.99)	0.000	61.9%
		<50	1[47]	5.98 (5.30, 6.66)	0.000	NA
Different intervention	Efficacy rate	Acupuncture	10[37–39, 42–46, 48–49]	1.19 (1.07, 1.33)	0.002	7.8%
		Electroacupuncture	2[41, 47]	1.10 (0.91, 1.33)	0.341	0.0%
	MMSE	Acupuncture	8[37–44, 49]	1.94 (0.40, 3.49)	0.014	99%
		Electroacupuncture	2[41, 47]	2.06 (–1.68, 5.80)	0.281	98.9%
	ADL	Acupuncture	7[37, 39–40, 43–44, 48–49]	–0.95 (–2.76, 0.86)	0.303	98.6%
		Electroacupuncture	1[47]	–1.48 (–2.0, –0.96)	0.00	NA

NA: not available

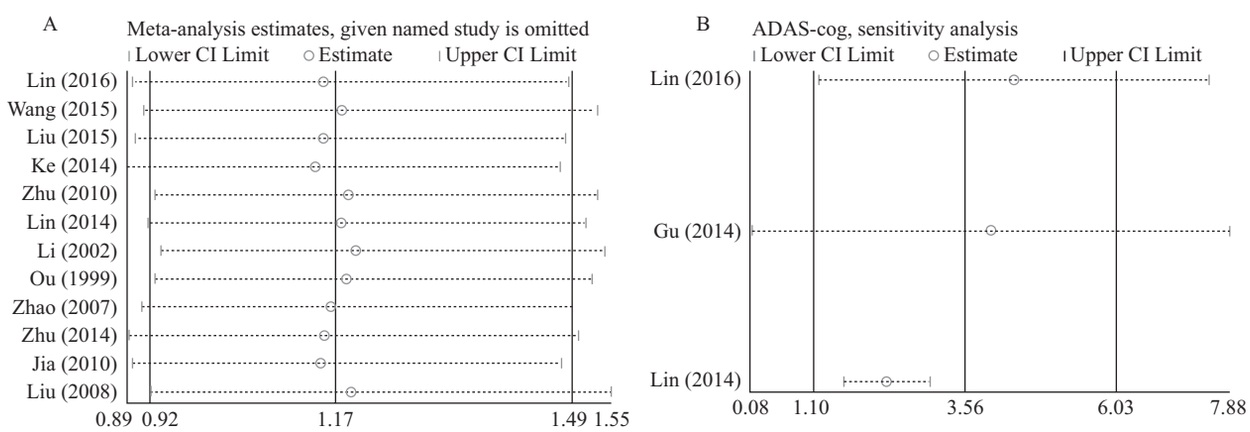


Fig. 4 A: sensitivity analysis of efficacy rate; B: sensitivity analysis of Alzheimer's Disease Assessment Scale-Cognition scores

reduced to I^2=61.9%. This may have been related to the small sample size of that study (18 cases in each group). Notably, the pooled changes were not altered, which demonstrated that the results were robust. Hence, potential sources of heterogeneity could not be determined from a clinical perspective. It may have been caused by the risks of bias or by the studies' designs.

2.6 Publication Bias

Egger's regression test and Harbord's test were used to assess publication bias. According to these tests, there was no evidence of significant publication bias for either of the parameters that could be reliably assessed, which were efficacy rate (t=–0.54, P=0.602) (fig. 5A) and MMSE (t=–0.54, P=0.606) (fig. 5B). The small numbers of studies involving ADL, ADAS-cog,

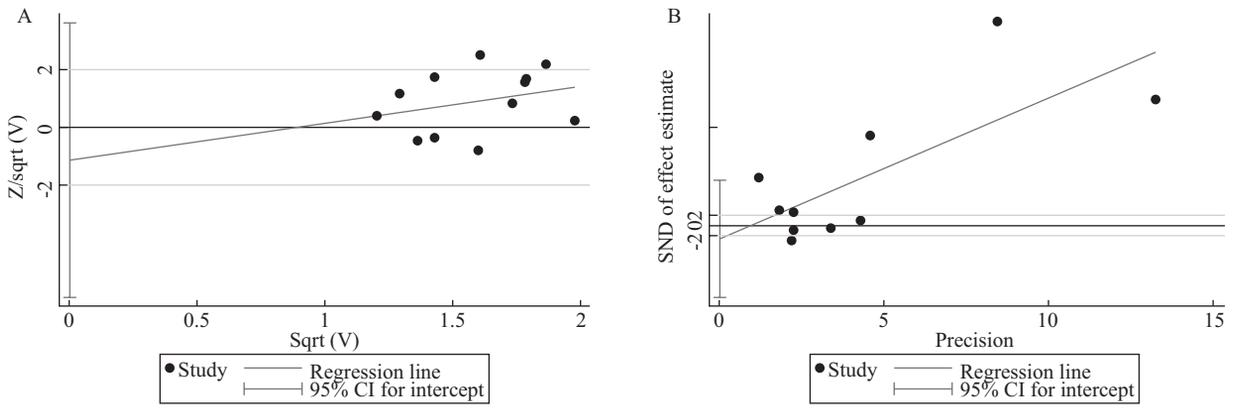


Fig. 5 A: funnel plot with pseudo 95% CIs to assess publication bias of efficacy rate (Harbord's test for publication bias, 95% CI= –5.8905 to 3.5990, *P*=0.602); B: funnel plot with pseudo 95% CIs to assess publication bias of Mini-Mental State Examination scores (Egger's test for publication bias, 95% CI=–14.3596 to 8.9342, *P*=0.606).

and HDS rendered the assessment of publication bias for those parameters unviable.

3 DISCUSSION

Our meta-analysis suggested significant superiority of acupuncture over medication therapy with regard to efficacy rate, MMSE scores, ADL scores, and ADAS-cog scores, but not HDS scores. The studies that examined HDS scores involved comparisons of acupuncture with nimodipine and almitrine. However, in the efficacy rate, MMSE scores and ADL scores, no evidence improved with acupuncture as well between the comparisons of acupuncture with nimodipine. Only one trial compared acupuncture with almitrine, and it concluded that acupuncture was not better than almitrine with regard to efficacy rate, MMSE scores, ADL scores, or HDS scores. Two studies compared efficacy rate between piracetam and acupuncture, only one study compared piracetam and acupuncture via MMSE and ADL scores, and a positive result for acupuncture was reported. "Meta-analysis" is not possible based on a single RCT however. With regard to acupuncture *vs.* donepezil, the collective results yielded a statistically significant positive effect of acupuncture. In subgroup analysis, we found that the efficacy of acupuncture treatment was superior to that of medication in studies reported since 2010. Additionally, there was no significant efficacy of acupuncture for AD in studies with sample sizes <50, or durations of intervention of 8–12 weeks.

Donepezil is a medication used in the palliative treatment of AD and recommended by the British Association for Psychopharmacology[50]. Evidence suggests that cholinesterase inhibitors should not be stopped in view of associated cognitive and functional benefits[50], but nimodipine, piracetam, and almitrine are not listed in the guidelines[50]. In the studies included in our meta-analysis, acupuncture was reportedly more effective than donepezil. However, all the results should be interpreted with caution because none of the trials included in the meta-analysis were methodologically rigorous. Due to their poor quality, it was not possible to draw firm conclusions about the efficacy of acupuncture for the treatment of AD. Additionally, the relative safety of acupuncture and medication could not be determined due to either poor descriptions, or a complete lack of descriptions in this regard.

Compared with a meta-analysis performed in 2009[21], the current analysis included more studies. Under similar literature quality conditions, the results of our analysis showed that the efficacy of acupuncture was superior to that of medication, which is contrary to the conclusion drawn in the 2009 analysis[21]. Compared with a systematic review in 2015[22], the current analysis not only included more studies, but also excluded studies with multiple interventions, which is arguably better with regard to understanding the efficacy of acupuncture. In addition, the current study conducted subgroup analyses based on different drugs, in an effort to clarify the efficacy of acupuncture *vs.* specific drugs. We incorporated effective rate funnel plotting, publication bias, sensitivity analysis, and other factors and analyzed the efficacy of acupuncture more scientifically and comprehensively.

Nevertheless, there are some limitations in the current meta-analysis. (1) All the studies included were published in Chinese journals, and thus there may have been publication bias due to Chinese cultural considerations. (2) In risk of bias analyses, most of the studies in the meta-analysis were classified as "unclear" in most domains. The majority did not describe details of the randomization method utilized, allocation concealment, or blinding, which may have led to performance bias, selective bias, and detection bias. Consequently, the authenticity of the results is questionable. (3) Substantial heterogeneity between

studies was detected in most respects, with I^2 values ranging from 0% to 99.2%. This may have caused expansion of the confidence intervals and led to false results. (4) The number of participants in most studies was very low, ranging from 30 to 141, upon which powerful evidence for a given result cannot be based.

Due to the improper design of the studies and their low quality, we could not perform an intention-to-treat analysis. Due to the existence of high heterogeneity, we could not completely rule out the source, so the results may be biased. Although the quality of the clinical trials was poor, in animal experiments acupuncture treatment of AD has been repeatedly confirmed[51–62]. Electro-acupuncture significantly increased neuroblast plasticity by elevating the levels of brain-derived neurotrophic factor and phosphorylated cyclic AMP response element-binding protein in the dentate gyrus of Wistar rats[52, 53]. It also reportedly preserved neuronal mitochondrial integration and decreased the levels of amyloid β (Aβ) plaques in the hippocampus in mice thereby improving learning-memory capacity[55, 57, 59]. Some studies also suggest that acupuncture stimulation at a specific acupoint improves the cognitive function of mice, and this may be related to the stimulation of neurogenesis potential in learning and memory and the reversion expression profiles of age-related genes[51, 54]. Additionally, acupuncture reportedly improves learning and memory deficits by reversing reduced acetylcholine neurotransmission, improving synaptic transmission, and decreasing oxidative damage in the hippocampus in AD rats[56, 60, 62]. In functional brain images of AD patients, acupuncture can increase the activity of the temporal lobe and prefrontal lobe, which are related to memory and cognitive function[58, 61]. Although only a small number of cases have been reported, they represent an extension of acupuncture research from animal models to human subjects. Future studies should adhere to rigorous participation reporting standards including correct randomization, appropriate blinding measures, clear allocation concealment, and a predetermined estimate of sample size.

Although the current meta-analysis suggested that acupuncture was more effective than donepezil and piracetam in the context of AD therapy, the quality of the studies included was too poor to give firm conclusions. All the trials included were conducted in China, so the findings could not be generalized. High-quality RCTs comparing acupuncture and medication for AD therapy are non-existent. It is too early to claim the superiority of acupuncture over medication for the treatment of AD. Rigorously designed large-scale trials are urgently needed. Trials comparing acupuncture with a placebo or no treatment as control interventions are also needed. Lastly, the long-term adverse effects of acupuncture should be critically assessed.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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