Acupuncture and Related Therapies for the Cognitive Function of Alzheimer's Disease: A Network Meta-Analysis

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Abstract

Background: Acupuncture and acupuncture-related therapies are effective for Alzheimer's disease (AD), therefore, we aimed to compare and rank the interventions that mainly focus on acupuncture-related therapies in the treatment of patients with mild to moderate AD.

Methods: We used network meta-analysis to evaluate the direct and indirect evidence shown in randomized controlled trials of AD. The data were analyzed using RavMan manager, Stata, and WinBUGS software after two researchers independently screened the literature, extracted the data, and assessed the risk of bias in the included studies.

Results: We analyzed a total of 36 eligible studies, including 2712 patients, involving 14 types of acupuncture-related therapies and comprehensive therapies. For Mini-Mental State Examination (MMSE), acupuncture (ACU) combined with cognitive and memory training (Training) was more effective than ACU, ACU+Chinese herb (CH), ACU+Donepezil (DON), CH, DON, DON+Nimodipine (NIM), Music therapy (Music), NIM, Placebo, and Training ($P<0.05$), while ACU+CH was batter than CH ($P<0.05$), and ACU+DON+NIM was better than DON+NIM ($P<0.05$). For Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-cog), ACU was more effective than DON and placebo ($P<0.05$). For Activities of Daily Living (ADL), ACU+DON was better than CH, DON, NIM, and Placebo ($P<0.05$). For the clinical effectiveness rate, ACU, ACU+CH, ACU+CH+DON, ACU+CH+DON+NIM, ACU+DON, CH, NIM were all more effective than DON+NIM ($P<0.05$), while ACU and ACU+CH were better than DON ($P<0.05$). The comprehensive ranking results show that ACU+training and ACU have the highest ranking probability.

Conclusion: ACU+Training and ACU may be the best therapies to improve the cognitive function of patients with mild to moderate AD, while the combination of acupuncture-related therapies and other therapies has a higher overall benefit.

Keywords: Acupuncture; Alzheimer's disease; Cognitive function; Network meta-analysis

Introduction

Alzheimer's disease (AD), mainly characterized by progressive memory and cognitive decline, can have a great effect on patients' daily living ability. According to the latest report from the Alzheimer's Association, the number of patients with AD has increased year by year, and nearly one million new cases will be added each year by 2050 (1). Notably, it has been more than a hundred years since AD was first discovered, however, it remains one of the world's biggest challenges (2). AD accounts for 80% of all types of dementia and is one of the main threats to the health of older people. Age is the most relevant risk factor besides genetic factors, with most sporadic AD patients' onset after the age of 65 (3). Gender is another important risk factor for the onset of AD. The meta-analysis shows that the prevalence of dementia is 19% to 29% higher in females than in males (3). In addition, vascular factors (such as cardiovascular disease, hypertension, hyperlipidemia, etc.) and unhealthy lifestyles are also important factors affecting the development of AD. And because of that, AD has become one of the most important medical and social problems in the world under the trend of global aging (4, 5). Currently, cholinesterase inhibitors are preferred as clinical drug therapies to alleviate symptoms, although they carry a high rate of adverse reactions (6-8). Although the National Medical Drugs Administration of China has conditionally approved the marketing of the mild to moderate AD drug Oligomannate (GV-971), the existing evidence does not fully demonstrate the pharmacological mechanism, long-term safety and efficacy of GV-971, and further experimental and clinical research evidence is still needed to support the feasibility of its clinical promotion (9).

In China, acupuncture has a long history of use in the treatment of brain diseases, and there is abundant evidence that acupuncture has satisfactory efficacy in the treatment of vascular dementia, Parkinson's disease, depression, and other diseases. In recent years, a series of basic and clinical studies have shown the potential of acupuncture in the treatment of AD. Results from recent systematic reviews and meta-analysis have shown that acupuncture may effectively improve the cognitive function of patients with AD (10-13). However, due to the wide variety of acupuncture therapies, we still lack comparative studies between the different acupuncture therapies.

In this study, we used a network meta-analysis to compare the efficacy of various therapies compared with acupuncture-related therapies for AD, in order to provide evidence-based medical evidence for selecting the best choice to improve the cognitive function in patients with mild to moderate AD.

Methods

This study was conducted following the preferred reporting items for systematic reviews and meta-analyses for network meta-analysis (PRISMA-NMA) checklist (14). The PRISMA-NMA checklist has revised 11 NMA-related items based on the 27 items in the PRISMA checklist and added 5 new items to guide and improve the writing and reporting of NMA (15).

Literature Retrieval

Our literature search was performed from database establishment until Feb 25, 2021, using the following databases: PubMed, Embase, the Cochrane Library, the Web of Science, the China Biology Medicine (CBM), the China National Knowledge Infrastructure (CNKI), Wanfang Data, and the Chinese Scientific Journal Database (VIP). The search was conducted using a combination of medical subject headings (MeSH) terms and free words.

Inclusion Criteria

For our analysis, we screened published clinical randomized controlled trial (RCT) involving acupuncture-related therapies for AD patients regardless of age or gender, clearly diagnosed with

mild to moderate AD by specific clinical guidelines (i.e., the American Psychiatric Association Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-R) (16), as well as the diagnostic criteria formulated by the Alzheimer's Association and National Institute on Aging (NIA-AA) (17) and operational criteria for the diagnosis of AD (OCDAD) (18), among other relevant clinical guidelines). Interventions include pharmacological therapies such as donepezil (DON), nimodipine (NIM), and Chinese Herbs (CH), or non-pharmacological therapies such as acupuncture and acupuncture-related therapies (ACU), music therapy (Music), cognitive or memory rehabilitation training (Training), or the combination of the above therapies. At least one of the following outcome indicators was included: Primary Outcome: Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-cog), Secondary Outcome: Activities of Daily Living (ADL) and Effectiveness Rate.

Exclusion Criteria

In our analysis, we excluded: ①Non-randomized controlled trials; ②No clear diagnostic criteria and/or efficacy evaluation criteria; ③Other types of dementia, such as vascular dementia; ④Without sufficient and/or clear original data; or ⑤Repeated studies and/or studies reporting the same results.

Two researchers, ZH and TJ, independently conducted the literature screen, data extraction, and cross-check. In any case of disagreement, they would discuss to reach a consensus or a third researcher, CY would assist in the final determination. A unified table was used for data extraction, which included: ①basic information (e.g., first author's name, publication year, among others); ②the baseline characteristics from each intervention group (e.g., sample size, age); ③intervention parameters (e.g., types of acupuncture, frequency, duration of treatment); and ④outcome indicators.

Our two researchers, JL and YW, evaluated the included studies following the bias risk assessment tool recommended on Cochrane Handbook 5.1 (19). Including seven parts: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

Statistical Analysis

STATA (ver. 15.0), RavMan manager (ver. 5.3), and WinBUGS (ver. 1.4.3) software were used in our statistical analysis (20, 21). The effectiveness rate was categorically variable, risk ratio (RR) with 95% confidence intervals (CI) was used. However, the MMSE, ADAS-cog, and ADL scores were numerical variables, standard mean difference (SMD) with 95% CI was used. The differences between baseline and after treatment were used as the effect size. If there were some data were not reported in some trials, we used the following formula to estimate the missing data (22):

$$\overline{X}_{change} = \overline{X}_{post-treatment} - \overline{X}_{baseline}$$

$$SD_{change} = \sqrt{(SD_{baseline})^2 + (SD_{post-treatment})^2 - 2 \times r \times SD_{baseline} \times SD_{post-treatment}}$$

Firstly, the standard pairwise meta-analysis was performed using the RavMan manager. We calculated the I-square (I^2) test to assess heterogeneity among RCTs (23). If $I^2 > 50\%$, they were analyzed using random-effects model; otherwise, fixed-effect model was chosen.

Second, we used the STATA to make NMA evidence diagram (24). We used the WinBugs to analyze the data, when running the WinBUGS program, four chains were used for simulation, the number of iterations was set to 100,000 times, the first 10,000 times were used for annealing to eliminate the influence of the initial value. Inconsistency factors (IF) with 95% CI were used to evaluate the consistency of each closed-loops. For closed-loops, if the IF with 95% CI contains 0, it indicates that the direct and indirect evidence were very consistent (25).

Third, we could judge whether there were small sample effects in this study by plotting the funnel plot (26).

Finally, the surface under the cumulative ranking curve (SUCRA) was generated using the STATA software to show the SUCRA scores, which means the probability of each intervention being ranked best, with a higher SUCRA score indicating a higher treatment level (27, 28).

Results

Study Search and Description

Overall, 8,045 related studies were retrieved from the databases, after deleting 3,149 duplicate studies, removing 4,815 studies by reading the title, abstract, and the full text, 36 studies were includ-

ed in the final analysis. Our analysis included three four-arm trials (29-31), one three-arm trial (32), and the remainder were two-arm trials. All the studies were from the USA (33), Japan (34), Hong Kong (35), Taiwan (36), and China mainland, involving 14 interventions: acupuncture and acupuncture-related therapies (ACU), Chinese Herbs (CH), donepezil (DON), nimodipine (NIM), music therapy (Music), cognitive or memory rehabilitation training (Training), placebo, and the combination of the above therapies, ACU+CH, ACU+CH+DON+NIM, ACU+DON, ACU+DON+NIM, ACU+Music, and ACU+Training. The basic characteristics of the included studies are shown in Table 1, while the results of the literature screening are shown in Fig. 1.

Table 1: Basic characteristics of the included studies

Studies (year)	country	Intervention			Control			course	outcomes
		Treatment	n	Years (mean±sd)/range	Treatment	n	Years (mean±sd)/range		
Zhu et al. (29)	China	CH	20	72.3±6	DON	20	72.3±6	8w	①
		ACU	20	72.3±6					
		ACU+CH	20	72.3±6					
Feng et al. (37)	China	ACU	20	68±9	DON	20	69±7	12w	①
Yan et al. (38)	China	ACU	20	60-78	DON	20	60-80	12w	①
Li et al. (30)	China	ACU+CH	35	67±4	NIM	14	65±7	8w	①③④
		ACU	37	65±6					
		CH	18	66±4					
Peng et al. (32)	China	ACU+CH	28	62-79	DON	28	60-78	12w	①③④
		CH	28	61-78					
Gu et al. (39)	China	ACU	72	75±7	DON	69	72±7	16w	①②③
Mu et al. (40)	China	ACU+CH	21	66.1±5.3	ACU	21	65.3±4.5	8w	①③④
Zhu et al. (41)	China	ACU	30	62.13±7.99	NIM	30	60.90±7.52	8w	①
Salloway et al. (33)	USA	DON	133	72.1±8.0	Placebo	137	72.7±8.0	24w	②
Doi et al. (34)	Japan	Music	67	76.2±4.6	placebo	67	76.0 ±4.9	40w	①

Study	Country	Intervention	N	Age	Control	N	Age	Duration	Outcomes
Li et al. (36)	Tai-wan, China	Music	21	76.7±8.45	placebo	20	80.8±5.94	6m	①
Grace et al. (35)	Hong kong, China	Training	7	77.7±6.07	placebo	6	77.7±6.07	3m	①
Ou et al. (42)	China	ACU	16	65.53±6.8	NIM	14	64.72±7.6	8w	③
Jia Y et al. (43)	China	ACU	43	75.11±6.53	DON	44	74.50±6.83	12w	②③
Cheng et al. (44)	China	ACU+CH+DON+NIM	30	64.7±3.7	DON+NIM	26	65.6±3.4	3m	①③④
Li et al. (45)	China	ACU+Training	40	68.43±7.56	Training	40	67.3±6.35	3m	①③④
Tang et al. (46)	China	ACU+CH	50	58-81	DON+NIM	50	58-81	12w	①④
Wang et al. (47)	China	ACU+CH+DON	45	68.89±3.22	DON	45	69.18±3.17	24w	③④
Yao et al. (48)	China	ACU+CH	24	76.52±6.365	DON	24	76.43±6.25	60d	①④
Wang et al. (49)	China	ACU	36	72.05±3.70	DON	36	70.31±3.79	12w	①③④
Yang et al. (50)	China	ACU+CH	36	80.5±7.8	ACU+DON	36	81.2±8.3	8w	①③④
Jiang et al. (31)	China	CH	20	60-80	DON	20	60-80	12w	①③
		ACU	20	60-80					
		ACU+CH	20	60-80					
Liu et al. (51)	China	ACU+DON+NIM	35	69.1±4.4	DON+NIM	35	68.9±4.3	8w	①②③
Jia Z et al. (52)	China	ACU	35	75.11±6.53	DON	36	74.50±6.83	12w	①②③④
Lin et al. (53)	China	ACU	18	73.44±3.37	DON	18	74.21±2.68	12w	①②③④
Zhao et al. (54)	China	ACU	16	67±2.12	NIM	16	67±2.12	2m	①③④
Dai et al. (55)	China	ACU+Training	47	71.06±5.45	Training	47	71.45±5.12	NR	①③④
Liu et al. (56)	China	ACU+Music	20	71.25±10.93	ACU	21	69.90±10.51	120d	①③
Zhou et al. (57)	China	ACU	13	71.6±8.1	placebo	13	74.4±8.6	6m	①②③
Sun et al. (58)	China	ACU	55	66.23±4.12	placebo	55	66.31±4.25	6m	①
Chen et al. (59)	China	ACU+DON	48	74.36±5.47	DON	48	75.13±5.81	3m	①③④
Bi et al. (60)	China	ACU	37	71.5±4.7	DON	37	70.2±4.6	12w	①④
Wang et al. (61)	China	ACU+DON	28	70.3±8.0	DON	27	70.7±9.1	20d	①②

Zhao et al. (62)	China	ACU+Music	60	72.0±10.9	placebo	60	5.71±0.86	4w	①③④
Xia et al. (63)	China	ACU+DON	30	49±11	DON	30	50±12	8w	①③④
Wang et al. (64)	China	ACU+DON	31	72.74±8.36	DON	31	75.77±7.03	8w	①②

ACU: acupuncture and related Therapies; CH: Chinese herb; DON: donepezil; NIM: nimodipine; Training: memory and cognitive function training; y: year; m: month; d: day;①: MMSE; ②:ADAS-cog; ③: ADL; ④:effectiveness rate.
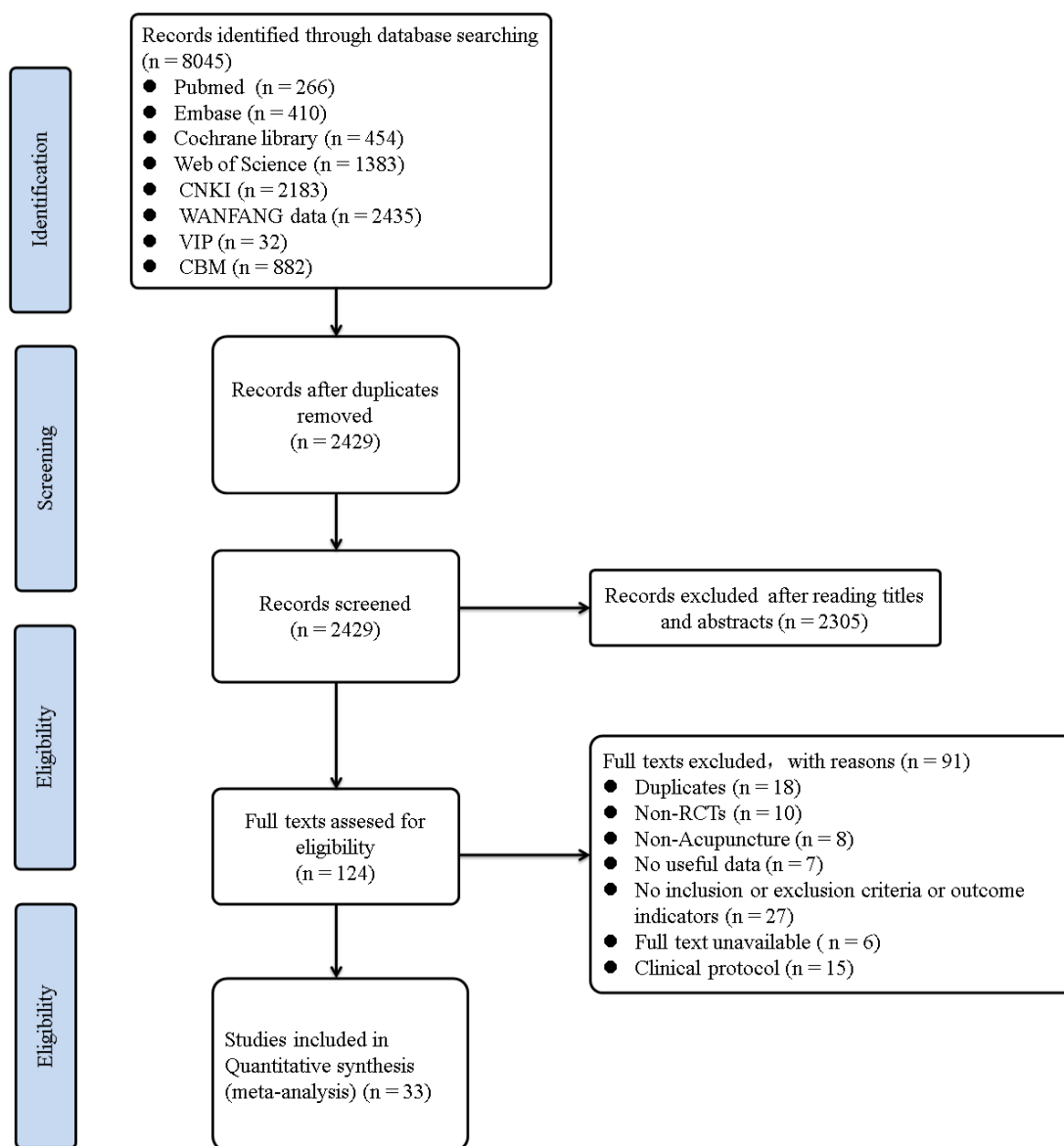
Fig. 1: Study flow diagram

Quality Assessment of Included Studies

Our two researchers, ZH and TJ, evaluated the included studies according to the bias risk assessment tool recommended by the Cochrane Handbook 5.1. However, acupuncture, music therapy, and memory and cognitive training were non-pharmacological therapies, so some participants and researchers involved in these studies were unable to be blinded. The results of risk evaluation are shown in Fig. 2.
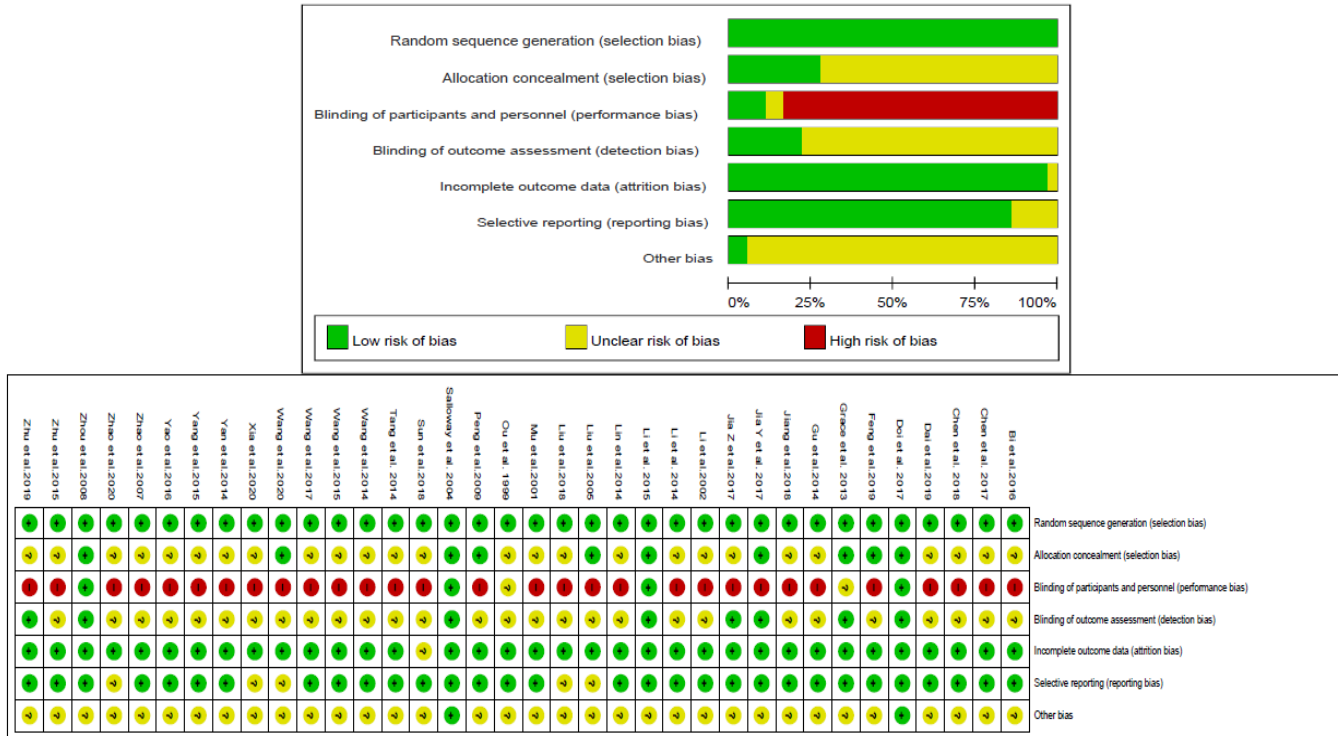
Fig. 2: Quality assessment of included studies.

Among the 36 trials, 36 trials (100%) represented a random sequence generation process. Ten trials (27.78%) described the use of allocation concealment methods, and eight trials (22.22%) described the blinding methods for participants or outcome assessment. 35 trials (97.22%) reported complete outcome data. Because of the particularity of the acupuncture operation, it is impossible to be blinded to the participants and personnel.

Results of Pairwise Meta-Analyses

Primary Outcome: MMSE and ADAS-cog

For the results of MMSE, ACU was more efficacious than the following interventions: DON (SMD:0.532, 95%CI:0.148,0.917), NIM (SMD:0.780, 95%CI:0.062,1.498), placebo (SMD:3.814, 95%CI:0.020,7.608). Acupuncture combined therapies were more efficacious than monotherapy, such as ACU+Training (SMD:6.979, 95%CI:4.569,9.389) was more efficacious than Traning, ACU+DON (SMD:2.837, 95%CI:1.031,4.643) was more efficacious than DON, ACU+CH (SMD:1.577, 95%CI:1.181,1.974) was more efficacious than

ACU, and ACU+CH (SMD:1.501, 95%CI:0.834,2.169) was more efficacious than CH. Regarding the ADAS-cog, ACU (SMD:-3.135, 95%CI:-3.95,-2.32) was more efficacious than DON.

### Secondary Outcome: ADL and Effectiveness Rate

For the result of ADL, ACU was more efficacious than the following interventions: DON (SMD:-0.976, 95%CI:-1.844,-0.109), NIM (SMD:0.780, 95%CI:0.431,1.129). ACU+CH was more efficacious than the following interventions: ACU (SMD:-2.399, 95%CI:-2.858,-1.940),

DON (SMD:-0.439, 95%CI:-0.656,-0.223), CH (SMD:-0.374, 95%CI:-0.599,-0.150). Regarding the effectiveness rate, ACU+CH (RR:4.214, 95%CI:1.399,12.690) was more efficacious than DON.

NMA Results

Primary Outcome: MMSE and ADAS-cog
As shown in Fig. 3A, 32 studies reported MMSE, involving 14 interventions. After the consistency test, the result included 9 closed-loops, whose IF with 95% CI of 7 closed-loops contained 0, indicating no obvious inconsistencies, whereas the IF with 95% CI of another 2 closed-loops failed to contain 0 (Fig. 4A).
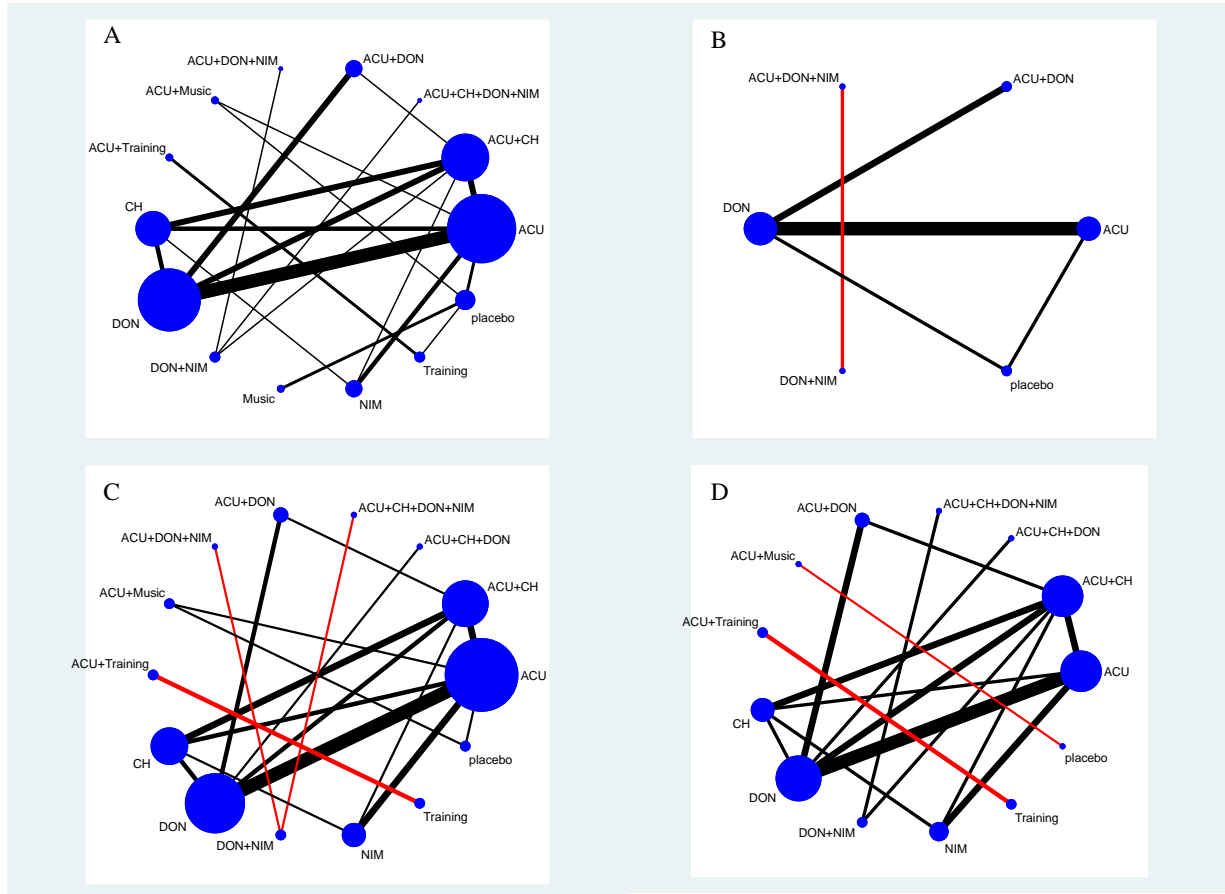
Fig. 3: Network diagram

The results of the NMA showed that ACU+Training was more efficacious than the following interventions: ACU (SMD:-7.22; 95%CI:-13.55,-0.67), ACU+CH (SMD:-7.22; 95%CI:-13.55,-0.67), ACU+DON (SMD:-8.72; 95%CI:-15.54,-1.69), CH (SMD:8.97; 95%CI:2.48,15.36), DON (SMD:9.30; 95%CI:2.87,15.57), DON+NIM (SMD:8.44; 95%CI:0.95,15.84), Music (SMD:11.22; 95%CI:5.15,17.25), NIM (SMD:8.70; 95%CI:1.78,15.20), Placebo (SMD:11.72; 95%CI:6.29,17.24), and Training (SMD:7.05; 95%CI:3.65,10.44). In addition, ACU+CH (SMD:1.77; 95%CI:0.09,3.49) was more efficacious than CH, ACU+DON+NIM (SMD:4.09; 95%CI:0.15,7.95) was more efficacious than DON+NIM, and ACU+Training (SMD:7.05; 95%CI:3.65,10.44) was more efficacious than Training, all of them indicated that acupuncture combined with other therapies could improve the

efficacy. The best therapy to improve MMSE was ACU + Training (86.6%), while the worst was Placebo (2.9%) (Fig. 5A).

As shown in Fig. 3B, 9 studies reported ADAS-cog, involving 6 interventions. The results of inconsistency test showed that there was 1 closed-loop that did not include 0 (Fig. 4B). The results of the NMA showed that ACU was more effica-

cious than DON (SMD:-3.45;95% CI:-6.00,-1.38) and Placebo (SMD:- 5.09; 95% CI:-9.34,-1.86). The most effective intervention for reducing the ADAS-cog was ACU (77.8%), while the worst was placebo (1.1%) (Fig. 5B). Therefore, ACU may be the best therapy for patients with mild to moderate AD to improve their cognitive function.
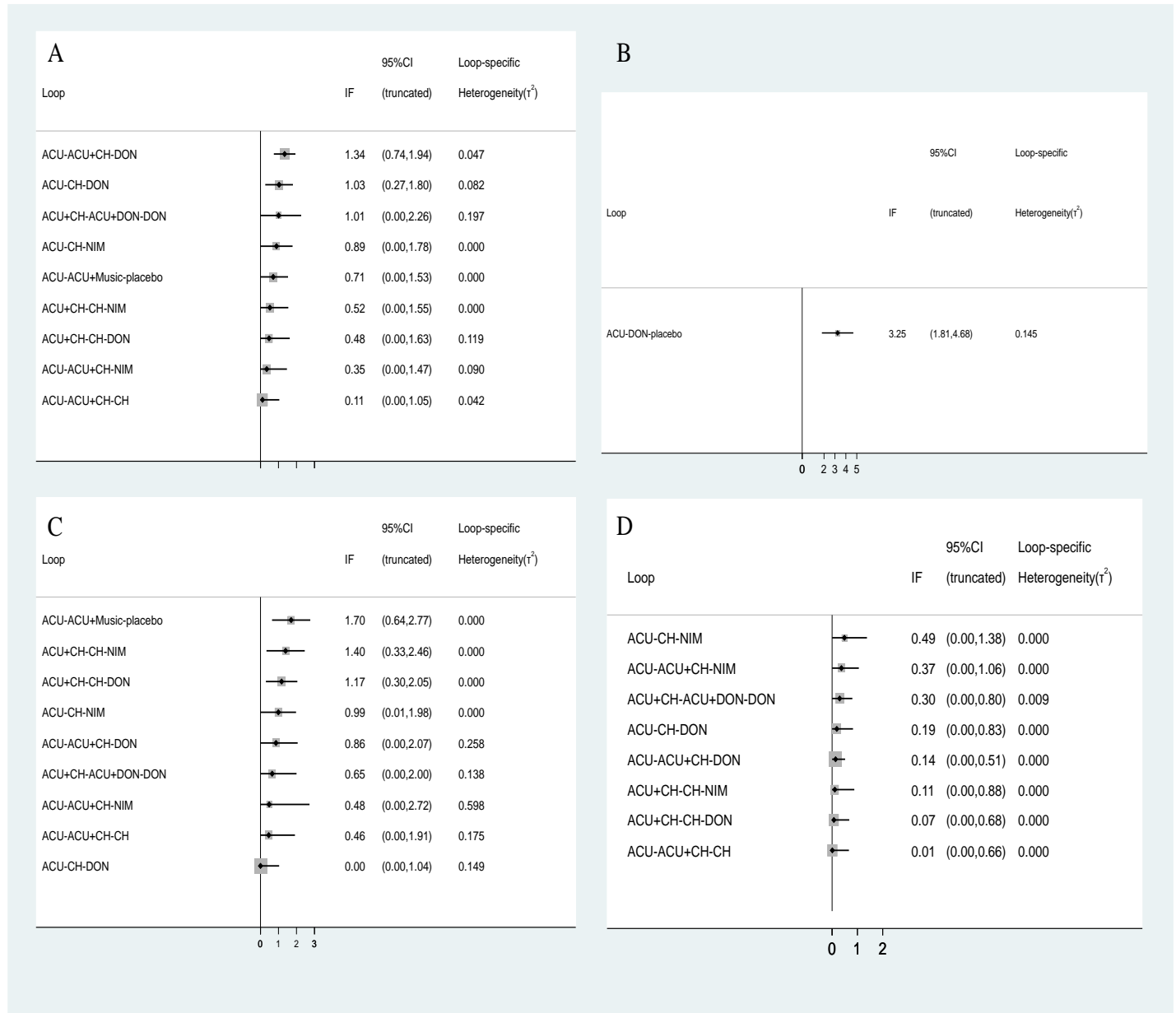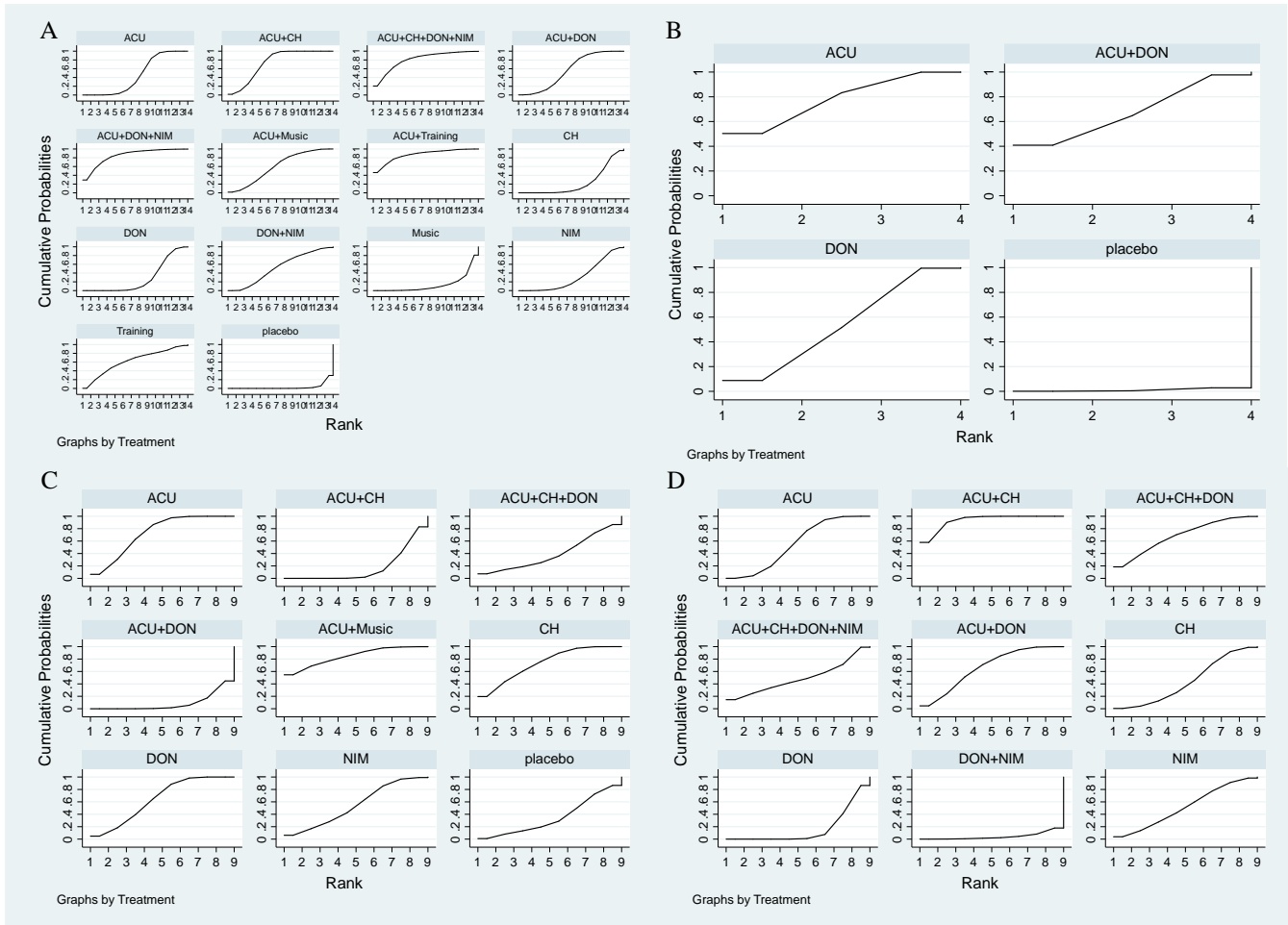

Fig. 4: Inconsistency test chart.

Fig. 5: Surface under the cumulative ranking curves

Secondary Outcome: ADL and Effectiveness Rate

As shown in Fig. 3C, 22 studies reported ADL, including 14 interventions. After the consistency test, the result included 9 closed-loops, whose IF with 95% CI of 5 closed loops contained 0, indicating no obvious inconsistencies, whereas the IF with 95% CI of another 4 closed loops failed to contain 0 (Fig. 4C). The results of the NMA showed that ACU+DON was more efficacious than the following interventions: CH (SMD:-5.93; 95%CI:-11.05,-2.05), DON (SMD:-5.29; 95%CI:-9.33,-1.87), NIM (SMD:-5.60; 95%CI:-11.32,-1.66), Placebo (SMD:-7.13; 95%CI:-20.03,5.78). The most effective intervention for improving the activity ability was ACU+Music (84.4%), while the worst was ACU+DON (8.7%) (Fig. 5C).

As shown in Fig. 3D, 18 studies reported the effectiveness rate, including 13 interventions. After the consistency test, the result included 8 closed-loops, whose IF with 95% CI contained 0, indicating no obvious inconsistencies (Fig. 4D). The following interventions were more efficacious than DON+NIM: ACU (RR:10.33; 95%CI:1.74,244.24), ACU+CH (RR:22.61; 95%CI:3.84,485.73), ACU+CH+DON (RR:13.98; 95%CI:1.57,445.27), ACU+CH+DON+NIM (RR:4.60; 95%CI:1.11,20.40), ACU+DON (RR:12.97; 95%CI:1.38,222.50), CH (RR:8.49; 95%CI:1.11,190.80), NIM (RR:0.11; 95%CI:0.00,0.79). ACU (RR:2.24; 95%CI:1.24,4.23) and ACU+CH (RR:4.71; 95%CI:2.32,11.27) were more efficacious than DON. The most effective intervention for the

effectiveness rate was ACU+CH (93.2%), while the worst was DON+NIM (4.4%) (Fig. 5D). All studies were symmetrically distributed around the X=0 vertical line, and the funnel plot was symmetrical, indicating that there was no evidence of small sample effects in the study network (Fig. 6).
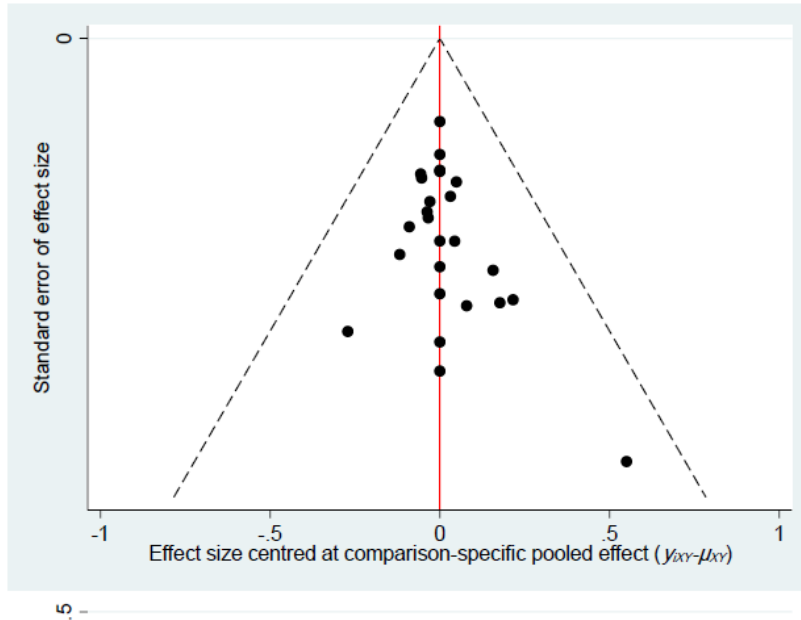

Fig. 6: Funnel diagram

Adverse Events

Of the 33 trials included, 9 trials reported adverse events occurred. Six trials reported adverse events related to gastrointestinal discomforts, such as diarrhea, nausea, vomiting, these interventions were mainly DON, CH, and NIM. Five trials reported dizziness, insomnia as adverse effects mainly related to DON. And 3 trials reported bleeding and ecchymosis at the acupuncture site as adverse events.

Discussion

AD is a neurodegenerative disease that currently has no specific drugs that can stop its deterioration (65). In recent years, TCM has been widely used in the treatment of AD (66, 67). Moreover, according to a previous meta-analysis, acupuncture-related therapies (10, 68) appear to be more advantageous than western medicine. In other words, acupuncture methods can be beneficial as complementary and alternative therapies for AD.

Our NMA consisted of 33 RCTs, which included 2,469 patients with mild to moderate AD. For these patients, there were three main findings in this NMA: ①ACU+Training may be the optimal therapy to improve MMSE scores; ②ACU may be most helpful in improving ADAS-cog scores and ADL scores; ③the combination of acupuncture-related therapies and other therapies has a higher overall benefit. Although some pharmacological treatments (such as donepezil, etc.) have shown slight efficacy, however, there were still some safety problems that exist. The adverse events reports showed that some participants experienced gastrointestinal reactions and insomnia due to DON, NIM and CH interventions. Overall, the possibility of adverse reactions to pharmacological treatment was higher than that of non-pharmacological treatment.

Compared with the previous meta-analysis (10, 12, 68, 69), the NMA methods were used in our research, we included more interventions for comparison and ranked the different interventions and calculated the probability of the best

intervention. In addition, we included more comprehensive data. Our findings reconfirm the safety and efficacy of acupuncture and acupuncture-related therapies in patients with mild to moderate AD.

In normal brain tissue, the amyloid-beta (Aβ) protein mainly exists in the form of Aβ40, and its generation and elimination are in a dynamic equilibrium state (70). Under physiological conditions, an appropriate amount of soluble Aβ can protect brain cells, while under pathological conditions, Aβ will be overexpressed, causing Aβ deposition and the formation of senile plaques (SP) that are detrimental to brain function (71). Moreover, Aβ can cause excessive phosphorylation of the tau protein (72), which leads to the formation of neurofibrillary tangles (NFTs) (73), and the number of NFTs is positively correlating to the degree of clinical dementia (74, 75). Acupuncture can reduce the levels of Aβ (76) and tau proteins (77), and activate low protein kinase signaling pathways to a certain extent (78), which could restore the learning and memory impairments of AD rats. In addition, acupuncture may have a neuroprotective effect in the AD brain (79, 80) and may also improve neural synaptic plasticity (81-83), activate related brain regions (84), and thus play a role in the prevention and treatment of AD.

Nonetheless, our study has some limitations. The majority of our studies being published in Chinese journals, there may be a publication bias due to Chinese cultural considerations. The risk bias assessment of those included studies was mostly unclear. All the studies analyzed were aimed at short-term efficacy observations, thus the long-term efficacy of acupuncture for AD still needs to be defined.

Conclusion

ACU+Training and ACU can improve MMSE score and cognitive function. Among the interventions we included, ACU+Training and ACU may be the best therapies to improve cognitive function, while the combination of acupuncture-related therapies and other therapies has a higher overall benefit.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Funding

Conflicts of interest

All authors declare that they have no potential conflicts of interest.

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