

Review Article

Aerobic exercise versus acupuncture as adjuncts to acetylcholinesterase inhibitors in Alzheimer's disease: a systematic review and Bayesian network meta-analysis

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Abstract: Background: Acetylcholinesterase inhibitors (AChEIs) remain the standard therapy for Alzheimer's disease (AD), yet their cognitive and functional benefits are limited, creating a strong need for effective adjunctive treatments. Aerobic exercise and acupuncture have been proposed as promising complements to AChEIs because of their potentially synergistic neurotrophic and cholinergic effects. To compare these treatment combinations, we carried out a Bayesian network meta-analysis (BNMA) of randomized controlled trials (RCTs). These studies were sourced from major English and Chinese databases and examined cognitive and functional outcomes. In total, 37 RCTs were included, covering 2,188 participants. Among all, combined acupuncture (SUCRA = 78.92%) and fire needle therapy (SUCRA = 78%) demonstrated the highest probability of improving Mini Mental State Examination scores, while moderate intensity aerobic exercise ranked best for the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog, SUCRA = 23.3%) and the Barthel Index (SUCRA = 71.1%). Combined acupuncture was ranked highest for the Alzheimer's Disease Assessment Scale-Activities of Daily Living (ADAS-ADL, SUCRA = 94.3%), although its effects did not reach statistical significance. Across analyses, heterogeneity was minimal ($I^2 \leq 4\%$), model convergence was stable, and no publication bias was detected. Overall, this BNMA suggests that combined or thermal acupuncture offers the strongest cognitive gains alongside AChEIs, whereas moderate-intensity aerobic exercise provides the most reliable functional support. Because overall functional improvements were modest and evidence for some interventions remains limited, the benefits appear selective rather than broad. Larger, standardized trials are needed to clarify these patterns and guide their use in practice.

Keywords: Alzheimer's disease, acetylcholinesterase inhibitors, aerobic exercise, acupuncture, cognitive outcomes, network meta-analysis

Introduction

Alzheimer's disease (AD) is the most common type of dementia and involves approximately 70% of the global dementia burden [1]. Characteristics of AD include progressive dismantling of the brain activity, accumulation of amyloid- β plaques and tau-protein tangles, and a slow yet irreversible deterioration of memory and cognitive skills [2]. Despite decades of studying the disease by scientists, the treatment capable of completely curing it has not been found. Current pharmacological treatments - mostly represented by acetylcholinesterase

inhibitors (AChEIs) like donepezil, rivastigmine, and galantamine - offer modest symptomatic relief and may often elicit gastrointestinal or cardiovascular adverse events [3]. Global prevalence is estimated to surpass 150 million by 2050, and the rising healthcare burden makes the development of supplementary interventions - one that can safely sustain cognition and functional independence when combined with standard drug therapy - particularly timely [4].

Among the available non-pharmacological approaches, interest has particularly been shifted

to aerobic exercise and acupuncture for their complementary yet converging modes of action that allow modulation of neuroplasticity [5]. Compared with resistance or flexibility exercises, aerobic exercise induces greater neurovascular and metabolic changes: it promotes hippocampal neurogenesis, enhances cerebrovascular perfusion, increases mitochondrial efficiency, and stimulates the expression of brain-derived neurotrophic factor (BDNF), thus enhancing long-term cognitive resilience [6-8]. Acupuncture affects neuroinflammation and neurotransmitter pathways, decreases overactivation of microglia by nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) signaling, and increases cholinergic transmission, thus improving synaptic activity and cortical metabolism. Both are thus promising adjuncts to enhance the cognitive efficacy of AChEI therapy [9, 10].

Previous reviews have tended to examine exercise and acupuncture on their own, rather than evaluating the two approaches directly against each other. Most of the work on exercise in this field has centered on fairly typical aerobic activities - walking routines, cycling sessions, or mixed endurance programs - usually delivered at intensities that range from mild to moderately vigorous. In nearly all of these studies, exercise was treated as an independent, non-pharmacological option, and while the results suggested a modest slowing of cognitive decline, only a small number of trials actually explored how exercise performs when combined with AChEIs [11-16]. Research on acupuncture has taken a somewhat different path. Here, meta-analyses have tended to focus on its use together with standard medical treatments, pairing various needling techniques with AChEIs, nimodipine, or herbal formulae. These combined approaches have generally produced more noticeable improvements in Mini Mental State Examination scores (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores than medication alone [17-23]. Even so, the overall evidence remains fragmented. Exercise trials vary considerably in terms of intensity and duration, acupuncture studies differ in point selection and technique, and almost none directly compare aerobic training with acupuncture-based interventions or attempt to rank them against each other. Because of this, our understanding of how these two approaches stack up when incorpo-

rated into real-world AChEI-based treatment plans is still incomplete. The present systematic review and Bayesian network meta-analysis (BNMA) bring together randomized controlled trials (RCTs) that have examined different intensities of aerobic exercise alongside a range of acupuncture modalities used as adjuncts to AChEIs in AD. The goal is to identify which intensity levels and which acupuncture techniques most effectively enhance cognitive outcomes and therapeutic synergy by integrating the pharmacological and non-pharmacological evidence within a single analytical framework.

Methods

This BNMA was registered prospectively in PROSPERO (CRD42024628390) and conducted in line with the PRISMA 2020 recommendations, including the extension for network meta-analyses [24].

Search strategy

To identify all relevant studies, we carried out an extensive search across nine major databases: PubMed, Embase, Web of Science, the Cochrane Library, Scopus, CNKI, CBM, VIP, and Wanfang. The search window spanned January 1, 2000, to September 30, 2024. We used a combination of MeSH terms and free-text keywords related to *Alzheimer's disease*, *acupuncture interventions*, and *aerobic training*. Because each database indexes material differently, the search syntax was tailored accordingly. We also screened the reference lists of eligible papers and related reviews to make sure no additional studies were missed.

Eligibility criteria

We included RCTs that enrolled adults aged 55 years or older diagnosed with AD according to DSM-IV, DSM-5, or NINCDS-ADRDA criteria. Participants had to be receiving a stable regimen of AChEIs - such as donepezil, rivastigmine, or galantamine. Studies were eligible if they evaluated aerobic exercise or acupuncture as adjuncts to AChEIs, while control groups used AChEIs alone. Aerobic interventions generally involved organized endurance-based activities - such as walking, cycling, treadmill sessions, or mixed training routines - performed several times a week, with each study specifying its own target intensity. Acupuncture was provided using a range of familiar techniques - including manual acupuncture, electroacupun-

cture, and fire needle therapy (FNT) - each applied to acupoints typically chosen for their known links to cognitive and neurovascular regulation. Our main focus was on how these treatments influenced cognitive measures, specifically shifts in MMSE and ADAS-Cog scores. Secondary outcomes included ADAS-ADL and the Barthel Index (BI). We limited inclusion to full-text RCTs published in English or Chinese. Studies were excluded if they lacked an appropriate comparison group, did not involve AChEi therapy, or failed to report at least one of the predefined outcomes.

Data extraction

Two reviewers (Z.Y. and Y.W.) went through all of the studies identified in the search, starting with the titles and abstracts and then moving on to the full texts. They recorded the necessary information using a template that had been prepared in advance. Whenever their interpretations differed, they discussed the point with a third researcher (F.S.) until they reached an agreement. The information they collected included details such as publication year, study design, sample size, participant characteristics, features of the interventions - such as their duration, frequency, type, and whether AChEIs were used at the same time - the comparison groups, and all outcomes that were reported. If a study included more than one intervention arm, each arm was entered separately to keep the analysis consistent.

Bias and quality control

Two reviewers (Z.Y. and H.L.) also reviewed the quality of the included studies and considered possible sources of bias. Any differences in judgment were resolved through discussion with a third investigator (Y.W.). The randomized trials were appraised using the Cochrane RoB 2 tool. To explore whether the evidence base might be influenced by publication bias or small-study effects, we examined comparison-adjusted funnel plots and applied a network-adapted Egger regression, allowing us to evaluate potential asymmetry within the structure of the evidence network.

Statistical analysis

All statistical procedures for the NMA were carried out in R (version 4.4.1). For this purpose, we relied on the gemtc package together with

rjags, which allowed the Bayesian models to be run through JAGS. Continuous outcomes were summarized as mean differences (MDs) and accompanied by 95% credible intervals (CrIs), and all analyses followed a random-effects approach. To run the Bayesian models, three Markov chains were initiated for each analysis. Each chain completed 50,000 iterations, although the initial 20,000 iterations were treated as burn-in and were not used for inference. Convergence was assessed both visually - by examining the chain trace plots - and numerically through the Gelman-Rubin statistic (potential scale reduction factor, PSRF), which provided an additional check on the stability of the posterior estimates. We examined the network geometry in R, preparing a network diagram for each outcome to illustrate how the evidence connected across interventions. In these figures, node sizes represented the number of participants assigned to each arm, and the thickness of the lines linking nodes showed how many studies informed each pairwise comparison. To compare treatments, we calculated SUCRA values. Model fit and heterogeneity across studies were evaluated using the deviance information criterion (DIC) and the I^2 statistic, respectively. We also carried out a leave-one-out sensitivity test in Stata 17.0 to determine whether the pooled estimates were being driven by any single trial. All visual outputs - including forest plots, SUCRA curves, rankograms, league tables, and funnel plots - were created in R, mainly with the help of ggplot2, which allowed the figures to be standardized across outcomes.

Results

Study selection

As outlined in the PRISMA flow chart (**Figure 1**), the search identified 1,543 records. After excluding 316 duplicates, 1,227 records remained for title and abstract screening. Of these, 1,120 were removed at this stage. The full texts of 107 articles were then examined, and 35 were excluded because the papers were inaccessible or did not satisfy the inclusion criteria. In total, 37 studies met all requirements and were included in the final analysis (**Figure S1**).

Study characteristics

Altogether, this BNMA incorporated 37 RCTs with a combined sample of 2,188 participants.

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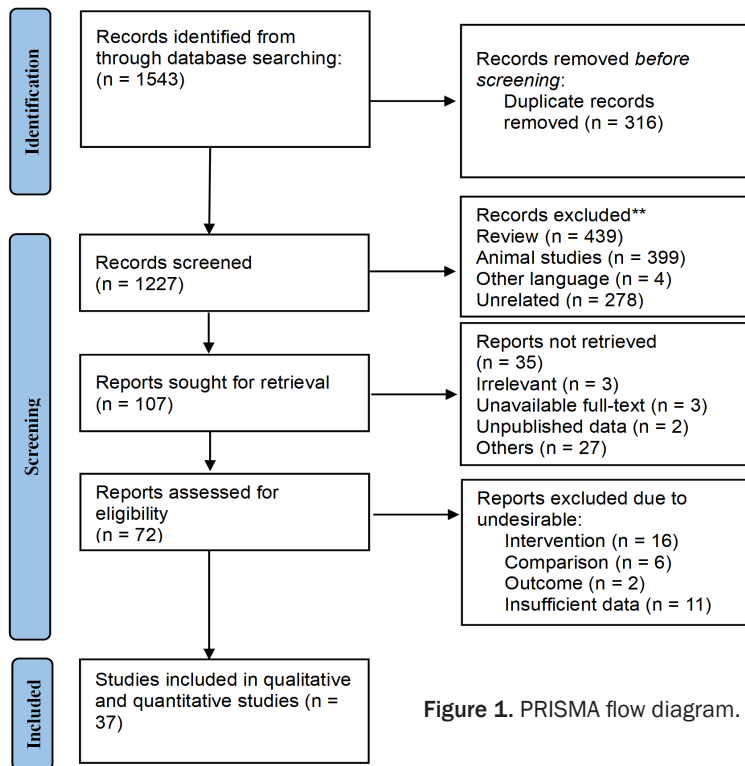


Figure 1. PRISMA flow diagram.

These studies evaluated either aerobic exercise or acupuncture used alongside AChEI therapy in AD. Twelve trials investigated acupuncture - manual acupuncture, electroacupuncture, combined acupuncture techniques, or FNT - while 25 studies examined aerobic exercise programs ranging from mild to high intensity, as detailed in [Tables S1, S2](#). Most studies were judged to have either a low risk of bias or to present minor concerns, usually related to deviations from the planned interventions or to issues in how outcomes were measured. Importantly, none of the trials were judged to have a high overall risk of bias. The complete assessment of reporting transparency according to the PRISMA NMA checklist is provided in [Table S3](#).

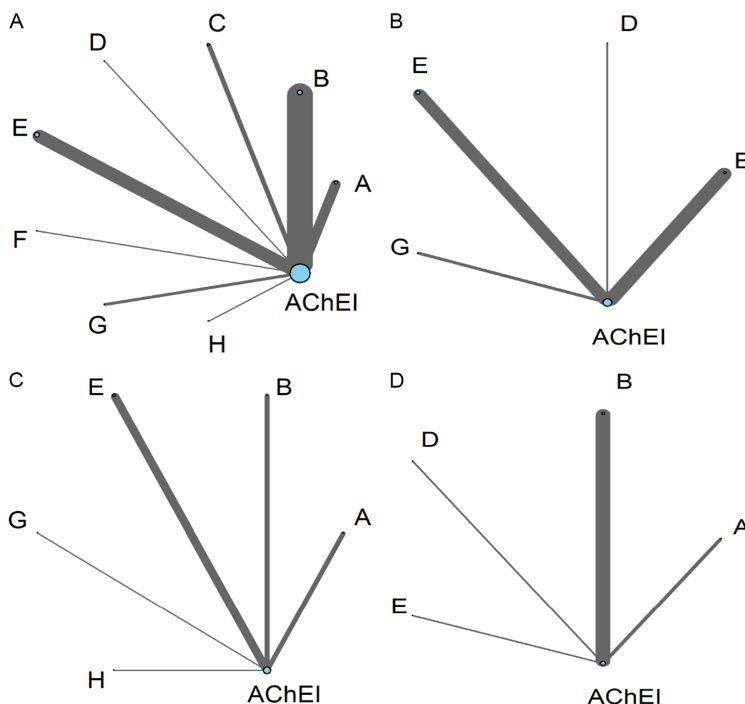


Figure 2. Network plots for (A) MMSE, (B) ADAS-Cog, (C) ADAS-ADL, and (D) BI. Nodes (blue circles) represent the total number of participants assigned to each treatment, and edges (gray lines) indicate the number of trials informing each comparison. MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADAS-ADL = Alzheimer's Disease Assessment Scale-Activities of Daily Living; BI = Barthel Index.

Network geometry

Across all outcomes, the treatment networks formed a star-shaped pattern centered on AChEI therapy, with each active intervention (A-H) branching outward from this common comparator (**Figure 2**). For MMSE, eight adjunct treatments were represented: mild-to-moderate aerobic exercise (A, n = 6), moderate aerobic exercise (B, n = 15), moderate-to-high aerobic exercise (C, n = 3), high-intensity aerobic exercise (D, n = 1), manual acupuncture (E, n = 8), electroacupuncture (F, n = 1), combined acupuncture (G, n = 2), and FNT (H, n = 1). For ADAS-Cog, the network included four interventions: moderate aerobic exercise (B, n = 8), high-intensity aerobic exercise (D, n = 1), manual acupuncture (E, n = 7), and combined acupuncture (G, n = 2). For ADAS-ADL, five interventions appeared: mild-to-moder-

ate aerobic exercise (A, n = 3), moderate aerobic exercise (B, n = 3), manual acupuncture (E, n = 5), combined acupuncture (G, n = 1), and FNT (H, n = 1). For the BI, the network included mild-to-moderate aerobic exercise (A, n = 2), moderate aerobic exercise (B, n = 8), high-intensity aerobic exercise (D, n = 1), and manual acupuncture (E, n = 1). Since none of the included trials offered direct head-to-head comparisons between active interventions, the networks relied fully on indirect evidence. This created uneven numbers of studies feeding each node, but the overall geometry still provided sufficient structure to support indirect comparisons across all outcomes.

Effects of adjunct therapies on cognitive outcomes

MMSE: Across 37 RCTs comparing eight adjunct interventions (A-H) plus AChEIs with AChEI monotherapy, most add-on treatments produced numerically higher MMSE scores. Statistically significant improvements were observed for G (MD = 3.93, 95% CrI 1.03-6.78), H (4.15, 0.16-8.15), B (2.35, 1.28-3.44), A (1.98, 0.35-3.65), and E (1.85, 0.39-3.28), whereas C (1.98, -0.49-4.41), D (1.52, -3.14-6.21), and F (3.53, -0.91-8.02) showed non-significant effects (**Figures 3A** and **S2A**). Based on SUCRA values, G had the highest probability of being the most effective (78.92%), followed closely by H (78.0%) and F (68.43%). Among the exercise-based interventions, B ranked highest (53.17%), followed by C (44.04%), A (43.87%), and D (38.21%), while AChEI monotherapy ranked lowest (5.2%) (**Figures 4A** and **S3A**). Taken together, acupuncture-based adjuncts (G, H, F) tended to rank best for MMSE, although estimates for F and H were imprecise, and B emerged as the leading exercise-based option.

ADAS-Cog: Across 18 RCTs comparing four adjunct interventions (B, D, E, G) used alongside AChEIs versus AChEI monotherapy, most add-on therapies resulted in numerically lower ADAS-Cog scores than AChEIs alone. Significant reductions were seen with B (MD = -3.43, 95% CrI -5.81 to -1.06) and E (-3.18, -5.67 to -0.72), while neither D (-2.79, -10.94 to 5.32) nor G (0.98, -3.74 to 5.69) showed a statistically meaningful difference (**Figures 3B** and **S2B**). Because lower ADAS-Cog scores indicate better cognitive performance, smaller SUCRA val-

ues correspond to higher efficacy. In line with this, B (23.25%) and E (27.33%) ranked as the most effective treatments, followed by D (38.59%). AChEI monotherapy (76.79%) and G (84.04%) ranked lowest (**Figures 4B** and **S3B**). Overall, B and E demonstrated the strongest improvements in ADAS-Cog scores compared with AChEIs alone, whereas G showed no clear benefit and considerable uncertainty due to limited indirect evidence.

Effects of adjunct therapies on functional outcomes

ADAS-ADL: Across 13 RCTs comparing five adjunct interventions (A, B, E, G, H) with AChEI monotherapy, most showed numerically higher ADAS-ADL scores, suggesting better functional ability. Although none of the comparisons reached statistical significance, G (MD = 22.25, 95% CrI -2.34 to 46.73) produced the largest mean improvement, hinting at a possible functional advantage (**Figures 3C** and **S4A**). SUCRA rankings placed G as the most likely to be effective (94.25%), followed by A (52.91%), B (39.83%), and AChEI monotherapy (39.6%), while E (37.29%) and H (36.12%) ranked lower (**Figures 4C** and **S3C**). Overall, the network suggested that G had the highest probability of enhancing daily functioning, although wide and overlapping credible intervals limit the certainty of this advantage.

BI: Across 12 RCTs assessing four adjunct interventions (A, B, D, E) combined with AChEIs versus AChEI monotherapy, most interventions led to numerically higher BI scores, reflecting improved functional independence. Among these, only B showed a statistically significant increase (MD = 4.07, 95% CrI 0.9-7.24). The improvements seen with A (3.12, -3.23 to 9.48), D (3.88, -5.07 to 12.94), and E (1.63, -7.42 to 10.58) were non-significant and accompanied by wide CrIs (**Figures 3D** and **S4B**). SUCRA rankings placed B highest (71.14%), followed by D (63.04%) and A (57.43%), whereas E (41.59%) and AChEI monotherapy (16.8%) ranked lowest (**Figures 4D** and **S3D**). Overall, the network suggested that B had the strongest likelihood of improving functional independence, while estimates for A, D, and E remained imprecise.

Sensitivity analysis

The sensitivity analysis showed that removing any single study did not change the overall pat-

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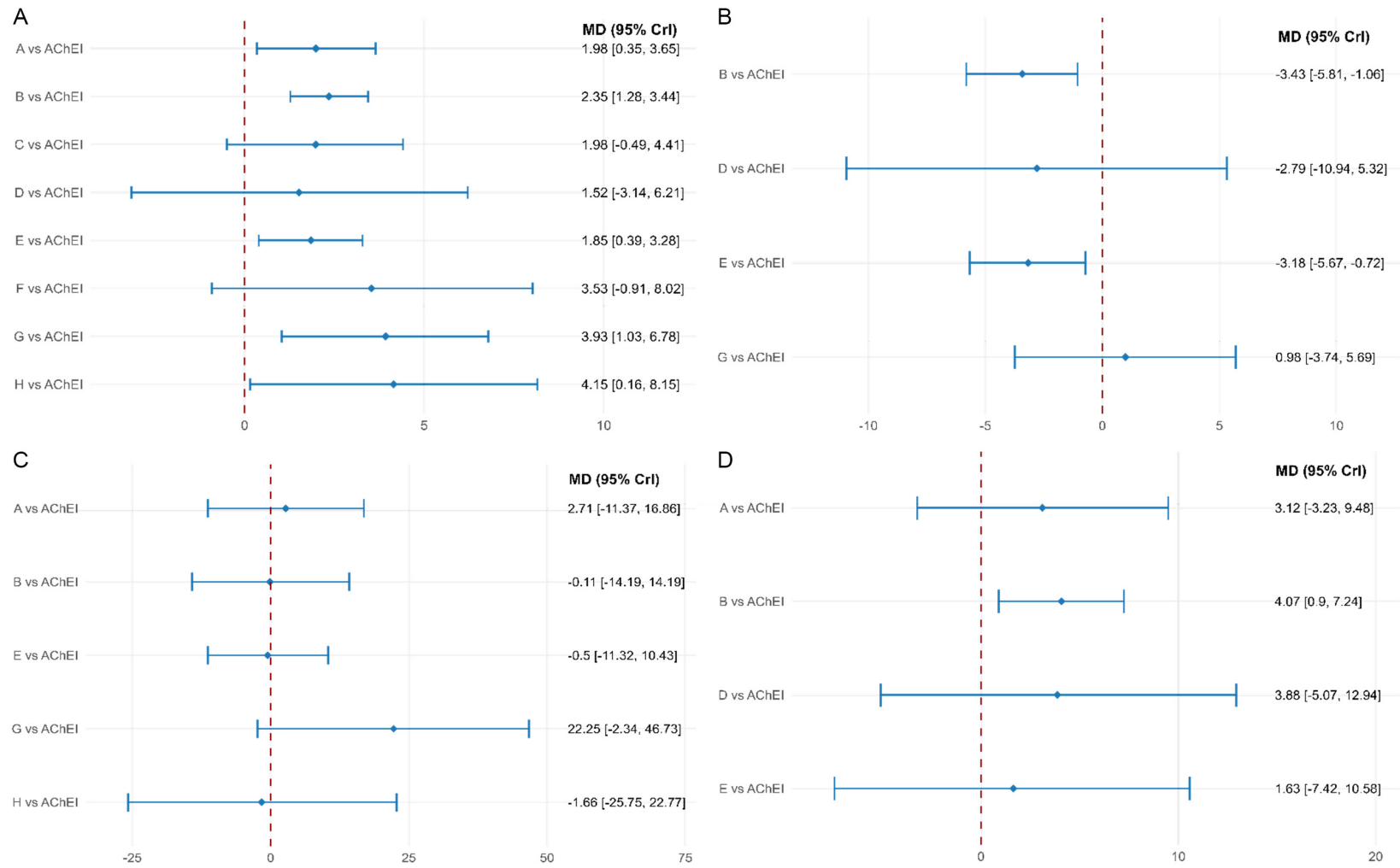


Figure 3. Forest plots of relative treatment effects for (A) MMSE, (B) ADAS-Cog, (C) ADAS-ADL, and (D) BI.

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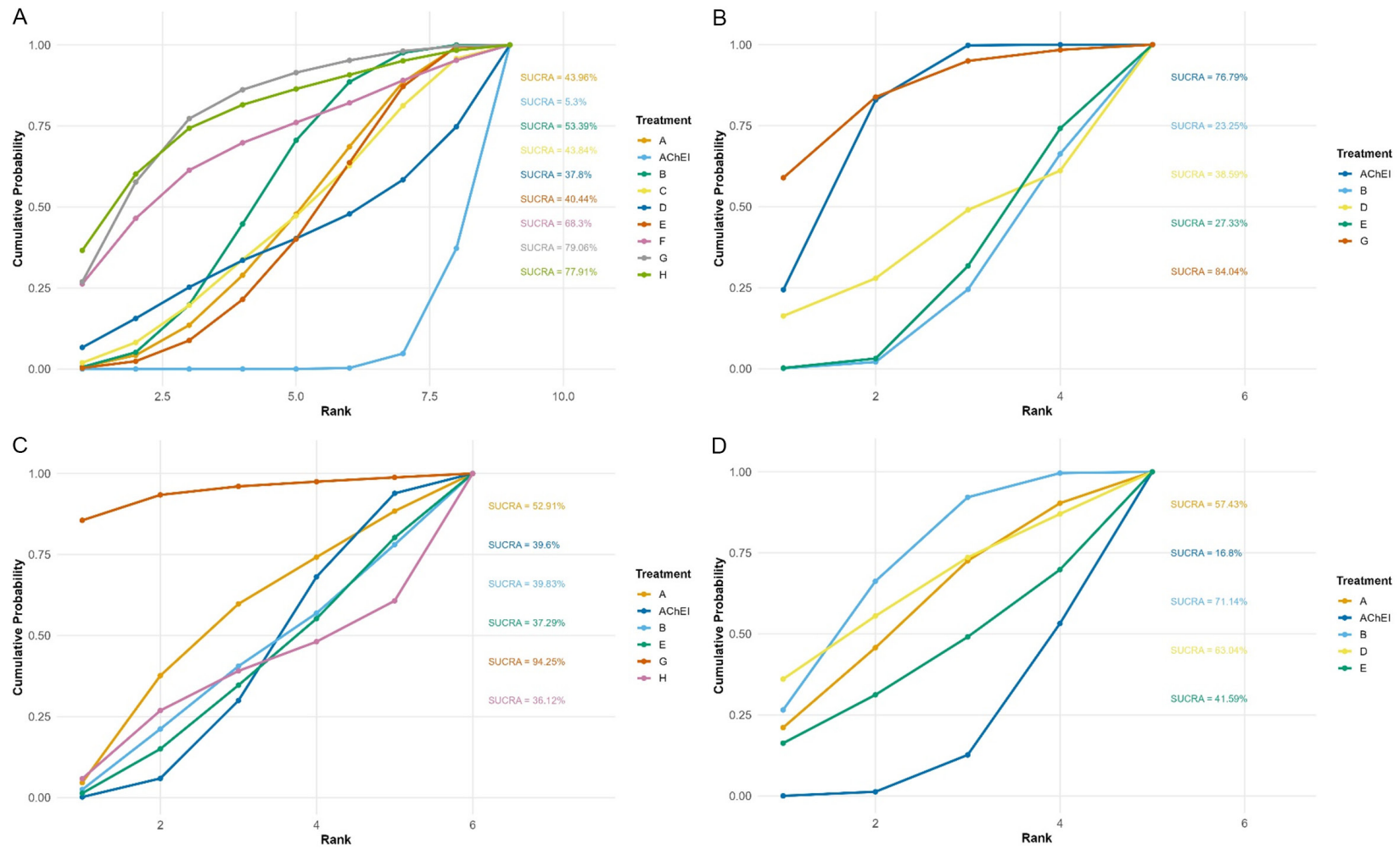


Figure 4. Plots of SUCRA values for (A) MMSE, (B) ADAS-Cog, (C) ADAS-ADL, and (D) BI. SUCRA = surface under the cumulative ranking curve.

tern of results, indicating that the findings were stable and robust (Figure S5).

Heterogeneity, model convergence, and publication bias

Across the different outcomes, the BNMA pointed to only minimal variation between studies, as shown by the low I^2 values - 1% for MMSE, 2% for ADAS-Cog, and 4% for both ADAS-ADL and BI. The DIC values also supported an acceptable model fit (145.22 for MMSE, 70.35 for ADAS-Cog, 51.98 for ADAS-ADL, and 47.87 for BI). In addition, the PSRF values were all close to 1, indicating that the Markov chains had reached stable convergence. Egger's regression tests did not identify statistically significant publication bias for MMSE ($P = 0.162$), ADAS-Cog ($P = 0.681$), ADAS-ADL ($P = 0.361$), or BI ($P = 0.609$), and funnel plots appeared largely symmetrical on visual inspection (Figure S6). Taken together, these results indicate acceptable model fit, consistent parameter convergence, and no clear evidence of small-study effects across the cognitive and functional outcomes.

Discussion

In this BNMA, we looked at whether adding either aerobic exercise or acupuncture to AChEI treatment could offer extra benefits for individuals with AD. Previous research indicate that both interventions may influence several key pathways involved in AD, including cholinergic signaling, neuroinflammatory activity, neurotrophic support, and cerebral blood flow [25, 26]. While aerobic exercise tends to bring about broad vascular and metabolic adaptations throughout the body, acupuncture is thought to exert more localized neuromodulatory and anti-inflammatory effects [26, 27]. While these mechanisms offer supportive context rather than direct proof, they outline biologically plausible ways in which each approach could enhance the therapeutic impact of standard AChEI treatment.

Most adjunct therapies produced numerically better cognitive and functional outcomes than AChEI monotherapy, although the extent of benefit varied across interventions. Combined acupuncture and FNT ranked highest for MMSE, followed by moderate-intensity aerobic exercise; however, these estimates were drawn

from a small number of trials with wide CIs, so they should be interpreted cautiously. Because MMSE captures global orientation and attention - domains influenced by cholinergic activity and cerebral perfusion - these patterns are broadly aligned with existing mechanistic hypotheses [28]. Previous mechanistic reviews suggest that acupuncture may enhance cholinergic signaling, modulate NF- κ B and NLRP3 pathways, reduce M1-type microglial activation, and help maintain astrocytic regulation of glutamate, although none of these mechanisms were directly examined in the RCTs included here [10]. FNT has likewise been proposed to act through TRPV-related and NO-cGMP-driven thermal pathways and to increase regional cerebral blood flow, but the supporting evidence in AD is still indirect [29, 30]. Meta-analyses have also reported MMSE gains with acupuncture combined with AChEIs, particularly in East Asian cohorts where thermal and combined techniques are more commonly used [19, 22, 31]. Altogether, the mechanistic evidence suggests that acupuncture and FNT may bolster the cognitive effects of AChEIs more effectively than moderate-intensity exercise, likely because they interact with cholinergic pathways in a more direct way [32]. This closer engagement can promote neurotransmitter production, strengthen synaptic activity, and help reduce neuroinflammatory responses [33]. Moderate aerobic exercise, by contrast, appears to influence cognition through slower-building neurotrophic and vascular changes - adaptations that take time to develop and rely on consistent, ongoing participation [34]. The less favorable results seen with high-intensity aerobic training and electroacupuncture are likely due to a combination of contributing factors. Very intense exercise can activate the sympathetic system excessively and increase oxidative stress and fatigue, which may counteract BDNF-related neuroplasticity [35]. For electroacupuncture, the variability in results is often linked to inconsistent protocols - such as differing stimulation frequencies, current strengths, or acupoint combinations - which makes it harder to reliably engage cholinergic and limbic circuits [36]. Many studies and reviews have pointed out that interventions that are too brief, overly intense, or insufficiently standardized often produce uneven cognitive outcomes [37, 38]. Overall, the evidence indicates that thermally enhanced and pharmacologically synergistic acupuncture approaches

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offer the strongest support for AChEI therapy by simultaneously engaging cholinergic, vascular, and inflammatory pathways.

In domain-specific cognition (ADAS-Cog), manual acupuncture and moderate-intensity aerobic exercise produced the strongest improvements, likely because both can influence hippocampal-frontoparietal circuits involved in memory, language, and praxis [39–40]. Moderate aerobic exercise activates neurotrophic and metabolic pathways by upregulating the BDNF-TrkB-CREB axis, together with IGF-1 and VEGF signaling. These processes promote hippocampal neurogenesis, increase dendritic branching, and enhance the brain's use of oxygen - while avoiding the stress-related suppression of neuroplasticity that can occur with excessively intense exercise [41–44]. As a result, the integrity of hippocampal-prefrontal networks is strengthened, which corresponds well with the cognitive domains measured by ADAS-Cog.

Manual acupuncture, although somewhat less potent than some other modalities, appears to complement these effects by modulating activity in hippocampal and parietal regions. It has been shown to increase choline acetyltransferase levels and to reduce inflammatory markers such as TNF- α , IL-1 β , and NF- κ B [33, 45], changes that help restore a healthier balance between excitatory and inhibitory signaling in the brain [46, 47]. In contrast, high-intensity aerobic training combined with AChEIs - and more complex acupuncture protocols - showed only limited benefit. When physical exertion becomes too intense, it can stimulate the HPA axis, raising cortisol and oxidative stress, which then suppress BDNF expression in the hippocampus and interfere with long-term potentiation [48]. Acupuncture results can also be inconsistent when there is wide variation in acupoint selection or stimulation parameters, since such differences make it harder to consistently engage cholinergic and limbic pathways [49]. These findings are in line with earlier meta-analyses showing that moderate aerobic exercise is the intervention most consistently associated with improvements in ADAS-Cog scores, whereas high-intensity or poorly standardized approaches often fail to deliver stable cognitive benefits [11, 17, 18]. Taken together, the evidence indicates that meaningful gains in domain-specific cognition are more likely when

interventions are physiologically balanced and carefully standardized so that BDNF-related plasticity can be maintained while metabolic stability is preserved.

When looking at functional outcomes, several adjunct therapies showed promising trends; however, none of them resulted in statistically significant improvements on the ADAS-ADL. This underscores how difficult it is to translate neurovascular or neurochemical improvements into meaningful, day-to-day functional behavior. The ADAS-ADL measures complex day-to-day abilities - such as planning, sequencing tasks, and maintaining motivation - that depend on coordinated fronto-subcortical networks and are also shaped by environmental context [50–52]. In line with this, earlier meta-analyses have shown that although acupuncture can improve global cognitive measures (MMSE, ADAS-Cog), its effects on daily functioning are often inconsistent or quite modest, likely due to short treatment durations, small sample sizes, and variability in treatment protocols [17, 18]. Large dementia cohorts show a similar pattern: physical activity may help preserve cognition, but functional improvements remain limited, implying that biological recovery may occur well before noticeable behavioral change [11]. Mechanistically, aerobic exercise promotes angiogenesis and synaptic development through BDNF- and VEGF-related pathways, while acupuncture influences cholinergic and dopaminergic activity by dampening NF- κ B/NLRP3-driven inflammation [42, 53]. Even though these mechanisms improve overall neural efficiency, they do not necessarily lead to immediate changes in the higher-order executive abilities assessed by the ADAS-ADL. Moreover, because AChEIs themselves have only modest effects on daily functioning, there may be a ceiling effect that limits how much additional improvement can be detected. Short intervention periods, a lack of functional training tailored to daily tasks, and limited caregiver engagement all make it less likely that physiological improvements will translate into noticeable gains in real-world functioning.

Overall, while both interventions help strengthen neurotrophic and cholinergic pathways, meaningful gains on the ADAS-ADL likely depend on longer-term, behavior-focused strategies that can connect underlying neural improvements with the practical demands of daily life.

The BI findings - most clearly improved through moderate aerobic exercise - suggest that functional independence is best supported by steady, manageable activation of motor and vascular systems [54]. Unlike the ADAS-ADL, which focuses on more complex cognitive-behavioral activities, the BI looks at much simpler, everyday functions such as basic mobility and routine self-care. These activities depend far more on neuromuscular endurance, coordinated motor control, and an efficient circulatory system [55]. Moderate-intensity aerobic exercise tends to support these capacities by boosting mitochondrial function, promoting eNOS-related vasodilation, and reinforcing synaptic connections within cortico-striatal and cerebellar pathways. All of these physiological shifts work together to improve balance and overall movement, without triggering the oxidative stress or fatigue often brought on by high-intensity exercise [56].

Meta-analyses from previous years similarly conclude that moderate-intensity exercise is generally seen to yield the most reliable functional gains among seniors with progressive neurodegenerative disorders [11, 13]. This benefit likely arises from how, during moderate aerobic exercise, vascular, metabolic, and cholinergic systems each contribute. When this form of exercise reinforces the cholinergic effects already provided by AChEIs, sensorimotor processing can be enhanced to assist the brain in coordinating executive and motor functions - skills that are especially important for maintaining daily independence.

Acupuncture, by contrast, while useful for cognitive and emotional symptoms [17, 18], tends not to act as directly on the motor pathways, thus helping to explain why its influence on BI scores tends to be more modest. Taking the studies together, the findings suggest that everyday functional abilities depend more on changes in peripheral motor and vascular function than on cognitive gains per se. The better BI outcomes seen with moderate aerobic exercise probably reflect a combination of enhanced neuroplasticity and steady improvements in physical endurance. When these physiological changes happen at the same time, they are far more likely to show up as real, everyday improvements in how well a person can carry out basic tasks on their own. Overall, the findings of this BNMA indicate that adding supplementary therapies to AChEIs can enhance treatment

effects, though the nature of these benefits differs depending on the specific outcome being measured. Each intervention seems to offer its own type of benefit: combined and thermal acupuncture were most likely to enhance global cognitive performance, while moderate-intensity aerobic exercise and manual acupuncture appeared to be more effective for specific cognitive functions. A similar pattern was seen for functional outcomes: combined acupuncture had the highest probability of improving more complex daily activities - although not to a statistically significant extent - whereas moderate aerobic exercise more reliably supported basic functional independence. These varied patterns of response align well with what is known about their underlying mechanisms, including cholinergic activation, engagement of neurotrophic pathways, anti-inflammatory actions, and enhanced cerebral blood flow. Taken together, the overall picture suggests that acupuncture-based approaches may be better positioned to support cognitive enhancement, whereas moderate aerobic exercise may play a more effective role in strengthening functional capacity in AD. Even with the low heterogeneity and solid model convergence observed in this BNMA, a number of limitations remain. Evidence for electroacupuncture and high-intensity exercise was sparse, and the variability in acupuncture protocols and exercise intensities likely added uncertainty to the effect estimates. Because none of the trials directly compared acupuncture with aerobic exercise, the reliability of the ranking results is reduced, and conclusions drawn solely from indirect evidence can naturally be inconsistent. One additional limitation is that many of the studies were quite small and followed participants for a relatively short period, making it difficult to know how well their findings would hold up over time. Looking ahead, it would be useful for future work in this area to follow more consistent intervention protocols and to incorporate biomarker testing and neuroimaging as part of the study design. Bringing these elements together would give researchers a clearer picture of the mechanisms at work and help them determine which treatment approaches genuinely offer the most benefit.

Conclusion

This BNMA suggests that the most notable cognitive gains alongside AChEI therapy come from combined and thermal acupuncture, whereas

moderate-intensity aerobic exercise and manual acupuncture tend to be more effective for sharpening specific cognitive functions. While the added therapies showed only modest effects on day-to-day functioning overall, moderate aerobic exercise was the intervention most consistently linked with improvements in basic independent activities. To confirm these outcome-specific patterns and determine the most effective way to integrate these approaches with AChEI therapy, larger and more rigorously designed trials will be essential.

Disclosure of conflict of interest

None.

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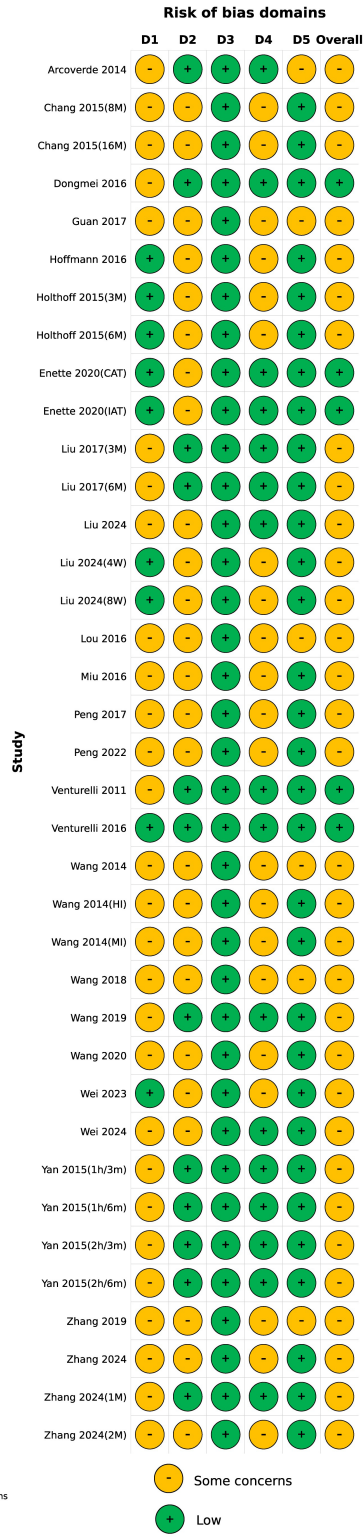
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A



B

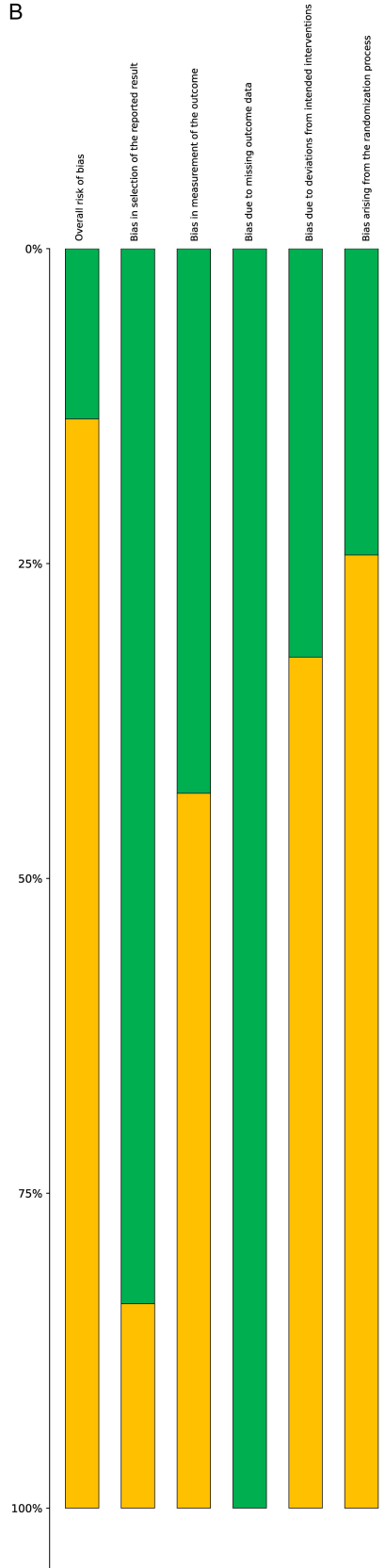
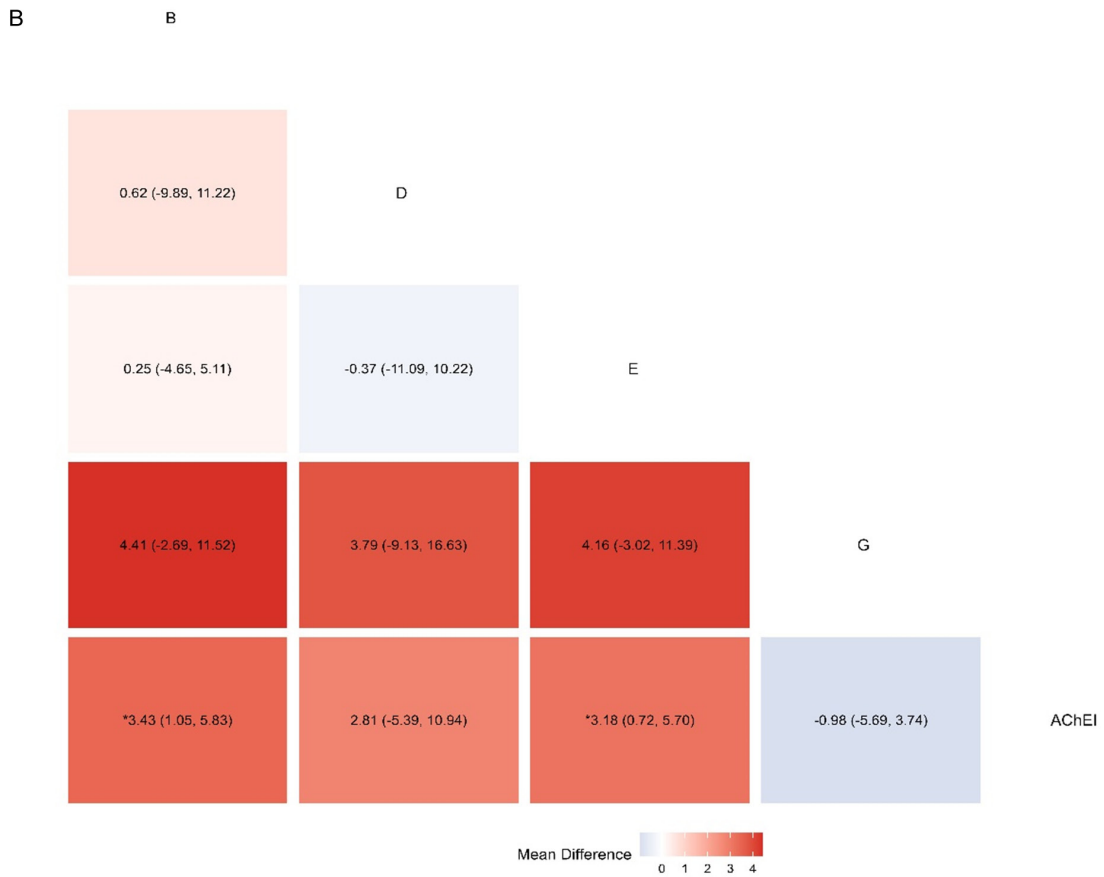
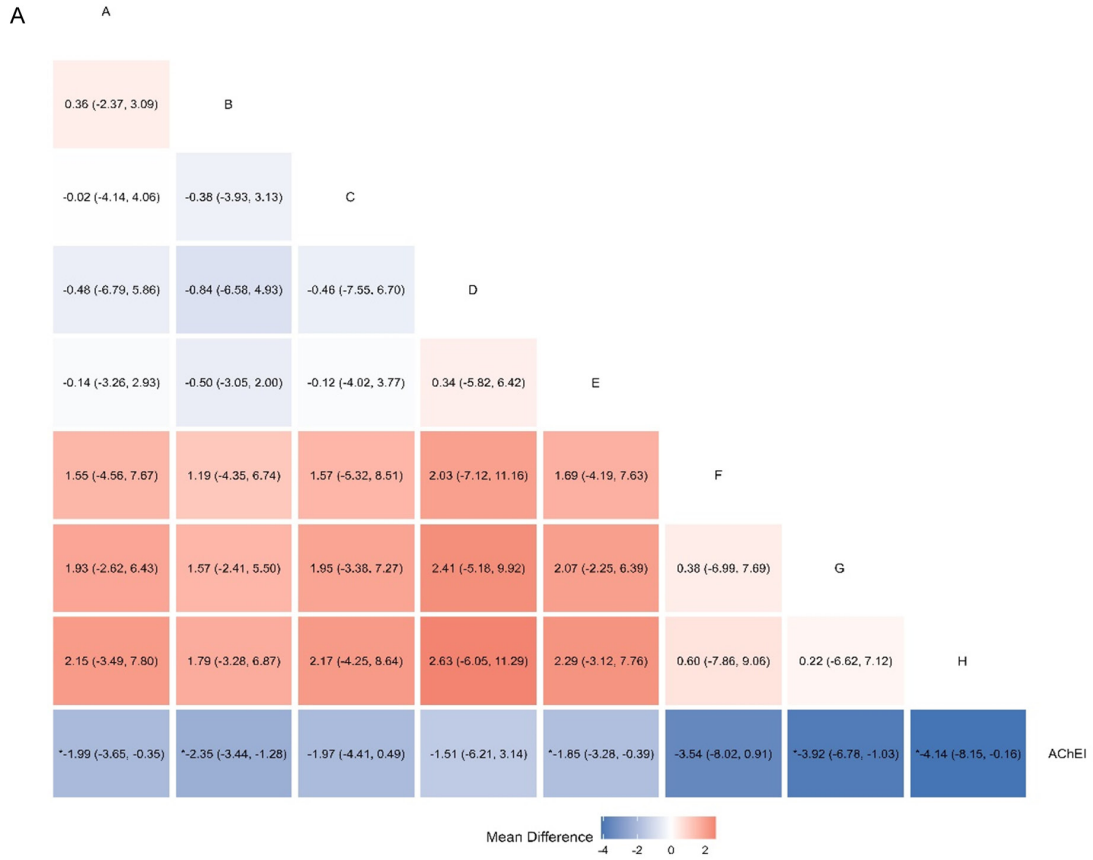


Figure S1. (A) graphical representation and (B) summary plot of the risk of bias assessment for included studies.

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Figure S2. Comparison of BNMA results for (A) MMSE and (B) ADAS-Cog. Color scale shows MD (95% CrI): red = greater improvement, blue = smaller or negative improvement. MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; MD, mean difference; CrI, credible interval; BNMA, Bayesian network meta-analysis.

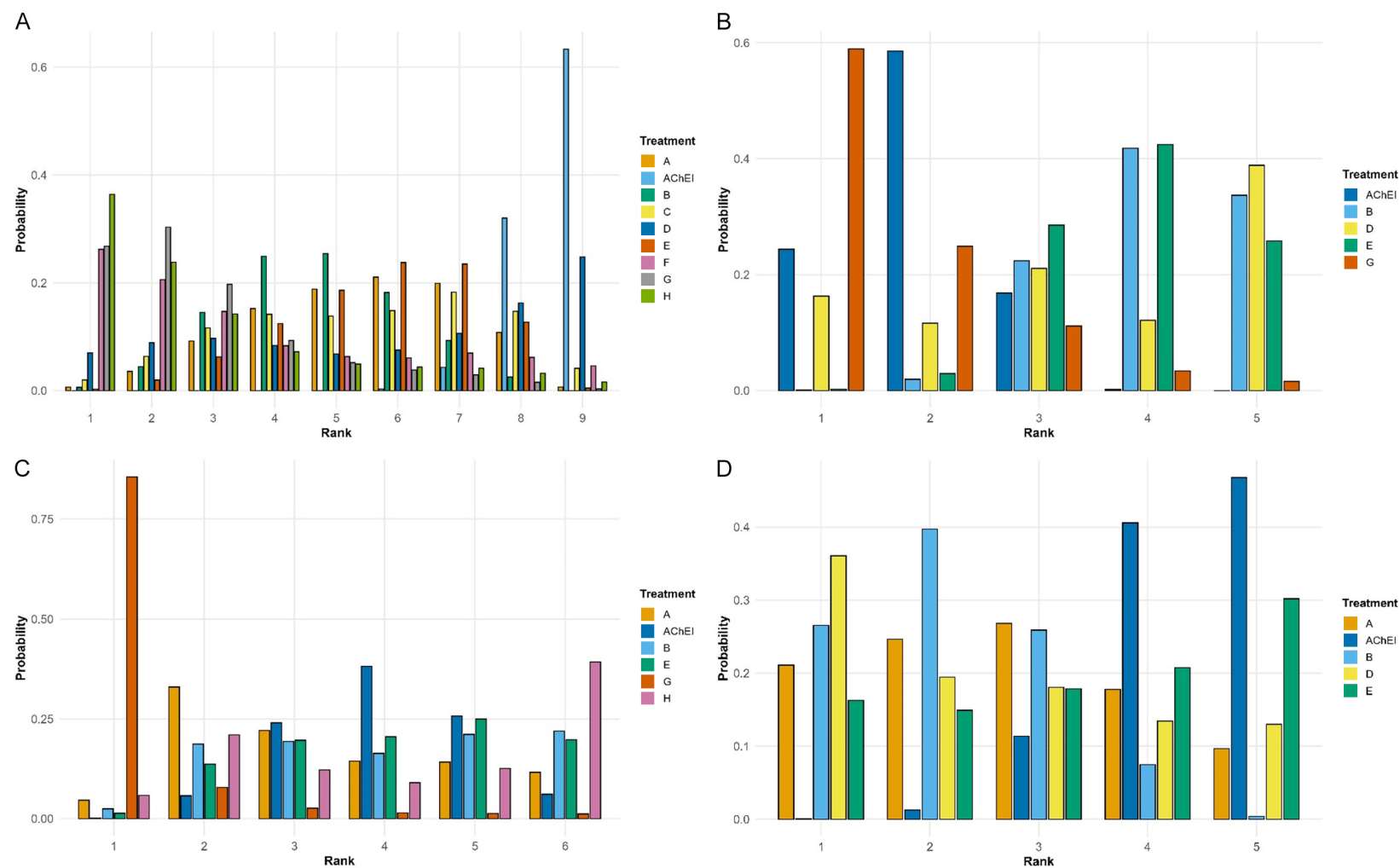
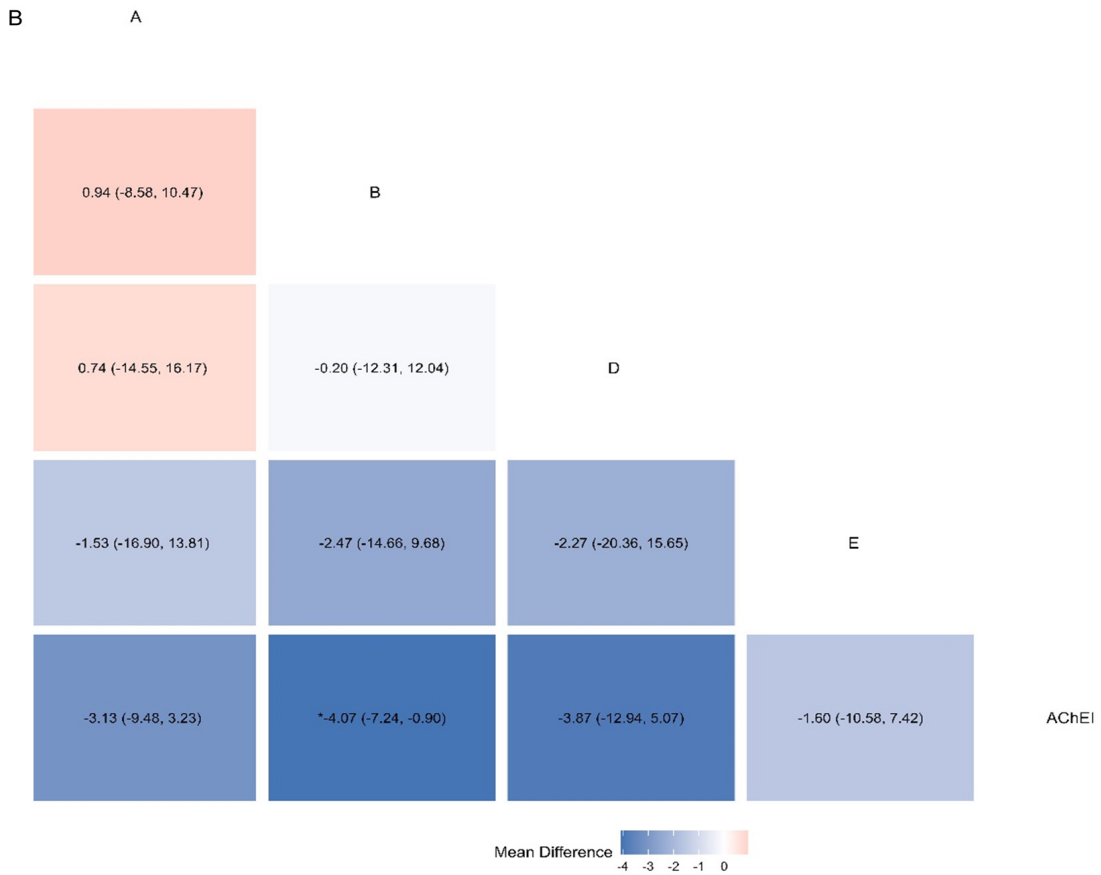
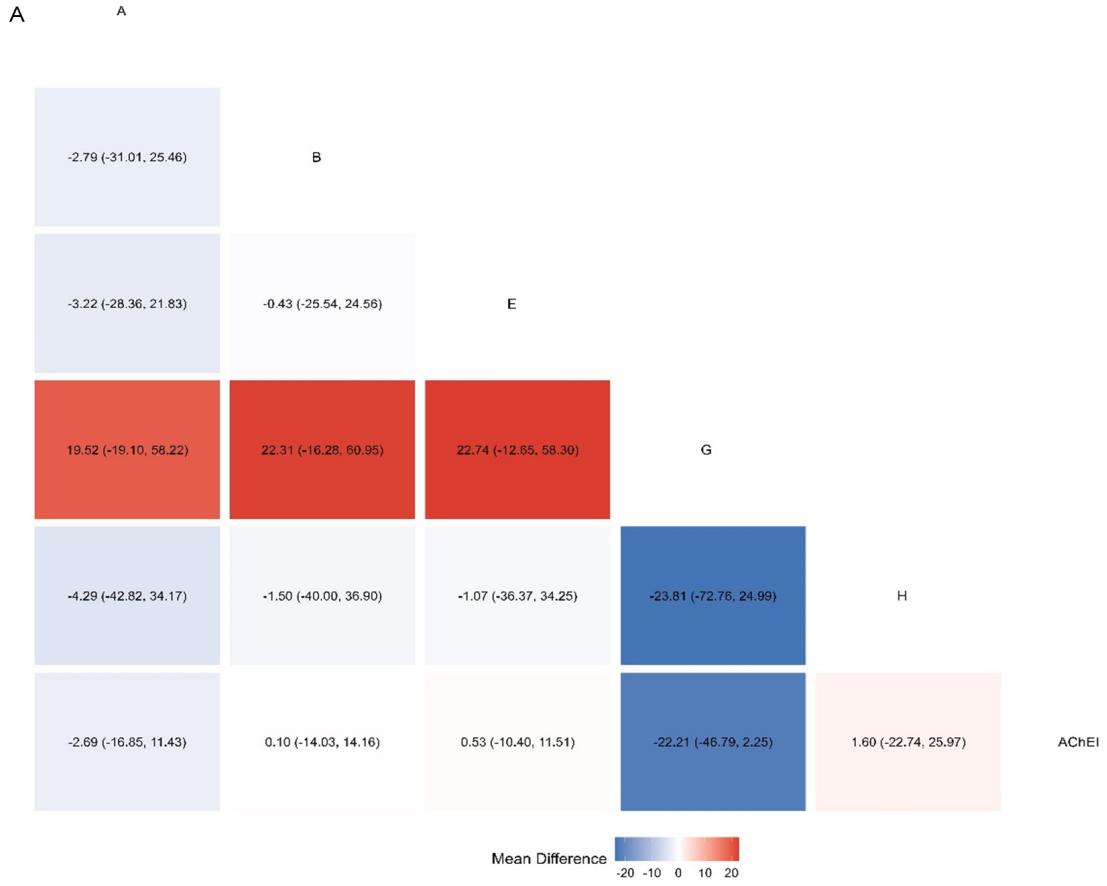


Figure S3. Ranking probability distributions of treatments across in the BNMA for (A) MMSE, (B) ADAS-Cog, (C) ADAS-ADL and (D) BI. ADAS-ADL, Alzheimer's Disease Assessment Scale-Activities of Daily Living; BI, Barthel Index.

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Figure S4. Comparison of BNMA results for (A) ADAS-ADL and (B) BI. Color scale shows MD (95% CrI): red = greater improvement, blue = smaller or negative improvement.

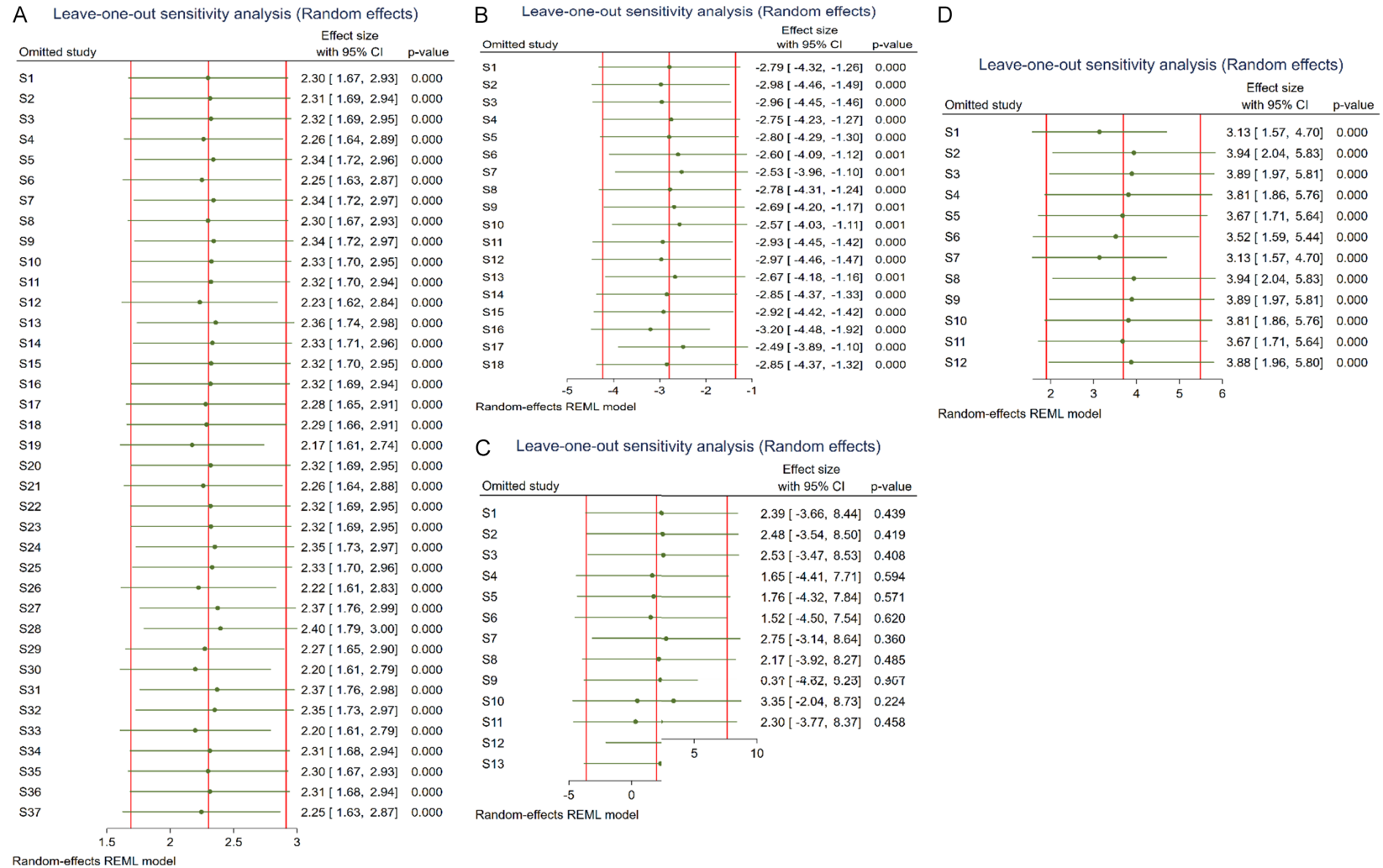


Figure S5. Sensitivity analysis of the (A) MMSE, (B) ADAS-Cog, (C) ADAS-ADL and (D) BI.

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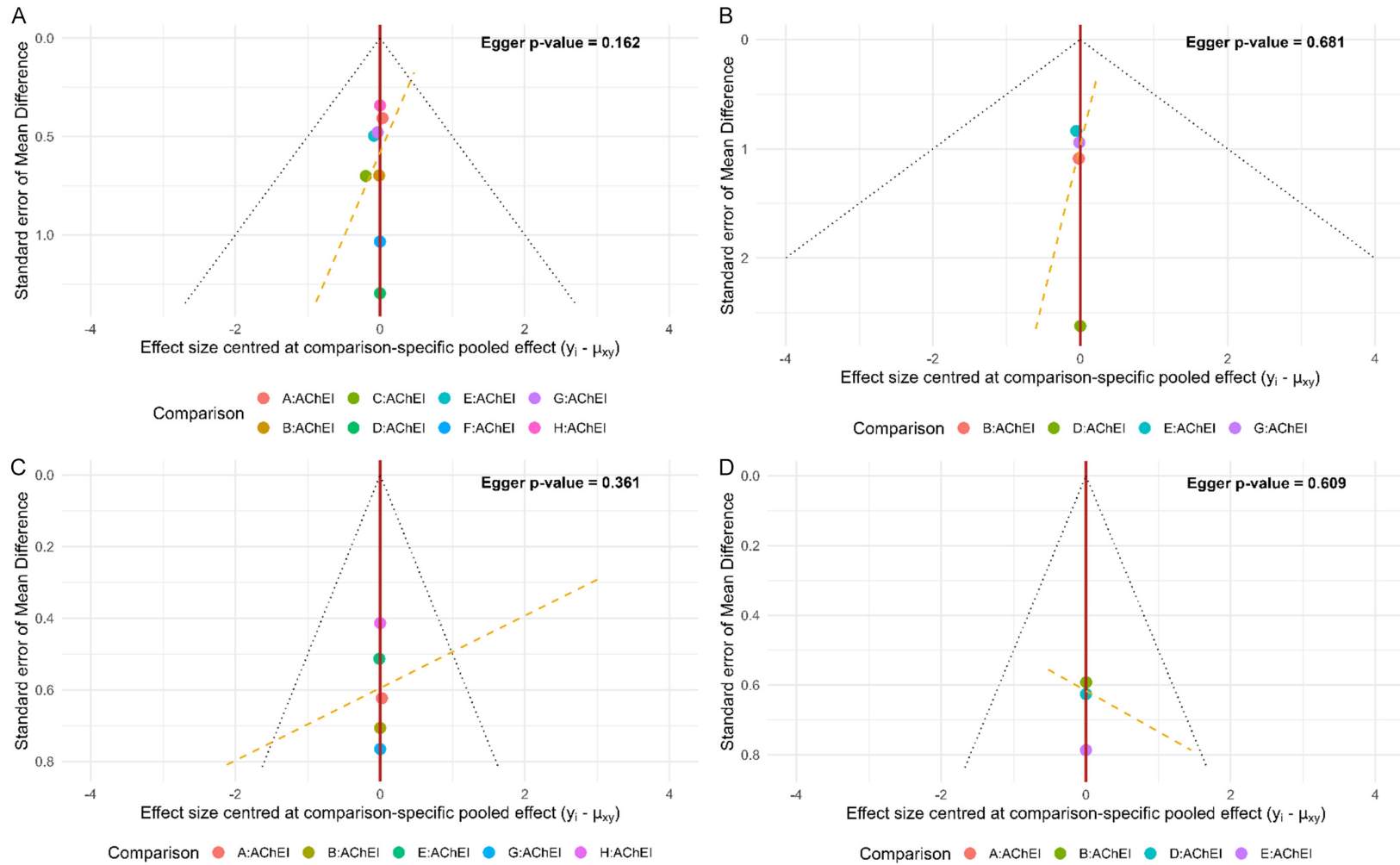


Figure S6. Funnel plots of BNMA for (A) MMSE, (B) ADAS-Cog, (C) ADAS-ADL and (D) BI.

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Table S1. Characteristics of included studies on adjunct aerobic exercise interventions with AChEIs in AD

Author & year	Country	Mean age (y/o)	Study type	Intervention (N)/intensity		Intervention Duration (months)	Session Frequency	Follow-up duration (months)	Ref.
				Exp.	Ctrl.				
Arcoverde 2014	China	78.8 ± 5	RCT	Treadmill walking + AChEIs (10)/Moderate	AChEIs (10)	4	2 sessions/week (30 minutes/session)	4	[1]
Chang 2015 (8 M)	China	70.74 ± 7.42	RCT	Stationary bicycle or treadmill + AChEIs (27)/Moderate	AChEIs (30)	2	3 sessions per week (60-90 minutes/session)	8	[2]
Chang 2015 (16 M)	China	70.74 ± 7.42	RCT	Stationary bicycle or treadmill + AChEIs (27)/Moderate	AChEIs (30)	4	3 sessions per week (60-90 minutes/session)	16	[2]
Dongmei 2016	China	72.9 ± 5.6	RCT	Mixed aerobic + AChEIs (50)/Mild to moderate	AChEIs (50)	3	4 sessions/day, 3 days/week (30 minutes/session)	3	[3]
Hoffmann K, 2016	China	70.5 ± 7.4	RCT	Mixed aerobic exercise + AChEIs (107)/Moderate-to-High	AChEIs (93)	4	7 sessions/week (60 minutes/session)	4	[4]
Enette 2020 (CAT)	France	77.9 ± 7.6	RCT	Stationary bicycle + AChEIs (14)/Moderate to high	AChEIs (21)	2.1	2 sessions/week (30 minutes/session)	1	[5]
Enette 2020 (IAT)	France	77.9 ± 7.7	RCT	Stationary bicycle + AChEIs (17)/Moderate to high	AChEIs (21)	2.1	2 sessions/week (30 minutes/session)	1	[5]
Liu J, 2024	China	72.2 ± 4.6	RCT	Stationary bicycle + AChEIs (20)/Moderate	AChEIs (20)	3	3 sessions/week (30-40 minutes/session)	3	[6]
Liu 2017 (3 M)	China	70.9 ± 9.2	RCT	Group-based full-body movements + AChEIs (24)/Moderate	AChEIs (24)	3	3 sessions/week (40 minutes/session)	3	[7]
Liu 2017 (6 M)	China	70.9 ± 9.2	RCT	Group-based full-body movements + AChEIs (24)/Moderate	AChEIs (24)	6.0	3 sessions/week (40 minutes/session)	6	[7]
Miu 2016	China	NS	RCT	Brisk walking + AChEIs (39)/Moderate	AChEIs (39)	4	≥ 3 sessions/week (20 minutes/session)	4	[8]
Venturelli 2011	Italy	84 ± 5	RCT	Walking + AChEIs (11)/Moderate	AChEIs (10)	6	4 sessions/week (30 minutes/session)	NA	[9]
Venturelli 2016	Italy	84 ± 7	RCT	Walking + AChEIs (20)/Moderate	AChEIs (20)	3	5 sessions/week (60 minutes/session)	NA	[10]
Wang 2019	China	NS	RCT	Group-based full-body movements + AChEIs (18)/Moderate	AChEIs (18)	3	3 sessions/week (35 minutes/session)	NA	[11]
Wang 2014 (MI)	China	NS	RCT	Stationary bicycle + AChEIs (13)/Moderate	AChEIs (26)	3	3 sessions/week (45 minutes/session)	NA	[12]
Wang 2014 (HI)	China	NS	RCT	Stationary bicycle + AChEIs (13)/High	AChEIs (26)	3	3 sessions/week (45 minutes/session)	NA	[12]
Wei 2024	China	NS	RCT	Baduanjin-based exercise + AChEIs (48)/Mild to moderate	AChEIs (50)	1	Daily (30 minutes/session)	NA	[13]
Yan 2015 (1 h/3 m)	China	72.1 ± 6.1	RCT	Stationary bicycle + AChEIs (18)/Moderate	AChEIs (18)	6	(1 hour) 2 sessions/week (30 min/session)	NA	[14]
Yan 2015 (1 h/6 m)	China	72.1 ± 6.2	RCT	Stationary bicycle + AChEIs (18)/Moderate	AChEIs (18)	6	(1 hour) 2 sessions/week (30 min/session)	NA	[14]
Yan 2015 (2 h/3 m)	China	71.5 ± 5.8	RCT	Stationary bicycle + AChEIs (18)/Moderate	AChEIs (18)	6	(2 hours) 3 sessions/week (40 min/session)	NA	[14]
Yan 2015 (2 h/6 m)	China	71.5 ± 5.9	RCT	Stationary bicycle + AChEIs (18)/Moderate	AChEIs (18)	6	(2 hours) 3 sessions/week (40 min/session)	NA	[14]

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Zhang 2024 (1 M)	China	NS	RCT	Mixed aerobic exercise + AChEIs (36)/Mild to moderate	AChEIs (36)	2	3-5 sessions/week (50 minutes/session)	NA	[15]
Zhang 2024 (2 M)	China	NS	RCT	Mixed aerobic exercise + AChEIs (36)/Mild to moderate	AChEIs (36)	2	3-5 sessions/week (50 minutes/session)	NA	[15]
Holthoff 2015 (3 M)	Germany	72.40 ± 4.34	RCT	Stationary bicycle + AChEIs (15)/Mild to moderate	AChEIs (15)	3	3 sessions/week (30 minutes/session)	3	[16]
Holthoff 2015 (6 M)	Germany	72.40 ± 4.34	RCT	Stationary bicycle + AChEIs (15)/Mild to moderate	AChEIs (15)	3	3 sessions/week (30 minutes/session)	6	[16]

AD: Alzheimer's disease, Exp.: Experimental group, Ctrl.: Control group, RCT: Randomized Controlled Trial, AChEIs: Acetylcholinesterase Inhibitors, y/o: years old, NS: Not specified, NA: Not available, CAT: Continuous Aerobic Training, IAT: Interval Aerobic Training, HI: High intensity, MI: Moderate intensity.

Table S2. Characteristics of included studies on adjunct acupuncture therapies with AChEIs in AD

Author & Year	Country	Mean age (y/o)	Study	Intervention (N)		Intervention Duration (months)	Session Frequency	Acupoints	Follow-up duration (months)	Ref.
				Exp.	Ctrl.					
Guan 2017	China	70.5 ± 9.3	RCT	MAC + AChEIs (30)	AChEIs (30)	2	6 sessions per week (NS)	Forehead midline (E zhongxian), vertex midline (Ding zhongxian), anterior temporal line (Nie qianxian), posterior temporal line (Nie houxian), Shenshu (BL23), Xuanzhong (GB39), Taixi (KI3), Zusanli (ST36), Shuigou (GV26)	2	[17]
Liu 2024 (4 W)	China	64.77 ± 2.68	RCT	MAC + AChEIs (30)	AChEIs (30)	2	6 sessions/week (30 minutes/session)	Baihui (GV20), Emotional area (three points including Yintang [EX-HN3] and two points 2 cm above the inner canthi), Sishencong (EX-HN1), Shuaigu (GB8, bilateral), Fengchi (GB20, bilateral), Neiguan (PC6, bilateral), Dazhong (KI4, bilateral), Zusanli (ST36, bilateral), and Sanyinjiao (SP6, bilateral)	4	[18]
Liu 2024 (8 W)	China	64.77 ± 2.68	RCT	MAC + AChEIs (30)	AChEIs (30)	2	6 sessions/week (30 minutes/session)	Baihui (GV20), Emotional area (three points including Yintang [EX-HN3] and two points 2 cm above the inner canthi), Sishencong (EX-HN1), Shuaigu (GB8, bilateral), Fengchi (GB20, bilateral), Neiguan (PC6, bilateral), Dazhong (KI4, bilateral), Zusanli (ST36, bilateral), and Sanyinjiao (SP6, bilateral)	8	[18]
Peng 2017	China	69.4 ± 5.4	RCT	EAC + AChEIs (25)	AChEIs (25)	2	7 sessions/week (25 minutes/session)	GV24 (Shenting), GV20 (Baihui), GV14 (Dazhui), GV16 (Fengfu), GV4 (Mingmen), KI1 (Yongquan)	NA	[19]
Peng 2022	China	68.9 ± 8.3	RCT	MAC + AChEIs (30)	AChEIs (30)	1	7 sessions/week (30 minutes/session)	Fengfu (GV16), Baihui (GV20), Shenting (GV24)	NA	[20]
Wang 2014	China	69.4 ± 7.2	RCT	MAC + AChEIs (27)	AChEIs (28)	2	6 sessions/week (30 minutes/session)	Along the cranial sutures: coronal suture, sagittal suture, lambdoidal suture, and frontotemporal sutures (α and β angles)	NA	[21]
Wei 2023	China	71.4 ± 7.7	RCT	MAC + AChEIs (30)	AChEIs (30)	1.5	6 sessions/week (30 minutes/session)	Baihui (GV20), Sishencong (EX-HN1), bilateral Shenmen (HT7), Neiguan (PC6), Zusanli (ST36), Sanyinjiao (SP6), and Xuanzhong (GB39)	1.4	[22]

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Zhang 2024	China	68.60 ± 7.79	RCT	CAC + AChEIs (30)	AChEIs (30)	2	7 sessions/week (30 minutes/session)	Baihui (GV20), Yintang (GV24+), Sishencong (EX-HN1), "Emotional area", Shenting (GV24), "Abdominal area 1", "Abdominal area 8", bilateral Fengchi (GB20), Taixi (KI3), Xuanzhong (GB39), Zusanli (ST36)	2	[23]
Lou 2016	China	65.82 ± 2.39	RCT	MAC + AChEIs (60)	AChEIs (60)	6	NR	Baihui (DU20), Sishencong (EX-HN1), Fengfu (DU16); <i>Additional points:</i> Yongquan (KI1), Taixi (KI3), Shenshu (BL23), Sanyinjiao (SP6), Zusanli (ST36), Fenglong (ST40); <i>Auricular points for patching:</i> Heart, Kidney, Forehead, Subcortex, Shenmen, Sympathetic Nerve	6	[24]
Wang 2018	China	70.88 ± 8.95	RCT	MAC + AChEIs (55)	AChEIs (54)	3	NR	Shanzhong (CV17), Zhongwan (CV12), Qihai (CV6), Xuehai (SP10, bilateral), Zusanli (ST36, bilateral)	NR	[25]
Wang 2020	China	72.74 ± 8.36	RCT	CAC + AChEIs (31)	AChEIs (30)	2	3 sessions/week (20 minutes/session)	Baihui (DU20), Yintang (EX-HN3), bilateral Toulinqi (GB15), bilateral Shuaigu (GB8), bilateral Fengchi (GB20), plus bilateral Hegu (LI4), Quchi (LI11), Zusanli (ST36), and Taichong (LR3)	NR	[26]
Zhang 2019	China	72.6 ± 9.2	RCT	FNT + AChEIs (46)	AChEIs (46)	3	1 session/week (NR)	Shenshu (BL23, bilateral), Pishu (BL20, bilateral), Baihui (GV20), Xinshu (BL15, bilateral), Zusanli (ST36, bilateral), and Sishencong (EX-HN1, 4 points)	3	[27]

MAC: Manual Acupuncture, CAC: Combined Acupuncture, EAC: Electroacupuncture, FNT: Fire Needle Therapy, GV: Governor Vessel (Du Meridian), CV: Conception Vessel (Ren Meridian), KI: Kidney meridian, GB: Gallbladder meridian, SP: Spleen meridian, ST: Stomach meridian, HT: Heart meridian, PC: Pericardium meridian, LI: Large Intestine meridian, LR: Liver meridian, BL: Bladder meridian.

Table S3. PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity</i> . Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	3
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4

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METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	5
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	6
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> ● Handling of multi-arm trials; ● Selection of variance structure; ● Selection of prior distributions in Bayesian analyses; and Assessment of model fit. 	6
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> ● Sensitivity or subgroup analyses; ● Meta-regression analyses; ● Alternative formulations of the treatment network; and ● Use of alternative prior distributions for Bayesian analyses (if applicable). 	N/A
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	7

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Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-11
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	12
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	1

PICOS = population, intervention, comparators, outcomes, study design. Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement. *Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section. #: number.

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