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Original Article

Comparative effects of some pharmacological and non-pharmacological interventions on cognitive function in Alzheimer's disease: A Bayesian network meta-analysis

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ABSTRACT

Background: Given the growing global public health burden of Alzheimer's disease, this study used the Bayesian network meta-analysis to assess the effects of pharmacological and non-pharmacological interventions on cognitive function in the population with Alzheimer's disease.
Methods: Two investigators screened the literature from English databases (PubMed, MEDLINE, Embase, Cochrane CENTRAL, and Web of Science) and three major Chinese bibliographical databases (China National Knowledge Infrastructure Database, Wanfang Database, and VIP Database). We assessed the risk of bias and publication bias of the selected literature. Subsequently, a Bayesian network meta-analysis and meta-regression were conducted to further investigate the comparative efficacy of different interventions on cognitive outcomes.
Results: A total of 4788 cases were initially identified. Photobiomodulation [SMD=0.66, 95%CrI (0.29, 1.02)], enriching environment [SMD=0.69, 95%CrI (0.08, 1.31)], pharmacological therapy [SMD=0.36, 95%CrI (0.17, 0.55)], cognitive stimulation therapy [SMD=0.32, 95%CrI (0.11, 0.55)] and exercise therapy [SMD=0.28, 95% CrI (0.06, 0.51)] showed considerable enhancements in cognitive function among individuals with Alzheimer's disease. Photobiomodulation and enriching environment stood out, with their effects more potent than those of other therapies, as indicated by the surface under the cumulative ranking curve — photobiomodulation clocked in at 87.3%, while enriching environment scored 83.8%, versus pharmacological therapy's 54.7%.
Conclusions: Among the interventions evaluated, photobiomodulation and enriching environment were associated with better improvements in cognitive function than pharmacological therapy. Exercise therapy and cognitive stimulation therapy also demonstrated beneficial effects. Music therapy showed no statistical difference from the control group. In addition, the research developed an innovative approach to contrast pharmacological and non-pharmacological treatments for Alzheimer's disease.
Registration: PROSPERO 2025 CRD420251075628. Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420251075628.

1. Introduction

Alzheimer's disease (AD) encompasses a family of progressive neurodegenerative syndromes that primarily lead to cognitive decline, often accompanied by language impairment, personality changes, and behaviour disturbances. As per the latest figures from Alzheimer's Disease International (ADI) in 2023, there are more than 55 million cases of AD around the world, and it is anticipated that the figure will reach 139 million by 2050 [1]. The burden is particularly pronounced in rapidly aging countries such as China. AD substantially reduces quality of life and imposes heavy caregiving and economic burdens on families and healthcare systems. Although no curative treatments for AD are

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currently available, abundant evidences indicate that pharmacological and non-pharmacological interventions may delay cognitive deterioration and partially alleviate symptoms.

Pharmacological treatments, including donepezil, memantine, and the recently approved sodium oligomannate, are commonly used in clinical practice. Memantine and donepezil are classified as Class I recommendations with C-EO level evidence for enhancing cognitive function for AD, and are guideline-recommended agents [2]. The cholinesterase inhibitor donepezil remains a cornerstone of treatment for mild to moderate AD [3], enhancing cholinergic transmission by inhibiting the breakdown of acetylcholine. In moderate to severe stages, the NMDA receptor antagonist memantine is utilized to modulate glutamatergic excitotoxicity and is frequently combined with cholinesterase inhibitors for synergistic effects [4]. In addition to common mechanisms such as reducing Aβ plaque deposition, tau protein phosphorylation, and inhibiting neuroinflammation, donepezil can inhibit acetylcholinesterase and enhance cholinergic signal transmission [3]; memantine, a non-competitive NMDA receptor antagonist, protects neurons from excitotoxic damage [4]. Sodium oligomannate, a new pharmacological agent in China, was included to reflect emerging therapeutic strategies supported by phase III trials in Asian populations. Sodium oligomannate can reshape the intestinal flora and reduce abnormal amino acid levels [5]. Long-term pharmacological intervention can significantly delay the progression of dementia [6]. However, concerns regarding adverse effects—such as bradycardia, gastrointestinal symptoms, and altered mental states—have prompted increasing interest in safer, more tolerable alternatives [7–13].

Non-pharmacological interventions are gaining momentum due to their non-invasive nature, safety profile, and accessibility. Widely studied modalities include photobiomodulation (PBM), enriching environment (EE), exercise therapy (ET), music therapy (MT), and cognitive stimulation therapy (CST). PBM is a non-invasive therapeutic technique that uses low-level light, typically red or near-infrared, to stimulate cellular functions, promote mitochondrial energy production [14], reduce neuroinflammation [15], and enhance tissue repair and neuroprotection [16]. EE provides multimodal, multisensory, comprehensive interventions that can enhance cognitive, social, and physical stimulation within a well-designed, structured environment or through activities such as discussions, puzzles, and themed games. Despite promising mechanisms and growing research interest, PBM and EE remain underexplored and have been selected infrequently to compare their effects on cognition in previous analyses. ET often refers to structured aerobic, resistance, or multicomponent training to enhance cognitive function, neurotrophic factor expression, and cerebrovascular health. Among non-pharmacological interventions, ET has been extensively studied and has demonstrated consistent beneficial effects on AD [17]. CST includes group or individual-based structured activities targeting multiple cognitive domains, such as memory, attention, language, and executive function. MT covers listening, singing, playing instruments, and composing. These activities are usually administered by a credentialed professional to address individualized physical, emotional, cognitive, and social needs within a therapeutic relationship. Besides, CST and MT have been incorporated into several clinical guidelines. Comprehensively considering both intervention effectiveness and economic evidence, the National Institute for Health and Care Excellence offers recommendations, such as a range of activities, music, and group cognitive stimulation therapy [18]. Furthermore, CST had direct comparative evidence with some interventions, such as ET and pharmacological therapy (PT). It can be taken for a shared intervention, bolstering the transferability of the network meta-analysis. Previous meta-analyses typically focused on a single intervention, with limited comparative insights into the efficacy of diverse pharmacological and non-pharmacological interventions.

To bridge this knowledge gap, we conducted a Bayesian network meta-analysis of randomized controlled trials, comprehensively assessing and ranking the efficacy of three pharmacological and five non-pharmacological interventions for cognitive function in people with AD. By synthesizing direct and indirect comparisons, this study aimed to provide robust, evidence-based guidance for clinical decision-making and promote more personalized and context-specific treatment strategies for the management of AD.

2. Methods

This protocol, a systematic review and network meta-analysis, was designed and performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [19] and adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [20]. The protocol was finalized before formal study screening, data extraction, and statistical analysis, and was then registered with PROSPERO (CRD420251075628).

2.1. Literature search strategies

Investigators searched English-language bibliographical databases such as PubMed, MEDLINE, Embase, Cochrane CENTRAL, and Web of Science, as well as Chinese-language bibliographical databases including China National Knowledge Infrastructure, Wanfang, and VIP Database. The selection and classification of interventions were informed by previously published reviews in the field of Alzheimer's disease and cognitive interventions [21–24]. This study was not intended to provide an exhaustive comparison of all possible interventions for Alzheimer's disease. Instead, we predefined a limited set of mainstream, cognition-oriented interventions that are most frequently evaluated in randomized controlled trials and recommended in clinical guidelines. The categorization was defined at the treatment-node level for analytical modeling purposes. Medical Subject Headings (MeSH) terms and relevant free-text keywords related to cognitive impairment or Alzheimer's disease in older adults were used in the search strategy. They utilized Medical Subject Headings and relevant text keywords focused on cognitive impairment or AD in older adults. For example, using the keyword ("Alzheimer's disease"), the terms for eight interventions ("Photobiomodulation", "Enriching environment", "Exercise therapy", "Music therapy", "Pharmacological therapies", "Donepezil", "Memantine", "Sodium Oligomannate"), and "Randomized controlled trial" were combined to search for relevant literatures.

We extracted eligible studies using the search strategy and search terms mentioned above for dementia interventions and included studies available in the literature from their inception to June 30, 2025, with no language restrictions. This date denotes the temporal coverage of the literature search rather than the completion of the review process. The search strategy was consistent with guidelines in the Cochrane Handbook [19]. **Supplementary material 1** is the comprehensive search strategy.

2.2. Selection criteria

The inclusion criteria kept to the PICOS principles: (1) Population: Individuals were diagnosed with AD by the National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines [25], the Diagnostic and Statistical Manual of Mental Disorders (DSMIV-TR) [26], and the Neurological and Communication Disorders or Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [27], as well as aged more than 65 years, while there were no other primary and secondary diseases accompanying. Studies were excluded if participants had primary or secondary conditions known to affect cognitive or neurological function, such as stroke, malignancies, or major depressive disorder. (2) Interventions: Interventions included non-pharmacological interventions, including PBM, EE, ET, MT, and CST, and pharmacological interventions, including donepezil, memantine, and sodium oligomannate, which were selected according to their pharmacology and were combined as PT. **Supplementary**

Table S2 presents a brief description of the pharmacological and non-pharmacological interventions in the included literature. (3) Comparison: Eligible groups within studies included usual care, placebo, or any other interventions included in the studies. (4) Outcomes: Cognition was evaluated by the validated tools, incorporating the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), or the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog). (5) Study design: Randomized controlled trials (RCTs).

Exclusion criteria included: (1) duplicate literature. (2) animal experiments, reviews, secondary studies, conference papers, and abstracts. (3) literature with incomplete data, outcome indicators without mean difference (MD) and standard deviation (SD), or data difficult to extract. (4) studies involving subjects diagnosed with other diseases affecting cognition, such as Parkinson's disease and vascular dementia.

2.3. Data collection and quality evaluation

According to the predetermined search strategy, two investigators searched the databases listed above and stored all relevant articles retrieved in EndNote X9, via which duplicate literature was deleted. They assessed the titles and abstracts to perform the initial screening. Subsequently, they assessed the full texts against inclusion and exclusion criteria and excluded abstracts that were irrelevant or unclear.

Two researchers independently extracted details for each study via a standardized data extraction table. The table covered the name of the first author, year of publication, country, dementia type of the study subjects, age, sample size, dropout rate, male-to-female ratio, types of interventions, duration and frequency of intervention, and outcome indicators such as MD and SD. Two investigators independently screened the literature in two rounds of screening and extracted data from the included studies. Then they cross-checked the collected data, with any disagreements being resolved by a third researcher.

The Cochrane Risk of Bias tool 2.0 (RoB 2.0) was utilized to evaluate risk of bias [19]. It assesses the overall quality of the included studies across six domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, selection of the reported results, and overall risk of bias. Two researchers rated these domains as "low risk", "some concerns", or "high risk". In case of discrepancies in rating, they would discuss with each other or consult a third investigator.

2.4. Data analysis

This network meta-analysis aimed to identify the optimal intervention for enhancing cognitive function in AD. Since all outcome indicators were continuous variables, the network estimates were presented as standard mean difference (SMD) and 95% Credible Interval (95%CrI) [19]. When data were missing (e.g., MD, SD, or p), we would try to contact the authors to retrieve missing data or calculate the SMD and 95%CrI by the RoB 2.0 in the Cochrane Handbook for Systematic Reviews of Interventions [28]. It was important to note that high heterogeneity may compromise the consistency and validity of network meta-analysis results [29,30]. To improve the effectiveness of the indirect comparison [29], we drew a boxplot (**Supplementary Figure S1**) to identify outliers, excluded the corresponding literature and data, and used the random-effects model to control potential heterogeneity [31,32].

The steps for the network meta-analysis were as follows. Firstly, a network plot was drawn to illustrate the available evidence construction and the comparisons between interventions. Each node represented a type of intervention, its size indicated the number of that intervention, and the lines connecting nodes showed the number of studies that directly compared those two interventions. Secondly, using the node-splitting method, the local inconsistency between the direct and indirect evidence across the network was calculated, and $p < 0.05$ indicated the presence of inconsistency [33]. Third, the network meta-analysis model was constructed within a hierarchical random-effects framework. A Markov Chain Monte Carlo (MCMC) simulation was employed to sample from the posterior distributions of the model parameters. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic, with a potential scale reduction factor (R-hat) of < 1.05 for all parameters, indicating satisfactory convergence. A league table was plotted to present a comprehensive matrix of relative effect estimates and confidence intervals for all pairwise comparisons, both direct and indirect, within the network. Then we ranked all interventions and the control group (CON) based on their surface under the cumulative ranking curve (SUCRA) scores. The SUCRA score ranged from 0% to 100%, and higher scores indicate greater potential to improve cognition [34]. Fourthly, the Q and I^2 statistics would be utilized to evaluate the magnitude and significance of heterogeneity if the network plot formed a closed loop. $p < 0.10$ and $I^2 > 50\%$ suggested significant heterogeneity, and the random-effects model would be selected. In other scenarios, the fixed-effects model would be selected as more appropriate for the analysis. Fifthly, a meta-regression was performed within the Bayesian random-effects framework to investigate the association between covariates and the outcome measures, with results expressed as the regression coefficient β and its 95%CrI. A positive value of β indicated that the covariate was positively correlated with the outcome index. When the 95%CrI included 0, it indicated that the covariates had no significant effect on the outcome measure. Sixthly, a funnel plot would be utilized to evaluate potential publication bias in outcomes if the number of included studies exceeded 10. The apparent asymmetry of the funnel plot demonstrated a high risk of bias [35].

The computational analysis in this study was carried out using R (version 4.3.2), and the adopted R packages included "*netmeta*", "*Meta*", "*coda*", "*gemtc*", and so on. Stata 16.0 was also used to generate the network plot and funnel plot.

3. Results

3.1. Literature screening process and results

A total of 4731 records were retrieved from database searches, with an additional 152 records sourced from other sources. 1965 studies were excluded because of duplicates. Another 2229 articles were eliminated after screening the titles and abstracts of the remaining records. Following a full-text assessment based on predetermined criteria, 632 studies were further excluded. Finally, 57 studies satisfied the inclusion criteria and were adopted in this network meta-analysis [36–93]. The detailed retrieval procedure is shown in Fig. 1. The detailed categories and reasons for study exclusion at the full-text screening stage are summarized in **Supplementary Table S1**.

3.2. Summary characteristics of the eligible studies

A total of 57 RCTs were retrieved using the search strategy described above, encompassing 6737 individuals with AD. 3077 individuals were in CON, and 3660 were in the intervention group. There were 7 studies involving PBM, 2 involving EE, 14 involving ET, 8 involving MT, 16 involving PT, and 17 involving CST. There were 55 two-arm trials and 2 three-arm trials. Double-blind methods were explicitly reported in 28 articles, whereas single-blind procedures were described in 15 articles. Table 1 presents the summary characteristics of the eligible studies.

3.3. Risk of bias and bias assessment

Among the 57 involved studies, 3 (5.3%) were rated as high risk of bias, 21 (36.8%) as moderate risk, and 33 (57.9%) as low risk. **Supplementary Figure S2** shows the distribution of potential bias across these included studies, and **Supplementary Table S3** shows the proportion of risk of bias in each intervention. In addition, the funnel plot (**Supplementary Figure S3**) appeared basically symmetrical.

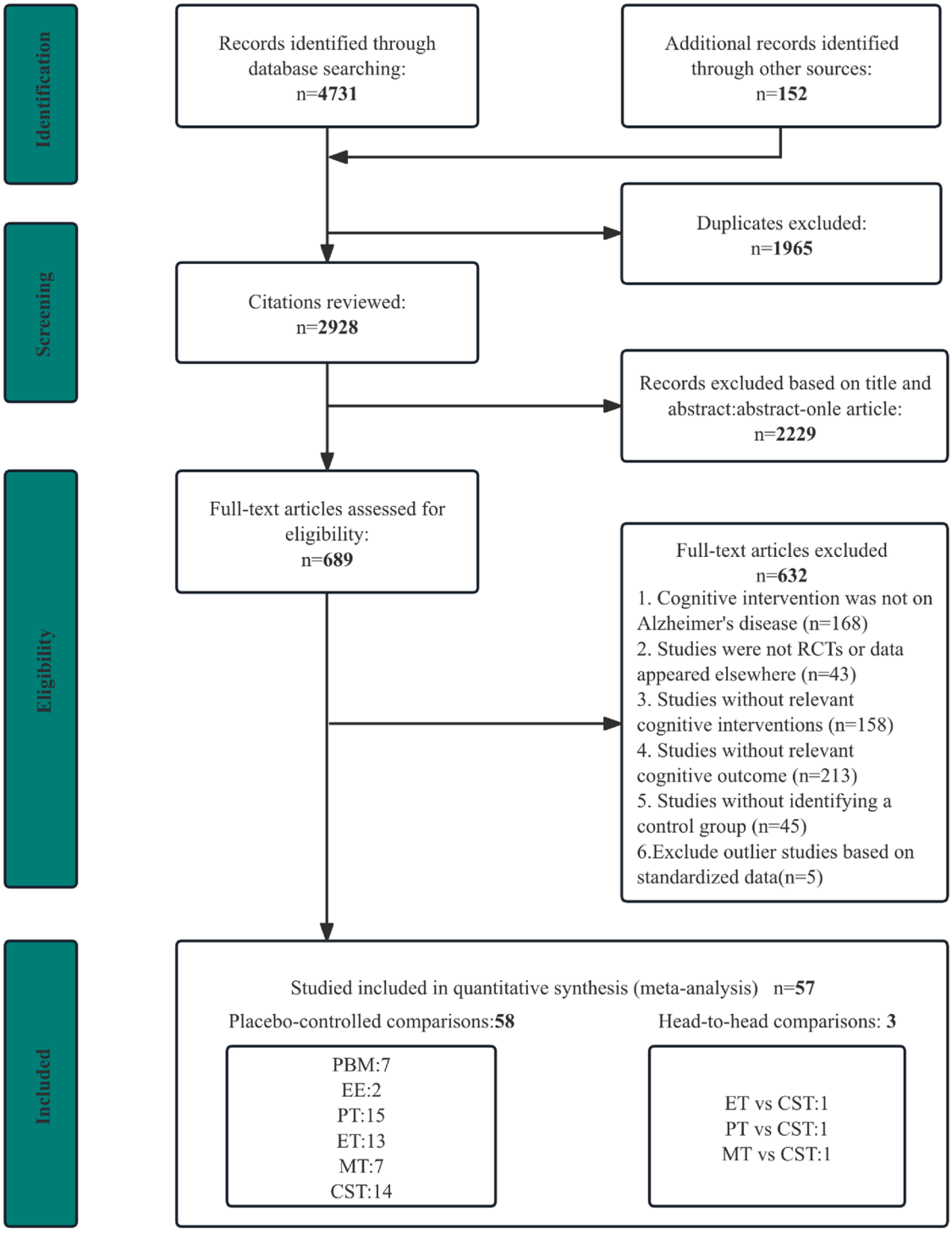

Fig. 1. Flow diagram for the literature search.
PBM: photobiomodulation; EE: enriching environment; ET: exercise therapy; MT: music therapy; PT: pharmacological intervention; CST: cognitive stimulation therapy; CON: control group.

Therefore, we conducted Egger's regression test ($t = 2.58$, $p = 0.012$) and Begg's test ($z = 2.24$, $p = 0.0251$), indicating the presence of publication bias.

3.4. Network diagram

The network covered 6 treatments, of which PBM (n = 7), EE (n = 2), ET (n = 12), MT (n = 7), CST (n = 14), and PT (n = 16) had direct comparisons with CON, respectively. Furthermore, the network evidence included direct comparisons of CST with MT (n = 1), ET (n = 1), and PT (n = 1), as well as key indirect comparisons involving these interventions and CON. Direct evidence for the different interventions is demonstrated in Fig. 2.

3.5. Network meta-analysis

The Brooks-Gelman-Rubin diagnostic indicated that all potential scale reduction factors (R-hat) were equal to 1, which proved excellent

Table 1
Characteristics of included comparative studies.

References	Country	Type	Diagnose	Age (Mean ± SD)		Sample		MMSE (baseline)		Duration (weeks)	Frequence (d/W)	Time (min)
				EXP	CON	EXP	CON	EXP	CON			
Xiaoming Qi (2021)	USA	PBM vs. CON	Mild AD/ ADRD	Male: 74 ± 7.5 Female: 73.8 ± 8.4		39	16	ALL:15–24		8	7	6
Damir Nizamutdinov (2021)	USA	PBM vs. CON	Dementia	72.4 ± 8.2	77.8 ± 5.2	29	28	23.2 ± 1.6	2.8 ± 2.6	9	7	6
Ali(2022)	Iran	PBM vs. CON	Dementia	78.13 ± 6.19	76.13 ± 7.53	16	16	6.0 ± 6.99	15.13 ±5.78	2	3	10
Nagy(2021)	Egypt	PBM vs. CON	AD	69.50 ± 2.0	70.00 ± 2.0	30	30	23.96 ±0.67	23.42 ±0.85	12	6	30
Chen(2023)	China	PBM vs. CON	AD	68.9 ± 9.05	72.1 ± 8.46	7	7	20.2 ± 4.98	18.5 ± 3.21	12	5	6
Guillaume Blivet (2022)	France	PBM vs. CON	AD	72.4 ± 7.0	73.7 ± 6.4	26	24	20.5 ± 3.6	20.2 ± 3.5	8	5	25
Mohammadreza Razzaghi (2024)	Iran	PBM vs. CON	AD	74.66 ±14.40	75.85±7.19	6	7	ALL:≥15		12	7	20
Zhou(2017)	China	EE vs. CON	AD	73.3 ± 2.1	71.3 ± 3.5	19	18	12.68 ±1.75	12.82 ±1.15	12	5	30
Xu(2017)	China	EE vs. CON	AD	79.05±9.48	78.86±9.74	42	42	18.21 ± 5.34	19.43 ± 5.08	25	5	60
Sarah E Lamb (2018)	UK	ET vs. CON	Dementia	ALL:77 ± 7.9		298	145	25.2 ± 12.3	23.8 ± 10.4	28	2	60–90
Marinda Henskensa (2018)	Netherlands	ET vs. CON	Dementia	85.14 ± 4.64	84.73 ± 4.55	16	16	12.1 ± 6.4	10.2 ± 5.7	24	3	30–45
Annika Toots (2017)	Switzerland	ET vs. CON	Dementia	84.4 ± 6.2	85.9 ± 7.8	81	85	15.4 ± 3.4	14.4 ± 3.5	16	5	45
Elisabeth Wiken Telenius(2015)	Norway	ET vs. CON	Dementia	87.3 ± 7.0	86.5 ± 7.7	72	68	15.5 ± 0.6	15.7 ± 4.9	12	2	50–60
Si-Yu Yang (2015)	China	ET vs. CON	AD	72.00 ± 6.69	71.92 ± 7.28	25	25	21.33 ±2.24	20.00 ±3.50	12	3	40
Paula Aguiar (2014)	Brazil	ET vs. CON	AD	78.6 ± 8.4	74.7 ± 7.4	17	17	20.1 ± 4.5	20.8 ± 4.0	24	2	40
Felipe de Oliveira Silva(2019)	Brazil	ET vs. CON	AD	81.22 ± 8.88	77.54 ± 8.05	12	7	20.66 ± 5.19	20.90 ± 4.34	12	2	60
Hannareeta €Ohman(2016)	Finland	ET vs. CON	AD	78.3 ± 5.1	78.1 ± 5.3	110	51	18.5 ± 6.3	17.7 ± 6.2	48	2	60
Elisabeth Wiken Telenius(2015)	Norway	ET vs. CON	Dementia	86.9 ± 7	86.4 ± 7.8	81	79	15.6 ± 5.0	15.8 ± 5.0	14	2	50–60
Cynthia Arcoverde (2013)	Brazil	ET vs. CON	AD	78.5 ±(64–81.2)	79 ±(74.7–82.2)	10	10	20.4 ± 2.7	19.9 ± 3.4	12	2	30
Gustavo Christofoletti (2007)	Brazil	ET vs. CON	Dementia	72.9 ± 2.3	79.4 ± 2.0	12	17	12.7 ± 2.1	14.6 ± 1.2	24	3	60
Wang wei(2014)	China	ET vs. CON	AD	71.19±7.04	70.04±8.90	26	28	0.23±3.60	19.36 ±4.11	12	3	40
AIMEE SPECTOR (2003)	British	CST vs. CON	Dementia	85.7 ± 6.2	84.7 ± 7.9	97	70	14.2 ± 3.9	14.8 ± 3.8	7	2	45
Martin Orrell (2014)	British	CST vs. CON	Dementia	82.7 ± 7.9	83.5 ± 7.2	106	106	17.8 ± 5.6	17.8 ± 5.4	7	2	45
Neslihan Lok (2020)	Turkey	CST vs. CON	AD	NA		30	30	17.60 (14.50-20.00)	16.50 (13.50-19.00)	7	2	45
Daphne Sze Ki Cheung (2019)	Hong Kong	CST vs. CON	Dementia	81.8 ± 7.41	85.3 ± 6.56	18	12	MoCA: CST:9.2 ± 3.9 CON:5.9 ± 4.5	MoCA: CST:9.2 ± 3.9 CON:5.9 ± 4.5	8	8	45–60
Sheung-Tak Cheng (2014)	Hong Kong	CST vs. PT vs. CON	Dementia	CST:81.9 ± 6.2 ET:81.8 ± 7.4	80.9 ± 7.2	CST:36 PT:39	35	CST:19.0 ± 3.2 ET:18.7 ± 3.9	18.9 ± 4.1	12	3	60

(*continued on next page*)

Table 1 (*continued*)

References	Country	Type	Diagnose	Age (Mean ± SD)		Sample		MMSE (baseline)		Duration (weeks)	Frequence (d/W)	Time (min)
				EXP	CON	EXP	CON	EXP	CON			
Fred Andersen (2012)	Norway	CST vs. CON	AD	81.6 ± 6.7	4.89±3.3	86	60	22.9 ± 4.6	23.5 ± 4.3	52	5	30
Katsuo Yamanaka (2013)	Japan	CST vs. CON	Dementia	84.12±5.52	83.73±6.44	23	24	17.00 ±0.83	16.87 ±0.77	7	2	45
Renate Stemmer (2018)	Germany	CST vs. CON	Dementia	80.2 ± 8.9	70.8 ± 10.0	24	30	19.3 ± 3.9	18.5 ± 3.8	26	1	30
Jennifer Cove (2014)	UK	CST vs. CON	Dementia	76.8 ± 6.62	77.8 ± 7.74	21	21	22.71 ±3.76	22.91 ±3.01	14	1	45
Emanuela Capotosto (2016)	Italy	CST vs. CON	Dementia	88.25 ± 5.15	86.52 ± 5.55	20	19	18.30 ± 3.14	18.20 ± 3.63	7	2	35
Luke Gibbor (2020)	UK	CST vs. CON	Dementia	86.24±5.19	77.19±12.38	16	13	20.94 ±2.98	22.50 ±3.95	7	2	45
E. Tsantali (2017)	Greece	CST vs. CON	AD	73.3 ± 4.9	74.2 ± 5.6	17	21	22.5 ± 0.9	23.1 ± 1.4	16	1	90
Yang (2019)	China	CST vs. CON	AD	75.74±5.86	75.24±7.00	42	42	18.48 ±2.02	18.21 ±1.97	7	2	30–45
Fred Andersen (2012)	Norway	PT vs. CST vs. CON	AD	PT:80.17 ± 6.4 CST: 81.89 ± 8.3	79.81 ± 8.1	PT:26 CST: 46	37	PT:23.7 ± 3.7 CST:22.9 ± 4.5	23.3 ± 4.9	48	7	NA
Sharon L(1996)	USA	PT vs. CON	AD	72.9 ± 7.5	70.6 ± 7.0	34	35	18.0 ± 5.00	18.2 ± 4.75	12	7	NA
Bengt Winblad (2006)	Sweden	PT vs. CON	AD	84.5 ± 6.0	85.3 ± 5.9	95	99	6.0 ± 3.0	6.2 ± 3.0	24	7	NA
Howard R(2012)	UK	PT vs. CON	AD	76.71±8.20	77.7 ± 8.0	109	59	9.10±2.64	9.1 ± 2.4	52	7	NA
Jared R. Tinklenberg (2007)	USA	PT vs. CON	AD	76.2 ± 8.1	78.4 ± 6.5	148	158	0.77 ± 4.28	19.36 ± 4.24	48	7	NA
Barry Reisberg (2003)	USA	PT vs. CON	AD	75.5 ± 8.16	75.8 ± 7.28	97	82	7.8 ± 3.76	8.1 ± 3.60	28	7	NA
Chris Fox(2012)	UK	PT vs. CON	AD	84.9 ± 6.7	84.4 ± 6.6	72	77	7.3 ± 6.2	7.3 ± 6.4	12	7	NA
S. Bakchine (2008)	France	PT vs. CON	AD	74.0 ± 7.4	73.3 ± 6.9	268	135	18.6 ± 3.3	18.9 ± 3.2	24	7	NA
Nunzio Pomara (2007)	USA	PT vs. CON	AD	78.0 ± 7.3	77.0 ± 8.2	165	167	17.4 ± 3.7	17.2 ± 3.4	24	7	NA
Elaine R. Peskind (2006)	USA	PT vs. CON	AD	78.0 ± 7.3	77.0 ± 8.2	160	162	17.4 ± 3.7	17.2 ± 3.4	24	7	NA
Chen xia(2007)	China	PT vs. CON	AD	ALL:49–89		94	95	11.8 ± 4.2	11.9 ± 4.0	16	7	NA
Zhang Baoli (2013)	China	PT vs. CON	AD	69.9 ± 5.5	69.7 ± 5.4	52	52	18.4 ± 4.2	18.5 ± 4.0	48	7	NA
Shifu Xiao(2021)	China	PT vs. CON	AD	69.6 ± 8.12	69.7 ± 8.20	334	344	19.4 ± 4.4	19.5 ± 4.5	36	7	NA
Tao Wang(2020)	China	PT vs. CON	AD	70.4 ± 8.5	70.3 ± 8.1	83	83	18.1 ± 4.4	17.5 ± 4.2	24	7	NA
Ling-Feng Zhang (2022)	China	PT vs. CON	AD	GV-971:67.67 ±4.92 DON:70.00 ±6.00	64.33±7.59	36	12	GV-971:16 ±3.27 DON:14.5 ± 0.5	16±1	48	7	NA
Jihui Lyu(2018)	China	MT vs. PT	AD	68.9 ± 7.1	69.9 ± 7.9	97	95	13.45 ± 3.66	13.22 ± 4.01	12	7	30–40
Anna Rita Giovagnoli (2018)	Italy	MT vs. CON	AD	74.3 ± 5.7	PT:72.0 ± 7.3	23	22	16.59 ± 4.01	PT:16.24 ± 4.10	24	2	40
A. R. Giovagnoli (2017)	Italy	MT vs. CON	AD	73.92 ± 7.74	71.69 ± 7.88	13	13	22.85 ± 6.28	23.62 ± 1.94	12	2	45
Enrico Ceccato, PsyD(2012)	Italy	MT vs. CON	Dementia	85.5 ± 5.9	87.2 ± 7.1	27	23	16.93 ± 3.66	16.39 ± 3.90	12	1	45
Li(2021)	China	MT vs. CON	AD	71.601 ±3.512	72.201 ±4.610	40	40	13.101 ±5.111	12.101 ±4.123	16	7	NA

(*continued on next page*)

Table 1 (*continued*)

References	Country	Type	Diagnose	Age (Mean ± SD)		Sample		MMSE (baseline)		Duration (weeks)	Frequence (d/W)	Time (min)
				EXP	CON	EXP	CON	EXP	CON			
Hsin Chu(2014)	China-Taiwan	MT vs. CON	Dementia	ALL:82±6.80		49	51	12.80 ±6.15	13.76 ±5.36	6	2	30
Eva M. Arroyo-Anlló(2013)	Spain	MT vs. CON	AD	74.38±3.56	75.15±4.23	20	20	19.30 ±3.68	19.90± 2.93	12	3	2–4
Masayuki Satoh (2015)	Japan	MT vs. CON	AD	78.1 ± 7.0	77.0 ± 6.1	10	10	19.1 ± 3.9	20.9 ± 3.5	24	1	60

PBM: photobiomodulation; EE: enriching environment; ET: exercise therapy; MT: music therapy; PT: pharmacological intervention; CST: cognitive stimulation therapy; CON: control group; AD: Alzheimer's disease.

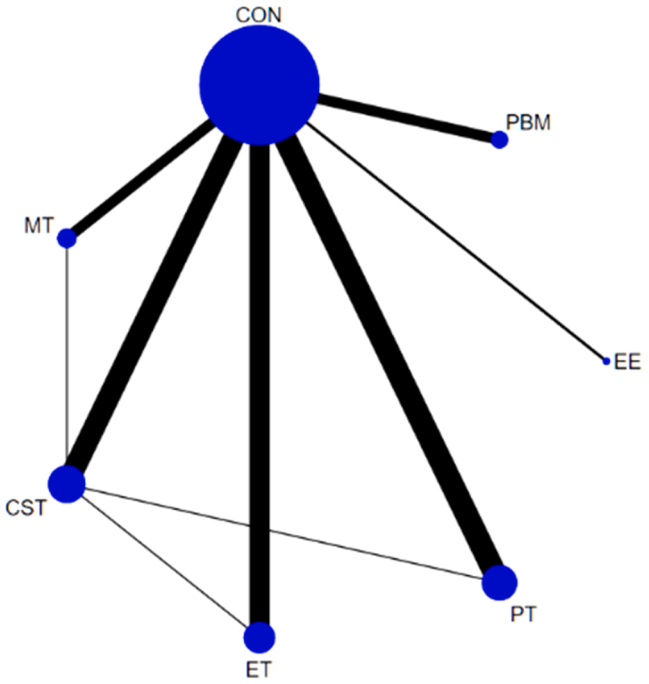

Fig. 2. Network evidence map of the effects of different cognitive interventions.
PBM: photobiomodulation; EE: enriching environment; ET: exercise therapy; MT: music therapy; PT: pharmacological intervention; CST: cognitive stimulation therapy; CON: control group.

convergence for all model parameters. The trace and density plots of the chains are shown in **Supplementary Figure S4**. The Bayesian network meta-analysis suggested that various interventions could enhance cognitive abilities in dementia patients. The relative effect estimates indicated that PBM [SMD = 0.66, 95%CrI (0.29, 1.02)], EE [SMD=0.69, 95%CrI (0.08, 1.31)], PT [SMD=0.36, 95%CrI (0.17, 0.55)], CST [SMD=0.32, 95%CrI (0.11, 0.55)], and ET [SMD=0.28, 95%CrI (0.06, 0.51)] were effective in enhancing cognitive function of AD patients compared to CON. However, MT [SMD=0.22, 95%CrI (−0.08, 0.52)] had no statistical significance. Fig. 3 illustrates the forest plot of the network meta-analysis.

The apparent loops within the network meant that there was both direct and indirect comparison evidence simultaneously for some interventions. It was essential to adopt the node-splitting approach to assess local inconsistency. Its results demonstrated a statistically significant inconsistency between direct and indirect evidence for the comparison of CST and CON (direct: [MD=0.34, 95%CrI (0.12, 0.57)], indirect: [MD=0.32, 95%CrI (−0.76, 1.4)], network: [MD=0.32, 95% CrI (0.12, 0.54)]). No significant inconsistencies were found in the other three paired comparisons (**Supplementary Figure S5**). In the previous manuscript, heterogeneity was assessed, indicating a moderate heterogeneity ($p < 0.01$, $I^2 = 67.3\%$). The interventions included in this study had various mechanisms. While it increased the comprehensiveness of our reviews and results, it may introduce clinical heterogeneity. We strongly recommend that clinicians, researchers, and policymakers carefully consider the diversity of interventions and integrate these insights with individualized patient assessments, local drug availability, and practical feasibility of implementation.

According to the cumulative ranking probabilities, PBM achieved the highest SUCRA value (87.3%), followed by EE (83.8%), PT (54.7%), CST (48.9%), ET (40.8%), and lastly MT (32.9%). However, the league table showed a slightly different result from this order. Mainly, the efficacy of EE was slightly superior to that of PBM. The league table and the SUCRA values are shown in Table 2. The cumulative ranking graph based on SUCRA values is shown in **Supplementary Figure S6**.

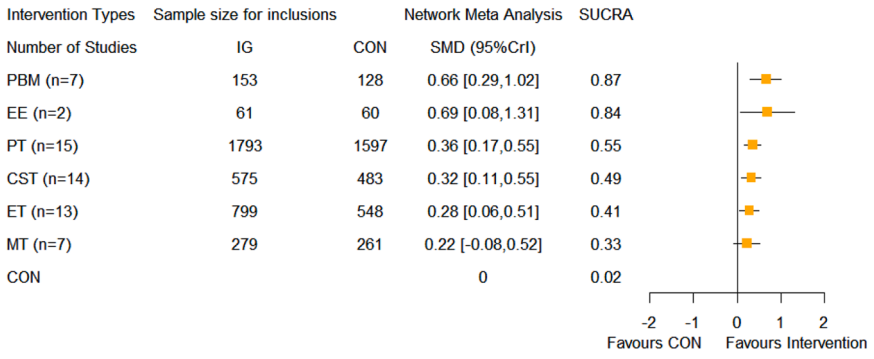

Fig. 3. Forest plot of network meta-analysis results.
PBM: photobiomodulation; EE: enriching environment; ET: exercise therapy; MT: music therapy; PT: pharmacological intervention; CST: cognitive stimulation therapy; CON: control group.

Table 2
League matrix table of critical outcome analyses (Significant results marked in bold).

0.84						
EE	0.87					
0.03 (-0.66, 0.78)	PBM	0.55				
0.34 (-0.3, 0.98)	0.3 (-0.12, 0.71)	PT	0.49			
0.37 (-0.29, 1.03)	0.33 (-0.09, 0.77)	0.03 (-0.25, 0.32)	CST	0.41		
0.41 (-0.23, 1.07)	0.37 (-0.07, 0.81)	0.07 (-0.24, 0.36)	0.04 (-0.25, 0.34)	ET	0.33	
0.47 (-0.2, 1.17)	0.42 (-0.04, 0.91)	0.13 (-0.23, 0.49)	0.1 (-0.26, 0.47)	0.05 (-0.33, 0.44)	MT	0.02
0.68 (0.08, 1.31)	**0.65 (0.29, 1.02)**	**0.35 (0.17, 0.54)**	**0.32 (0.11, 0.53)**	**0.28 (0.06, 0.52)**	0.22 (-0.08, 0.54)	CON

PBM: photobiomodulation; EE: enriching environment; ET: exercise therapy; MT: music therapy; PT: pharmacological intervention; CST: cognitive stimulation therapy; CON: control group.

3.6. Meta-regression and sensitivity analysis

Three study design indicators (baseline, duration of intervention, and frequency of intervention) and the participants' characteristics (age) were selected as covariates. The network meta-regression revealed that only the baseline of the outcome measures [$\beta = 0.28$, 95%CrI (0.07, 0.48)] was statistically significant for the effect on global cognitive function, demonstrating a positive correlation. Other results of network meta-regressions were as follows: duration of intervention [$\beta = -0.07$, 95%CrI (−0.30, 0.17)], frequency of intervention [$\beta = -0.14$, 95%CrI (−0.40, 0.11)], and age of subjects [$\beta = -0.03$, 95%CrI (−0.25, 0.18)].

Since the I^2 statistic (67.3%) indicated moderate heterogeneity, a sensitivity analysis was conducted by eliminating high-risk, small-sample, and outlier studies. The heterogeneity decreased marginally to 66.2% after removing three high-risk studies, indicating that the results were not substantially influenced by these studies. Besides, excluding 15 small-sample studies did not alter the SUCRA of any intervention, demonstrating high robustness of the findings to their removal. However, after excluding 6 outlier studies, the SUCRA for EE decreased from 0.84 to 0.45 following the removal of one study that used EE as treatment. This may be attributed to the limited number of studies on EE, rendering the results sensitive to the exclusion of any one of them. The SUCRA for each intervention, after removing small-sample and outlier studies, is shown in **Supplementary Table S4**.

4. Discussion

This Bayesian network meta-analysis was to comprehensively compare the efficacy of diverse interventions for improving cognitive function in AD. The evaluated interventions included non-pharmacological interventions (PBM, EE, ET, MT, and CST) and a combined pharmacological group (donepezil, memantine, and sodium oligomannate). Based on the SUCRA values, PBM demonstrated the highest probability of being the optimal intervention in cognitive improvement, followed by EE, PT, CST, ET, and finally MT. However, MT did not show a statistically significant effect compared to other interventions.

4.1. Summary and interpretation of findings

PBM demonstrated greater enhancement in cognitive function contrasted to PT, highlighting its potential for dementia treatment. There are no independent meta-analyses of PBM, but the clinical applications of PBM have been increasing rapidly in recent years, proving the therapeutic effect of PBM for dementia [94,95]. PBM uses low-level light absorbed by cellular photoreceptors [96,97] (such as in mitochondria) to enhance cellular energy (ATP) [14], reduce neuroinflammation [15] and amyloid-beta (Aβ) [98], promote nerve regeneration, and enhance excitatory neurotransmission and oxidative metabolism [16], thereby improving cognitive function. PBM can improve memory and executive function in patients with mild-to-moderate dementia. However, its clinical applicability has not been tested in a large-scale patient population. The encouraging findings provide preliminary support for planning an expanded design of larger trials. With an estimated device cost of €2000 to €10,000, PBM represents one of the most economical non-invasive brain stimulation techniques, aside from sensory stimulation [99]. In these included studies, the light sources were light-emitting diodes and low-level lasers, with wavelengths mainly ranging from 800 to 1080 nm. In addition to the commonly irradiated sites such as the cranium and eyes, some studies also exposed the abdomen and wrists. Treatment sessions ranged from 6 to 30 min, with frequencies of 3 to 14 sessions per week and durations of 2 to 12 weeks. In clinical practice, PBM typically plays an adjuvant role in standard pharmacological treatments for AD. A detailed explanation of its specific implementation methods in clinical practice is provided in **Supplementary Table S5**. The implementation of PBM mostly relies on specific devices and health professionals, so caregiver burden does not pose a barrier to carrying out the intervention. Future research can be directed towards developing individualized treatment protocols to address the specific symptom profiles of AD patients, such as optimizing energy density and duration.

EE significantly improves cognitive function in AD patients through multiple mechanisms, such as enhancing hippocampal synaptic density [100], increasing microRNA-146a secretion [101] and brain-derived neurotrophic factor (BDNF) levels [102], and reducing Aβ plaques [102,103]. One study assessed the feasibility of virtual reality-assisted occupational therapists for cognitive treatment in patients with mild cognitive impairment or dementia, reporting scores exceeding 5 out of 7 across acceptability, expectation effectiveness, satisfactoriness, and stability metrics [104]. Because EE modalities—such as virtual reality, enriched gardens, and music— were multifarious, factors including caregiver burden, cost-effectiveness, and resource allocation may vary widely [105,106]. The heterogeneity also limited the comparability and reliability of findings across studies. Future studies should standardize intervention protocols to facilitate more consistent and generalizable

conclusions.

The effect of CST was also significant. Its mechanisms include elevating BDNF, reducing proinflammatory cytokines (TNF-α, IL-6) [107,108], improving brain connectivity, and promoting synaptogenesis [109]. Notably, the therapeutic benefits of CST exhibit time-dependent characteristics (peaking then declining) [110]. While effective, CST did not outperform other interventions, such as PBM and EE, warranting further mechanistic research. CST was recommended for individuals with mild to moderate dementia. One study suggested that caregivers attended structured training and adhered to the intervention protocols [111]. Although there was some burden for caregivers, satisfactory levels of acceptability and treatment fidelity were critical to ensuring intervention efficacy [111,112]. As for cost-effectiveness, this therapy can be conducted economically through training programs for nurses, caregivers, or employees of care facilities [113]. A comprehensive evaluation conducted in the UK demonstrated that CST was superior in cost-effectiveness to usual care over 3 months, with a mean cost of £1223 per one-point improvement on the MMSE [114]. Overall, CST is appropriate for patients with mild to moderate dementia, and its combination with acetylcholinesterase inhibitors may offer superior effectiveness and cost-efficiency [114].

Some network meta-analyses [17,115,116] showed that multimodal exercise, aerobic exercise, and high-intensity functional training had superior outcomes, which were consistent with this study. The proposed mechanisms encompass: enhancing hippocampal signaling (FNDC5/irisin, BDNF) [117,118], reducing pathological proteins (P-tau, Aβ) [119], improving brain plasticity (astrocyte regulation, blood flow) [120,121], modulating systemic factors (phospholipase D1) [122], and supporting mitochondrial energy metabolism [123]. However, the extent of these effects appears to vary with exercise modality, intensity, and frequency, demonstrating the need for further investigation. Most caregivers showed positive affect, general health, and low burden, but might have mild depressive symptoms [124]. Although ET is effective and economical, safety concerns may further contribute to caregivers' reluctance to engage in exercise interventions [125].

No statistically significant improvement in cognitive function was observed with MT in this study, which was consistent with previous meta-analyses [126,127]. Some studies reported that MT offered modest benefits in specific cognitive domains in mild to moderate dementia and potentially modulated biomarkers, such as telomere length and Aβ [128], or influenced neural circuitry, including prefrontal-hippocampal pathways [129]. But the current evidence for its efficacy and mechanisms remains limited and inconsistent. Significant heterogeneity in intervention formats, duration, and frequency across studies complicated comparative analysis and outcome interpretation [130]. Personalized music intervention was a straightforward and economical approach with potential therapeutic value. However, MT did not achieve significant effects on depression, anxiety, quality of life, or caregiver burden among participants [131]. Caregivers received training and practical support on selecting preferred music and creating individualized playlists. Moreover, it was evaluated that the expense was $20.00 per personalized playlist, based on a standard of 10 songs [132].

In addition to common mechanisms such as reducing Aβ plaque deposition, tau protein phosphorylation, and inhibiting neuroinflammation, donepezil can inhibit acetylcholinesterase and enhance cholinergic signal transmission [3]; memantine, a non-competitive NMDA receptor antagonist, protects neurons from excitotoxic damage [4]. The cholinesterase inhibitor donepezil is established as the first-line standard pharmacotherapy for mild to moderate AD. The non-competitive NMDA receptor antagonist memantine is commonly used in the treatment of moderate to severe AD. It was proven that the combination of these two drugs could enhance the therapeutic effect of improving cognition. An increasing number of new drugs have been developed and studied recently. Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab has shown potential in the treatment of AD in recent years, which was approved for the treatment of early AD and was recommended to be diluted in accordance with the standard of 10 mg/kg and once every 2 weeks by the Food and Drug Administration (FDA) in 2023 [133]. It is a humanized IgG1 antibody that primarily targets soluble Aβ fibrils. Clinical research showed that lecanemab significantly reduced Aβ plaques and delayed cognitive decline [134]. Future research can explore the potential to enhance efficacy by combining such targeted medicines with non-pharmacological interventions based on the results of clinical studies.

4.2. Advantages

The Bayesian network meta-analysis framework offered several methodological strengths. It could integrate direct and indirect evidence, enable robust effect estimates through posterior probability distributions, and rank them by relative efficacy. These advantages enhanced the comprehensiveness and interpretability of results within complex treatment networks, particularly when direct comparisons were scarce.

4.3. Limitations

There were several limitations in this study. First, the relatively small number of studies on EE may reduce the precision and reliability of the estimates. Secondly, most pharmacological and non-pharmacological interventions lacked direct comparative evidence and instead relied on indirect comparisons within the network. Thirdly, there was an inevitable and obvious publication bias. Fourthly, the star-shaped structure limited the reliability of indirect comparisons, as these relied on the unverifiable consistency assumption. Fifthly, this network meta-analysis focused on a predefined set of cognition-oriented interventions. Importantly, the most effective strategies in clinical practice are often multimodal or combined interventions. Such combined approaches were not included in the present network because component-based modelling was beyond the scope of this analysis. Therefore, our findings should be interpreted as comparisons among selected single-intervention categories rather than definitive rankings of all possible therapeutic strategies. Moreover, as with all network meta-analyses, the validity of indirect comparisons depends on the transitivity assumption. Although we assessed key potential effect modifiers across studies, residual violations of transitivity cannot be entirely excluded.

4.4. Enlightenment for practice, policy, and research

Delaying cognitive decline is a critical goal in the clinical management of AD. This study holds relevant implications for clinical practice, health policy, and further research. Considering factors such as costs, efficacy, and adverse effects, healthcare professionals could integrate non-pharmacological interventions either as alternatives or adjuncts to pharmacological interventions to delay the decline of brain function in AD patients. The National Action Plan for Addressing Dementia in Older Age (2024–2030) in China recommended the construction of dementia care areas within elderly care institutions. Establishing standardized protocols for non-pharmacological interventions in dementia care areas could not only reduce family burden but also enable more efficient use of resources, such as occupational therapy staff and medical equipment. In addition, the National Healthcare Security Administration of China has included non-invasive neuromodulator therapies on the list of medical service price items, enabling reimbursement and enhancing their accessibility for AD patients. Larger clinical trials focusing on PBM and EE could be conducted to further validate their effectiveness in improving cognitive function and directly compare their outcomes with those of conventional pharmacological interventions. This study focused solely on the effects of selected single non-pharmacological interventions on cognitive improvement. Future research is warranted to employ component network meta-analysis to explore the effects of combined interventions. Such an approach would yield insights of

greater translational value for the prevention of mild-to-moderate AD.

5. Conclusions

In conclusion, among the evaluated interventions, PBM and EE were associated with the most substantial improvements in cognitive function, followed by PT, CST, and ET. In contrast, MT did not yield statistically significant improvements in cognition compared to CON. Future research should prioritize exploring the differential effects of these interventions across clinical subgroups, such as mild-to-moderate versus severe dementia, to provide robust scientific evidence for precise intervention strategies and individualized clinical decision-making.

Data availability statement

The data used in this study are all based on previously published research. The original data can be obtained by searching relevant literature. Additionally, the supporting data for the research results and the R software code can be obtained from the corresponding author upon reasonable request.

Abbreviations

AD: Alzheimer's disease; ADI: Alzheimer's Disease International; PBM: photobiomodulation; EE: enriching environment; ET: exercise therapy; MT: music therapy; CST: cognitive stimulation therapy; PT: pharmacological therapy; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; NIA-AA: National Institute on Aging and Alzheimer's Association; DSMIV-TR: Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA: Neurological and Communication Disorders or Stroke-Alzheimer's Disease and Related Disorders Association; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; RCTs: Randomized controlled trials; MD: mean difference; SD: standard deviation; RoB 2.0: Risk of Bias tool 2.0; SMD: standard mean difference; 95%CrI: 95% Credible Interval; MCMC: Markov Chain Monte Carlo; CON: control group; SUCRA: surface under the cumulative ranking curve; BDNF: brain-derived neurotrophic factor; FDA: Food and Drug Administration.

Declaration of generative AI

Generative AI was used to assist with a few grammar edits.

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Availability of data, code, and other materials

Template data collection forms, data extracted from included studies, data used for all analyses, and analytic code are available only to collaborators under agreement. Upon reasonable request, with the author's consent and after obtaining ethical approval, they can be provided.

Multiple publications

This study shares a similar set of included literature with only one study [135]. The former study was published in *Frontiers in Aging Neuroscience* in 2023. It compared the effects of non-pharmacological interventions (enriched environment, PBM, ET, computerized cognitive training, and CST) on the cognitive function of patients with dementia. The new study differs from the former in the following ways.

First, the new study updated the database search time. Second, it selected new interventions based on reliable opinions, such as international guidelines, especially adding pharmacological interventions. Additionally, it calculated the SUCRA value to make the ranking results more comprehensive and reliable. Third, we chose a Bayesian network meta-analysis to make the results of this small sample study more stable and reliable. Fourthly, the new study conducted meta-regression and sensitivity analysis to explore the sources of heterogeneity. Fifthly, it focused on comparing the effects of mainstream non-pharmacological and pharmacological interventions on cognitive function and explored whether non-pharmacological interventions were more effective than pharmacological ones.

CRediT authorship contribution statement

Yuning Zhao: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis. **Guangxin Luo:** Supervision, Methodology, Data curation, Conceptualization. **Can Huang:** Supervision, Investigation. **Zhenyang Chen:** Supervision, Investigation. **Yu Wei:** Supervision, Investigation. **Qiaosen Chen:** Validation, Supervision. **Fang Wang:** Validation, Supervision. **Yong Gan:** Validation, Supervision. **Xiaoxv Yin:** Validation, Supervision, Project administration, Funding acquisition.

Conflict of competing interest

The authors declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100564.

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