Journal of NeuroEngineering and Rehabilitation

REVIEW

Open Access

Efficacy of non-invasive brain stimulation interventions on cognitive impairment: an umbrella review of meta-analyses of randomized controlled trials

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Abstract

Background The impact of noninvasive brain stimulation (NIBS) on cognitive and mental outcomes in Alzheimer's disease (AD) and mild cognitive impairment (MCI) remains under debate due to contradictory findings from systematic reviews and meta-analyses (SRMAs). To synthesize evidence from SRMAs assessing the effectiveness of NIBS techniques on cognitive and mental outcomes in AD and MCI populations. By comparing our findings to recent reviews and clinical guidelines, we highlight how this study addresses current limitations in the literature, provides a more holistic perspective on NIBS interventions, and guides future research and clinical practice.

Methods We searched four databases from inception to May 15, 2024, reviewing SRMAs that analyzed the effects of NIBS. Effect sizes, 95% confidence intervals (CIs), and prediction intervals were computed for each meta-analysis. The methodological quality of the SRMAs was evaluated using the Measurement Tool to Assess Systematic Reviews 2, and the quality of evidence was assessed through the Grading of Recommendations, Assessment, Development, and Evaluation criteria.

Findings Ten SRMAs detailing 22 associations were analyzed, focusing on two NIBS techniques across 12 unique outcomes. Significant improvements were observed in global cognition, language, executive function, and memory. Repetitive transcranial magnetic stimulation (rTMS) significantly enhanced short-term global cognition (standardized mean difference [SMD], 0.44; 95% CI 0.02–0.86), language (SMD, 1.64; 95% CI 1.22–2.06), executive function (SMD, 1.64; 95% CI 0.18–0.83), and long-term global cognition (SMD, 0.29; 95% CI 0.07–0.50). Transcranial direct current stimulation (tDCS) was effective in improving memory (SMD, 0.60; 95% CI 0.32–0.89) and executive function (SMD, 0.39; 95% CI 0.08–0.71). NIBS interventions showed no significant correlation with neuropsychiatric symptoms but demonstrated good tolerability in terms of safety and acceptability.

Interpretation This umbrella review indicates that NIBS techniques, particularly rTMS and tDCS, can significantly improve cognitive functions such as global cognition, language, executive functions, and memory in patients with AD and MCI. Despite potential benefits, results should be interpreted cautiously due to study heterogeneity and methodological limitations. Future studies should investigate their long-term effects and applicability across dementia types.

Keywords Non-invasive brain stimulation, Mild cognitive impairment, Alzheimer's disease, GRADE, Umbrella review

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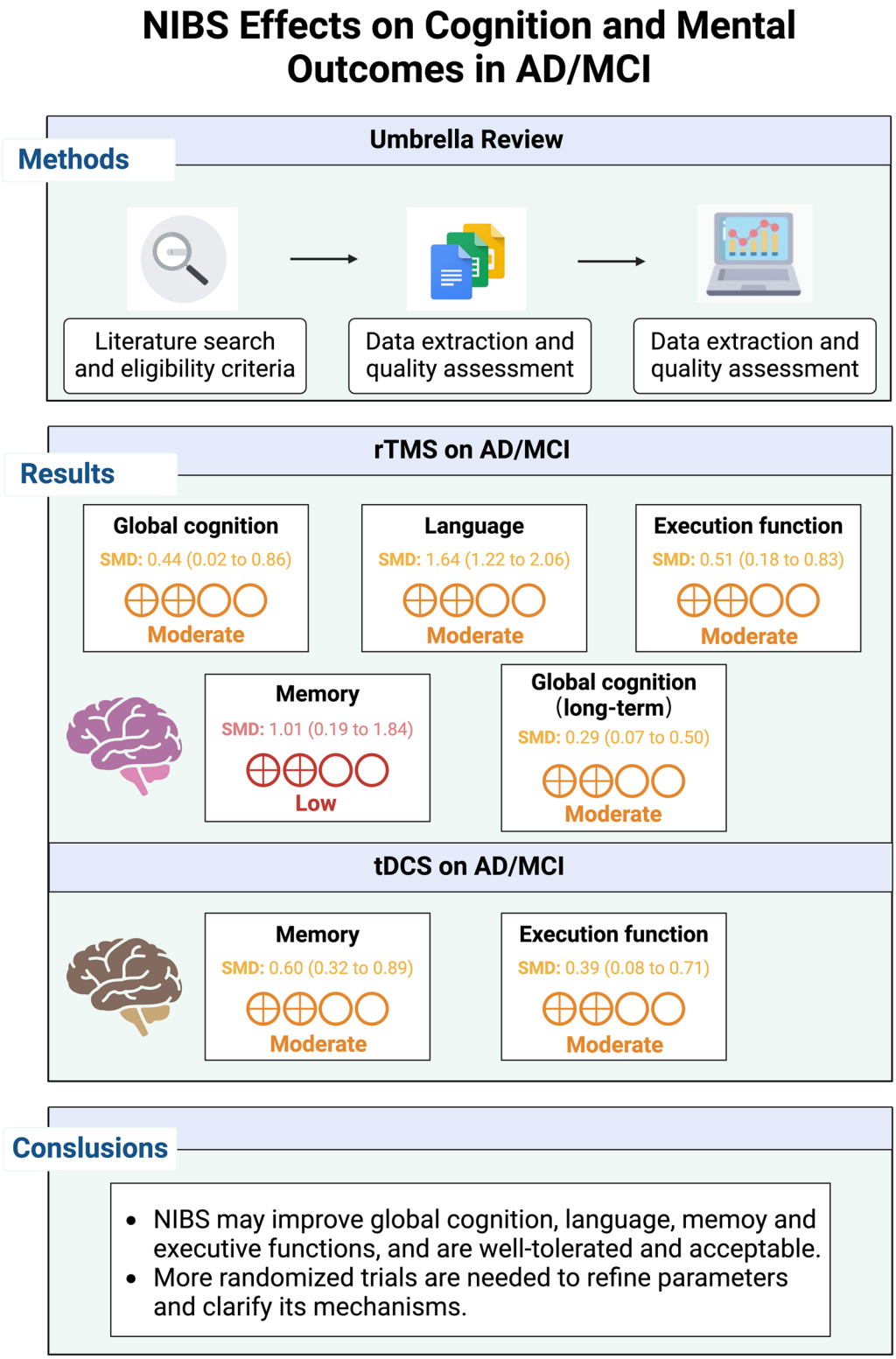
Graphical Abstract



Introduction

With an increasing aging population, dementia has become an urgent global public health challenge. According to the World Health Organization, approximately 55 million people worldwide are diagnosed with dementia annually, and this number is expected to rise to 82 million by 2030, with 60–70% of cases attributed to Alzheimer's disease (AD) [1]. AD is a chronic progressive neurodegenerative disease characterized by persistent cognitive decline [2] and neuropsychiatric symptoms (NPS) [3] that severely affect quality of life. Mild cognitive impairment (MCI) represents the transitional state from normal aging to AD, affecting 10–15% of the population aged > 65 years [4]. Approximately 30–40% of people with MCI, especially with memory difficulties, progress to AD and other forms of dementia within five years of diagnosis [5]. The Alzheimer's Association estimates that by 2023, the total expenditure for treating AD and other types of dementia will reach $345 billion [6]. The gradual functional impairment of patients with AD imposes significant costs on society and healthcare systems. Therefore, managing, preventing, and treating MCI and AD to reduce their incidence and healthcare costs represent current challenges.

Standard interventions for AD currently involve pharmacological treatments, specifically acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonists [7]. However, these medications are associated with strong side effects and poor compliance, and therapeutic outcomes often fail to deliver satisfactory results. Non-invasive brain stimulation (NIBS) is a cost-effective supplementary and alternative therapeutic approach frequently used to treat MCI and age-related neurodegenerative diseases [8, 9]. The most widely used NIBS techniques for AD and MCI treatment include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Mechanistically, rTMS uses strong magnetic fields to generate focal currents through a coil to stimulate the brain, which can activate or inhibit neural activity in specific brain areas through high- or low-frequency stimulation, respectively [10, 11]. Conversely, tDCS delivers low-intensity electrical currents via electrodes on the scalp, modulating synaptic transmission by altering the polarization of the neuronal membrane, thereby promoting or inhibiting the generation of neural signals. It is worth noting that other TMS protocols (e.g., theta-burst stimulation) and transcranial electrical stimulation modalities (e.g., transcranial alternating current stimulation and transcranial random noise stimulation) are less frequently employed in clinical trials or routine care, possibly due to their less well-defined mechanisms and the absence of standardized treatment guidelines.

However, systematic reviews and meta-analyses (SRMAs) on the effect of NIBS interventions on cognitive function and neuropsychiatric symptoms in patients with MCI or AD have yielded varying results [12]. The reliability of study outcomes, which may be affected by reporting biases and inadequate statistical power due to small sample sizes, remains a key issue in NIBS research. Additionally, variations in inclusion and exclusion criteria, analytical methods, and risk of bias in SRMAs can lead to inconsistent results and conclusions. These factors may have contributed to the over-representation of significant findings in SRMAs. Furthermore, most SRMAs focus solely on one type of intervention (either rTMS or tDCS) and on specific domains (cognitive function or apathy) [2], which hampers a comprehensive understanding of the subject. Moreover, recent guidelines and reviews often do not integrate findings across different NIBS modalities and a range of cognitive and mental health outcomes, leaving gaps in the literature and unanswered questions regarding the comparative and collective value of these interventions.

Umbrella reviews are valuable tools for synthesizing evidence; identifying, integrating, and evaluating evidence from published SRMAs; and assessing the strength and validity of the evidence based on sample size, effect size, and biases [13, 14]. In this umbrella review, we systematically and comprehensively assessed the relationship between NIBS and cognitive and mental outcomes to provide evidence-based decision-making support to clinicians and rehabilitation specialists.

Method

We strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the standardized methods and principles for umbrella reviews (Supplementary Table S1) [15, 16]. The study is registered in PROSPERO under the registration number CRD42024537045.

Literature search

We searched PubMed, Embase, Web of Science, and the Cochrane Library from their inception to May 2024. Our search strategy used a combination of terms related to NIBS (e.g., rTMS and tDCS), disorders (e.g., AD, MCI, and dementia), and meta-analyses. No restrictions were placed on publication status, or study design during the search, and references from relevant systematic reviews were manually screened. Detailed information regarding the search strategy is provided in Supplementary Table S2.

Eligibility criteria

Studies were included based on the Population, Intervention, Comparator, Outcome, and Study design (PICOS) criteria, as described below.

1 Population: Participants diagnosed with AD or MCI according to recognized standardized criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), National Institute on Aging and Alzheimer's Association (NIA-AA), or Petersen's MCI [17].

Diagnoses confirmed by medical experts (i.e., neurologists and psychiatrists) and supported by laboratory results (i.e., computed tomography scans, magnetic resonance imaging, positron emission tomography scans, or lumbar punctures) were also considered. No restrictions were placed on race or geographic location.

2 Intervention: The NIBS interventions included TMS, tDCS, theta burst stimulation, transcranial pulse stimulation (TPS), and transcranial alternating current stimulation (tACS). These interventions can be administered alone or in combination with pharmacological or psychotherapeutic interventions.

3 Comparator: The control group received a combination of standard treatments, such as sham stimulation, rehabilitation, usual care, or pharmacotherapy. In contrast, the intervention group received only the addition of NIBS modalities to the same standard treatments as those in the control group.

4 Outcome: Cognitive function was assessed using global cognitive function tests, such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog). Performances in specific cognitive domains, such as executive function, attention, memory, language, processing speed, visuospatial skills, and visual perception, were also evaluated. The NPS was measured using the Neuropsychiatric Inventory (NPI), Geriatric Depression Scale (GDS), Apathy Evaluation Scale (AES), Cornell Depression Scale (CDS), and Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD). Acceptability and safety were evaluated by the proportion of participants who discontinued or dropped out owing to adverse events, the proportion of participants experiencing adverse reactions, and the severity of these reactions during the study period.

5 Study design: SRMAs of randomized controlled trials (RCTs) were conducted.

Studies with the following features were excluded: (1) other research designs (e.g., narrative reviews, network meta-analyses, observational studies, and animal studies); (2) participants with Parkinson's disease, stroke, or multiple sclerosis; (3) meta-analyses or systematic reviews that provided insufficient data (e.g., mean and standard deviation [SD]) for quantitative analysis; and (4) meta-analyses published in languages other than English.

Data extraction and quality assessment

Two reviewers (MW and WS) independently extracted the data, and any disagreements were resolved by consulting a third reviewer (JZ). Subsequently, two other reviewers (LT and JL) used the updated A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 to assess the methodological quality of the included meta-analyses [18]. SRMAs were rated as "no," "partial yes," or "yes." Nine non-critical items and seven critical items that influence the validity of the assessment were included. These items cover protocol registration, comprehensiveness of search strategies, reasons for excluding studies, assessment of risk of bias in studies, appropriateness of statistical methods in meta-analyses, use of risk of bias in the interpretation/discussion process, and evaluation of publication bias [18]. Although these scoring criteria could be adjusted based on the context of the umbrella review, no changes were made in this study. Our methodology was rigorous, and the credibility of our umbrella review was rated as high (no critical flaws and at most one non-critical flaw), moderate (more than one non-critical flaw), low (one critical flaw, regardless of non-critical flaws), or very low (more than one critical flaw, regardless of non-critical flaws) [19].

For each eligible article, we recorded the following data: characteristics of the study, namely the first author, year of publication, study population, study design, subject characteristics (age, sex, and number), number of studies included, total sample size, interventions, control groups, and outcomes; results of the studies, namely effect size (weighted mean difference [WMD], standardized mean difference [SMD], relative risk [RR], odds ratio [OR]) and their 95% confidence intervals (CIs) and/or P values; heterogeneity (I^2); publication bias; source of funding; and conflicts of interest.

If multiple meta-analyses assessed the same intervention and outcomes, we selected the one with the greatest number of primary studies to ensure a broader and more robust evidence base, thereby enhancing the statistical stability and representativeness of the pooled results. If the numbers of studies were equal, we chose the most

recently published meta-analysis, as it is more likely to reflect the latest evidence and current clinical practice. This is consistent with the umbrella review method [15, 16, 20].

Data synthesis

For each association, owing to the anticipated high heterogeneity, the pooled effect sizes and their 95% CIs were recalculated using a generic inverse variance method and random effects model (DerSimonian and Laird) [21]. Statistical significance was defined as a two-sided P value of <0.05. Heterogeneity was assessed using the I^2 statistic [22]. Small-study effects were evaluated using Egger's regression test for asymmetry, where a P value of <0.10 was considered statistically significant [23]. Additionally, the 95% prediction interval (PI) for the pooled random effects was calculated, providing an estimate of the potential range of effect sizes for future studies.

A sensitivity analysis of the identified associations was conducted by excluding small studies (25th percentile) and those with high risks of bias.

The quality of evidence for each study was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, which involves the following five domains: (1) risk of bias in individual studies, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias [24]. The GRADE classifies the strength of evidence into the following four categories: high, moderate, low, and very low.

All analyses were performed using R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) using the packages meta and metafor.

Result

Study selection

A total of 1018 records were identified through the literature search, and 348 duplicate records were removed. Based on title/abstract screening, 582 records were excluded, resulting in 89. After reading the full texts, 79 records were excluded for reasons listed in Supplementary Table S3. Finally, 10 meta-analyses that met the eligibility criteria were included [12, 17, 25–32]. Figure 1 shows a flowchart of the study selection.

Characteristics of meta-analyses

The 10 included SRMAs were published between 2021 and 2024 and involved 12 unique associations. Specifically, 4 SRMAs exclusively reviewed rTMS [25–27, 32], 5 focused solely on tDCS [12, 17, 28, 29, 31], and 1 SRMA encompassed both techniques [30] (Table 1). Among all the studies, two types of NIBS were used, rTMS (n = 84; 53%) and tDCS (n = 76; 47%). Although we planned to

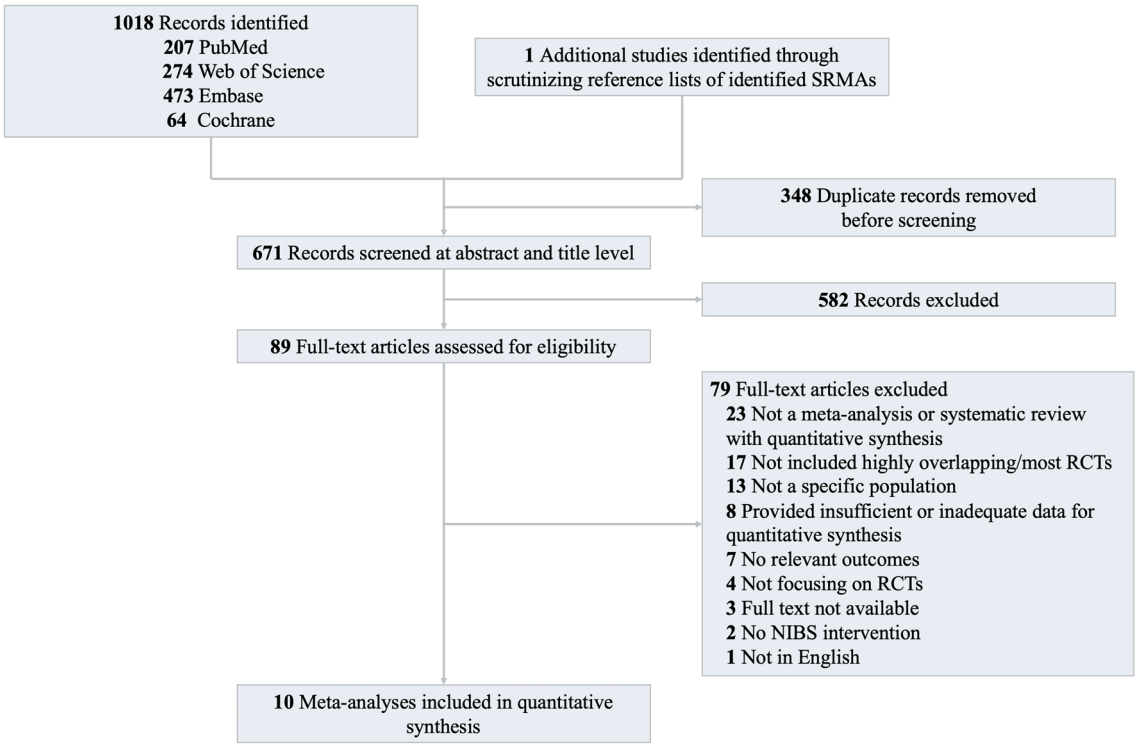


Fig. 1 Flowchart of the selection process

Table 1 Characteristics of meta-analyses of randomized clinical trials investigating non-invasive brain stimulation

Source	Population	Type of NIBS	No. of included studies	Mean age range (years)	Total participants	Duration of NIBS (weeks/sessions)	Stimulation site	Comparator	Outcomes
Pagali et al. [25]	MCI/AD	rTMS	24	53.12–79.6	931	1–10/5–42	L-DLPFC, B-DLPFC, Broca's area, Wernicke's area, B-parietal lobe, Angular gyrus, L-LPC, Precuneus, B-PSAC, B-dorsal, B-cerebellum, L- LTL, Parietal P3/P4, Posterior temporal T5/T6	Sham	Global cognition (MMSE, MoCA, ADAS-Cog)
Li [26]	AD	rTMS	16	63.87–79.6	655	1–24/5–32	B-DLPFC, L-DLPFC, B-AG, Hippocampus, Precuneus, B-cerebellum, Parietal P3/P4, Posterior temporal T5/T6, B-FPTR	Sham	Global cognition (MMSE, MoCA, and ADAS-cog); Executive function (TMS, CDT, FAB); NPS (NPI, GDS, PHQ-9, CDS, IADL); Side effect
Jin [27]	MCI/AD	rTMS	3	65.6–77.3	49	4/10–20	B-DLPFC, L-DLPFC	Sham	Apathy (AES)
Jiang et al. [32]	MCI	rTMS, rTMS + CT/ drug	9	63.4–74	369	2–8/10–48	B-DLPFC, L-DLPFC, R-DLPFC, L-PFC, B-anterior temporal	Sham, piracetam, CT, drug	Global cognition (MoCA, MMSE); Drop out; Adverse effect
Wang T [30]	MCI/AD	rTMS tDCS (Anode, Cathodal Anode + ICMT)	15 13	64–77.6	374	1–6/5–30	B-DLPFC, L-DLPFC, R-DLPFC, R-STG, R-IFG, Precuneus, B-FPTR, Parietal P3/P4, Posterior temporal T5/T6 B-DLPFC, L-DLPFC, R-DLPFC, B-temporal lobes, L-temporal lobes, B-TP, L-PFC	Sham Sham, Sham + ICMT	Memory; Language; Executive function (TMT, FAB, Executive Function Contrasting Program, CAMCOG-Executive function) Memory; Language
Saleh [13]	MCI	tDCS (Anode, Anode + SMART/LOCATO/CCT/TC/CT)	11	62.58–76.8	429	1–12/3–36	L-IFG, R-IFG, L-DLPFC, R-DLPFC, L-temporal area (T3)	Sham, Sham + SMART/LOCATO/CCT/TC/CT	Global cognition (MoCA); Attention (TMT-A); Executive function (TMT-B)
Chen et al. [28]	MCI/AD	tDCS (Anode, Cathodal Anode + ICMT/SMART/CT/WMT)	16	62.58–81.6	616	1–32/3–180	B-temporal lobes, L-temporal lobes, L-DLPFC, L-IFG, B-TP, L-frontotemporal cortex, B-TP, L-LTL, R-DLPFC	Sham, Sham + ICMT/SMART/CT/WMT	Global function (MMSE, ADAS-cog); Attention (Forward Digital Span); Executive function (Clock Drawing Test)
Majdi [17]	AD	tDCS (Anode, Cathodal Anode + CT)	13	63.8–81.6	317	1–32/3–180	B-DLPFC, L-DLPFC, B-temporal lobes, B-TP, L-frontotemporal cortex, L-temporal lobes	Sham, Sham + CT	Attention
Teselink [29]	MCI/AD	tDCS (Anode, Cathodal Anode + ICMT)	13	63.8–81.6	330	1–24/5–180	B-temporal lobes, L-temporal lobes, L-DLPFC, L-frontotemporal cortex, B-TP, R-DLPFC	Sham, Sham + ICMT	NPS (NPI, GDS, CDS, AES, BEHAVE-AD)
Saxena [31]	MCI/AD	tDCS (Anode, Cathodal Anode + ICMT/ CT)	10	63.8–80.6	369	1–32/3–180	B-temporal lobes, B-DLPFC, L-DLPFC, L-LTL, L-temporal lobes, B-TP	Sham, Sham + ICMT/ CT	Drop out; Adverse effect

3MS: Modified-Mini Mental State Examination; AD: Alzheimer's Disease; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; AES: Apathy Evaluation Scale; B-AG: Bilateral Angular Gyrus; B-DLPFC: Bilateral Dorsolateral Prefrontal Cortex; B-FPTR: Bilateral frontal parietal-temporal regions; BEHAVE-AD: Behavioural Pathology in Alzheimer's Disease; CCT: Computerized Cognitive Training; CDT: Clock Drawing Test; CDS: Cornell Depression Scale; CT: Cognitive Training; FAB: Frontal Assessment Battery; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; ICMT: Individualized Computerized Memory Training; L-DLPFC: Left Dorsolateral Prefrontal Cortex; L-LPC: Left lateral parietal cortex; L-LTL: Left lateral temporal lobe; L-PFC: Prefrontal cortex; LOCATO: Object-Location Memory Paradigm; MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; NIBS: Non-invasive Brain Stimulation; NPI: Neuropsychiatric Inventory Questionnaire; NPS: Neuropsychiatric Symptoms; PHQ-9: Patient Health Questionnaire-9; PSAC: Parietal somatosensory association cortices; rTMS: Repetitive Transcranial Magnetic Stimulation; R-IFG: Right inferior frontal gyrus; R-STG: Right superior temporal gyrus; SMART: Strategic Memory and Advanced Reasoning Training; tDCS: Transcranial Direct Current Stimulation; TC: Tai Chi; TMT: Trail Making Test; TP: temporoparietal; WMT: Working-Memory Training

consider other NIBS techniques, such as theta-burst stimulation, transcranial alternating current and transcranial random noise, no SRMAs related to these treatments were retrieved.

Primary studies in the included SRMAs were predominantly from the United States, Europe, and Asia, with a few from African countries. The number of studies included in the SRMAs was 3–24, with total number of participants of 49–931 and average age of the participants of 53.12–81.6 years. The duration of the interventions was 1–32 weeks, and the number of intervention sessions was 3–180.

Table 2 and Supplementary Table S4 list all 22 associated summaries. According to the random effects model, 10 of the 22 associations (45.5%) were statistically significant at $p < 0.05$. Among these, 3 associations (30%) exhibited high heterogeneity ($I^2 > 75\%$), 5 (50%) included null values within their 95% PIs, and 3 (30%) showed evidence of small study effects.

Methodological quality and quality of the evidence

According to the overall assessment by AMSTAR 2, the methodological qualities of the seven and three included publications were rated as low and very low, respectively. None of the publications were rated as high or moderate quality. The detailed results of the AMSTAR 2 analysis are presented in Supplementary Table S5.

Using the GRADE assessment system, 63.6% (n = 14), 22.7% (n = 5), and 13.6% (n = 3) of the meta-analyses were rated as moderate, low, and very low quality, respectively. None of the meta-analyses were rated as high-quality. Among the associations with moderate evidence quality, seven were statistically significant. The details of the GRADE assessments are listed in Supplementary Table S6.

Therapeutic effect of NIBS on AD and MCI

rTMS in AD and MCI

Six SRMAs were used to evaluate the effects of rTMS on patients with AD or MCI. rTMS had statistically significant effects on improving cognitive functions, including global cognition, memory, language, and executive function. One SRMA of moderate quality found that, compared with sham stimulation, treatment with 5–42 sessions of rTMS improved global cognition in patients with AD/MCI (SMD, 0.44; 95% CI 0.02–0.86) [25]. Additionally, in SRMAs studying the long-term effects of rTMS (lasting ≥ 6 weeks), only one association (global cognition) reported moderate-quality evidence and was statistically significant (SMD, 0.29; 95% CI 0.07–0.50) [26]. An SRMA reported two statistically significant associations supported by moderate-quality evidence [30]. In elderly individuals with AD/MCI (aged 65.1–77.6 years), compared with those following sham stimulation, the scores for language and executive function significantly increased after 2–4 weeks with 10–20 rTMS sessions. Specifically, language and executive function scores increased by 1.64 (95% CI 1.22–2.06; $p < 0.0001$) and 0.51 (95% CI 0.18–0.83; $p = 0.0024$), respectively.

Moreover, two SRMAs involving 353 participants with AD or MCI that compared rTMS with sham stimulation reported no significant effects on neuropsychiatric symptoms (NPI, GDS, apathy, and instrumental activities of daily living [IADL]), with associations based on low- and very low-quality evidence [26, 27]. This suggests that while rTMS may improve certain cognitive metrics, its effects on NPS may not be significant and should be considered when implementing rTMS interventions. Notably, dropout rates and side effects had moderate-quality support in the associations. No significant difference was observed in dropout rates during rTMS treatment (OR 1.08; 95% CI 0.02–0.86; $p = 0.9090$), potentially indicating high acceptance among patients with AD and MCI [32]. Two SRMAs with different primary studies each reported an association of side effects (OR 2.14; 95% CI 1.12–4.10; $p = 0.0220$, and OR 2.26; 95% CI 1.00–5.08; $p = 0.0492$, respectively) [26, 32]. These side effects were minor and included headaches, scalp tingling, and dizziness. Although the side effects were significant, they did not lead to significant treatment dropouts, suggesting that, in most cases, the side effects were manageable.

tDCS in AD and MCI

Only one SRMA showed a significant effect of tDCS on the association between memory and executive function, with moderate-quality evidence supporting these findings [30]. Specifically, the scores for memory and executive function improved by 0.60 (95% CI 0.32–0.89; $p < 0.0001$) and 0.39 (95% CI 0.08–0.71; $p = 0.0151$), respectively.

The remaining six SRMAs covering six independent associations (global cognition, attention, NPS, language, dropout, and adverse effects) did not reach statistical significance, with evidence quality ranging from very low to moderate. Four of these SRMAs, involving independent associations between global cognition, attention, language, and dropout, reported moderate-quality evidence. In addition, one SRMA reported that tDCS was safe and acceptable [31]. However, the study cautioned that the wide CI for adverse reactions (i.e., 95% CI 0.69–24.59) should be interpreted with caution.

Sensitivity analyses

Multiple sensitivity analyses were conducted to assess whether the quality of evidence changed when using the GRADE system. After excluding RCTs with small sample

sizes (25th percentile), the two associations experienced a downgrade from moderate to low quality [26, 32]. Specifically, mild adverse reactions were observed in patients with AD and MCI after 2–8 weeks and 2–24 weeks of rTMS intervention, respectively, compared with those following sham stimulation. Another association was downgraded from low to very low quality, concerning the impact of rTMS intervention on memory improvement in patients with AD or MCI [30], compared with sham stimulation (Supplementary Table S7). Additionally, after excluding RCTs with high risks of bias, one of the associations was downgraded from low to very low quality [32]. Compared with sham stimulation, 10–48 sessions of rTMS intervention over 2–8 weeks preserved global cognitive function (SMD, 3.94; 95% CI − 0.97–8.86) in patients with MCI (Supplementary Table S8).

Discussion

Principal findings and possible explanations

To the best of our knowledge, this study is the first umbrella review to assess the cognitive and mental outcomes of different types of NIBS (rTMS and tDCS) in patients with AD and MCI, encompassing numerous published RCT meta-analyses. We employed standardized random effects analysis methods to replicate each meta-analysis for a better comparison of the different outcomes. We assessed the methodological quality of the meta-analyses using standard methods and conducted sensitivity analyses to provide additional evidence from high-quality RCTs to further enhance the reliability of the results. Additionally, we evaluated the evidence using the recognized GRADE criteria, with most associations rated as moderate. Some associations were rated as low or very low evidence owing to significant imprecision and heterogeneity. Our findings contribute to a better understanding of the current research in this field.

Our study results indicate that rTMS intervention is significantly associated with the six independent factors global cognition, follow-up global cognition (≥6 weeks), memory, language, executive function, and adverse effects. Among these, moderate-quality evidence supports associations with global cognition, follow-up global cognition, adverse effects, language, and executive function. These findings were consistent with those of previous studies [11]. A component network meta-analysis comprising 27 RCTs and 1070 participants demonstrated that compared with sham stimulation, rTMS had short-term (mean difference [MD], 1.08; 95% CI 0.35–2.40) and long-term (MD 1.65; 95% CI 0.77–2.54) positive impacts on global cognition in patients with AD and MCI, respectively (followed up after 1 month). In addition, rTMS significantly improved memory function (MD 0.72; 95% CI 0.05–1.39). Other associations, such as NPS, apathy, IADL, and dropout rates, showed no statistically significant differences, with moderate-quality evidence for NPS and dropout rates. Associations between low and very low evidence quality may be attributed to small sample sizes in the imprecision domain of the studies, which could impact the statistical power and precision of the results, thereby being rated as serious or very serious. As the FDA expert panel has not yet supported the use of rTMS interventions for NPS aspects (depression and apathy) in patients with AD or MCI in real clinical settings (NCT03665831, NCT04562506), fewer patients may receive rTMS interventions as clinicians and therapists implement the protocols.

Regarding tDCS, multiple previous SRMAs have confirmed that the improvements of cognitive abilities in MCI and AD through tDCS show considerable variability [12, 17]. Our findings identified significant effects of tDCS only on memory. However, no statistically significant differences were observed in other cognitive subdomains, such as global cognition, executive function, language, and attention. The reproducibility of tDCS studies and variability in stimulation effects were high [33, 34]. These differences were partly attributed to variations in study design, such as changes in stimulation intensities, number of treatments, durations, and stimulation sites. Notably, even when similar parameters, such as stimulation protocols and outcome measures, have been used, studies have reported inconsistent results [34, 35]. Additionally, the individual characteristics of participants, including variations in brain anatomy and pathology, may significantly affect how currents influence cortical neurons. Given that tDCS may act through cortical excitability and neuroplasticity, the integrity of neural networks is crucial in determining its beneficial effects. Therefore, future studies should consider assessing individual brain structures and resting-state functional connectivity using magnetic resonance imaging to predict favorable outcomes of tDCS. These assessments can help researchers understand the varying effects of tDCS on different individuals and enhance the personalization and precision of treatment. To further validate the impact of tDCS on cognitive function and reduce variability in research outcomes, more studies with larger sample sizes and longer follow-up periods are needed to provide more conclusive evidence and better understand its positive impacts and mechanisms.

Currently, clinical practice guidelines for dementia suggest that pharmacological treatments should only be recommended for NPS that is resistant to treatment and when non-pharmacological interventions have failed to produce positive results with close monitoring of risk factors and adverse effects [36, 37]. The lack of clinical evidence may impede the beneficial effects of

Table 2 Summary of Significant Findings from Associations Between Non-invasive Brain Stimulation and Cognitive and Mental Outcomes in MCI/AD

Source	Outcome	Population	Type of NIBS	No. of studies	Sample size (NIBS/control)	Metric	Random effect size (95% CI)	*P* value	I^2, %	95% Predictive interval (95% PI)	Egger's test p-value	GRADE rating	AMSTAR-2 rating
Pagali et al. [25]	Global cognition[a]	MCI/AD	rTMS	31	508/481	SMD	0.44 (0.02 to 0.86)	0.0420	86	− 0.91 to 0.98	0.1458	Moderate	Low
Li [26]	Global cognition (follow-up)	AD	rTMS	8	182/163	SMD	0.29 (0.07 to 0.50)	0.0089	0	0.07 to 0.47	0.6012	Moderate	Low
Jiang et al. [32]	Global cognition[b]	MCI	rTMS	7	151/145	SMD	2.25 (0.13 to 4.38)	0.0374	93.5	− 0.79 to 0.99	0.0924	Low	Low
Wang [30]	Memory	MCI/AD	rTMS	12	215/214	SMD	1.01 (0.19 to 1.84)	0.0160	89.9	− 0.87 to 0.99	0.0133	Low	Low
Wang [30]	Language	MCI/AD	rTMS	6	63/63	SMD	1.64 (1.22 to 2.06)	< 0.0001	20.5	0.70 to 0.99	0.2313	Moderate	Low
Wang [30]	Executive	MCI/AD	rTMS	5	73/77	SMD	0.51 (0.18 to 0.83)	0.0024	0	0.18 to 0.68	0.0998	Moderate	Low
Wang [30]	Memory	MCI/AD	tDCS	13	172/168	SMD	0.60 (0.32 to 0.89	< 0.0001	36.1	− 0.08 to 0.86	0.1714	Moderate	Low
Wang [30]	Executive	MCI/AD	tDCS	7	94/91	SMD	0.39 (0.08 to 0.71)	0.0151	8.4	− 0.02 to 0.67	0.3459	Moderate	Low
Li [26]	Adverse effect[c]	AD	rTMS	9	210/185	OR	2.14 (1.12 to 4.10)	0.0220	0	1.11 to 4.10	0.7475	Moderate	Low
Jiang et al. [32]	Adversed effect[d]	MCI	rTMS	7	170/157	OR	2.26 (1.00 to 5.08)	0.0492	0	1.00 to 5.08	0.1772	Moderate	Low

NIBS: Non-invasive Brain Stimulation; rTMS: Repetitive Transcranial Magnetic Stimulation; tDCS: Transcranial Direct Current Stimulation; AD: Alzheimer's Disease; MCI: Mild Cognitive Impairment; SMD: Standardized Mean Difference; OR: Odds Ratio; CI: Confidence Interval; PI: Prediction Interval; GRADE: Grading of Recommendations Assessment: Development and Evaluation; AMSTAR: A Measurement Tool to Assess Systematic Reviews

[a, b] None of the primary literature is the same

[c, d] None of the primary literature is the same

non-pharmacological treatments, such as NIBS techniques, on non-cognitive symptoms in patients with dementia. An SRMA involving six RCTs with 185 participants showed that rTMS improved NPS (SMD 0.78; 95% CI 0.03–1.53; $p = 0.40$; $I^2 = 80.4$), compared with a control group [29]. An SRMA conducted by Wang et al. in 2021 based on four RCTs published between 2012 and 2019 showed that rTMS intervention was more effective than sham stimulation [30]. These inconsistent results regarding the effect of rTMS on NPS symptoms in patients with AD may be attributed to several factors, including variations in sample size and duration. Wang et al.'s SRMA had a total sample size of 166 with a duration of 1–6 weeks, Teselink et al.'s SRMA had a total sample size of 185 with a duration of 1–6 weeks, and our study had a total sample size of 298 with a duration of 1–24 weeks. Smaller sample sizes may lead to higher heterogeneity, which in turn may lead to reporting bias and insufficient statistical power. Shorter durations may not adequately capture the durability of the treatment effects and potential long-term impacts. In this study, we aimed to minimize the potential effects of time by extracting data at the final follow-up; however, the relatively short follow-up duration (average of 12 weeks) may still be confounded by time. Therefore, we encourage future randomized controlled trials to employ longer follow-up periods (i.e., at least 6–12 months). Furthermore, two SRMAs studying tDCS reported no evidence of effective NPS, which is consistent with our findings [38, 39]. Notably, evidence for certain NPS factors (agitation, psychosis, anxiety, and aggression) remains insufficient to determine whether NIBS has an actual impact on patients with AD and MCI. This may be attributed to our study design, which did not identify other types of dementia, such as anxiety in Lewy body dementia or agitation and aggression in frontotemporal dementia [40]. We recommend that future researchers conduct high-quality RCTs on patients with other types of dementia.

As NIBS techniques are increasingly integrated into routine medical care, it is crucial to thoroughly assess their safety and treatment adherence. Studies have shown that, among 18,000 NIBS sessions conducted on 8,000 healthy subjects and patients with neurological and psychiatric disorders, no serious adverse events were reported [41]. Consistent with our findings, we observed that adverse events during NIBS treatment were generally mild and manageable, such as headaches, dizziness, and fatigue. Notably, the elderly population frequently presents with comorbid conditions—such as cardiovascular disease, diabetes, or other chronic illnesses—that may heighten their sensitivity to treatment-related adverse effects [42]. Although current evidence suggests that rTMS and tDCS can be applied safely in older adults, further data are needed to clarify how these comorbidities influence overall tolerability and whether certain patient subgroups may require more cautious monitoring or individualized treatment protocols [43].

Dropout rates are a key indicator when assessing treatment acceptability and tolerance, as higher rates may suggest severe adverse events or general patient dissatisfaction with the treatment. Therefore, we closely examined the relationship between dropout rates and adverse events to better understand how these minor side effects may affect patient adherence. Our data indicate that, despite minor adverse events, the dropout rate observed during rTMS treatment did not significantly differ (OR 1.08; 95% CI 0.02–0.86), suggesting these events were insufficient to cause treatment discontinuation in AD/MCI patients. However, given that only two SRMAs evaluated adverse events and one evaluated dropout rates, the relative lack of data poses challenges for a comprehensive assessment of the clinical risks and benefits of NIBS across diverse patient populations. Future research should focus on developing and implementing standardized guidelines for reporting adverse events, with an emphasis on stratifying data by patient subgroups, including those with common comorbidities. Such guidelines are essential to ensure consistent and reliable data collection, guide clinical practice, ensure patient safety, and maximize therapeutic outcomes.

The quality assessment of the included SRMAs revealed varying degrees of bias. We conducted a thorough search of authoritative databases, with two authors systematically and independently performing rigorous screening, data extraction, effect size recalculations, methodological quality assessment, and certainty of evidence evaluations. However, according to AMSTAR 2, all included systematic reviews and meta-analyses were rated as low or very low quality. Specifically, of the 10 SRMAs included, 9 received low ratings for critical items such as providing a list of excluded SRMAs and justifying their exclusion, and 8 failed to report funding sources for the included SRMAs (Supplementary Table S5). Additionally, another SRMA did not adequately address publication bias assessment [30], resulting in an overall low quality for these SRMAs [22]. Moreover, the SRMAs by Teselink et al. [29], Majdi et al. [17], and Saxena et al. [31] received particularly low ratings due to the absence of a registered study protocol or a failure to retrieve one [13, 23, 34]. Beyond the methodological flaws highlighted here, existing SRMAs have not sufficiently explained the rationale behind the inclusion of specific study designs. Furthermore, comprehensive literature search strategies are often overlooked, such as whether researchers searched the reference lists of included studies, clinical trials, research registration platforms, consulted experts,

or searched grey literature. This variability in study quality underscores the need for transparent reporting and robust methodology in future evaluations to optimize NIBS treatment protocols.

While our umbrella review has demonstrated the potential benefits of NIBS on various outcomes, ensuring the reliability and clinical applicability of these results may be complicated by differences in sample characteristics (age, sex, disease duration, ethnicity, and region), specifics of stimulation protocols (electrode placement and stimulation intensity), and variations in outcome measurement methods (use of different scales or assessment time points). This complexity may explain why previous SRMAs have reported inconsistent findings on the effects of NIBS on cognitive functions and NPS in MCI or AD patients. Although we focused on SRMAs of RCTs to ensure evidence quality, we observed significant diversity in NIBS parameters within the original RCTs, including inconsistencies in electrode placement, polarity, intensity, session duration, and total treatment course (Table 1), reflecting a clear lack of standardized protocols. This variability in parameters may indicate a placebo effect of neuromodulation therapies, thereby complicating the estimation of NIBS's true effect size and hindering the development of standardized treatment protocols [44, 45]. Our analysis found that 8 of the 22 reported associations exhibited moderate to high heterogeneity. Despite our efforts to explore the impact of potential moderating variables, such as NIBS parameters, demographic data, and baseline disease characteristics, the control and testing of these variables remained limited due to the data constraints of the original studies. We recommend that future studies strengthen the integration and reporting of these potential moderating variables, particularly in meta-analyses, to gain a deeper understanding of which patient groups may benefit most from specific types of NIBS. This approach would support the advancement of personalized medicine and provide a foundation for developing more precise treatment protocols and clinical guidelines, ensuring patients receive the most appropriate treatment based on their specific needs and conditions.

In modern medical practice, the potential of NIBS in AD and MCI treatment remains uncertain. Although traditional meta-analysis results and CIs provide some quantification of treatment effects, these statistical methods often fail to capture variability in treatment effects across different patient groups. In contrast, PI offers a broader perspective, depicting not only the possible range of treatment effects, but also the potential for ineffectiveness or adverse outcomes under certain circumstances. Based on our results, the PIs of the reanalyzed meta-analyses indicated that half of the patients with AD and MCI experienced clinical improvement. However, the wide span of the PI indicates a high level of uncertainty, reminding clinicians to interpret these findings with caution in practice. To more robustly integrate NIBS into clinical decision-making, it is essential to consider individual patient differences, comorbidities, economic factors, and patient preferences. In summary, NIBS showed potential therapeutic promise; however, a deeper investigation into its long-term effects and individual differences in patient responses is necessary before it can be widely implemented in clinical practice. Such efforts will ultimately facilitate the development of more rational and tailored interventions for patients.

Policy implication

Our umbrella review highlights the potential of NIBS as an emerging treatment modality for AD and MCI, underscoring the need for policy adjustments to accommodate these technological advancements. The positive effects of NIBS on cognitive function suggest that health policymakers should consider incorporating NIBS into standard treatment protocols, particularly when traditional therapeutic approaches are ineffective or unsuitable [46]. Given the portability and ease of operation of NIBS devices, there is significant potential for developing NIBS as a home-based treatment option [47], which would expand accessibility and provide patients with more convenient therapeutic choices.

However, to ensure that NIBS becomes a safe and effective component of routine care, several key steps must be taken. First, establishing standardized intervention protocols, including parameters such as stimulation intensity, frequency, and duration. Second, identifying biomarkers that predict individual responses to NIBS may guide personalized treatment strategies, ensuring that patients with specific disease characteristics or levels of cognitive decline receive the most benefit. Third, rigorous long-term monitoring frameworks, including regular follow-up assessments and detailed adverse event reporting, will be essential to confirm sustained efficacy and safety over time. Furthermore, as patient-specific factors (e.g., brain structure, age, gender, disease duration) may influence treatment response, comprehensive individualized assessments prior to initiating NIBS are advisable. Utilizing advanced imaging techniques (e.g., MRI) and predictive modeling can inform personalized parameter adjustments and optimize outcomes [47]. Therefore, policy development should not only promote the adoption of these promising technologies but also ensure stringent regulation of their clinical application.

Limitations

This study had several limitations that must be considered when interpreting the results. First, most studies did not follow a priori methods, lacked a list of specific reasons for excluding articles, and lacked information about fundings, resulting in low or very low methodological quality according to AMSTAR 2. Second, our umbrella review relied on primary studies within the published SRMAs and did not consider the latest high-quality RCTs. Moreover, to avoid high overlap, we selected the largest SRMAs, which might have excluded relevant individual RCTs or earlier high-quality SRMAs. Third, from the existing SRMAs, the long-term effects of NIBS on memory, attention, executive function, and other associated outcomes for patients with AD and MCI remain unclear. Therefore, we encourage future RCTs with longer follow-up periods (at least 2–6 months). Fourth, we combined patients with AD and MCI as our study sample, which may have enhanced the statistical power and generalizability of our study results. Finally, we have not yet fully understood the potential mechanisms and appropriate parameters of NIBS for improving cognitive and mental outcomes in patients with AD and MCI. To assess its efficacy more accurately, the evaluation of vital parameters, such as intensity, frequency, duration, and location of stimulation, must be standardized. Additionally, increasing the number of participants and utilizing multimodal brain imaging techniques will help explore the pathophysiological mechanisms underlying these interventions in greater depth.

Conclusion

Our umbrella review systematically included numerous published clinical trials using SRMAs to examine the evidence hierarchy for the efficacy of NIBS interventions on cognitive and mental outcomes in patients with AD and MCI. Although these associations are supported by moderate-quality evidence, the presence of heterogeneity and low methodological quality necessitates a cautious interpretation of these findings. Due to variations in NIBS parameters, participant characteristics, and treatment duration, the variability in effects highlights the need for further research to standardize and optimize treatment protocols. Future studies should focus on larger-scale, longer-term (>6 months) RCTs to confirm the sustained effects of NIBS and explore its broader applicability across different types of dementia.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12984-025-01566-3.

Supplementary Material 1.

Acknowledgements

We extend our heartfelt gratitude to Huize Lin for the invaluable insights and guidance provided during the development of this manuscript. Her contributions were instrumental in shaping the direction and execution of our research.

Author contributions

MW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: MW, QT, LZ. Acquisition, analysis, or interpretation of data: MW, WS, LT, JL, JZ, BW, DY. Drafting of the manuscript: MW, QT, LZ. Critical review of the manuscript for important intellectual content: WS, LT, JL, JZ. Statistical analysis: MW, XW, XL, HJ. Administrative, technical, or material support: LZ, QT. Supervision: LZ.

Funding

The work was supported by the National Key Research and Development Program [Grant Numbers 2023YFC3603902]; National Natural Science Foundation of China [Grant Numbers 82174477]; Heilongjiang Key R&D Program [Grant Numbers 2022ZX06C24]; Heilongjiang University of Chinese Medicine Outstanding Cultivation Fund Project [Grant Numbers 2019JC03].

Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have approved this manuscript for publication. This manuscript has not previously been published and is not pending publication elsewhere.

Competing interests

The authors declare no competing interests.

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Received: 22 August 2024 Accepted: 30 January 2025
Published online: 05 February 2025

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