Effects of Oral Probiotic Supplementation on Cognitive Function in Adults with Mild Cognitive Impairment: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Vanessa Esteves-Mesquita
vaeste01@ucm.es
Complutense University of Madrid
África Peral-Suárez
Complutense University of Madrid
Aránzazu Aparicio
Complutense University of Madrid
Iván Cavero-Redondo
University of Castilla-La Mancha
Laura M Bermejo
Complutense University of Madrid
Ana M López-Sobaler
Complutense University of Madrid

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Abstract

Purpose

Probiotic supplementation has emerged as a microbiota-targeted nutritional strategy with potential to modulate gut–brain communication in mild cognitive impairment (MCI). However, randomized evidence remains limited. This systematic review and meta-analysis aimed to quantify the effects of oral probiotic supplementation on cognitive outcomes in adults with MCI and explore whether effects differed by formulation.

Methods

Eight databases were searched according to PRISMA. Eligible studies were randomized controlled trials (RCTs) of oral probiotic supplementation in adults with MCI. Risk of bias was assessed with RoB 2. Random-effects meta-analyses estimated standardized mean differences (SMDs) with 95% confidence intervals (CIs). Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. An exploratory network meta-analysis was conducted to compare probiotic categories.

Results

Six RCTs including 474 participants were included. Compared with placebo/control, probiotics produced a small improvement in global cognitive performance (SMD 0.19, 95% CI 0.04 to 0.34; I^2 = 75.9%). Small favorable effects were observed for memory (SMD 0.14, 95% CI 0.02 to 0.25) and visuospatial/constructional function (SMD 0.24, 95% CI 0.06 to 0.41). No clear effects were detected for attention/processing speed, language, or orientation. Multi-strain formulations ranked highest in the exploratory network meta-analysis.

Conclusion

In adults with MCI, probiotic supplementation may yield modest improvements in global cognition and selected cognitive domains, but clinical relevance remains uncertain. Current evidence supports probiotics as a promising, not established, nutritional strategy. Larger strain-specific trials using harmonized cognitive outcomes, longer follow-up, safety assessment, and microbiota/inflammatory biomarkers are needed.

1. Introduction

Neurodegenerative diseases constitute a significant global health challenge due to the progressive and irreversible loss of neuronal structure and function[1]. Currently, Alzheimer's disease (AD), the most prevalent neurodegenerative disorder, has an estimated global prevalence of between 34 and 40 million people, according to the World Health Organization [2]. In Europe, AD affects approximately 5% of individuals aged 65 years and older, with prevalence rates sharply increasing with age—from around 1% among those aged 65–74 years to over 20% in individuals aged over 85 years [3]. As the population ages, the absolute number of individuals affected by AD is projected to double by 2040, posing an unprecedented burden on healthcare systems and societies worldwide [4]. Consequently, there is an urgent need for effective early intervention strategies to delay or prevent progression from the initial stages of cognitive decline to AD and other dementias [4]. In particular, mild cognitive impairment (MCI) has been identified as an intermediate stage between normal cognitive aging and dementia, characterized by measurable cognitive deficits exceeding those expected for an individual’s age and educational level, yet not significantly interfering with daily activities [5, 6]. This condition represents a critical intervention window since it carries an elevated risk for progression to more severe forms of neurodegeneration, with annual conversion rates reported between 10% and 15% [7].

From a pathophysiological perspective, cognitive impairment and progression to AD have been closely linked to neurodegenerative processes, such as amyloid-beta deposition and tau phosphorylation, leading to neuronal hyperexcitability due to disrupted GABAergic/glutamatergic balance [8, 9]. Despite decades of research, therapeutic interventions capable of significantly modifying the clinical course of MCI or AD remain scarce. Recently approved pharmacological treatments, such as the monoclonal antibody Aducanumab, have raised concerns due to adverse effects and limited evidence of clinical efficacy [10].

Therefore, research efforts have increasingly shifted toward modifiable lifestyle interventions targeting factors such as hypertension, hyperlipidemia, obesity, physical inactivity, and poor dietary habits, all associated with elevated dementia risk [11]. In recent years, the gut-brain axis (GBA), a bidirectional communication pathway linking the gastrointestinal tract and the central nervous system, has emerged as a promising target [12]. Numerous studies have demonstrated significant alterations in gut microbiota composition in patients with MCI and AD, characterized by a decrease in beneficial anti-inflammatory genera (e.g., *Bifidobacterium*) and an increase in potentially pro-inflammatory genera (e.g., *Bacteroides*). These changes may contribute to low-grade systemic inflammation and could potentially exacerbate cognitive decline [13, 14].

Probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, have recently gained attention as potential modulators of the GBA [15]. Specifically, certain strains of *Lactobacillus* (such as *Levilactobacillus* and *Lactiplantibacillus*) and *Bifidobacterium* have shown promising results in animal models, improving cognitive deficits and reducing biomarkers associated with neuroinflammation and oxidative stress [16, 17]. The potential mechanisms underlying these effects include the production of neurotransmitters (e.g., gamma-aminobutyric acid (GABA) and acetylcholine (ACh)), reinforcement of intestinal barrier integrity, modulation of systemic inflammation, and restoration of intestinal microbiota homeostasis [18, 19]. Clinical trials evaluating probiotic supplementation in cognitive impairment are relatively limited and have yielded mixed results. While some studies suggest improvements in cognitive performance in MCI patients following probiotic intervention [16, 17], others have reported only modest benefits on inflammatory markers and metabolic parameters, particularly in populations already diagnosed with AD [20]. This variability indicates that probiotics may be more beneficial during earlier stages of cognitive decline, such as MCI, rather than advanced dementia. Given this context, exploring probiotic supplementation as a non-pharmacological intervention to enhance cognitive function in individuals with MCI represents a highly relevant scientific inquiry.

This systematic review and meta-analysis aim to comprehensively evaluate and synthesize current evidence regarding the efficacy of probiotic supplementation on cognitive functions in individuals diagnosed with MCI. The primary objective is to assess the effect of oral probiotic supplementation on cognitive function in adults diagnosed with MCI, compared with placebo. Secondary objectives include exploring potential sources of heterogeneity across studies and assessing the quality of the cumulative evidence.

2. Material & Methods

This systematic review was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, considering the methodological recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Online Resource 1) [21]. The protocol for this systematic review was registered in PROSPERO (CRD420251037930). The literature search was last updated on June 05th, 2025. To formulate the research question and guide the selection of search terms, the PICOS framework (Population, Intervention, Comparator, Outcome, Study Design) was applied. The research question was structured as follows: In individuals with mild cognitive impairment (Population), does oral probiotic supplementation (Intervention), compared to placebo (Comparator), improve cognitive function (Outcome), as assessed in randomized controlled trials (Study Design)?

2.1 Data sources and search strategy

A comprehensive literature search was conducted across the following databases: Web of Science Core Collection, MEDLINE®, Current Contents Connect, BIOSIS Previews, ProQuest Dissertations & Theses Citation Index, SciELO Citation Index, Scopus, and PubMed, with the aim of identifying randomized controlled trials (RCTs) evaluating the effects of oral probiotic supplementation on cognitive function in individuals with MCI. The search strategy included both Medical Subject Headings (MeSH) and relevant keywords identified from previous systematic reviews and original research. The complete search strategies for each database are detailed in Table 1. No restrictions were imposed regarding publication date or language. Additionally, the reference lists of all included studies and relevant reviews were manually screened to identify further eligible studies.

Table 1
Search strategies used in each database.

Database	Search strategy
Scopus	(TITLE-ABS-KEY ("probiotic*" OR "levilactobacillus brevis" OR "lactobacillus plantarum") AND TITLE-ABS-KEY ("cognitive dysfunction" OR "cognitive disorder" OR "cognitive impairment" OR "cognitive decline" OR "mild cognitive impairment" OR "mild neurocognitive disorder" OR "elderly cognitive impairment" OR "cognitive function") AND TITLE-ABS-KEY ("randomized controlled trial"))
Web of Science	(Probiotic* OR Levilactobacillus brevis OR Lactobacillus plantarum) AND (cognitive dysfunction OR cognitive disorder OR cognitive impairment OR cognitive decline OR mild cognitive impairment OR mild neurocognitive disorder OR elderly cognitive impairment OR cognitive function) AND (randomized controlled trial)
PubMed	("probiotic"[tiab] OR "probiotics"[Title/Abstract] OR "probiotics"[MeSH Terms] OR "levilactobacillus brevis"[tiab] OR "lactobacillus plantarum"[tiab] OR "lactiplantibacillus plantarum"[tiab] OR "lactobacillus plantarum"[MeSH Terms]) AND ("cognitive dysfunction"[tiab] OR "cognitive disorder"[tiab] OR "cognitive impairment"[tiab] OR "cognitive decline"[tiab] OR "mild cognitive impairment" [tiab] OR "mild neurocognitive disorder" [tiab] OR "elderly cognitive impairment"[tiab] OR "cognitive function"[tiab] OR "cognition disorders"[MeSH Terms] OR "mild cognitive impairment"[MeSH Terms]) AND ("randomized"[tiab] OR "randomised"[tiab] OR "trial"[tiab] OR "RCT"[tiab])

2.2. Eligibility criteria and selection process

The articles included in the systematic review and meta-analysis were selected based on the following eligibility criteria, established according to the PICOS framework (Table 2):

Table 2
Inclusion and exclusion criteria for the articles included in the review according to the PICOS framework.

Terms	Inclusion criteria	Exclusion criteria
Population	Adults diagnosed with MCI, based on any recognized diagnostic criteria*	Adults without an objective diagnosis of MCI or any neurological conditions other than mild cognitive impairment
Intervention	Oral probiotic supplementation. Only studies that explicitly reported the dose and duration of the probiotic intervention were considered	Studies were excluded if the intervention did not involve oral probiotics or combined probiotics administration with other therapeutic interventions
Comparator	Placebo or standard care without any probiotic supplementation	Studies were excluded if no comparator group was used
Outcome	Primary outcome: Cognitive function assessed through standardized cognitive tests Secondary outcomes: Domain-specific cognitive improvements, and biochemical parameters relevant to cognitive function	Studies were excluded if cognitive function was not assessed as an outcome or data was not available
Study type	Randomized controlled trials	Reviews, editorials, letters, protocols, case reports, systematic reviews, meta-analysis and studies examining unrelated interventions were also excluded

* Recognized diagnostic criteria for MCI included fulfillment of commonly accepted clinical standards such as: (1) subjective memory complaints reported by the individual or an informant, (2) objective cognitive impairment demonstrated by scores in screening tools, (3) preserved global functioning and independence in activities of daily living; and (4) absence of dementia, often supported by a Clinical Dementia Rating (CDR) of 0.5 [22].

All records identified through database searches and manual screening of reference lists were imported into Rayyan for deduplication. The process of selection of the studies was carried out independently by two reviewers (Vanessa Esteves-Mesquita. and África Peral-Suárez). Any discrepancies between reviewers were resolved through discussion or, when necessary, by consultation with a third reviewer (Aránzazu Aparicio). To assess the consistency between reviewers during the first stage of study selection (title and abstract screening), Cohen's kappa coefficient was calculated [23].

2.3. Data extraction, risk of bias assessment, and certainty of evidence assessment

The data extraction process was conducted by one reviewer (Vanessa Esteves-Mesquita). To minimize potential errors and reduce bias, a second reviewer (África Peral-Suárez) independently verified the accuracy and completeness of the data extracted for all included studies. From each eligible study, the following information was collected and synthesised in summary tables: first author, year of publication, country, sample size, diagnose criteria, participants characteristics, details of the probiotic intervention (strains, dosage, duration), cognitive assessment tools used, outcomes measured, and main findings related to cognitive function.

The risk of bias in the included randomized controlled trials was assessed using the RoB 2 tool (Revised Cochrane risk-of-bias tool for randomized trials) [21]. This tool evaluates five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain was judged as having low risk, some concerns, or high risk of bias. The overall risk of bias for each study was determined according to the criteria established by the tool. Two investigators (Vanessa Esteves-Mesquita and África Peral-Suárez) independently performed the assessment, and a third investigator (Iván Cavero-Redondo) resolved any disagreements as required.

The certainty of evidence for the main cognitive outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24]. The certainty of evidence was rated as high, moderate, low, or very low based on the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.4. Statistical analysis

The impact of probiotics on cognitive performance was assessed by calculating the mean difference in the change of cognitive scores from baseline between intervention and control groups. Given the heterogeneity of neuropsychological instruments across studies, results were synthesized as standardized mean differences (SMD) with 95% confidence intervals (CIs), allowing for direct comparison across different cognitive scales. Separate meta-analyses were conducted for both overall cognitive test scores and for specific cognitive domains, and the results for each outcome were visually summarized using forest plots. To enable direct comparison across studies using different cognitive instruments, domain scores from the MoCA (Montreal Cognitive Assessment Scale), RBANS (Repeatable Battery for the Assessment of Neuropsychological Status), Cognitrax, ADAS-cog (Japanese version of the Alzheimer's Disease Assessment Scale – Cognitive Subscale), MMSE (Mini-Mental State Examination), and NIH Toolbox were systematically classified into primary cognitive domains (memory, attention and processing speed, language, orientation, and visuospatial/constructional). This domain classification was based on the dominant cognitive process each domain score is designed to assess.

Meta-analyses were performed using both classical pairwise methods and frequentist network meta-analysis (NMA). Between-study heterogeneity was assessed using Cochran's Q test and the I^2 statistic. Fixed-effects models were applied when heterogeneity was low ($I^2 < 50\%$ or $p > 0.1$); otherwise, random-effects models were used. To compare the relative

efficacy of different probiotic interventions across cognitive domains, a network meta-analysis was conducted, comparing multi-strain probiotic formulations, single-strain probiotics (*Bifidobacteriaceae* and *Lactobacillaceae*), and placebo. For each intervention, pooled SMDs, confidence intervals, and surface under the cumulative ranking curve (SUCRA) values were calculated. Results were visualized with network plots, rankograms, and comparison tables for each cognitive domain.

Potential publication bias was assessed visually using funnel plots and statistically using Egger's test. All statistical analyses were conducted using Stata (version 3.3.4; R StataCorp, College Station, TX, USA) and the R software (version 3.3.4; R Foundation for Statistical Computing, Vienna, Austria), with the "netmeta", "gemtc", and "bnma" packages.

3. Results

3.1 Systematic literature search and eligibility screening

A total of 906 records were initially identified through systematic searches of Web of Science, Scopus, and PubMed databases. After removing duplicates using Rayyan (n = 623), 283 unique records were screened by title and abstract. There was substantial agreement between reviewers at this screening stage (Cohen's kappa, κ = 0.74; SE = 0.096; 95% CI: 0.55–0.93). Eligibility was assessed according to the predefined inclusion and exclusion criteria summarized in Table 2. Following this initial screening, 12 studies were selected for full-text review. Of these, six randomized controlled trials met all inclusion criteria and were subsequently included in the final synthesis (Fig. 1).

3.2. Characteristics of the included studies

The main characteristics of the randomized controlled trials included in this review, along with the description of the probiotic supplementation and the cognitive outcomes assessed in each study, are summarized in Table 3 and Table 4.

Table 3. Characteristics of studies included in the systematic review and meta-analysis.

Study	Country	Population	Diagnose Criteria	Participants characteristics					
				Participants (*n*)		Age (mean ± SD)		Sex (male (M) / female (F)) (*n*; %)	
				IG	PG	IG	PG	IG	PG
Fei et al., 2023 [25]	China	42 individuals, aged > 60 years	Peterson diagnostic criteria of MCI	21	21	76.4 ± 9.6	75.3 ± 9.7	M (10; 47.6%) F (11; 52.4%)	M (11; 52.4%) F (10; 47.6%)
Asaoka et al., 2022 [17]	Japan	115 individuals, aged 65-89 years	Satisfied with the clinical criteria of MCI (DSM-5): 1) Memory complaint by subject or family; 2) MMSE score 22-26; 3) CDR = 0.5	55	60	77.2 ± 5.8	78.9 ± 4.3	M (26; 47.3%) F (29; 52.7%)	M (25; 41.7%) F (35; 58.3%)
Sakurai et al., 2022 [26]	Japan	78 individuals, aged > 65 years	Japanese version of the MCI Screen: 1) MPI < 60 points	39	39	76.8 ± 4.6	76.9 ± 4.9	M (18; 46.2%) F (21; 53.8%)	M (18; 46.2%) F (21; 53.8%)
Xiao et al., 2020 [27]	Japan	80 individuals, aged 50-79 years	MMSE score ≥ 22	40	40	61.3 ± 7.7	60.9 ± 6.9	M (19; 47.5%) F (21; 52.5%)	M (20; 50.0%) F (20; 50.0%)
Sanborn et al., 2020 [28]	USA	42 individuals, aged 52-75 years	Petersen/Winblad criteria (one or more NIH Toolbox t scores ≤ 35)	19	23	65.6 ± 5.3	62.7 ± 5.3	M (10; 52.6%) F (9; 47.4%)	M (8; 34.8%) F (15; 65.2%)
Kobayashi et al., 2019 [16]	Japan	117 individuals, aged 50-80 years	MMSE score between 22-27	59	58	61.5 ± 6.8	61.6 ± 6.4	M (29; 49.2%) F (30; 50.8%)	M (29; 50.0%) F (29; 50.0%)

IG: Intervention group; PG: Placebo group; SD: Standard deviation; MCI: Mild cognitive impairment; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating; MPI: Memory Performance Index.

Table 4
Description of probiotic supplementation and the cognitive outcomes assessed in the included studies.

Study	Species of probiotic used**	Time of intervention	Probiotic dosage and daily intake	Outcomes studied	Main findings
Fei et al., 2023 [25]	*Lactobacillus plantarum* BioF-228, *Lactococcus lactis* BioF224, *Bifidobacterium lactis* CP-9, *Lactobacillus rhamnosus* Bv-77, *Lactobacillus johnsonii* MH-68, *Lactobacillus paracasei* MP137, *Lactobacillus salivarius* AP-32, *Lactobacillus acidophilus* TYCA06, *Lactococcus lactis* LY-66, *Bifidobacterium lactis* HNO19, *Lactobacillus rhamnosus* HNO01, *Lactobacillus paracasei* GL-156, *Bifidobacterium animalis* BB-115, *Lactobacillus casei* CS-773, *Lactobacillus reuteri* TSR332, *Lactobacillus fermentum* TSF331, *Bifidobacterium infantis* BLI-02, *Lactobacillus plantarum* CN2018	12 weeks	> $2x10^{10}$ CFU/g (2 g/day) Equivalent* CFU dosage/day: > $4x10^{10}$ CFU/day	Neuropsychological tests: - MMSE - MoCA Biochemical parameters: - BDNF levels	After 12 weeks, the probiotic group achieved significantly higher MMSE (24.75 ± 2.47 vs. 20.95 ± 1.36; $p < 0.001$) and MoCA scores (22.05 ± 2.14 vs. 20.10 ± 1.45; $p = 0.00$) compared to placebo
Asaoka et al., 2022 [17]	*Bifidobacterium breve* A1 MCC1274	24 weeks	≥ $2×10^{10}$ CFU/sachet (1 sachet/day) Equivalent* CFU dosage/day: ≥ $2×10^{10}$ CFU/day	Neuropsychological tests: - ADAS-Jcog - MMSE - VSRAD	*B. breve* MCC1274 supplementation led to significant improvements in cognitive subdomains, including ADAS-Jcog "orientation" ($p = 0.022$), MMSE "orientation in time" ($p = 0.006$), "repetition" ($p = 0.026$), and "writing" ($p = 0.045$)
Sakurai et al., 2022 [26]	*Lactiplantibacillus plantarum* OLL2712	12 weeks	> $5×10^{9}$ CFU/g (1g/day) Equivalent* CFU dosage/day:	Neuropsychological tests: - Cognitrax (Japanese version of the CNSVS): VIM and VBM tests	*L. plantarum* OLL2712 supplementation for 12 weeks significantly improved visual memory ($p = 0.044$) and showed a trend toward improvement in composite memory ($p = 0.058$)

Study	Species of probiotic used**	Time of intervention	Probiotic dosage and daily intake	Outcomes studied	Main findings
			> 5×10^9 CFU/day		
Xiao et al., 2020 [27]	*Bifidobacterium breve* A1 MCC1274	16 weeks	≥ 1×10^{10} CFU/capsule (2 capsules/day) Equivalent* CFU dosage/day: ≥ 2×10^{10} CFU/day	Neuropsychological tests: - RBANS - JMCIS Other outcomes: - Bood pressure - Pulse rate - BMI	*B. breve* A1 significantly improved RBANS total score ($p < 0.0001$), with notable effects in immediate memory, visuospatial/constructional, and delayed memory domains (all $p < 0.0001$).
Sanborn et al., 2020 [28]	*Lactobacillus rhamnosus* GG	12 weeks	1×10^{10} CFU/capsule (2 capsules/day) Equivalent* CFU dosage/day: 2×10^{10} CFU/day	Neuropsychological tests: - NIH Toolbox Total - Cognition Score Other outcomes: - Blood pressure - BMI	Three-month supplementation with *Lactobacillus rhamnosus* GG led to improved neuropsychological test performance in adults with cognitive impairment
Kobayashi et al., 2019 [16]	*Bifidobacterium breve* A1	12 weeks	> 1×10^{10} CFU/capsule (2 capsules/day) Equivalent* CFU dosage/day: > 2×10^{10} CFU/day	Neuropsychological tests: - MMSE - RBANS Other outcomes: - BMI - Blood pressure - Pulse rate - Biochemical and metabolic parameters (ALT; LDH; ALP; γ-GTP; CREA; LDL; HDL; HbA1c; h-CRP)	Both *B. breve* A1 and placebo groups showed significant improvements in RBANS and MMSE scores at 12 weeks, with no significant differences between groups

CFU: Colony Forming Unit; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment Scale; ADAS-Jcog: Japanese version of the Alzheimer's Disease Assessment Scale – Cognitive Subscale; VSRAD: Voxel-based Specific Regional Analysis System for Alzheimer's Disease; CNSVS: Central Nervous System Vital Signs; VIM: Visual memory test; VBM: Verbal memory test; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; JMCIS: Japanese version of the MCI Screen; BDNF: Brain-derived neurotrophic factor; BMI: Body mass index. ALT: alanine amino transferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; γ-GTP: gamma-glutamyl transferase; CREA: creatine; LDL: low density lipoprotein; HDL: high density lipoprotein; HbA1c: hemoglobin A1c; h-CRP: high-sensitivity C-reactive protein. *For consistency across the included trials, the investigators converted the reported probiotic dosages into equivalent colony-

forming units (CFU). This methodological approach was adopted to facilitate clarity of interpretation and allow for a more accurate comparison of daily intake levels across studies. ** The probiotic species listed in this table reflect the nomenclature reported in the original clinical trials. Although several taxa have undergone recent taxonomic reclassification, we retained the names as presented by the study authors to ensure fidelity to the primary sources.

All included randomized controlled trials were published within the last five years and enrolled 474 individuals with clinically diagnosed MCI [16, 17, 25–28]. Most studies were conducted in East Asia, mainly Japan [16, 17, 26, 27], and others were conducted in China [25] and the United States [28]. Consistent application of established clinical criteria ensured the MCI diagnosis across all trials (Table 3). The study populations represented by older adults, with three studies including participants aged 50 years and older [16, 27, 28], and the other three enrolling those over 60 years [17, 25, 26]. All studies had balanced gender distributions and comparable group sizes, supporting internal validity.

The interventions consisted mainly of single-strain probiotic supplements from the *Bifidobacteriaceae* (*Bifidobacterium breve* A1) [16, 17, 27] and *Lactobacillaceae* (*Lactiplantibacillus plantarum* OLL2712 and *Lactobacillus rhamnosus* GG) [26, 28] families, and one study evaluated a multi-strain formulation comprising 19 distinct strains belonging to three different families *Lactobacillaceae, Bifidobacteriaceae and Streptococcaceae* [25]. Across the included studies, some consistency was observed in probiotic regimens, with four trials administering a daily dosage of ≥ 2×10^{10} CFU/day [16, 17, 27, 28] and four others implementing a 12-week supplementation protocol [16, 25, 26, 28]. Only two studies employed higher dosages [25, 26] and two investigated longer intervention durations [17, 27]. Encapsulation and sachet delivery were used to maintain blinding, with matched placebos.

Cognitive outcomes were evaluated predominantly through validated neuropsychological tests. Only a single study incorporated neuroimaging to capture structural brain changes [17], while another measured circulating BDNF (brain-derived neurotrophic factor) levels [25]. Most trials observed significant improvements in global or domain-specific cognitive performance with probiotic supplementation, particularly in memory and orientation domains. However, results were not uniformly consistent, suggesting variability depending on the probiotic strain, outcome measure, or baseline cognitive status.

3.3. Risk of bias assessment of the selected studies

The risk of bias assessment is summarized in Fig. 2. *Overall, one study was judged to have low risk of bias, three studies raised some concerns, and two studies were judged to have high risk of bias (*Fig. 2A*). Most studies showed low risk regarding the randomization process, outcome measurement, and selection of the reported result. However, concerns were identified mainly in* Fig. 2. Risk of bias assessment of studies included in the systematic review. (**A**) Risk of bias summary. (**B**) Risk of bias graph. Note: D1: Randomisation process; D2: Deviations from the intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result.

relation to deviations from intended interventions and missing outcome data (Fig. 2B).

3.4. Meta-analysis and network meta-analysis main findings

A total of six randomized controlled trials reporting cognitive outcomes in adults with MCI were included in the meta-analysis [16, 17, 25–28]. Pooled results for the overall cognitive test scores showed a statistically significant positive effect of probiotic supplementation compared to placebo (SMD: 0.19, 95% CI: 0.04 to 0.34), although substantial heterogeneity was observed (I^2 = 75.9%, p = 0.002) (Fig. 3). When analyzing specific cognitive domains, statistically significant effects were observed for both memory (SMD: 0.14, 95% CI: 0.02 to 0.25; I^2 = 68.3%, p = 0.008) and visuospatial/constructional function (SMD: 0.24, 95% CI: 0.06 to 0.41; I^2 = 56.6%, p = 0.075), indicating a beneficial impact of probiotics on these domains. For attention and processing speed, language, and orientation, the meta-analyses did not show statistically significant improvements with probiotic supplementation (Fig. 3).

The network meta-analysis was used as an exploratory comparative framework to summarize and compare the available evidence across probiotic categories, rather than to establish definitive comparative efficacy. In this analysis, multi-strain probiotic formulations showed the largest estimated effect on global cognitive function compared with placebo/control (SMD: 0.99; 95% CI: 0.37 to 1.61). By contrast, single-strain probiotic interventions classified within the *Bifidobacteriaceae* (SMD: 0.22; 95% CI: −0.71 to 1.14) and *Lactobacillaceae* families (SMD: 0.37; 95% CI: −0.52 to 1.26) showed smaller estimates, with wide confidence intervals crossing the null. Across domain-specific cognitive outcomes, including attention and processing speed, memory, language, orientation, and visuospatial/constructional function, no statistically significant network estimates were observed for any probiotic category. Although point estimates generally favored multi-strain formulations, these findings should be interpreted cautiously given the limited number of trials, the sparse structure of the evidence network, and the heterogeneity of probiotic strains, doses, intervention durations, and cognitive outcome measures (Fig. 4A).

Ranking analyses based on SUCRA values were broadly consistent with these exploratory estimates. Multi-strain formulations showed the most favorable ranking probability for global cognition, with a SUCRA value of 84.7%, followed by *Lactobacillaceae*-based probiotics, Bifidobacteriaceae-based probiotics, and placebo/control, with SUCRA values of 51.0%, 40.8%, and 22.4%, respectively (Fig. 4B). Multi-strain formulations also ranked highest for attention and processing speed, memory, and visuospatial/constructional function, with SUCRA values of 85.7%, 80.6%, and 76.5%, respectively. Rankings were less clearly differentiated for language and orientation, although multi-strain formulations still showed the highest SUCRA values in these domains. Importantly, SUCRA values represent probabilistic rankings and do not, by themselves, demonstrate clinically meaningful superiority or high certainty of evidence. Therefore, these rankings should be considered hypothesis-generating and should not be interpreted as definitive evidence that multi-strain probiotics are clinically superior to single-strain formulations.

3.5. Assessment of Potential Publication Bias and Sensitivity Analyses

Assessment of publication bias using the Egger's test and visual inspection of funnel plots revealed no evidence of publication bias for either the total neuropsychological test scores or any of the individual cognitive domains, with all *p*-values being non-significant ($p > 0.05$) (Online Resource 2). Furthermore, sensitivity analyses using a "leave-one-out" approach showed that the exclusion of any individual study did not substantially altered the overall effect estimates, supporting the robustness of the findings to the influence of single studies.

3.6. Certainty of evidence assessment of the selected studies

The certainty of evidence assessed using the GRADE approach is summarized in Table 5, with detailed reasons for downgrading rationale provided in Online Resource 3. Overall, the certainty of evidence was rated as low across all cognitive outcomes. Certainty was downgraded for risk-of-bias concerns across all outcomes. In addition, evidence for global cognition, memory, and visuospatial/constructional function was downgraded because of inconsistency, whereas evidence for attention and processing speed, language, and orientation was downgradad due to imprecision. Publication bias was not formally downgraded, as funnel plot inspection and Egger's regression tests did not suggest statistically significant asymmetry. However, this assessment was limited by the small number of studies available for each outcome.

Table 5
Summary of findings and certainty of evidence according to GRADE

Outcome	No. of studies / participants	Effect estimate	Heterogeneity	Certainty of evidence	Interpretation
Global cognition	5 RCTs / n = 396	SMD 0.19 95% CI 0.04 to 0.34	I^2 = 75.9% *p* = 0.002	⊕⊕○○ Low	Probiotic supplementation may be associated with a small improvement in global cognition, but confidence in the effect estimate is limited.
Attention and processing speed	5 RCTs / n = 396	SMD 0.05 95% CI − 0.13 to 0.23	I^2 = 0.0% *p* = 0.677	⊕⊕○○ Low	The evidence suggests little or no clear effect on attention and processing speed.
Memory	6 RCTs / n = 474	SMD 0.14 95% CI 0.02 to 0.25	I^2 = 68.3% *p* = 0.008	⊕⊕○○ Low	Probiotic supplementation may be associated with a small improvement in memory, but the certainty of evidence is limited.
Language	4 RCTs / n = 354	SMD 0.02 95% CI − 0.09 to 0.13	I^2 = 0.0% *p* = 0.771	⊕⊕○○ Low	The evidence does not show a clear effect on language outcomes.
Orientation	3 RCTs / n = 274	SMD 0.08 95% CI − 0.12 to 0.27	I^2 = 0.0% *p* = 0.889	⊕⊕○○ Low	The effect on orientation is uncertain.
Visuospatial/constructional function	4 RCTs / n = 354	SMD 0.24 95% CI 0.06 to 0.41	I^2 = 56.6% *p* = 0.075	⊕⊕○○ Low	Probiotic supplementation may be associated with a small improvement in visuospatial/constructional performance, but confidence in the estimate is limited.

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; SMD, standardized mean difference.

4. Discussion

This systematic review and meta-analysis provides an up-to-date synthesis of the evidence on the effects of oral probiotic supplementation on cognitive function in individuals with MCI. Our findings suggest that probiotics may contribute to improvements in overall cognitive performance in this population and might also be associated with positive effects on specific cognitive domains, particularly memory and visuospatial/constructional abilities. Notably, exploratory subgroup analyses indicate that multi-strain probiotic formulations were associated with greater improvements in global cognitive function compared with single-strain probiotic supplementation, suggesting that the combined action of multiple bacterial strains may enhance cognitive benefits, potentially through synergistic effects along the gut-brain axis.

These findings may have meaningful clinical implications for the management of individuals with MCI. Although the observed effect sizes are modest, even small improvements in global cognition and specific domains such as memory and visuospatial/constructional abilities can translate into enhanced daily functioning, better quality of life, and prolonged autonomy in older adults [29]. Given that MCI represents a high-risk state for progression to dementia, interventions that yield cognitive benefits may contribute to delaying clinical deterioration and the onset of functional dependence [30, 31]. Crucially, a recent systematic review and meta-analysis shows that a meaningful proportion of individuals (around 31%) with MCI can revert to a normal cognitive state, particularly when modifiable factors such as physical engagement and baseline cognitive and functional status are favorable [32]. In this context, probiotic supplementation emerges as a low-risk, accessible, and potentially scalable strategy that could complement existing lifestyle and pharmacological approaches.

While several previous systematic reviews and meta-analyses have examined probiotic supplementation and cognitive outcomes, they typically combined individuals with Alzheimer's disease and MCI and, in some cases, pooled probiotics with prebiotic or synbiotic formulations. In contrast, to our knowledge, the present review is the first meta-analysis restricted exclusively to adults with a formal diagnosis of MCI and to trials comparing probiotic supplements alone with placebo, thereby providing a more targeted and clinically relevant estimate of the cognitive effects of probiotics in this initial stage [33–39].

4.1. Cognitive decline and probiotic modulation of the gut–brain axis

A biologically plausible explanation for the modest cognitive effects observed in this review is that probiotic supplementation may modulate several interconnected pathways within the microbiota–gut–brain axis. MCI is an early stage of cognitive vulnerability in which chronic low-grade inflammation, oxidative and nitrosative stress, mitochondrial dysfunction, altered neurotransmission, blood–brain barrier (BBB) vulnerability, and impaired synaptic plasticity may already contribute to neuronal dysfunction before the onset of clinically established dementia [40–44]. In this context, gut dysbiosis may amplify systemic and central processes involved in cognitive decline.

Alterations in the gut microbiota have been reported in MCI and Alzheimer's disease, including reduced microbial diversity, depletion of beneficial taxa such as *Bifidobacterium* and *Lactobacillus*, and expansion of potentially pro-inflammatory microbial profiles [45–47]. Beyond these taxonomic changes, the functional consequences of dysbiosis may be particularly relevant. Reduced production of short-chain fatty acids (SCFAs), especially butyrate, may weaken epithelial barrier integrity and increase intestinal permeability [48]. Butyrate supports tight-junction assembly and the expression of barrier-related proteins such as claudin-1, occludin, and zonula occludens-1 (ZO-1) [49–52]. Therefore, reduced SCFA availability may facilitate systemic exposure to microbial products such as lipopolysaccharide (LPS).

LPS is a major outer-membrane component of Gram-negative bacteria and a canonical pathogen-associated molecular pattern. Once in the circulation, LPS can activate Toll-like receptor 4 (TLR4) signaling in immune and endothelial cells, engaging myeloid differentiation primary response 88 (MyD88)- and TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathways and promoting nuclear factor kappa B (NF-κB) activation [53–57]. This LPS/TLR4/NF-κB axis increases the transcription of pro-inflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), inducible nitric oxide synthase, and cyclooxygenase-2. In MCI, this peripheral inflammatory burden may be relevant because systemic inflammation, endothelial activation, BBB dysfunction, and microglial priming are closely linked to neurodegenerative vulnerability [40, 48, 58].

Probiotic supplementation may act upstream in this cascade. At the intestinal level, selected strains may help restore microbial balance, compete with LPS-producing pathobionts, reinforce mucus and tight-junction integrity, and increase beneficial metabolites such as acetate, lactate, butyrate-related cross-feeding substrates, and indole derivatives [52, 59]. Through these effects, probiotics may reduce endotoxin translocation and attenuate TLR4/NF-κB-mediated inflammatory signaling. This mechanism is supported mainly by preclinical evidence. In aged senescence-accelerated mouse prone 8

(SAMP8) mice, a multi-strain probiotic mixture composed of *Bifidobacterium lactis*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus acidophilus* improved memory deficits, attenuated intestinal and BBB disruption, reduced plasma and cerebral LPS concentrations, and inhibited TLR4/retinoic-acid-inducible gene I (RIG-I)-mediated NF-κB signaling [60]. A subsequent SAMP8 study further showed that the same multi-strain probiotic mixture restored intestinal tight-junction proteins and reduced bacteria-related inflammatory signaling through caspase-11/caspase-1 and alpha-kinase 1 (ALPK1)-related pathways [61]. Similarly, *Lactobacillus rhamnosus* GG attenuated LPS-induced intestinal inflammation and barrier dysfunction by modulating mitogen-activated protein kinase (MAPK)/NF-κB signaling in piglets [62], while *Lactobacillus rhamnosus* CY12 reduced LPS-induced oxidative stress, inflammation, and tight-junction disruption in Caco-2 cells [63]. Although these experimental models are not directly equivalent to human MCI, they support a plausible gut barrier–endotoxin–inflammation pathway through which probiotics may influence cognitive vulnerability.

Probiotics may also modulate oxidative stress and neuroactive signaling, two pathways closely related to cognitive vulnerability in MCI. Persistent activation of the LPS/TLR4/NF-κB axis can increase reactive oxygen and nitrogen species through mitochondrial dysfunction, NADPH oxidase activation, and inducible nitric oxide synthase expression, contributing to lipid peroxidation, protein oxidation, synaptic injury, and impaired long-term potentiation [41, 44]. By reducing endotoxin-driven inflammation and modulating microbial metabolites, probiotics may help improve redox balance and endogenous antioxidant defenses, although oxidative biomarkers were rarely assessed in the trials included in this review [64]. These redox-related effects may also intersect with neurotransmission, as oxidative and inflammatory stress can disrupt excitatory–inhibitory balance and impair synaptic signaling. Consistently, reduced GABA levels in the anterior and posterior cingulate cortex have been associated with executive dysfunction in individuals with MCI [65]. In this context, several *Lactobacillus* and *Bifidobacterium* strains may influence GABAergic, serotonergic, and tryptophan-related pathways through microbial metabolism, enteroendocrine signaling, enteric nervous system activity, and vagal afferent communication [18, 66]. These effects should be interpreted as gut–brain signaling mechanisms rather than direct central neurotransmitter replacement.

In addition, probiotic effects may converge on pathways related to neuroplasticity. Brain-derived neurotrophic factor (BDNF) is relevant to MCI because hippocampal plasticity, synaptic maintenance, and memory formation depend on adequate neurotrophic support [67]. Rather than treating BDNF as an isolated mechanism, it may be better understood as a downstream pathway potentially influenced by reduced inflammation, improved redox balance, microbial metabolites, and vagal signaling. Some experimental and emerging clinical evidence suggests that probiotics may influence BDNF-related pathways, but this remains insufficiently demonstrated in human MCI [68, 69]. Therefore, BDNF should be considered a plausible neuroplasticity-related mechanism, not a confirmed mediator of the effects observed in this meta-analysis.

4.2. Multi-strain probiotic formulations

The findings of our exploratory network meta-analysis indicate that multi-strain probiotic formulations from three different families (*Lactobacillaceae*, *Bifidobacteriaceae* and *Streptococcaceae*) may exert greater effects on cognitive performance than single-strain interventions in individuals with MCI (Fig. 4).

Multi-strain probiotics act through several complementary pathways. They restore gut microbial balance, enhanced colonization, increase beneficial taxa, suppress pathogenic bacteria, and modulate immune responses by attenuating pro-inflammatory cytokine production and oxidative stress [70, 71]. By combining strains, a multi-strain formula can yield a more diverse pool of neurotransmitters and neuromodulatory metabolites, which collectively support cognitive processes [70]. Indeed, it has been proposed that multi-strain probiotics more effectively boost neurotransmitter production than single strains, thanks to synergistic cross-feeding of metabolites and complementary enzymatic pathways [70]. Additionally, multi-strain probiotics often exert stronger or broader immune regulation than single strains. Different bacterial strains can stimulate the host's immune system in complementary ways, promoting an overall anti-inflammatory milieu [71]. Transcriptomic and immunological studies show that multi-strain combinations can synergistically regulate

signaling pathways, like NF-κB, leading to greater reductions in neuroinflammation by suppressing excessive cytokine production and improved cellular homeostasis attenuating the neurodegenerative process [71, 72].

Species from the *Lactobacillaceae* family, particularly *Lactobacillus plantarum* and *Lactobacillus rhamnosus*, are well known for their ability to produce neuroactive compounds such as GABA, serotonin, and dopamine precursors [73–75]. These metabolites have been implicated in modulating stress responses, enhancing synaptic transmission, and regulating mood and cognition. Besides, certain *Lactobacillus* strains possess strong immunomodulatory properties. *L. plantarum* OLL2712 has demonstrated high IL-10-inducing capacity, leading to systemic reductions in pro-inflammatory markers [26].

Moreover, species within the *Bifidobacteriaceae* family have shown similarly promising effects in individuals with MCI. Mechanistic studies suggest that they may downregulate hippocampal expression of inflammation- and immune-related genes, while increasing circulating levels of acetate, known to regulate microglial activity and maintain BBB integrity [76]. Additionally, *Bifidobacterium* species contribute to tryptophan metabolism, enhance gut barrier function, and suppress systemic inflammation, all of which are implicated in the pathophysiology of neurodegenerative conditions [68, 76].

Furthermore, the multi-strain probiotic showing the greatest effect in this network meta-analysis also includes species from the *Streptococcaceae* family, which are frequently included in multi-strain products and may contribute additional metabolic benefits. These include promotion of butyrate-producing taxa via cross-feeding, and biosynthesis of B-vitamins such as folate and riboflavin, which support methylation pathways and neuronal integrity [77]. Though their isolated effects on cognition remain to be elucidated, their role in shaping microbial networks and enhancing functional diversity likely amplifies the impact of co-administered *Lactobacillus* and *Bifidobacterium* strains [78].

4.3. Factors influencing the cognitive response to probiotic supplementation

The heterogeneity observed in the cognitive effects of probiotic supplementation across trials likely reflects differences in both participant characteristics and intervention protocols. Although all included studies focused on older adults with clinically diagnosed MCI, age thresholds varied, ranging from ≥ 50 to ≥ 60 years. Given that advancing age is the strongest non-modifiable risk factor for MCI, and that prevalence increases exponentially after the age of 65, it is plausible that earlier intervention may yield greater benefits [79]. Younger individuals with MCI may retain higher neuroplastic potential and a lower inflammatory and neuropathological burden, which could enhance responsiveness to microbiota-targeted strategies [5, 6]. However, no trial to date has formally examined age-stratified responses, limiting firm conclusions.

Probiotic dose and treatment duration represent additional sources of variability. Across the included RCTs, daily doses ranged from > 5×10^9 to 2×10^{10} CFU/day, consistent with doses commonly used in gut-–brain axis interventions [5]. Despite good tolerability, there is currently no consensus on a minimum effective dose for cognitive outcomes, and evidence for a clear dose-–response relationship remains inconclusive. While higher doses may exert stronger anti-inflammatory effects, these have not been consistently associated with superior cognitive improvements [5]. Additionally, intervention length may also play an important role. A minimum of 12 weeks of probiotic intervention was sufficient to produce measurable cognitive gains in MCI patients, and there is an indication that longer exposure enhances these benefits [16, 25, 26, 28]. Xiao et al. (2020) reported markedly improved memory scores after 16 weeks of *B. breve* supplementation [27]. Similarly, Asaoka et al. (2022) observed that 24 weeks of daily *B. breve* (2×10^{10} CFU) not only led to subtle cognitive improvements on select subscales, but also significantly slowed brain atrophy progression on magnetic resonance imaging compared to placebo [17]. In contrast, that study found no overt shifts in overall gut microbiota composition despite the prolonged regimen, suggesting that probiotic effects on the brain may occur via functional or metabolic changes rather than broad taxonomic overhaul [17]. Such findings imply that current probiotic dosing and durations are adequate to elicit central and peripheral changes relevant to cognition. Longer trials might be needed to determine if probiotics can affect hard clinical outcomes like MCI conversion rates or sustained cognitive trajectories.

Interpretation of probiotic-related cognitive effects is also influenced by the outcome measures used across trials. Almost all trials evaluated cognitive efficacy only with test batteries, which may lack sensitivity to subtle changes in MCI populations. Only one study incorporated structural neuroimaging (VSRAD), showing a slower progression of Alzheimer-type brain atrophy in probiotic-treated participants, providing objective support for a potential neuroprotective effect [17]. Moreover, evidence on biological markers associated with cognitive change was limited. BDNF increases were reported in parallel with cognitive improvements in one trial, while peripheral inflammatory and metabolic markers were assessed in only a single study, leaving their contribution to cognitive changes incompletely characterized [16, 25].

4.4. Strengths and limitations

This systematic review and meta-analysis has several strengths. It provides a focused synthesis of placebo-controlled randomized trials evaluating oral probiotic supplementation in adults with mild cognitive impairment (MCI), while excluding studies conducted exclusively in Alzheimer's disease, synbiotic interventions, and multi-component nutritional approaches. This design allowed a more specific assessment of probiotics as a microbiota-targeted intervention in an early stage of cognitive decline. The review was reported in accordance with PRISMA guidelines, and key review procedures, including study selection and risk-of-bias assessment, were performed independently by two reviewers. Data extraction was conducted by one reviewer and independently verified by a second reviewer. In addition, probiotic strains, formulations, doses, intervention durations, cognitive assessment tools, and domain-specific outcomes were systematically characterized. The use of RoB 2 and GRADE further increased the transparency of the assessment of risk of bias and certainty of evidence.

Nevertheless, the findings should be interpreted cautiously. The main limitation is the small evidence base, as only six randomized controlled trials including 474 participants met the eligibility criteria, with some domain-specific analyses based on even fewer studies. This limits statistical power, reduces the robustness of subgroup and sensitivity analyses, and restricts the ability to explore potential effect modifiers. Although probiotic supplementation was associated with a statistically significant improvement in global cognition, the effect size was small (SMD 0.19), and its clinical relevance remains uncertain. Moreover, the certainty of evidence was rated as low across cognitive outcomes, mainly because of risk-of-bias concerns, inconsistency, and imprecision.

Substantial heterogeneity was observed, particularly for global cognition, and the included trials differed in probiotic strains, single- versus multi-strain formulations, dose, intervention duration, participant characteristics, geographic setting, and cognitive assessment tools. Therefore, probiotics should not be interpreted as a homogeneous intervention, and the pooled estimates may not be directly generalizable to all probiotic formulations or MCI populations. Effects across cognitive domains were also inconsistent: small positive effects were observed for memory and visuospatial/constructional function, whereas no clear effects were found for attention and processing speed, language, or orientation.

The network meta-analysis should also be interpreted with caution. Although multi-strain formulations ranked highest in the SUCRA analyses, the evidence network was sparse and based on a limited number of heterogeneous trials. Accordingly, these rankings should be considered exploratory and hypothesis-generating rather than confirmatory evidence of comparative clinical superiority. Publication bias was not statistically evident based on funnel plots and Egger's tests, but it could not be reliably excluded because fewer than ten studies were available for each outcome.

In general, the present findings suggest a small and preliminary signal of benefit of probiotic supplementation on global cognition and selected cognitive domains in adults with MCI. However, the limited number of trials, modest effect sizes, heterogeneity, risk-of-bias concerns, and low certainty of evidence indicate that these results should be interpreted as preliminary rather than confirmatory. Larger, adequately powered, strain-specific randomized controlled trials with standardized cognitive outcomes are needed before probiotic supplementation can be considered for routine clinical use in MCI.

5. Conclusions

This systematic review and meta-analysis provides a focused synthesis of randomized evidence on oral probiotic supplementation in adults with mild cognitive impairment. Overall, the findings suggest a modest and preliminary improvement in global cognitive performance, with small positive effects also observed for memory and visuospatial/constructional function. However, no clear effects were found for attention and processing speed, language, or orientation, indicating that the potential cognitive benefit is not consistent across all domains.

Although these findings suggest a modest signal of benefit, they should be interpreted cautiously because the evidence base remains limited, heterogeneous, and of low certainty. The clinical relevance of the small standardized effects observed for global cognition and selected cognitive domains therefore remains uncertain.

The exploratory network meta-analysis suggested that multi-strain probiotic formulations may have more favorable ranking probabilities than single-strain interventions. Nevertheless, because the evidence network was sparse and probiotic formulations differed substantially across trials, these rankings should be considered hypothesis-generating rather than evidence of definitive comparative superiority.

Overall, current evidence suggests that probiotic supplementation may represent a promising microbiota-targeted approach for further investigation in MCI, but it does not yet provide a sufficient basis for firm clinical recommendations or routine implementation. Future randomized controlled trials should be larger, adequately powered, strain-specific, and designed with standardized cognitive outcomes, longer follow-up, comprehensive safety reporting, and mechanistic biomarkers related to the microbiota–gut–brain axis.

Declarations

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Author contributions

Conceptualization: V.E.-M., A.M.L.-S.; Data curation: V.E.-M., A.P.-S.; Formal analysis: I.C.-R.; Investigation: V.E.-M., A.P.-S., A.A.; Methodology: V.E.-M., A.P.-S., A.A., I.C.-R., L.M.B., A.M.L.-S.; Visualization: V.E.-M., I.C.-R.; Writing - original draft: V.E.-M.; Writing - review & editing: V.E.-M., A.P.-S., A.A., I.C.-R., L.M.B., A.M.L.-S.

Conflict of interest

All authors declare no potential conflict of interest.

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Figures

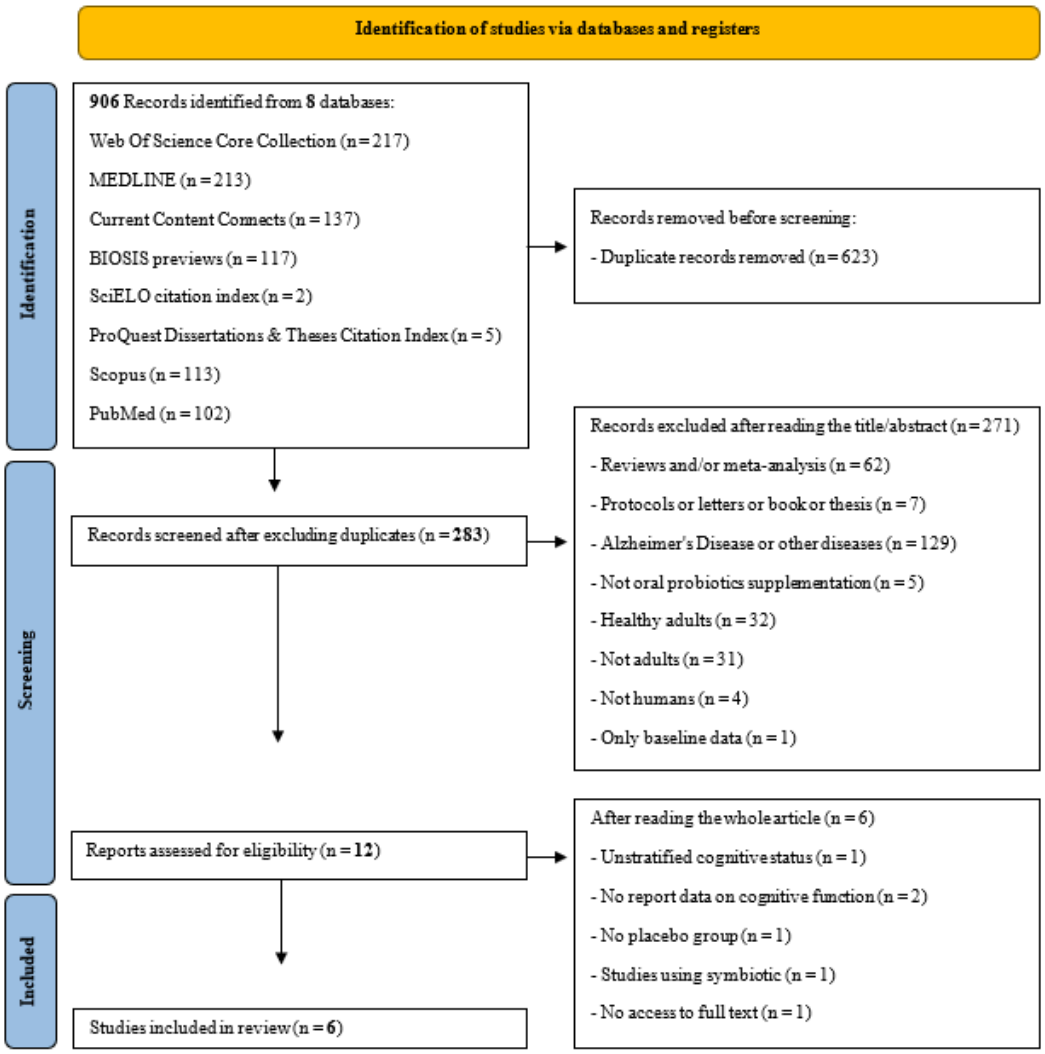

Figure 1

PRISMA 2020 flow diagram for new systematic reviews, retrieved from Page et al. 2021. One asterisk indicates that records were removed by automatization tools while two asterisks indicate that records were removed by the researchers.

Figure 2

Risk of bias assessment of studies included in the systematic review. (**A**) Risk of bias summary. (**B**) Risk of bias graph. Note: D1: Randomisation process; D2: Deviations from the intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result.

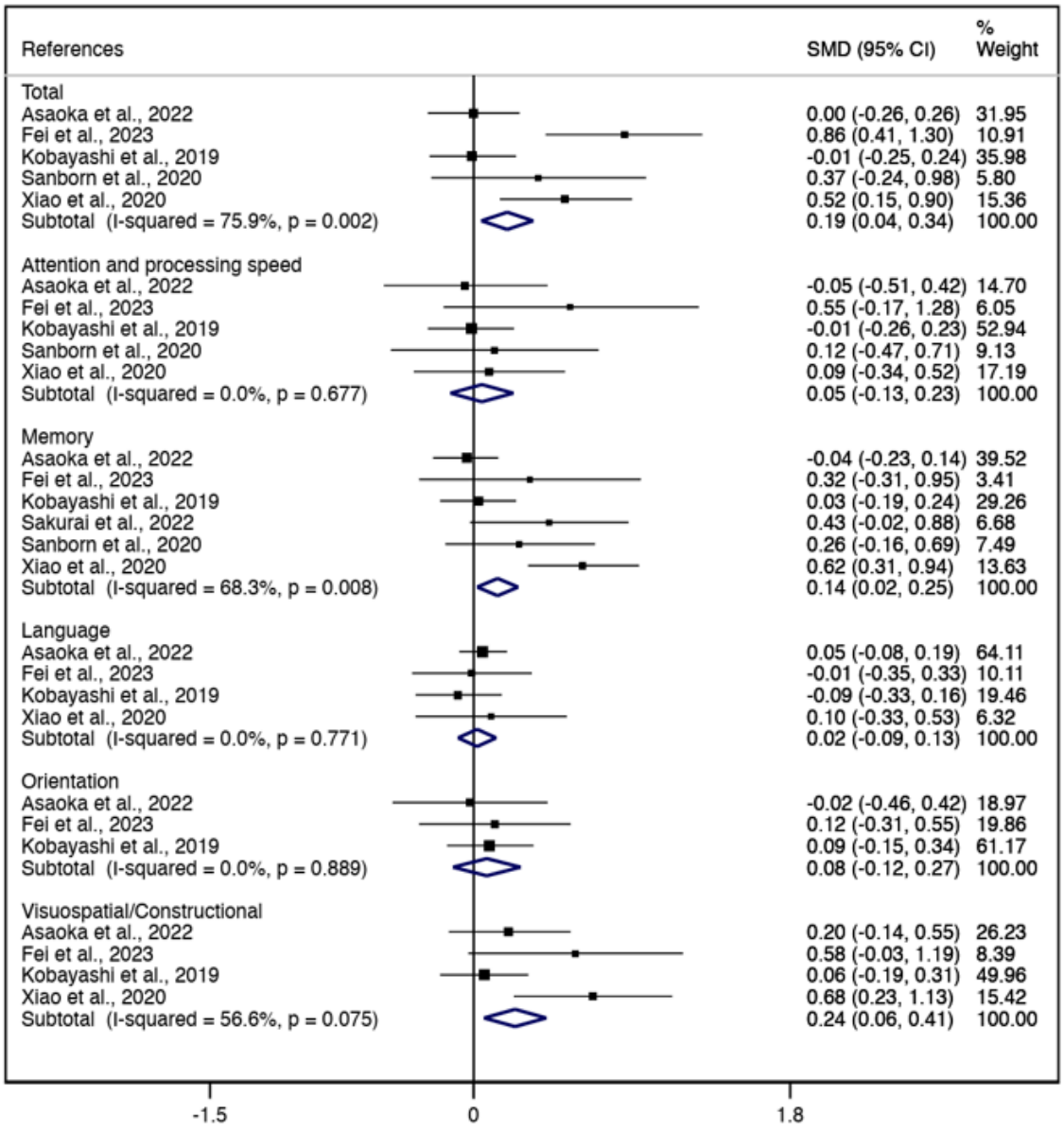

Figure 3

Meta-analysis of the effect of probiotics on cognition by cognive domains. SMD: standard mean difference; 95% CI: 95% confidence interval.

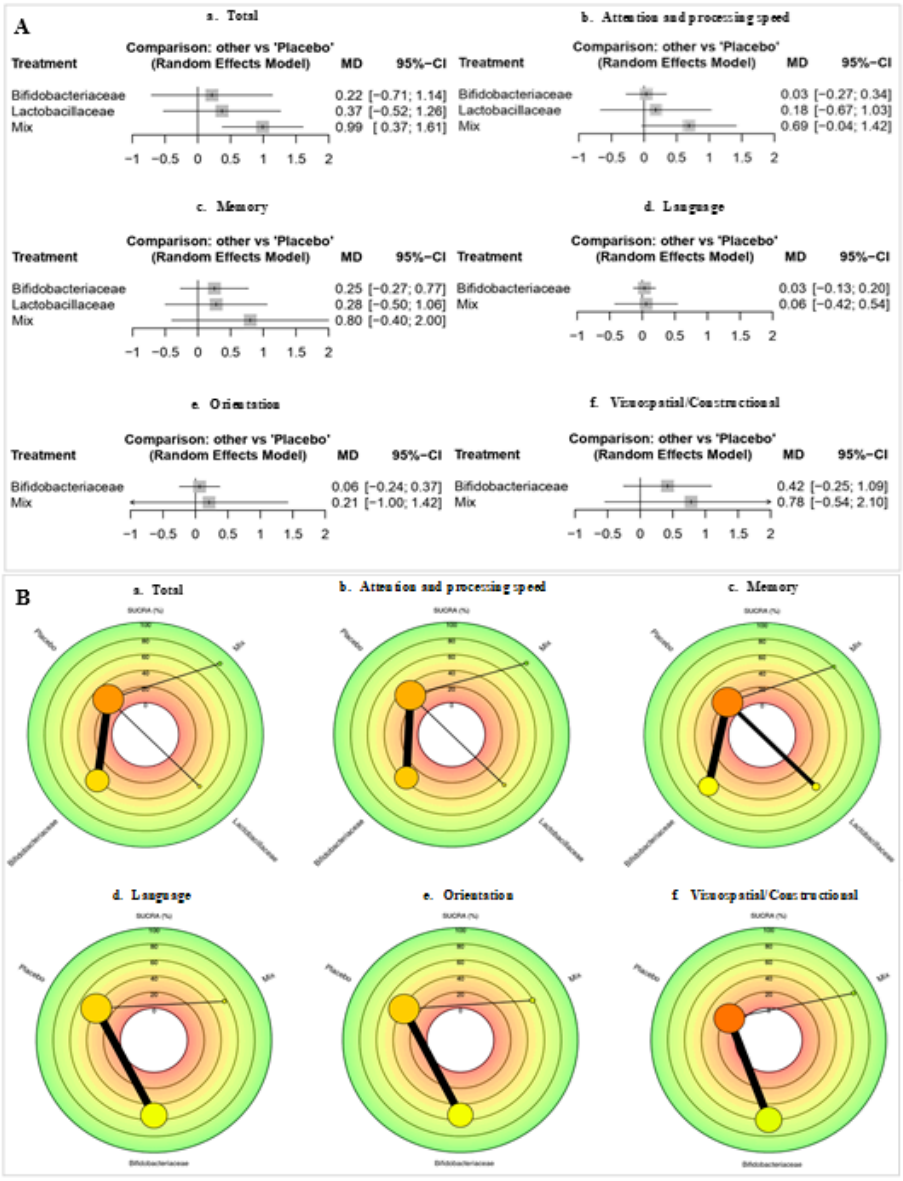

Figure 4

Network meta-analysis evaluating the impact of different probiotic formulations on cognitive performance by domain. (**A**) Forest plot showing the standardized mean differences (SMD) and 95% confidence intervals (CI) for the effects of Bifidobacteriaceae, Lactobacillaceae, and multi-strain probiotics compared to placebo across cognitive domains, based on the network meta-analysis. (**B**) SUCRA plot showing the probability of each intervention (multi-strain probiotics, Lactobacillaceae, Bifidobacteriaceae, and placebo) being among the most effective treatments according to the network meta-analysis

Supplementary Files

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