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Review Article

The association between gut microbiota and cognitive decline: A systematic review of the literature[☆]



Sofia Libriani^a, Gabriella Facchinetti^{b,c,d,*}, Flavio Marti^{c,e}, Maria Ymelda Tolentino Diaz^f, Elena Sandri^g

^aDepartment of Urology, Santa Rosa Hospital, Viterbo, Italy

^bNational Center for Clinical Governance and Excellence in Care, Istituto Superiore di Sanità, Roma, Italy

^cSchool of Nursing and Midwifery, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy

^dDepartment of Medicine and Surgery, Campus Bio-Medico of Rome University, Rome, Italy

^eDepartment of Health Profession, San Camillo Forlanini Hospital, Rome, Italy

^fArea for Training, Professional Development and Research, U.O.C. Care for the Person, Rome, Italy

^gFaculty of Medicine and Health Sciences, Catholic University of Valencia San Vicente Mártir, Valencia, Spain

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ABSTRACT

The gut–brain axis has emerged as a key pathway in the pathogenesis of neurodegenerative disorders, with age-related shifts in gut microbiota potentially contributing to cognitive decline and dementia progression. This systematic review evaluated the effects of microbiota-targeted interventions on cognitive outcomes in adults aged >45 years with cognitive impairment or at risk of dementia. Randomized controlled trials and quasi-experimental studies published up to June 2025 were identified through PubMed, COCHRANE, CINAHL, Web of Science, and EMBASE. Methodological quality, assessed using the Joanna Briggs Institute Critical Appraisal Checklist, ranged from moderate to high. Fifteen studies involving 4,275 participants across Europe, Asia, North America, and the Middle East met inclusion criteria. Interventions included probiotic supplementation, fecal microbiota transplantation, and dietary strategies such as Mediterranean and ketogenic diets. Cognitive outcomes were measured using validated tools, including the Mini-Mental State Examination, Montreal Cognitive Assessment, and Repeatable Battery for the Assessment of Neuropsychological Status. Narrative synthesis indicated that microbiota modulation was associated with im-

[☆] Abbreviations: FMT, fecal microbiota transplantation; Keto, ketogenic; MCI, mild cognitive impairment; Med, Mediterranean; SCFA, short-chain fatty acid

* Corresponding author at: Department of Medicine and Surgery, Campus Bio-Medico of Rome University, Via Alvaro del Portillo, 21, 00128, Rome, Italy. Tel.: +39-3284443838.

E-mail addresses: g.facchinetti@unicampus.it, gabriella.facchinetti@iss.it (G. Facchinetti).

provements in memory, executive function, and global cognition, particularly in individuals with prodromal or mild cognitive impairment. Reported benefits correlated with increased microbial diversity, enhanced short-chain fatty acid production, and reduced neuroinflammatory markers. In contrast, effects were limited in advanced Alzheimer's disease. Overall, gut microbiota modulation represents a promising nonpharmacological strategy to support cognitive health, with early intervention appearing crucial for optimal benefit. Nevertheless, heterogeneity in study design and intervention protocols highlights the need for large-scale, longitudinal randomized controlled trials to confirm efficacy and clarify underlying biological mechanisms.

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1. Introduction

Major neurocognitive disorder and cognitive decline are chronic conditions marked by progressive and irreversible neurological deterioration, often developing insidiously over a period of decades [1]. Rising life expectancy will lead to a significant increase in age-related neurodegenerative diseases, especially Alzheimer's [2]. Early stages of cognitive impairment, including mild cognitive impairment (MCI), are associated with subtle yet measurable cognitive and functional deficits, which may progress to overt dementia if left unmanaged [3]. MCI is characterized by cognitive decline exceeding normal age-related changes, without significantly impairing daily functioning. In contrast, dementia involves more severe cognitive deterioration that disrupts daily activities. MCI is classified into two types: amnesic, primarily affecting memory, and nonamnesic, involving other domains like executive function or attention. Diagnosis of MCI requires the absence of severe functional impairment and the exclusion of other potential causes, such as medical or psychiatric conditions. Symptoms must persist for at least 6 months [4]. This type of cognitive impairment is the one most commonly associated with the risk of Alzheimer's disease (AD) (the first cause of dementia worldwide) [5]. In the field of dementia prevention research, the concept of the gut–brain axis, describing the bidirectional communication between the gastrointestinal tract and the central nervous system via neural, endocrine, and immune pathways, has gained increasing attention since its initial description in the late 20th century. Over the past two decades, research has gradually shifted from exploratory animal studies to human investigations, establishing the gut microbiota as a pivotal regulator of neurodevelopment, mood, and cognition [6–8]. Recent studies suggest that gut microbiota, influenced by age and diet, may contribute to neurodegeneration through dysbiosis. This imbalance is linked to increased neuroinflammation, compromised blood–brain barrier (BBB), and accumulation of amyloid- β and tau proteins, hallmarks of AD [9,10]. Modifiable lifestyle-related factors, including nutrition and microbiota-targeted interventions, are gaining attention as plausible strategies for dementia prevention [11]. Probiotics, prebiotics, dietary supplementation, and fecal microbiota transplantation (FMT) are among the most studied interventions aimed at restoring microbial balance. [12,13]. Although prior reviews have addressed indi-

vidual interventions such as probiotics or dietary patterns, they rarely incorporate a unified analytical framework that contrasts the mechanisms and outcomes across intervention types [2,5,14,15]. Moreover, many earlier reviews have not sufficiently accounted for the historical evolution of research on the gut microbiota's role in cognitive decline—from early observational studies to recent mechanistic trials—which hampers our ability to contextualize current findings within a broader research framework. Addressing this gap is critical to advancing both translational research and the clinical application of microbiota-targeted interventions.

By systematically evaluating the effectiveness of microbiota-targeted interventions—including dietary strategies, probiotics, and FMT—this review aims to offer an original contribution beyond prior work, highlighting both mechanistic insights and clinical implications. This review aims to evaluate whether modulation of the gut microbiota can prevent or manage MCI and serve as a complementary therapeutic strategy alongside pharmacological treatments, thereby helping to preserve cognitive function and reduce the incidence of dementia in individuals with MCI and at risk of developing dementia.

2. Methods and materials

2.1. Review methodology and protocol registration

This systematic review was reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidance [16]. Preliminary searches of the main databases did not identify any existing or ongoing systematic reviews with this aim. The study protocol was previously registered on PROSPERO (registration number CRD420251068851).

2.2. Formulation of the research question

The present review was guided by the research question: “Can interventions targeting gut microbiota modulation in adults with, or at risk of, dementia effectively prevent or mitigate cognitive decline?”. This question was structured according to the PICO framework [17], facilitating a systematic delineation of its core elements. The population (P) comprised individuals aged over

45 years diagnosed with dementia, cognitive impairment, or comorbidities associated with elevated risk of neurocognitive disorders. Microbiota-targeted interventions are strategies designed to influence gut microbiota composition or activity, either directly (e.g., probiotics, synbiotics, FMT) or indirectly through specific diets (e.g., Mediterranean, ketogenic, methyl donor intake). These interventions are defined by their mechanistic link to microbiota modulation, distinguishing them from general nutritional or lifestyle changes.

To classify interventions as “microbiota-targeted,” only those strategies explicitly intended to alter gut microbial composition or activity were considered. Such interventions were identified as either direct—by administering live microorganisms (probiotics or synbiotics) or replacing the existing microbiota (FMT)—or indirect—by modifying nutrient intake through specific diets (e.g., Mediterranean or ketogenic diets) known to influence the microbiota.

Dietary strategies indirectly modulate microbiota by altering nutrient intake. The most commonly studied nutritional interventions in the literature include the Mediterranean diet, ketogenic diet, omega-3 Supplementation, and methyl donor nutrient supplementation. These interventions are frequently examined due to their proven effects on inflammation, oxidative stress, and metabolic health, all of which can influence the gut microbiome. The Mediterranean diet, rich in polyphenols and fibers, supports beneficial bacteria [18], while the ketogenic diet may shift microbiome composition by reducing carbohydrate intake [19]. Omega-3 supplementation is linked to anti-inflammatory effects [20], and methyl donor nutrients are essential for DNA methylation processes, which can modulate microbial community structure and function [21].

Probiotic and synbiotic supplementation act more directly by introducing live microorganisms, enhancing microbial diversity. FMT offers the most immediate modulation, replacing entire microbial communities from healthy donors. Only studies employing such interventions and assessing cognitive outcomes were included, with gut microbiota monitored through fecal analyses or relevant biomarkers to evaluate diversity, taxonomy, and associations with cognition. The comparison (C) groups involved placebo, standard care, or alternative nutritional interventions. The primary outcomes (O) were cognitive performance measures evaluated using validated tools such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Studies that assessed only physiological or biochemical parameters without cognitive endpoints were excluded. Secondary outcomes encompassed serum and fecal biomarkers indicative of inflammation, microbial diversity, and neurodegenerative processes (e.g., short-chain fatty acids [SCFAs], inflammatory cytokines, lipid profiles).

2.3. Eligibility criteria

Primary studies were included based on the following eligibility criteria: participants aged ≥ 45 years diagnosed with dementia, cognitive impairment, or comorbidities associated with increased risk of cognitive decline. Eligible interventions were those explicitly designed to modulate the gut microbiota, including the administration of probiotics, prebi-

otics, synbiotics, FMT, or defined dietary interventions (e.g., Mediterranean or ketogenic diets) aimed at altering microbial composition. Only studies implementing a protocolized microbiota-targeted intervention and reporting cognitive outcomes were considered. Primary outcomes comprised cognitive performance assessed using validated neuropsychological tools such as the MMSE, MoCA, or RBANS. Secondary outcomes included serum and fecal biomarkers related to inflammation, microbial diversity, or neurodegeneration, such as SCFA concentrations, inflammatory cytokines, and lipid profiles.

Exclusion criteria encompassed studies lacking methodological or clinical relevance, including observational studies, narrative reviews, editorials, animal experiments, and non-clinical reports. Studies without full-text availability or insufficient data for extraction were also excluded. Clinical trials were excluded if participants were under 45 years of age, did not present cognitive impairment or dementia, or if the intervention was not explicitly intended to modulate the gut microbiota.

2.4. Search strategy

A comprehensive bibliographic search was performed on the PubMed, CINHAL, and COCHRANE databases in June 2025 with no time limits. Medical subject headings and free terms were searched for the following keywords: “dementia”; “gut microbiota”; “gastrointestinal microbiome”; “cognitive impairment”; along with their synonyms and related phrases. Boolean operators (AND, OR) were strategically applied to combine these terms to provide both a comprehensive and focused search (Supplementary Table S1 in Supplementary File). Search strategies were checked by three reviewers (GF, ES, SL).

2.5. Study selection and data collection

Study screening was conducted independently by three reviewers (GF, ES, SL) using the “Rayyan” application [22]. First, titles and abstracts, and then full texts selected from the first round were reviewed based on the inclusion criteria. Conflicts regarding study inclusion were resolved by mutual agreement between reviewers. The data from the full texts selected were extracted independently by three authors (GF, ES, SL). The extracted data included the first author, year of publication, country, sample (clinical setting, patient age, and pathology), description of the intervention, intervention outcomes, quality assessment tool used with scores. No automation tools were employed in the screening or data extraction processes.

2.6. Quality assessment

The methodological quality of each included study was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Randomised Controlled Trials and Quasi-Experimental Studies [23]. This tool evaluates domains including participant selection, allocation concealment, blinding, outcome measurement, and completeness of follow-up. Two reviewers independently assessed risk of bias, and disagreements were resolved through discussion. No automa-

tion tools were used in the assessment process. Each study received an overall quality score.

2.7. Data synthesis and analysis

Following PRISMA guidelines and established methodological standards for systematic reviews, data from included studies were synthesized narratively and presented in both tabular and textual formats. Results were categorized by intervention type and corresponding cognitive outcomes. Primary outcomes focused on cognitive function, assessed via validated tools such as the MMSE, MoCA, RBANS, Clock Drawing Test (CDT), and other standardized neuropsychological measures. Extracted data encompassed baseline and postintervention scores, longitudinal changes, and group comparisons. Secondary outcomes included serum biomarkers (e.g., inflammatory cytokines, lipid profiles), gut microbiota diversity indices (α and β diversity), microbial species abundance, and fecal SCFA levels. Additional extracted variables comprised intervention characteristics (type, dosage, duration, delivery), sample size, and participant demographics (age, sex, comorbidities, cognitive status).

3. Results

3.1. Study selection

The database search yielded 1431 unique records, with 851 duplicates removed. Of the 580 remaining articles, 254 were excluded based on title and abstract screening. Full-text review of the 15 remaining studies confirmed their eligibility, and all were included in the systematic review. The study selection process is detailed in the PRISMA flow diagram (Fig. 1).

3.2. Study and sample characteristics

All included studies were published in peer-reviewed journals between 2012 and 2025 (Table 1). The clinical trials were conducted across a range of countries, including Spain, China, the United States, South Korea, Finland, Australia, Iran, Norway, Sweden, and the Netherlands. Among these, two large-scale trials were conducted in Spain by Martínez-Lapiscina et al. [5,24], while studies by Chen et al. [25] and Kim et al. [26] were carried out in China and South Korea, respectively. A multicen-

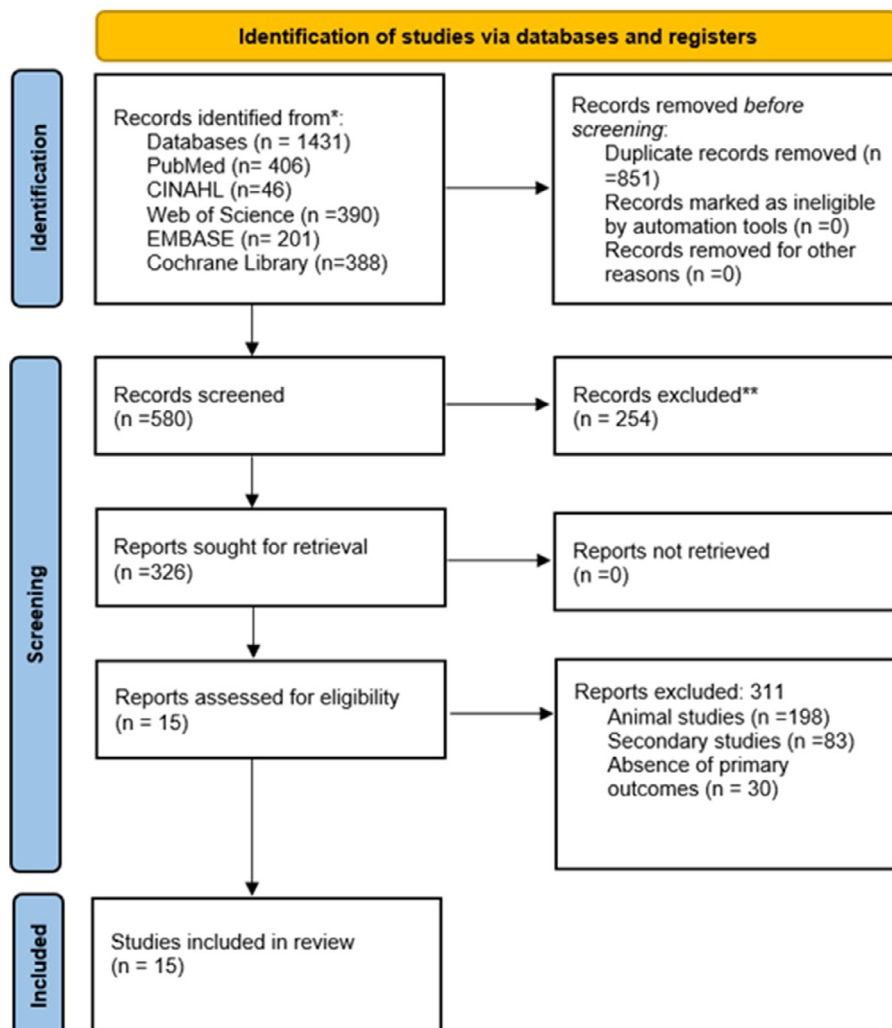


Fig. 1 – PRISMA flowchart.

Table 1 – Characteristics of the 15 studies investigating the association between gut microbiota and cognitive decline included in this systematic review.

Study Country	Type of study	Intervention/type of monitoring/type of exposure	Type of dementia or comorbidities	Assessed for eligibil- ity/randomized	Associations of characteristic microorganisms/experimental intervention with cognitive tests or main outcomes (+ =significant relationship) >better performance on multiple cognitive tests in case group <worst performance on multiple cognitive tests in case group	
(Martínez-Lapiscina et al. [24]) Spain	Randomized trial	MED DIET +EVOO or MED DIET + nuts vs a low-fat control diet 6.5 y	Type 2 diabetes mellitus or (2) three or more vascular risk factors	1055/522	MMSE CDT	+> +>
(Martínez-Lapiscina et al. [5]) Spain	Randomized controlled trial	intervention comparing two MedDiets (supplemented with either EVOO or mixed nuts) vs a low-fat control diet 6.5 mo	People aged, 65 y with mild cognitive impairment	285/268	MMSE CDT	+> +>
(Geleijnse et al. [27]) The Netherlands	Randomized, double-blind, placebo-controlled trial	margarines that provided 400 mg/d of EPA–DHA, 2 g/d of ALA, both EPA–DHA and ALA, or placebo for 40 mo	Stable myocardial infarction patients	5665/4837	MMSE	Ns
(Azuma et al. [28]) Japan	Randomized, double-blind, placebo-controlled trial	Intake of GCL2505 and inulin (a prebiotic) 12 wk	Japanese men and women between the ages of 50 and 80 y with MCI	80/67	Cognitrix test Blood inflammation markers	+> +
(Hu et al. [15]) China	Randomized, double-blind, and placebo-controlled trial	Probiotics (<i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> , <i>Enterococcus faecalis</i>) or placebo treatment 1 wk	Elderly patients undergoing hip or knee arthroplasty	106/96	Hopkins verbal learning test-revised test Hopkins verbal learning test	+> +>
(Dilmore et al. [9]) USA	Primary pilot trial	Low-fat American Heart Association diet or high-fat MMKD for 6 wk; then, after a 6-wk	Adults, either with MCI or CN	23/20	Mild cognitive impairment GABA levels and gut-transit time	+ +

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Table 1 (continued)

Study Country	Type of study	Intervention/type of monitoring/type of exposure	Type of dementia or comorbidities	Assessed for eligibility/randomized	Associations of characteristic microorganisms/experimental intervention with cognitive tests or main outcomes (+ =significant relationship) >better performance on multiple cognitive tests in case group <worst performance on multiple cognitive tests in case group	
(Lee et al. [29]) Korea	Randomized controlled trial	Group A, the multidomain intervention with nutritional supplements; group B, nutritional supplements only; and a control group 8 wk	Participants with mild cognitive impairment or mild dementia and positive in the amyloid PET study	76/49	RBANS total scale index score gut microbiota changes	+> +
(Handajani et al. [30]) China	Experimental study	Probiotic supplementation isolated from tempeh for 12 wk intervention	Subjects with age >60 y, and memory impairment	200/93	CDT	+>
(Kim et al. [26]) Korea	Preliminary study	FMT 3 mo post-FMT	AD patients	5	MMSE score MoCA scores	+> +>
(Soininen et al. [2]) Finland, Germany, the Netherlands, and Sweden	Randomized, controlled, double-blind, parallel-group, multicenter trial	Active product (125 mL once-a-day drink containing Fortasyn connect) or control product 24 mo	Prodromal Alzheimer's disease	382/311	NTB score CDR-SB MMSE	Ns +> +>
(Xiao et al. [10]) Japan	Randomized, double-blind, placebo-controlled trial	Probiotic (<i>Bifidobacterium breve</i> A1, 2×10^{10} CFU) or placebo for 16 wk	Older adults suffering from mild cognitive impairment	315/80	RBANS	+>
(Sinn et al. [31]) Australia	Randomized, triple-blind, placebo-controlled trial	Supplement rich in EPA, DHA, or the n – 6 PUFA linoleic acid for 6 mo	Aged people >65 y with MCI	118/54	Memory functioning questionnaire Rey auditory verbal learning test Digits forward Executive function/working memory letter-number sequencing Stroop color-word test Geriatric depression score	+> Ns +> +> Ns +>

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Table 1 (continued)

Study Country	Type of study	Intervention/type of monitoring/type of exposure	Type of dementia or comorbidities	Assessed for eligibility/randomized	Associations of characteristic microorganisms/experimental intervention with cognitive tests or main outcomes (+ =significant relationship) >better performance on multiple cognitive tests in case group <worst performance on multiple cognitive tests in case group
(Mehmandoust et al. [32]) Iran	Randomized, placebo-controlled, double-blind clinical trial	Symbiotic supplementation (2 capsules daily, 7 probiotic strains + prebiotic) for 12 wk	Mild to moderate Alzheimer's disease; comorbidities included hypertension, diabetes, dyslipidemia	60/52 completed	MMSE Barthel index Significant metabolic changes - -
(Jung et al. [33]) Republic of Korea	Randomized, double-blind, parallel-group, noncomparative trial	MH-Pro (<i>Lactocaseibacillus rhamnosus</i> CBT-LR5 + skim milk), low vs high dose, for 12 wk	MCI; some had hypertension, dyslipidemia	20 screened/20 (10 low dose, 10 high dose)	1×10^{10} CFU/d of LR5 and 1622 mg/d of skim milk): MOCA-K naming and delayed recall; decrease in amyloid- β 1 40/42 (1×10^{10} CFU/d of LR5 and 4055 mg/d of skim milk): improvement in orientation; no adverse events reported +> +>
(Chen et al. [25]) China	Prospective single-center RCT (TALENTs)	Assessment of dietary MDNs: folate, choline, VB12, etc. + gut microbiome analysis 4 mo	Cognitive impairment (MCI & dementia), chronic diseases considered as covariates	301 assessed/290 included with valid fecal samples	MoCA gut microbiota diversity (beta diversity) +> +
Abbreviations: AD, Alzheimer's dementia; CDR-SB, clinical dementia rating sum of boxes; CDT, Clock Drawing Test; CN, cognitively normal; EVOO, extravirgin olive oil; FMT, fecal microbiota transplantation; MCI, mild cognitive impairment; MDNs, methyl donor nutrients; MMKD, modified Mediterranean KD; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NTB, neuropsychological test battery; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.					

ter trial by Soininen et al. [2] included research centers across four European countries.

Across the 15 studies, a wide demographic spectrum was observed. Most participants were over the age of 60, with inclusion criteria requiring a minimum age of 45 years. The total number of participants varied across trials, ranging from small-scale pilot studies with 5 to 20 individuals (e.g., Kim et al., Jung et al.) to large-scale interventions involving over 1200 participants (e.g., Coley et al., Soininen et al.).

The cognitive status of participants ranged from cognitively normal older adults at risk for decline, to individuals with MCI, or diagnosed with early to moderate AD. In some studies, additional comorbidities were present, such as prediabetes, cardiovascular disease, or metabolic syndrome.

The interventions under review included probiotic supplementation, synbiotics, modified ketogenic or Mediterranean diets, omega-3 fatty acid intake, and FMT.

Baseline assessments of cognitive function included tools such as MMSE, MoCA, RBANS, CDT, and Cognitrax, with follow-up periods ranging from 8 weeks to over 6 years, depending on the study. Biomarker data, including inflammatory and metabolic markers and fecal microbiota composition, were collected as secondary outcomes.

3.3. Quality assessment

The quality appraisal of included studies is summarized in Tables 2 and 3, using the Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled trials or equivalent tools for quasi-experimental designs. Two randomized controlled trials studies, Sinn et al. [31] and Jung et al. [33], achieved a 100% quality score, reflecting rigorous methodology with double-blinding, randomization, comprehensive outcome reporting, and appropriate statistical controls.

Other studies presented methodological limitations. For instance, Kim et al. [26], despite its novel use of FMT, was limited by a small sample size ($n = 5$) and short follow-up (3 months), lowering its quality score. Chen et al. [25] lacked

blinding and random sampling but was strengthened by its incorporation into the larger TALENTs trial and thorough microbial and nutritional analyses.

The studies by Chen et al. [25], Lee et al. [29], and Martínez-Lapiscina et al. [5,24] received comparatively lower quality scores (85.7%, 84.6%, and 76.9%, respectively). Given the inherent lack of blinding in nutritional interventions, findings from these studies were interpreted with caution, acknowledging the higher risk of performance bias compared to double-blind probiotic trials. Dietary exposures cannot be feasibly masked from participants or clinicians, and attempts to impose blinding may compromise adherence, ecological validity, or ethical considerations. Consequently, the inherent impossibility of full blinding in nutrition-based trials introduces a higher susceptibility to performance and expectation bias. This limitation does not invalidate the findings but necessitates cautious interpretation and appropriate weighting within the overall synthesis.

Overall, quality scores for the remaining studies ranged from 76.9% to 100%, indicating adequate methodological rigor to support data synthesis.

3.4. Intervention characteristics

The reviewed studies encompassed a variety of dietary and microbiota-targeted interventions aiming to prevent or mitigate cognitive decline in older adults with or at risk of dementia.

3.4.1. Dietary interventions (Mediterranean diet, ketogenic diet, omega-3 supplementation, methyl donor nutrient supplementation)

Martínez-Lapiscina et al. [5,24] conducted two parallel randomised clinical trials investigating the effects of two variations of the Mediterranean diet (with extravirgin olive oil or mixed nuts) in individuals at high vascular risk. After 6.5 years, cognitive performance was assessed via MMSE and the CDT. Dilmore et al. [9] ran a crossover pilot trial in individuals with MCI, prediabetes, or normal cognition. Participants

Table 2 – JBI Critical appraisal of quasi-experimental studies assessing the relationship between gut microbiota composition and cognitive decline included in this systematic review.

JBI checklist for quasi-experimental studies	(Handajani et al. [30])	(Kim et al. [26])	(Dilmore et al. [9])
Is it clear in the study what is the “cause” and what is the “effect” (i.e., there is no confusion about which variable comes first)?	Yes	Yes	Yes
Was there a control group?	Yes	No	Yes
Were participants included in any comparisons similar?	Yes	Nv	Yes
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Yes	Nv	Yes
Were there multiple measurements of the outcome, both pre- and postintervention/exposure?	Yes	Yes	Yes
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes
Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes
Was appropriate statistical analysis used?	Unclear ½	Yes	Yes
Score	94.4%	85.7%	100%

Table 3 – JBI Critical Appraisal Checklist applied to randomized controlled trials assessing the relationship between gut microbiota composition and cognitive decline, included in this systematic review.

JBI Critical Appraisal Checklist for randomized controlled trials	(Hu et al. [15])	(Lee et al. [29])	(Soininen et al. [2])	(Xiao et al. [10])	(Sinn et al. [31])	(Martínez-Lapiscina et al. [24])	(Martínez-Lapiscina et al. [5])	(Azuma et al. [28])	(Geleijnse et al. [27])	(Chen et al. [25])	(Jung et al. [33])	(Mehmandoust et al. [32])
Was true randomization used for assignment of participants to treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was allocation to treatment groups concealed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were treatment groups similar at the baseline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were participants blind to treatment assignment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Were those delivering treatment blind to treatment assignment?	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Were outcomes assessors blind to treatment assignment?	No	No	No	No	Yes	No	No	Yes	No	No	Yes	Yes
Were treatment groups treated identically, other than the intervention of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Score	92.3%	84.6%	92.3%	92.3%	100%	84.6%	84.6%	92.3%	92.3%	76.9%	100%	92.3%

alternated between a low-fat diet and a modified Mediterranean ketogenic diet over 12 weeks. Cognitive impairment was assessed using standard neuropsychological measures (MMSE). Soininen et al. [2] led a 24-month multicenter RCT (LipiDiDiet) assessing the multinutrient drink Fortasyn Connect in patients with prodromal AD. Cognitive and neuroimaging outcomes were evaluated, with follow-up extending to 36 months. Chen et al. [25], within the TALENTs trial, examined the link between methyl donor nutrient intake and cognitive impairment, including dietary assessments, fecal 16S rRNA sequencing, MoCA testing, and microbial predictions via PICRUST2. Sinn et al. [31] examined omega-3 supplementation (DHA, EPA, linoleic acid) in 50 elderly participants with MCI for 6 months. Outcomes included verbal fluency and working memory. Geleijnse et al. [27] conducted the Alpha Omega Trial in 2911 elderly coronary patients, randomizing them to omega-3-enriched margarine or placebo for 40 months. MMSE was used to assess cognition. Lee et al. [29] evaluated a multidomain intervention (“Superbrain”) in individuals with MCI or mild AD, comparing nutritional supplementation, lifestyle changes, and no intervention. Cognitive function (RBANS) and microbial composition were assessed before and after 8 weeks.

3.4.2. Probiotics and synbiotics

Azuma et al. [28], a double-blind, placebo-controlled trial with 80 participants receiving the probiotic *Bifidobacterium animalis* subsp. *lactis* GCL2505 and inulin for 12 weeks. Cognition was assessed using the Cognitrax battery. Hu et al. [15] evaluated perioperative probiotics (*Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis*) in elderly patients undergoing elective arthroplasty, with cognitive and microbial assessment. Handajani et al. [30] trialed a probiotic derived from tempeh in 93 older adults with memory impairment. Cognitive performance improved after 12 weeks, with 16S rRNA sequencing revealing beneficial strains encoding GABA genes. Xiao et al. [10] ran a double-blind RCT in elderly individuals with MCI who received *Bifidobacterium breve* A1 or placebo for 16 weeks. Cognitive changes and biomarkers were evaluated. Mehmandoust et al. [32] tested a 12-week synbiotic supplementation (Gerilact) vs placebo in 60 patients with mild to moderate AD. Cognitive function and metabolic markers were assessed pre- and postintervention. Jung et al. [33] conducted a double-blind RCT in 20 older adults with suspected MCI, receiving either low or high doses of *Lactocaseibacillus rhamnosus* CBT-LR5 with skimmed milk for 12 weeks. Cognitive testing, serum biomarkers, and fecal microbiota composition were evaluated.

3.4.3. FMT

Kim et al. [26]—Conducted a preliminary study of FMT in five Alzheimer’s patients. Cognitive scores were tracked at baseline, one, and 3 months post-FMT, alongside microbial and gene expression analyses.

3.5. Comparative benefits of gut microbiota-targeted interventions on cognitive function

Across the 15 studies analyzed, 4275 participants were included, ranging from healthy older adults at risk of dementia

to patients with MCI or AD. Interventions comprised Mediterranean and ketogenic diets, probiotic and synbiotic supplementation, methyl donor nutrient intake, and FMT. Rather than considering the findings in isolation, we compare how different strategies act on the microbiota and their associated cognitive effects.

3.5.1. Outcomes of dietary interventions (Mediterranean diet, ketogenic diet, omega-3 supplementation, methyl donor supplementation)

Martínez-Lapiscina et al. [2,24] found that older adults on a Mediterranean diet with EVOO or mixed nuts showed significantly better MMSE and CDT scores compared to low-fat controls (MMSE difference: +0.62, +0.57; $P = .005$, $P = .015$). Chen et al. [25] linked higher methyl donor intake with significantly improved MoCA scores and healthier gut microbiota, suggesting microbiota-mediated epigenetic modulation. Dillmore et al. [9] showed ketogenic and low-fat diets enhanced SCFA production and GABA-related metabolites, improving cognition ($P = .03$). Geleijnse et al. [27] reported that omega-3 supplementation had modest effects on cognition, with DHA supplementation linked to improved physical symptoms, particularly reduced bodily pain. Sinn et al. [31] found that DHA improved verbal fluency in MCI patients ($P = .04$). Soininen et al. [2] reported that Fortasyn Connect (which contains EPA and DHA, phospholipids, vitamins C and E, B vitamins, choline, L-carnitine, N-acetylcysteine) slowed hippocampal atrophy and improved memory ($P = .03$) and executive function ($P = .04$). Lee et al. [29] found that a multidomain intervention (dietary supplementation, cognitive training, physical exercise) significantly improved cognitive function (MMSE, ADAS-Cog; mean difference = 2.3, $P = .04$) and increased gut microbiome diversity, notably *Bifidobacterium* and *Lactobacillus* ($P = .03$) in early AD. These studies highlight dietary interventions’ potential to reshape gut microbiota, enhance SCFAs, stabilize neurotransmitter networks, and reduce neuroinflammation, promoting cognitive health.

3.5.2. Outcomes of probiotic and synbiotic interventions

Probiotic and synbiotic interventions [10,15,28,30,32,33] improve executive function, memory, and verbal fluency, alongside increased microbial diversity and altered neurotransmitter pathways. *Lactobacillus fermentum* and *B. breve* specifically enhance GABA synthesis and reduce amyloid- β . Azuma et al. [28] reported improvements in executive function and microbial diversity with *B. animalis* GCL2505 and inulin ($P < .05$). Hu et al. [15] demonstrated significant reductions in postoperative cognitive dysfunction with perioperative probiotics (26.7% vs 56.9%, $P = .003$). Handajani et al. [30] showed *L. fermentum* A2.8 enhanced memory and verbal fluency ($P < .05$). Xiao et al. [10] observed significant RBANS score improvements in MCI patients ($P < .0001$). Jung et al. [33] found cognitive benefits and reduced amyloid- β ($P < .05$) with *L. rhamnosus* CBT-LR5. Mehmandoust et al. [32] found cognitive improvement in the synbiotic group (+1.8 MMSE), though between-group differences were not significant ($P = .53$). However, lipid and vitamin D markers showed significant time-treatment interactions ($P = .04$).

3.5.3. FMT

FMT [26] demonstrated preliminary but striking results, with Alzheimer's patients showing improved MMSE and MoCA scores alongside increased microbial richness. Compared with dietary or probiotic interventions, FMT appears to induce more rapid and pronounced microbial shifts, though long-term stability and safety remain uncertain. Kim et al. [26] found that five Alzheimer's patients improved significantly on MMSE (pre- and post-FMT were 13.00 and 18.00) and MoCA after FMT, with post-FMT analyses indicating increased bacterial richness and changes in lipid-related gene expression.

4. Discussion

The reviewed interventions appear to mediate cognitive benefits by modulating the gut microbiota and its metabolic outputs. Dietary interventions, for example, have been demonstrated to increase the abundance of SCFA-producing bacteria, which in turn enhances gut barrier function, modulates neuroinflammation, and promotes neurotransmission via enteroendocrine signaling [34,35]. Probiotics directly introduce bacteria that are capable of synthesizing neurotransmitters such as GABA, thereby mitigating excitotoxicity associated with MCI and AD [36,37]. FMT interventions, although still in a preliminary phase, have the potential to cause rapid shifts in the microbial ecosystem that may favor neuroprotective pathways [36,38].

One of the novel aspects of the present review is its integrative approach, which combines and contrasts multiple classes of interventions while highlighting their individual mechanistic pathways. Unlike previous reviews that examined single approaches, this review provides a comprehensive synthesis that contextualizes recent findings within the historical evolution of research on the microbiota and cognitive decline. It is now appreciated that early studies established a correlation between gut dysbiosis and cognitive impairment, but it is only in recent years that mechanistic insights—such as the role of SCFAs, neurotransmitter modulation, and lipid metabolism—have been elucidated [38,39].

Historically, research on the gut microbiota and cognitive decline was punctuated by a shift from descriptive correlations observed in small animal studies to more sophisticated human clinical trials. Early investigations in the 1990s primarily focused on characterizing microbial diversity in healthy vs diseased subjects. Over the past 20 years, advances in high-throughput sequencing and metabolomic profiling have allowed for detailed characterization of gut microbial communities and their bioactive metabolites. These developments have paved the way for interventional studies that now dissect the specific contributions of dietary patterns, probiotic strains, and even FMT on cognitive parameters. This historical perspective is critical as it reinforces how far the field has advanced and underscores the urgency for integrated reviews that capture the evolution of scientific thought on the gut-brain axis [36,39].

It is well established that metabolic dysregulation and inflammation occur in tandem with cognitive decline over the course of AD [11].

Recent evidence indicates that disruption of intestinal epithelial tight-junction integrity promotes the systemic translocation of microbial-associated molecular patterns, leading to chronic low-grade endotoxemia and inflammation. These inflammatory signals impair BBB integrity, facilitating neuroinflammation, neuronal dysfunction, and synaptic loss, thereby contributing to cognitive decline in ageing and neurodegenerative conditions.

Furthermore, the gut dysbiosis can trigger immune dysregulation, characterized by altered monocyte and macrophage activity, T-cell senescence, and impaired B-cell responses [40]. This immune imbalance promotes chronic systemic inflammation, which in turn can compromise the integrity of the BBB. In this way, the microbiome, immune system, and brain are engaged in a continuous dialogue, where perturbations in one component can reverberate throughout the system, creating a vicious cycle that promotes cognitive decline.

Other evidence in literature [41] support that microbial metabolites such as SCFAs and certain bile acids may exert neuroprotective effects by reducing oxidative stress, supporting mitochondrial electron transport chain function, promoting mitophagy, and enhancing the clearance of A β and tau. These microbiome-derived factors modulate mitochondrial signaling (e.g., via AMPK), influencing neuronal, astrocytic, and microglial function and impacting cognitive outcomes.

In comparing interventions, our analysis indicates that dietary strategies are effective in sustaining microbial diversity and promoting a stable, anti-inflammatory profile over the long term. For instance, adherence to the Mediterranean diet not only provides essential nutrients that modulate the microbiome but also exerts systemic antioxidant effects that benefit neural integrity [40]. Probiotics, while offering a more immediate effect on neurotransmitter production and immune modulation, require careful strain selection to ensure reproducible outcomes; studies have revealed that *Lactobacillus* and *Bifidobacterium* strains can increase GABA levels and reduce neuroinflammatory markers [37,40]. FMT stands apart by its ability to produce rapid and dramatic changes in microbial composition, though the heterogeneity in donor microbiota and the lack of standardized protocols pose significant challenges to interpreting its long-term cognitive benefits [37,40].

FMT study, in this review, shows that altered microbial communities can modulate lipid-metabolism gene expression in patients with AD, coinciding with cognitive improvements. FMT results in the increased expression of three genes (ACAA1, EHHADH, and B2M) associated with lipid metabolism and the downregulation of one gene (FABP6) [26]. After synbiotic (probiotic and prebiotic) formulation in the study of Mehmandoust et al. [32], there were significant time pretreatment interaction effects for the serum concentrations of LDL-c, total cholesterol, and 25(OH)D in the case group. Complementary evidence from ketogenic and low-fat diet indicates that microbiota-driven SCFA production alters circulating lipid-related metabolites, which may reduce neuroinflammatory signaling [9]. The regulation of lipid metabolism by the intestinal microbiota has also been corroborated by other studies, which confirm that bile acids, produced in the liver and modified by gut bacteria, regulate systemic and cerebral cholesterol metabolism. In the brain, where cholesterol

is largely synthesized locally, bile acids influence cholesterol turnover and neuronal lipid homeostasis, which are essential for membrane integrity, myelination, and neurotransmitter synthesis. SCFAs regulate host lipid metabolism through mechanisms including G-protein coupled receptor activation and histone deacetylase inhibition, influencing both gene transcription and systemic lipid profiles. Furthermore, in this review, Dillmore et al. [9] reported that participants following a ketogenic diet showed a significant improvement in cognitive outcomes concurrently with a notable increase in the relative abundance of *Akkermansia muciniphila*, a mucin-degrading bacterium that resides in the gut mucus layer and maintains gut barrier integrity by stimulating mucus production and strengthening tight junctions between epithelial cells. *Akkermansia* interacts with the host immune system to promote anti-inflammatory effects, stimulating regulatory T cells and modulating cytokine production. This contributes to reduce systemic inflammation and may indirectly explain the cognitive outcomes. The study of Chen [25] showed that specific colonic taxa can synthesize B vitamins, facilitate microbiota–host nutrient exchange, and influence the nervous system via neurotransmitter production, in accord with other studies which indicate that specific gut microbes can produce vitamins (K, B2, B9, B12) that support brain function. With regard to the production of neuromodulators, *L. rhamnosus*, in this review, has been shown to increase the Brain-Derived Neurotrophic Factor (BDNF), thereby reducing the production of proinflammatory cytokines (such as IL-1 β and TNF- α) through neuroprotective signaling pathways, linking probiotic supplementation to cognitive resilience [33].

The Mediterranean diet, rich in extravirgin olive oil and nuts, conferred in participants protection against vascular comorbidities and dementia through antioxidant and anti-inflammatory mechanisms [5,24]. This dietary pattern is characterized by a high intake of monounsaturated fatty acids—particularly oleic acid—derived from extravirgin olive oil, alongside polyphenols such as hydroxytyrosol and oleuropein, which exert potent free-radical-scavenging and anti-inflammatory effects. These compounds reduce oxidative stress, inhibit lipid peroxidation, and modulate key inflammatory pathways, including NF- κ B signaling, thereby attenuating chronic low-grade inflammation associated with neurodegenerative processes. Although the LipiDiDiet study reported no significant effects on dementia progression [2], multinutrient interventions analyzed in this study produced cognitive benefits and structural brain improvements, potentially modifying Alzheimer's pathology. These findings accord with observations in other studies, demonstrating that various probiotic combinations can restore hippocampal synaptic plasticity and ameliorate stress-induced impairments in spatial learning and memory. Nutritional interventions such as Ketogenic and low-fat diets in this review showed to increase GABA-related metabolites associated with cognitive resilience [9].

One point that remains uncertain in both the original and revised texts is the relationship between dietary margarine enriched in EPA/DHA and *n* – 6 polyunsaturated fatty acids (PUFAs) and the gut microbiota. Although some studies have indicated that specific fatty acids can reduce systemic in-

flammation and consequently modulate gut microbial composition, the evidence linking margarine-based interventions with cognitive outcomes is less definitive [40]. It is conceivable that while EPA and DHA may improve vascular and anti-inflammatory profiles, the matrix in which these fatty acids are delivered (such as margarine) may contain other lipid components (e.g., *n* – 6 PUFAs) that could counterbalance these effects. Hence, further research is essential to clarify whether these compounds act synergistically or antagonistically with respect to gut microbiota modulation and cognitive outcomes. Inizio moduloFine modulo

Several studies [2,11,14] have examined links between gut microbiome composition and AD, including Apolipoprotein E ϵ 4 (APOE4)-associated differences that connect genetic risk with microbial profiles (Fig. 2). APOE4, one of three major APOE isoforms (APOE2, APOE3, APOE4) encoded on chromosome 19, alters the structure and function of the apolipoprotein essential for lipid transport and cholesterol homeostasis in the central nervous system. Relative to other isoforms, APOE4 markedly increases AD susceptibility by impairing amyloid- β clearance, promoting tau hyperphosphorylation, activating chronic microglial inflammation, and disrupting neuronal lipid and mitochondrial metabolism. It also compromises BBB integrity, facilitating peripheral inflammatory ingress.

Emerging human evidence indicates that APOE ϵ 4 carriers exhibit distinct gut microbial and metabolite signatures associated with neuroinflammatory pathways and amyloid pathology. APOE-dependent disruptions in lipid metabolism and bile acid signaling may influence intestinal microbial ecology, while heightened systemic inflammation and impaired mucosal immunity in ϵ 4 carriers may reinforce dysbiosis and gut barrier dysfunction. These convergent mechanisms suggest that APOE ϵ 4 may potentiate AD risk partly through microbiota-mediated pathways.

These insights raise the prospect that microbiome-targeted interventions—such as dietary modification, probiotics, or FMT—could exert genotype-specific effects, although robust evidence from APOE-stratified clinical trials remains limited. Integrated metagenomic, metabolomic, and central biomarker studies will be essential to clarify whether modulating the gut microbiota can mitigate APOE ϵ 4-related neurodegenerative vulnerability.

4.1. Limits of the review

The systematic review exhibits several methodological limitations that affect the strength and generalizability of its conclusions. First, the heterogeneity among the included studies—in terms of intervention type, dosing regimens, duration, and outcome metrics—precluded a meta-analytic synthesis and mandated a narrative review approach. In addition, the search strategy was confined to English-language publications, which may have introduced language bias. The review also encompassed studies with varied methodological quality, ranging from rigorously blinded randomized controlled trials to quasi-experimental designs, thereby potentially confounding the overall interpretation of the results. Interventions ranged from Mediterranean and ketogenic diets [5,24] to supplementation with probiotics, synbiotics, or methyl donor nutrients [25,28,32], differing in composition, duration, and regimen.

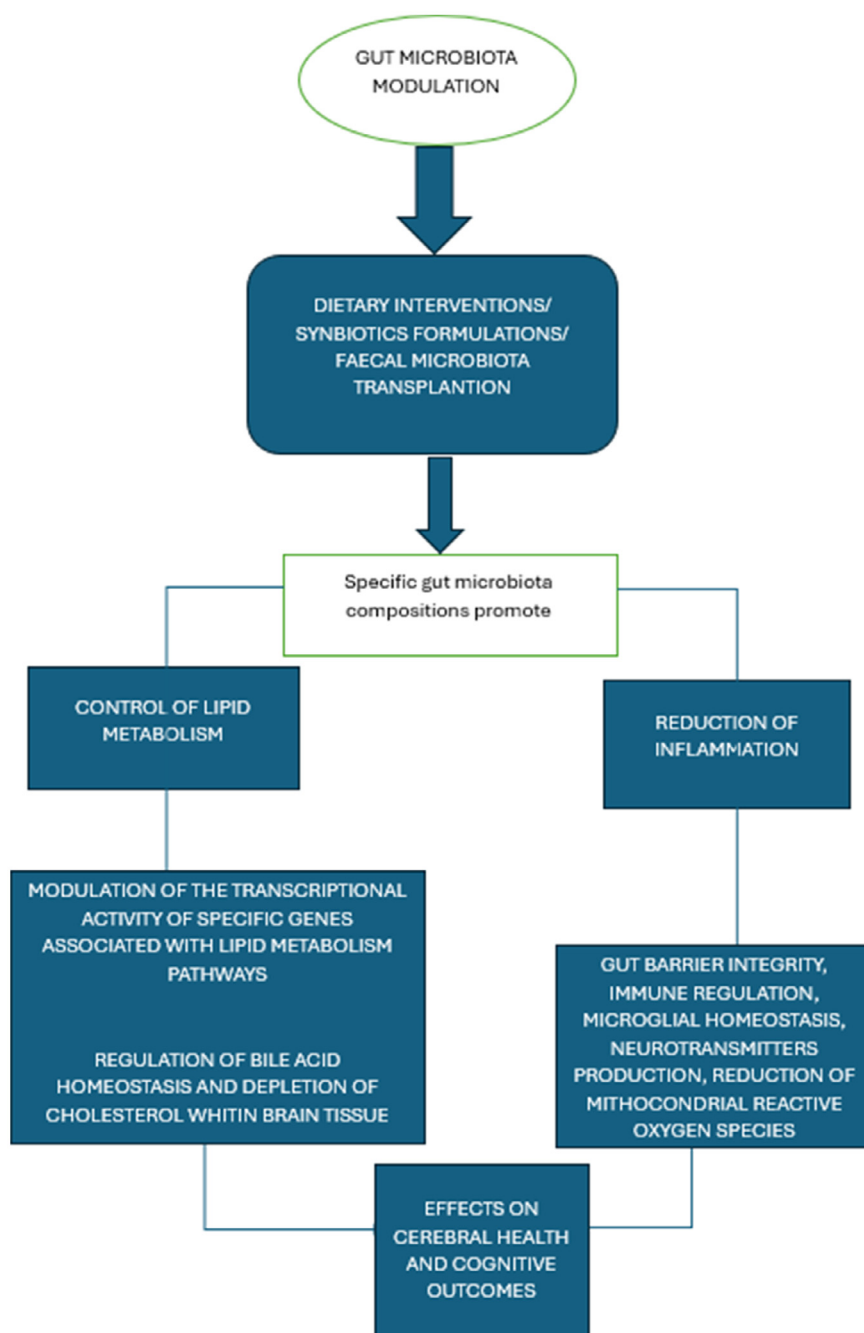


Fig. 2 – Apolipoprotein E ϵ 4 (APOE4) gene and Alzheimer's disease.

Population characteristics also varied, including age, baseline cognitive status, and comorbidities, further limiting comparability.

Methodological quality was mixed: while some studies were fully randomised, double-blind, placebo-controlled trials [28,27,15], others were quasi-experimental or noncomparative [19,20]. With regard to Mediterranean and ketogenic diet interventions, double-blind designs were inherently unfeasible; this limitation has been considered in interpreting the results.

Cognitive outcomes were assessed with diverse instruments, from global scales to domain-specific tests, complicating direct comparisons. The review also relied predominantly

on published English-language studies, introducing potential publication and language bias.

Overall, these factors warrant cautious interpretation and highlight the need for more standardized, adequately powered, and methodologically robust studies. Harmonization of intervention protocols, population selection, and cognitive assessments will be crucial for deriving more definitive conclusions on the effects of nutritional and microbiome-targeted interventions on cognition.

Furthermore, the preliminary study by Kim et al. [26] illustrates several limitations of FMT in Alzheimer's patients. The small sample size, absence of a control group, and nonblinded

design limit statistical power and generalizability. Additionally, variability in donor microbiota, preparation methods, and administration routes introduces potential confounding and complicates replication. The mechanisms underlying cognitive improvements remain unclear, and the short follow-up precludes assessment of long-term efficacy and safety. These factors underscore the need for larger, randomised, controlled, and standardized studies to establish the therapeutic potential of FMT in cognitive disorders.

4.2. Implications for practice, policy, and future research

The reviewed evidence demonstrates that distinct microbiota-targeted interventions—ranging from diet and probiotic supplementation to FMT—can beneficially influence cognitive outcomes in older adults or in prodromal AD. According to current evidence, although these interventions do not provide a cure for dementia, their effects converge on mechanisms involving lipid metabolism and neuromodulation, which have been shown to improve specific cognitive aspects such as memory and executive function, reinforcing the plausibility of gut microbiota as a therapeutic target.

This integrative perspective highlights the potential of microbiota-targeted strategies as part of a holistic and multidisciplinary approach to dementia prevention.

This review offers a substantive and original contribution to the existing body of literature by integrating, for the first time, the full spectrum of microbiota-targeted interventions—dietary strategies, probiotic and synbiotic supplementation, and FMT—and by examining their mechanistic links to cognitive outcomes in adults with, or at risk of, dementia. Whereas previous reviews have typically focused on isolated interventions or on descriptive associations between gut microbiota and neurocognitive decline, the present work synthesizes evidence across intervention modalities and explicitly connects clinical findings with underlying pathways involving SCFAs, lipid metabolism, immune regulation, and neuroinflammation.

Furthermore, this review uniquely emphasizes the differential effectiveness of microbiota modulation across the cognitive continuum, demonstrating that benefits are most pronounced in individuals with MCI or early symptomatic AD. By comparing interventions not only on clinical endpoints but also on mechanistic biomarkers—including microbial diversity, fecal metabolites, bile-acid profiles, and neurotrophic signaling—this review provides an integrated, systems-level perspective that is currently lacking in the literature.

Taken together, the review advances the field by offering a comprehensive, mechanistically grounded synthesis that clarifies how distinct microbiota-targeted strategies converge on shared biological pathways relevant to cognitive ageing. It thereby lays the groundwork for the development of standardized, evidence-based, and potentially personalized microbiome-focused interventions for the prevention and management of cognitive decline.

A distinctive feature of this review is its in-depth examination of the metabolic mechanisms contributing to AD. The analysis demonstrates how gut-derived metabolites, lipid-regulatory pathways, and mitochondrial signaling interact to influence neurodegenerative processes. By elucidating these

metabolic determinants, the study moves beyond purely descriptive associations and situates microbiota-modulating strategies within a mechanistically grounded framework of Alzheimer's pathophysiology.

At a population level, community education, nutritional counselling during midlife, and the inclusion of microbiota-supportive diets in national guidelines could provide scalable and cost-effective means of extending cognitive healthspan and reducing the burden of dementia.

Large-scale, longitudinal, multicenter randomized controlled trials are warranted to validate the cognitive benefits of microbiota-targeted strategies and to establish standardized protocols across interventions. Future research should particularly focus on achieving greater methodological consistency and mechanistic clarity. Standardization of probiotic strains, dosages, and delivery methods is crucial to ensure reproducibility and comparability across studies. In parallel, detailed mechanistic investigations are needed to explore the complex interplay between gut-derived metabolites—such as SCFAs—and host factors, including genetic predispositions like the APOE genotype and common metabolic comorbidities.

Moreover, direct comparative trials between different intervention modalities—dietary strategies, probiotic supplementation, and FMT—are essential to delineate their respective effects on the gut microbiome and neural substrates. Particular attention should also be given to clarifying the influence of specific dietary components, such as margarines enriched in EPA and DHA, and the dietary balance of $n-6$ PUFAs, in modulating inflammatory and metabolic pathways that may contribute to cognitive decline. Finally, the evaluation of multidomain interventions combining dietary modifications with cognitive training and physical exercise represents a promising avenue to investigate potential synergistic effects on cognitive function and overall brain health.

5. Conclusions

To summarize, the augmented analysis presented in this review highlights several key points: First, the necessity for an integrative assessment of microbiota-targeted interventions arises from the fragmented nature of prior reviews and the evolving understanding of gut-brain communication. Second, the original contribution of this review lies in its capacity to simultaneously compare distinct intervention modalities and the elucidation of their mechanistic underpinnings, set against the backdrop of a historical evolution in the field. Third, the clear delineation of intervention grouping—dietary, probiotic, and FMT—provides a framework for future research aimed at optimizing cognitive outcomes. Fourth, despite promising findings, considerable challenges remain, including heterogeneity of study designs, a need for standardized intervention protocols, and unresolved ambiguities surrounding the impact of specific nutrients, such as margarine-based EPA/DHA formulations, on microbial-host metabolic interactions. The overall message is that microbiota modulation is a promising therapeutic target that complements existing pharmacological and lifestyle interventions. However, rigorous, standardized, and well-powered clinical trials with mechanistic endpoints are essential to confirm these preliminary

findings and to drive forward the translation of this promising strategy into clinical practice.

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Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that Gen AI was used in the creation of this manuscript. During the preparation of this work, the author used DeepL Write to correct the manuscript's syntax and grammar. After using this tool, the author reviewed and edited the content as necessary and takes full responsibility for its publication. No generative AI was used in designing the study, developing the methodology, analyzing the data, or interpreting the results.

Author declarations

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CRediT authorship contribution statement

Sofia Libriani: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **Gabriella Facchinetti:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Flavio Marti:** Writing – review & editing, Writing – original draft, Visualization. **Maria Ymelda Tolentino Diaz:** Writing – review & editing, Writing – original draft, Visualization. **Elena Sandri:** Writing – review & editing, Writing – original draft, Visualization, Investigation.

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Supplementary materials

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