Received: 29 August 2024 | Revised: 29 October 2024 | Accepted: 27 November 2024

DOI: 10.1002/dad2.70057

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

REVIEW ARTICLE

A systematic review and meta-analysis of basal microbiota and cognitive function in Alzheimer's disease: A potential target for treatment or a contributor to disease progression?

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Funding information
Ministry of Science and Innovation, Grant/Award Number: PID2023-151715OB-IOO; European Union NextGeneration EU/PRTR, Grant/Award Numbers: PLEC2022-009464, CPP2022-009646

Abstract

A systematic review and meta-analysis examined the impact of gut microbiota in Alzheimer's disease (AD) pathogenesis. Dysbiosis may influence neurodegeneration by affecting gut permeability and neurotrophic factors, leading to cognitive decline. The study analyzed microbiome differences between patients with AD and healthy individuals, as well as the impact of various interventions in both preclinical and clinical studies. Of 60 studies reviewed, 12 were excluded from the meta-analysis due to unsuitable data or lack of control groups. Meta-analyses revealed significant cognitive impairment in AD patients and animal models, with specific tests identifying these deficits. Notably, *Bacteroides* levels were higher in patients with AD, whereas probiotics improved *Prevotella* levels. Natural treatments increased Bacteroidetes and reduced Firmicutes in animal models. The findings emphasize the need for standardized methods to develop therapies targeting the gut microbiota to restore cognition in AD. Understanding individual dysbiosis could further clarify the cognitive effects of the gut–brain axis.

KEYWORDS
Alzheimer´s disease, cognition, dysbiosis, gut microbiome, therapy

Highlights

- Dysbiosis in the gut microbiota is linked to cognitive decline in Alzheimer's disease (AD).
- Patients with AD show significant differences in *Bacteroides* levels compared to healthy individuals.
- Probiotic treatments increase *Prevotella* levels in AD animal models.
- Natural agents boost *Bacteroidetes* and reduce *Firmicutes* in AD animal models.
- Human studies show no consistent effects of gut microbiota interventions on cognitive function in AD.

1 | BACKGROUND

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. According to the World Health Organization, dementia affects 50 million people globally, with patients with AD comprising 60%–70% of these cases. Furthermore, this number is projected to double every 5 years, potentially reaching 152 million by 2050.[1] Considering the widespread occurrence of AD, the increasing number of studies where gut microbiota interventions have positively impacted different biomarkers of the disease, and the challenges associated with an effective treatment, it becomes imperative to understand the baseline differences in patients with AD that could be effectively treated by gut microbiota interventions in order to delay and/or ameliorate the cognitive deficits associated to this disease.

Recent advances in research on the etiology of AD suggest that microbiota dysbiosis throughout life can trigger a systemic inflammatory response and affect the immune response of microglial cells in the brain. Increasing experimental and clinical data confirm the key role of gut dysbiosis and the interaction of gut microbiota with the host in the development of neurodegeneration.[2] In addition, over time, the persistent permeability of the intestinal mucosa and the blood–brain barrier increases, creating a vicious cycle that irreversibly destroys neurons.

In fact, it has been suggested that the gut microbiota may be involved in the neuropathology of AD. A study comparing the microbiota of 25 AD cases with 25 controls showed a decrease in microbial diversity in these patients. The investigators also observed a reduction in the number of *Firmicutes* and an increase in the percentage of *Bacteroidetes*.[3] Another study comparing the microbiome of patients without dementia to those with dementia found that *Bacteroides* were reduced in patients with dementia compared to those without it.[4] Similarly, a study conducted on the Chinese population, including patients with AD, patients with mild cognitive impairment, and healthy individuals, showed that fecal microbiota diversity was reduced in patients with AD compared to patients with mild cognitive impairment and healthy subjects. In addition, there was a decrease in the number of *Firmicutes* and an increase in the number of *Proteobacteria*.[5]

These changes in gut microbiota populations in AD have been linked to certain disease biomarkers. Indeed, some species of enterobacteria and/or fungi can produce amyloid peptides or a curly-type amyloid fiber that leads to amyloid aggregation in the brain.[6,7] Microbial amyloids have also been shown to increase the nucleation of amyloid beta (Aβ) peptide aggregates and trigger an inflammatory response.[8] Furthermore, bacterial amyloid peptides also enhance the aggregation of other misfolded proteins, such as α-synuclein.

In this line, a reduction in amyloid accumulation was observed in human amyloid beta precursor protein (*APP*)/human presenilin 1 (PS1) transgenic mice, an animal model of AD, when the gut microbiota was absent.[6] In addition, the microbiota of the transgenic mouse model differs from that of the wild-type, causing amyloid protein accumulation in wild-type mice transplanted with the microbiota from the AD transgenic mouse model.[8] These results demonstrate how impaired bacterial microbiota can alter the levels of amyloids and bacterial metabolites in the body, thereby potentially playing a triggering role in the onset and exacerbation of neurodegeneration in AD.

In this context, the discovery of therapies capable of restoring gut microbiota in AD offers hope for mitigating neurodegeneration. Indeed, Xiang et al.[9] conducted a systematic review and meta-analysis on the use of probiotics in AD and Parkinson's disease (PD), suggesting that probiotics may improve AD outcomes, possibly through anti-inflammatory pathways, as evidenced by a decrease in glutathione (GSH) levels, an indication of oxidative stress and inflammation, following probiotic supplementation. It has been shown that interventions with single- or multi-strain probiotics can positively impact cognitive and memory deficits in AD animal models.[10,11] In this regard, a study from Medeiros et al.[12] with a supplemented diet in 3xTg-AD mice with two *Lactobacillus* strains showed a significant increase in the abundance of *Bacteroidetes* in 10-month-old AD mice receiving *Lactobacillus*, which was accompanied by the positive effects observed in memory performance after 12 weeks of probiotic treatment.

Consistent with these findings, manipulation of the microbiome, which extends beyond probiotic supplementation, has been demonstrated to mitigate inflammation and consequently reduce disease burden. For instance, a recent phase-3 clinical trial[13] highlighted the efficacy of GV-971, a sodium oligomannate capable of reshaping gut microbiota, in alleviating gut dysbiosis and mitigating phenylalanine/isoleucine accumulation. This intervention led to a reversal of cognitive impairment in patients with mild cognitive impairment associated with AD.[14] In addition studies suggest that fecal microbiota transplantation (FMT) may ameliorate cognitive symptoms in patients with AD.[15,16]

Certain dietary patterns influencing gut microbiota composition may present an effective strategy in averting the onset of AD. The ketogenic diet (KD) has emerged as a potential therapeutic intervention for AD, targeting the commonly observed impaired glucose metabolism in the condition. The KD redirects metabolic pathways from glucose, which has a toxic metabolic route, toward fatty acids and ketone bodies. Consequently, the brain is shielded from the inflammatory and toxic ramifications stemming from impaired glucose metabolism. In addition, the KD exhibits multifaceted potential targets, including the modulation of gut microbiota.[5] Ma et al.[17] demonstrated that a 16-week KD regimen in an animal study augmented the relative abundance of putatively beneficial gut microbiota, such as *Akkermansia muciniphila* and *Lactobacillus*, while concurrently diminishing putatively proinflammatory taxa such as *Desulfovibrio* and *Turicibacter* during the early stages of AD.

Other diets, such as the modified Mediterranean-ketogenic diet (MMKD), which emphasizes olive oil and fish as primary sources of healthy fats and proteins, permit slightly higher carbohydrate intake to facilitate increased consumption of vegetables and fruits. Nagpal et al.[18] demonstrated that MMKD induces alterations in gut microbiome composition and short-chain fatty acids (SCFAs), which are correlated with improved cerebrospinal fluid (CSF) AD biomarkers in older adults. Conversely, Park et al.,[19] in a study involving rats injected with Aβ into the hippocampus and subjected to an 8-week KD (AD-KD), intermittent fasting (AD-IMF), a 30% fat diet (AD-CON), or a

high carbohydrate (starch) diet (AD-CHO), investigated changes in gut microbiota and memory, among other factors. AD-KD exacerbated gut dysbiosis by elevating *Proteobacteria* levels, whereas AD-CHO ameliorated it by increasing *Bacteroidetes* levels. Moreover, they found that AD-CON, AD-IMF, and AD-CHO, but not AD-KD, reduced hippocampal Aβ deposition and improved memory performance.

Given the diverse impact of different strategies targeting the microbiome in AD to recover the associated cognitive deficits, this study endeavors to investigate the baseline differences in microbiota diversity between healthy subjects and those with AD, study their differences in diversity, and study the impact on various aspects of cognition with the aim of increasing knowledge for designing effective strategies to improve cognitive impairment in AD. This exploration seeks to unveil common gut microbiota populations that could underlie the cognitive deficits observed in AD. Adopting this comprehensive perspective may provide valuable insights into developing treatments that target specific microbiota populations to address cognitive deficits in AD.

2 | METHODS

2.1 | Research strategy

A systematic bibliographic search was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Independent searches for original research articles related to microbiota differences between healthy individuals and patients with AD and their relationship with cognitive deficits were performed in four electronic databases: PubMed, Web of Science (WoS), Science Direct, and Scopus. The search was carried out by two researchers (M.V. and A.J.G.) on July 30, 2024, using the following terms and search combinations: (Alzheimer's disease) and/or (neurodegeneration) and/or (dementia) and (gut microbiome or microbiota or gut-brain axis or metabolites or short-chain fatty acids or SCFA or dietary fiber or oral-brain axis or probiotics or prebiotics or fermented foods or fecal microbiota transplant diet or exercise) and (cognitive functions or memory or learning or behavior or attention or cognition or brain health or emotion). No chronological or methodological filters were applied to the search engines, apart from filtering by titles, keywords, and abstracts, and all resulting data sets were exported and compiled in Mendeley and Excel.

2.2 | Study selection

After removing duplicates, all remaining titles and abstracts were reviewed to determine their eligibility. Epidemiological studies and articles that did not specifically address microbiota differences between healthy individuals and patients with AD and their relationship with cognitive deficits were considered ineligible. After the initial selection phase, the full texts of the selected studies were retrieved and reviewed in detail according to the inclusion criteria. For a study to be included in the systematic review, it had to (1) involve experimental cases related to AD, (2) show measurements of the gut microbiota of the experimental subjects, and (3) study cognitive changes in the experimental subjects.

2.3 | Meta-analysis

A continuous random-effects model with a standard mean difference (SMD) was employed to conduct the meta-analysis on cognitive changes, whereas a continuous random-effects model with a log odds ratio was used to analyze the effect of AD on microbial populations. A total of 48 studies were included in the meta-analysis: 7 in humans and 41 in the animal model (mice; $n = 39$ and rats; $n = 2$) studies. Of the 60 studies included in this systematic review, 12 articles were excluded from the meta-analysis for various reasons. Two studies were excluded as they were single-case reports.[15,16] Eight studies were omitted because they did not provide extractable data suitable for meta-analysis.[12,20–26] In addition, two studies were excluded due to the lack of a control or comparable group.[27,28] Significance did not influence the selection process, and studies reporting null findings were included. Raw data extraction was performed using the online data extraction tool PlotDigitizer. Means, standard deviations (SDs), and sample sizes were entered into R Studio software version 4.3.1, which automatically calculated the SMD, confidence intervals (CIs), heterogeneity, and overall effect size for cognitive and microbiota changes. For studies reporting frequencies instead of means and SDs, numerical data extraction was performed, and a continuous random-effects model with a log odds ratio was employed to analyze the effect of AD on microbial populations. The 'metafor' package in R Studio was utilized to calculate the log odds ratio, CIs, heterogeneity, and overall effect size for this analysis.

3 | RESULTS

Searches conducted in the electronic databases PubMed, Scopus, Science Direct, and WoS yielded 2833, 291,476, and 2188 articles, respectively, reaching a total of 96,488 publications, of which 1317 were identified as duplicates and removed from the data set, and 87,886 were marked as ineligible by automated tools in the database. The titles and abstracts of the remaining 7285 articles were evaluated for eligibility, and 4901 publications were deemed out of scope for the systematic review and excluded because they were systematic reviews, meta-analyses, reviews, books, or conference communications. A total of 2384 articles were retrieved, thoroughly reviewed in their entirety, and assessed based on the inclusion criteria. Of these, 58 studies met the eligibility requirements for inclusion in the systematic review. In addition, three articles were identified through alternative methods, and following evaluation against the study's inclusion and exclusion criteria, two were deemed eligible and included. Thus a total of 60 references were incorporated into the systematic review (see Figure 1).

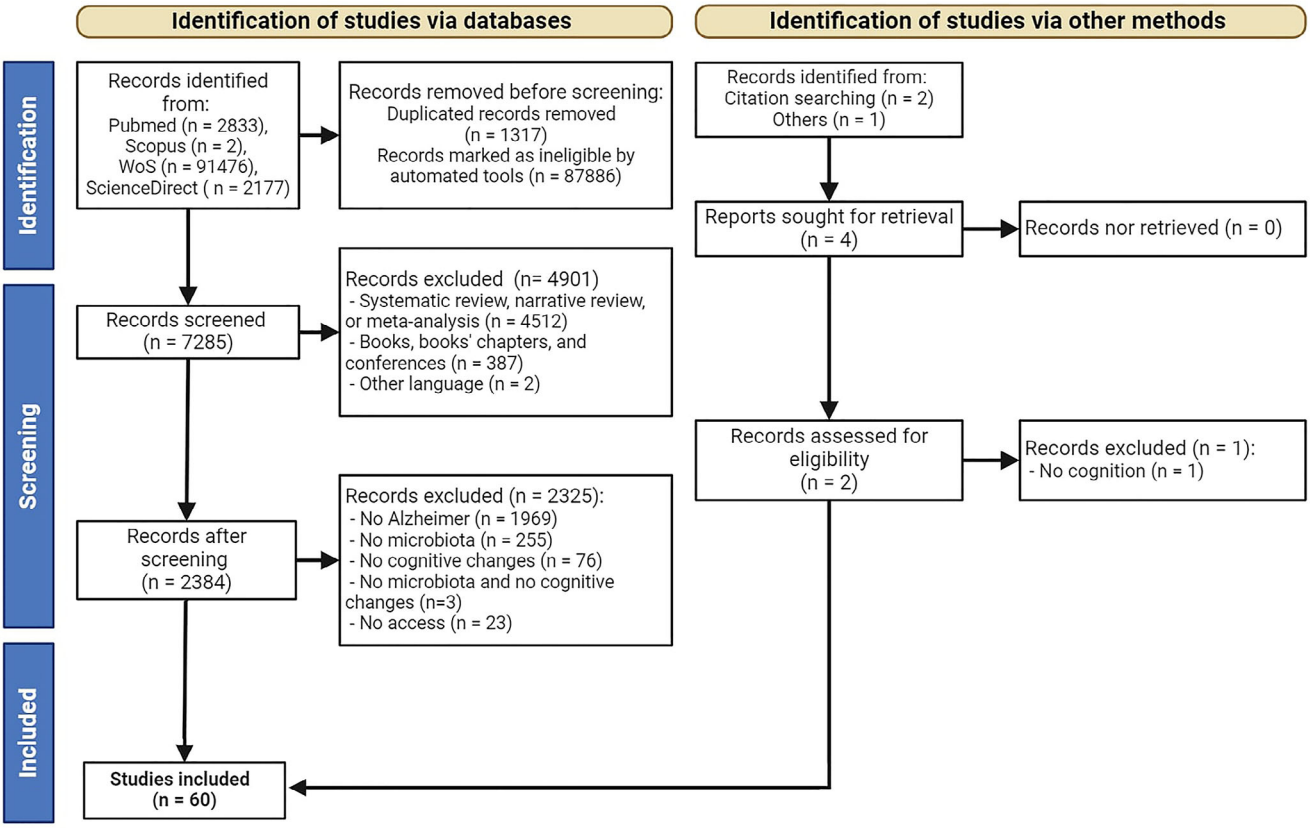

FIGURE 1 PRISMA flow chart of selection of publications for inclusion in review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

3.1 | General characteristics of selected studies

The studies selected for inclusion in the systematic review were published between 2016 and 2024 (n = 60). These studies include 45 experimental designs involving animal models, and 15 studies with Alzheimer's patients. Among the animal studies, 26 involved *APP/PS1* mice with the *APPswe* and *PSEN1dE9* mutations; 6 used *C57BL/6* mice, 3 of which involved AD induced by an Aβ1-42 oligomer injection; and 3 employed other AD-related models, such as D-galactose/AlCl3-induced models (n = 2) or streptozotocin-induced models (n = 1). In addition, six studies utilized 5x*FAD* mice, four used 3xTg-AD mice, and one employed transgenic (Tg2576)) mice. Two employed other AD-related models like *SAMP8* or scopolamine-induced models. Furthermore, 15 studies included human participants, evaluating a total of 1028 patients, both with and without AD, for comparative purposes. The average age of the participants was 74.7 years, with a gender distribution of ≈51% women and 49% men. All studies incorporated samples from these 1028 patients for further analysis.

Regarding gut microbiota, most studies focused on 34 microbial populations: *Bacteroides*, *Prevotella*, *Ruminococcus*, *Akkermansia*, *Bifidobacterium*, *Lactobacillus*, *Alistipes*, *Rikenella*, *Helicobacteraceae*, *Desulfovibrionaceae*, *Odoribacter*, *Clostridia*, *Bacilli*, *Verrucomicrobiae*, *Erysipelotrichales*, *Allobaculum*, *Muribaculaceae*, *Roseburia*, *Parasutterella*, *Agathobacter*, *Turicibacter*, *Klebsiella*, *Escherichia*, *Shigella*, *Pseudomonas*, *Parabacteroides*, *Barnesiella*, *Atopobiaceae*, *Enterobacteriaceae*, *Lachnospiraceae*, *Firmicutes*, *Megamonas*, *Rhodococcus*, and *Proteus*.

Furthermore, spatial working and reference memory tests were conducted using the Morris Water Maze (MWM) in 29 studies (n = 27 for spatial reference memory and n = 5 for working memory). Reference memory was also evaluated using the Barnes test (n = 3), whereas working memory was assessed with the Y maze (n = 11) and the T maze (n = 1). Object recognition memory in animals was assessed in 15 studies. Cognition was also assessed with the nest-building test (n = 3). Other evaluations that measured anxiety in animals included the open field test (n = 3), the contextual fear conditioning test (n = 1), the elevated plus maze (n = 1), the tail-suspension test (n = 1), and the passive avoidance test (n = 1). In addition, human studies assessed cognitive functions using the Mini-Mental State Examination (MMSE), reported in 14 articles, and the Montreal Cognitive Assessment (MoCA), compared in 8 studies. The Clinical Dementia Rating (CDR) was also utilized in seven studies to assess cognitive impairment. Other instruments that were used to assess cognition were the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; n = 2), the Activities of Daily Living (ADL; n = 2) scale, and the Thai Mental Status Exam (TMSE; n = 1).

A range of treatments were utilized across the studies. Exercise interventions were applied in three studies, using methods such as running on a motor-driven treadmill. Probiotics were employed in 10 studies, with various formulations including combinations

like SLAB51, *Bifidobacterium lactis* and *Probio-M8*, *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI, as well as others such as *Lactobacillus rhamnosus* and *Bifidobacterium longum*, Tibetan fermented milk, and *Clostridium butyricum*. Probiotics were also used in combination with exercise and environmental enrichment. Dietary interventions were explored in two studies, involving non-fermented sorghum and caloric restriction. Prebiotics were assessed in four studies, including neoagarotetraose, mannan oligosaccharide, sesamol, and a polysaccharide derived from *Sparassis crispa*-1 (SCP-1). Microbiota-based therapies were utilized in four studies, with methods such as FMT, indoles, and SCP-1. Natural therapeutic agents were used in five studies, including Huanglian Jiedu decoction, silibinin and silymarin, curcumin, quercetin-3-O-glucuronide, defatted walnut powder, and black ginseng.

3.2 | Microbiota differences

All 60 studies included in the analysis observed changes in the aforementioned 34 bacterial populations. A consistent increase was observed in *Ruminococcus*, *Akkermansia*, *Rikenella*, *Helicobacteraceae*, and *Lactobacillus* in the *APPswe/PSEN1dE9* AD animal model, with a similar increase in *Rikenella* in the Aβ1–42 injection animal model. In addition, a notable decrease was observed in *Bacteroidetes*, *Bifidobacterium*, *Desulfovibrionaceae*, and *Lachnospiraceae* either in animal models or patients with AD.

Several studies reported contrasting findings when comparing the control group to the *APPswe/PSEN1dE9* transgenic animal model. *Prevotella*, *Firmicutes*, *Muribaculaceae*, and *Bacteroidetes* showed an increase, whereas *Helicobacteraceae* and *Rikenella* decreased significantly. However, there were discrepancies among publications regarding reductions in bacterial groups. Xu et al.[29] highlighted reductions in *Alistipes* and *Rikenella*, whereas Shen et al.[30] reported decreases in *Odoribacter* and *Helicobacteraceae*. Similarly, Sun et al.[31] observed reductions in *Helicobacteraceae* and *Rikenella*, and Qian et al.[32] found decreases in *Desulfovibrionaceae*, *Enterobacteriaceae*, *Turicibacter*, and *Ruminococcus*. Furthermore, other studies identified reductions in groups such as *Akkermansia*, *Alistipes*, and *Odoribacter*,[33,34] highlighting the variability in microbiota changes across Alzheimer's models compared to controls.

In studies involving Alzheimer's patients, diverse changes were observed in bacterial groups compared to healthy subjects. A consistent finding across several studies was the increased abundance of specific bacterial groups in Alzheimer's patients such as *Eisenbergiella*[35] and *Proteobacteria*.[5] Laske et al.[22] further observed increases in *Moritella*, *Parabacteroides*, *Basfia*, *Arsenophoonus*, *Acidothermus*, *Sureimonas*, *Candidatus Arthromitus*, and *Asaia*, suggesting significant microbial shifts in Alzheimer's patients. In addition, *Parabacteroides*, *Alistipes*, *Tannerella*, and *Actinobacteria* were found to be enriched after FMT in patients with AD.[36]

Conversely, decreases were noted in several microbiota populations; indeed, Liu et al.[5] observed reductions in *Firmicutes*, *Clostridiaceae*, and *Ruminococcaceae*, whereas Yamashiro et al.[35] reported decreases in *Anaerostipes* and *Roseburia* when compared to healthy subjects. Moreover, Li et al.[37] highlighted reductions in *Alistipes*, *Bacteroides*, *Parabacteroides*, *Sutterella*, and *Paraprevotella*, indicating a shift away from a balanced microbiome. In addition, Guo et al.[38] found decreased levels of *Bacteroides*, *Lachnospira*, and *Ruminiclostridium 9* in patients with AD compared to healthy participants, further emphasizing the microbial dysbiosis linked to AD.

3.3 | Cognitive differences

All included studies investigated cognitive differences using standard cognitive tests for human or animal models. In human studies, cognition was assessed using the MMSE (n = 12), the MoCA (n = 7), or the CDR (n = 7). MMSE and CDR results highlighted significant differences, that indicated cognitive impairment, with lower MMSE scores and higher CDR in patients with AD. MoCA results also showed that patients with AD had significantly lower scores when compared to the control group, specifically in visuospatial/executive functions, naming, attention, language, and orientation.

In animal models of AD, cognitive functions were assessed using various paradigms. Spatial working memory deficits were evident in the MWM (n = 2), the Y maze (n = 9), and the T maze (n = 1). Specifically, in the *APPswe/PSEN1dE9* transgenic model (n = 5) and the 5x*FAD* mice (n = 1), significant impairments in working memory were observed, with notable reductions in spontaneous alternation in both the Y and T mazes. Furthermore, in the *APPswe/PSEN1dE9* transgenic model, performance in the MWM showed prolonged escape latency, fewer crossings of the target area, and reduced time spent in the target quadrant, indicating additional impairments in spatial working memory.

Regarding the spatial reference memory, assessments conducted in the *APPswe/PSEN1dE9* model (n = 16), the 5x*FAD* (n = 4), the scopolamine-induced AD animal model (n = 2), the Aβ1–42 injection model (n = 2), D-galactose/AlCl3 induced AD (n = 2), the 3xTg-AD (n = 1), and the *SAMP8* (n = 1) showed consistent impairments. In the former, increased escape latency over time and decreased time spent on the platform suggested compromised spatial reference memory. Similarly, the Aβ1–42 injection model and the D-galactose/AlCl3 induced displayed increased latency compared to its counterpart, reinforcing the presence of spatial reference memory deficits in AD models.

Age-related changes in spatial reference memory were also observed, highlighting the progressive nature of Alzheimer's pathology. Shen et al.[30] noted significant differences between 6-month-old and 8-month-old *APPswe/PSEN1dE9* mice, with the latter exhibiting higher escape latency. This suggests a decline in spatial memory performance with disease progression, pointing out the relevance of these models in studying AD progression.

Finally, in object recognition studies using the *APPswe/PSEN1dE9* model (n = 47), a decline in the discrimination index was observed, indicating impaired cognitive abilities related to parahippocampal cortices damage. A detailed description of all features is provided in Table 1

TABLE 1 Description of gut microbiota changes in AD animal models and the associated cognitive changes found in the described peer-reviewed studies.

Source	*Population/ sample*	*AD model*	*Microbiota changes*	*Cognitive changes*
Bello-Medina et al.[39]	Mice	Triple transgenic 3xTg-AD (*PS1M146VA*, *PPSwe*, *TauP301L*) at 3 and 5 months	For the transgenic mice, at 3 months old, the abundances in the 3xTg-AD female showed an increase in the genus *Lactobacillus* (phylum *Firmicutes*), whereas at 5 months old, it showed an increase in the genera *Dorea*, *Gemella*, *Lachnobacterium*, *Peptoniphilus*, *and Ruminococcus* (phylum *Firmicutes*). The 3xTg-AD male mice at 3 months old showed an increase in the family *Koribacteraceae* (phylum *Acidobacteria*); the family *Streptomycetaceae*; the genera *Atopobium*, *Collinsella*, *Nesterenkonia*, and *Rothia* (phylum *Actinobacteria*); the genus *Pedobacter* (phylum *Bacteroidetes*); the genera *Allobaculum*, *Eubacterium*, *Lactococcus*, *Selenomonas*, and *Veillonella* (phylum *Firmicutes*); the families *Beijerinckiaceae*, *Oxalobacteraceae*, *Phyllobacteriaceae*, *Rhodospirillaceae*, *Xanthomonadaceae*; the genera Aeromonas, *Campylobacter*, *Erythrobacter*, *Flexispira*, and *Neisseria* (phylum *Proteobacteria*); and the genus S1 (phylum *Thermotogae*). The 3xTg-AD male at 5 months old showed an increase in the family *Christensenellaceae* (phylum *Firmicutes*).	In the NOR test, the results showed that exploration time was higher than familiar-object place in female and male control mice. The effect observed in female control mice was opposite in male 3xTg-AD mice. No differences were found in exploration time between Nov and Fam objects in female 3xTg-AD mice. On the other hand, the Bonferroni test showed statistical differences in exploration time of object displaced in female control and female 3xTg-AD. This same effect was also observed in male control in comparison with male 3xTg-AD.
Cuervo-Zanatta et al.[40]	Mice	*APP/PS1 (APPswe, PSEN1dE9)* at 4 months	At the phylum level, we found a higher abundance of *Bacteroidetes* in female AD compared to male AD. At the class level, a higher relative abundance of *Bacilli* was observed in male AD compared to female AD. At the order level, higher abundances of *Lactobacillales* and *Turicibacterales* were observed in male AD compared to female AD mice and compared to female wild-type only for *Turicibacterales*. At the family level, *Clostridiaceae* abundance was higher in female wild-type (WT) compared to male WT mice. *Lactobacillaceae* relative abundance was higher in male AD compared to the rest of the groups. *S24-7* showed an increase in female AD compared to male AD, and *Turicibacteraceae* was higher in male AD compared to female AD and female WT. At the genus level, the abundance of *Klebsiella* was higher in female AD compared to female WT and male-wild type, whereas *Lactobacillus* was higher in male AD compared to female AD. *Lactococcus* showed higher proportions in male AD compared to the other three groups, and *SMB53* showed a higher abundance in female WT compared to male WT and female AD, increasing its abundance in male AD in comparison to male WT mice.	**Working memory** was evaluated by the T maze, the percentage of spontaneous alternations was higher in control compared to AD mice. Male control also showed better working memory than AD male mice. In the **NOR**, impaired recognition memory was observed in both AD mice, as they presented lower discrimination indexes compared to their WT counterparts. Finally, spatial reference memory was evaluated in the Morris Water Maze (MWM). Average time to find the escape platform during all learning trials indicate that AD male mice had higher latencies compared to their WT counterparts.
Feng et al.[41]	Mice	*APP/PS1 (APPswe, PSEN1dE9)* at 7 months	In *APP/PS1* mice, the *Firmicutes/Bacteroidota* ratio was notably higher compared with WT mice. Beneficial bacteria such as *Candidatus saccharimonas* and *Rikenellaceae* decreased in *APP/PS1* mice. In addition, *Erysipelotrichaceae* and *Proteobacteria* increased in *APP/PS1* mice. Finally, changes in *Lactobacillus reuteri*, *Alistipes*, *Eryslpelotrichales*, *Gammaproteobacteria*, and *Burkholderiales* were also observed in the AD group.	The **spatial reference memory** in the MWM did not show differences between groups in escape latency, number of platform-site crossovers and effective-area crossovers. In addition, significant differences were observed in percent time and distance in the target quadrant, and latency to first target-site crossover.

(Continues)

TABLE 1 (Continued)

Source	*Population/ sample*	*AD model*	*Microbiota changes*	*Cognitive changes*
Jin et al.[42]	Mice	*APP/PS1 (APPswe, PSEN1dE9)* at 12 months	The prevalence of various bacterial taxa such as *Bacteroidales*, *Bacteroidia*, *Bacteroidetes*, *Prevotellaceae*, and *Prevotella* was elevated in 12-month-old *APP/PS1* mice. Conversely, there was a notable increase in the abundance of proinflammatory bacteria, including *Bacteroides*, *Prevotella*, and *Ruminococcus*, in these mice at 12 months of age, whereas certain beneficial gut bacteria such as *Akkermansia*, *Bifidobacterium*, and *Lactobacillus* exhibited a decrease.	The AD model exhibited lower scores in **spatial working memory** in the Y-maze, as well as in the **NOR task**; however, they showed similar performance in working memory tasks conducted in the MWM.
Li et al.[43]	Mice	*APP/PS1 (APPswe, PSEN1dE9)* at 2, 5, 10, and 12 months	The microbiota was categorized into three enterotypes. Enterotype 1 was characterized primarily by the presence of *Lactobacillus*, enterotype 2 by *Bacteroides*, and enterotype 3 by an over-representation of the *Lachnospiraceae NK4A136* group, which had an inverse relationship with *Lactobacillus* abundance. In the WT group, enterotype 1 was predominant in 2-month-old mice, whereas enterotype 2 appeared only in the 12-month-old mice. As the mice aged, the enterotypes transitioned from 1 to 3 and then to 2, suggesting that enterotype changes were driven by age. In the AD-prone (PAP) group, the shift from enterotype 1 to enterotype 2 occurred earlier, with enterotype 2 forming as early as 5 months.	When evaluating the **spatial working memory** in the Y maze, the analysis revealed that AD mice had a lower spontaneous change rate when compared to the age-matched WT mice, and the difference was highly significant.
Lorenzini et al.[44]	Mice	Transgenic Tg2576 mice at 2.5 months	The Tg2576 mice exhibit significant changes in gut microbiota compared to WT mice, including an increase in *Firmicutes* and *Lactobacillus*, and a decrease in *Clostridia_UCG-014*, *Dubosiella spp.*, and *Turicibacter spp.*	**MWM.** The Tg2576 mice showed severe impairment in both the acquisition phase and the probe trial compared to the WT mice. The Tg2576 mice traveled a slightly longer distance and at a somewhat higher speed than the WT mice, although these differences were not statistically significant.
Shen et al.[30]	Mice	*APP/PS1 (APPswe, PSEN1dE9)* at 3, 6, and 8 months	At the family and genus levels, the average abundance of *Helicobacteraceae* and *Desulfovibrionaceae* in *APP/PS1* mice was significantly higher than in WT mice. At the genus level, *Odoribacter*, *Helicobacter*, and *Prevotella* in *APP/PS1* mice were significantly more abundant compared to WT mice. Throughout the time points, there was a significant increase in *Coriobacteriaceae* in AD at 6 and 8 months compared to WT. In addition, *Ruminococcus* is significantly more abundant in WT mice than in *APP/PS1* mice at the genus level.	No differences were found in **spatial reference memory** at 3 months of age between the experimental groups. At 6 months of age, the escape latency of *APP/PS1* mice was significantly higher than WT, which worsened at 8 months. Likewise, the percentage of time in the target quadrant in *APP/PS1* mice decreased compared to WT mice, and this difference was more significant in the 8-month group.
Sun et al.[45]	Mice	*APP/PS1 (APPswe, PSEN1dE9)* at 4 months	*Libanicoccus massiliensis*, *Paraprevotella clara*, and *Lactobacillus amylovorus* were increased significantly in PAP mice, whereas *Turicibacter sanguinis*, *Dubosiella newyorkensis*, and *Prevotella oris* were greatly reduced.	AD mice demonstrated a lower percentage of spontaneous alternation in **Y maze**, as compared to WT mice. In the performance of **spatial reference memory** in the **MWM**, the escape latency of AD mice was significantly longer than that of WT mice. Furthermore, a significant decrease in both the frequency of platform crossings and time spent in the target quadrant was observed in AD mice compared to control mice.

(Continues)

TABLE 1 (Continued)

Source	*Population/ sample*	*AD model*	*Microbiota changes*	*Cognitive changes*
Wei et al.[46]	Mice	Triple transgenic 3xTg-AD (*PS1M146VA*, *PPSwe*, *TauP301L*) at 3, 6, and 9 months	At the phylum level, from 3 to 9 months of age, there was a decrease in the abundance of *Actinobacteriota*, *Verrucomicrobiota*, and *Acidobacteriota*. A decrease was observed for *Bacteroidota*, *Deferribacteres*, *Campylobacterota*, and *Proteobacteria* in 3×Tg-AD mice from 3 to 6 months of age, whereas at 9 months of age, a highest abundance of these phyla were detected for *Bacteroidota*, *Deferribacteres*, *Campylobacterota*, and *Proteobacteria*, respectively. *Firmicutes* were more abundant in 6-month-old 3×Tg- AD mice than at 3 months or 9 months. Similarly, *Desulfobacterota* were more abundant at 6 months vs 3 months or 9 months.	The **NOR** showed that the recognition index for new object location was decreased significantly in the 6- and 9-month-old AD mice. Analysis of the discrimination index show that the 9-month-old mice have significantly lower discrimination index than the WT mice. There were no significant differences in the speed of WT and 3×Tg mice in the three groups.
Yan et al.[47]	Rats	D-galactose/AlCl3 induced AD-like rats (130-150 g)	At the level of phylum, the top five phyla were *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Bacteroidetes*, and *TM7*. There were no significant differences between groups in relative abundance in the top five phyla. At the genus level, *Psychrobacter*, *Enterococcus*, and *Aerococcus* accounted for 50% of the community in the control group, whereas in the AD group, *Aerococcus* constituted 81.98%.	The **spatial reference memory** measured in the MWM showed that the escape latency of the AD group was increased significantly from day 2 to day 4 when compared with the control group. In addition, the track of rats in the control group was concentrated mainly in and around the target quadrant (the first quadrant), whereas rats in the AD group moved disorderly or presented marginal movement, and rarely enter the target quadrant. Moreover, the AD group had a significantly decreased number of times across the platform than the control group.

for animal studies without treatment and in Table S1 for those with treatment.

3.4 | Meta-analysis

3.4.1 | Evaluation of cognition in human studies

A total of $k = 7$ studies were included in the analysis of participants' cognitive impairment measured with the MoCA, the MMSE, and the CDR. Among them, a total of $k = 5$ studies assessed cognitive impairment with the MMSE. The results showed SMDs ranged from −2.94 to −2.44, with all of them being negative. The results were shown to be heterogeneous ($Q_{(4)} = 14.37$, $p = 0.006$, $tau^2 = 0.06$, $I^2 = 73.87\%$). Significant differences were found in MMSE ($Z = -20.79$; $p < 0.001$). On the other hand, a total of $k = 4$ studies examined cognitive impairment with the MoCA. The observed SMDs ranged from −3.53 to −2.11, with all of them negative. The results were not shown to be heterogeneous ($Q_{(3)} = 0.89$, $p = 0.83$, $tau^2 = 0.00$, $I^2 = 0.00\%$). Significant differences were found in MoCA ($Z = -41.88$; $p < 0.001$). Similar results were found with the CDR, which included a total of $k = 3$ studies. The observed SMDs ranged from 1.90 to 4.56, all of which were positive. The results were shown to be heterogeneous ($Q_{(2)} = 65.95$, $p < 0.001$, $tau^2 = 1.16$, $I^2 = 98.23\%$). Significant differences were found in CDR ($Z = 4.76$; $p < 0.001$) (Figure S1).

3.4.2 | Evaluation of microbiota in human studies

The impact of AD on **bacterial phyla** was evaluated by analyzing *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* (see Table 2).

For *Firmicutes*, data from four studies ($k = 5$) were analyzed. The log odds ratios ranged from −1.0448 to 0.2961, with no detected heterogeneity ($Q_{(4)} = 3.30$, $p = 0.51$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The overall effect was not statistically significant ($Z = -1.0448$, $p = 0.2961$), suggesting that AD does not significantly alter *Firmicutes* levels. In the case of *Bacteroidetes*, four studies ($k = 5$) were examined. The log odds ratios ranged from −0.5107 to 0.3565, with moderate heterogeneity ($Q_{(4)} = 8.39$, $p = 0.0784$; $tau^2 = 0.1041$, $I^2 = 44.25\%$). The overall effect was not significant ($Z = -0.3485$, $p = 0.7275$), indicating no significant impact of AD on Bacteroidetes. For *Proteobacteria*, two studies ($k = 3$) provided data. Log odds ratios ranged from −0.6126 to 1.5042, with significant heterogeneity ($Q_{(2)} = 6.0208$, $p = 0.0493$; $tau^2 = 0.5777$, $I^2 = 66.60\%$). The overall effect was not significant ($Z = 0.9622$, $p = 0.3360$), suggesting no notable impact of AD on *Proteobacteria* levels.

TABLE 2 Description of gut microbiota changes in AD and the associated cognitive changes in patients with AD found in the described peer-reviewed studies.

Source	*AD model*	*Microbiota changes*	*Cognitive changes*
Grabrucker et al.[26]	Sixty-four patients diagnosed with AD (61% female) with a mean age of 71.4 ± 7.9 years. Sixty-nine healthy controls (53% female) with a mean age of 74.8 ± 7.3 years.	At the phylum level, patients with AD showed a higher abundance of *Bacteroidetes*, which includes many proinflammatory species, and a lower abundance of the phyla *Firmicutes* and *Verrucomicrobiota* compared to controls. At the genus level, AD patients had a significant reduction in the abundance of *Clostridium sensu stricto 1* and *Coprococcus* compared to controls. In addition, the pathobiont genus *Desulfovibrio* was significantly increased in AD patients compared to controls.	**MMSE** showed that patients with AD had a lower score than healthy controls.
Guo et al.[38]	Twenty AD and 20 healthy participants who were 60 years old.	Patients with AD had decreased *Bacteroides*, *Lachnospira*, and *Ruminiclostridium_9* and increased *Prevotella* at the genus level compared with healthy controls.	AD patients had lower **MMSE** and **MoCA** scores.
Hazan[15]	A case of an 82-year-old man with AD who underwent two FMTs.	Erradication of *Clostridioides difficile* infection after FMT at the 2-month follow-up visit was reported.	**MMSE** scored 20, indicating mild cognitive impairment with significant impairments in the areas of memory and semantic language abilities, nonverbal learning, and divided attention and response inhibition. at the pre-FMT stage. MMSE scored 26 at the post-FMT stage indicating normal cognition at 2 months follow-up visit and 29 at 6 months post-FMT.
Khedr et al.[48]	Twenty-five patients diagnosed with AD (44% female) with a mean age of 68.92 ± 7.56 years. Twenty-five healthy controls (44% female) with a mean age of 66.76 ± 8.8 years.	In the AD group, a greater abundance of bacterial species, including *Akkermansia*, *Enterobacteria*, *Bacteroidetes*, *Bacillus cereus*, *Prevotella*, and *Clostridium cluster IV*, was found compared to the control group. However, in the AD group, the abundance of *Bifidobacterium*, *Firmicutes*, and *Actinobacteria* was significantly lower.	Patients with AD had lower **MMSE** and **MoCA** scores.
Kim et al.[36]	Five patients with AD (two men and three women) with a mean age of 74 years. FMT.	There was an increase in *Bacteroidaceae* and a decrease in *Enterococcaceae* when comparing pre- and post-FMT. The abundance of each genus before and after the transplantation showed that the proportions of *Bacteroides*, *Parabacteroides*, *Alistipes*, *Tannerella*, and Actinobacteria were relatively enriched in fecal samples after FMT. By contrast, *Enterococcus* proportions were reduced after FMT compared to before.	**MMSE and MoCA** showed an increase in scores in the AD after FMT that was maintained over time up to 3 months. **CDR-SB** scores decreased post-FMT and were maintained up to 3 months in all patients.
Laske et al.[22]	Seventy-five amyloid-positive AD patients and 100 cognitively healthy controls.	At the genus level, higher levels in the healthy controls were found in *Aliivibrio*, *Propionibacterium*, *Orrella*, *Veillonella*, *Muchinivorans*, *Paenarthrobacter*, *Plesiomonas*, *Roseovariusm Lactococcus*, and Su*lfuricella*. The patients with AD showed increased *Moritella*, *Parabacteroides*, *Basfia*, *Arsenophoonus*, *Acidothermus*, *Sureimonas*, *Candidatus Arthromitus*, and *Asaia*. At the phylum level, higher levels in healthy controls were found in *Preoteobacteria*, *Actinobacteria*, *Firmicutes*, and *Bacteroidetes*; whereas in the patients with AD the higher levels were found in *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, and *Firmicutes*.	**MMSE** showed that patients with AD had a lower score than healthy controls.

(Continues)

TABLE 2 (Continued)

Source	*AD model*	*Microbiota changes*	*Cognitive changes*
Li et al.[37]	Thirty patients with AD age- and gender-matched with normal control subjects	The abundance of 7 genera in the fecal microbiota (*Lactobacillus*, *Akkermansia*, *Dorea*, *Bifidobacterium*, *Streptococcus*, *Acinetobacter*, and *Blautia*) was higher in the AD group, whereas the abundance of 11 genera (*Parabacteroides*, *Alistipes*, *Bacteroides*, *Alloprevotella*, *Haemophilus*, *Paraprevotella*, *Succinivibrio*, *Sutterella*, *Prevotella*, *Barnesiella*, and *Butyricimonas*) was lower. After adjusting for possible confounding factors (age, gender, BMI, and constipation) 11 genera in the feces increased in AD: *Dorea*, *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Blautia*, and *Escherichia*; and decreased in AD: *Alistipes*, *Bacteroides*, *Parabacteroides*, *Sutterella*, and *Paraprevotella*.	**MMSE** showed that patients with AD had a lower score than normal controls.
Liu et al.[5]	Thirty-three patients with AD (14 women and 19 men) with a mean age of 74.85 years. Thirty-two healthy control patients (16 women and 16 men) with a mean age of 76.88 years.	Compared to the control group, patients with AD exhibited a marked decrease in the relative abundance of *Firmicutes*. Meanwhile, *Proteobacteria* were highly enriched in AD patients compared to the control group. Unexpectedly, *Bacteroidetes* decreased in the AD group to the normal level. The decrease in *Firmicutes* in patients with AD was primarily explained by the reduced abundance in three families: *Lachnospiraceae* and *Ruminococcaceae* compared to controls. Particularly, the most abundant genera *Blautia* and *Ruminococcus* of the *Firmicutes* phylum also exhibited a reduction in AD compared to controls. There was a prevalence of *Enterobacteriales* and the *Enterobacteriaceae* family in the control group compared to AD.	**MoCA**: Patients with AD had significantly lower scores in visuospatial/executive function, naming, attention, language, and orientation compared to the control groups. Only patients with AD had reduced abstraction function scores. In addition, patients with AD had lower scores in delayed recall function compared to control patients. **MMSE**: Scores were lower in the AD groups than in the controls.
Park et al.[16]	A case of a 90-year-old woman with AD who underwent two FMTs.	Decrease in *Clostridioides difficile* infection after the second FMT.	**MMSE, MoCA, and CDR** scores improved immediately after the first FMT, with an increasement over her results after the second FMT.
Verhaar et al.[24]	A total of 170 patients from the Amsterdam Dementia Cohort, comprising 33 with AD dementia (with a mean age of 66 ± 8 years, 46% female), 21 with mild cognitive impairment (MCI) (64 ± 8 years, 43% female), and 116 with subjective cognitive decline (SCD) (62 ± 8 years, 44% female).	Higher abundance of *Clostridium leptum* and lower abundance of *Eubacterium ventriosum* group spp., *Lachnospiraceae* spp., *Marvinbryantia* spp., *Monoglobus* spp., *Ruminococcus torques* group spp., *Roseburia hominis*, and *Christensenellaceae R-7* spp., was associated with higher odds of amyloid positivity. We found associations between lower abundance of *Lachnospiraceae* spp., *Lachnoclostridium* spp., *Roseburia hominis*, and *Bilophila wadsworthia* and a higher odds of positive phosphorylated tau status.	**MMSE** scores where higher than 16 for all the three groups; however, the AD groups showed significantly lower scores compared to MCI and SCD, whereas MCI showed increased scores compared to AD only,
Wanapaisan et al.[49]	Twenty AD and 20 healthy participants who were 70 years of age	The significantly higher abundance of bacteria in non-dementia patients belonged to the *Clostridiales* order, including *Clostridium sensu stricto* 1, *Fusicatenibacter*, *Lachnospiraceae*, *Agathobacter*, and *Fecalibacterium*. In contrast, *Escherichia*, *Shigella*, *Bacteroides*, *Holdemanella*, *Romboutsi*, and *Megamonas* were the dominant genera in the AD group.	The **Thai Mental Status Exam (TMSE)** was lower in AD patients compared to normal cognitive healthy controls.
Yamashiro et al.[35]	Cognitively normal control (NC) ($n = 19$), and AD ($n = 18$) groups, ages 79 to 82.	*Anaerostipes*, *Roseburia*, *Lachnospiraceae UCG-004*, *Ruminococcaceae UCG-013*, and *[Ruminococcus] gnavus* group were significantly lower in the AD group than in the NC group. Conversely, *Eisenbergiella* was significantly higher in the AD group than in the NC group.	MMSE, MoCA, ADAS-Cog, and CDR-SB scores were significantly different among the groups, with lower scores in the AD group in the MMSE and MoCA, whereas higher scores were obtained in the AD group for the ADAS-Cog and CDR-SB compared to NC subjects.

(Continues)

TABLE 2 (Continued)

Source	*AD model*	*Microbiota changes*	*Cognitive changes*
Zhou et al.[50]	Sixty AD patients and 32 sex- and age-matched healthy controls	Genus *Bifidobacterium* and species *Actinomyces viscosus* from *Actinobacteria*; genus *Sphingomonas*, *Bilophila*, and *Neorhizobium* all from *Proteobacteria*; and genus *Flavobacterium*, *Moheibacter*, *Lactobacillus*, *Weissella*, *Blautia*, *Clostridium XlVa*, and *Solobacterium* were significantly enriched in the feces of patients with AD compared with the HC group, whereas the genera *Odoribacter*, *Eubacterium*, *Anaerobacterium*, and *Papillibacter* were significantly enriched in the HC group compared to the AD group.	The AD group had significantly lower **MMSE** scores and higher **CDR** than those of the HC group.
Zhu et al.[25]	Ninety-four NC participants were recruited from the Shanghai Aging Study (SAS) and 83 patients with AD from the Shanghai Memory Study (SMS)	Patients with AD had increased bacterial taxa including *Erysipelatoclostridiaceae*, *Erysipelotrichales*, *Patescibacteria*, *Saccharimonadales*, and *Saccharimonadia*, compared with the NC group.	A gradual worsening in **ADL, CDR, MMSE, MoCA**, and cognitive performance in various domains (Z_memory, Z_attention, Z_visuospatial, Z_executive, and Z_language) was observed.
Zhuang et al.[51]	Forty-three patients with AD and 43 age- and gender- matched controls with normal cognition.	At the phylum level, *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* were the dominant bacteria. A mild decrease was observed in the abundance of *Bacteroidetes* among AD patients, whereas *Actinobacteria* were slightly more abundant. Although *Verrucomicrobia* decreased in AD patients, the difference was not statistically significant. *Firmicutes* were almost the same between the two groups. At the class level, *Clostridia*, *Gammaproteobacteria*, *Bacteroidia*, *Bacilli*, *Negativicutes*, and *Actinobacteria* were the dominant bacteria. We found that the relative abundance of *Actinobacteria* and *Bacilli* increased, whereas that of *Negativicutes* and *Bacteroidia* decreased significantly in the AD group compared with the control group. At the family level, *Lachnospiraceae*, *Ruminococcaceae*, *Enterobacteriaceae*, *Bacteroidaceae*, *Veillonellaceae*, *Erysipelotrichaceae*, and *Enterococcaceae* were the dominant bacteria. In patients with AD, the relative abundance of *Ruminococcaceae*, *Enterococcaceae*, and *Lactobacillaceae* increased, whereas that of *Lanchnospiraceae*, *Bacteroidaceae*, and *Veillonellaceae* decreased significantly compared with the control group.	**MMSE and CDR** showed significant differences between groups where the AD group had lower scores than the normal control subjects. **ADL** showed significant differences with increased scores in the AD group.

Subsequent analyses focused on **bacterial genera**, including *Agathobacter*, *Escherichia Shigella*, *Prevotella*, *Fusicatenibacter*, *Blautia*, *Faecalibacterium*, and *Bacteroides*. For *Agathobacter*, two studies ($k = 2$) revealed log odds ratios from −5.1613 to 1.8620, with significant heterogeneity ($Q_{(1)} = 4.1617$, $p = 0.0413$). The overall effect was not significant ($Z = -0.9207$, $p = 0.3572$), indicating no significant impact of AD. *Escherichia Shigella* was analyzed in three studies ($k = 3$), with log odds ratios from −1.0548 to 5.7507 and significant heterogeneity ($Q_{(2)} = 43.3510$, $p < 0.0001$). The overall effect was not significant ($Z = 1.3524$, $p = 0.1763$), suggesting no significant impact of AD. *Prevotella* was examined in two studies ($k = 2$), showing log odds ratios from −1.8515 to 3.6904, with significant heterogeneity ($Q_{(1)} = 4.2344$, $p = 0.0396$). The overall effect was not significant ($Z = 0.6504$, $p = 0.5154$), indicating no significant impact of AD. For *Fusicatenibacter*, two studies ($k = 2$) showed log odds ratios from −1.1355 to 0.1662, with no heterogeneity detected ($Q_{(1)} = 0.0705$, $p = 0.7906$). The overall effect was not significant ($Z = -1.4594$, $p = 0.1445$), suggesting no significant impact of AD. *Faecalibacterium*, analyzed in two studies ($k = 2$), had log odds ratios from −2.7802 to 1.1806, with significant heterogeneity ($Q_{(1)} = 4.7669$, $p = 0.0290$). The overall effect was not significant ($Z = -0.7915$, $p = 0.4286$), indicating no significant impact of AD. *Blautia* was assessed in two studies ($k = 2$), with log odds ratios from −1.0659 to 0.6853, and no detected heterogeneity ($Q_{(1)} = 0.6622$, $p = 0.4158$). The overall effect was not significant ($Z = -0.4259$, $p = 0.6701$), suggesting no significant impact on *Blautia*. Finally, *Bacteroides* was analyzed in three studies ($k = 3$), showing log odds ratios from −1.9405 to −0.0407, with significant heterogeneity ($Q_{(2)} = 7.9826$, $p = 0.0185$). A significant impact of AD was found

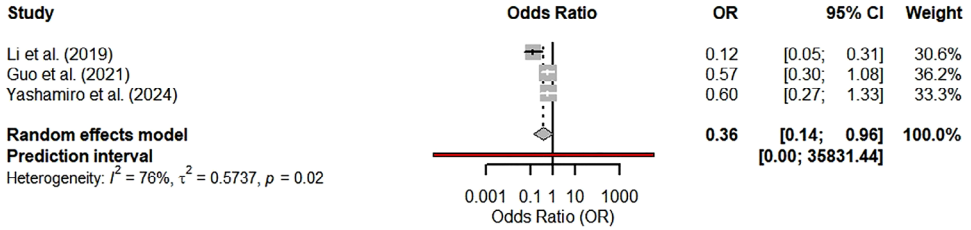

FIGURE 2 Meta-analysis using a random-effects model of selected studies for the *Bacteroides* changes in the human microbiota when comparing AD versus healthy subjects. The plot shows the effect estimates and corresponding CIs for each study included in the meta-analysis. The relative weight or contribution of each study to the overall effect estimate is also included in percentages. The overall weighted effect is indicated by a diamond at the bottom of the figure. The figure was generated with R software version 4.3.1. AD, Alzheimer's disease; CI, confidence interval.

($Z = -2.0439$, $p = 0.0410$), indicating that AD significantly affects *Bacteroides* levels (see Figure 2).

Further analysis focused on **bacterial families**: *Lachnospiraceae*, *Ruminococcaceae*, and *Enterobacteriaceae*. Two studies ($k = 2$) examined *Lachnospiraceae*, with log odds ratios ranging from −0.7782 to 0.1571, and no heterogeneity ($Q_{(1)} = 0.0329$, $p = 0.8561$). The overall effect was not significant ($Z = -1.3015$, $p = 0.1931$), suggesting no impact of AD. For *Ruminococcaceae*, two studies ($k = 2$) reported log odds ratios from −1.1284 to 1.0861, with moderate heterogeneity ($Q_{(1)} = 3.6845$, $p = 0.0549$). The overall effect was not significant ($Z = -0.0375$, $p = 0.9701$), indicating no significant impact of AD. *Enterobacteriaceae*, also analyzed in two studies ($k = 2$), had log odds ratios from −1.2137 to 3.4319, with heterogeneity detected ($Q_{(2)} = 7.2137$, $p = 0.0072$). The overall effect was not significant ($Z = 0.9358$, $p = 0.3494$), suggesting no significant impact of AD.

Finally, **bacterial orders** *Bacteroidales*, *Bifidobacteriales*, *Clostridiales*, *Enterobacteriales*, *Erysipelotrichales*, *Lactobacillales*, and *Verrucomicrobiales* were analyzed. *Bacteroidales*, studied in two studies ($k = 2$), showed log odds ratios from −1.0461 to 0.0280, with no heterogeneity ($Q_{(1)} = 0.1871$, $p = 0.6654$). The overall effect was not significant ($Z = -1.8577$, $p = 0.0632$), suggesting no significant impact of AD. *Bifidobacteriales*, also analyzed in two studies ($k = 2$), had log odds ratios from −0.5824 to 2.2188, and no heterogeneity ($Q_{(1)} = 0.4720$, $p = 0.4921$). The overall effect was not significant ($Z = 1.1450$, $p = 0.2522$), indicating no significant impact of AD. *Clostridiales*, with two studies ($k = 2$), had log odds ratios from −3.4765 to 1.2506, with significant heterogeneity ($Q_{(2)} = 26.1115$, $p < 0.0001$). The overall effect was not significant ($Z = -0.9229$, $p = 0.3561$), suggesting no significant impact of AD. *Enterobacteriales*, studied in two studies ($k = 2$), had log odds ratios from −0.9671 to 0.3318, with no heterogeneity ($Q_{(1)} = 0.5525$, $p = 0.4573$). The overall effect was not significant ($Z = -0.9585$, $p = 0.3378$), suggesting no significant impact of AD. *Erysipelotrichales*, also analyzed in two studies ($k = 2$), showed log odds ratios from −1.1100 to 1.5627, and no heterogeneity ($Q_{(1)} = 0.0922$, $p = 0.7614$). The overall effect was not significant ($Z = 0.3320$, $p = 0.7399$), indicating no significant impact of AD. *Lactobacillales*, studied in two studies ($k = 2$), had log odds ratios from −0.1828 to 1.7105, with no heterogeneity ($Q_{(1)} = 0.7965$, $p = 0.3721$). The overall effect was not significant ($Z = 1.5815$, $p = 0.1138$), suggesting no significant impact of AD. Finally, *Verrucomicrobiales*, with two studies ($k = 2$), had log odds ratios from −0.4652 to 2.3133, and no heterogeneity ($Q_{(1)} = 0.7352$, $p = 0.3912$). The overall effect was not significant ($Z = 1.3036$, $p = 0.1924$), indicating no significant impact of AD.

3.4.3 | Evaluation of cognition in animal studies

The escape latency in the MWM test was analyzed on the first and last days of testing across two age groups of animals: those 0–5 months of age (early-stage AD) and those 6 months of age or older (late-stage AD).

For animals younger than 5 months, nine studies ($k = 9$) assessed escape latency on the first day. The SMDs ranged from 1.0219 to 3.4614, all positive, indicating significant heterogeneity ($Q_{(8)} = 231.0065$, $p < 0.001$, $tau^2 = 3.1911$, $I^2 = 97.67\%$). A significant increase in latency was observed ($Z = 3.6020$, $p = 0.0003$), suggesting that early-stage AD leads to higher escape latency. On the last day, eight studies ($k = 8$) reported similar findings, with SMDs ranging from 1.1365 to 3.7942. Again, high heterogeneity was noted ($Q_{(7)} = 229.7663$, $p < 0.001$, $tau^2 = 3.3423$, $I^2 = 95.75\%$), and significant differences in escape latency persisted ($Z = 3.6362$, $p = 0.0003$) (Figure S2).

For animals 6 months or older, 11 studies ($k = 11$) examined escape latency on the first day, showing SMDs from 0.0565 to 3.4442, with 90.9% positive. The results indicated high heterogeneity ($Q_{(10)} = 347.6264$, $p < 0.0001$, $tau^2 = 8.0136$, $I^2 = 99.28\%$) and a significant effect on escape latency ($Z = 2.0254$, $p = 0.0428$). On the last day, 14 studies ($k = 14$) revealed SMDs from 1.1205 to 3.2175, with 85.71% positive. High heterogeneity persisted ($Q_{(13)} = 367.7692$, $p < 0.0001$, $tau^2 = 3.6851$, $I^2 = 97.90\%$), with a significant overall effect ($Z = 4.0545$, $p < 0.0001$), indicating a substantial impact of AD on escape latency (Figure S3).

Similar trends were observed for the crossing times of the target in the MWM. Six studies ($k = 6$) focused on rats of 5 months or younger, with negative effect sizes ranging from −4.8232 to −1.4277, indicating high heterogeneity ($Q_{(5)} = 35.6162$, $p < 0.0001$, $tau^2 = 3.8767$, $I^2 = 88.94\%$). A significant effect was found ($Z = -3.6082$, $p = 0.0003$), suggesting a notable impact on crossing times. For older rats, 10 studies ($k = 10$) measured the percentage of time spent in the target zone, with effect sizes ranging from −2.7846 to −0.1560, 80% of which were

negative. High heterogeneity was again observed ($Q_{(9)}$ = 101.4617, $p < 0.0001$, tau^2 = 4.1093, I^2 = 93.32%), with significant differences detected ($Z = -2.1926$, $p = 0.0283$) (Figure S4).

For the percentage of time spent in the target zone, five studies (k = 5) on younger rats reported negative effect sizes ranging from −3.0564 to −0.5904, with high heterogeneity ($Q_{(4)}$ = 34.1630, $p < 0.0001$, tau^2 = 1.6603, I^2 = 85.61%). A significant overall effect was noted (Z = −2.8985, p = 0.0037) (Figure S5). For older rats, six studies (k = 6) indicated mixed effect sizes ranging from −3.1560 to 2.0010, with no significant overall effect (Z = −0.4390, p = 0.6607), despite high heterogeneity ($Q_{(9)} = 133.2347$, $p < 0.0001$, $tau^2 = 8.5881$, $I^2 = 99.28\%$).

Regarding the time spent on the target in the MWM, five studies (k = 5) on older rats reported negative effect sizes ranging from −6.2290 to −2.6225, with high heterogeneity ($Q_{(5)}$ = 107.5815, $p < 0.0001$, tau^2 = 4.1088, I^2 = 90.02%). A significant impact of AD was observed (Z = −4.8103, $p < 0.0001$) (Figure S5). For alternation performance in the Y maze, five studies (k = 5) on older rats showed a range of effect sizes from −2.8990 to 0.2587, with high heterogeneity ($Q_{(5)} = 58.0289$, $p < 0.0001$, $tau^2 = 3.0616$, $I^2 = 95.88\%$). However, no significant overall effect was found ($Z = -1.6388$, $p = 0.1013$).

Finally, in the analysis of recognition memory using the Novel Object Recognition (NOR) index, four studies ($k = 4$) on younger rats revealed effect sizes ranging from −3.0621 to 3.2705, with high heterogeneity ($Q_{(3)}$ = 37.4067, $p < 0.0001$, tau^2 = 9.9661, I^2 = 98.69%). No significant impact of AD on recognition memory was observed (Z = 0.0645, p = 0.9486). Similarly, in older rats, NOR analysis across two studies showed no significant overall effect (Z = −0.4405, p = 0.6596) despite substantial heterogeneity ($Q_{(1)}$ = 49.1036, $p < 0.0001$, tau^2 = 6.0346, I^2 = 97.96%).

3.4.4 | Evaluation of microbiota in animal studies

The analyses of changes in microbiota in animal models of AD have not yielded significant results for any of the bacterial populations. The results of this section are detailed in Appendix S1.

3.4.5 | Changes in microbiota after an intervention

The different applied treatments focused on microbiota and AD will be considered in the following section. These include prebiotics, probiotics, exercise, diet, and natural therapeutic agents in animal models (Table S1).

Probiotics

The analysis focused on changes in **bacterial phyla** after a probiotic treatment in AD animal models included *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*.

A total of k = 8 studies were included in the analysis, focusing on measuring *Firmicutes*. The estimated heterogeneity was significant ($Q_{(7)}$ = 49.2405, $p < 0.0001$; tau^2 = 0.5632, I^2 = 85.25%), indicating high variability among the studies. The estimated log odds ratio ranged from −0.1047 to 1.0240. The overall effect estimate was not significant (Z = 1.5964; p = 0.1104), suggesting that there was no significant impact of the intervention on *Firmicutes* levels in AD animal models after a probiotic treatment.

A total of k = 8 studies were included in the analysis, focusing on measuring *Bacteroidetes*. The results indicated high heterogeneity ($Q_{(7)}$ = 47.1989, $p < .0001$; tau^2 = 0.6293, I^2 = 86.69%). The estimated log odds ratio ranged from −0.9853 to 0.2082. The overall effect estimate was not significant (Z = −1.2761; p = 0.2019), suggesting that there was no significant impact of the intervention on *Bacteroidetes* levels in AD animal models after a probiotic treatment.

A total of k = 6 studies were included in the analysis, focusing on measuring *Proteobacteria*. The estimated heterogeneity was not significant ($Q_{(5)} = 1.1752$, $p = 0.5132$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.4605 to 0.9403. The overall effect estimate was not significant ($Z = 0.6713$; $p = 0.5021$), suggesting that there was no significant impact of the intervention on *Proteobacteria* levels in AD animal models after a probiotic treatment.

A total of k = 3 studies were included in the analysis, focusing on measuring *Actinobacteria*. The results indicated no heterogeneity ($Q_{(2)}$ = 1.2322, p = 0.5401; tau^2 = 0.00, I^2 = 0.00%). The estimated log odds ratio ranged from −1.2815 to 0.5124. The overall effect estimate was not significant ($Z = -0.8403$; $p = 0.4007$), suggesting that there was no significant impact of the intervention on *Actinobacteria* levels in AD animal models after a probiotic treatment.

A total of k = 2 studies were included in the analysis, focusing on measuring *Verrucomicrobia*. The results indicated no heterogeneity ($Q_{(1)}$ = 0.1808, p = 0.6707; tau^2 = 0.00, I^2 = 0.00%). The estimated log odds ratio ranged from −1.9313 to 0.5268. The overall effect estimate was not significant ($Z = -1.1199$; $p = 0.2627$), suggesting that there was no significant impact of the intervention on *Verrucomicrobia* levels in AD animal models after a probiotic treatment.

On the other hand, the analysis focused on changes in **bacterial genera**, specifically *Bacteroides* and *Prevotella*, following the administration of a probiotic in AD animal models.

A total of k = 2 studies were included in the analysis, focusing on measuring *Bacteroides*. The results indicated low heterogeneity ($Q_{(1)}$ = 1.1318, p = 0.2874; tau^2 = 0.0549, I^2 = 11.65%). The estimated log odds ratio ranged from −0.2450 to 1.3749. The overall effect estimate was not significant ($Z = 1.3670$; $p = 0.1716$), suggesting that there was no significant impact of the intervention on *Bacteroides* levels in AD animal models after a probiotic treatment.

A total of k = 2 studies were included in the analysis, focusing on measuring *Prevotella*. The results indicated low heterogeneity ($Q_{(1)}$ = 0.8749, p = 0.3496; tau^2 = 0.00, I^2 = 0.00%). The estimated log odds ratio ranged from −0.2450 to 1.3749. The overall effect estimate was significant (Z = −2.3591; p = 0.0183), suggesting that there was a significant impact of the intervention on *Prevotella* levels in AD animal models after a probiotic treatment (Figure 3).

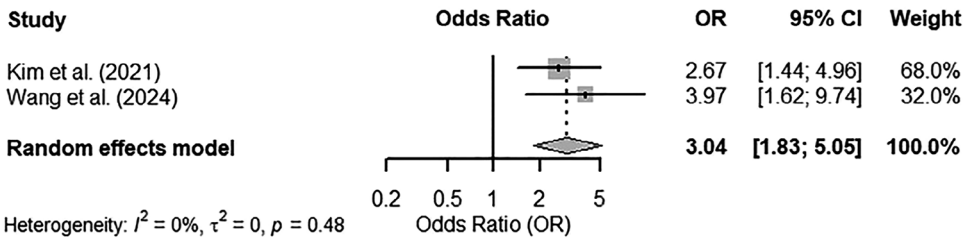

FIGURE 3 Meta-analysis using a random-effects model of selected studies for the *Prevotella* changes in the animal microbiota after a treatment with natural therapeutic agents. The plot shows the effect estimates and corresponding CIs for each study included in the meta-analysis. The relative weight or contribution of each study to the overall effect estimate is also included in percentages. The overall weighted effect is indicated by a diamond at the bottom of the figure. The figure was generated with R software version 4.3.1. CI, confidence interval.

Prebiotics

The analysis focused on changes in **bacterial phyla** after a prebiotic treatment in AD animal models included *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Firmicutes*. The estimated heterogeneity was significant ($Q_{(2)} = 7.5011$, $p = 0.0235$; $tau^2 = 0.2360$, $I^2 = 72.91\%$), indicating a moderate variability among the studies. The estimated log odds ratio ranged from −0.7039 to 0.5839. The overall effect estimate was not significant ($Z = -0.1826$; $p = 0.8551$), suggesting that there was no significant impact of the prebiotics on *Firmicutes* levels in AD animal models.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Bacteroidetes*. The results indicated no heterogeneity ($Q_{(4)} = 1.5097$, $p = 0.4701$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.5583 to 0.1760. The overall effect estimate was not significant ($Z = -1.0206$; $p = 0.3074$), suggesting that there was no significant impact of the intervention on *Bacteroidetes* levels in AD animal models.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Proteobacteria*. The results indicated no heterogeneity ($Q_{(4)} = 0.1409$, $p = 0.9320$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.4962 to 1.3532. The overall effect estimate was not significant ($Z = 0.9083$; $p = 0.3637$), suggesting that there was no significant impact of the prebiotic intervention on *Proteobacteria* levels in AD animal models.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Actinobacteria*. The results indicated no heterogeneity ($Q_{(2)} = 0.1792$, $p = 0.9143$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −1.4702 to 0.6436. The overall effect estimate was not significant ($Z = -0.7664$; $p = 0.4434$), suggesting that there was no significant impact of the intervention on *Actinobacteria* levels in AD animal models.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Verrucomicrobia*. The results indicated no heterogeneity ($Q_{(2)} = 0.3654$, $p = 0.8330$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −2.4264 to 1.0947. The overall effect estimate was not significant ($Z = -0.7413$; $p = 0.4585$), suggesting that there was no significant impact of the prebiotics on *Verrucomicrobia* levels in AD animal models.

On the other hand, the analysis focused on changes in **bacterial genera** after a prebiotic treatment in AD animal models included only *Lactobacillus* ($k = 2$) studies. The results indicated low heterogeneity ($Q_{(1)} = 1.5212$, $p = 0.2174$; $tau^2 = 0.6516$, $I^2 = 34.26\%$). The estimated log odds ratio ranged from −1.5616 to 1.4525. The overall effect estimate was not significant ($Z = -0.0710$; $p = 0.9434$), suggesting that there was no significant impact of the intervention on *Lactobacillus* levels in AD animal models after a treatment with prebiotics.

Exercise

The analysis focused on changes in **bacterial phyla** after exercise in AD animal models including *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Firmicutes*. The estimated heterogeneity was significant ($Q_{(2)} = 53.0169$, $p < 0.0001$; $tau^2 = 5.3585$, $I^2 = 96.60\%$), indicating high variability among the studies. The estimated log odds ratio ranged from −4.1336 to 1.2055. The overall effect estimate was not significant ($Z = -1.0749$; $p = 0.2824$), suggesting that there was no significant impact of the intervention on *Firmicutes* levels in AD animal models after exercise.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Bacteroidetes*. The results indicated moderate heterogeneity ($Q_{(2)} = 4.7657$, $p = 0.0923$; $tau^2 = 0.1306$, $I^2 = 58.81\%$). The estimated log odds ratio ranged from −0.3585 to 0.7084. The overall effect estimate was not significant ($Z = 0.6429$; $p = 0.5203$), suggesting that there was no significant impact of the intervention on *Bacteroidetes* levels in AD animal models after exercise.

A total of $k = 2$ studies were included in the analysis, focusing on measuring *Proteobacteria*. The estimated heterogeneity was not significant ($Q_{(1)} = 0.4275$, $p = 0.5132$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.5303 to 1.5617. The overall effect estimate was not significant ($Z = 0.9663$; $p = 0.3339$), suggesting that there was no significant impact of the intervention on *Proteobacteria* levels in AD animal models after exercise.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Actinobacteria*. The results indicated no heterogeneity ($Q_{(2)} = 1.5016$, $p = 0.4720$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −1.9357 to 1.5285. The overall effect estimate was not significant ($Z = -0.2304$; $p = 0.8178$), suggesting that there was

no significant impact of the intervention on *Actinobacteria* levels in AD animal models after exercise.

A total of $k = 3$ studies were included in the analysis, focusing on measuring *Verrucomicrobia*. The results indicated high heterogeneity ($Q_{(2)} = 10.3548$, $p = 0.0056$; $tau^2 = 4.2268$, $I^2 = 85.86\%$). The estimated log odds ratio ranged from −2.0021 to 3.0623. The overall effect estimate was not significant ($Z = 0.4103$; $p = 0.6816$), suggesting that there was no significant impact of the intervention on *Verrucomicrobia* levels in AD animal models after exercise.

Natural therapeutic agents

On the other hand, the analysis focused on changes in **bacterial phyla**, specifically *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*, following the administration of a natural therapeutic agent in AD animal models.

A total of $k = 4$ studies were included in the analysis, focusing on measuring *Firmicutes*. The estimated heterogeneity was moderate ($Q_{(3)} = 6.1902$, $p = 0.1027$; $tau^2 = 0.1021$, $I^2 = 51.63\%$), indicating high variability among the studies. The estimated log odds ratio ranged from −0.9173 to −0.0450. The overall effect estimate was significant ($Z = -2.1623$; $p = 0.0306$), suggesting that there was a significant impact of the intervention on *Firmicutes* levels in AD animal models after treatment with natural therapeutic agents (Figure 4A).

A total of $k = 5$ studies were included in the analysis, focusing on measuring *Bacteroidetes*. The results indicated moderate heterogeneity ($Q_{(4)} = 7.5199$, $p = 0.1108$; $tau^2 = 0.0806$, $I^2 = 46.92\%$). The estimated log odds ratio ranged from 0.1302 to 0.8573. However, the overall effect estimate was significant ($Z = 2.6619$; $p = 0.0078$), suggesting that there was a significant impact of the intervention on *Bacteroidetes* levels in AD animal models after treatment with natural therapeutic agents (Figure 4B).

A total of $k = 5$ studies were included in the analysis, focusing on measuring *Proteobacteria*. The results indicated high heterogeneity ($Q_{(4)} = 28.2995$, $p < .0001$; $tau^2 = 10.2705$, $I^2 = 91.05\%$). The estimated log odds ratio ranged from −4.4924 to 1.4777. The overall effect estimate was not significant ($Z = -0.9897$; $p = 0.3223$), suggesting that there was no significant impact of the natural therapeutic agents on *Proteobacteria* levels in AD animal models.

A total of $k = 2$ studies were included in the analysis, focusing on measuring *Actinobacteria*. The results indicated no heterogeneity ($Q_{(2)} = 0.7988$, $p = 0.3714$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.5639 to 1.1681. The overall effect estimate was not significant ($Z = 0.6838$; $p = 0.4941$), suggesting that there was no significant impact of the intervention on *Actinobacteria* levels in AD animal models.

A total of $k = 2$ studies were included in the analysis, focusing on measuring *Verrucomicrobia*. The results indicated no heterogeneity ($Q_{(1)} = 0.0000$, $p = 1.0000$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −3.3803 to 1.1630. The overall effect estimate was not significant ($Z = -0.9565$; $p = 0.3388$), suggesting that there was no significant impact of the intervention on *Verrucomicrobia* levels in AD animal models.

On the other hand, the analysis focused on changes in **bacterial genera** after natural therapeutic agents in AD animal models included *Bacteroides*, *Helicobacter*, *Lactobacillus*, *Parabacteroides*, *Prevotella*, *and Barnesiella*.

A total of $k = 5$ studies were included in the analysis, focusing on measuring *Bacteroides*. The results indicated no heterogeneity ($Q_{(4)} = 3.1931$, $p = 0.5261$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.1568 to 0.8642. The overall effect estimate was not significant ($Z = 1.3581$; $p = 0.1744$), suggesting that there was no significant impact of the natural therapeutic agents on *Bacteroides* levels in AD animal models.

A total of $k = 5$ studies were included in the analysis, focusing on measuring *Helicobacter*. The results indicated no heterogeneity ($Q_{(4)} = 4.6444$, $p = 0.5902$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −0.1278 to 0.8894. The overall effect estimate was not significant ($Z = 1.4673$; $p = 0.1423$), suggesting that there was no significant impact of the intervention on *Helicobacter* levels in AD animal models.

A total of $k = 7$ studies were included in the analysis, focusing on measuring *Lactobacillus*. The results indicated low heterogeneity ($Q_{(6)} = 5.8034$, $p = 0.4456$; $tau^2 = 0.0485$, $I^2 = 14.04\%$). The estimated log odds ratio ranged from −0.5469 to 0.3225. The overall effect estimate was not significant ($Z = -0.5058$; $p = 0.6130$), suggesting that there was no significant impact of the intervention on *Lactobacillus* levels in AD animal models.

A total of $k = 4$ studies were included in the analysis, focusing on measuring *Parabacteroides*. The results indicated no heterogeneity ($Q_{(3)} = 0.2250$, $p = 0.8936$; $tau^2 = 0.00$, $I^2 = 0.00\%$). The estimated log odds ratio ranged from −1.1252 to 1.5590. The overall effect estimate was not significant ($Z = 0.3168$; $p = 0.7514$), suggesting that there was no significant impact of the natural therapeutic agents on *Parabacteroides* levels in AD animal models.

A total of $k = 2$ studies were included in the analysis, focusing on measuring *Prevotella*. The results indicated high heterogeneity ($Q_{(1)} = 24.4837$, $p < .0001$; $tau^2 = 1.8353$, $I^2 = 90.09\%$). The estimated log odds ratio ranged from −1.1252 to 1.5590. The overall effect estimate was not significant ($Z = -0.9215$; $p = 0.3568$), suggesting that there was not a significant impact of the intervention on *Prevotella* levels in AD animal models.

A total of $k = 2$ studies were included in the analysis, focusing on measuring *Barnesiella*. The results indicated high heterogeneity ($Q_{(1)} = 15.1070$, $p = 0.0017$; $tau^2 = 0.4478$, $I^2 = 80.37\%$). The estimated log odds ratio ranged from −2.0638 to 0.7438. The overall effect estimate was not significant ($Z = 0.1122$; $p = 0.9106$), suggesting that there was not a significant impact of the intervention on *Barnesiella* levels in AD animal models after a treatment with natural therapeutic agents.

4 | DISCUSSION

A growing body of evidence indicates that gut microbiota engages in bidirectional communication through multiple pathways, collectively referred to as the gut–brain axis. The brain communicates with the

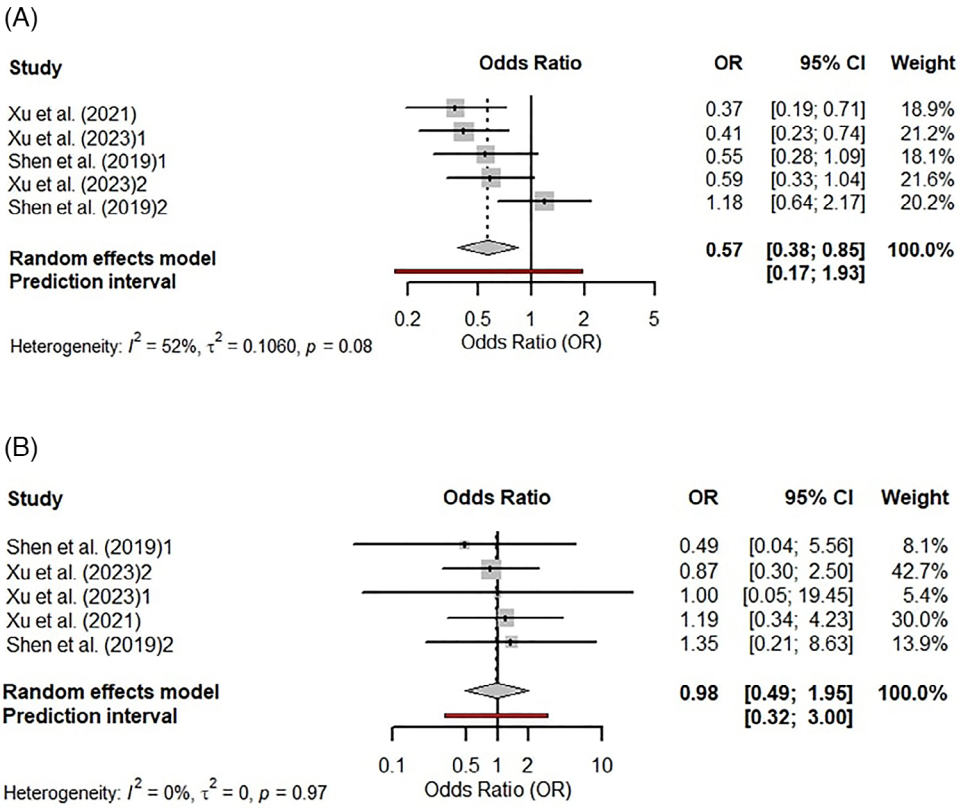

FIGURE 4 Meta-analysis using a random-effects model of selected studies for the *Firmicutes* (A) and *Bacteroidetes* (B) changes in the animal microbiota after a treatment with natural therapeutic agents. The plot shows the effect estimates and corresponding CIs for each study included in the meta-analysis. The relative weight or contribution of each study to the overall effect estimate is also included in percentages. The overall weighted effect is indicated by a diamond at the bottom of the figure. The figure was generated with R software version 4.3.1. The number indicated silymarin-administrated group (1) and silibinin-administrated group (2) in Shen et al.,[32] and medium (1) and high (2) doses of defatted walnut powder in Xu et al.[57] CI, confidence interval.

gut via neuronal and hormonal pathways, including the hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal axis. The vagus nerves transmit most signals from the brain to the gut, coordinating stress and anti-inflammatory activities with the HPA axis to regulate gut motility, intestinal permeability, and mucosal immune activity. Concurrently, gut microbiota can influence the brain by producing and releasing various molecules, such as metabolites, neurotransmitters, and cytokines; these molecules can reach the brain through multiple pathways and may play a key role in modulating neurodegenerative disorders.[52]

This study is the first systematic review and meta-analysis to date synthesizing the current evidence from clinical and preclinical studies that examined the basal differences of microbiome between healthy and AD conditions. In addition, we explored any pattern in gut dysbiosis, or improvement associated with gut microbiota interventions. Our meta-analysis demonstrated that whereas AD condition has been linked to specific cognitive changes along the progression of the disease in humans and animal models, the microbiome baseline levels were not associated with AD in any animal models, whereas in humans, changes in *Bacteroides* were observed in patients with AD.

The comprehensive analysis of bacterial phyla, genera, and families in AD animal models versus control conditions indicates that AD does not significantly alter the gut microbiome at these taxonomic levels. Across all the phyla examined—*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*—no significant impact of AD models on their levels was observed, despite varying degrees of heterogeneity among the studies. Similarly, the analysis of bacterial genera such as *Bacteroides*, *Helicobacter*, *Lactobacillus*, *Akkermansia*, *Parabacteroides*, and *Bifidobacterium* revealed no significant differences in their levels between AD and control groups.

Regarding intestinal microbiota in human studies, analyses of various bacterial genera such as *Agatobacter*, *Escherichia Shigella*, *Prevotella*, *Fusicatenibacter*, *Faecalibacterium*, *and Blautia* showed no significant association with AD. However, among the bacterial groups analyzed, *Proteobacteria*, *Escherichia Shigella*, and *Prevotella* exhibited the highest variability in terms of heterogeneity, reflecting substantial differences across studies. These results could partly support the initial suggestions of a potential involvement of certain bacterial genera in AD, such as *Agatobacter and E. shigella*. Conversely, *Firmicutes* and *Fusicatenibacter* showed minimal variability, indicating more consistent findings across studies.

In this regard, it is important to mention the study by Li et al.,[52] which observed lower relative proportions of *Ruminococcus*, *Faecalibacterium*, *Lachnospira*, *Dialister*, *Lachnoclostridium*, and *Roseburia* (all

from the *Firmicutes* phylum) in a 69% Chinese population sample with mild cognitive impairment and AD in comparison to healthy subjects. In contrast, the genera *Phascolarctobacterium*, *Lactobacillus* (Firmicutes phylum), and *Akkermansia muciniphila* (Verrucomicrobia phylum) were found to be significantly higher in these patients. Furthermore, regional variations may have influenced the abundance of intestinal microbes such as *Bacteroides*, *Alistipes* (Bacteroidetes phylum), and *Bifidobacterium* (Actinobacteria phylum) in this population.

Extending this analysis further to bacterial families, including *Lactobacillaceae*, *Ruminococcaceae*, *Desulfovibrionaceae*, and *Bacteroidaceae*, also showed no significant impact of AD. The results from these family-level analyses were consistent, with none of the families demonstrating significant changes in response to AD. Regional differences were also observed in the enrichment of the *Desulfovibrio* genus, which was significantly increased 59 days post-FMT in rats colonized with Alzheimer's human microbiota from an Italian cohort.[26]

Moreover, it is important to note the analysis for *Bacteroides* across three human studies indicating that AD is associated with notable changes in the abundance of *Bacteroides*, which was accompanied by a high level of variability, suggesting that the impact of AD on *Bacteroides* levels differs considerably between the studies included in the analysis. In addition, the uncertain direction of the effect suggests variability in the direction and magnitude of the effect, meaning that although AD appears to affect *Bacteroides* levels, the specific nature and extent of this impact may differ across studies.

Those observations could be supporting *Bacteroides* as a potentially significant player. Indeed, decreased levels of *Bacteroides* in patients with AD suggest a possible link between this genus and cognitive impairment associated with the disease. Regarding the causal relationship, clinical and experimental evidence linking gut microbiota to AD has given rise to the theory of "age-related dysbiosis," which suggests that AD may develop as part of the aging immune system. Studies have shown that aging is associated with changes in gut microbiota composition and neuroprotective molecules such as SCFAs.[53,54] Furthermore, a loss of microbiome function, particularly genes encoding SCFAs, has been linked to increased circulating proinflammatory cytokines in healthy elderly individuals.[55] In this line, *Bacteroides* plays a crucial role in regulating the immune system and modulating inflammation. A reduction in *Bacteroides* may disrupt the balance of the gut microbiota, leading to altered immune responses and increased systemic inflammation. Chronic inflammation is a known contributor to the pathogenesis of AD, potentially leading to neuroinflammation and neuronal damage.[3] In healthy individuals, *Bacteroides* is involved in producing metabolites such as SCFAs, which have anti-inflammatory effects and support brain health. Consequently, lower levels of *Bacteroides* in patients with AD may reduce the production of these beneficial metabolites, negatively impacting brain function and contributing to cognitive decline.[5] Furthermore, *Bacteroides* helps maintain the integrity of the intestinal barrier. Reduced levels of this genus could increase intestinal permeability, allowing harmful substances, such as endotoxins, to enter the bloodstream and exacerbate neuroinflammation associated with AD.[3,4]

It is important to mention that although the current study shows no significant changes in overall gut microbiome composition between patients with AD and controls at the phylum, genus, or family levels, *Bacteroides* appears to be an exception with notable changes across multiple studies. However, the inconsistent direction of the changes in *Bacteroides* levels across studies suggests that although AD might influence this genus, the exact nature of this relationship remains unclear. IN addition, this variability could be due to geographical differences, sample collection methods, or individual differences in microbiota.

Of interest, our review did not reveal consistent differences between the gut microbiota of AD models and the changes observed in humans. This may reflect, in part, the existing differences between the gut microbiota of these two-mammalian species. Along these lines, an intriguing study by Grabrucker et al.[26] explored the effects of colonizing rats, pretreated with antibiotics, with fecal material from Alzheimer's donors. The findings revealed that human AD-colonized rats showed distinct metabolomic profiles. By the end of the experiment (59 days post-FMT), a decline in newly acquired taxa was observed in the rats colonized with Alzheimer's microbiota, suggesting a tendency for their microbiota to return to its original state. Approximately 40% of the donor taxa engrafted into the recipient rats. In contrast, rats colonized with microbiota from cognitively healthy individuals maintained a relatively stable microbial diversity over time. Those receiving Alzheimer's donor microbiota, however, experienced greater alterations in taxa composition between 10 and 59 days post-FMT. Notably, *Desulfovibrio*, a genus also significantly enriched in patients with AD, showed increased abundance at day 59, suggesting both a potential link to AD in this cohort and a certain cross-species microbiota compatibility.

In line with these findings, it is crucial to consider the results from qualitative synthesis, which indicated that microbiome-modulating interventions might reduce inflammation and improve certain biomarkers of AD when compared to untreated groups or specific study controls. Indeed, our study revealed that the probiotics and the natural therapeutic agents notably impact the levels of *Prevotella*, *Firmicutes*, and *Bacteroidetes* in AD animal models, particularly when compared to other interventions such as exercise, probiotics, or prebiotics. These findings underscore the potential efficacy of these natural treatments in modulating these specific bacterial phyla. However, the variability across studies hinders the identification of a specific microbiome profile associated with the disease. Despite the potential benefits of these interventions, the relationships and mechanisms linking gut microbiome modulation to clinical outcomes remain inconclusive. This is largely due to the lack of high-quality preclinical studies and clinical trials, inconsistencies in study design, and the varied diets administered in the included studies, which likely influence microbiome diversity in AD and obscure any baseline differences. Other microbiota-based therapies, such as FMT, *Candida rugosa lipase* (CRL), or *SCP-1*, could not be included in the meta-analysis due to the insufficient number of studies that met the necessary criteria for meaningful comparison. The limited availability of rigorous and comparable data for these interventions highlights the need for

further research to evaluate their potential efficacy and to establish standardized protocols for their use in clinical settings.

The variability in individual responses to changes in intestinal microbiota could be a crucial factor in cognitive decline related to AD. This implies that the impact of microbiota on cognitive health is not uniform and may be influenced by individual differences such as genetics, lifestyle, and other environmental factors. In this regard, the meta-analysis results in humans with AD, which included an analysis of seven studies assessing cognitive impairment using the MoCA and the MMSE, revealed negative SMDs, whereas the CDR revealed positive SMDs, indicating significant cognitive decline characteristic of participants with AD. The observed high heterogeneity suggests considerable variation among studies, possibly due to differences in participant characteristics, methodology, or environmental factors. Despite this heterogeneity, the statistical significance confirms a robust association between AD and measured cognitive decline, underscoring the severity of cognitive impact in the disease, and more importantly, underscores the relevance of these tools in capturing different dimensions of cognitive decline. The lack of heterogeneity in the MoCA results suggests a consistent pattern of cognitive decline measured by this tool, whereas the MMSE displayed some variability, highlighting potential differences in sensitivity or population characteristics. Conversely, the CDR results were positive and heterogeneous, reflecting its utility in assessing the progression and severity of dementia in patients with AD. These findings emphasize the importance of employing a combination of cognitive assessments to obtain a comprehensive understanding of cognitive impairment in AD, as each tool offers unique insights into the nature and extent of cognitive decline.

In animal models, the analysis of escape latency in the MWM test revealed significant differences between animals of 5 months or younger and those of 6 months or older, on both the first and last days of the test. Similar differences were observed when analyzing the number of times the animals crossed the target area, with significant variations between the younger and older groups. Conversely, the analysis of behavioral parameters related to time spent in the target area yielded mixed results. Although the percentage of time spent in the target area in the MWM test showed significant effects in animals of 5 months or younger but not in those of 6 months or older, crossing times did not reveal significant differences for either age group. However, significant differences were found for animals of 6 months or older when considering the time spent in the target area, as opposed to the percentage of time. Therefore, these results highlight the sensitivity of these cognitive tests for studying the progression of cognitive impairment associated with the disease. Notably, alternation performance in the Y maze and recognition memory as measured by the NOR index of discrimination showed significant effects in older animals, indicating specific cognitive deficits associated with AD progression.

Finally, it is important to note that differences in sampling methods, analysis techniques, and microbiota characterization can lead to divergent outcomes among studies, making direct comparisons and the identification of consistent patterns challenging. In addition, variations in age, animal strain, experimental conditions, and factors such as diet can influence the microbiota's response to the disease, complicating the detection of effects, particularly in studies with limited sample sizes. We also observed a lack of standardized methods for assessing and manipulating gut microbiota across different studies. The variability in animal models used to mimic AD, along with differences in the sources of these models, diets, and housing conditions, contributes to the associated heterogeneity in gut microbiota diversity. Meanwhile, human studies are mostly observational and cross-sectional, which limits their ability to establish causality or directionality between gut microbiota and neurodegenerative disorders[1,56]

Although the involvement of the intestinal microbiota in AD is an area of growing interest, our results highlight the need for more rigorous and well-designed research to better understand this relationship. In conducting this study, we encountered a wide variability of studies that perform interventions on patients or models with AD, directly comparing them under the same experimental condition, but often lacking a healthy control group. These results suggest that the observed differences may not be attributable to variations at the genus or phylum level, but rather to the underlying dysbiosis or the compromised state of the subject. Finally, our findings indicate that certain interventions are more effective than others in restoring an altered gut microbiome under AD conditions. This could illuminate the potential pathways through which specific interventions may contribute to cognitive improvement.

5 | CONCLUSION

This study highlights the complex relationship between gut microbiota and AD and its influence on cognitive function. Although no significant differences were found in the overall gut microbiome composition between AD patients and controls at the phyla, genera, or family levels, Bacteroides stood out with notable changes across multiple studies, showing a significant link to cognitive decline in humans. Of interest, AD animal models did not exhibit signs of dysbiosis. However, when human AD microbiota was transplanted into rats, the results were similar to those observed in human studies, reinforcing the potential role of gut microbiota in AD. However, our findings revealed notable variability across studies, particularly concerning *Prevotella*, *Bacteroidetes*, and *Firmicutes*, whose levels were restored when natural therapeutic agents or probiotics were applied. This points not only to their association with AD improvement but also to the potential effectiveness of specific interventions in managing the disease.

ACKNOWLEDGMENTS

This work was supported by the Ministry of Science and Innovation (PID2023-151715OB-IOO), and by the European Union NextGeneration EU/PRTR [PLEC2022-009464 and CPP2022-009646].

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Informed consent was not necessary for this study.

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REFERENCES

1. Nichols E, Szoeke CEI, Vollset SE, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):88-106.
2. Kowalski K, Mulak A. Brain-gut-microbiota axis in Alzheimer's disease. *J Neurogastroenterol Motil*. 2019;25(1):48-60.
3. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. *Sci Rep*. 2017;7(1):13537.
4. Saji N, Niida S, Murotani K, et al. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in japan. *Sci Rep*. 2019;9(1):1008.
5. Liu P, Wu L, Peng G, et al. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. *Brain Behav Immun*. 2019;80:633-643.
6. Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L. Different brain regions are infected with fungi in Alzheimer's disease. *Sci Rep*. 2015;5(1):15015.
7. Lundmark R, Doherty GJ, Howes MT, et al. The GTPase-activating protein GRAF1 regulates the CLIC/GEEC endocytic pathway. *Curr Biol*. 2008;18(22):1802-1808.
8. Harach T, Marungruang N, Duthilleul N, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. *Sci Rep*. 2017;7(1):41802.
9. Xiang S, Ji J, Li S, et al. Efficacy and safety of probiotics for the treatment of Alzheimer's disease, mild cognitive impairment, and Parkinson's disease: a systematic review and meta-analysis. *Front Aging Neurosci*. 2022;14:730036.
10. Nimgampalle M, Kuna Y. Anti-Alzheimer properties of probiotic, *lactobacillus plantarum* MTCC 1325 in Alzheimer's disease induced albino rats. *J Clin Diagn Res*. 2017;11(8):KC01-KC05.
11. Athari Nik Azm S, Djazayeri A, Safa M, et al. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β-amyloid (1-42) injected rats. *Appl Physiol Nutr Metab*. 2018;43(7):718-726.
12. Medeiros D, McMurry K, Pfeiffer M, et al. Slowing alzheimer's disease progression through probiotic supplementation. *Front Neurosci*. 2024;18:1309075.
13. Xiao S, Chan P, Wang T, et al. A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. *Alzheimers Res Ther*. 2021;13(1):62.
14. Wang X, Sun G, Feng T, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res*. 2019;29(10):787-803.
15. Hazan S. Rapid improvement in alzheimer's disease symptoms following fecal microbiota transplantation: a case report. *J Int Med Res*. 2020;48(6):030006052092593.
16. Park S, Lee JH, Shin J, et al. Cognitive function improvement after fecal microbiota transplantation in alzheimer's dementia patient: a case report. *Curr Med Res Opin*. 2021;37(10):1739-1744.
17. Ma D, Wang AC, Parikh I, et al. Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. *Sci Rep*. 2018;8(1):6670.
18. Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. Modified mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. *EBioMedicine*. 2019;47:529-542.
19. Park S, Zhang T, Wu X, Yi Qiu J. Ketone production by ketogenic diet and by intermittent fasting has different effects on the gut microbiota and disease progression in an Alzheimer's disease rat model. *J Clin Biochem Nutr*. 2020;67(2):188-198.
20. Su Y, Wang D, Liu N, Yang J, Sun R, Zhang Z. Clostridium butyricum improves cognitive dysfunction in ICV-STZ-induced Alzheimer's disease mice via suppressing TLR4 signaling pathway through the gut-brain axis. *PLoS One*. 2023;18(6):e0286086.
21. Su I, Hsu C, Shen S, et al. The beneficial effects of combining anti-aβ antibody NP106 and curcumin analog TML-6 on the treatment of Alzheimer's disease in APP/PS1 mice. *Int J Mol Sci*. 2022;23(1):556.
22. Laske C, Müller S, Munk MHJ, et al. Prognostic value of gut microbiome for conversion from mild cognitive impairment to Alzheimer's disease dementia within 4 years: Results from the AIzBiom study. *Int J Mol Sci*. 2024;25(3):1906.
23. Liang L, Zhou H, Zhang S, Yuan J, Wu H. Effects of gut microbiota disturbance induced in early life on the expression of extrasynaptic GABA-A receptor α5 and δ subunits in the hippocampus of adult rats. *Brain Res Bull*. 2017;135:113-119.
24. Verhaar BJH, Hendriksen HMA, de Leeuw FA, et al. Gut microbiota composition is related to AD pathology. *Front Immunol*. 2022;12:794519.
25. Zhu Z, Ma X, Wu J, et al. Altered gut microbiota and its clinical relevance in mild cognitive impairment and Alzheimer's disease: Shanghai aging study and shanghai memory study. *Nutrients*. 2022;14(19):3959.
26. Grabrucker S, Marizzoni M, Silajdžić E, et al. Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis. *Brain*. 2023;146(12):4916-4934.
27. Yanguas-Casás N, Torres-Fuentes C, Crespo-Castrillo A, et al. High-fat diet alters stress behavior, inflammatory parameters and gut microbiota in tg APP mice in a sex-specific manner. *Neurobiol Dis*. 2021;159:105495.
28. Kim N, Jeon SH, Ju IG, et al. Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice. *Brain Behav Immun*. 2021;98:357-365.
29. Xu M, Huang H, Mo X, et al. Quercetin-3-*O*-Glucuronide alleviates cognitive deficit and toxicity in A$\beta_{1\text{-}42}$ -Induced AD-Like mice and SH-SY5Y cells. *Mol Nutr Food Res*. 2021;65(6):e2000660.
30. Shen L, Liu L, Ji H. Alzheimer's disease histological and Behavioral manifestations in Transgenic mice correlate with Specific Gut microbiome state. *J Alzheimers Dis*. 2017;56(1):385-390.
31. Sun Z, Li X, Wang S, Shen L, Ji H. Bidirectional interactions between curcumin and gut microbiota in transgenic mice with Alzheimer's disease. *Appl Microbiol Biotechnol*. 2020;104(8):3507-3515.
32. Qian X, Hai W, Chen S, Zhang M, Jiang X, Tang H. Multi-omics data reveals aberrant gut microbiota-host glycerophospholipid metabolism in association with neuroinflammation in APP/PS1 mice. *Gut Microbes*. 2023;15(2).
33. Shen L, Liu L, Li X, Ji H. Regulation of gut microbiota in Alzheimer's disease mice by silibinin and silymarin and their pharmacological implications. *Appl Microbiol Biotechnol*. 2019;103(17):7141-7149.
34. Zhu J, Liu S, Zhang H, et al. Dynamic distribution of gut microbiota during Alzheimer's disease progression in a mice model. *APMIS*. 2023;131(9):480-490.
35. Yamashiro K, Takabayashi K, Kamagata K, et al. Free water in gray matter linked to gut microbiota changes with decreased butyrate producers in Alzheimer's disease and mild cognitive impairment. *Neurobiol Dis*. 2024;193:106464.
36. Kim J, Park H, Lee J, et al. Effect of altered gene expression in lipid metabolism on cognitive improvement in patients with Alzheimer's

dementia following fecal microbiota transplantation: a preliminary study. *Ther Adv Neurol Disord*. 2024;17:17562864231218181.
37. Li B, He Y, Ma J, et al. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimers Dement*. 2019;15(10):1357-1366.
38. Guo M, Peng J, Huang X, Xiao L, Huang F, Zuo Z. Gut microbiome features of Chinese patients newly diagnosed with Alzheimer's disease or mild cognitive impairment. *J Alzheimers Dis*. 2021;80(1):299-310.
39. Bello-Medina PC, Hernández-Quiroz F, Pérez-Morales M, et al. Spatial memory and gut microbiota alterations are already present in early adulthood in a pre-clinical transgenic model of Alzheimer's disease. *Front Neurosci*. 2021;15:595583.
40. Cuervo-Zanatta D, Garcia-Mena J, Perez-Cruz C. Gut microbiota alterations and cognitive impairment are sexually dissociated in a transgenic mice model of Alzheimer's disease. *J Alzheimers Dis*. 2021;82(s1):S195–S214.
41. Feng M, Hou T, Zhou M, et al. Gut microbiota may be involved in alzheimer's disease pathology by dysregulating pyrimidine metabolism in APP/PS1 mice. *Front Aging Neurosci*. 2022;14:967747.
42. Jin J, Xu Z, Zhang L, et al. Gut-derived β-amyloid: likely a centerpiece of the gut–brain axis contributing to Alzheimer's pathogenesis. *Gut Microbes*. 2023;15(1):2167172.
43. Li Z, Zhu H, Guo Y, Du X, Qin C. Gut microbiota regulate cognitive deficits and amyloid deposition in a model of Alzheimer's disease. *J Neurochem*. 2020;155(4):448-461.
44. Lorenzini L, Zanella L, Sannia M, et al. Experimental colitis in young Tg2576 mice accelerates the onset of an Alzheimer's-like clinical phenotype. *Alzheimers Res Ther*. 2024;16(1):116.
45. Sun P, Zhu H, Li X, et al. Comparative metagenomics and metabolomes reveals abnormal metabolism activity is associated with gut microbiota in Alzheimer's disease mice. *Int J Mol Sci*. 2022;23(19):11560.
46. Wei Z, Li D, Shi J. Alterations of spatial memory and gut microbiota composition in Alzheimer's disease triple-transgenic mice at 3, 6, and 9 months of age. *Am J Alzheimers Dis Other Demen*. 2023;38:153331752311741.
47. Yan C, Diao Q, Zhao Y, et al. *Fusobacterium nucleatum* infection-induced neurodegeneration and abnormal gut microbiota composition in Alzheimer's disease-like rats. *Front Neurosci*. 2022;16:884543.
48. Khedr EM, Omeran N, Karam-Allah Ramadan H, Ahmed GK, Abdelwarith AM. Alteration of gut microbiota in Alzheimer's disease and their relation to the cognitive impairment. *J Alzheimers Dis*. 2022;88(3):1103-1114.
49. Wanapaisan P, Chuansangeam M, Nopnipa S, et al. Association between gut microbiota with mild cognitive impairment and Alzheimer's disease in a Thai population. *Neurodegener Dis*. 2022;22(2):43-54.
50. Zhou Y, Wang Y, Quan M, Zhao H, Jia J. Gut microbiota changes and their correlation with cognitive and neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dis*. 2021;81(2):583-595.
51. Zhuang Z, Shen L, Li W, et al. Gut microbiota is altered in patients with Alzheimer's disease. *Alzheimers Dis*. 2018;63(4):1337-1346.
52. Li H, Cui X, Lin Y, Huang F, Tian A, Zhang R. Gut microbiota changes in patients with Alzheimer's disease spectrum based on 16S rRNA sequencing: a systematic review and meta-analysis. *Front Aging Neurosci*. 2024;16:1422350.
53. Lambert J, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009;41(10):1094-1099.
54. Caracciolo B, Xu W, Collins S, Fratiglioni L. Cognitive decline, dietary factors and gut–brain interactions. *Mech Ageing Dev*. 2014;136-137:59-69.
55. Claesson MJ, Jeffery IB, Conde S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature*. 2012;488(7410):178-184.
56. Feigin VL, Vos T, Nichols E, et al. The global burden of neurological disorders: translating evidence into policy. *Lancet Neurol*. 2020;19(3):255-265.
57. Xu X, Ding Y, Zhang X, et al. Potential anti-Alzheimer's disease effect of defatted walnut powder through remodeling gut microbiota and modulating amino acid metabolite levels. *J Funct Foods*. 2023;111:105891.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jimenez-García AM, Villarino M, Arias N. A systematic review and meta-analysis of basal microbiota and cognitive function in Alzheimer's disease: A potential target for treatment or a contributor to disease progression? *Alzheimer's Dement*. 2024;16:e70057.
https://doi.org/10.1002/dad2.70057