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Review

Gut Microbiota Dysbiosis in Mild Cognitive Impairment: Alzheimer's Disease Diagnostic Potential and Nutritional Modulation

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressively deteriorating neurodegenerative condition that poses a substantial burden on society. Current diagnostic methods of AD are often considered complex and costly. Mild Cognitive Impairment (MCI) is defined as the transitional stage before AD. Alterations in the gut microbiota (dysbiosis) are observed in MCI and preclinical AD and are hypothesized to contribute to disease pathogenesis.

Aim: The objective of this review was to evaluate gut microbiota profiles as non-invasive, low-cost indicators and tailor diagnostic biomarkers. The diagnostic potential and the efficacy of nutritional modulation strategies across the AD continuum were assessed.

Methods: The mechanisms by which dysbiosis promotes neurodegeneration were analyzed, including increased intestinal permeability, Lipopolysaccharide (LPS) leakage, and reduced production of short-chain fatty acids (SCFAs). Taxonomic shifts were summarized, documenting the depletion of SCFA producers (e.g., Firmicutes) and the enrichment of general pro-inflammatory. The quantitative performance of machine learning models utilizing microbial data for disease classification was reviewed.

Results: High predictive accuracy for AD incidence was achieved by machine learning classifiers based solely on gut microbiome profiles, with Area Under the Curve (AU-ROC) values reaching up to 0.927. Nutritional interventions, including probiotics (Lactobacillus, Bifidobacterium) and prebiotics, were found to modulate the gut effectively by enhancing SCFA production, reinforcing intestinal barrier integrity, and suppressing systemic neuroinflammation.

Conclusion: Robust potential is demonstrated by gut microbial profiles as high-performance, non-invasive screening tools for early detection in the AD continuum. However, future validation is required through large-scale, long-term randomized controlled trials (RCTs) focusing on establishing causation and developing personalized gut-based therapies.

Keywords: Alzheimer, microbiota, dysbiosis, neurodegeneration

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INTRODUCTION

Alzheimer's disease (AD) is a progressively deteriorating neurodegenerative condition that poses a substantial burden on society (Wang et al., 2025). Diagnosis of AD has historically relied on the detection of hallmark pathologies, such as extracellular amyloid-beta (Aβ) plaques and hyperphosphorylated tau protein neurofibrillary tangles (Wang et al., 2025), often confirmed through clinical signs, brain imaging, and cerebrospinal fluid (CSF) analysis (Girodon & Hauet, 2025). However, current AD treatment strategies, which predominantly utilize single-target therapies or symptomatic management, have shown limited efficacy in influencing disease progression (Wang et al., 2025). Attempts to develop Aβ-targeting agents,

such as BACE and γ-secretase inhibitors, have often failed due to limited ability to improve cognitive function or substantial toxicity. Furthermore, existing diagnostic methods can be complex and costly (Girodon & Hauet, 2025), and biomarker confirmation of Aβ or tau pathology is not always available in clinical studies, which restricts interpretation within a biological framework (Sepúlveda-rivera et al., 2025). These limitations underscore the urgent need to investigate novel diagnostic and therapeutic strategies (Wang et al., 2025).

Mild Cognitive Impairment (MCI) is defined as an intermediate stage between normal cognition and dementia, characterized by noticeable cognitive deficits that do not significantly interfere with daily activities (Alaeddin et al., 2025). MCI is considered the earliest transitional stage before the onset of AD, corresponding to prodromal AD within the clinical continuum.(Aathira et al., 2025; Dong et al., 2025) Individuals diagnosed with MCI have a significantly higher annual risk of progressing to AD, with probabilities ranging from 40% to 75% (Dong et al., 2025; Fan et al., 2025). Recent research highlights that alterations in the composition of the gut microbiota (gut dysbiosis) are observed in individuals with MCI and preclinical AD (Alaeddin et al., 2025; Kang et al., 2025). These early microbial changes are increasingly hypothesized to contribute to AD pathogenesis (Girodon & Hauet, 2025).

Given the challenges associated with complex and costly conventional diagnostic methodologies, exploring alternative markers is essential. Gut dysbiosis is viewed as a potentially modifiable risk factor for AD (Kang et al., 2025). which can promote neuroinflammation and Aβ aggregation, leading to its identification as a potential early AD biomarker (Aathira et al., 2025). The objective of this review is to enhance understanding of AD by adopting a "gut microbiome-centric approach" to tailor diagnostic biomarkers (Sharma et al., 2025). and evaluate gut microbiota profiles as non-invasive, low-cost indicators that could complement current complex examinations for early detection and intervention in the AD continuum (Wang et al., 2025).

Mechanisms Linking Dysbiosis to Neurodegeneration

Dysbiosis, characterized by alterations in the composition and diversity of the gut microbiota, plays a significant role in promoting neurodegenerative processes through the disruption of physiological barriers and the subsequent release of inflammatory mediators and microbial products into the systemic circulation and central nervous system (CNS) (Koumpouli et al., 2025; Zhao et al., 2025; Zhou et al., 2025).

Intestinal Permeability ('Leaky Gut') and Associated Markers

Gut dysbiosis is frequently associated with a weakening or disruption of the intestinal epithelial barrier, a condition colloquially known as a "leaky gut" (Koumpouli et al., 2025; Marizzoni et al., 2026; Sharma et al., 2025). This alteration results in increased intestinal permeability (Aathira et al., 2025; Flynn et al., 2025; Koumpouli et al., 2025; Pfaffinger & Seeley, 2025). The integrity of the intestinal barrier is regulated by specific structures, including tight junction proteins such as zona occludens-1 (ZO-1), claudin-1, and occludin (Koumpouli et al., 2025; Sharma

et al., 2025; Skawratananond et al., 2025; Wang et al., 2025; Zhou et al., 2025). The compromise of this barrier allows gut microbes, microbial metabolites, and lipopolysaccharides (LPS) to breach the gut and enter the bloodstream, thereby initiating systemic inflammatory cascades (Koumpouli et al., 2025; Wang et al., 2025; Zhou et al., 2025). In patients with Alzheimer's dementia, elevated fecal calprotectin is an indicator of a leaky gut (Marizzoni et al., 2026). Furthermore, systematic reviews have identified consistently increased circulating levels of the tight-junction protein zonulin as a key marker associated with gut dysbiosis in many neurological disorders (Theis et al., 2025).

Table 1. Microbiome Shifts in Mild Cognitive Impairment

Bacteria Name	Increased/Decreased	Source Citation
Phylum: Bacteroidetes	Increased	(Fan et al., 2025)
Phylum: Firmicutes	Decreased	(Fan et al., 2025)
Phylum: Enterobacteriaceae	Altered abundance (direction relative to HC not specified)	(Wang et al., 2025)
Anaerostipes (Genus)	Progressive Decrease (HC to MCI to AD)	(Zhao et al., 2025)
Anaerostipes hadrus (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Anaerostipes (Genus)	Decreased (Implied by association of reduction with reduced SCFAs)	(Zhao et al., 2025)
Limosilactobacillus (Genus)	Progressive Decrease (HC to MCI to AD)	(Zhao et al., 2025)
Sphingomonas (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Staphylococcus (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Stenotrophomonas (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Massilia (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Variovorax (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Bacillus (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Bosea (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Dyella (Genus)	Progressive Increase (HC to MCI to AD)	(Zhao et al., 2025)
Blautia (Genus)	Decreased (More abundant in cognitively normal individuals)	(Fan et al., 2025)
Lachnospira (Genus)	Decreased (More abundant in cognitively normal individuals)	(Fan et al., 2025)
Escherichia (Genus)	Increased (More prevalent in AD spectrum, including MCI)	(Fan et al., 2025)
Prevotella (Genus)	Increased (More prevalent in AD spectrum, including MCI)	(Fan et al., 2025)

Bacteria Name	Increased/Decreased	Source Citation
Faecalibacterium (Genus)	Decreased	(Fan et al., 2025)
Faecalibacterium (Genus)	Decreased (Higher abundance in controls)	(Sepúlveda-Rivera et al., 2025)
Adlercreutzia equolifaciens (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Alistipes communis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Bifidobacterium dentium (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Bifidobacterium pseudocatenulatum (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Clostridium scindens (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Clostridium symbiosum (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Enterococcus faecium (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Fusicatenibacter saccharivorans (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Lacrimispora amygdalina (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Parasutterella excrementihominis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Phocaeicola dorei (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Prevotella copri clade C (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Roseburia faecis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Ruminococcus lactaris (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Ruminococcus torques (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Streptococcus anginosus (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Anaerobutyricum soehngenii (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)

Bacteria Name	Increased/Decreased	Source Citation
Butyricimonas virosa (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Holdemanella biformis (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Neobittarella massiliensis (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Parabacteroides merdae (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Bacteroides salyersiae (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Blautia obeum (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Dialister invisus (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Enterocloster bolteae (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Hungatella hathewayi (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Klebsiella variicola (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Lachnospira eligens (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Romboutsia timonensis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Ruminococcus bromii (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Anaerotruncus rubiinfantis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Barnesiella intestinihominis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Blautia faecis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Blautia luti (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Dorea formicigenerans (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Faecalimonas umbilicata (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Flavonifractor plautii (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Fusobacterium mortiferum (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)

Bacteria Name	Increased/Decreased	Source Citation
Fusobacterium varium (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Intestinimonas butyriciproducens (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Streptococcus australis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Streptococcus salivarius (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Walterella intestinalis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Allisonella histaminiformans (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Anaerotruncus colihominis (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Bacteroides clarus (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Holdemanella porci (Genus)	Decreased (Negative association with MCI)	(Fan et al., 2025)
Streptococcus cristatus (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Streptococcus mitis (Genus)	Increased (Positive association with MCI)	(Fan et al., 2025)
Methanobrevibacter (Genus)	Increased (Observed in preclinical stage AD subjects)	(Girodon & Hauet, 2025)
Dialister (Genus)	Decreased (Implied by association of increased abundance in cognitively normal participants)	(Fan et al., 2025)

The Role of Lipopolysaccharides (LPS) in Systemic Inflammation

Lipopolysaccharide (LPS), an endotoxin primarily derived from the outer membrane of gram-negative bacteria in the gut microbiota, is a crucial mediator of inflammation (Skawratananond et al., 2025; Wang et al., 2025). When intestinal barrier dysfunction occurs, gut-derived LPS translocates into the systemic circulation (Aathira et al., 2025; Skawratananond et al., 2025; Wang et al., 2025). This translocation triggers systemic inflammation (Marziyeh et al., 2025; Pfaffinger & Seeley, 2025; Theis et al., 2025; Zhou et al., 2025). LPS exerts its effect by binding to pattern recognition receptors, specifically toll-like receptor 4 (TLR4), on gut epithelial cells and immune cells (Pfaffinger & Seeley, 2025; Skawratananond et al., 2025; Wang et al., 2025) This binding activates the TLR4/MyD88 signaling pathway, which leads to the subsequent production and release of proinflammatory cytokines, including TNF-∝, IL-1β, and IL-6 (Aathira et al., 2025; Pfaffinger & Seeley, 2025; Sharma et al., 2025; Wang et al., 2025). The resulting systemic inflammatory state can be transmitted to the CNS (Aathira et al., 2025; Skawratananond et al., 2025;

Wang et al., 2025; Zhou et al., 2025). LPS can cross the Blood-Brain Barrier (BBB) via a lipoprotein-mediated transport mechanism (Skawratananond et al., 2025), where it activates innate immune cells, such as microglia and astrocytes, leading to a central nervous system inflammatory response known as neuroinflammation (Dong et al., 2025; Marizzoni et al., 2026; Pfaffinger & Seeley, 2025; Wang et al., 2025). Consistent with this mechanism, LPS has been detected in the neocortex, hippocampus, and Aβ plaques of postmortem AD brains (Skawratananond et al., 2025).

Gut Metabolites (SCFAs) and the Blood-Brain Barrier (BBB)

The gut microbiota significantly impacts the CNS through the production of metabolites, notably short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which are formed by the fermentation of dietary fiber (Alaeddin et al., 2025; Marziyeh et al., 2025; Pfaffinger & Seeley, 2025; Zhou et al., 2025). In states of gut dysbiosis, reduced levels of SCFA-producing bacteria and consequently decreased SCFA concentrations are often observed (Pfaffinger & Seeley, 2025; Skawratananond et al., 2025; Theis et al., 2025). SCFAs modulate the integrity and function of the Blood-Brain Barrier (BBB) (Alaeddin et al., 2025; Basgaran et al., 2025; Fan et al., 2025; Koumpouli et al., 2025; Pfaffinger & Seeley, 2025; Zhou et al., 2025), which serves as a highly selective barrier separating the CNS from the systemic circulation (Koumpouli et al., 2025; Pfaffinger & Seeley, 2025). Butyrate has been specifically demonstrated to strengthen intestinal barrier integrity (Aathira et al., 2025; Flynn et al., 2025). and decrease BBB permeability by upregulating tight junction proteins (Zhou et al., 2025). Conversely, reduced SCFA levels impair neuroprotection and can accelerate neurodegeneration (Aathira et al., 2025). SCFAs can cross the BBB and directly influence glial cell function (Dong et al., 2025; Marziyeh et al., 2025; Zhou et al., 2025). When the BBB is compromised, the entry of microbial products and inflammatory mediators can activate innate immune cytokines in the CNS, worsening neurodegenerative pathology (Zhou et al., 2025). The disruption of the BBB's integrity is recognized as being involved in the pathology and development of neurodegenerative disorders (Koumpouli et al., 2025).

Taxonomic Alterations in MCI

The transition from normal cognition to Mild Cognitive Impairment (MCI) and subsequent Alzheimer’s Disease (AD) is marked by significant alterations in gut microbiota composition, a phenomenon termed gut dysbiosis (Fan et al., 2025; Zhou et al., 2025). Analysis of microbial taxa across the AD continuum reveals directional shifts characterized by a reduction in generally beneficial, short-chain fatty acid (SCFA)-producing bacteria and an expansion of potentially pro-inflammatory taxa (Fan et al., 2025). As shown on Table 1, the following microbial genera and phyla were reported to be significantly altered in patients diagnosed with Mild Cognitive Impairment (MCI) or displaying a progressive change along the continuum from healthy controls (HC) through MCI to AD.

Depleted Beneficial Taxa

The loss of beneficial taxa, particularly those associated with SCFA production, is a defining feature of gut dysbiosis in the MCI stage (Fan et al., 2025). The phylum Firmicutes is broadly observed to be diminished in patients with neurological disorders compared to healthy controls (Marizzoni et al., 2026; Sepúlveda-rivera et al., 2025; Wang et al., 2025). At the genus level, there is progressive decrease in the relative abundance of Limosilactobacillus and Anaerostipes from healthy controls (HC) through MCI to AD (Zhao et al., 2025). Consistent with this finding, the SCFA-producing species Anaerostipes hadrus exhibited a negative association with MCI (Fan et al., 2025). Since Anaerostipes utilizes dietary inositol for SCFA production, its decreased abundance may lead to reduced SCFA levels, which are critical for regulating the nervous system (Zhao et al., 2025).

Numerous other general typically recognized for protective properties or SCFA production demonstrate decreased abundance or negative association with MCI. Faecalibacterium displayed lower abundance in MCI patients relative to controls (Fan et al., 2025; Sepúlveda-rivera et al., 2025). Fusicatenibacter saccharivorans showed a negative association with MCI (Fan et al., 2025), and the genus Fusicatenibacter is generally considered beneficial for intestinal health (Marizzoni et al., 2026). Blautia, typically more abundant in cognitively normal individuals, showed negative associations with MCI, including species like Blautia obeum, Blautia faecis, and Blautia luti (Fan et al., 2025). Other key species showing negative associations with MCI included Roseburia faecis, Enterococcus faecium, Roseburia faecis, Lacrimispora amygdalina, Adlercreutzia equolifaciens, and Alistipes communis (Fan et al., 2025).

Enriched Pro-inflammatory Taxa

In parallel with the depletion of beneficial taxa, the MCI stage is characterized by an increase in potentially pathogenic or pro-inflammatory bacteria. Several genera display a progressive increase in relative abundance from HC to MCI to AD (Zhao et al., 2025). This progressive increase was observed for Sphingomonas, Staphylococcus, Stenotrophomonas, Massilia, Variovorax, Bacillus, Bosea, and Dyella (Zhao et al., 2025). The phylum Proteobacteria, which includes many gram-negative bacteria, was also reported as increased in patients with neurological disorders (Marizzoni et al., 2026; Wang et al., 2025). Furthermore, increases were noted in potentially pathogenic genera such as Escherichia and Prevotella in the AD spectrum, which includes MCI (Fan et al., 2025). The decreased abundance of these beneficial species contributes to impaired neuroprotection and accelerated neurodegeneration due to reduced SCFA levels (Aathira et al., 2025).

Specific species demonstrating positive association with MCI risk include: Clostridium scindens and Clostridium symbiosum, which are capable of converting primary bile acids to secondary bile acid compounds (Fan et al., 2025). Bifidobacterium dentium, Anaerobutyricum soehngenii, Butyricimonas virosa, Holdemanella biformis, Neobittarella massiliensis, and Parabacteroides merdae (Fan et al., 2025). The methane-producing archaea Methanobrevibacter smithii was found to be increased in preclinical stage AD subjects, associated with neuroinflammation (Girodon & Hauet, 2025). Species such as Prevotella copri clade

C, Streptococcus anginosus, Streptococcus cristatus, and Streptococcus mitis were also positively associated with MCI (Fan et al., 2025).

Table 2. Diagnostic Utility of Gut Microbiome Profiles in Neurological Disorders, Assessed by Machine Learning

Model/Classifier	Features Used	Target Outcome	Performance Metric (Value)	Source Citation
SIAMCAT (Atlas Dataset)	Microbiome Profile	AD Incidence Prediction	Area under the receiver operating characteristic (AU-ROC): **0.889**	(Basgaran et al., 2025)
SIAMCAT (Curated Dataset)	Microbiome Profile	AD Incidence Prediction	AU-ROC: **0.927**	(Basgaran et al., 2025)
Support Vector Machine (SVM)	DTI + Microbiome (*Proteobacteria*)	Classify Early-Stage Parkinson's Disease (PD)	Diagnostic Accuracy: **95%**	(Wu et al., 2025)
Multimodal ML Model	Microbiota Diversity + Plasma Inflammatory Markers (IL-6, TNF-α) + Neuroimaging	Predicting AD Disease Progression	Area Under the Curve (AUC): **0.89**	(Wu et al., 2025)

Statistical Inference of Associations between Microbial Composition And host phenoTypes (SIAMCAT)

Contradictory Findings

Analysis at the species level challenges simple genus- or phylum-level classifications, revealing conflicting associations for high-abundance taxa (Fan et al., 2025). While the phylum Bacteroidetes was suggested to be increased in MCI in one report (Marizzoni et al., 2026) other findings suggest that this phylum is reduced in AD compared to controls (Fan et al., 2025). Species within the same genus frequently exhibited opposite effects on MCI risk (Fan et al., 2025). Specifically, Bacteroides eggerthii was negatively associated with MCI, while Bacteroides thetaiotaomicron showed a positive association with MCI (Fan et al., 2025). Similarly, contradictory results were observed within the Ruminococcus genus, where Ruminococcus torques was positively associated with MCI, but Ruminococcus lactaris and Ruminococcus bromii showed negative associations (Fan et al., 2025). Finally, Akkermansia muciniphila correlated with reduced amyloid burden, suggesting a protective role; conversely, its role remains controversial due to its reported increase in other neurodegenerative conditions like Parkinson's disease (Fan et al., 2025).

Diagnostic Utility of Microbiome Classifiers

Machine learning (ML) methodologies have been utilized to evaluate the predictive and diagnostic capabilities of gut microbiome profiles in neurological disorders, particularly Alzheimer's disease (AD) (Wu et al., 2025). These

computational models aim to quantify the relationship between microbial signatures and disease status, offering objective performance metrics (Wu et al., 2025).

Quantitative Performance Metrics

Studies employing supervised learning models (Table 2), such as those using the Statistical Inference of Associations between Microbial Composition And host phenoTypes (SIAMCAT) package, have demonstrated high predictive value for AD incidence based on population microbiome profiles (Basgaran et al., 2025), while the SVM model targeting PD achieved a diagnostic accuracy of 95% (Wu et al., 2025).

Comparison of Microbiome-Only vs. Combined Models

Emerging evidence suggests that integrating microbiome data with clinical features enhances predictive value, despite the absence of standardized quantitative comparison metrics. Two independent analyses predicted Alzheimer's disease (AD) incidence using gut microbiome profiles alone, achieving AU-ROC values of 0.889 in the Atlas Dataset and 0.927 in the Curated Dataset (Basgaran et al., 2025). In contrast, combined approaches demonstrate broader utility. For example, a multimodal machine learning model that incorporated intestinal microbiota diversity, plasma inflammatory markers, and multimodal neuroimaging achieved an AUC of 0.89 in predicting AD progression, explicitly defined as a combined approach (Wu et al., 2025). Similarly, Girodon and Hauet (2025) evaluated a Random Forest model integrating biological parameters, cerebrospinal fluid (CSF) analysis, and cerebral imaging. When transcriptomic gut microbiota data were added, diagnostic specificity improved, enabling identification of pre-clinical AD patients who had previously been classified as healthy. However, the study did not report exact quantitative gains, such as changes in AUC or specificity values, resulting from this integration.

Nutritional Modulation of the Prodromal Gut

Targeting gut dysbiosis through nutritional interventions represents a leading strategy for modulating the pathogenesis of neurodegenerative conditions like Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). These interventions aim to normalize microbial composition, reinforce the intestinal barrier, and enhance the production of beneficial microbial metabolites, thereby counteracting the reported depletion of beneficial taxa and the enrichment of pro-inflammatory species.

Probiotics and Synbiotics

Probiotics, defined as live microorganisms that confer health benefits to the host, and synbiotics, which combine probiotics with selective substrates (prebiotics), have been extensively investigated as therapeutic modalities (Sharma et al., 2025; Zhou et al., 2025). Probiotic supplementation has been proposed to suppress neuroinflammatory responses and strengthen gut barrier integrity (Dong et al., 2025). The primary mechanism involves modulation of gut microbial composition to enhance beneficial factors. For instance, probiotic strains such as Lactobacillus and

Bifidobacterium are widely utilized to increase short-chain fatty acid (SCFA) production, thereby supporting metabolic balance (Dong et al., 2025; Sharma et al., 2025; Upadhyay et al., 2025). Administration of Bifidobacterium breve A1 has been shown to elevate plasma acetate levels (Dong et al., 2025), while Clostridium butyricum reduced amyloid-β deposition and mitigated neuroinflammation in mouse models (Zhou et al., 2025). In clinical studies, probiotic interventions in patients with probable Alzheimer's disease (AD) increased butyrate and indole concentrations while reducing valerate levels (Marizzoni et al., 2026).

Beyond metabolic effects, probiotics contribute to taxonomic restoration, as demonstrated by reductions in the Firmicutes/Bacteroidetes ratio in AD mouse models, suggesting improved microbial balance in dysbiosis (Sharma et al., 2025). They also reinforce gut barrier integrity by upregulating tight junction proteins such as ZO-1, Occludin, and Claudin-1, thereby preventing lipopolysaccharide (LPS) leakage (Flynn et al., 2025; Wang et al., 2025). Furthermore, probiotic supplementation has been associated with suppression of inflammatory mediators, including IL-6, MIF, NLRP3, and TNF-α, alongside increased levels of the anti-inflammatory cytokine IL-10 (Marizzoni et al., 2026). Similar effects include reductions in serum IL-1β and enhanced antioxidant enzyme activity, such as superoxide dismutase (SOD) (Dong et al., 2025; Zhou et al., 2025). Synbiotic formulations, such as fructooligosaccharides (FOS) combined with Bifidobacterium, have also demonstrated therapeutic efficacy in AD mouse models by restoring anti-inflammatory indices to baseline levels (Dong et al., 2025).

Prebiotics and Dietary Fiber

Prebiotics, composed primarily of fibers and oligosaccharides, selectively stimulate the proliferation and metabolism of beneficial gut bacteria (Dong et al., 2025; Sharma et al., 2025; Zhou et al., 2025). Their therapeutic potential in Alzheimer's disease (AD) is largely attributed to the promotion of short-chain fatty acid (SCFA) producers. Compounds such as inulin and fructooligosaccharides (FOS) act as substrates that enhance the growth of SCFA-producing taxa, including Anaerostipes and Faecalibacterium, which are typically depleted along the mild cognitive impairment (MCI) continuum (Koumpouli et al., 2025). Prebiotic intake has also been associated with improved intestinal barrier integrity, evidenced by reductions in plasma zonulin and calprotectin levels (Koumpouli et al., 2025). Taxonomic shifts further highlight their role in modulating gut ecology: inulin supplementation decreased the abundance of the pro-inflammatory phylum Proteobacteria and pathogenic Escherichia coli, while FOS consumption increased beneficial genera such as Bifidobacterium and Lactobacillus (Dong et al., 2025; Koumpouli et al., 2025). Beyond microbial modulation, SCFAs derived from fiber fermentation exert epigenetic effects. Butyrate, in particular, functions as a histone deacetylase (HDAC) inhibitor, which has been proposed to enhance all-trans retinoic acid (ATRA) bioavailability, thereby strengthening intestinal barrier integrity (Skawratananond et al., 2025). Collectively, these findings underscore the multifaceted mechanisms through which prebiotics contribute to gut homeostasis and neuroprotection in AD.

Whole Dietary Patterns

Specific comprehensive dietary patterns have demonstrated the capacity to reshape the entire microbial ecosystem. Adherence to the Mediterranean diet, characterized by high intake of fruits, vegetables, and legumes, has been associated with a reduction in the Firmicutes/Bacteroidetes (F/B) ratio and an increased relative abundance of short-chain fatty acid (SCFA)-producing strains such as Dorea, Roseburia, and Coprococcus, thereby shifting the microbiota away from the dysbiotic profile often linked to neurological disorders (Theis et al., 2025). A modified Mediterranean–ketogenic diet (MMKD) has similarly been shown to modulate gut microbiome composition and SCFA levels, correlating with improvements in cerebrospinal fluid (CSF) biomarkers of amyloid-β deposition in individuals with mild cognitive impairment (Zhou et al., 2025). In contrast, the classical ketogenic diet, characterized by high fat and low carbohydrate intake, has been reported to selectively inhibit the growth of Bifidobacteria and reduce pro-inflammatory Th17 cells, potentially alleviating gut inflammation (Zhou et al., 2025). Collectively, these findings highlight the capacity of dietary interventions to induce taxonomic and functional shifts in the gut microbiome, with implications for neuroprotection and disease modification.

Traditional Chinese Medicine Polysaccharides (TCMPs)

Traditional Chinese medicinal polysaccharides (TCMPs) function as natural prebiotics, offering a multi-target approach to gut modulation (Wang et al., 2025; Zhou et al., 2025). Polysaccharides derived from Schisandra chinensis (SCP2) have been shown to restore the altered abundance of Firmicutes, Bacteroidetes, and Lactobacillus species while simultaneously boosting short-chain fatty acid (SCFA) levels, particularly acetic acid (Wang et al., 2025). Similarly, polysaccharides from Poria cocos were reported to rebalance the Firmicutes/Bacteroidetes ratio and repair intestinal barrier integrity compromised by oxidative stress, primarily through the upregulation of tight junction protein ZO-1 expression (Wang et al., 2025). In addition, polysaccharides extracted from Lycium barbarum increased the abundance of Akkermansia and other beneficial taxa, thereby promoting SCFA synthesis and reinforcing intestinal barrier function (Wang et al., 2025). Collectively, these findings highlight the potential of TCMPs to restore microbial balance, enhance barrier integrity, and strengthen host–microbiota interactions, underscoring their therapeutic relevance in gut–brain axis modulation.

DISCUSSION

The increasing understanding of the microbiota–gut–brain axis offers a compelling rationale for exploring gut dysbiosis as a diagnostic and therapeutic target in the Alzheimer's disease (AD) continuum (Marziyeh et al., 2025; Sharma et al., 2025). The collective findings presented here underscore the capacity of gut microbial profiles, derived from non-invasive fecal samples, to serve as robust classifiers for neurodegenerative risk (Basgaran et al., 2025; Sharma et al., 2025). Machine learning models predicated on population-level gut microbiome data demonstrated high predictive accuracy for the incidence of AD, achieving mean Area

Under the Curve (AUC) values of 0.889 and 0.927 (Basgaran et al., 2025). Furthermore, a model combining fecal microbial and metabolite indicators achieved an AUC of 0.955 in classifying AD, suggesting exceptional diagnostic potential (Sharma et al., 2025).

The inclusion of microbiota analysis also enhanced diagnostic specificity in predicting preclinical AD patients who were otherwise classified as healthy by conventional diagnostic methods (Girodon & Hauet, 2025). Given these quantitatively high performance metrics, the evaluation of gut microbiota profiles through stool testing holds significant promise as a non-invasive, low-cost Tier-1 screening tool that could effectively complement complex and expensive current examinations for the early detection and intervention in Mild Cognitive Impairment (MCI) and AD (Girodon & Hauet, 2025).

Limitations of Current Research

Despite the encouraging association between taxonomic alterations and diagnostic capability, several substantial limitations constrain the interpretation and translational readiness of current research findings. A major constraint across multiple studies is the small sample size of cohorts, particularly within subgroups stratified by AD biomarkers, which compromises the statistical power and limits the generalizability of conclusions (Fan et al., 2025; Flynn et al., 2025; Kang et al., 2025; Koumpouli et al., 2025; Sepúlveda-rivera et al., 2025). The reliance on cross-sectional study designs in many investigations precludes the establishment of temporal dynamics and causal relationships between gut microbiome features and neurodegeneration (Fan et al., 2025; Kang et al., 2025; Zhao et al., 2025). For intervention trials, the uncontrolled design often used prevents definitive conclusions regarding the causality of observed effects following interventions like probiotic administration (Marizzoni et al., 2026).

Furthermore, methodological heterogeneity introduces significant variability, stemming from differences in diagnostic criteria, selection of probiotic strains and dosages, intervention durations, sequencing protocols (16S rRNA vs. shotgun metagenomics), and the specific cognitive assessment tools utilized (Dong et al., 2025; Fan et al., 2025; Koumpouli et al., 2025; Quansah et al., 2025; Upadhyay et al., 2025). The highly variable nature of the inter-individual microbiome composition further complicates the design of generalized therapeutic protocols (Koumpouli et al., 2025; Sepúlveda-rivera et al., 2025; Upadhyay et al., 2025).

Confounding variables, such as unmeasured lifestyle factors, dietary patterns, or the concurrent use of medications (including antibiotics, oral probiotics, or anti-dementia drugs), are recognized to influence microbial composition and may confound outcomes, yet are often not fully controlled for in analyses (Fan et al., 2025; Pfaffinger & Seeley, 2025; Sepúlveda-rivera et al., 2025; Zhao et al., 2025). Finally, several studies noted the absence of biomarker confirmation of AD pathology (e.g., Aβ or tau) in their clinical populations, which constrains the biological interpretation of microbial changes (Marizzoni et al., 2026; Sepúlveda-rivera et al., 2025).

Future Directions

To bridge the gap between correlation and causation and to realize the clinical potential of the gut–brain axis, future research must address current limitations through targeted experimental designs.

First, there is a critical need for large-scale, long-term randomized controlled trials (RCTs) to validate the efficacy, safety, and sustained effectiveness of microbiota-modulating strategies across the Alzheimer's disease (AD) continuum, with intervention periods extending beyond 12 weeks to adequately capture disease progression (Dong et al., 2025; Quansah et al., 2025; Sepúlveda-Rivera et al., 2025; Sharma et al., 2025).

Second, mechanistic studies should move beyond observational correlations to establish causal relationships between specific gut microbial features and AD pathology, focusing on molecular and neuropathological pathways through which metabolites such as short-chain fatty acids (SCFAs) and lithocholic acid influence neuroimaging and cognitive outcomes (Fan et al., 2025; Kang et al., 2025; Zhao et al., 2025).

Third, advancing personalized medicine requires the development of tailored gut-based therapies using specific strains, prebiotics, or metabiotics matched to individual microbiome profiles, with careful determination of optimal types, dosages, and timing of interventions (Pfaffinger & Seeley, 2025; Sharma et al., 2025; Upadhyay et al., 2025; Zhou et al., 2025).

Fourth, integrating multi-omics and longitudinal datasets—including microbiota sequencing, metabolomics, immune profiling, neuroimaging, and detailed clinical and dietary records—will enable comprehensive models of disease pathogenesis and enhance biomarker discovery (Fan et al., 2025; Wang et al., 2025; Wu et al., 2025; Zhao et al., 2025). Fifth, species- and strain-level analyses are essential to uncover novel pathological mechanisms, as pathogenic potential can vary even within the same genus (Fan et al., 2025; Pfaffinger & Seeley, 2025). Finally, future studies must optimize delivery systems, such as encapsulation or protective coatings, to ensure the viability and targeted colonization of therapeutic bacterial strains (Zhou et al., 2025). Collectively, these directions will strengthen causal inference, refine therapeutic strategies, and accelerate translation of gut–brain axis research into clinical practice.

CONFLICT OF INTEREST

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