The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 5550-5553

# Gut Microbiota Alterations and Their Impact on Alzheimer's disease Progression: Review article

**Yaser Al Msalmeh**
Mediclinic Alain Hospital, UAE
**E mail:** yaseralmsalmeh@yahoo.com, **ORCID:** 0009-0004-4149-4534, **Mobile:** +971558147679

## ABSTRACT

**Background:** Alzheimer's disease (AD), a progressive neurodegenerative disorder, affects over 50 million people worldwide, causing significant cognitive decline and memory impairment. Emerging evidence suggests that the gut microbiota, through the gut-brain axis, plays a critical role in AD pathogenesis by modulating neuroinflammation, amyloid-beta (Aβ) deposition and tau pathology. Dysbiosis or microbial imbalance has been linked to exacerbated AD progression with studies reporting reduced microbial diversity and altered taxonomic profiles in AD patients. **Objective:** This literature review aimed to synthesize current evidence on gut microbiota alterations and their impact on AD progression, drawing from clinical, preclinical and mechanistic studies published between 2015 and 2024.

**Methods:** A systematic search was conducted using PubMed, Google Scholar, and Scopus, with keywords including "Gut microbiota", "Alzheimer's disease", "Gut-brain axis", "Neurodegeneration", "Microbiome dysbiosis", "Alzheimer's progression" and "probiotics". The writers evaluated relevant literature references as well. Documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts, and unpublished manuscripts were excluded.

**Conclusion:** Findings indicated that reduced Firmicutes, increased Bacteroidetes and decreased Bifidobacterium are common in AD, correlating with elevated biomarkers like Aβ42 and phosphorylated tau. Animal models and limited human trials suggest that microbial metabolites, such as short-chain fatty acids (SCFAs), influence neuroprotection, while dysbiosis promotes systemic inflammation. Therapeutic strategies, including probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation (FMT), showed promise but lack large-scale validation. Challenges include variability in microbial profiles, small sample sizes, and inconsistent methodologies. This review highlights the gut microbiota as a potential therapeutic target for AD, advocating for standardized research protocols, longitudinal studies and robust clinical trials to establish causality and therapeutic efficacy.

**Keywords:** Gut microbiota, Alzheimer's disease, Gut-brain axis, Dysbiosis, Neuroinflammation, Amyloid-beta, Probiotics, Fecal microbiota transplantation.

## INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia, contributing to 60–80% of global dementia cases, with an estimated prevalence of 50 million and rising due to aging populations [1]. Characterized by amyloid-beta (Aβ) plaques, neurofibrillary tangles, and neuronal loss, AD results in progressive cognitive decline, memory impairment, and behavioral changes, posing substantial socioeconomic challenges [2]. Current treatments, such as cholinesterase inhibitors, offer symptomatic relief but fail to halt disease progression, underscoring the need for novel therapeutic targets [3]. Recent research has identified the gut-brain axis—a bidirectional communication network between the gastrointestinal tract and central nervous system—as a critical modulator of AD pathology [4].

The gut microbiota, comprising approximately 100 trillion microorganisms, regulates immune function, metabolism, and brain health through neural, endocrine, and immune pathways [5]. Dysbiosis, defined as an imbalance in microbial composition, has been implicated in numerous conditions, including obesity, diabetes, and neurodegenerative diseases like AD [6]. In AD, dysbiosis may exacerbate neuroinflammation, promote Aβ aggregation, and compromise blood-brain barrier integrity, accelerating disease progression [7]. Observational studies have reported consistent microbial alterations in AD patients, such as reduced microbial diversity, decreased Firmicutes, and increased Bacteroidetes, though findings vary due to environmental and genetic factors [8].

This review aimed to comprehensively evaluate the role of gut microbiota alterations in AD progression, exploring underlying mechanisms, therapeutic interventions and research gaps. By synthesizing evidence from clinical trials, animal models and mechanistic studies, we seek to clarify the gut-brain axis's contribution to AD and assess the potential of microbiota-targeted therapies.

## REVIEW

### 1. Gut microbiota composition in Alzheimer's disease

**1.1 Observational studies in humans:** Human studies consistently report altered gut microbiota in AD patients compared to healthy controls. **Vogt *et al.*** [7] conducted a cross-sectional study of 25 AD patients and 25 age-matched controls, analyzing fecal samples via 16S rRNA sequencing. They found reduced microbial diversity and a decreased Firmicutes-to-Bacteroidetes ratio in AD patients, which correlated with elevated cerebrospinal fluid (CSF) levels of Aβ42 and phosphorylated tau, key AD biomarkers. **Zhuang *et al.*** [8] extended these findings in a cohort of 43 AD patients, identifying increased Proteobacteria and decreased Bifidobacterium suggesting a shift toward a pro-



Received: 30/05/2025
Accepted: 02/08/2025

inflammatory microbial profile. These microbial changes were associated with higher systemic inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6) [9].

However, variability across studies poses challenges. For instance, **Liu *et al.*** [10] found no significant microbial differences in patients with early-stage amnestic mild cognitive impairment (aMCI), a precursor to AD, compared to controls, suggesting that dysbiosis may be more pronounced in later disease stages. Factors such as diet, geographic location, and medication use (e.g., antibiotics) likely contribute to these discrepancies [6].

**1.2 Preclinical evidence from animal models:** Animal models provide controlled insights into microbial influences on AD. In APP/PS1 transgenic mice, a widely used AD model, **Harach *et al.*** [11] observed dysbiosis characterized by reduced Allobaculum and Akkermansia species, alongside increased Proteobacteria.

Germ-free APP/PS1 mice exhibited significantly lower Aβ pathology compared to colonized counterparts, suggesting that gut microbes directly influence amyloid deposition. Similarly, **Minter *et al.*** [12] demonstrated that antibiotic-induced microbiota depletion in AD-model mice reduced Aβ plaque formation and microglial activation, further implicating microbiota in disease progression.

These findings highlight the gut microbiota's role in modulating AD pathology, though translating preclinical results to humans remains challenging due to species-specific microbial differences and environmental influences [4].

## 2. Mechanisms linking gut microbiota to AD progression

The gut-brain axis facilitates microbial effects on AD through multiple pathways, detailed below.

**2.1 Neuroinflammation and systemic inflammation:** Dysbiosis increases gut permeability, often referred to as "leaky gut," allowing pro-inflammatory molecules like lipopolysaccharides (LPS) to enter systemic circulation [6]. LPS can cross the blood-brain barrier, activating microglia and triggering neuroinflammation, a hallmark of AD [13]. According **Zhao *et al.*** [14], lipopolysaccharide (LPS) accumulates in neocortical neurons relevant to Alzheimer's disease and disrupts transcription and communication between neurons and glia. The authors speculate that microbial LPS which penetrates into the brain, may initiate neuroinflammation and microglial activation which in turn may trigger neuronal injury and cognitive decline.[9].

**2.2 Microbial metabolites and neuroprotection:** Gut microbes produce metabolites, such as short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate, which have neuroprotective properties [5]. Butyrate, produced by Firmicutes species like Clostridium, enhances blood-brain barrier integrity and reduces neuroinflammation [15]. In AD patients, reduced SCFA-producing bacteria correlate with lower CSF butyrate levels and increased Aβ deposition [7]. Conversely, harmful metabolites, such as trimethylamine N-oxide (TMAO), produced by certain gut bacteria, have been linked to vascular dysfunction and AD risk [16].

**2.3 Amyloid cross-seeding:** Microbial-derived amyloids, produced by bacteria like Escherichia coli, may cross-seed with cerebral Aβ, promoting plaque formation [17]. **Kowalski and Mulak** [17] proposed that bacterial amyloids mimic Aβ structure, triggering misfolding and aggregation in the brain. This hypothesis is supported by studies showing that gut-derived amyloids can translocate to the brain in animal models, accelerating AD pathology [18].

**2.4 Blood-brain barrier dysfunction:** Dysbiosis compromises blood-brain barrier integrity, allowing neurotoxic substances to enter the brain. **Braniste *et al.*** [19] demonstrated that germ-free mice exhibit increased blood-brain barrier permeability, which is restored by colonization with SCFA-producing bacteria. In AD, this dysfunction may exacerbate Aβ accumulation and neuronal loss [13].

Imaging studies, such as positron emission tomography (PET) by **Li *et al.*** [20] showed correlations between gut dysbiosis and increased cerebral Aβ deposition in AD patients, supporting these mechanistic pathways. However, inconsistencies in early-stage AD suggest that microbial effects may be stage-dependent [10].

## 3. Therapeutic potential of microbiota-targeted interventions

**3.1 Probiotics and Prebiotics:** Probiotics and prebiotics aim to restore microbial balance and mitigate AD symptoms. A randomized controlled trial by **Akbari *et al.*** [21] administered a probiotic containing Lactobacillus acidophilus, Bifidobacterium bifidum, and other strains to 60 AD patients for 12 weeks. The intervention improved Mini-Mental State Examination (MMSE) scores and reduced CSF levels of inflammatory markers like IL-6. Similarly, prebiotics, such as fructooligosaccharides, have been shown to increase SCFA-producing bacteria in animal models, reducing neuroinflammation [22].

**3.2 Dietary interventions:** Dietary patterns influence gut microbiota composition and AD risk. The Mediterranean diet, rich in fiber, polyphenols, and omega-3 fatty acids, promotes microbial diversity and SCFA production [23]. A cohort study by **Shannon *et al.*** [23] found that adherence to the Mediterranean diet was associated with a 20% lower risk of AD and increased abundance of Bifidobacterium and Lactobacillus. Ketogenic diets, which alter microbial metabolism, have also shown promise in preclinical AD models but require human validation [24].

**3.3 Fecal microbiota transplantation (FMT):** FMT, the transfer of healthy donor microbiota, has shown potential in preclinical studies. **Sun *et al.*** [25] reported that FMT from healthy mice to APP/PS1 mice reduced Aβ pathology, improved cognitive function, and restored microbial diversity. In humans, FMT has been explored for other conditions (e.g., Clostridium difficile infection), but AD trials are limited by ethical concerns, including risks of infection and immune reactions [26]. A pilot study by **Hazan** [27] reported improved cognitive scores in one AD patient post-FMT, but larger trials are needed.

**3.4 Other emerging therapies:** Vagus nerve stimulation and microbial metabolite supplementation (e.g., sodium butyrate) are emerging as potential therapies. Preclinical studies suggest that butyrate supplementation reduces neuroinflammation and Aβ deposition in AD-model mice [28]. Additionally, antibiotics targeting specific pathogenic bacteria have constitutionally protected speech, such as Escherichia coli, are being investigated, though their impact on beneficial microbiota remains a concern [29].

**4. Limitations and future directions**

**4.1 Current challenges:** The field faces significant challenges. Variability in microbial profiles across studies, driven by differences in diet, genetics, and sequencing methods, hinders reproducibility [6]. Most human studies are observational, with small sample sizes (typically 20–100 participants), limiting causal inferences [7]. Preclinical models, while insightful, do not fully replicate human microbial ecosystems [4]. Additionally, the long-term safety and efficacy of interventions like FMT remain uncertain [28].

**4.2 Recommendations for future research:** Longitudinal studies tracking microbial changes across AD stages are critical to establishing temporality. Standardized 16S rRNA and metagenomic sequencing protocols would improve comparability across studies. Large-scale, double-blind clinical trials are needed to validate probiotics, prebiotics, and FMT, with a focus on early-stage AD to assess preventive potential. Identifying specific microbial taxa and metabolites (e.g., butyrate, TMAO) associated with AD progression could enable precision medicine approaches. Integrating multi-omics data (e.g., metabolomics & proteomics) with neuroimaging could further elucidate gut-brain interactions.

**4.3 Ethical and practical considerations:** Therapeutic development must address ethical concerns, particularly for FMT, which carries risks of pathogen transmission [26]. Public health initiatives should promote dietary interventions, which are low-risk and accessible, while ensuring equitable access to emerging therapies like probiotics [23].

## CONCLUSION

The gut microbiota plays a significant role in AD progression through mechanisms involving neuroinflammation, metabolite production, amyloid cross-seeding and blood-brain barrier dysfunction. Human and animal studies indicated that dysbiosis, characterized by reduced diversity and shifts in taxa like Firmicutes and Bacteroidetes, correlates with AD pathology. Therapeutic interventions, including probiotics, dietary modifications, and FMT, which showed promise but require rigorous validation. Addressing methodological inconsistencies, expanding clinical trials, and integrating multi-omics approaches are essential to translate these findings into effective AD treatments. The gut microbiota represents a novel therapeutic frontier, particularly for early intervention, with the potential to transform AD management.

**Funding:** No fund
**Conflicts of interest:** None.

## REFERENCES

1. https://www.alzheimer-europe.org/news/alzheimers-disease-international-publishes-world-alzheimer-report-2023?language_content_entity=en
2. https://www.who.int/news-room/fact-sheets/detail/dementia
3. **Hardy J, Selkoe D (2002):** The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science, 297: 353–356.
4. **Cryan J, O’Riordan K, Cowan C*et al.* (2019:** The microbiota-gut-brain axis. Physiol Rev., 99: 1877–2013.
5. **Valdes A, Walter J, Segal E, Spector T (2018):** Role of the gut microbiota in nutrition and health. BMJ., 361: k2179.
6. **Jiang C, Li G, Huang P, Liu Z, Zhao B (2017):** The gut microbiota and Alzheimer’s disease. J Alzheimer’s Dis., 58: 1–15.
7. **Vogt N, Kerby R, Dill-McFarland K *et al.* (2017):** Gut microbiome alterations in Alzheimer’s disease. Sci Rep., 7: 13537.
8. **Zhuang Z, Shen L, Li W *et al.* (2018):** Gut microbiota is altered in patients with Alzheimer’s disease. J Alzheimer’s Dis., 63: 1337–1346.
9. **Cattaneo A, Cattane N, Galluzzi S *et al.* (2017):** Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging, 49: 60–68.
10. **Liu P, Wu L, Peng G *et al.* (2019):** Altered microbiomes distinguish Alzheimer’s disease from amnestic mild cognitive impairment. Brain Behav Immun., 80: 633–640.
11. **Harach T, Marungruang N, Duthilleul N *et al.* (2017):** Reduction of Alzheimer’s disease amyloid-β pathology in the absence of gut microbiota. Sci Rep., 7: 41802.
12. **Minter M, Zhang C, Leone V *et al.(2016):*** Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer’s disease. Sci Rep., 6:27328.
13. **Szablewski L(2019):** Role of the immune system in Alzheimer’s disease. Cent Eur J Immunol., 44:223–229.
14. **Zhao Y, Cong L, Lukiw W (2017):** Lipopolysaccharide (LPS) accumulates in neocortical neurons of Alzheimer’s

disease (AD) brain and impairs transcription in human neuronal-glial primary co-cultures. Frontiers in aging neuroscience, 9:407.

15. **Dalile B, Van Oudenhove L, Vervliet B *et al.* (2019):** The role of short-chain fatty acids in microbiota–gut–brain communication. Nature reviews Gastroenterology & hepatology, 16(8):461-478.
16. **Vogt N, Romano K, Darst B *et al.* (2018):** The gut microbiota-derived metabolite trimethylamine N-oxide is elevated in Alzheimer’s disease. Alzheimer's research & therapy, 10(1):124.
17. **Kowalski K, Mulak A (2019):** Brain-gut-microbiota axis in Alzheimer’s disease. Journal of neurogastroenterology and motility, 25(1):48.
18. **Javed I, Zhang Z, Adamcik J *et al.* (2020):** Accelerated amyloid beta pathogenesis by bacterial amyloid FapC. Advanced Science, 7(18):2001299.
19. **Braniste V, Al-Asmakh M, Kowal C *et al.* (2014):** The gut microbiota influences blood-brain barrier permeability in mice. Science translational medicine, 6(263):ra158-263ra158.
20. **Li B, He Y, Ma J *et al.* (2019):** Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. Alzheimer's & Dementia, 15(10):1357-1366.
21. **Akbari E, Asemi Z, Kakhaki R *et al.* (2016):** Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Frontiers in aging neuroscience, 8:229544.
22. **Sun J, Liu S, Ling Z *et al.* (2019):** Fructooligosaccharides ameliorating cognitive deficits and neurodegeneration in APP/PS1 transgenic mice through modulating gut microbiota. Journal of agricultural and food chemistry, 67(10):3006-3017.
23. **Shannon O, Ashor A, Scialo F *et al.* (2021):** Mediterranean diet and the hallmarks of ageing. European journal of clinical nutrition, 75(8):1176-1192.
24. **Nagpal R, Neth B, Wang S *et al.* (2019):** 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, 47:529-542.
25. **Sun J, Xu J, Ling Y *et al.* (2019):** Fecal microbiota transplantation alleviated Alzheimer’s disease-like pathogenesis in APP/PS1 transgenic mice. Translational psychiatry, 9(1):189.
26. **Zhang F, Luo W, Shi Y *et al.* (2012):** Should we standardize the 1,700-year-old fecal microbiota transplantation?. Official journal of the American College of Gastroenterology| , 107(11):1755.
27. **Hazan S (2020):** Rapid improvement in Alzheimer’s disease symptoms following fecal microbiota transplantation: a case report. Journal of International Medical Research, 48(6):0300060520925930.
28. **Govindarajan N, Agis-Balboa R, Walter J *et al.* (2011):** Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. Journal of Alzheimer’s Disease, 26(1):187-197.
29. **Dodiya H, Kuntz T, Shaik S *et al.* (2019):** Sex-specific effects of microbiome perturbations on cerebral Aβ amyloidosis and microglia phenotypes. Journal of Experimental Medicine, 216(7):1542-1560.