Medical Science

To Cite:
Steć G, Brzyska A, Siemianowski J, Kotnis W, Pawlak M, Prolejko S, Gajęcki B, Kopala J, Kucharski T, Buczek W. The role of gut microbiota in the pathogenesis of Alzheimer's disease: A review of the literature. *Medical Science* 2025; 29: e165ms3654
doi: https://doi.org/10.54905/disssi.v29i163.e165ms3654

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Peer-Review History
Received: 27 May 2025
Reviewed & Revised: 14/June2025 to 25/August/2025
Accepted: 05 September 2025
Published: 16 September 2025

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Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

The role of gut microbiota in the pathogenesis of Alzheimer's disease: A review of the literature

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, amyloid-beta (Aβ) accumulation, and neuroinflammation. While classical hypotheses—the amyloid cascade, tau protein pathology, and chronic inflammation—have long been the predominant explanations of AD pathogenesis, recent evidence highlights the fundamental role of the gut microbiota in affecting brain health. This review article describes the pathway through which gut dysbiosis contributes to AD by elevated intestinal permeability, systemic inflammation, disruption of the blood–brain barrier (BBB), and altered production of microbial metabolites. Experimental findings indicate that microbial imbalance in animal models and human groups leads to reduced microbial diversity, elevated levels of proinflammatory cytokines, and increased amyloid pathology. Moreover, gut-derived metabolites such as short-chain fatty acids (SCFAs), bile acids, and neurotransmitters regulate microglial function, synaptic health, and Aβ formation. Therapeutic strategies aimed at the restoration of microbiota homeostasis—dietary intervention, probiotics, prebiotics, and fecal microbiota transplantation (FMT)—have been successful in improving cognitive status and reducing neurodegeneration in preclinical models. Causality is still under investigation, but the microbiota-gut-brain axis is a productive area for future AD research and therapy. Further large-scale, long-term studies will be required to explain the mechanisms and to aid in the development of microbiota-based interventions.

Keywords: Alzheimer's disease; gut microbiota; neuroinflammation; gut-brain axis; blood–brain barrier

1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition that represents the most frequent cause of dementia and a growing global public health concern. With over 47 million people currently affected worldwide, experts predict that the number of cases will reach 82 million by 2030 and 152 million by 2050, primarily due to the aging population. AD mainly affects individuals over the age

of 65 and imposes a significant social, medical, and financial strain on people living with the disease, their families, and the healthcare system.

The AD typical symptoms usually develop slowly and get worse over time (Atri, 2019; Scheltens et al., 2021). Early signs often involve mild disturbances in short-term memory or recalling recent events. Additionally, patients might forget recent conversations or become disoriented in familiar environments. Difficulties with word-finding, decreased planning and organization skills, confusion, and mood changes such as irritability or apathy can also occur.

With the disease progression, symptoms become more pronounced and interfere with daily life. Patients may have trouble recognizing familiar people, experience greater difficulties with speech and understanding language, and suffer from disorientation in time and place. Repetitive behaviors, forgetting basic tasks, and difficulty with daily activities often occur. Psychological symptoms, such as anxiety, depression, delusions, or even aggression, may also appear.

In the advanced stages of AD, individuals lose the ability to function independently. Cognitive and communicative abilities severely decline - patients may no longer recognize loved ones or speak coherently. Motor difficulties, problems with eating and swallowing, and loss of bladder and bowel control become common. The person becomes entirely dependent on caregivers in their daily functioning.

AD multifactorial pathogenesis involves a complex interplay between genetic, molecular, and environmental factors; however, scientists still lack a complete understanding of the complex molecular mechanisms involved in AD pathophysiology.

The disease begins years before the onset of clinical symptoms, in a preclinical phase characterized by cellular and molecular alterations in the brain.

A hallmark of AD pathology is the cerebral accumulation of abnormal proteins that are insoluble and resistant to degradation. These include: amyloid beta (Aβ) peptide and hyperphosphorylated tau protein (Bloom, 2014; Hardy and Higgins, 1992). Amyloid precursor protein (APP), a transmembrane protein involved in neuroprotection and axonal transport, is cleaved into soluble fragments by a properly functioning alpha-secretase under physiological conditions, after fulfilling its functional role.

APP is cleaved into fragments known as beta-amyloid peptides in AD. The peptides aggregate to form extracellular plaques, which initiate a chain of pathologic events. One of the main effects of the process is hyperphosphorylation of tau protein, leading to intracellular neurofibrillary tangles. The brain accumulation of the two compounds causes accumulating neuronal loss and disrupted interneuronal transmission.

As the disease progresses, all the neuropathological changes lead to a decline in neurotransmitter levels, particularly acetylcholine (Akyuz et al., 2024). Dysfunctions also affect the serotonergic, noradrenergic, and dopaminergic systems, as well as signal transduction components such as adenylate cyclase, phosphoinositides, and protein kinase C.

Neuroinflammation also plays a vital role in the course of AD. The presence of Aβ and tau aggregates in the brain triggers chronic activation of the specialized immune cells of the central nervous system (CNS) - microglia (Singh, 2022). Typically, the role of microglia is to maintain brain homeostasis and respond to injury or infection. In AD, prolonged activation of microglia and the resulting constant inflammatory response contribute to neurotoxic damage.

Genetic risk factors, such as mutations in APOE (apolipoprotein E) and TREM2, can promote this activation (Sheppard and Coleman, 2020). These genes are essential for controlling microglia, processing lipids, and clearing amyloid deposits. Improper regulation of microglial function can result in neurotoxic damage.

Additional factors involved in AD pathogenesis include oxidative stress, mitochondrial dysfunction, vascular problems, and impaired clearance systems. These factors work together to worsen synaptic dysfunction, lead to neuronal loss, and cause cerebral atrophy. Lifestyle behaviors such as poor diet and reduced physical activity, as well as environmental and metabolic risk factors, including diabetes, cerebrovascular disease, head injury, and stress, are also considered essential players in increasing the risk of the disease. Dominant mutations in three genes encoding APP, PSEN1 (presenilin 1), and PSEN2 (presenilin 2) account for a small fraction of AD cases, typically associated with early-onset forms of the disease (Sheppard and Coleman, 2020).

Growing evidence suggests a link between gut microbiota dysbiosis and AD (Cattaneo et al., 2017; Liu et al., 2019; Vogt et al., 2017). The composition of gut microbiota in patients with AD differs from that of healthy individuals, particularly in terms of microbial diversity and the relative abundance of specific bacterial species, which may support the hypothesis of a link between gut microbiota composition and the pathogenesis of AD.

2. REVIEW METHODS

In this review, we synthesize and critically analyze current evidence of the role of gut microbiota in the pathogenesis and potential treatment of Alzheimer's disease. Our search of the literature covered several digital databases, such as PubMed, Scopus, and Google Scholar, for articles published up to April 2025. We used the following keyword operators in various combinations: "Alzheimer's disease", "gut microbiota", "gut-brain axis", "neuroinflammation", "dysbiosis", "amyloid-beta", "short-chain fatty acids", "microbiome", "fecal microbiota transplantation", "probiotics", and "blood-brain barrier"

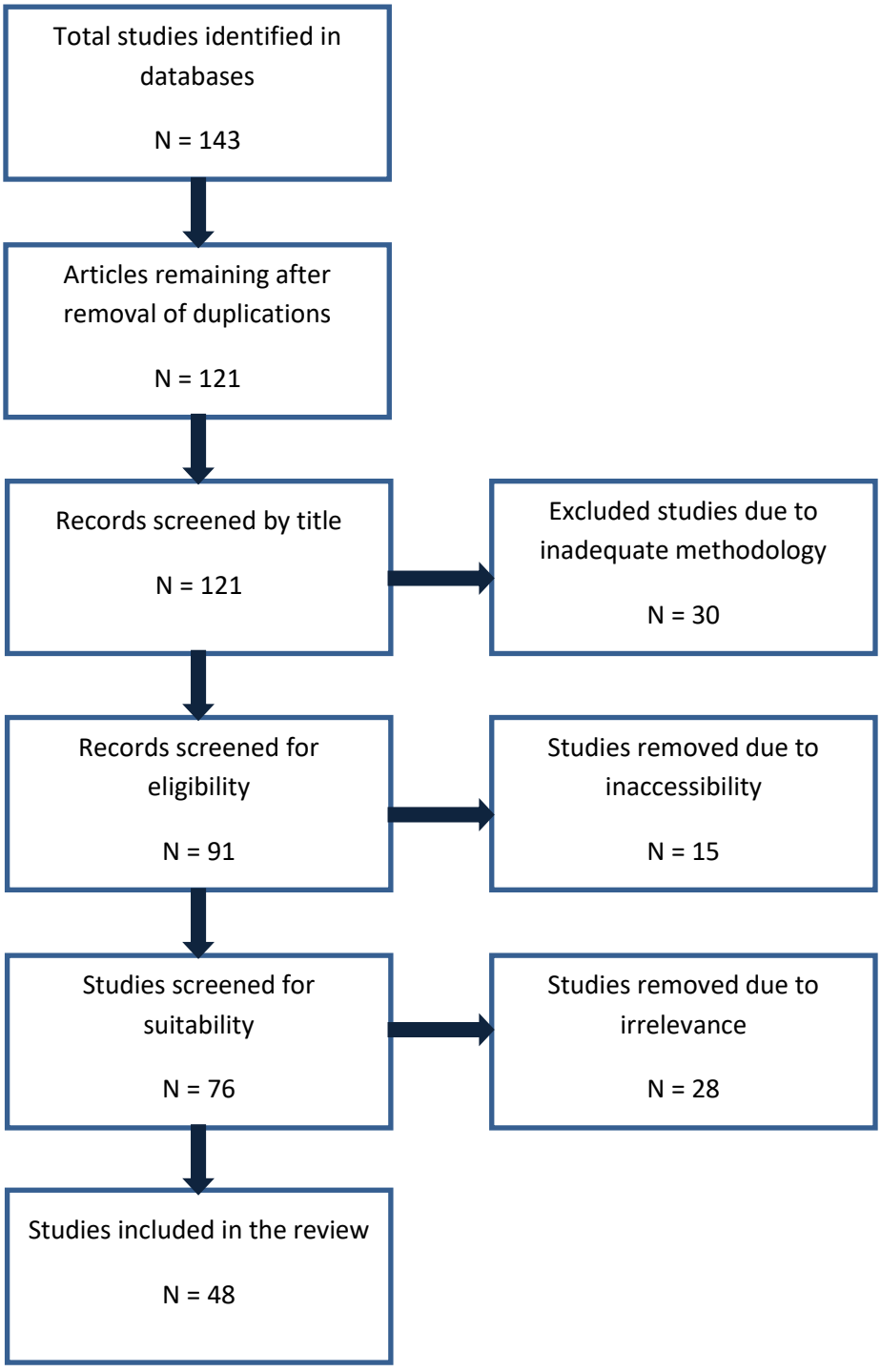

Figure 1 PRISMA chart

This review integrates human and animal studies to provide translational data, with preselection of peer-reviewed original research articles, systematic reviews, and meta-analyses. The inclusion criteria were publications that provided data or discussion relevant to the microbiota-AD relationship (Figure 1). We excluded articles focusing solely on other neurodegenerative diseases without mention of Alzheimer's pathology.

3. RESULTS AND DISCUSSION

Microbiota alterations in AD: evidence from human and animal studies

One of the first studies to explore the microbiome in AD was that of Cattaneo et al., (2017) who utilized qPCR to investigate six groups of microbes in an Italian cohort. The researchers observed that amyloid-positive participants had increased levels of Escherichia/Shigella and reduced levels of Bacteroides fragilis and Eubacterium rectale compared with amyloid-negative individuals. Another study by Vogt et al. examined the gut microbiome of 25 Alzheimer's patients and 25 matched healthy controls in the USA (Vogt et al., 2017). Using 16S rRNA sequencing, they determined a decrease in Firmicutes and Actinobacteria, and an increase in Bacteroidetes in patients with AD. Moreover, specific bacterial genera correlated with cerebrospinal fluid biomarkers of AD, including Aβ-42/Aβ-40 ratios and phosphorylated tau (pTau) (Vogt et al., 2017). Liu et al. further analyzed gut microbiome alterations, comparing fecal samples from AD patients, individuals with aMCI, and healthy controls (Liu et al., 2019). The results indicated significant diminished microbial diversity in AD patients compared to both aMCI and HC groups. Microbial composition differed across all three groups, with AD patients showing the highest abundances of Deferribacteres, Bacteroidetes, and Phascolarctobacterium. At the same time, the relative abundances of Clostridiaceae, Lachnospiraceae, and Ruminococcaceae were reduced compared to healthy controls. The overall abundance of the phylum Firmicutes was also lower in AD patients. In contrast, Proteobacteria were significantly enriched, with a progressive increase in Gammaproteobacteria, Enterobacteriales, and Enterobacteriaceae from HC to aMCI to AD. Further, the abundance of altered microbiota was found to correlate significantly with the clinical severity score of AD patients' symptoms (Liu et al., 2019).

Research on animal models also indicates a possible link between gut microbiota and brain functioning. This connection has been studied using, among other methods, germ-free (GF) mice - animals raised in completely sterile environments without any microorganisms - which have helped reveal important ways the microbiota affects brain function. For instance, GF Swiss-Webster mice demonstrated impaired non-spatial memory performance, suggesting a key role of the microbiota in cognitive function. Moreover, the expression of brain-derived neurotrophic factor (BDNF)—a molecule essential for synaptic plasticity and often diminished in AD—varied by sex in GF mice, being elevated in females but reduced in males (Gareau et al., 2011).

In another study, shifts in microbiota composition, resulting from long-term broad-spectrum antibiotic treatment in APP/PS1 transgenic mice, lead to reduced amyloid plaque buildup but increased levels of soluble Aβ and changes in immune signaling. These shifts also reduce glial activation around plaques and change microglial shape, suggesting that gut microbiota diversity plays a vital role in controlling immune responses that affect amyloid pathology (Minter et al., 2016).

Similarly, ampicillin-treated rats exhibited impaired spatial memory, as well as reduced NMDA receptor expression in the hippocampal region of the brain (Wang et al., 2015). In contrast, other studies reported that antibiotic exposure reduced neurogenesis in the hippocampus and caused memory deficits in mice (Möhle et al., 2016). These findings highlight the meaningful impact of microbiota integrity on brain health and AD-related neurodegeneration. The summary of key findings from human studies and animal studies on the relationship between gut microbiota and AD are presented in Tables 1 and 2.

Table 1. Summary of key findings from human studies on the relationship between gut microbiota and AD.

Study	Method	Key Microbiota Changes	Other Key Findings
Cattaneo et al., 2017	Microbial DNA qPCR assay	↑ Escherichia/Shigella, ↓ Bacteroides fragilis, ↓ Eubacterium rectale	Association with amyloid status; Correlations between bacteria abundance and cytokine levels
Vogt et al., 2017	16S rRNA sequencing	↓ Firmicutes, ↓ Actinobacteria (notably ↓ Bifidobacterium), ↑ Bacteroidetes	Correlation of specific genera with CSF biomarkers (Aβ42/Aβ40, p-tau)

Liu et al., 2019	16S rRNA sequencing	↓ Microbial diversity in AD; ↑ Deferribacteres, Bacteroidetes, Phascolarctobacterium; ↓ Clostridiaceae, Lachnospiraceae, Ruminococcaceae; ↓ Firmicutes; ↑ Proteobacteria (Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae)	Microbiota abundance correlated with clinical severity of AD

Table 2. Summary of key findings from animal studies on the relationship between gut microbiota and AD.

Study	Model	Key Findings
Gareau et al., 2011	Germ-free Swiss-Webster mice	Impaired non-spatial memory; sex-dependent BDNF expression (↑ in females, ↓ in males)
Minter et al., 2016	APP/PS1 transgenic mice, long-term broad-spectrum antibiotics	↓ Amyloid plaques, ↑ soluble Aβ, altered immune signaling; reduced glial activation, changed microglial morphology
Wang et al., 2015	Ampicillin-treated rats	Impaired spatial memory; ↓ NMDA receptor expression in hippocampus
Möhle et al., 2016	Antibiotic-treated mice	Reduced neurogenesis in hippocampus; memory deficits

The role of gut microbiota in the pathogenesis and progression of AD

Increased Intestinal Permeability and Systemic Inflammation

Gut dysbiosis, mainly characterized by an increased Firmicutes-to-Bacteroidetes ratio, contributes to increased intestinal permeability, a condition known as "leaky gut syndrome" (LGS) (Bischoff et al., 2014). As a result, bacterial components such as lipopolysaccharides (LPS) can translocate into systemic circulation.

Researchers found that LPS is present in increased amounts in the brains of individuals with AD, particularly accumulating around the nuclei of brain cells in the regions affected explicitly in AD, such as the neocortex and hippocampus (Zhao et al., 2017). Zhan et al., (2016) detected elevated LPS levels in both the gray and white matter of AD brains compared to controls. Moreover, immunofluorescence analysis showed co-localization of LPS with Aβ1–40/42 within amyloid plaques.

Toll-like receptors (TLRs), specifically TLR4, detect LPS in the human body and initiate cascade signaling, which results in the discharge of proinflammatory cytokines like TNF-α, IL-6, IL-8, and IL-12 (Paik et al., 2003). Additionally, LPS activates NF-κB signaling, which upregulates proinflammatory microRNAs, such as miRNA-146a and miRNA-155, ultimately suppressing complement factor H and potentially initiating AD-related pathology (Alexandrov et al., 2019). Chronic, low-grade systemic inflammation—a recognized risk factor for AD—is thus perpetuated (Cryan et al., 2019). Moreover, gut dysbiosis was associated with early APP deposition in the intestines (Brandscheid et al., 2017). Significantly, Aβ deposition and innate immune activation in the enteric nervous system precede CNS inflammation in mouse models, reinforcing the concept of gut-originating neurodegeneration (Semar et al., 2013).

Blood-Brain Barrier Dysfunction and Neuroinflammation

Gut dysbiosis also affects blood-brain barrier (BBB) integrity, which is critical for the regulation of central nervous system (CNS) homeostasis (Kadry et al., 2020). Elevated circulating bacterially derived bile acids (BAs) have been found to destabilize tight junction proteins in the BBB, increasing permeability and allowing peripheral toxins and cholesterol to enter the CNS (Quinn et al., 2014). This flooding causes an accumulation of cholesterol in the brain, where it directly engages with APP and enhances its insertion into lipid raft domains, facilitating amyloidogenic processing and enhanced production of Aβ (Gamba et al., 2012). Besides, BAs also trigger the farnesoid X receptor activation, which inhibits the expression of CYP46A1, a key enzyme in cholesterol homeostasis, worsening the

retention of cholesterol and Aβ deposits (Jia et al., 2020). Interestingly, evidence from postmortem analyses and MRI scans of individuals with AD reveals BBB disruption, which correlates with impaired memory and learning abilities (Montagne et al., 2015).

Secondly, increased permeability of the BBB facilitates entry of peripheral inflammatory mediators and microbial metabolites, such as trimethylamine N-oxide (TMAO), into the brain. TMAO has been implicated in AD pathology by enhancing β-secretase activity, which promotes further Aβ accumulation and cognitive decline (Gao et al., 2019).

Amyloid plaques make microglia become active and gather around them. Active microglia help keep inflammation going, which might limit some damage (Hansen et al., 2018). However, continuous activation of microglia might worsen the loss of nerve cells.

Microbial Metabolites

Specific metabolites, such as short-chain fatty acids (SCFAs), produced by commensal gut bacteria, play a pivotal role in maintaining microglial maturation and function. Recolonization with a complex microbiota community resulted in improved microglial features (Erny et al., 2015). SCFAs also interfere with protein-protein interactions critical for Aβ aggregation, potentially mitigating amyloid plaque formation (Ho et al., 2018). A growing body of evidence supports a link between AD and branched-chain amino acids (BCAAs) - essential amino acids, which come from a diet and microbial production in the gut. Some human population studies showed that higher circulating levels of BCAAs correlate with a lower risk of AD (Tynkkynen et al., 2018).

Effect of the Gut Microbiota on Neurotransmission

Neurotransmitters, such as acetylcholine (ACh), norepinephrine (NE), gamma-aminobutyric acid (GABA), dopamine (DA), and histamine (His), are bioactive molecules that mediate communication between neurons at chemical synapses. Alterations in neurotransmitter systems have been strongly implicated in the course of AD (Akyuz et al., 2024). Among these, the cholinergic deficit is the most consistently associated with AD pathology, and cholinesterase inhibitors such as donepezil remain one of the few approved symptomatic treatments (Stanciu et al., 2019). The gut microbiota produces and responds to several of these neurotransmitters, influencing brain function via the bloodstream or vagal signaling pathways (Strandwitz, 2018). AD is also marked by neuronal loss in brain regions responsible for the production of norepinephrine and histamine, namely the locus coeruleus and the tuberomammillary nucleus, respectively (Oh et al., 2019). Consequently, neurotransmitters of microbial origin may play an essential role in AD.

Overall, the evidence converges on a model in which gut dysbiosis is the initiator of a cascade of events that contribute to both amyloid aggregation and changes in microglial activity. This process begins with increases in permeability of the intestinal wall and systemic inflammation, and is followed by a disruption of the BBB, triggering an inflammatory response in the brain. Altered microbial metabolites also contribute to these outcomes.

All these interactions together suggest the potential of modulating the gut microbiota as a promising approach for the prevention or treatment of Alzheimer's disease, through interventions such as dietary modifications, probiotic use, or other strategies. Nevertheless, causal relationships have yet to be established, highlighting the strong need for further research in this field.

Gut Microbiota—Potential Therapeutic Strategies in AD

Dietary habits shape the composition of our gut microbiota (Liu et al., 2019). The Mediterranean diet, known for its anti-inflammatory foods, has been linked to reduced AD risk, improved cognition, and increased levels of beneficial gut bacteria and SCFA production. A meta-analysis by Loughrey et al., (2017) demonstrated that the Mediterranean diet improved cognitive functions and episodic memory in older adults, while Taylor et al., (2021) showed that higher intake of carbohydrates in the diet correlated with increased cerebral levels of Aβ in a subset of individuals.

In human studies, probiotic supplementation has improved cognitive performance and metabolic profiles in AD patients, although the findings are inconsistent (Lanctôt et al., 2004; Papalini et al., 2019). In animal models, mice with early-stage AD treated with multi-strain probiotic - SLAB51 showed reduced brain damage and amyloid beta buildup compared to untreated mice (Bonfili et al., 2018). As a result, cognitive decline in the probiotic-treated group was slower compared to controls, suggesting beneficial effects of probiotics in modulating disease progression.

In addition, prebiotics, which promote the growth of beneficial gut bacteria, also showed some positive effects in several AD models. For example, the prebiotic Morinda officinalis improved cognitive functions, elevated neurotransmitter levels, and reduced oxidative stress in rat models of AD (Chen et al., 2017). Supplementation with xylooligosaccharide also helped preserve mitochondrial and synaptic function and improved memory in rats fed with a high-fat diet (Chunchai et al., 2018). Likewise, fructooligosaccharide

(FOS) treatment improved behavioral deficits, reduced Aβ deposition, and increased the expression of synaptic plasticity markers, such as PSD-95 and synapsin, in APP/PS1 mice (Sun et al., 2019; Liu et al., 2019).

Another promising strategy for restoring healthy gut microbial communities is fecal microbiota transplantation (FMT). In GF APP/PS1 mice, FMT from conventional APP/PS1 donors increased cerebral Aβ levels, while transplantation from wild-type (WT) donors did not, indicating a microbial contribution to amyloidosis (Harach et al., 2017). Furthermore, FMT from WT to APPswe/PS1dE9 mice led to improved memory and reduced Aβ and tau pathology, along with normalization of synaptic and inflammatory markers (Sun et al., 2019).

4. CONCLUSION

While we already know that things like amyloid buildup, tau problems, and long-lasting inflammation explain partially the process behind AD development, more and more research shows that gut bacteria might also have an important part to play. An increasing number of studies suggest that gut bacteria can affect neuroinflammation, amyloid buildup, and synaptic function through different pathways. To fully understand this link, large-scale studies integrating genomic, metabolomic, and transcriptomic data are essential. These could reveal how microbial dysbiosis influences AD at a molecular level and potentially open new avenues for personalized microbiome-targeted therapies.

Acknowledgments

The authors have no acknowledgments to disclose.

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Tomasz Kucharski: Conceptualization, writing- rough preparation
Weronika Buczek: Writing - Review and editing, supervision
All authors have read and agreed to the published version of the manuscript.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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