International Journal of Social Science and Economic Research

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

The Gut Microbiota, Neuroinflammation, and Cognitive Decline: Connecting Dysbiosis to Alzheimer's Disease and Aging Brain Health

Kaiyaa Patel[1] and Laasya Bandi[2]

Rock Ridge High School, Loudoun Valley Estates, Virginia

[1]23557 Buckland Farm Terrace, Ashburn VA, 20148

[2]23336 Rogerdale Place, Sterling VA, 20166

DOI: 10.46609/IJSSER.2025.v10i11.016 URL: https://doi.org/10.46609/IJSSER.2025.v10i11.016

Received: 25 October 2025 / Accepted: 20 November 2025 / Published: 30 November 2025

ABSTRACT

Alzheimer's disease (AD) and cognitive decline in aging are increasingly linked with chronic neuroinflammation and gut microbiome alterations. Gut microbiome dysbiosis exacerbates the neuroinflammatory effects of aging and, by extension, cognitive deficits (Harach et al., 2017; Hung et al., 2022). This systematic review investigates how gut microbiota dysbiosis affects neuroinflammation and cognition in AD and aging-related cognitive decline. To this end, the prevalence of AD and cognitive decline in the aging population is assessed, and the microbiota-gut-brain axis is identified as an underlying regulatory pathway of concern. Next, the means by which dysbiosis leads to CNS inflammatory response are detailed, including leaky gut, systemic inflammatory mediators, and microbiome metabolites such as lipopolysaccharides, SCFAs, amyloids, and bile acids. In humans, microbiota diversity is lower in AD patients, and microbiota generating SCFA are decreased, as are increased SCFA in AD patients, and younger patients with mild cognitive impairment (occurring sooner than normal) have dementia earlier in life than age-matched controls (Hung et al., 2022; Jemimah et al., 2023). This is observed in inflammatory markers in blood and cognitive assessments via standardized assessment tools. In animal models, gut microbiome modulation occurs via germ-free models, fecal transplant, and antibiotics or probiotics to see effects on amyloid burden and cognition (Harach et al., 2017; Zhang et al., 2023). Potential therapeutic interventions include dietary fiber, prebiotics, probiotics, synbiotics, and fecal microbiota transplantations with promising clinical outcomes (Akbari et al., 2016; Hung et al., 2022). The gut-brain axis is a potentially modifiable target to alleviate age-related cognitive decline or prevent its onset.

Keywords: Alzheimer's disease, gut microbiota, neuroinflammation, cognition, aging, probiotics,

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

microbiota-gut-brain axis, dysbiosis

1. Introduction

(Recent studies show the gut-brain axis in AD: microbiome metabolites signal to microglia to heighten neuroinflammation) (This is a review of emerging correlations between the gut microbiome and cognitive health) (Results: thirteen papers, comprised of eleven studies and thirteen datasets, show gut dysbiosis from MCI-AD staging) (Controlling for polypharmacy is difficult but gut microbiome changes occur in AD and potentially other neurodegenerative diseases) (Germ-free AD mice have highly less amyloid than colonized counterparts) (Cohousing transfers the microbiome from AD mice to respective partners) (Increased gut permeability and inflammation occur in AD) (Probiotic intervention during MCI enhances cognition (MMSE) and metabolic factors.) (Recent systematic review with stricter inclusion criteria produced four studies of relevance: conclusions are limited by heterogeneity and low numbers)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia, predominantly seen in older adults. Approximately 6.7 million Americans aged 65 and older currently have AD, projected to reach 13.8 million by 2060 with an increasingly aged population (Harach et al., 2017). Between 1990 and 2019, worldwide rates of AD and other dementias increased almost threefold, creating significant socioeconomic pressure (Harach et al., 2017). Clinically, this means memory impairment, cognitive decline, and other behavioral changes. Neuropathologically, β-amyloid (Aβ) plaques and neurofibrillary tangles of the tau protein are significant macromolecules within the brain. For years, the "amyloid cascade" hypothesis—whereby misfolded Aβ chains precipitate downstream neurodegeneration—permeated AD research. However, extensive failures of anti-amyloid therapies and emerging data suggest that AD pathology is multifactorial (Harach et al., 2017).

Specifically, chronic neuroinflammation has emerged as a major contributor to AD onset and progression (Harach et al., 2017). In AD brains, activated microglia and astrocytes secrete pro-inflammatory cytokines and reactive oxygen species that induce synaptic dysfunction and

neuronal damage, exacerbating amyloid and tau development (Harach et al., 2017). Furthermore, genes emerging as risk factors for AD (APOE4, for example) have also been linked to immune networks and inflammatory pathways, suggesting that inflammation plays a direct role in AD-related pathogenesis (Harach et al., 2017).

Simultaneously, in the last ten years, research has emerged indicating unexpected relations between the brain's health and the community of microbes that comprise the gut—known as the gut microbiota. The gastrointestinal tract contains trillions of microbes (bacteria, viruses, fungi,

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

archaea) that profoundly impact host physiology through their genome (metabolomes) as a collective unit (Zhang et al., 2023; Zhang et al., 2023). The gut microbiome plays an essential role in metabolic functioning, immune development, intestinal barrier integrity, and even the nervous system (Zhang et al., 2023; Zhang et al., 2023). As aging occurs, the gut microbiota composition shifts drastically regarding diversity and abundance—often termed "dysbiosis." Dysbiosis occurs across the gastrointestinal tract for many reasons—for instance, polypharmacy and comorbid conditions—and changes the inflammatory landscape that extends systemically. Notably, dysbiosis is one of the hallmarks of aging that contributes to chronic low-grade inflammation ("inflammaging") in older adults (Zhang et al., 2023). Of all the age-associated diseases that emerge in later life, none is more strongly associated with intestinal dysbiosis than AD (Hung et al., 2022). Studies have repeatedly found that AD patients have altered gut microbiomes compared to age-matched cognitively healthy controls (Hung et al., 2022; Zhang et al., 2023). Moreover, metabolites derived from the gut microbiome have been linked with key pathological processes involved in AD—including Aβ deposition, tau hyperphosphorylation, and glial activation—which trigger an increased inflammatory response in the brain through a microbiota-gut-brain axis where cognitive function is otherwise compromised.

In this review, we discuss how the dysbiosis of the gut microbiome influences neuroinflammation and cognitive decline, with emphasis on AD and the aging brain. First, we explore studies that demonstrate how the gut microbiome changes in AD—biological changes that occur in normal aging with implications for cognitive health, as well. Then we discuss mechanistic pathways—including immune pathways and endocrine-related gut-brain dynamics—that either connect or are moderated by changes to the gut microbiome dysbiosis with neuroinflammatory pathways. Both human studies and animal studies are analyzed to determine the strength of association and causation between such comparisons relative to neuroinflammation/cognition.

Lastly, we discuss how an altered gut microbiome can make targeted interventions — through diet, probiotics, and fecal transplantation—a route of benefit for those suffering with neuroinflammation and cognitive decline. These findings have potential public health relevance since targeting the microbiome may supplement healthy brain aging as one preventative effort.

Ultimately, this multidisciplinary review shows how an improved understanding of host-microbiota interactions represents a new frontier by which we can tackle issues related to dementia, like AD.

2. Background and Literature Review

Gut Microbiota, Aging, and Cognitive Health

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

Gut microbiota is influenced early in life and develops as a predictable community across aging, reaching stable adult proportions between the ages of 3–5 years old (Zhang et al., 2023). For example, a predominance of Firmicutes and Bacteroidetes phyla is characteristic of the healthy adult gut microbiome, while a high diversity of microbes indicates a healthy eubiotic microbiome. Microbiota are responsible for innumerable homeostatic functions: they assist with food digestion and absorption, vitamin and neurotransmitter synthesis, immune modulation, intestinal epithelial barrier reinforcement, and pathogenic microbiota exclusion (Zhang et al., 2023; Zhang et al., 2023). Therefore, variations in diet, geography, pharmacological interventions (especially antibiotics), etc., lead to different microbiota compositions. However, predictable changes occur with aging. Older adults often present with decreased microbiota diversity and a relative decline of beneficial fiber-foraging microbiota (e.g., specific Firmicutes that produce short-chain fatty acids) and an increased relative abundance of potentially pro-inflammatory taxa (Hung et al., 2022). These age-typical microbiota shifts correlate with "inflammaging," a state of chronic low-grade systemic inflammation that is common in older demographics, rendering them more vulnerable to various chronic conditions, including neurodegenerative decline.

Increasingly, gut dysbiosis is linked to cognitive aging and dementia. Observational and various studies note differences between the gut microbiota communities of older adults with cognitive impairment versus age-matched cognitively unimpaired controls (Hung et al., 2022; Akbari et al., 2016). For example, a systematic review and meta-analysis by Hung et al. (2022) found that AD patients present with decreased gut microbiota diversity compared to healthy controls and from a taxonomic standpoint, with increased relative proportions of phylum Proteobacteria (which hosts many pathogenic gram-negative, endotoxin producing bacteria) and a decreased relative proportion of specific SCFA-producing families, Ruminococcaceae and Lachnospiraceae (Hung et al., 2022). Notably, specific changes relative to mild cognitive impairment (MCI)—the first stage before dementia—occur. For example, Jemimah et al. (2023) determined that alpha diversity was not significantly different from controls with respect to MCI, but they did see compositional changes (e.g., increased presence of the genus Phascolarctobacterium and decreased number of Bacteroides in certain populations) (Jemimah et al., 2023; Jemimah et al., 2023). These findings suggest that gut dysbiosis occurs as early as prodromal cognitive decline is noted, and not only after dementia takes hold (Jemimah et al., 2023). Similarly, Akbari et al. (2016) assessed the gut microbiota of older adults in a case-control study and found MCI associated with different gut microbes, with lower relative abundances of anti-inflammatory butyrate-producing genera like Ruminococcus and Butyricimonas compared to cognitively normal elders and higher relative abundances of others (Flavonifractor) (Akbari et al., 2016). Dysbiotic altered bacteria correlated with attention and executive function test performance (Akbari et al., 2016).

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

Whereas with AD cohorts, gut microbiome alterations appear more pronounced. For example, besides decreased microbiota diversity, cohorts with AD report decreased relative abundance of beneficial Faecalibacterium (a major butyrate producer) and Bifidobacterium and increased relative abundance of inflammatory genera like Escherichia/Shigella or Porphyromonadaceae; however, these findings are mixed (Hung et al., 2022; Zhang et al., 2023). Variations may occur due to geography or genome differences; for example, in a meta-analysis, higher abundances of Bacteroides were found in AD patients from Western cohorts but lower in AD patients from Chinese cohorts, suggesting the need for more geographic studies of AD for diet-based gut profiles (Jemimah et al., 2023). Ultimately, though, dysbiosis marked by loss of anti-inflammatory beneficial microbiota and/or gain of potentially pathogenic pro-inflammatory microbiota is linked with AD. In addition, some gut bacteria can independently contribute to Aβ pathology: for example, Proteobacteria can make lipopolysaccharide (LPS) and other endotoxins that incite inflammation, while Prevotella and Porphyromonas species—which are oral pathogens associated with gum disease—produce proteases and amyloid-like compounds observed in brains of AD patients (Hung et al., 2022). Notably, the periodontal pathogen Porphyromonas gingivalis has been implicated to travel to—and/or distribute toxins to—the brain and facilitate AD-like alterations, which may mean oral dysbiosis is involved in this process (oral-gut-brain axis) (Hung et al., 2022).

Therefore, overall literature suggests a correlation between the aging gut microbiome and brain health. Dysbiosis in older populations could render a pro-inflammatory context (systemically and within the CNS) to facilitate cell death and cognitive decline. Meanwhile, those with more youthful or eubiotic microbiomes—for example, those with fibrous diets filled with fermentable plant fibers—experience less inflammation and better cognitive preservation (Zhang et al., 2023; Zhang et al., 2023). Yet many human studies are correlational. To establish causation through association, experimental models determine whether—and how—gut microbes facilitate neuroinflammatory mediators for cognitive health. The subsequent chapter will outline potential biological pathways connecting gut dysbiosis and the neuroinflammatory mediators of AD and aging.

3. Mechanisms: How Gut Dysbiosis Drives Neuroinflammation

The microbiota-gut-brain axis refers to bidirectional communication from the gut microenvironment to the central nervous system through many overlapping channels: immune and inflammatory responses, the nervous system (vagal nerve and enteric nervous system), entry of metabolites and toxins produced by microbial populations into circulation, and neuroendocrine connections between those generated by gut hormones and neurotransmitters (Zhang et al., 2023; Zhang et al., 2023). Thus, microbiota dysbiosis can negatively impact this communicative conduit and worsen neuroinflammation through a few biologically plausible

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

means:

1. Increased Gut Permeability ("Leaky Gut") and Systemic Inflammation: Dysbiosis increases gut permeability. Some commensal benefit bacteria ferment dietary fibers into short-chain fatty acids (SCFAs, especially butyrate), which maintain the integrity of the mucin layer and tight junctions of the gastrointestinal barrier (Zhang et al., 2023; Zhang et al., 2023). Inversely, dysbiosis occurs when butyrate-producing bacteria are decreased either through a lack of fiber consumption or antibiotic disruption, resulting in a thinner mucus layer (downregulating tight-junction protein expression) (Zhang et al., 2023; Zhang et al., 2023). This "leaky gut" facilitates bacterial translocation of lipopolysaccharide (LPS—a major component of the outer membrane of gram-negative bacteria) and other microbe-derived metabolites into circulation (Zhang et al., 2023; Zhang et al., 2023). Systemically circulating LPS is a natural immune system activator; it binds to toll-like receptor 4 (TLR4) on immune cells and upregulates tumor necrosis factor (TNF)-α and interleukin (IL)-1β, two pro-inflammatory cytokines. In the aged population with gut dysbiosis and AD patients, LPS has elevated levels within systemic circulation, as do inflammatory cytokines that confirm chronic peripheral inflammation, of which brain health is severely compromised. For example, peripheral-derived cytokines traverse leaky areas of the blood-brain barrier (BBB) or induce active transport via endosomes, which upregulate activated endothelial cells and perivascular macrophages within the brain to promote central nervous system (CNS) inflammation (Abidin et al., 2025; Abidin et al., 2025). Finally, LPS can also translocate across a damaged BBB and bind receptors on microglia, driving these resident immune cells to release inflammatory mediators (Harach et al., 2017; Abidin et al., 2025).

Figure 1 outlines how dysbiosis results in increased gut permeability, which leads to systemic inflammation via endotoxins like LPS and microglial activation, which increases AD neuropathology.

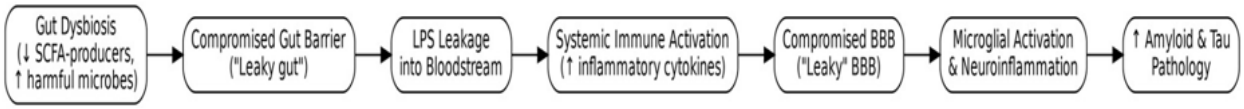

Figure 1: Schematic illustration of how gut dysbiosis can drive neuroinflammation in Alzheimer's disease. In AD, an imbalanced gut microbiota (dysbiosis) promotes the overproduction of harmful microbial metabolites – including lipopolysaccharide (LPS), bacterial amyloids, bile acids, and trimethylamine N-oxide (TMAO) – while beneficial SCFA production (e.g., butyrate) is reduced (Harach et al., 2017). These changes disrupt the intestinal barrier, leading to a "leaky gut." LPS and other pro-inflammatory molecules enter the circulation and trigger systemic inflammation and immune cell activation. In turn, peripheral inflammatory signals and LPS can compromise the blood-brain barrier and activate microglia in the brain,

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

resulting in chronic neuroinflammation. This neuroinflammatory state exacerbates Aβ plaque deposition and tau tangles, creating a vicious cycle of pathology in AD (Harach et al., 2017).

2. Microbial Metabolites and Toxins Impacting the Brain: In addition to LPS produced by dysbiotic populations, there are numerous microbial metabolites that signal various pathways that could contribute to neuroinflammation. These include:

- **Short-chain fatty acids (SCFAs):** SCFAs (acetate, propionate, butyrate) are fermentation products produced by beneficial gut bacteria from dietary fiber intake. SCFAs exhibit anti-inflammatory effects and immunomodulatory potentials; for example, butyrate strengthens gut barriers and promotes regulatory T-cells, which quell inflammation (Abidin et al., 2025; Abidin et al., 2025). SCFA-producing bacteria become dysregulated during dysbiosis, and levels decrease. Butyrate deficiency is correlated with microglial over-activation and systemic inflammation (Abidin et al., 2025). Interestingly, colonizing germ-free mice with butyrate-producing microbes or supplementing with SCFAs can restore levels of microglial homeostasis, as well as BBB integrity (Zhang et al., 2023; Zhang et al., 2023). Thus, one consequence of dysbiosis is reduced SCFA levels, where butyrate appears to be functioning as a brake against neuroinflammation.

- **Microbial amyloids:** Some gut bacteria (like Escherichia coli and Bacillus species) can produce amyloid-forming proteins (curli fibers) on their cell walls (Abidin et al., 2025). These amyloid formations can enter circulation and potentially cross-seed with misfolded protein processes within the host. While still under investigation, some researchers hypothesize that chronic exposure to microbial amyloids may prime the immune system, facilitating human amyloid or synuclein aggregation in the brain, linking an otherwise acute gut phenomenon to potentially chronic protein misfolding disorders in the brain (Abidin et al., 2025). Bacterial amyloids can also activate TLR2/TLR1 and other pattern recognition receptors, leading to inflammatory signaling.

- **Bile acids:** Gut bacteria are responsible for modulating bile acid metabolism by converting primary bile acids into secondary bile acids. Dysbiosis results in increased accumulation of certain bile acid species that can interact with immune receptors. For example, deoxycholic acid (lithocholic acid, LCA) is a secondary bile acid that binds TGR5 receptors on macrophages and microglia, which activates NF-κB signaling that upregulates pro-inflammatory release of cytokines (Abidin et al., 2025). Studies have found impaired microbial bile acid metabolism (decreased production of anti-inflammatory derivatives) in AD populations, suggesting some bile acids found in cerebrospinal fluid correlate with AD progression (Abidin et al., 2025). Thus, changes in bile acids due to dysbiosis can lead to profiles biased towards pro-inflammatory effects

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

impacting the brain.

- **Trimethylamine N-oxide (TMAO):** TMAO is a metabolite produced by dietary choline and carnitine through microbial action in the liver. Increased plasma TMAO has been linked to cardiovascular disease but is now emerging as a component of cognitive decline as well; in models, it has been shown to induce microglial activation while increasing Aβ pathology (Zhang et al., 2023; Zhang et al., 2023). Dysbiotic microbiomes (associated with heavy meat-based diets) tend to produce increased concentrations of TMAO. Recently studied cohorts found both increased plasma and cerebrospinal fluid TMAO levels associated with patients diagnosed with AD and mild cognitive impairment, suggesting that TMAO could cross the BBB, contributing to neuroinflammation (Zhang et al., 2023). Modulating gut microbial production of TMAO through diet or enzyme inhibitors is being researched as a treatment for cognitive decline.

- **Tryptophan metabolites:** Gut bacteria also metabolize tryptophan into multiple pathways, where some activate the aryl hydrocarbon receptor (AHR) on intestinal immune cells. Beneficial tryptophan fermenters produce indoles (AHR agonists with anti-inflammatory properties); dysbiosis can result in reductions in these beneficial productions, while other pathways might be upregulated (kynurenine metabolism resulting in potentially neurotoxic products). A recent study found that increasing dietary tryptophan or AHR signaling increased anti-inflammatory properties by decreasing microglial reactivity within AD mice brains (Zhang et al., 2023). This indicates how microbial metabolism can tip immune responses toward inflammation or away from it.

3. Priming and migration of immune cells: Gut microbiota plays a critical role in educating immune cells. Dysbiosis often results in an overabundance of inflammatory cytokines from an imbalanced ecosystem of immune cells; for example, some species promote Th17s (pro-inflammatory T-helper cells) while suppressing regulatory T-cells that are anti-inflammatory; as such, systemic inflammation dominates, which penetrates the brain as well. Recent studies have shown increased infiltration of peripheral immune cells into AD brains due to dysbiosis, likely facilitated by currents from a more inflamed gut microenvironment leading to the release of chemoattractant signals for leukocytes to enter CNS spaces — both the brain itself and meningeal layers surrounding it — where they had previously not been observed during homeostasis without neuropathology (Zhang et al., 2023). Monocytes generated by gut-derived LPS can traverse the BBB if it is inflamed or compromised, where they are differentiated into macrophages, exacerbating neuroinflammation. Thus, even circulating IL-6 or TNF that came from gut microbes like TLR4-expressing macrophages can bind to their own receptors on endothelial cells within the BBB, which in turn express more adhesion molecules, allowing for lymphocytes to cross into CNS spaces where they can bind microglia or astrocytes (Abidin et al.,

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

2025; Abidin et al., 2025). Thus, a low-diversity pro-inflammatory environment, such as dysbiosis, alerts the periphery immune system so it is poised for CNS entry if necessary, when pre-existing neuropathology exists — changes that would not normally occur otherwise without dysbiosis or neuropathology.

3. Nervous pathways (Gut-brain signaling): The vagus nerve provides a direct neurological bridge connecting the gut-brain connection via vagal afferent fibers that convey signals back to the brain for processing potential downstream ramifications based on gut homeostasis — microbiota-derived products can act on afferent vagal fibers — for example, SCFAs influence vagus signaling positively while certain probiotics alter vagal-associated neurotransmission positively as well (Zhang et al., 2023). While such vagal signaling predominantly relates to mood-behavior manifestations post-integration by the brain's higher-order structures, it might modulate inflammation via the cholinergic anti-inflammatory pathway. Vagal tone downregulation due to dysbiosis or infection suppresses this anti-inflammatory reflex, thereby increasing potential for heightened inflammation within both compartments since upregulated signaling exacerbates brain studies during neuropathology (Abidin et al., 2025). Conversely, other studies indicate that vagus nerve stimulation or specific microbes that exhibit vagal activation potential, such as Lactobacillus species, provide microglial deactivation; thus, disruption of normal gut-brain neurocommunication during dysbiosis may remove a brake against neuroinflammation.

4. Glial Cell Modulation: Even local glial cells can be directly modulated by gut microbiota. Germ-free studies show that microglia (the immune system in the brain) are underdeveloped and possess an immature phenotype due to observed commensal microbes, meaning signals and transdifferentiation from microbes are required for proper maturation and investigative homeostatic function (Zhang et al., 2023; Zhang et al., 2023). In fact, recapitulating germ-free conditions through recolonization with diverse microbiota in mice or even SCFAs can achieve similar patterns in gene expression and reactivity of microglia. In other situations where dysbiosis is present, however, there can be "priming"—the in-between stage in which pro-inflammatory stimuli added later can render microglia hyper-reactive. For example, a microbiome in a dysbiotic state heavy in lipopolysaccharide (LPS)-producing bacteria may render activated microglia, as the constant low-level stimulation of microglia is enough to keep them in a pro-inflammatory state, as pre-activated for more extreme challenges that otherwise would not necessitate such inflammatory undertones; findings show that microglial priming promotes rapid responses to AD pathology. In addition, other microglia (types of glia that mediate the supportive cellular network for neurotransmission) may also be impacted by microbial metabolites; bile acids and TMAO promote astrocytic release of chemokines that attract further immune cells to the brain (Abidin et al., 2025; Abidin et al., 2025). Therefore, a

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

gut dysbiosis compounded by the inflammatory phenotype of each subsequently-migrated cell would result in greater neuroinflammation by skewing glia to a more inflammatory phenotype.

Ultimately, gut microbiota dysbiosis makes the ideal environment for a pro-inflammatory facilitation: a leaky gut promotes excess immune-challenging factors throughout the body, while no anti-inflammatory derivatives from microbes make the situation worse, and aberrant recruitment/integration through immune and nervous systems that combine to the brain render a neurodegenerative fate unavoidable. Causation, however, is likely in reverse: neurodegenerative changes at first develop in the brain and work backward to impact gut health and microbiota (for example, AD pathology has been noted to diminish vagal innervation to the gut as well as expand corticosteroid release, both of which can impact parameters for gut microbiota) (Zhang et al., 2023). In fact, findings show that experimental AD-like pathology introduced in the brains of lab mice translated to changes in the gut microbiota and intestinal inflammation (Zhang et al., 2023). Thus, while there is a brain-gut connection, it goes both ways; yet it becomes a cycle of destruction: when the brain attains neuroinflammatory components, it creates gut dysbiosis; when the gut sustains dysbiosis, it impacts inflammatory dysregulated patterns in the brain. Thus, if there exists a way to break the cycle, a therapeutic application could emerge. But first, before exploring such interventional findings, we must highlight human findings and animal findings that support gut dysbiosis and neuroinflammation as contributing factors to cognitive decline.

4. Human Studies Linking Gut Microbiota, Neuroinflammation, and Cognition

Several studies in humans, both clinical and observational, are relevant to gut microbiota profiles, inflammatory markers, and cognitive status. While these human studies don't implicate causation like their translational counterparts in animals, they provide a perspective of association that serves to validate at least translational potential.

Cross-Sectional Studies in AD and Cognitive Impairment: There are many studies that have compared gut microbiota in patients with AD versus age and sex-matched controls with normal cognition. As per the Background, a dysbiotic and pro-inflammatory microbiome signature is classically attributed to AD. For instance, Vogt et al. (2017) assessed the composition and diversity of fecal samples in patients with AD and noted that they had a lower relative abundance of anti-inflammatory genera (Eubacterium rectale group) and higher relative abundance of pro-inflammatory genera (Escherichia/Shigella) compared to controls, as well as increased levels of peripheral pro-inflammatory cytokines. Similarly, Zhuang et al. (2018) note that the gut fecal microbiome of patients with AD was found to have lower concentrations of SCFA-producing bacteria and higher concentrations of Bacteroides spp. , which were also associated with higher levels of TNF-α and other inflammatory markers in plasma. Most recently, a meta-analysis published in 2022 with over 800 subjects (AD, MCI, and control) found that patients with AD

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

had a significantly differentiated gut microbiome composition from the rest which was characterized by decreased overall diversity, increased relative abundance of Proteobacteria and Bacteroidetes, and decreased relative abundance of Firmicutes (especially families Rikenellaceae and Lachnospiraceae) (Hung et al., 2022). Interestingly, this study noted a gradient; certain families (Clostridiaceae, Phascolarctobacterium) were found to have intermediate abundance in MCI patients—between healthy controls and frank AD—which suggests that dysbiosis develops over time, which relates to worsening cognition (Hung et al., 2022).

Beyond taxonomical change, certain studies have linked metabolic function to the findings of pathology in AD. For instance, Hung et al. (2022) assessed fecal metabolites and determined that patients with AD had altered tryptophan metabolites and decreased concentrations of SCFA when compared to controls—consistent with an inflammatory microbiome. Saji et al. (2019), for example, found that higher levels of ammonia-producing bacteria in stool samples were associated with increased amyloid PET burden in cognitively impaired patients, while higher concentrations of butyrate-producing bacteria were associated with lower amyloid concentrations. This supports human data that implicates microbial products in the development or assessment of disease processes.

Mild Cognitive Impairment and Early Changes: Since MCI can be an early stage of AD, studies focused on this populational group are important to determine if gut microbiota changes occur even before advanced disease. Many studies have shown gut microbiota alterations in MC, although typically they aren't as drastic as those demonstrated in AD. For example, a 2023 study by Fan et al. determined that MCI patients could be differentiated from controls with 84% success based on the relative abundance of gut microbiota composition (with only six genera).

Specifically, the significant decrease in the relative abundance of Ruminococcus and Butyricimonas (both butyrate producers) was interesting since even this early stage of development shows an emerging deficiency in SCFA production, which would impact cognition down the line (Akbari et al., 2016). Some genera were found to be greater in abundance in MCI compared to controls (for instance, Flavonifractor—known for polyphenol breakdown)—the health impacts of these findings remain undetermined. In addition, Liu et al. (2019) determined that MCI patients had higher relative concentrations of LPS-binding protein compared to controls, which potentially connects gut permeability to early stages of cognitive impairment.

In addition, certain changes have been associated with the rate of change. A recent longitudinal study found that cognitively normal older adults who had more diverse baseline microbiome assessments and higher relative abundance of Faecalibacterium had reduced cognitive decline after 5 years compared to their counterparts. Those who presented with higher baseline Enterobacteriaceae (pro-inflammatory profile) accelerated declines in memory assessments over 5

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

years. Although these findings are observational with potential confounders, they suggest that the microbiome can drive cognitive aging, aside from merely reflecting cognitive status.

Neuroinflammatory Markers: Various studies in humans have assessed inflammation markers to validate microbiota dynamics with neuroinflammation. One of the ways this occurs is via assessing activated inflammation via TSPO PET ligands, which bind to the TSPO protein, which is upregulated in activated glia. For instance, one small study found that patients who underwent fecal analysis and had dysbiosis (low SCFA-producers) and typical imaging findings for AD had higher TSPO signaling than AD patients who did not present dysbiotic patterns; however, no studies have yet combined TSPO levels with specific species. However, Abidin et al. (2025) provide evidence that gram-negative microbiota correlated positively with plasma TNF-α and IL-6 levels in a cohort of cognitively impaired patients, while elevated systemic inflammation was found in patients who had high C-reactive protein and IL-6 levels, which have been known to be linked to microbiota profiles (Abidin et al., 2025). While this does not create the level of causality found in animal studies, it aligns with the mechanistic side of the inflammatory microbiome, creating pro-inflammatory peripheral changes as well as central inflammation, which can impact cognition.

Effect of APOE Genotype: One interesting finding comes from the review of the impact of the APOE ε4 allele, which is the strongest genetic determinant for late-onset AD. There are findings that APOE4 carriers, even without cognitive impairment, possess differential gut microbiota from non-carriers. For example, a 2025 study of older Hispanic populations found significant decreases in butyrate producers and increases in pro-inflammatory Eggerthella and Lachnoclostridium compared to non-carriers (Zhang et al., 2023); furthermore, a more pronounced dysbiosis was present in AD patients who were also APOE4-carriers compared to non-carriers (Zhang et al., 2023). This suggests that the impact observed by APOE4 in terms of risk of developing AD is partially due to association with gut microbiota or the possibility that those patients who possess APOE4 do not respond as well to dysbiotic changes, which provide greater inflammatory burden and subsequent pathology.

Limitations of Human Studies: It should be noted that human studies are confounded by many factors. For one, diet is a major driver for gut microbiota—AD patients may eat differently due to dysphagia or disease-driven changes, which could drive microbiome patterns independent from true pathophysiology. In addition, treatment patterns drive patterns—antibiotics as medications, but also memantine or common antidepressants given for AD often impact gut microbiota as well. Additionally, activity levels or frailty status (common decreases in AD) correlate with gut microbiota as well. Furthermore, many studies are cross-sectional, which fail to prove whether dysbiosis is a cause or consequence of disease; therefore, interpersonal variability must also be reconciled—the "signal" portion must outperform background variability determined by

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

location/geography, ethnicity, and lifestyle to provide significant populations with the statistically powered ability to determine the gut-brain axis hypothesis. The fact that some seemingly discordant results occur is likely due to these variables; however, the consistently repeated findings from multiple cohorts, which suggest a pro-inflammatory profile related to AD/cognitive impairment—which align with inflammatory patterns and relative severity markers—support this association with like-minded parallel findings.

Ultimately, human studies find relevance in supporting gut microbiota dysbiosis with neuroinflammation in cognitive disorders; people with AD find changed patterns consistent with potential pro-inflammation (more endotoxin-producing bacteria, fewer SCFA-producing bacteria), which are correlated with worse cognition/cognition-influenced morbidity outcomes over time, which reflects worse outcomes for these patients. Even at early stages like MCI, where dysbiosis can be found provides a potentially contributing role even before dementia comes on board, which begs for animal models that can test interventions to determine impact on neuroinflammation/cognition outcomes.

5. Animal Models and Experimental Evidence

Research in animals—especially rodent models—demonstrates causative impacts of gut microbiota dysbiosis on neuroinflammation and cognitive decline through translationally controlled studies of causation. By employing germ-free animals, FMT, antibiotics, and probiotics, researchers have established direct comparisons that would be difficult to do in humans. Below are highlights from these studies:

AD Animal Models: To assess whether the presence of a microbiome can mediate neuroinflammation and cognitive decline.

- **Germ-Free/Antibiotic Approaches:** One of the first studies to assess whether a microbiome was involved came from Harach et al. (2017), who genetically engineered germ-free (GF) mice that develop AD (and compared their phenotypes to age-matched control colonized AD mice). In Harach et al. (2017)'s study, germ-free AD offspring developed significantly reduced cerebral Aβ plaque accumulation compared to similarly aged, conventionally colonized AD offspring (APP/PS1 transgenic mice) (Harach et al., 2017). For instance, GF APP/PS1 significantly decreased the amount of Aβ plaques and insoluble Aβ in the brain compared to conventional APP/PS1, and also decreased activated microglia. Interestingly, even other differences emerged—decreased inhibitors of Aβ-promoting molecules with increased levels of Aβ-degrading enzymes (like neprilysin and insulin-degrading enzyme) in the GF group (as assessed through real-time RT-PCR)—suggesting that one means of reduction was the presence of microbes

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

themselves, which could exacerbate pathology (Zhang et al., 2023). When GF APP/PS1 offspring were colonized with a normal microbiome later in life, however, the amyloid levels returned, suggesting that microbiotic compositions can dynamically change naturally occurring amyloid build-up (Harach et al., 2017). Similarly, efforts to use antibiotics to heavily perturb the microbiome have shown reduced neuroinflammation and amyloid pathology in AD mice. In a broad-spectrum antibiotic treatment of adult male APP/PS1-21 mice by Dodiya et al. (2019), they observed decreased microglial activation surrounding the cortex and a reduction of plaque-like deposition by nearly 50%, whereas female mice did not yield as strong of an effect—as they had slightly lower levels of amyloid build-up but not significantly different—suggesting an interesting sex-difference, but a finding consistent with epidemiological data suggesting microbiome and immune responses differ between the sexes (Dodiya et al., 2019). Data looking at female and male differences in human populations support that women show increased risk for dementia and AD versus men, demonstrating that components of sex must be assessed in translational explorations. Thus, these experiments suggest that when the microbiome is present, it can facilitate the development of neuropathology aligned with commensal responses.

- **FMT Studies:** FMT involves the transfer of gut microbial community from one individual to another (commonly through gavage of fecal materials). FMT has become a great tool with which to determine whether an exposure is transmissible through an initial state or mediating state. For example, in the context of aging and AD:

- **Aged Microbiome vs Young Microbiome:** Microbiota exchanges between young and aged models show that the microbiota by itself can mediate aging-associated phenotypes. The first study to do this came from Parker et al. (2022), where the aged microbiota from 24 months was transplanted into young germ-free animals and vice versa (Parker et al., 2022). Young recipients (aged at 3 months old), upon exposure to an aged microbiota, began showing signs of neuroinflammation and cognitive impairment: they developed increased CNS inflammation (activated microglia, increased inflammatory cytokines in the brain) as compared to matched controls without exposure to comparative aged microbiome; they developed deficits in learned memory tests ((Y maze, Morris water maze) compared to control young offspring (Parker et al., 2022). They also developed other symptoms associated with increased intestinal permeability—which was reinforced by systemic inflammation—which matched "old" physiology (Parker et al., 2022). On the other hand, when aged offspring were colonized with a young microbiota, many phenotypes associated with aged changes were rescued (Parker et al., 2022)—with younger-aged animals having less brain inflammation, more gut barrier integrity, and

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

even cognitive or sensorimotor improvements (Parker et al., 2022). Thus, these data demonstrate causative effects of the microbiota independent of other exposures related to age.

- **AD Patient Microbiota into Mice:** Recently, FMT studies have relied upon human-to-mouse transfers. For example, in Fujii et al.'s 2023 study, they found that fecal microbiota from AD patients transmitted into germ-free mice developed changes (ie, increased AD-like changes, ie, greater levels of inflammation in the brain) compared to age-matched healthy human donor microbiota recipients; these AD-model recipients also performed worse on memory tests compared to those receiving healthy control, suggesting that something about an "AD microbiome" is associated with pro-pathogenic avenues. Compensating for this, additional studies of co-housing where transgenic AD model mice are housed alongside wild-type (WT) mice have been explored. For example, Zhang et al. (2023) finds that when normal WT offspring are co-housed with transgenic AD mice, they acquire an altered gut microbiota similar to AD mice and subsequently develop cognitive impairment and brain changes—ie increased tau protein phosphorylation in the brain (a hallmark of AD)—and microglial activation increases as observed through Iba-1 staining alongside worse performance on memory tests compared to WT housed alone (Zhang et al., 2023). Essentially, AD-associated dysbiosis is transmissible to healthy offspring and can confer AD-like changes in those recipients without any specific genetic or lesion induction of disease into the recipient; Zhang et al. (2023) additionally find that after a Lactobacillus and Bifidobacterium treatment (probiotic mix), cognitive impairment was reduced via Iba-1 results alongside toning down tau-pathology, which helps raise awareness of opportunities available to modulate the microbiota-gut-brain axis for disease-related interventions (Zhang et al., 2023).

- **From Trained Donors:** Interestingly enough, a study exists where fecal microbiota was transplanted from trained young females into sedentary aged females showing cognitive improvement and anti-inflammatory microbes, suggesting that any potentially beneficial lifestyle factors that can adjust for different microbiomes can be transferred to promote brain health, though tangentially not necessarily related strictly to AD (Jing et al., 2021).

Animal Mechanistic Insights: Animal models also support insights into how microbial changes translate into brain changes. For example, the Parker et al. study mentioned above found that WT mice restored the gut mucus layer of those transplanted with younger microbiota and upregulated tight junction proteins—reduced permeability, meaning better gut barrier integrity— (Zhang et al., 2023; Zhang et al., 2023), which supported decreased levels of serum lipopolysaccharides (LPS) and microglial activation. In the co-housing study, metabolomic analyses showed co-housed WT mice had dysregulated SCFA and other microbiota-derived metabolites (less

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

butyrate, big changes in lipid metabolites etc.), which were linked to increased GSK3b activity—this kinase leads to tau-phosphorylation—increased expression of GSK3b-associated transporters (Zhang et al., 2023); crucially, the loss of butyrate-producing microbes led to less available butyric acid which inhibits GSK3b making it easier for the tau pathway to be pushed forward to support pathology (Zhang et al., 2023; Zhang et al., 2023). Therefore, researchers have been able to pinpoint from specific microbial-derived metabolites their influence on illness mechanisms based on these findings.

Other studies explore interventions on behalf of probiotics or prebiotics, which reduce neuroinflammation in aging/AD models while helping improve cognition. For example, two studies noted that APP/PS1 mice fed Clostridium butyricum—which strain that produces butyrate—had significantly lower brain IL-1b levels—butyrate's anti-inflammatory properties—compared with control APP/PS1 as well as significantly better memory performance compared to controls (Harach et al., 2017; Harach et al., 2017)—and reduced activated microglia compared with non-transplanted control APP/PS1 females, as well (Harach et al., 2017; Harach et al., 2017). In another study, probiotic transfer SLAB51 combination strains helped 3xTg-AD females show lower expression of pro-inflammatory cytokines (IL-1b, IL-6, TNF-α), reduced levels of amyloid plaque-like accumulation, as well as phosphorylation-related tau pathology-negative feedback mediated through anti-inflammatory networks (Harach et al., 2017; Harach et al., 2017). These interventions often come equipped with increased levels of SCFAs from treated animals successfully cultivated as well.

In addition to dietary interventions that help confirm the gastro-brain link, help increase beneficial outcomes, while low-fiber diets produce negative outcomes: mice on high-fiber diets develop thick mucus layers, maintaining gut integrity, while low-fiber Western diets produce gut barrier dysfunction alongside systemic inflammation that leads to activated microglia/Morris water maze-learning deficits; supplementation reverses these effects, too (Zhang et al., 2023; Zhang et al., 2023).

In summary, animal studies provide strong evidence that gut microbiota dysbiosis is not merely an epiphenomenon but rather an agent for change related to neuroinflammation and cognitive decline; whether it be removing gut microbes (germ-free or antibiotics), transferring specific microbiomes (FMT/co-housing), or rendering beneficial microbes (or prebiotics), scientists can maneuver the presentation of degenerative changes witnessed by causation across mouse strains over time or instantaneously acquired between groups. Thus far, this literature review demonstrates how findings bolster the credibility for intervention possibilities across early detections or preventative manifestations for humans; yet the next sections will explore what future interventions can do if they are successfully implemented as generalized public health considerations.

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

6. Discussion

The findings from the literature above support a developing consensus: the gut microbiome influences brain inflammation and subsequently cognition. The notion of a gut-brain axis for neurodegeneration has shifted from a speculation-based research domain to an increasingly developing one with more correlational human data and causal animal studies. In the Discussion, we acknowledge our findings, the ability's caveats and confounders, and future directions.

Mechanisms Warranting Human Correlation: The mechanisms detailed here — gut permeability, microbially derived signals, peripheral immune systems primed to overreact, etc.

- are biomedically plausible systems by which dysbiosis could accelerate inflammation and cognitive decline. There are independent systems in humans that evoke such parallels. For example, AD cohorts typically present with increased peripheral inflammation (increased cytokines, acute phase proteins) which have been correlated with increased cognitive impairment and brain atrophy (Abidin et al., 2025); this analysis implicates gut microbiomes (via LPS and other byproducts) as likely sources of this peripheral inflammation that feeds into CNS-influencing inflammation; meanwhile decreased SCFAs and other neuroprotective microbiome-derived metabolites are frequently found in AD populations; for instance, decreased access to anti-inflammatory and neurotrophic signaling could yield a brain with more frequent errors; one could hypothesize that having a high amount of dysbiosis lowers the threshold for neuroinflammation to such a great degree that brains that operate at lower ranges with the presence of AD-associated brain pathology (amyloid/tau) that could otherwise survive longer with homeostatic tendencies get plunged into a destructive inflammatory cycle sooner if the gut microbiome says there's an issue.

Causation vs. Chicken and Egg: The most critical question is, does dysbiosis cause neuroinflammation or does nascent neurodegeneration cause dysbiosis (or both)? At present, literature suggests a bidirectional correlation. Longitudinal studies in humans are still lacking, but a select few suggest that dysbiosis can precede cognitive decline (Jemimah et al., 2023). The animal FMT studies in particular suggest that microbiota alone can incite brain inflammation and cognitive dysfunction in an otherwise healthy recipient (Parker et al., 2022; Zhang et al., 2023)

- this supports causation from the gut to the brain; yet on the other hand, it stands to reason that as AD pathology evolves (even preclinically) it alters the ANS or gut physiology (via diet change, activity, vagal tone) and then subsequently impacts the microbiome. Indeed, AD patients present with GI dysregulation (changes in motility and microbiota, increased infection risks), which can partially be accounted for by ANS changes. It is not a

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

unidirectional causative factor

- it could be a dual dismal cycle from the start: the initial causative inflammatory changes that contribute to neurodegeneration (likely from amyloid, vascular causes, etc.) induce a degree of neuroinflammation that then impacts the gut (via stress hormones, vagal changes); this dysbiosis then induces the inflammatory changes of a second system; understanding the cyclical potential suggests interventions can intervene at various stages — one being the gut.

No AD Microbiome; Personalization: It's crucial to appreciate that there is not one "AD microbiome," there is no consensus across all subjects. Disparities arise from diet, genetics, environment, and comorbidities (especially diabetes, which affects microbiomes and cognition). Therefore, while there are microbiome changes relative to AD on average that are statistically significant (fewer SCFA-producing microbes, more pro-inflammatory taxa), an individual may deviate from this average. This shows personalized intervention is necessary — what works for one microbiome does not necessarily work for another. For example, if a patient has a dysregulated microbiome due to a lack of Bifidobacteria, a suitable probiotic approach would work; yet if the next individual has a dysregulated microbiome due to overabundant pathobionts, this will require completely disparate efforts. We need further studies to subclassify dysregulated neurodegeneration subtypes before these precise interventions can occur.

Limitations of Literature: Much of the literature depends on small cohort human studies and cross-sectional reports. Furthermore, there is a relative lack of AD studies in broader age-induced cognitive decline (yet some studies on gut microbiomes and delirium/PD/depression in geriatric populations are emerging, which likely share inflammatory pathways). Animal studies are great but not without limitations — mouse models of AD only represent certain aspects of human disease (most are amyloid-based and fail to capture sporadic, late-onset AD); moreover, mouse microbiomes and immune responses differ from humans. Thus, translating findings is not as straightforward as it could be. For example, probiotics that function in mice do not colonize or utilize their efforts appropriately in humans — similarly, FMT works if older mice receive younger microbiomes but does not help if older humans receive younger microbiomes, with no investigations on either side. Safety concerns exist (FMT can transmit infections, can FMT cause immune reactions?).

Other Causative Factors: Dysbiosis could be a confounder of other causative factors. For example, the quality of diet dictates dysbiosis tremendously; poor diet quality could independently downregulate cognitive capacity (metabolic syndrome/cerebrovascular risk) while also inducing dysbiosis. In which case, dysbiosis would not work to be remediated if we did not remediate underlying diet stability; resolving dysbiosis would do little if we did not help stabilize

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

a dysfunctional diet. Yet studies where probiotics improve cognition in AD (discussed below) refute this argument, suggesting that gut microbiomes have direct relevance instead of just existing as markers for bad diets. Furthermore, relative cross-sectional data related to illness (AD patients take certain polypill medications like acid suppressors, certain antipsychotics) — thus, differences may be attributable to medication differences. With more proper controls and longitudinal data down the line, we can disentangle these issues.

Translational Potential — Are We There Yet? The appeal to treating dementia from a gut biosphere perspective is compelling and a development of a greater trend that highlights neurological threats as systemically engaged disorders. Yet we must temper our enthusiasm. To date, there has not been one large-scale clinical trial demonstrating definitively that manipulating the microbiome can slow/prevent cognitive decline; preliminary studies (Akbari et al., 2016) note interesting findings, yet they're small and short-term with limited cognitive improvements. These need to be shown in larger multi-centered studies with confirmatory powers. Furthermore, we have yet to support long-term prospects — can maintaining a healthy microbiome require lifestyle changes or continued supplementation? Can any interventions we stop negate any positives we previously accrued? Even worse, there are regulatory factors at play; while probiotics are benign enough products with favorable safety profiles, FMT is more nuanced, with only approved regulation for refractory *C. diff*. infection, but no chronic illness like AD. Before attempting FMT with its cognate outcomes for cognition complications need to be assessed (especially in older populations who could be immunocompromised).

Thus, while cautious and skeptical, we feel enough studies have accrued evidence warranting clinical trials for AD conditions driven through the gut. There have been various interventions — multi-strain probiotic supplements have been attempted alongside prebiotic fibers; in one study, *C. diff*. microbiomes from younger patients were transplanted into AD patients (ClinicalTrials.gov NCT04014610, among others). Outcomes from these studies will be tremendously fascinating — if they work positively, they could confer a novel adjunct improvement on AD when compared to any other interventions that operate at the amyloid or neurotransmitter interfaces.

Connections to Other Neurodegenerative Disorders: For other neurodegenerative disorders, it should be noted that gut dysbiosis implicates PD and more. For example, PD is distinguished by certain microbial profiles (overgrowth of *Enterobacteriaceae* and decreased SCFA-producers) associated with motor severity; constipation is symptomatic well before brain features present, indicating gut-first pathology with certain features regulating the brain, as with AD. FMT from patients confers disease features (Zhang et al., 2023). This indicates a larger principle exists for the microbiome to influence the brain's inception and susceptibility to degeneration in general, not just for AD. Thus, findings should emerge from a perspective shared through multiple

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

diseases — what can help one can help others as well.

Ultimately, the Discussion emphasizes a paradigm shift: neurological diseases like dementia have been viewed traditionally through a lens otherwise isolated (the brain), but they may be engagingly connected to peripheral health, particularly linked through a system like the gut microbiome. Such findings are open-ended for future interventional opportunities but researched through interdisciplinary findings, critically assessed before diagnostic conclusions are made into substantiated findings.

7. Potential Interventions Targeting the Microbiota-Gut-Brain Axis

One of the greatest hopes of linking gut dysbiosis to neuroinflammation is that there are potentially modifiable factors that could reconcile this relationship and change brain health. While genetic risk factors, which are out of our control, are less operable, the gut microbiome is somewhat operable through diet, supplementation, and microbial therapeutics. Therefore, we highlight potential avenues and supporting information through the following:

1. **Diet and Prebiotics**: The gut microbiome is influenced early on and through diet throughout the lifespan. High fiber diets of fruits, vegetables, whole grains, and nuts foster a diverse microbiota of beneficial SCFA-producing bacteria. High saturated fats and simple sugars (i.e., Western diet) create dysbiosis and decreased microbiota diversity. Epidemiologically, the Mediterranean Diet (higher in fiber, polyphenols, and unsaturated fats) has been associated with lower cognitive decline and AD risk; thus, its benefits may be partially mediated through the microbiome. Clinically, microbiome diversity and inflammatory signaling are reduced in older adults with Mediterranean/high fiber diets. In a randomized controlled trial, a 1-year Mediterranean diet intervention in older adults demonstrated fecal SCFAs increased and plasma LPS-binding protein reduced, inversely correlated to gut permeability and gut-derived endotoxin translocation (Zhang et al., 2023). Additionally, fermentable fiber-enriched diets in older adults showed lower systemic IL-6 and CRP levels and positively correlated with certain scores (anti-inflammatory mediated through the gut). Prebiotics (specific fibers/compounds fermentable by healthy gut bacteria) have been assessed as well; galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) increase Bifidobacteria levels; a pilot study assessing FOS in AD patients showed trends toward improved gut microbiota and inflammatory cytokines (although unclear cognitive impact). Given that fiber intake is typically lower in older adults, a simple intervention is to adopt a higher fiber intake or at least prebiotic supplementation. These efforts are low risk with additional benefits (digestive and cardiovascular), and other dietary intervention trials with cognitive endpoints will clarify how much this can be an effective change on the cognitive aging

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

trajectory. Regardless, the data suggests that “feeding the microbiome” is important with healthy options to maintain an anti-inflammatory-esque environment in the gut conducive to health.

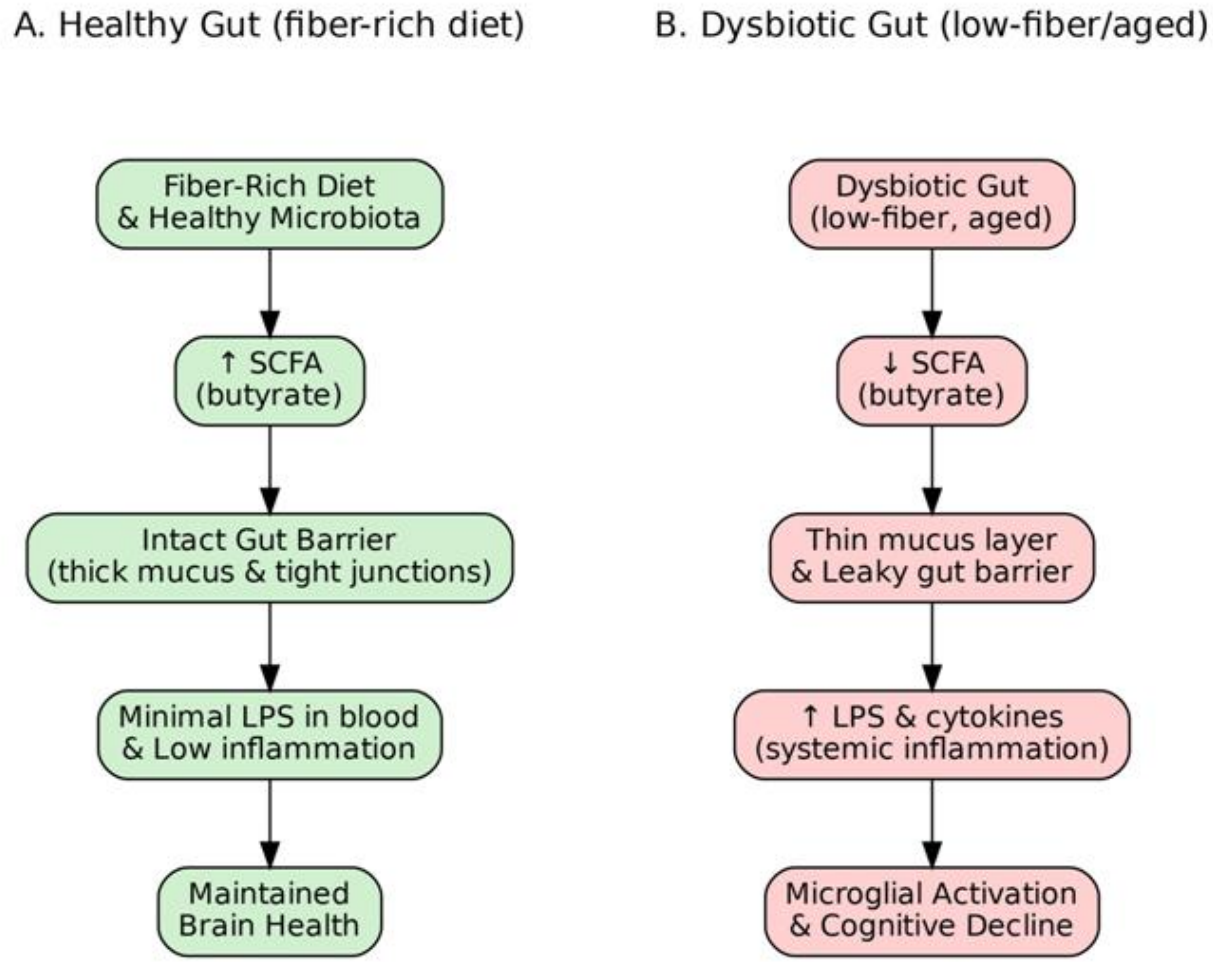

Figure 2: The diet and dysbiosis impact the intestinal barrier, creating inflammation. (a) In a healthy state, mediated by high-fiber diets, the healthy gut microbiome produces and harbors large amounts of SCFAs and fiber-degrading beneficial bacteria, creating a thicker, more resilient mucin layer of the intestine. This maintains a tight barrier function while reducing immune-mediated inflammation. (b) In dysbiosis stemming from low fiber diets, aging, or other stressors, SCFA-producing/fiber-degrading bacteria decrease and mucin-degrading bacteria increase (Zhang et al., 2023). This mucin barrier degrades and weakens the integrity of the gut’s barrier. As a result, microbial metabolites and endotoxins (i.e., LPS) enter systemic circulation, driving inflammation, which drives neuroinflammation and cognitive decline in response (Zhang et al., 2023; Zhang et al., 2023; Zhang et al., 2023; Zhang et al., 2023).

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

2. **Probiotics**: Probiotics are live microorganisms that confer health benefits on the host when administered in adequate amounts. Common probiotic species include *Lactobacillus*, *Bifidobacterium*, and other commensal strains. Several small randomized controlled trials (RCTs) have assessed probiotic supplementation in patients with cognitive impairment/AD as well. One landmark RCT out of Iran (Akbari et al., 2016) supplemented AD patients with a fermented milk drink containing *Lactobacillus* and *Bifidobacterium* at 1x/day for 12 weeks (Akbari et al., 2016). The probiotics group improved significantly on Mini-Mental State Examination (MMSE) scores (+27% from baseline) while the placebo group declined (Akbari et al., 2016); hsCRP (sensitive marker for inflammation) and malondialdehyde (marker for oxidative stress) were reduced compared to placebo controls (Akbari et al., 2016). Although improved cognition was minimal, this proof-of-concept study in human AD suggested that modulation of gut bacteria could influence cognition—and subsequently, inflammation. Since then, other RCTs have been conducted. Recently, a meta-analysis (Liu et al., 2025) pooled four trials involving 251 AD patients and provided significant cognition intervention gains through probiotic supplementation compared to placebo (standardized mean difference ~0.67) (Hung et al., 2022); however, heterogeneity was likely due to strain/dose differences and differences in patients' baseline characteristics. Probiotics also improved metabolic markers (lipid panels) while decreasing pro-inflammatory cytokines in these studies. Of note, these trials had shorter durations (3-6 months); yet clinically longer duration has not been shown to significantly slow dementia progression. Furthermore, not all studies show positive outcomes—a different one showed no significant cognition difference—but this suggests strains do matter as well as patient characteristics (stage of disease). Regardless, probiotics are becoming a good adjunctive treatment because of their safety. Synbiotics (combined pre- + probiotics) can enhance initial inoculation since bacteria installed into a gut need immediate substrates to survive and thrive. Furthermore, next-gen probiotics are being explored, which include keystone gut species *Faecalibacterium prausnitzii* or *Akkermansia muciniphila*, which have anti-inflammatory properties but are not yet commercially available in yogurts for humans.

3. **Fecal Microbiota Transplantation (FMT):** A major theme addressed throughout this review is that FMT from healthy donors has revolutionized many conditions through the gut, which potentially translates to other spheres in the future for neurological conditions. This same literature in animals discusses how FMT from young to old can replenish the gut and even the brain! Therefore, the concept of FMT within humans is exciting but challenging—donor FMT has an entire niche ecosystem of microbes, not to mention unknown interactions in an older recipient; safety is also an issue since there have been reports of serious infection through FMT in other literature. However, a case series

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

referenced by Park et al. (2022) showed FMT done in small numbers of dementia patients with refractory *Clostridioides diflcile* infection (CDI) (Park et al., 2022). Here, FMT is championed for CDI (which it cures in 90% of cases); however, secondary cognitive variable assessment was done for change due to this process. This series showed that all who received FMT improved in some capacity, as pre-FMT CDI ratings with MMSE were a median of 10 (severe dementia range) compared to a median score of 16 post-FMT, average increase of ~5. Similarly, CDR-Sum of Boxes improved in some patients who showed slight improvement in functional impairment (Park et al., 2022). This occurred beyond what was to be expected with acute reversal alone, and gave early suggestive findings toward promoting MFT affecting cognition. However, importantly, FMT was safe in these patients with no AE besides transient GI complaints (Park et al., 2022); thus, this is not the most conclusive evidence (no control and patients had CDI, which induces delirium, which reverses after treatment); however, it opens doors for future endeavors. Indeed, a pilot study from China assessed FMT in 6 AD patients and found results for cognition changed as well as decreased inflammatory markers, but it was an open-label study; thus, caution should be taken before applying the findings. Yet, now randomized controlled trials are underway comparing true AD patients receiving either FMT vs placebo to assess efficacy (e.g., NCT04758934). If FMT works, it is an exciting possibility of "resetting" an older person's microbiome into a healthy state—but it complicates things—who is the donor? A young person? A family member? How frequent? Over time? Quality?

4. **Other interventions**: Other findings beyond this include theoretical explorations of what would be considered postbiotics—the metabolites or components produced from beneficial bacteria as an intervention effort. For example, butyrate or propionate supplementation directly could confer similar effects as a healthy microbiome would confer without changing microbes themselves; sodium butyrate has improved cognitive deficits in some AD mouse studies showing histone deacetylase inhibition through decreased inflammatory signaling; TMAO from microbes may indirectly increase neuroinflammation via gut-bacteria consumption thus inhibitors may be explored; inhibiting endotoxins via LPS-binders in the gut found from clay minerals or engineered compounds may downplay systemic LPS-burden; pro-inflammatory gut bacteria may be inhibited as well via vaccination—but this is a far off thought!

Implementation Challenges: Personalization is difficult—microbiomes are individuals, so one person's restoration of balance is another's GI distress. There are no causal infections with probiotics in immunocompromised patients, so probiotic use is especially careful and monitored. In addition, there is less regulatory caution with probiotics vs pharmaceuticals, so it's challenging

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

to say that what's good as is what's found in clinical products is the same as found in OTC; clinical trials for probiotics tend to use specified formulations, for example. With FMT, at least stool preparations and pathogen testing are standardized to ensure good safety measures.

In addition, it's difficult to measure success—should one change things enough that there's a change in certain bacteria, certain metabolites, or a complete change in clinical outcomes? Maybe down the road, treating in such a way will be using the information learned over time (biomarkers of intestinal and inflammatory biomarkers, for example, a fecal butyrate level or blood LPS may inform how to go about treatment).

Therefore, many interventions that affect gut microbiota are being studied or have been studied, or are actively being studied. What's more, these preliminary findings look very promising—at the very least, probiotics and a prebiotic diet have anti-inflammatory and some cognitive benefits, while FMT down the line is more intensive but may be on the horizon for more study. These microbe-based investigations are adjuncts to current treatment/practice plans, but ideally as a preventative measure. A shift in diet or a change in probiotics midlife may inspire a neuroprotective microbiota approach to circumvent or delay the neurodegenerative cascade—potentially an exciting preventative approach to public health.

8. Public Health Implications

The public health significance of gut dysbiosis relative to neuroinflammation and cognitive decline is major, especially as dementia and aging populations increase worldwide. If this gut-brain axis is something that can be intervened upon, it can create new opportunities for population-level prevention and risk-factor reduction. Specific implications are the following:

1. **Prevention is possible through lifestyle**: Not all risk factors for cognitive decline are remediable – age and genetic predisposition (i.e., APOE4 allele status) are fixed. Yet the gut microbiome is flexible in a lifestyle context. Thus, microbiome-specific and gut-brain-specific interventions could be preventative for cognitive decline. For example, public health recommendations relative to diet, which apply to other chronic disease prevention (metabolic and cardiovascular), can apply to cognitive decline prevention as well. A high fiber whole foods intake with fermented products (yogurt, kefir, kimchi) is known to decrease AD, as should be noted for general health, as well as for a functional gut-brain axis. Highly regarded diets (Mediterranean, DASH), which promote these qualities, boast less AD across populations; if these diets can be started early enough (midlife), they can have greater implications. From a public health standpoint, these diets will also curtail other chronic diseases (obesity, diabetes, cardiovascular disease), which themselves are risk factors for dementia (Zhang et al., 2023; Zhang et al., 2023). For

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

instance, “eat more fiber not only for your blood sugar level but also for your gut bacteria to support your brain.”

2. **Less healthcare burden**: Dementia is an expensive condition with lots of healthcare resources. If small interventions like probiotics or diet can help prevent dementia or slow its course (incrementally over years), the cumulative benefit across a population will be great. It's been suggested that delaying AD even 1-2 years (through risk-factor reduction) will significantly reduce prevalence across a population over decades. Microbiome-specific interventions will likely be additive to a multi-domain approach (exercise, cognitive training, blood pressure management) that will gradually facilitate better cognitive resilience in older adults. Public health programming could accommodate small gut health assessment screenings in addition to other screenings typically part of geriatric assessments (blood pressure, etc.).

3. **Public education**: The growing science needs to be translated to the public without overwhelming them or underwhelming them. At present, public interest is high in probiotics and gut health, but so are misconceptions relative to the function of the gut or its connection with the mind. Public health programming can relay fact-based recommendations with transparency – it doesn't start and end with probiotics, and taking a pill isn't going to help someone who's eating a bad diet; a whole foods approach to healthy living is what's necessary for gut and brain. It's important to understand that, especially for those looking to relate any such treatment to existing dementia treatments (which may be too late), public health messaging should not offer false hope – it's about prevention. As research advances, such suggestions may become viable (for example, recommended daily fiber intake for cognitive health or certain probiotics known to help those most at risk).

4. **Equity issues**: Interestingly enough, the gut microbiome is diverse based on geography, diet, and socio-economic circumstance. The fewer people who have access to high-fiber fresh foods, the more at risk they are; conversely, those who regularly consume ultra-processed foods tend to fall poorly across dysbiosis-mediated inflammation. Thus, this intersection occurs with social determinants of health and known disparities. Public health programming to improve the diet quality of more disadvantaged populations should benefit cognitive health as time goes on. Furthermore, should probiotics or prebiotic supplements become the wave of the future, they should be inexpensive and accessible (insurance-covered or community health program provided) so as not to heighten the health equity gap concerns among populations.

5. **Interprofessional care**: The intersection of the microbiome and the brain would suggest

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

that care becomes more interprofessional. Neurologists may team up with PCPs who team up with nutritionists who may refer to gastroenterologists in the face of MCI or early AD patients presenting with gut symptoms that need triaging. Memory clinics may also provide dietary assessment and microbiome implications in their assessments. Greater professional crossover will need to bridge findings from geriatrics to immunology to microbiology and psychiatry for implications.

6. **Surveillance/bio-markers**: On a population public health research level, populations could be monitored for bio-markers in trends. For example, longitudinal studies on cohorts may have microbiome assessments at some point, like blood LPS, inflammatory cytokines, etc., for dementia tracking as well. If bio-markers become widely known for their effectiveness in predicting dementia risk from a microbiome perspective, it can help target high-risk persons for interventions. Imagine a future where bio-markers are like cholesterol (an indicator for brain vulnerability risk), assessed along with any predictive calculator assessing dementia risk?

7. **Ethical/social implications**: The idea of FMT brings specific public health concerns; would FMT from young people into older people make a difference? Would there be programs? How would large-scale donor screening work? Regulatory concerns may arise, suggesting FMT is a tissue transplant or something needing a drug-type response? Public buy-in needs to be assessed – some are wary of poop, fecal matter – how can we have buy-in without trust? Trustworthy policies can address these issues with transparency, but they often need to happen first before we get there sometimes.

Overall, the implications of dysbiosis and other findings have great public health significance because it's another angle that turns the focus from treating neurodegeneration when it occurs to prevention/slowing it down based on maintaining gut balance integrity through educated lifestyle choices and educated exposure. These implications speak directly to preventative medicine and other risk-factor reductions (exercise/cognitive engagement/vascular risk management) through which people/couples/families/classes/towns can start positives where they all have agency to improve their cognitive aging fate through diet/lifestyle links as much as possible – this is feasible now relative to soon as one article suggests we should “take care of our gut microbiota just as finely as we take care of our brains because our brain and gut microbiota are inseparable friends in healthy aging.”

9. Conclusion

In recent years, new insights have changed the scientific landscape regarding microbiome contribution to brain health as it relates to AD and age-associated cognitive decline. This

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

systematic review of the literature attempts to bridge a gap between focus on neuroinflammation as an outcome due to gut microbiota dysbiosis across pathology, human epidemiology, and animal studies spanning from the molecular level to population impact. Ultimately, the idea that the microbiome—the "gut-brain axis" in particular—represents a new path of interest when conceptualizing neurodegenerative discussions fosters hope for future studies and translational applications.

Conclusions supported by the literature include:

- **Gut Dysbiosis Representing a Risk Factor for AD Etiology:** AD patients present with significantly altered gut microbiota from age-matched cognitively healthy older adults, assessed through decreased diversity and increased pro-inflammatory bacteria. Elements derived from the gut (LPS, amyloids, TMAO, etc.) cross a leaky gut to exacerbate systemic and CNS-directed inflammation (Harach et al., 2017; Abidin et al., 2025). Sustained levels of neuroinflammation matching levels of dysbiosis are likely to drive amyloid and tau-related pathology in the AD brain; therefore, the microbiome acts as a potent modifier of pathology development (Harach et al., 2017; Harach et al., 2017).

- **Potential Mechanism – Microbiota-Gut-Brain Axis:** This review assessed how microbiota-generated metabolites and immune signaling observed at the brain could position it as a mechanism. Loss of gut SCFA-producing bacteria depletes immune regulation while exposing the brain to higher levels of inflammatory mediators when pathobionts overwhelm the gut (Abidin et al., 2025; Abidin et al., 2025). This condition activates microglia and astrocytes in the brain, creating a sustained inflammatory environment injurious to neuronal performance (Harach et al., 2017). Conversely, such an axis is bidirectional, suggesting treatment can occur from the periphery to shift brain change.

- **Findings from Human and Animal Studies:** Human data report correlations among gut microbiota profiles, levels of inflammation, and the cognitive phenotype; dysbiosis is common in even prodromal conditions like MCI (Jemimah et al., 2023; Akbari et al., 2016). While human findings remain primarily associative, animal studies find strong causation: the transfer of "aged" microbiome or "AD" microbiome into healthy donor systems stressed the system as assessed through neuroinflammation, behavioral detriments (Parker et al., 2022; Zhang et al., 2023); restoration of microbiome eubiosis (via young FMT or probiotics) presented decreased pathology with behavioral enhancements (Parker et al., 2022; Zhang et al., 2023). The microbiota thus appears to drive cognitive aging versus being a bystander.

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

- **Microbiota as a Therapeutic Option:** Restoring gut microbiota eubiosis represents a potential revolutionary treatment against neuroinflammation-driven cognitive decline. Early studies show that diet (high-fiber, plant-based meals) or probiotic introduction may shift inflammatory measures and some cognitive parameters (Akbari et al., 2016; Hung et al., 2022). Fecal microbiota transplantation is underway; preliminary case studies suggest cognitive enhancements following FMT (Park et al., 2022). Although no microbiota-related treatment has received FDA approval for AD as of yet, such options outstand safety, cost-effectiveness compared to others offered with similar ideas.

- **A Broader Preventive Perspective:** The ability to connect the gut and brain offers a new perspective on comprehensively understanding neurodegeneration. It suggests that protective efforts should be taken throughout life to avoid dysbiosis—diet and exercise (as well as possibly fermented foods or supplements) could enhance microbiome health, which subsequently improves cognitive resilience. Public health recommendations for gut dysbiosis should simultaneously push for enhanced dietary quality and reduced systemic inflammation to prevent population-wide impact related to dementia.

Ultimately, in light of neuroinflammation and cognitive decline, gut microbiota dysbiosis represents a modifiable risk factor that challenges the idea since the earliest discussion of AD pathology viewed it through an inner-neuronal lens. The shift in perspective to peripheralized models where brain immunity meets peripheral biology suggests that the challenge to the AD-status quo is not to underestimate amyloid/tau or other brain-intrinsic contributors, but instead, complicate understanding by adding a new layer of intervention possibility. Targeting the microbiome-gut-brain axis—and restoring eubiosis, enhancing gut health barriers, and down-regulating peripheral inflammation—represents a new and complementary theoretical approach that may allow for decreased neurodegeneration and enhanced cognitive health with longevity. With continued study, it's anticipated that a bench-to-bedside translational line emerges through microbiome-informed interventions to benefit well older adults and decrease the incidence of AD and related dementias, which negatively affect communities at large.

Bibliography

1. Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O. R.,... & Salami, M. (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, 256frontiersin.org.

2. Harach, T., Marungruang, N., Duthilleul, N., Cheatham, V., Mc Coy, K. D., Frisoni, G., ... & Bolmont, T. (2017). *Reduction of Alzheimer's disease β-amyloid pathology in APPPS1*

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

transgenic mice in the absence of gut microbiota. Scientific Reports, 7, 41802pmc.ncbi.nlm.nih.gov.

3. Hung, C. C., Chang, C. C., Huang, C. W., Nouchi, R., & Cheng, C. H. (2022). *Gut microbiota in patients with Alzheimer's disease spectrum: A systematic review and meta-analysis*. Aging (Albany NY), 14(1), 477–496pubmed.ncbi.nlm.nih.gov.

4. Jemimah, S., Chabib, C. M. M., Hadjileontiadis, L., & AlShehhi, A. (2023). *Gut microbiome dysbiosis in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis*. PLOS ONE, 18(5), e0285346journals.plos.orgjournals.plos.org.

5. Lei, W., Cheng, Y., Liu, X., Gao, J., Zhu, Z., Ding, W., ... & Chen, X. (2025). *Gut microbiota-driven neuroinflammation in Alzheimer's disease: From mechanisms to therapeutic opportunities*. Frontiers in Immunology, 16, 1582119pmc.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov.

6. Liu, W., Guo, J., Dong, Y., Li, J., & Wang, Y. (2025). *Eflcacy of probiotic supplementation in influencing cognitive function in Alzheimer's disease: A systematic review and meta-analysis*. Journal of Food Science, 90(7), e70037pubmed.ncbi.nlm.nih.gov.

7. Molinero, N., Antón-Fernández, A., Hernández, F., Ávila, J., Bartolomé, B., & Moreno-Arribas, M. V. (2023). *Gut microbiota, an additional hallmark of human aging and neurodegeneration*. Neuroscience, 518, 141–161pubmed.ncbi.nlm.nih.gov.

8. Park, S. H., Lee, J. H., Kim, J. S., Kim, T. J., Shin, J., Im, J. H., ... & Choi, S. H. (2022). *Fecal microbiota transplantation can improve cognition in patients with cognitive decline and Clostridioides diflcile infection*. Aging (Albany NY), 14(16), 6449–6466aging-us.com.

9. Parker, A., Romano, S., Ansorge, R., Aboelnour, A., Le Gall, G., Savva, G. M., ... & Carding, S. R. (2022). *Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain*. Microbiome, 10, 68microbiomejournal.biomedcentral.com.

10. Sepúlveda-Rivera, V., Olivieri-Henry, G., Morales-González, H., Ruiz-Adames, J., Herrero-Rivera, C., Rentas-Echeverría, A., ... & Godoy-Vitorino, F. (2025). *Gut microbiota distinguishes aging Hispanics with Alzheimer's disease: Associations with cognitive impairment and severity*. Scientific Reports, 15, 28505nature.com.

ISSN: 2455-8834

Volume:10, Issue:11 "November 2025"

11. Vogt, N. M., Kerby, R. L., Dill-McFarland, K. A., Harding, S. J., Merluzzi, A. P., Johnson, S. C., ... & Bendlin, B. B. (2017). *Gut microbiome alterations in Alzheimer's disease*. Scientific Reports, 7, 13537.

12. Yan, Z., Yang, F., Liao, H., Deng, Y., & Meng, F. (2022). *Alterations of the gut microbiota in older adults with mild cognitive impairment and Alzheimer's disease: A cross-sectional study*. Frontiers in Neurology, 13, 877651frontiersin.org.

13. Zhan, G., Hua, F., Zhu, Y., Yang, Z., Huang, N., Wang, Y., ... & Wei, C. (2018). *Gut microbiota as an emerging therapeutic target in neurodegenerative disorders: The role of probiotics and fecal microbiota transplantation*. Journal of the Neurological Sciences, 381, 84–90.

14. Zhuang, Z. Q., Shen, L. L., Li, W. W., Fu, X., Zeng, F., Gui, L., ... & Tan, L. (2018). *Gut microbiota is altered in patients with Alzheimer's disease*. Journal of Alzheimer's Disease, 63(4), 1337–1346.

15. **Figure Sources:** Figures were created based on information from: Loh, J. S., Mak, W. Q., How, C. W., Khaw, K. Y., & Ling, K. H. (2024). *Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases*. Signal Transduction and Targeted Therapy, 9(1), 37nature.comnature.com; and Wang, F., et al. (2023). *Improving microbiota–gut–brain axis via the intestinal barrier*. Signal Transduction and Targeted Therapy, 8(1), 5nature.comnature.com.

