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REVIEW

Gut Microbiota, Insulin Resistance, and Alzheimer's Disease: A Narrative Review of Mechanistic Links and Therapeutic Perspectives

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Abstract: Alzheimer's disease (AD) is increasingly regarded as a "neurometabolic syndrome" wherein systemic insulin resistance exacerbates cerebral glucose hypometabolism, tau hyperphosphorylation, and neuroinflammation. We hypothesize that gut microbiota dysbiosis produces metabolites that are associated with peripheral insulin sensitivity, potentially contributing to disruptions in cerebral insulin signaling and an increased risk of AD. We conducted integrated search of PubMed, Web of Science, and Scopus to synthesize evidence showing: (i) consistent taxonomic shifts in AD, highlighting reduced Firmicutes and increased Proteobacteria and Bacteroidetes, depletion of *Ruminococcaceae* and enrichment of *Blautia* and *Bilophila*; (ii) functional consequences of dysbiosis, leading to lower short-chain fatty acids, altered secondary bile-acid signaling, elevated lipopolysaccharide and trimethylamine-N-oxide, and perturbed tryptophan catabolism; (iii) these microbial metabolites compromising gut and blood-brain barrier integrity, thereby triggering chronic inflammation, potentially modulating the PI3K-Akt-GSK-3β pathway, and linking peripheral insulin resistance to cerebral dysfunction; and (iv) a translational discussion of therapeutic strategies that target both microbiota and insulin pathways, including dietary modulation, probiotics and prebiotics, fecal microbiota transplantation, intranasal insulin, metformin, and metabolite-based agents, show promise. This review uniquely integrates taxonomic, functional, and therapeutic literature to propose a mechanistic microbiota–insulin resistance–AD axis and highlights the need for longitudinal and interventional trials.

Keywords: Alzheimer's disease, gut microbiome alterations, insulin resistance

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Introduction

Alzheimer's disease (AD) remains the leading cause of dementia worldwide. Although several anti-amyloid monoclonal antibodies have now demonstrated modest, statistically significant slowing of cognitive decline in Phase III trials and obtained regulatory approval in selected jurisdictions, the overall clinical impact remains limited.[1–3] Converging epidemiological and mechanistic evidence now positions AD as a "neurometabolic syndrome" where systemic insulin resistance accelerates cerebral glucose hypometabolism, tau hyperphosphorylation and neuroinflammation.[4,5] This metabolic paradigm shift is encapsulated by the concept of "type 3 diabetes", which emphasizes the desensitization of brain insulin receptors.[5]

The gut microbiome plays a pivotal role in immunity regulation across various conditions, from cancer to autoimmune diseases,[6–10] and is a critical in regulating insulin sensitivity. For instance, compared to lean individuals, the microbiota of obese subjects exhibits a reduced capacity to produce short-chain fatty acids (SCFAs), which can improve

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peripheral insulin sensitivity.[11] High-fat diets can reshape the gut microbial composition, thereby contributing to insulin resistance and metabolic dysfunction. Moreover, fecal microbiota transplantation (FMT) from insulin-resistant mice to germ-free recipients can transmit the insulin-resistant phenotype.[12] Through both direct metabolic actions and neuroendocrine pathways, the microbiome influences energy balance and insulin action.[13]

Gut-brain communication occurs through several converging channels, including vagal afferents, immune signaling, endocrine hormones, and microbial metabolites, which together modulate intestinal and blood-brain barrier (BBB) integrity.[14,15] Dysregulation of this axis is increasingly implicated in AD pathogenesis, potentially via mechanisms such as heightened inflammation and increased gut permeability.[16] The emerging term "microbiota-gut-brain axis" highlights the critical contribution of gut microbes in the pathogenesis of central nervous system (CNS) disorders, including AD.[17,18] These microbial shifts can provoke neuroinflammation and modulate the immune response of the brain, thereby facilitating Aβ deposition and tau pathology.[19,20]

Despite the growing recognition of the gut microbiota and insulin resistance as contributors to AD, their interactions remain underexplored. To encapsulate potential interactions among them, we conducted a comprehensive, though not systematic, review of the literature indexed in databases such as PubMed, Web of Science, and Scopus from January 2001 through November 2025. Utilizing search terms centered on AD, neurodegenerative diseases, neuroinflammation, gut microbiota, metabolites, and insulin resistance, we identified, organized, and integrated pertinent studies to describe the principal achievements in this area according to the following inclusion criteria: (i) peer-reviewed original research; (ii) studies specifically investigating the gut microbiota–insulin signaling–AD mechanistic links and therapeutic interventions; and (iii) articles published in English; as well as the exclusion criteria: (i) conference abstracts or unpublished preprints and (ii) studies with no clear neurodegeneration or metabolic focus. Evidence from longitudinal cohorts and randomized controlled trials was prioritized to minimize bias. Findings from small-scale exploratory studies are interpreted with caution as they often lack sufficient power.

This review proposes a stepwise cascade as a unifying hypothesis: (i) microbial dysbiotic shifts may decrease SCFA production and increase pro-inflammatory metabolites like lipopolysaccharide (LPS) and trimethylamine-N-oxide (TMAO); (ii) these shifts probably impair peripheral insulin sensitivity and promote systemic inflammation; (iii) this inflammation, coupled with metabolite translocation, likely compromises BBB integrity; (iv) consequently, reduced insulin transport and altered receptor signaling within the brain potentially modulate PI3K-Akt-GSK-3β signaling activity, favoring tau hyperphosphorylation and Aβ accumulation; (v) the resulting neurodegeneration may perpetuate a feedback loop that further destabilizes gut homeostasis.

In contrast to previous reviews that largely catalog taxonomic alterations,[21,22] this review integrates gut-derived metabolites with cerebral insulin-signaling cascades, prioritizing those with the translational evidence. By proposing a unifying mechanistic model that connects dysbiosis-driven metabolic perturbations to tau hyperphosphorylation and BBB breakdown, the guidance of future experimental and therapeutic strategies is expected.

Gut Microbiota Landscape in AD

Taxonomic Shifts and Functional Metabolic Consequences

Numerous studies have demonstrated that individuals with gut microbiota dysbiosis have a heightened risk of developing AD.[21,23] At the phylum level, the dominant bacterial groups Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes have been characterized by large-scale metagenomic cohort projects from the Metagenomics of the Human Intestinal Tract Project including 249 newly sequenced samples and the Human Microbiome Project including 22 newly sequenced fecal metagenomes.[24,25] In an observational research, 25 patients with AD exhibited a decreased relative abundance of Firmicutes and Actinobacteria, alongside an increased abundance of Bacteroidetes and Proteobacteria in fecal samples, compared with cognitively normal populations.[26] This phylum-level shift is associated with a pro-inflammatory environment, characterized by reduced production of beneficial SCFAs, typically derived from Firmicutes, and an increased load of LPS associated with Gram-negative Bacteroidetes and Proteobacteria.

At a finer taxonomic resolution, several families and genera were consistently altered (Figure 1). Within Firmicutes, families such as Ruminococcaceae, *Turicibacteraceae*, Peptostreptococcaceae, Clostridiaceae, and Mogibacteriaceae

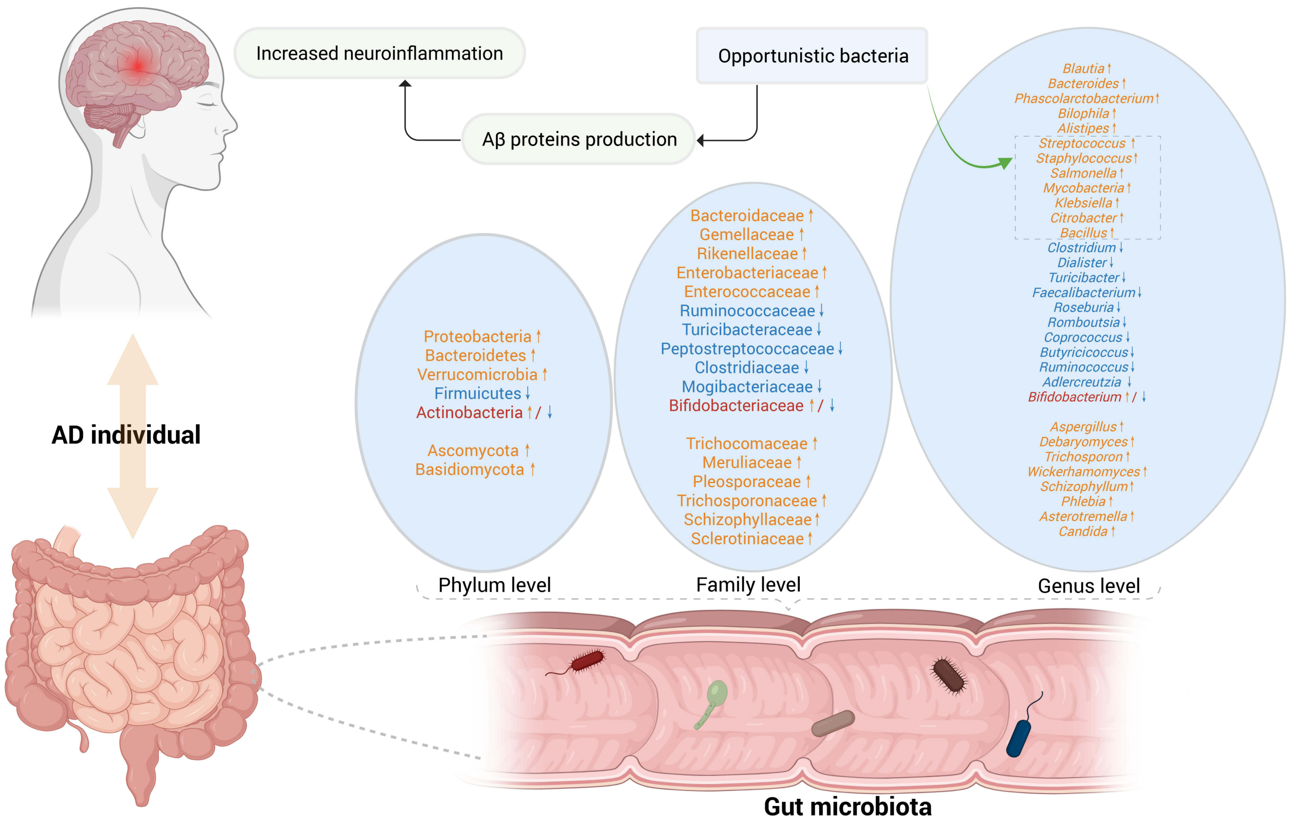

Figure 1 Gut microbial alterations in individuals with AD. At the phylum level, there is a decreased relative abundance of Firmicutes and an increased abundance of Proteobacteria, Bacteroidetes, and Verrucomicrobia. The abundance of Actinobacteria increases during the prodromal stage but decreases at the later stages of AD progression. At the family level, Ruminococcaceae, *Turicibacteraceae*, Peptostreptococcaceae, Clostridiaceae, Mogibacteriaceae, and Bifidobacteriaceae are reduced in AD patients, while Gemellaceae, Rikenellaceae, Verrucomicrobiaceae, Coriobacteriaceae, Erysipelotrichaceae, Enterococcaceae, and Corynebacteriaceae show increased abundance. Notably, Bifidobacteriaceae are elevated specifically in Chinese AD patients. At the genus level, AD patients exhibit lower levels of *Dialister, Clostridium, Turicibacter, Faecalibacterium, Romboutsia, Coprococcus, Butyricicoccus*, and *Adlercreutzia*, but higher levels of *Blautia, Phascolarctobacterium, Bilophila*, and *Alistipes*. The abundance of *Bifidobacterium* exhibits both increases and decreases. Furthermore, several opportunistic bacteria, including *Streptococcus, Staphylococcus, Salmonella, Mycobacterium, Klebsiella, Citrobacter*, and *Bacillus*, have the capacity to produce Aβ-like proteins that promote inflammation in the central nervous system. In addition to bacterial dysbiosis, alterations in gut fungi have been observed in AD individuals, characterized by increased levels of Ascomycota and Basidiomycota. Families such as Trichocomaceae, Meruliaceae, Pleosporaceae, Trichosporonaceae, Schizophyllaceae, and Sclerotiniaceae are more prevalent in cases of AD. The upward arrows indicate increased abundance, while the downward arrows decreased abundance.
Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β.

were reduced in patients with AD.[26] Notably, the reduction in butyrate-producing Ruminococcaceae implies a compromised ability to maintain intestinal barrier integrity and suppress neuroinflammation. Conversely, *Gemellaceae* was enriched. Within Bacteroidetes, Bacteroidaceae and Rikenellaceae were more abundant, potentially contributing to an elevated synthesis of pro-inflammatory cytokines. The family Bifidobacteriaceae from the phylum Actinobacteria was decreased. At the genus level, patients with AD showed lower levels of *Dialister, Clostridium*, and *Turicibacter* but higher levels of *Blautia, Phascolarctobacterium*, and *Gemella*. In addition, the Bacteroidetes-derived genera *Bacteroides* and *Alistipes* were abundant. These genera are often linked to pro-inflammatory indole production and bile acid dysregulation, which may further play a role in metabolic disturbances in AD. Within Actinobacteria, the genera *Bifidobacterium* and *Adlercreutzia* exhibited decreased abundance, while the genus *Bilophila* within the phylum Proteobacteria was found in greater abundance.[26] The depletion of *Bifidobacterium* is particularly significant given its role in producing neurotransmitters like Gamma-aminobutyric acid and modulating gut permeability. Another randomized clinical trial involving 100 human subjects with mild cognitive impairment showed an increase in Actinobacteria abundance, including an increase in the families Bifidobacteriaceae and genus *Bifidobacterium*.[27]

Cohort studies conducted in China have revealed region-specific patterns. In an observational study with 100 AD patients, those exhibited increased abundances of Actinobacteria and Verrucomicrobia, together with a marked reduction in Firmicutes.[28] Families such as Bifidobacteriaceae, Verrucomicrobiaceae, Coriobacteriaceae, Erysipelotrichaceae,

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Enterococcaceae, and Corynebacteriaceae were elevated, whereas Ruminococcaceae, Lachnospiraceae, and Clostridiaceae were depleted. The genera *Faecalibacterium, Roseburia, Clostridium sensu stricto, Gemmiger, Dialister, Romboutsia, Coprococcus*, and *Butyricicoccus* were reduced.[28] Since *Faecalibacterium, Roseburia*, and *Coprococcus* are prolific butyrate producers, their depletion suggests a severe deficit in neuroprotective metabolites that support the BBB function and microglia homeostasis. In another cohort study on 33 Chinese AD patients, the phylum Firmicutes showed a marked decrease in abundance, while Proteobacteria were enriched. Bacteroidetes were significantly enriched in the pre-onset stage of AD (compared with 32 patients with mild cognitive impairment) and unexpectedly decreased in later stages.[29] At the family level, Clostridiaceae, Lachnospiraceae, and Ruminococcaceae had decreased abundance. Notably, the genus *Blautia* was the most abundant, whereas *Ruminococcus* of the phylum Firmicutes showed a reduction in AD (Figure 1). The functional impact of enriched Proteobacteria, particularly the class Gammaproteobacteria, order Enterobacteriales, and family Enterobacteriaceae, is critical. These taxa are potent sources of endotoxins like LPS. Elevated systemic LPS can promote amyloidogenesis and increase BBB permeability, thereby facilitating the infiltration of immune cells into the CNS.

Fungal dysbiosis has also been reported (Figure 1). In an retrospective case control study, both Ascomycota and Basidiomycota dominate the microbiome in 88 AD and 65 non-AD individuals, yet families such as *Incertae sedis*, Trichocomaceae, Meruliaceae, Pleosporaceae, *Trichosporonaceae*, Schizophyllaceae, and Sclerotiniaceae are more prevalent in AD cases.[30] At the genus level, *Candida*, *Aspergillus, Debaryomyces*, *Trichosporon, Wickerhamomyces*, *Schizophyllum, Phlebia*, and *Asterotremella* are commonly detected, with *Candida albicans, Candida tropicalis*, and *Candida parapsilosis* being the most abundant species.[30] While less functionally characterized than bacteria, the overgrowth of *Candida* species may contribute to AD pathology through the secretion of candidalysin, a toxin that can damage epithelial barriers, or by potentially inducing Th17-mediated immune responses.

Importantly, diverse opportunistic bacteria, including *Streptococcus, Staphylococcus, Salmonella, Mycobacteria, Klebsiella, Citrobacter*, and *Bacillus*, have the ability to produce functional amyloid-like proteins, which proved through in vitro basic research,[31,32] such as TasA produced by *Bacillus*.[33] These microbial amyloids may prime hosts; innate immune system or trigger the misfolding of endogenous proteins through cross-seeding mechanisms, thereby contributing to neuroinflammation and Aβ-like pathology,[34] rather than directly forming human Aβ plaques within the CNS.

It must be noted that these reported taxonomic shifts vary across studies due to differences in sequencing platforms like 16S rRNA and shotgun metagenomics, and diagnostic criteria. Meanwhile, these can be influenced by confounders such as dietary fiber intake, the use of proton pump inhibitors, and the institutionalization of elderly patients, which are variables not always fully adjusted for in current literature. Consequently, the taxa highlighted herein should be interpreted as recurrent patterns rather than universally applicable biomarkers. Furthermore, genomic abundance does not always correlate linearly with metabolic output; thus, future multi-omics studies combining metagenomics with metabolomics are essential to definitively map these taxonomic shifts to specific functional pathways in AD.

Functional Metabolite Mechanisms in AD Pathogenesis

The taxonomic shifts described above translate into profound functional consequences through the production of key metabolites (Figure 2). SCFAs, primarily acetate, propionate, and butyrate, are fermentation products derived from digestive dietary fibers that exert multiple neuroprotective actions, which represent the primary communication channel between the gut microbiota and the host brain. The functional consequence of the depletion of SCFA-producing taxa is therefore multifaceted. SCFAs are known to play a key part in sustaining colonocyte energy metabolism, reinforcing intestinal barrier integrity, and modulating the BBB permeability. Neurologically, they function as histone deacetylase inhibitors and ligands for G-protein coupled receptors like FFAR2/FFAR3.[35] Through these signaling pathways, butyrate, in particular, upregulates the expression of tight-junction proteins including occludin and zonula occludens in cerebral endothelial cells, thereby preserving the BBB structure and limiting the infiltration of peripheral inflammatory mediators, which is a key link in the occurrence of neurodegenerative diseases such as AD.[36]

Beyond barrier maintenance, SCFAs shape neuroimmunity by promoting the differentiation of peripheral colonic regulatory T cells (Tregs) via FOXP3 induction. In the intestinal mucosal environment, SCFAs promote FOXP3$^+$ Treg development in a germ-free mouse model by acting on dendritic cells or directly on T cells. When SCFAs are severely reduced,

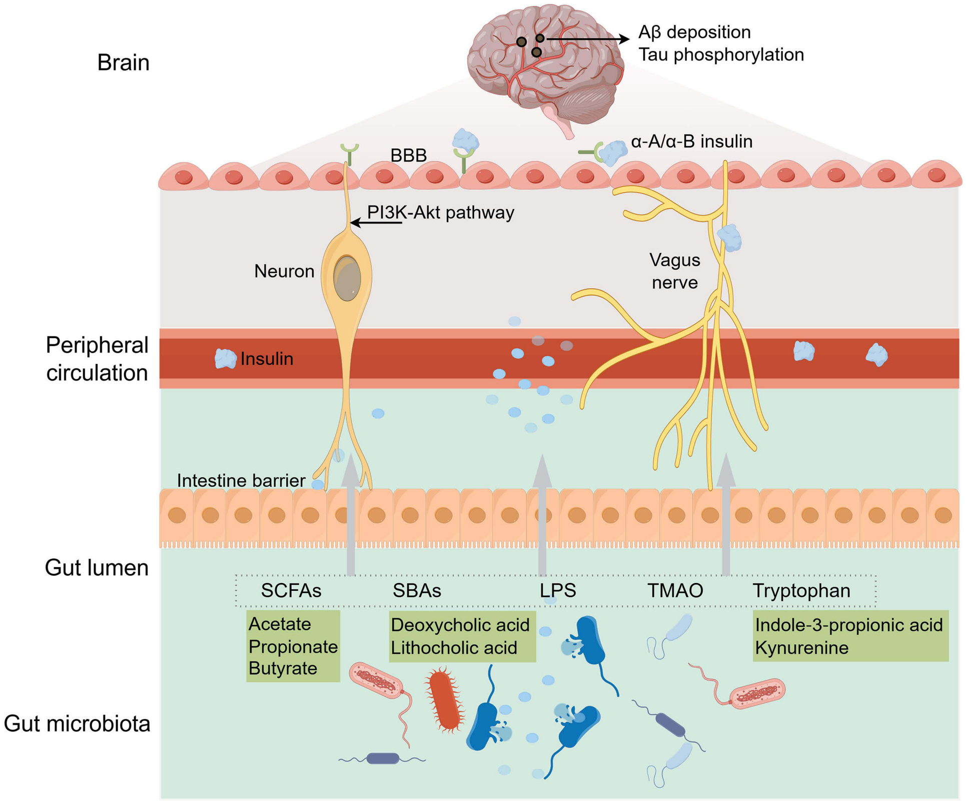

Figure 2 Functional gut metabolite production and its association with insulin sensitivity in individuals with AD. SCFAs, SBAs, LPS, TMAO, and tryptophan represent the primary gut metabolites in AD individuals. These metabolites play critical roles in regulating host glucose and energy metabolism while directly influencing insulin sensitivity. They can activate the downstream PI3K-Akt-GSK-3β pathway, promoting glucose utilization, supporting neuronal survival, and inhibiting tau hyperphosphorylation. Additionally, they may facilitate the translocation of endotoxins, such as LPS, into peripheral circulation, which probably increase the risk of or accelerate AD progression. Furthermore, insulin signaling intersects with pathways involving mTOR, autophagy, mitochondrial function, oxidative stress, and inflammatory responses. SCFAs, including acetate, propionate, and butyrate, sustain colonocyte energy metabolism, reinforce intestinal barrier integrity, and modulate BBB permeability. SBAs, such as deoxycholic acid and lithocholic acid, have evolved from being mere detergents to functional signaling molecules that interact with the central nervous system. They can activate FXR farnesoid X receptor and GPBAR1, regulating neuroinflammation, oxidative stress, and metabolic pathways associated with AD. LPS, as a prototypical endotoxin, can translocate across a compromised BBB, activating NF-κB signaling and upregulating neurotoxic microRNAs. TMAO compromises cerebral lymphatic endothelial cell function, potentially hindering the clearance of metabolic waste from the brain, including Aβ. TMAO is also associated with accelerated cognitive decline and neurodegenerative changes through mechanisms such as promoting oxidative stress, activating NLRP3 inflammasomes, disrupting mitochondrial function, and compromising BBB integrity.
Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; SCFAs, short-chain fatty acids; SBAs, secondary bile acids; LPS, lipopolysaccharides, TMAO, trimethylamine N-oxide; FXR, farnesoid X receptor; GPBAR1, G protein-coupled bile acid receptor 1; BBB, blood-brain barrier.

the number of RORγt$^+$ Tregs in the intestine decreases significantly.[37] Crucially, circulating SCFAs can cross the BBB to directly modulate microglial phenotype, shifting them from a pro-inflammatory (M1-like) to a neuroprotective (M2-like) state. The disruption of this "SCFA-microglia axis", driven by the loss of genera like *Faecalibacterium*, leads to unchecked neuroinflammation and Aβ accumulation, suggesting that SCFA deficiency may serve as a mechanistic bridge linking gut dysbiosis to AD pathology by disrupting the BBB, promoting inflammation, and altering glial cell function.[38,39]

Secondary bile acids (SBAs), notably deoxycholic acid and lithocholic acid converted from primary bile acids through bacterial metabolism, have transitioned from mere detergents to functional signaling molecules that interact with the CNS.[40] (Figure 2) Dysbiosis in AD typically is associated with an altered SBA profile, which may interfere with signaling via the farnesoid X receptor (FXR) and membrane receptor GPBAR1 (TGR5) expressed on neurons and glia. Through these receptors, SBAs regulate neuroinflammation, oxidative stress, and metabolic pathways implicated in AD.[41,42] Recent metabolomic studies have demonstrated that altered serum SBA profiles correlate with cerebrospinal fluid (CSF) tau/Aβ ratios and reduced cerebral glucose metabolism in AD patients.[43]

LPS, a component of the outer membrane of gram-negative bacteria, is a prototypical endotoxin (Figure 2). The expansion of Gram-negative Proteobacteria described earlier translates functionally into a chronic "endotoxin burden". Elevated LPS levels have been detected in the serum and CSF of patients with AD and mild cognitive impairment,

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supporting the "endotoxin hypothesis" that peripheral LPS translocates across a compromised BBB, activating the NF-κB inflammatory cascade. Mechanistically, this activation upregulates neurotoxic microRNAs such as miRNA-30b, miRNA-34a, miRNA-146a, and miRNA-155, leading to the downregulation of synaptic proteins and failure of phagocytosis. Specific pathways detailed in recent literature, such as the "LPS–NF-κB–miRNA-30b–neurofilament light chain" axis, illustrate how gut-derived toxins directly compromise neuronal cytoskeletal integrity.[44,45] In addition, recent studies have linked dietary LPS with cognitive function, suggesting that reducing dietary sources rich in LPS, advanced glycation end products, and arachidonic acid may lower the risk of AD by mitigating chronic neuropathy.[46] However, there is currently no standard protocol regarding dietary interventions, probiotics, antibacterial strategies, barrier enhancement, drug treatment, and long-term safety must also be considered.

Elevated TMAO, which is generated from dietary choline and carnitine via gut microbial conversion, for instance, by *Proteobacteria*, to trimethylamine and subsequent hepatic oxidation by flavin monooxygenase 3,[47] can impair cerebral lymphatic endothelial cells, which may negatively affect the clearance of brain metabolic waste, including Aβ aggregates (Figure 2). Furthermore, TMAO may accelerate cognitive decline and neurodegenerative changes by promoting oxidative stress, activating NLRP3 inflammasomes, disrupting mitochondrial function, and compromising BBB integrity.[48] While a large prospective cohort with 3143 participants has shown modest associations between plasma TMAO levels and dementia risk, this association is notably weak in individuals with renal impairment.[49]

Conversely, tryptophan catabolism yielded indole-derived metabolites like indole-3-propionic acid and kynurenine (Figure 2). Unlike the neurotoxic agents above, indole-3-propionic acid acts as a potent antioxidant and aryl hydrocarbon receptor agonist, possessing antioxidant and anti-inflammatory properties that can slow neuroinflammation and oxidative damage and thus help prevent AD.[50] Those indoles can also modulate mitochondrial function and endosomal trafficking, thereby influencing neuronal survival.[51] The imbalance between these toxic (TMAO) and protective (Indoles) metabolites further defines the metabolic signature of AD.

Insulin-Resistance Mechanisms in AD

Peripheral Insulin Resistance and Cerebral Consequences

Peripheral insulin resistance, commonly associated with type 2 diabetes and metabolic syndrome, not only affects systemic metabolism but may also affect brain function through several pathways, increasing the risk or accelerating the progression of AD (Figure 2). It stands an independent risk factor for cardiovascular and cerebrovascular disease. While the brain was traditionally considered "insulin independent", contemporary research demonstrates that the brain is sensitive to insulin, which regulates neuronal energy metabolism, synaptic plasticity, autophagy, and oxidative defence.[52] Chronic hyperinsulinemia can desensitize insulin receptor at the BBB, impairing insulin transport into the CNS and disrupting downstream signaling.[53] Moreover, systemic inflammation, lipotoxicity, oxidative stress, and vascular dysfunction associated with insulin resistance compromise BBB integrity, further limiting cerebral insulin availability. Thus, the brain finds itself in a state of both hormone deficiency and cellular resistance. The early identification of insulin resistance and lifestyle-based interventions holds promise not only for metabolic health, but also for reducing the risk of AD.

Molecular Nodes in Cerebral Insulin Signaling

In healthy neurons, insulin activates the downstream PI3K-Akt pathway through the insulin receptor, promoting glucose utilization, neuronal survival, and synaptic plasticity, while concurrently inhibiting overactivated glycogen synthase kinase 3β (GSK-3β) (Figure 2), a key kinase driving tau hyperphosphorylation.[53] Recent data suggest that insulin receptors expressed on cerebral microvascular endothelium, rather than solely on neurons, constitute the principal entry point for insulin into the brain.[53] Patients with AD display an altered α-A/α-B insulin receptor isoform ratio, which attenuates insulin-mediated Aβ clearance across the BBB.[54] Beyond the PI3K-Akt-GSK-3β pathway, insulin signaling intersects with mTOR, autophagy, mitochondrial function, oxidative stress, and inflammatory response.[55] Dysregulation of any of these nodes probably exacerbate neuronal injury and neurodegeneration.

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Potential Modulation by Microbial Metabolites

The concept of the microbiota-gut-brain axis (MGBA) has recently been used to describe how the gut microbiota affects systemic metabolism, including insulin sensitivity, brain function, and cognition through metabolites. Here, we synthesize the evidence that gut-derived metabolites constitute a mechanistic bridge, linking the dysbiosis to cerebral insulin resistance (Figure 2).

The gut microbiota influences host glucose metabolism and insulin sensitivity through several inter-related mechanisms. Specific bacterial taxa have shown to influence carbohydrate availability. Genera within the Lachnospiraceae family, such as *Blautia* and *Dorea* tend to release host-accessible monosaccharides that promote adiposity, hepatic lipogenesis, and systemic inflammation, thereby fostering insulin resistance. In contrast, species from *Alistipes* and *Bacteroides* reduce monosaccharide flux, mitigate fat deposition, and preserve insulin resistance. For example, oral administration of *Alistipes indictus* induces high-fat diet in mice to prevent diet-induced obesity and insulin resistance,[56] highlighting the therapeutic potential of specific commensal bacteria in metabolic disorders.

As synthesized in Figure 2, dysbiosis of the gut microbiota compromises intestinal barrier function, facilitating the translocation of endotoxins such as LPS into the peripheral circulation.[57] Crucially, circulating LPS is a potent inducer of pro-inflammatory cytokines like TNF-α and IL-6, which activate stress kinases such as c-Jun N-terminal kinase. These kinases phosphorylate insulin receptor substrate-1 (IRS-1) at inhibitory serine residues like Ser307 rather than functional tyrosine residue, uncoupling the insulin receptor from downstream PI3K/Akt signaling, a hallmark of molecular insulin resistance.[58,59] This suggests a feedforward loop wherein chronic inflammation and metabolic dysfunction may mutually reinforce one another.[46]

Specific metabolites directly modulate key checkpoints in insulin signaling and AD pathology. SCFAs can activate G-protein-coupled receptors such as GPR41, 43, and 109 and upregulate metabolic genes such as *GLUT4, PPAR alpha*, and *SREBP1c*,[60,61] thereby restoring insulin sensitivity. SBAs, through the signaling of FXR and Takeda G protein-coupled receptor 5 (TGR5), also influence hepatic gluconeogenesis and peripheral insulin action.[50] Conversely, a preclinical model suggested that TMAO aggravates insulin resistance and implies a further mechanistic link to AD neurodegeneration.[62]

Systemic insulin resistance directly impacts CNS pathology through competition for the Insulin-Degrading Enzyme (IDE). IDE is responsible for the catabolism of both insulin and Aβ.[63] In states of hyperinsulinemia driven by gut dysbiosis, IDE is preferentially occupied by excess insulin, thereby reducing its capacity to clear Aβ peptides.[63] IDE competition results in the accumulation of neurotoxic Aβ plaques.[57,64] Furthermore, defective insulin signaling compromises neuronal glucose transport. Insulin resistance downregulates the expression and membrane translocation of glucose transporters, specifically GLUT3 and GLUT1,[65,66] leading to a state of cerebral energy starvation. This bioenergetic deficit impairs synaptic plasticity and promotes tau hyperphosphorylation, accelerating neurodegeneration.

Given the crucial role of gut microbiota in regulating the IRS-1/PI3K/Akt axis and IDE activity,[67,68] therapeutic modulation of the microbiota, such as dietary fiber enrichment, probiotics, and FMT, has demonstrated the capacity to restore a favorable microbial profile, elevate SCFA production, lower HOMA insulin resistance scores, and rescue neuronal insulin signaling in both animal models and early stage human trials.[69]

A Unified Mechanistic Pattern: The Microbiota-Insulin-AD Axis

Rather than viewing gut dysbiosis and insulin resistance as parallel independent risk factors, our synthesis suggests they are sequentially interdependent. Specifically, the “leaky gut” allows for chronic systemic endotoxemia, which initiates a systemic metabolic inflammation. This inflammation is considered a key driver in IRS-1 serine phosphorylation, a modification that can interfere with the coupling of brain insulin receptors from their survival-signaling pathways (PI3K-Akt). This unified model offers a framework for understanding why dietary or microbiota-targeted interventions may fail if they do not simultaneously address the established insulin desensitization, and vice versa, providing a comprehensive and multidimensional therapeutic blueprint.

Therapeutic Implications

Dietary Interventions (Level of Evidence: High)

High-fiber, low-saturated-fat diets are supported by extensive epidemiological data as particularly effective strategies for promoting the growth of SCFA-producing bacteria.[70–72] These dietary patterns are integral in maintaining intestinal health and reducing systemic inflammation (Figure 3), potentially attenuating LPS-mediated endotoxemia linked to AD.[73] In addition to fiber, the Mediterranean diet, rich in polyphenols, represents the gold standard for nutritional neuroprotection, showing consistent beneficial effects on metabolic and cognitive health in large cross-sectional study with 689 older individuals.[73] Polyphenols, abundant in foods like fruits, vegetables, whole grains, and olive oil, possess anti-inflammatory and antioxidant properties that mitigate oxidative stress, a key driver of neurodegeneration in AD.[74,75] Moreover, polyphenols may modulate bile acid metabolism and reduce TMAO production, linking dietary patterns directly to insulin resistance reduction in an in vitro human colon model.[76] Unlike pharmacological interventions, dietary modification offers a universally applicable, low-risk foundation for AD prevention.

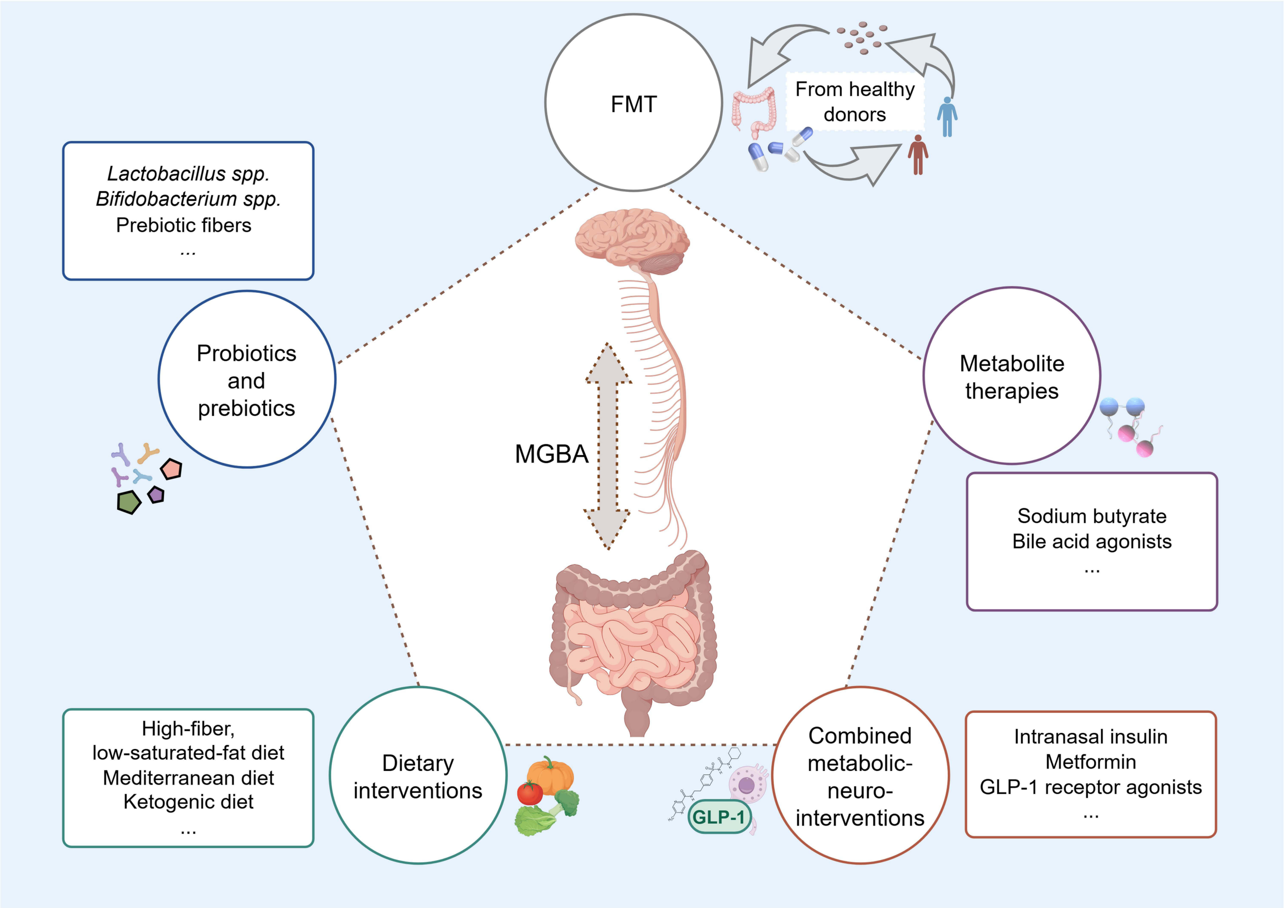

Figure 3 Potential therapeutics for individuals with AD. Various therapeutic approaches are summarized, including dietary therapies, probiotics and prebiotics, FMT, metabolite therapies, and combined metabolic-neurointerventions. High-fiber, low-saturated-fat diets contribute to maintaining intestinal health and reducing systemic inflammation. Notably, the Mediterranean diet, rich in polyphenols, has been shown to mitigate oxidative stress that contributes to neurodegeneration in AD. Probiotics and prebiotics, such as *Lactobacillus* spp. and *Bifidobacterium* spp., are known to reinforce intestinal barrier function, suppress systemic inflammation, and improve peripheral insulin sensitivity, thereby indirectly protecting cerebral insulin signaling. FMT can lead to increased butyrate production, which is associated with anti-inflammatory and neuroprotective effects, ultimately enhancing cognitive function and stabilizing AD progression. Oral or intranasal delivery of SCFAs and bile acid agonists may help restore insulin sensitivity and positively influence insulin signaling pathways, which are often compromised in individuals with AD. Furthermore, combined therapies that integrate metabolites with conventional neurointerventions, such as intranasal insulin, metformin, or GLP-1 receptor agonists, can exert synergistic effects in mitigating AD progression.
Abbreviations: AD, Alzheimer's disease; FMT, fecal microbiota transplantation; GLP-1, glucagon-like peptide-1.

Probiotics and Prebiotics (Level of Evidence: Adjuvant)

Comparatively, specific probiotic strains, such as *Lactobacillus* spp. and *Bifidobacterium* spp., function as adjuvant therapies. They have been shown to enhance the production of SCFAs,[77–80] reinforcing intestinal barrier function, suppressing systemic inflammation, and improving peripheral insulin sensitivity (Figure 3). While these mechanisms theoretically protect cerebral insulin signaling, a pathway that is often disrupted in neurodegenerative diseases, such as AD, clinical outcomes in AD patients remain heterogeneous. A pre-clinical study reported modest improvements in cognitive scores like Mini-Mental State Examination and inflammatory biomarkers like C-reactive protein,[78] but effect sizes vary widely based on strain selection and duration. Additionally, probiotic fibers can promote gut microbiota diversity, potentially enhancing the efficacy of probiotics.[81] Thus, while probiotics show promise for metabolic regulation, standardized protocols for their use in neurodegenerative disease management are still under development.

FMT (Level of Evidence: Early Phase)

FMT represents a novel, investigational approach aimed at comprehensive microbiota restoration (Figure 3). The theory posits that transferring stool from cognitively healthy donors can reset the dysbiotic Firmicutes/Bacteroidetes ratio and restore butyrate levels.[82] Currently, the strongest efficacy data come from transgenic mouse models, where FMT successfully ameliorated Aβ plaques and tau pathology.[83,84] In humans, evidence is limited to case series and small pilot safety trials. Preliminary data indicate potential stability in cognitive function and inflammatory profiles.[85,86] However, devoid of rigorous Phase III trials, FMT remains an experimental procedure due to concerns regarding donor variability and long-term immunological safety. Further research is critical to determine if these preclinical benefits translate into clinically meaningful outcomes for AD patients.

Targeted Metabolite Therapies (Level of Evidence: Preclinical)

Moving beyond live bacterial therapeutics, direct administration of bioactive metabolites offers a precise, albeit largely preclinical, avenue. Oral or intranasal delivery of SCFAs, including sodium butyrate, has been shown to enhance BBB integrity in rodent models,[87] effectively preventing neurotoxic substances from entering the brain (Figure 3). In these animal models, such treatment reduced neuroinflammation and restored insulin-responsive signaling pathways, which are typically disrupted in insulin resistance.[88] Similarly, bile acid agonists, such as FXR and TGR5 ligands, show potential in modulating the gut-brain axis by reducing endotoxin load that can exacerbate neuroinflammation.[89,90] Importantly, while these metabolites influence insulin signaling pathways in vitro and in vivo, their bioavailability and therapeutic window in human AD subjects remain to be established.[36]

Combined Metabolic-Neurointerventions (Synergistic Potential)

Finally, recognizing the multifactorial nature of AD, combined approaches represent the frontier of validation. Merging systemic metabolic therapies such as intranasal insulin, metformin, and glucagon-like peptide-1 receptor agonists, along with microbiota-modulating strategies,[91,92] may potentially exert synergistic effects by simultaneously targeting both the peripheral drivers and the central consequences of insulin resistance (Figure 3). Intranasal insulin has shown moderate clinical efficacy in improving cognitive.[93] Metformin, a widely used drug for the management of type 2 diabetes, is another key therapeutic agent in this combined approach. In addition to its effects on glucose metabolism, metformin has been shown to exert neuroprotective effects through mechanisms such as the activation of AMP-activated protein kinase and the reduction of oxidative stress.[94] Glucagon-like peptide-1 receptor agonists are accumulating encouraging signals from ongoing clinical trials for their neuroprotective properties.[95] Integrating these pharmacological agents with gut-microbiota modulation offers a personalized therapeutic strategy, though clinical protocols for such combinations are currently undefined.

Limitations and Future Research Directions

The findings discussed in this review are subject to several limitations. First, the majority of clinical evidence is cross-sectional, making it difficult to determine if gut dysbiosis precedes AD or is a consequence of disease-related lifestyle changes (reverse causality). Second, technical heterogeneity ranging from diverse 16S rRNA primers to varying bioinformatic pipelines limits the comparability of taxonomic data across different geographical cohorts. Third, small sample sizes in FMT and probiotic trials necessitate larger, multicenter randomized controlled trials to validate therapeutic efficacy. Finally, publication bias cannot be excluded, as studies with positive findings are more likely to be published than those reporting null results.

Advancing our understanding of MGBA in AD will require a coordinated series of investigations guided by a mechanistic framework. First, large-scale, multicenter, longitudinal studies employing both 16S rRNA sequencing and shotgun metagenomics should be conducted to identify specific microbial taxa or community structures that can most reliably predict disease progression or possess therapeutic potential. Second, targeted metabolomics, coupled with measurements of the BBB permeability using techniques such as PET-CT and CSF analysis, will enable the characterization of dose-response relationships for SCFAs, SBAs, TMAO, and other metabolites in cerebral insulin signaling pathways. Third, causal links between gut microbes and central insulin resistance must be tested using advanced preclinical models, such as humanized mouse models that receive FMT or colonized with engineered microbial strains, followed by phosphoproteomic and metabolic profiling of brain tissue. Fourth, double-blind randomized controlled trials should evaluate combined interventions, including dietary modification, probiotic supplementation, and insulin-sensitizing agents, using cognitive composites, FDG-PET imaging, and peripheral insulin sensitivity indices as primary outcomes. Fifth, developing precision-medicine platforms that integrate microbial, metabolic, and clinical datasets using machine learning algorithms will facilitate individualized therapeutic recommendations. Finally, long-term safety surveillance of microbiota-targeted therapies is essential to assess potential adverse effects, including immune dysregulation, metabolic disturbances, and the emergence of antimicrobial resistance. Collectively, these research directions provide a mechanistic framework for translating microbiome-based strategies into clinically effective AD interventions.

Conclusions

Accumulating evidence supports a transition from a mere association to a causal axis linking gut dysbiosis to AD pathology through the lens of metabolic failure. This review proposes a unifying hypothesis: taxonomic shifts that are characterized by the depletion of SCFA-producing Firmicutes and the enrichment of LPS-producing Proteobacteria may contribute to a bioenergetic crisis. Mechanistically, the elevation of pro-inflammatory metabolites like LPS and TMAO and the deficit in SCFAs are hypothesized to collectively trigger peripheral insulin resistance, which can compromise the BBB and potentially lead to the desensitization of cerebral insulin receptors. This peripheral-to-central metabolic failure is thought to disrupt the PI3K-Akt signaling cascade, thereby reducing the inhibition on GSK-3β, which plays a central role in tau hyperphosphorylation and accelerates Aβ deposition. From a translational perspective, this axis suggests that future AD therapies must move beyond amyloid-centric models toward multi-target metabolic restoration. Precision microbial modulation via metabolite-based agents or targeted probiotics offers a unique window to restore cerebral insulin sensitivity before irreversible neurodegeneration occurs. Future longitudinal trials should prioritize biomarkers of the PI3K-Akt pathway to validate this microbiota-insulin-AD axis as a viable therapeutic target, moving the field closer to a precision metabo-psychiatry approach for AD prevention and treatment.

AI Disclosure Statement

DeepSeek V3.2 was used to improve the grammar, clarity and readability of the manuscript. The authors take full responsibility for the authenticity and accuracy of the content of this manuscript.

Data Sharing Statement

Data presented in this study are available upon request from the corresponding author (H. S.).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report there are no competing interests to declare for this work.

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