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Expanding the Understanding of Gut Microbial Dysbiosis in Alzheimer's Disease

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Commentary

Alzheimer's disease (AD) represents a persistent and growing global health challenge. It is a progressive, and largely sporadic neurodegenerative condition characterized not only by a reduction in brain volume and weight but also by widespread and progressive atrophy of the cerebrum. The disease involves substantial loss of neurons, particularly in the hippocampus and the medial temporal lobes, as confirmed through pathological studies [1]. The physical, emotional, and financial burdens imposed by AD on affected individuals, their caregivers, and society as a whole highlight the urgent need for a deeper understanding of its complex pathophysiology. While traditional research has primarily focused on hallmark pathological features such as amyloid-β plaques and tau neurofibrillary tangles, increasing attention has shifted toward broader systemic mechanisms, including inflammation, metabolic dysregulation, and microbial influences. Such knowledge is essential for developing effective preventive and therapeutic strategies.

Over the past decade, growing attention has been directed toward the intricate communication between the gut microbiome and the central nervous system, commonly known as the gut–brain axis. This expanding field has generated significant interest in understanding the potential role of gut microbiota in the development and progression of neurodegenerative diseases. A recently published umbrella review by Kumari *et al.* [2] examining the association between gut microbiota dysbiosis and AD highlights the emerging importance of microbial alterations in the pathophysiology of this debilitating condition. By integrating findings from 12 systematic reviews, the authors present a comprehensive overview of current evidence linking changes in gut microbial composition to cognitive decline and neurodegeneration. The collective findings consistently indicate that individuals with AD display less abundant microbial diversity as well as distinct alterations in their gut microbial communities compared with cognitively healthy individuals. In particular, differences involving major bacterial phyla, such as Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, were frequently reported. Building on these observations, it is important to move beyond compositional changes and consider the functional consequences of the microbiome. Specifically, the metabolites produced by gut microbes and the ways in which microbial communities can be modulated may play a crucial role in influencing the development and progression of AD. Exploring these mechanistic pathways may provide deeper insight into how the gut microbiome contributes to neurodegeneration and may open new avenues for preventive and therapeutic strategies.

The gut microbiota comprises trillions of diverse microorganisms, along with the metabolites they produce, collectively forming the gut microbiome ecosystem. The mechanisms through which gut microbiota and their metabolites influence disease initiation and progression are complex, multifactorial, and bidirectional. These interactions involve multiple physiological systems, including the central and autonomic nervous systems, as well as neuro-immune, neuro-endocrine, and entero-endocrine signaling pathways [3]. Together, these interconnected pathways constitute an intricate communication network commonly referred to as the microbiota–gut–brain–immune axis, which functionally links the gastrointestinal tract with the brain. Communication from the brain to the gut occurs primarily through the sympathetic and parasympathetic branches of the autonomic nervous system, in addition to hormonal signaling pathways. Conversely, signals from the gut to the brain are transmitted through several mechanisms, including the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, and a wide array of microbially derived molecules [4].

Gut microbiota produce a wide range of bioactive molecules that influence the microbiota–gut–brain axis and play an important role in AD pathogenesis. These include bacterially synthesized neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine, serotonin, and noradrenaline, as well as metabolites such as branched-chain amino acids, short-chain fatty acids (SCFAs), aryl hydrocarbon receptor agonists, bile acids, and lipid derivatives including sphingolipids and phospholipids [5]. These microbial products can regulate key pathogenic mechanisms in AD, including β-amyloid metabolism, tau phosphorylation, and neuroinflammation. Among them, SCFAs produced through the fermentation of dietary fibers, play a central role in gut–brain communication by supporting blood–brain barrier integrity, reducing microglial activation, and enhancing synaptic plasticity, although excessive or imbalanced levels may also promote β-amyloid deposition [6]. Other microbiota-derived metabolites such as tryptophan-derived indoles, kynurenine pathway metabolites, trimethylamine N-oxide (TMAO), and secondary bile acids also influence neurodegenerative processes. Protective indole derivatives can reduce oxidative stress and inflammation, whereas elevated TMAO levels are associated with endothelial dysfunction, neuroinflammation, and increased β-amyloid aggregation [7]. Metabolomic studies further show that individuals with AD often exhibit decreased levels of beneficial metabolites, including SCFAs and indole derivatives, along with increased TMAO levels, which correlate with disease severity indicators such as Mini-Mental State Examination (MMSE) scores, brain atrophy, and cerebrospinal fluid β-amyloid levels [8]. Collectively, these findings highlight that gut-derived metabolites act as active regulators of neural, immune, and metabolic pathways, suggesting that microbiome-targeted strategies and metabolomic profiling may offer promising approaches for precision medicine in AD.

Kumari *et al.* discussed several lifestyle factors that may influence the prevention or progression of AD, with particular emphasis on dietary patterns such as the mediterranean, ketogenic, and western diets. Nutrition and dietary habits are critical determinants of both gut microbiome composition and neurodegenerative processes. Increasing evidence indicates that diet significantly shapes the gut microbiota, which plays an essential role in maintaining the proper functioning of multiple physiological systems, including the nervous system. Individuals with AD often experience a decline in taste perception, which can lead to reduced food intake and fewer meals. Additionally, cognitive impairment associated with the disease frequently alters eating behaviors. Poor nutritional status in individuals with chronic dementia can further aggravate disease symptoms, including sleep disturbances, hallucinations, and apathy [9]. Evidence suggests that specific dietary patterns, such as the Mediterranean diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and the MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay) diet, may exert beneficial effects on the gut microbiome and potentially reduce the risk or progression of AD [10]. Therefore, a comprehensive understanding of the interactions between diet, the gut microbiota, and the nervous system could contribute to the development of targeted dietary strategies and lifestyle interventions aimed at preventing or delaying AD.

Beyond diet and nutrition, several modern lifestyle factors, such as chronic stress, sleep disruption, sedentary behavior, and environmental stressors like noise, can significantly influence the gut microbiome and contribute to the pathogenesis of AD. The gut microbiota is highly sensitive to external lifestyle conditions, most of which are recognized risk factors for AD [11]. Lifestyle interventions such as regular physical activity appear to exert neuroprotective effects by enhancing the production of antioxidant enzymes and neurotrophic growth factors, while reducing reactive oxygen species, neuroinflammation, and the accumulation of β-amyloid plaques and tau protein in the brain [12]. Sleep quality is another important factor; improved sleep in older adults has been associated with better cognitive performance and increased abundance of beneficial microbial phyla such as Verrucomicrobia and Lentisphaerae [13]. Furthermore, aging, one of the strongest risk factors for AD, is accompanied by physiological changes that alter the gut microbiome. Studies have shown that aging is associated with shifts in microbial composition, including increased numbers of facultative anaerobes, alterations in species dominance, and relative stability in the overall abundance of anaerobic bacteria, which may collectively contribute to cognitive decline and dementia risk [14].

Another important area of study is pre/pro/post-biotic intervention. Growing evidence indicates that microbiome-targeted interventions, including probiotics, prebiotics, synbiotics, and postbiotics, may exert beneficial effects on neuroinflammation and cognitive function. These strategies modulate the composition and activity of the gut microbiome, thereby influencing systemic and central inflammatory processes through the gut–brain axis. Probiotic supplementation, for instance, has been shown to alter neuropeptide expression in the brain in parallel with shifts in gut microbial composition. Experimental studies suggest that the hippocampus, a brain region critical for learning and memory, exhibits particular sensitivity to probiotic interventions, indicating a potential mechanism through which microbiome modulation may influence cognitive outcomes [15]. Prebiotics including soluble and insoluble dietary fibres are associated with production of functional neurotrasnsmitters and regulating cytokine production, essential for protecting neurodegeneration [16]. In addition, synbiotics, which combine probiotics and prebiotics, can generate bioactive metabolites with neuroprotective

properties. Certain synbiotic-derived compounds, including polyphenols, have demonstrated potential in attenuating Alzheimer's-related neuropathological processes by inhibiting β-amyloid aggregation and preventing tau fibril formation [17]. Similarly, postbiotics, defined as metabolic byproducts produced by beneficial microorganisms during fermentation or growth, represent an emerging concept in the field of microbiome-based therapeutics. These compounds exhibit a wide range of biological activities, including immunomodulatory, anti-inflammatory, antioxidant, and anti-proliferative effects. Mechanistically, postbiotics have been shown to influence key inflammatory signaling pathways such as NF-κB and MAPK, thereby contributing to the regulation of immune responses and maintenance of host health. By suppressing the synthesis of pro-inflammatory cytokines, postbiotics may help attenuate neuroinflammation associated with the development and progression of Alzheimer's disease [18]. Although human clinical evidence is limited in this area, findings from microbiome-based interventions involving prebiotics, probiotics, synbiotics, and postbiotics represent a promising avenue for modulating gut–brain interactions and may offer novel preventive and therapeutic strategies for managing AD.

Future research should therefore prioritize longitudinal cohort studies that track microbial changes across the preclinical and early symptomatic stages of AD. Such studies would help clarify whether specific microbial patterns as well as their metabolites can serve as early biomarkers for disease risk or progression. In addition, randomized controlled trials investigating microbiome-targeted interventions, such as dietary modifications, lifestyle modification, prebiotic supplementation, or probiotic therapies, may provide valuable insights into the therapeutic potential of modulating the gut microbiota.

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