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Nutritional Intervention Strategies for Alzheimer's Disease from the Perspective of the Gut-Brain Axis

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Abstract. As a progressive neurodegenerative disorder, Alzheimer's disease (AD) currently lacks curative treatments. Recent studies have demonstrated that gut dysbiosis modulates neuroimmune and metabolic pathways via the gut–brain axis and plays a pivotal role in AD pathological progression, which opens up new avenues for nutritional intervention. This paper systematically reviews multiple nutritional intervention strategies based on gut microecology regulation, including probiotics, prebiotics, polyphenolic antioxidants, omega-3 fatty acids, and fecal microbiota transplantation (FMT). Such interventions exert certain protective effects by modulating gut microbiota composition, alleviating neuroinflammation, preserving blood-brain barrier integrity, and slowing cognitive decline. Although existing clinical investigations have yielded several positive outcomes, the field is still confronted with prominent limitations such as high heterogeneity of intervention regimens, short follow-up durations, small sample sizes, and inconsistent biomarkers and detection criteria. These drawbacks result in low levels of evidence, making it difficult to directly guide clinical practice. Furthermore, factors including poor patient adherence and interference from comorbidities and concomitant medications hinder the stable evaluation of intervention efficacy. Future research should rely on long-term, multicenter, large-sample randomized controlled trials (RCTs), combined with integrated multi-omics analysis and individualized stratification strategies, to identify the most effective intervention combinations and their applicable populations. This review elaborates on mechanisms underlying the gut-brain axis, major nutritional intervention strategies, available clinical evidence, and prevailing challenges, aiming to provide references for subsequent research and translational applications in this field.

Keywords: Alzheimer's Disease, Nutritional intervention, Gut-brain axis

1. Introduction

Alzheimer's disease (AD) stands as a degenerative cognitive disorder that gains high prevalence among elderly groups, which faces expanding patient groups as the whole global population gradually enters an aging phase. Global health authorities keep long-term tracking work for cognitive impairment disorders of this kind, which can reflect the overall spreading trend of such diseases from various research records [1]. Conventional intervention drugs adopted in current clinical practice only relieve physical discomfort for targeted symptoms, which include two

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mainstream medicines that aim at brain receptors with distinct functional mechanisms. Such pharmaceutical preparations can merely ease external clinical manifestations, which fail to deliver radical curative effects or block the onset of related diseases in advance. Research circles carry out intensive studies on diet and nutritional regulation plans, which can cut down the risk of Alzheimer's disease and delay the initial onset of relevant pathological signs. Continuous innovative outcomes emerge in the field of pharmaceutical research and development, which take slowing pathological progression as the core target for all medical intervention methods. Actual functional effects of these medicines have not obtained comprehensive authoritative verification, which will be jointly influenced by disease progression phases, individual physical conditions and adverse reactions induced by relevant drugs. All sorts of diseases may be due to nutritional intervention and associated with energy metabolism disorders, oxidative stress, chronic inflammation, blood-brain barrier effects and gut microbiota effects. They have numerous targets in the body, they are long acting and they have a good safety track record.

Alzheimer's disease (AD) originates as a neurological condition, yet its effects extend beyond the brain to involve immune system alterations, intestinal microbial shifts, and disturbances in metabolic processes. Current scientific opinion holds that irregularities in the communication pathway between the digestive tract and the brain contribute to the progression of this neurodegenerative illness. The host's energy homeostasis and immunological responses are influenced by commensal bacterial populations and the bioactive compounds they produce, which in turn appear to shape cognitive performance. Multiple investigative approaches, including high-throughput biological profiling and laboratory trials with animal models, have additionally pointed toward a role for the microbiome–metabolism–neural axis in the pathological cascade of AD [2]. To date, no single herbal agent or purified natural compound has been confirmed as an effective remedy for this disease. For this reason, dietary strategies and nutritional support are increasingly viewed as valuable complements to conventional medical care, offering potential benefits both for reducing disease risk and for intervening at initial stages of the condition.

The present paper will summarize the research results on AD and review systematically the main strategies of nutritional modification of the intestinal microflora. Among these are probiotics, prebiotics, polyphenols, omega-3 fatty acids and faecal microbiota transplantation (FMT). The newest clinical data will also be introduced and problems in the design and application of this study will be discussed, directions for clinical application and research will be put forward.

2. Mechanism of gut-brain axis in AD

2.1. The basic concept of the intestinal microbiota

2.1.1. Composition and physiological functions

There are about 10^{13}~ 10^{14}microorganisms in the adult gastrointestinal tract, and most of them live in the colon. Good state of the gut microbiota is an ecosystem that is stable and has many functions for the body. The gut microbiota plays multiple roles in human health. It not only participates in nutrient metabolism and synthesis, but also influences immune system balance through various bioactive molecules. Meanwhile, these microorganisms can communicate with the nervous system to regulate emotional and behavioral responses. Changes in the composition of the gut microbiota have been found to be associated with many common diseases. For this reason, the academic community has recently regarded it as a functional "invisible organ," whose importance is no less than that of traditionally defined solid organs.

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2.1.2. Gut microbial metabolites and key pathological processes in Alzheimer's disease

Firmicutes and Bacteroidetes represent bacterial phyla which are capable of digesting dietary fiber and subsequently generating several types of short-chain fatty acids (SCFAs), including acetic acid, propionic acid and butyric acid. These metabolites serve as key intermediaries which link the intestinal microbial community to a wide range of physiological operations throughout the organism [3, 4]. GPR41/43/109A and HDAC are associated with inflammation, changes in metabolism and gene expression. Research on animals has shown that SCFAs enhance learning and memory, regulate emotions, microglial activation, synaptic plasticity, etc. A small number of SCFAs in the AD model are associated with heightened inflammation and impaired cognition [5]. Tryptophan metabolism will also affect neurotransmitter synthesis and neuroinflammation in this way. Tryptophan metabolism in the gut also leads to the formation of 5-hydroxytryptamine and other indole derivatives by gut bacteria [6]. Microbiota are related to changes in the tryptophan-5-HT pathway and mood or cognition, etc. Some indole metabolites are agonists of the aryl hydrocarbon receptor (AhR) and regulate the inflammatory response of astrocytes and microglia; thus, they can induce neuroinflammation and neuronal death [3]. Dysregulation of Tryptophan metabolism has been associated with mood disorders and cognitive decline in many models of neurodegenerative diseases; secondary bile acids arise from primary bile acids through the metabolic actions which are carried out by microbial populations residing in the intestinal tract. These molecules can affect cholesterol and glucose metabolism and the inflammatory response by acting on FXR and TGR5 receptors; thus, they may alter the condition of the endothelium and inflammation, change cerebrovascular and BBB homeostasis. When the bacterial ecosystem within the intestines undergoes compositional fluctuations, the processing of both bile acids and choline becomes correspondingly altered. Such metabolic perturbations are capable of interfering with the organism's baseline biochemical state, and through this route, they may ultimately influence neural activities. An additional factor of interest is trimethylamine-N-oxide (TMAO), which arises from the breakdown of choline and carnitine by gut microbes, with trimethylamine (TMA) being an intermediate product that the liver subsequently converts into TMAO. Circulatory levels of this oxidized amine have been found to correlate with diminished cognitive test results among patients diagnosed with Alzheimer's disease (AD), as well as among those who exhibit cognitive deficits attributed to vascular pathology. Based on animal studies, it has been found that high levels of TMAO in the external environment lead to mitochondrial dysfunction in the hippocampus, oxidative stress, neuroinflammation, impaired learning and memory, synaptic damage, etc.; therefore, it is proposed that TMAO can promote the pathology of AD through a multi-pathway mechanism of "vessel-metabolism-neuroinflammation", and these metabolites may ultimately change molecules involved in neuroplasticity, such as brain-derived neurotrophic factor (BDNF). Brain-derived neurotrophic factor (BDNF) is necessary for synaptic plasticity and the learning-memory process of the brain. Some studies have found that certain prebiotics, such as Galacto-oligosaccharides (GOS), polyphenols and fermentable dietary fibre, can increase the expression of BDNF in the hippocampus by modifying the microbiota and altering the SCFA/tryptophan metabolic profile, thus promoting cognition and emotional behavior [7].

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2.2. Key signaling pathways of the gut–brain axis

2.2.1. Neural pathway: the vagus nerve and the enteric nervous system

Among the various afferent routes which constitute the gut-brain communication axis, the vagal nerves rank as the foremost pathway, and they are responsible for transmitting mechanical stimuli, chemical cues, and inflammatory indicators upward to the brainstem region. A number of experimental investigations have revealed that certain strains of lactic acid bacteria, along with SCFAs, can modify both behavioral responses and physiological reactions to stressful conditions, provided that the vagal innervation remains surgically undisturbed. However, once vagotomy has been performed, these microbial and metabolic influences become markedly diminished or even completely absent. The enteric nervous system (ENS), which operates in close coordination with the vagal nerves, is capable of detecting inflammatory states, compositional fluctuations within the intestinal microbial population, and metabolic signals originating from the digestive tract. Following such detection, this integrated neural network relays information upward to the central nervous system, which in turn channels these inputs toward the hypothalamic-pituitary-adrenal (HPA) axis, a system which governs emotional regulation, cognitive processing, and stress management.

2.2.2. Immune–inflammatory pathway

When the microbial population within the digestive tract experiences compositional shifts, the inflammatory processes which are related to Alzheimer's disease undergo corresponding modifications. A compromised integrity of the intercellular junctions which exist between intestinal epithelial cells may permit the entry of lipopolysaccharides (LPS) and various other molecular entities into the bloodstream. This event subsequently triggers the activation of the TLR4/NF-κB signaling cascade, which is then followed by the secretion of numerous pro-inflammatory mediators. Evidence derived from population-based investigations further indicates that elevated levels of systemic inflammatory markers are correlated with a heightened susceptibility to Alzheimer's disease, as well as with a premature deterioration of cognitive abilities among elderly cohorts [5]. When these observations are considered collectively, a coherent picture emerges which suggests that low-grade inflammation circulating throughout the organism serves as a plausible intermediary that links microbial imbalances in the intestinal environment to the degenerative processes which occur within neural tissues (see Figure 1).

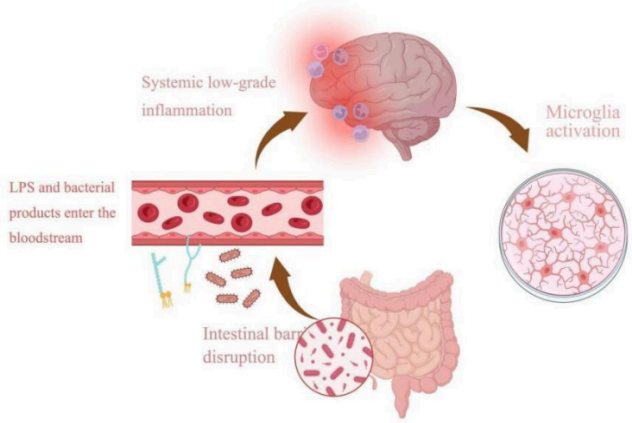

Figure 1. Mechanisms by which "gut-brain axis" immune-inflammatory pathways affect Alzheimer's disease (picture credit: original)

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2.2.3. Microbial metabolites and blood–brain barrier regulation

The well-structured blood-brain barrier maintains homeostasis within cerebral tissue by blocking toxic compounds from penetrating its core regions. However, metabolic products from the digestive tract and inflammation-related molecular factors can exhibit marked fluctuations under different physiological and pathological conditions. Over the past decade, numerous studies have revealed that intestinal microorganisms and their metabolites produced within the digestive cavity can regulate blood-brain barrier (BBB) function. In current academic circles, short-chain fatty acids (SCFAs) are recognized as metabolic substances generated by resident gut microbes. In vitro experiments demonstrate that SCFAs can increase the abundance of endothelial tight junction structures and preserve the structural integrity of the BBB. Trials on isolated human brain microvascular endothelial cells (HBMECs) provide clear evidence that propionate moderately upregulates tight junction protein expression and alleviates LPS-induced BBB injury. Furthermore, multiple cell culture studies on cerebral endothelial layers confirm that propionic acid directly enhances the protective barrier function of HBMVECs and partially repairs structural damage caused by LPS exposure. The decrease of endothelial tight junction proteins, and increase of BBB permeability is triggered by TNF-α, IL-1β, IL-6, etc. in systemic inflammatory disorders. A storm of LPS and inflammation due to damage to the intestinal barrier will increase the susceptibility of the brain to toxic metabolites and create a peripheral inflammatory environment in the brain tissue [4].

3. Nutritional intervention strategies based on intestinal microecology

3.1. Neuroprotective dietary patterns

At present, the two most popular neuroprotective diets are the Mediterranean Diet (MD) and the Mediterranean-DASH Intervention Diet for Neurodegenerative Diseases (MIND). The above diets recommend increasing the intake of whole grains, vegetables, fruits, etc., and reducing the consumption of red meat, processed food and refined sugar; polyphenols and ω-3 fatty acids in the Mediterranean diet can reduce oxidative stress, Aβ deposition and abnormal phosphorylation of Tau to provide neuroprotection. Many prospective cohort studies of the Mediterranean diet have shown that people who have been eating this diet for a long time have a low risk of Alzheimer's disease and a relatively slow decline in all kinds of cognitive functions. Therefore, the diet will help foster a good gut microflora in people. It is rich in dietary fibre, polyphenols and unsaturated fatty acids; therefore, it can promote the growth of Bifidobacterium, Lactobacillus and some butyrate-producing bacteria, increase the diversity of intestinal microorganisms, and enhance the production of short-chain fatty acids (SCFAs). The elevation of short-chain fatty acids in the human body can effectively improve intracranial inflammatory responses, which can repair and maintain the complete state of the blood-brain barrier and regulate the physiological activity of intracranial microglia. This core mechanism can ameliorate various pathological damages that occur in the progression of Alzheimer's disease [8]. Various population studies and clinical trials have confirmed the positive effects of long-term scientific dietary maintenance, which can provide stable protection for the overall health of human brain tissues. The professional dietary model for brain health has been officially proposed in academic circles, which can reduce the risk of cognitive degenerative diseases according to relevant systematic research [8]. Multiple long-term follow-up studies and large-scale clinical verifications have proven the value of standardized dietary patterns, which can delay the deterioration of cognitive abilities and stabilize multiple core physiological functions of the human brain. Long-term consumption of the Mediterranean and MIND diets may reduce the risk of

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dementia [9], but currently, most of the available evidence on people's dietary patterns is observational studies, and a causal relationship has not been confirmed. Dietary culture in different areas of the country is not the same, so the degree of adherence and dissemination also varies accordingly. In the future, more long-term, multi-centre randomised controlled trials that are also based on the microbiome will be needed to better understand why different diets and changes in gut microbiota cause Alzheimer's disease pathology.

3.2. Probiotics and psychobiotics

Probiotics are beneficial microorganisms that maintain the healthy state of human intestinal tracts, which include a special subtype called psychobiotics that regulate human emotions, thinking patterns and behaviors through gut-brain axis modulation [10]. Probiotics can optimize the steady state of intestinal microecology and produce healthy metabolites that improve intestinal immune functions and suppress internal inflammatory responses in the human body. Specific probiotic strains can synthesize a variety of neuroactive substances that adjust neurotransmitter metabolism and modify the plasticity of brain synapses. For pathological changes caused by Alzheimer's disease, probiotics can inhibit abnormal microglia activation in the brain and reduce the release of pro-inflammatory substances that stabilize the physiological function of the blood-brain barrier [3]. Authoritative controlled clinical studies have verified the positive effects of specific probiotic interventions on cognitive performance that protect brain tissue structures and preserve basic cognitive functions in early disease stages. Various probiotic preparations can regulate systemic inflammation and protect the human nervous system that improve multiple core cognitive abilities of people with mild cognitive impairment. Current academic studies still have obvious limitations that prevent the formation of unified application standards for clinical practice, which require systematic research on early-stage patients and standardized evaluation systems for probiotic strains.

3.3. Prebiotics

Various natural dietary prebiotics act as vital substances that regulate intestinal microecology, which can selectively boost the proliferation of beneficial intestinal flora and support the production of beneficial metabolites in the human body [11]. Prebiotics can protect the health of the intestinal barrier and relieve systemic inflammatory conditions, which optimize the state of the brain barrier and curb the progression of brain inflammation and cognitive degeneration. These substances can adjust the metabolism of key substances and the expression of neurotrophic factors which effectively improve the learning and memory abilities of human bodies [11]. Relevant experimental studies have confirmed the powerful brain-protective effects of different prebiotic components [8]. Such active ingredients can optimize the intestinal flora structure and cognition-related functions of elderly individuals which help improve and maintain the overall cognitive state of the human brain [10]. In clinical trials, Fructo-oligosaccharides (FOS), GOS and other prebiotics were shown to have a beneficial effect on the improvement of executive functions and attention of older individuals with all types of cognitive impairment. Most research on prebiotics has been done in animals and the optimal dose, length of treatment and long-term safety in older people with dementia remain to be established [3]. Their study will be taken to the next level in the future with the combination of metabolomics and the microbiome (Figure 2).

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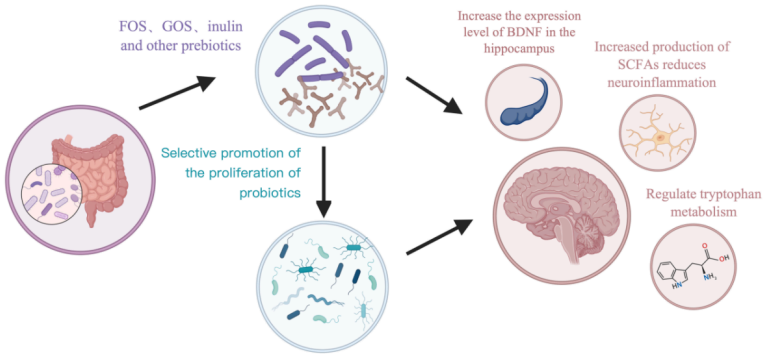

Figure 2. Pathways through which prebiotics and probiotics influence brain function (picture credit: original)

3.4. Polyphenols and antioxidants

Many common natural daily ingredients are rich in active polyphenolic components which rely on the decomposition and transformation of intestinal flora to exert antioxidant and anti-inflammatory physiological effects in the human body. These natural substances have a limited direct absorption efficiency in the small intestine which restricts their immediate biological utilization in human tissues. Polyphenolic ingredients can regulate the abnormal changes of key proteins in the brain which deliver essential protective effects for maintaining the health of human brain nerves [3]. Anthocyanins and prebiotics contained in daily diets can positively adjust the cognitive state of the human body which effectively improves the memory, executive ability and attention performance of elderly groups. So, polyphenols are not readily absorbed and there are numerous varieties of components in all foods and drinks.

3.5. Omega-3 fatty acids

Omega-3 unsaturated fatty acids can adjust the overall structure of intestinal microflora which expand beneficial metabolic bacteria and suppress intestinal microbes that trigger inflammatory responses in human tissues. Such lipid substances carry both anti-inflammatory and neuroprotective values which include two core components that sustain the activity of nerve cell membranes and take part in signal transmission inside the human brain. Dietary supplementation of these fatty acids can protect the synaptic structures of groups with early cognitive injuries which optimize various performance indicators related to human cognitive functions [12]. Other related studies have also reported some degree of protection of synaptic plasticity and memory function in patients with mild cognitive impairment (MCI) and early Alzheimer's disease (AD) with all types of EPA and DHA supplementation, but the findings have been inconsistent and the magnitude of the effect is small. Omega-3 supplements will work differently for different ages, different times while sick and different diets. The combined effects of the Omega-3 fatty acids, probiotics and prebiotics will be further investigated in future studies.

3.6. Other potential approaches

To change the makeup of a person's gut bacteria through the addition of good donor bacteria, Fecal Microbiota Transplantation (FMT) is employed. Engineered bacteria and metabolic targeting strategies can be employed to achieve therapeutic effects by modifying some types of

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microorganisms or metabolic pathways significantly [13], and in AD animal models such as APP/PS1 mice, FMT has shown that it can improve learning and memory and reduce Aβ deposition and Tau hyperphosphorylation. Engineered bacteria can target SCFAs, GABA and other antioxidants; thus, it is hoped that they will be used to protect the nervous system [13]. Although most of the current research on FMT is based on cases, some studies have found that it can improve cognition and behavior; thus far, there has been some preliminary support for future clinical trials. At present, the problems of donor selection, safety risk control and the lack of norms in FMT have not been solved.

4. Clinical research evidence and challenges

4.1. Recent clinical trial findings

Academic circles have launched multiple clinical observations at present which explore the regulatory effects of various nutritional intervention schemes on the intestinal microecology of crowds with degenerative cognitive illnesses. Intervention approaches include dietary optimization, supplementation of multiple intestinal regulatory active substances and chrono-nutrition conditioning modes which face common limitations such as single experimental sites and insufficient observation cycles in most existing relevant investigations. Most of the main results have been concentrated on specific areas of cognition, emotion and quality of life, and the results show that many interventions are positively affecting people's general cognition or certain parts of their cognition, such as memory and executive functions [11]. There has been a slight rise in the scores for depression and anxiety, as well as in people's sense of well-being. Most of the effect sizes are relatively small or medium, and neither strong statistical evidence nor reproducibility has been obtained; therefore, so far there have been no large-scale, systematic multicenter randomised controlled trials on the effects of nutritional microbial interventions for AD (Table 1).

Table 1. Summary of representative clinical trials and cognitive improvement effects of nutritional interventions based on gut microecology in Alzheimer's disease

Categories of Intervention	Representative trials and design	Core findings with affected cognitive domains
Dietary patterns	Randomised controlled trials of the MIND diet; Large multicenter RCT of the Mediterranean diet	Long-term adherence decreased the risk of all-cause dementia. In the healthy elderly, the rate of global cognitive decline is slowed, but the reversal of core pathology is not obvious in the patient population.
Probiotics/prebiotics	single-strain or multi-strain compound preparation RCT; FOS/GOS dietary fiber intervention.	It can significantly improve immediate memory, executive function and selective attention in patients with mild cognitive impairment (MCI). The levels of proinflammatory cytokines in peripheral blood were decreased.
Polyphenols /ω-3	High-purity EPA/DHA supplement trials; intervention with dark berry extracts rich in anthocyanins.	ω-3 has a protective effect on early synaptic plasticity; after polyphenol intervention, the subjects showed mild to moderate improvements in working memory, verbal fluency, and anxiety/depression symptoms.
Time series nutrition	Limiting meal times (Time-Restricted Eating, TRE, such as 16:8 fasting) and regulating dietary intake according to the circadian rhythm.	By restoring the circadian rhythm of the gut microbiota, the sleep quality of the subjects was improved, their peripheral insulin sensitivity was enhanced, and their daytime attention was indirectly improved.

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Most of the studies were single-centre, had a small number of subjects, and were conducted for a short time. Most studies have concentrated on a few areas of cognition. Although many interventions have some good effects on cognition and memory, they are not pronounced and cannot be continuously applied. At present, there is no official randomised controlled trial that can provide more evidence on the effect of nutritional intervention on Alzheimer's disease. Most of the research that has been conducted so far is single-centre in nature, and relatively few people have taken part over a short period. Most studies have shown some positive effects on certain aspects of cognition, mood and quality of life, and while many interventions have achieved minor or moderate improvements in cognition, memory, executive functions, depression, anxiety, sleep quality, etc., the effect sizes are generally small to moderate. In addition, the reproducibility of the results has not been confirmed so far, and more experiments need to be conducted [3].

4.2. Key challenges in clinical trials

The screening links of biological markers still hold many unresolved difficulties which multiple studies analyze the fluctuation conditions of intestinal microbes and their metabolites inside human body fluids. These research works combine humoral pathological indicators and brain imaging detection methods which observe abnormal physical changes induced by cognitive lesions from multiple dimensional perspectives. Various studies have employed different types of biomarkers and detection methods, so there is no single standard for them, and their results are difficult to compare. In the future, many particular but simple-to-obtain indicators will be combined to help personalise the construction of nutrition plans and observe the results of these plans [3].

Trial Design is not standardised, and since there are many components to microecological and nutritional interventions, they are difficult to standardise. There will be a longer time before any changes in cognition can be observed in practice. Most of the available trials have had a short follow-up period and are not easy to observe. Trials often have many lifestyle factors at the same time, so it is difficult to analyse and speculate on the reasons for such trials.

Dieting and changes in daily life were also difficult for the people to practice in reality. It is difficult for the patient to follow the specified diet plan and supplement regimen for a long time, so it cannot be applied in practice. At the same time, older patients with AD or MCI often have several chronic diseases and are on many different medications at the same time; these drugs may interact and reduce the effectiveness of treatment [12].

There are many batches and many differences in platforms for the measurement and data analysis of gut microbiome sequencing and metabolomics detection. The steps of collection, storage, extraction of DNA from and analysis of the data for the samples are not the same. Microbiome and multi-omics data are high-dimensional and highly correlated with many other variables, so multivariate modelling, network analysis, machine learning methods, etc., need to be employed in the analysis. The analysis pipelines and statistical thresholds of the different research groups are quite different, so they cannot be combined and used together as evidence.

At present, some initial results have been obtained from the beginning of clinical trials on the feasibility of prevention and early treatment of Alzheimer's disease using "nutritional intervention targeting intestinal microecology", but the data are still scarce and scattered. In the future, longer follow-up and stricter design will be required to integrate multi-omics data, biomarkers, information on individual differences, etc., to provide stronger support for the clinical application of new drugs.

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5. Conclusion

Current studies have confirmed that gut microecological dysregulation profoundly participates in the progression of AD through neural transmission, immune inflammation and metabolic pathways of the gut-brain axis. In terms of interventions, the Mediterranean diet and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet optimize gut microbiota diversity and SCFA production via abundant polyphenols and omega-3 fatty acids. Specific probiotics and prebiotics improve memory, executive function and peripheral inflammatory markers in patients with mild cognitive impairment (MCI). Supplementation with polyphenolic antioxidants and omega-3 fatty acids synergistically alleviates oxidative stress and synaptic damage, and fecal microbiota transplantation (FMT) has also shown potential to reduce amyloid-β (Aβ) deposition and improve cognitive function in animal models; all these strategies exert neuroprotective effects.

Nevertheless, existing clinical evidence is highly fragmented. Prominent limitations include high heterogeneity of intervention regimens, short follow-up durations, insufficient sample sizes and inconsistent testing standards for biomarkers. Combined with poor patient adherence and confounding effects of concomitant medications, most interventions yield modest effect sizes that are difficult to replicate, failing to meet the evidence threshold required for clinical translation.

Future research should be built on long-term, multicenter, large-sample randomized controlled trials (RCTs). Integrative analysis of metagenomic, metabolomic and host stratification data, combined with artificial intelligence, enables the construction of individualized dynamic "microbiota-metabolism-immunity" networks to precisely identify optimal responders and intervention windows. Driven by bidirectional translation between evidence-based medicine and multi-omics research, nutritional interventions targeting gut microecology are expected to evolve from auxiliary adjuvants into core disease-modifying components within the comprehensive management of AD.

References

[1] World Alzheimer Report (2025): Reimagining life with dementia - the power of rehabilitation (June 28, 2026). Available from: https: //www.alzint.org

[2] Seo, D.-O., & Holtzman, D. M. (2024). Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. *Experimental and Molecular Medicine, 56*(1), 86–94.

[3] Loh, J. S., Mak, W. Q., Tan, L. K. S., Ng, C. X., Chan, H. H., Yeow, S. H., Foo, J. B., Ong, Y. S., How, C. W., & Khaw, K. Y. (2024). Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduction and Targeted Therapy, 9*(1), 37.

[4] Moțățăianu, A., Șerban, G., & Andone, S. (2023). The role of short-chain fatty acids in microbiota–gut–brain cross-talk with a focus on amyotrophic lateral sclerosis: A systematic review. *International Journal of Molecular Sciences, 24*(20), 15094.

[5] Qian, X.-H., Xie, R.-Y., Liu, X.-L., Chen, S.-D., & Tang, H.-D. (2022). Mechanisms of short-chain fatty acids derived from gut microbiota in Alzheimer's disease. *Aging and Disease, 13*(4), 1252–1266.

[6] Wasser, C. R., Werthmann, G. C., Hall, E. M., Kuhbandner, K., Wong, C. H., Durakoglugil, M. S., & Herz, J. (2023). Regulation of the hippocampal translatome by Apoer2-ICD release. *Molecular Neurodegeneration, 18*(1), 62.

[7] Vogt, N. M., Kerby, R. L., Dill-McFarland, K. A., Harding, S. J., Merluzzi, A. P., Johnson, S. C., Carlsson, C. M., Asthana, S., Zetterberg, H., Blennow, K., Bendlin, B. B., & Rey, F. E. (2017). Gut microbiome alterations in Alzheimer's disease. *Scientific Reports, 7*(1), 13537.

[8] Azuma, N., Mawatari, T., Saito, Y., Tsukamoto, M., Sampei, M., & Iwama, Y. (2023). Effect of continuous ingestion of bifidobacteria and dietary fiber on improvement in cognitive function: A randomized, double-blind, placebo-controlled trial. *Nutrients, 15*(19), 4175.

[9] Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S. J., Scott, K., Stanton, C., Swanson, K. S., Cani, P. D., Verbeke, K., & Reid, G. (2017). Expert consensus document: The International

DOI: 10.54254/2753-8818/2026.35600

Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology, 14*(8), 491–502.

[10] Dalile, B., Van Oudenhove, L., Vervliet, B., & Verbeke, K. (2019). The role of short-chain fatty acids in microbiota–gut–brain communication. *Nature Reviews Gastroenterology & Hepatology, 16*(8), 461–478.

[11] Zhang, T., Gao, G., Kwok, L. Y., & Sun, Z. (2023). Gut microbiome-targeted therapies for Alzheimer's disease. *Gut Microbes, 15*(2), 2271613.

[12] Xiang, W., Xiang, H., Wang, J., Jiang, Y., Pan, C., Ji, B., & Zhang, A. (2023). Fecal microbiota transplantation: A novel strategy for treating Alzheimer's disease. *Frontiers in Microbiology, 14*, 1281233.

[13] Sun, J., Xu, J., Ling, Y., Wang, F., Gong, T., Yang, C., Ye, S., Ye, K., Wei, D., Song, Z., Chen, D., & Liu, J. (2019). Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. *Translational Psychiatry, 9*(1), 189.