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REVISIÓN SISTEMÁTICA

Exploring the connections between Microbiome and Dementia: systematic review

Explorando las conexiones entre Microbioma y Demencia: revisión sistemática

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ABSTRACT

Introduction: disturbance in the balance of the intestinal microbiota, as an ecosystem, determines states of dysbiosis and dysregulation of the immune system, which are crucial for the onset of gastrointestinal and systemic diseases. Dementia is defined as an acquired syndrome, characterized by cognitive impairment and changes in mood or personality, which are severe enough to hinder social and occupational performance.
Objectives: to describe the scientific evidence on the relationship between the gut microbiome and the onset/progression of dementia, and how it influences the underlying pathological mechanisms of different types of dementia.
Methods: a search was conducted in Pubmed, Scopus, Web of Science from January 2000 to October 2022. Selecting abstracts of cohort and case-control studies evaluating the relationship between the gut microbiome and the onset/progression of dementia.
Results: the results of this review suggest that there is a significant interaction between gut microbiota and mental health, supporting the idea that the gut and brain are bidirectionally connected through the gut-brain axis. However, it is important to note that many of these studies have limitations, such as small sample sizes and varied research designs, making it difficult to draw definitive conclusions. Therefore, more research is needed to fully understand the underlying mechanisms and clinical relevance of these relationships.
Conclusions: this systematic review provides a comprehensive overview of the interaction between gut microbiota and mental health in diverse populations. The results suggest that gut microbiota may play an important role in mental health, but further studies are needed to confirm and better understand these relationships. These results have significant implications for research and the development of interventions targeting the gut microbiota as a potential approach to improve mental health in various conditions.

Keywords: Microbiota; Dementia; Neuroscience; Neuropathology; Systematic Review.

RESUMEN

Introducción: la perturbación en el equilibrio del microbiota intestinal, como ecosistema, determina estados de disbiosis y desregulación del sistema inmunológico, que son cruciales para la aparición de enfermedades gastrointestinales y sistémicas. Demencia se define como un síndrome

adquirido, que se caracterizado por deterioro cognitivo y cambios en el estado de ánimo o la personalidad, los cuales son suficientemente graves como para obstaculizar el desempeño social y laboral.
Objetivos: describir la evidencia científica sobre la relación entre el microbioma intestinal y la aparición/progresión de la demencia, y cómo influye en los mecanismos patológicos subyacentes de diferentes tipos de demencia.
Métodos: se realizó una búsqueda en Pubmed, Scopus, Web of Science desde enero de 2000 hasta octubre de 2022. Seleccionando resúmenes de estudios de cohorte y de casos y controles que evalúen la relación entre el microbioma intestinal y la aparición/progresión de la demencia.
Resultados: los resultados de esta revisión sugieren que existe una interacción significativa entre el microbiota intestinal y la salud mental, lo que apoya la idea de que el intestino y el cerebro están conectados bidireccionalmente a través del eje intestino-cerebro. Sin embargo, es importante señalar que muchos de estos estudios tienen limitaciones, como el pequeño tamaño de las muestras y los variados diseños de investigación, lo que dificulta la extracción de conclusiones definitivas. Por lo tanto, se necesita más investigación para comprender plenamente los mecanismos subyacentes y la relevancia clínica de estas relaciones.
Conclusiones: esta revisión sistemática proporciona una visión global de la interacción entre el microbiota intestinal y la salud mental en diversas poblaciones. Los resultados sugieren que el microbiota intestinal puede desempeñar un papel importante en la salud mental, pero se necesitan más estudios para confirmar y comprender mejor estas relaciones. Estos resultados tienen implicaciones significativas para la investigación y el desarrollo de intervenciones dirigidas al microbiota intestinal como un enfoque potencial para mejorar la salud mental en diversas condiciones.

Palabras clave: Microbiota; Demencia; Neurociencia; Neuropatología; Revisión Sistemática.

INTRODUCTION

Seventy percent of the entire human microbiome is located in the gut, and the trillions of microbes normally found at that level are called the microbiota. Thus, it is the organ with the highest number of microbes in the body, and they belong to 9 different tribes: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia, Cyanobacteria, Fusobacteria, Spirochaetes and Saccharibacteria. Although fungi and archaea may also be resident, they represent only 1 % of the total. The majority are Firmicutes and Bacteroidetes.[1,2,3]

The density and composition of the microbiota in different parts of the intestine are influenced by chemical, nutritional and immunological factors. The small intestine has faster transit and greater absorption of antimicrobials and nutrients. These functions help limit the growth of bacteria, which is limited to those that can adhere to the epithelium or the mucus covering it and multiply rapidly. On the other hand, conditions in the large intestine lead to a dense and diverse community of mainly anaerobic bacteria that are able to anchor themselves to the mucus and digest indigestible carbohydrates from the diet or the mucus itself.[4]

The development of the intestinal microbiota depends on several factors, such as type of birth, gestational age, diet, health status and lifestyle. How individuals are born is the primary means of colonization. Those born by vaginal delivery receive the microbiota found in the vagina and maternal fecal matter. In contrast, infants born by cesarean section pick up microbiomes found on the skin of their mothers, health care workers and the hospital environment. From the first year of life, microbial diversity increases until it reaches adult-like characteristics around 2-3 years of age. There are no significant differences or changes in adulthood, except those related to genetic predisposition, gender or environmental exposure.[2,3]

Prebiotics are substrates that are selectively utilized by the host microbiota and provide health benefits. Evidence from a variety of diseases supports the possibility that prebiotics have health-

promoting effects in healthy populations. Probiotics are defined as live microorganisms that, when ingested in sufficient quantities, provide health benefits to the host. A symbiotic couples at least one probiotic and one prebiotic.[5]

The metabolic functions of the intestinal microbiota are related to the degradation of complex polysaccharides and bile acids, the synthesis of short-chain fatty acids (SCFA) and vitamins, linked to nutritional effects on the intestinal barrier and the immune system. Thus, food is inferred as an essential element in the balance of the microbiota and host, and conceives its formation in children, as well as its function and structure in adults. In addition to food composition, nutrients, dietary patterns, there are other important factors that modulate the microbiota: medications, hygienic conditions, circadian rhythms, intermittent fasting, seasonal changes and industrialization.[5]

Microbial assemblages that stably constitute a given ecological niche live in homeostasis, determined by species richness and commensalism and mutualism relationships with the host, so that both benefit from symbiosis. This condition is known as eubiosis. In contrast, dysbiosis is a state of disequilibrium, where there is an alteration in the symbiotic state and is identified by qualitative and/or quantitative variations in the constitution and functioning of the microbiota. The use of antibiotics and other drugs, stress, genetic, dietary and lifestyle factors are associated with the cause of dysbiosis.[5]

Disturbance in the balance of the gut microbiota, as an ecosystem, determines states of dysbiosis and dysregulation of the immune system, which are crucial for the onset of gastrointestinal and systemic diseases.[3]

The gut-brain axis is a neural, hormonal and immune signaling connection system between the gut and the brain and allows the gut microbiota and its metabolites a potential pathway to the brain.[6]

This axis involves the gut microbiome, autonomic nervous system, central nervous system, enteric nervous system, neuroendocrine system, and neuroimmune system.7

It functions as a bidirectional system, allowing the brain to influence the digestive tract (such as peristalsis, mucin release and synthesis), and the immune system (regulation of cytokines produced by mucosal immune cells).[6]

The vagus nerve is one of the main sources of information transmission from the microbiota to the central nervous system. Neurohormones (serotonin, catecholamines, dopamine) are released from neuroendocrine cells in the gut to directly or indirectly regulate behavior.[7]

In addition to the microbiota intervening in the regulation, production and release of neurohormones, it is involved in the synthesis of SCFA at the intestinal level, which cross the blood-brain barrier and reach the hypothalamus, where it stimulates production of anorexigenic peptides, adjusts GABA levels and helps maintain the integrity of the blood-brain barrier.[7]

Microbiota activity also affects the hypothalamic-pituitary-adrenal axis and regulates cortisol discharge. Stressful situations or emotional instability can lead to changes in gastrointestinal peristalsis and permeability of the epithelium at that level. This may increase the risk of opportunistic infections of the microbiome or the entry of components of microbial metabolism that can damage tissues, trigger inflammatory responses, and alter the balance between the immune system and the microbiome.[2,7]

During the onset and development of the senile state, physiological changes occur that affect the entire organism, including the dynamics and functioning of the digestive and immune systems, leading to changes in the composition and dynamics of the microbiota. Given the important role of the microbiota in mental health, dysregulation and/or changes in its composition are believed to contribute to the development and progression of neurodegenerative diseases such as Alzheimer's and Parkinson's.[8]

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Dementia is defined as an acquired syndrome, which is characterized by cognitive impairment and changes in mood or personality, which are severe enough to impair social and occupational performance.[9]

In addition to impaired cognitive activities (memory, language, executive function, etc.), dementia also has several neuropsychiatric symptoms, including: delusions, hallucinations, agitation/aggressiveness, altered motor activity, anxiety, restlessness, euphoria, euphoria, dishibition, apathy, irritability, changes in diet.[10]

Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disorder associated with cognitive impairment. This is related to the extracellular accumulation of ß-amyloid (Aß) peptides in the form of senile plaques and the intracellular accumulation of hyperphosphorylated tau protein that forms neurofibrillary tangles. In addition, it is closely related to neuroinflammatory conditions.[11]

Although the etiology of AD is not completely understood, it is known to originate from an interplay of genetic and environmental factors. Age is the most important risk factor, in addition to family history, susceptibility genes, and recently it has been proposed that the gut microbiome plays an important role in the development of the disease by regulating brain activity through the microbiota-gut-brain axis.[12]

Mild cognitive impairment (MCI) is considered a preclinical stage of AD, indicating that the mnestic alterations do not coincide with the memory loss typical of normal senescence, although they are not significant enough to produce changes in daily life. Furthermore, the term MCI does not necessarily indicate a future development of dementia.[13]

Parkinson's disease (PD) is a neurodegenerative and systemic event due to the deposition of α-synuclein in the somas of neurons, leading to the formation of Lewy bodies and neuronal loss in the substantia nigra of the midbrain. Thus, as a result, motility symptoms appear, characterized by the tetrad of: rigidity, bradykinesia, resting tremor, gait and taxia disorders, and several non-motor symptoms such as dementia, depression, anosmia and changes at the level of the gastrointestinal tract, among which constipation is the most prominent.[14]

Objective: To describe the scientific evidence on the relationship between the gut microbiome and the onset/progression of dementia, and how it influences the underlying pathological mechanisms of different types of dementia.

METHODS

Study Design

Taking into account that there is abundant scientific literature on the subject under study, the research results were synthesized by means of a systematic review. If the quantitative data are sufficiently standardized, a meta-analysis will be performed.

This systematic review will be governed according to the PRISMA guidelines (preferred reporting elements for systematic reviews and meta-analyses).[15]

Study population

Scientific Papers addressing the relationship between the gut microbiome and the onset/progression of dementia, in the period January 2000 to October 2022, were included.

Inclusion Criteria

- Original articles with IMRyD typology developing cohort studies, clinical trials, other systematic reviews and meta-analyses.

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Exclusion Criteria

- Review articles, Scientific Letters/Letters to the Editor, Clinical Cases, Editorials, Original Articles that correspond to preclinical studies and Observational Studies.

Selection and Sample Size

A search was performed in Pubmed, Scopus, Web of Science from January 2000 to October 2022. Selecting abstracts of cohort and case-control studies evaluating the relationship between the gut microbiome and onset/progression of dementia.

Data collection planning

- A literature search was performed in databases using as MESH descriptors: "Microbiota" and "Dementia".
- The publications were classified and according to the inclusion and exclusion criteria those that will form the study were selected.
- A critical reading of the abstracts and articles in extenso was carried out to assess their inclusion according to their relevance.
- The studies were classified according to levels of evidence and quality

Ethical and legal considerations

This study included secondary data sources and therefore does not correspond to an analysis from the ethical point of view, given that no experimentation or evaluations were performed on human beings/experimental animals.

RESULTS AND DISCUSSION

The systematic review analyzed a number of studies related to mental health and gut microbiota in diverse populations. Key findings are then discussed and compared with previous research, methodological limitations and errors are identified, conclusions are reached, and needs for future research are highlighted.[16,17,18,19]

Regarding the relationship between aerobic exercise and mental health, studies showed that aerobic training increases plasma Cathepsin B (CTSB) enzyme levels, which correlates with improved cognitive performance. However, brain-derived neurotrophic factor (BDNF) levels decrease with exercise. This suggests that exercise may have beneficial effects on brain function through mechanisms related to CTSB and BDNF. These results are consistent with previous research that has demonstrated the positive effects of exercise on mental health.[20,21,22,23,24,25]

Regarding the effects of gut microbiota on brain structure and function, studies revealed significant differences in microbiota composition between patients with schizophrenia and normal controls. In addition, a correlation was found between gut microbiota alpha diversity and brain gray matter volumetry (GMV) in patients with schizophrenia. These findings suggest that the gut microbiota may play a role in the observed alterations in brain structure and function in schizophrenia, supporting previous research that has explored the connection between microbiota and mental health.[26,27,28,29,30,31,32,33,34]

Another important aspect was the relationship between APOE genotype and gut microbiota in the context of Alzheimer's disease. Specific microbiota profiles associated with APOE genotypes were found, and APOE4 carriers showed a loss of butyrate-producing bacteria in their microbiota. These findings indicate that the gut microbiota may play a role in modulating the risk of developing Alzheimer's disease in individuals with different APOE genotypes, supporting previous research on the relationship between microbiota and Alzheimer's disease.[35,36,37,38,39,40,41,42,43,44]

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Study	Country	Aim	Intervention	Type of research	Sample	Main results	Clinical/practical implications
Effects of Aerobic Exercise Training on Systemic Biomarkers and Cognition in Late Middle-Aged Adults at Risk for Alzheimer's Disease	United States, South Korea	To determine whether metabolomic profiles related to brain health are beneficially altered following 26 weeks of aerobic exercise training	Enhanced Physical Activity (EPA): 150min/week moderate-vigorous aerobic exercise Usual Physical activity (UPA): mantain sedentary status	Randomized controlled trials	23 asymptomatic late middle-aged adults, with familial and genetic risk for AD	Aerobic exercise training increases plasma Cathepsin B (CTSB) levels, which correlate with cognitive performance. Brain-derived neurotrophic fator (BDNF) levels, on the other hand, decrease with exercise training. Klotho levels remain unchanged but are closely associated with changes in VO2 peak. Metabolomic analysis reveals increased levels of polyunsaturated free fatty acids (PUFAs) and reductions in ceramides, sphingo- and phospholipids with exercise. Multiple metabolites (~30 %) correlate with changes in BDNF, but not CTSB or klotho. The positive association between CTSB and cognition, as well as the modulation of lipid metabolites implicated in	Aerobic exercise training can increase plasma Cathepsin B (CTSB) levels, which are positively associated with cognitive performance, suggesting that exercise may have beneficial effects on brain function in individuals at risk for Alzheimer's disease. Exercise-induced changes in lipid metabolites, such as reductions in ceramides and phospholipids, and increased levels of polyunsaturated free fatty acids (PUFAs), may have neuroprotective effects and be relevant to Alzheimer's disease. Monitoring CTSB, brain-derived

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	dementia, support the beneficial effects of exercise training on brain function. Phospholipids are key constituents of the plasma membrane, and sphingolipids are multifunctional lipids that can regulate cell structure and signaling. Sphingolipids are transported by lipoproteins, primarily by LDL. Reductions in several ceramides are observed with exercise. Exercise training also leads to increased levels of polyunsaturated fatty acids (PUFAs) such as dihomo-linolenate, arachidonate, docosapentaenoate, and docosahexaenoate. No significant changes are noted in saturated fatty acids.	neurotrophic factor (BDNF), and klotho levels can serve as exercise biomarkers for evaluating the effects of lifestyle interventions on brain function. The findings of this study highlight the importance of aerobic exercise training as a potential preventive or delaying strategy for Alzheimer's disease and provide insights into the metabolic and biomarker changes associated with exercise-induced cognitive improvements. These results suggest that exercise interventions targeting CTSB and lipid metabolites may have practical implications for promoting brain

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							health and reducing the risk of dementia in late middle-aged adults at risk for Alzheimer's disease
The gut microbiome is associated with brain structure and function in schizophrenia	China, USA, Japan	To explore whether such diferences were associated with brain structure and function between patients with schizophrenia (SZ) and Demographically matched normal controls (NCs)	16S rRNA sequencing with structural magnetic resonance imaging (sMRI) and resting-state functional (rs-fMRI)	Cohort study	Patients with schizophrenia (SZ): 38 Demographically matched normal controls (NCs): 38	The study found that patients with schizophrenia (SZ) had significantly different gut microbiota compared to normal controls (NCs), with lower abundance of Ruminococcus and Roseburia and higher abundance of Veillonella. MRI analysis revealed that SZ patients had lower gray matter volume (GMV) and regional homogeneity (ReHo) in certain brain regions, as well as higher amplitude of low-frequency fluctuation. The alpha diversity of the gut microbiota showed a strong linear relationship with both GMV and ReHo.	The study suggests that the gut microbiome may play a role in the alterations of brain structure and function observed in schizophrenia. Characterizing the gut microbiome in schizophrenia patients could provide valuable clues for the diagnosis and prognosis of the disorder. Understanding the relationship between the gut microbiome and brain structure and function in schizophrenia could lead to the development of new therapeutic approaches.

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			In SZ patients, the abundance of the genus Roseburia was negatively correlated with ReHo indexes in the right STC, left cuneus, and right MTC. These findings suggest that the gut microbiome may play a role in the alterations of brain structure and function observed in schizophrenia.	Targeting specific bacterial taxa, such as Ruminococcus, Roseburia, and Veillonella, could potentially be explored as a treatment strategy for schizophrenia. The findings highlight the importance of considering the gut-brain axis and the potential impact of the gut microbiome on mental health disorders. Further research in this area could lead to the development of personalized interventions that target the gut microbiome to improve brain structure and function in schizophrenia patients.

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APOE genotype influences the gut microbiome structure and function in humans and mice: relevance for Alzheimer's disease pathophysiology	Ireland, United Kingdom	Explore the hypothesis that polipoprotein E (APOE) variation influences the microbiome composition and its subsequent metabolism	Healthy participants: analysis of their gut microbiota speciation Targeted-replacement (TR) transgenic mice: bacterial genomic DNA was extracted from fecal samples	Statistical analysis	56 healthy participants 32 targeted-replacement (TR) transgenic mice	APOE genotype is associated with specific gut microbiome profiles in both humans and APOE-targeted replacement (TR) mice. Several bacterial taxa, including Prevotellaceae and Ruminococcaceae, showed significantly different relative abundance between APOE genotypes. APOE4 carriers have a loss of butyrate-producing bacteria and short-chain fatty acids (SCFAs) in their gut microbiome. No significant differences were observed in the levels of haptoglobin and LBP (biomarkers of intestinal integrity) according to APOE genotype. The findings suggest a possible role of gut microbiota butyrate-producing bacteria as	The study highlights the association between APOE genotype and specific gut microbiome profiles in both humans and mice, suggesting that the gut microbiome could be a potential target for mitigating the deleterious impact of the APOE4 allele on cognitive decline and the prevention of Alzheimer's disease (AD). The findings indicate that APOE4 carriers have a loss of butyrate-producing bacteria and short-chain fatty acids (SCFAs) in their gut microbiome, which may contribute to the neuropathology associated with the APOE4 allele.

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			an intervention point to mitigate the impact of APOE genotype in the development of Alzheimer's disease.	This suggests that interventions targeting the restoration of butyrate-producing bacteria in the gut microbiota could potentially help mitigate the impact of APOE genotype in the development of AD. The study also found no significant differences in the levels of haptoglobin and LBP (biomarkers of intestinal integrity) according to APOE genotype, indicating that the impact of APOE genotype on the gut microbiome is not mediated through changes in intestinal integrity.

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							Overall, these findings provide insights into the potential role of the gut microbiome in the pathophysiology of Alzheimer's disease and suggest that modulating the gut microbiota could be a promising avenue for therapeutic interventions.
Effects of Lactiplantibacillus plantarum OLL2712 on Memory Function in Older Adults with Declining Memory: A Randomized Placebo-Controlled Trial	Japan	To verify the Lactiplantibacillus plantarum OLL2712 (OLL2712) protective effects on memory function in older adults	Active group: consumed either powder containing heat-treated OLL2712 cells Placebo group: a stick filled with 1 g of TK-16AG dextrin without OLL2712	Double-blind placebo-controlled trial randomizing	Active group: 39 Placebo group: 39	The active group showed significant improvements in composite memory and visual memory scores compared to the placebo group. The active group also had a lower abundance ratio of Lachnoclostridium, Monoglobus, and Oscillibacter genera, which are involved in inflammation. The analysis of the effects of OLL2712 on memory function without the influence	The study provides evidence for the efficacy of Lactiplantibacillus plantarum OLL2712 (OLL2712) in improving memory function in older adults with declining memory. This suggests that OLL2712 could be used as an intervention for neurodegenerative conditions that cause dementia, as it has the ability to modulate neuroinflammatory responses via the

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				of daily nutritional intake and participant characteristics also showed positive results. The study demonstrated the efficacy of OLL2712 in improving memory function in older adults with early memory decline.	microbiome-gut-brain axis. The findings highlight the potential of probiotics, specifically OLL2712, as a preventive or therapeutic approach for memory decline in older adults. This could have significant implications for the aging population, as memory decline is a common issue in older individuals. The study also identified specific genera, such as Lachnoclostridium, Monoglobus, and Oscillibacter, which are involved in inflammation and were found to have a lower abundance in the active group. This suggests that OLL2712 may have

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	anti-inflammatory effects, further supporting its potential as a therapeutic intervention for memory decline. The research contributes to the growing body of evidence on the role of the gut microbiota in cognitive function and highlights the importance of considering the microbiome-gut-brain axis in the development of interventions for cognitive decline. Overall, the findings of this study suggest that OLL2712 supplementation could be a promising strategy for improving memory function in older adults and potentially preventing or managing

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							neurodegenerative conditions associated with memory decline.
Orthopedic Surgery Causes Gut Microbiome Dysbiosis and Intestinal Barrier Dysfunction in Prodromal Alzheimer Disease Patients	China	To investigate gut microbiota and intestinal barrier function changes after orthopedic surgery in elderly patients with either normal cognition (NC) or a prodromal Alzheimer disease phenotype (pAD) comprising either subjective cognitive decline (SCD) or amnestic mild cognitive impairment (aMCI).	The gut microbiota, bacterial endotoxin (lipopolysaccharide), tight junction (TJ) protein, and inflammatory cytokines in blood were measured before surgery and on post-surgical day 1, 3, and 7 (or before discharge)	Prospective Observational Cohort Study	Total: 135 patients Normal cognition (NC): 40 Subjective cognitive decline (SCD): 58 Amnestic mild cognitive impairment (aMCI): 37	Preoperative concentrations of plasma endotoxin were significantly higher in the prodromal Alzheimer disease (pAD) groups compared to the normal cognition (NC) group. Postoperative plasma endotoxin levels increased in both NC and pAD groups, peaking on postoperative day 3. The short-chain fatty acid (SCFA)-producing bacteria were lower, while gram-negative bacteria and plasma claudin were higher preoperatively in the pAD groups compared to the NC group. After surgery, there was a decrease in SCFA-producing bacteria and an increase in both gram-negative bacteria and plasma claudin in the pAD groups relative to the NC group.	Orthopedic surgery in elderly patients with prodromal Alzheimer's disease (pAD) can exacerbate gut microbiota dysbiosis and intestinal barrier dysfunction, leading to cognitive deterioration. Surgery-induced perioperative metabolic stress and inflammatory responses are associated with gut microbiota alterations. Reduced abundance of short-chain fatty acid (SCFA)-producing bacteria and increased levels of gram-negative bacteria and lipopolysaccharide were observed in pAD patients

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			The Shannon index, a measure of microbial diversity, was significantly reduced in the aMCI group on postoperative day 7 compared to baseline. The Sobs index and Shannon index were lower in the aMCI group than in the NC group on postoperative day 7.	before and after surgery. The long-term impact of gut microbiota and barrier changes induced by surgery and subsequent trauma requires further study. Preventing hypoperfusion of the gut and using anti-inflammatory medicine during the perioperative period may protect intestinal barrier function in pAD patients. Promoting microbiome diversity and intestinal barrier function through physical exercise, vegetarian diets, weight control, probiotics, and fecal microbiota transplantation may benefit gut bacteriome diversity.

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							Overall, this study highlights the importance of considering the gut microbiota and intestinal barrier function in elderly patients with pAD undergoing orthopedic surgery, as these factors can impact cognitive outcomes and systemic inflammation.
Combination of gut microbiota and plasma amyloid-β as a potential index for identifying preclinical Alzheimer's disease: a cross-sectional analysis from the SILCODE study	China	To characterize the gut microbiota in the preclinical stage of Alzheimer's disease (AD), to assess whether plasma Aβ indexes (Aβ40, Aβ42, and the ratio of Aβ40 and Aβ42) were changed in preclinical AD, and (3) to investigate the discriminative power of the combined gut microbiota and plasma Aβ indexes in identifying	Each participant underwent routine clinical evaluation, standardized neuropsychological assessments, blood sample tests, fecal sample amplicon sequencing, and Aβ-PET scans. T	Statistical analysis	34 Aβ-negative cognitively normal (CN−) participants 32 Aβ-positive cognitively normal (CN+) participants	The study found that individuals with preclinical Alzheimer's disease (AD) had significantly reduced plasma amyloid-β (Aβ) levels compared to cognitively normal individuals without amyloidosis (CN-). The relative abundance of phylum Bacteroidetes was significantly enriched, while phylum Firmicutes and class Deltaproteobacteria were significantly decreased in individuals with	The combination of gut microbiota and plasma amyloid-β (Aβ) markers may serve as a potential screening tool for identifying individuals with preclinical Alzheimer's disease (AD). Targeting gut microbiota could offer novel strategies for the therapeutic management of AD-related cognitive decline.

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	individuals with preclinical AD.		preclinical AD compared to CN- individuals. The combination of plasma Aß markers, altered gut microbiota, and cognitive performance showed good discriminative power in identifying individuals with preclinical AD from CN- individuals. A Venn diagram showed that there were 1929 shared amplicon sequence variants (ASVs) between the preclinical AD and CN- groups. The study also reported a negative association between global brain Aß burden and plasma Aß 42 /Aß 40, family Desulfovibrionaceae, genus Bilophila, and genus Faecalibacterium in all cognitively normal participants. The alpha diversity of gut microbiota did not	The findings of this study highlight the importance of considering gut microbiota alterations in the early stages of AD and suggest that interventions targeting the gut microbiota could potentially delay or prevent the progression of AD. The study provides insights into the association between gut microbiota, plasma Aß levels, and brain amyloidosis, which could contribute to the development of non-invasive diagnostic methods for preclinical AD. Future studies with larger sample sizes and standardized protocols are needed to further validate the

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						show significant differences among the CN-, CN, and cognitive impairment (CI) groups	potential of gut microbiota and plasma Aß markers as diagnostic and therapeutic targets for AD
Effects of oral health intervention strategies on cognition and microbiota alterations in patients with mild Alzheimer's disease: A randomized controlled trial	China	explored the effects of an oral health intervention on the oral microbiome and cognitive function of patients with mild Alzheimer's disease (AD) and determined the influence on disease progression	Intervention group: received a 24-week oral health intervention Control group: Received a 24-week routine care	Randomized controlled trial	Sixty-six patients with mild AD	After 24 weeks of oral health intervention, significant differences were observed in Kayser-Jones Brief Oral Health Status Examination (BOHSE), Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Nursing Home Adjustment Scale (NHAS), and Alzheimer's Disease Cooperative Study-ADL (ADCS-ADL) scores between the intervention and control groups . The intervention group showed a higher abundance of normal oral flora in subgingival plaque compared to the control group. The intervention group had a higher proportion of alphaproteobacterial,	Improving oral health through intervention strategies can have positive effects on cognition and microbiome in patients with mild Alzheimer's disease (AD). The oral health intervention led to significant improvements in Kayser-Jones Brief Oral Health Status Examination (BOHSE), Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Nursing Home Adjustment Scale (NHAS), and Alzheimer's Disease Cooperative Study-

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			betaproteobacteria, and flavobacteria, while the control group had higher abundance ratios of actinobacteria, spirochaete, and synergistic bacteria. The intervention had statistically significant effects on BOHSE scores, MMSE scores, NPI scores, NHAS scores, and ADCS-ADL scores in both the intervention and control groups . The intervention group showed significant within-group differences in BOHSE scores, MMSE scores, NPI scores, NHAS scores, and ADCS-ADL scores . The control group also showed significant within-group differences in BOHSE scores, MMSE scores, NPI scores, NHAS scores, and ADCS-ADL scores	ADL (ADCS-ADL) scores. The intervention group showed a higher abundance of normal oral flora in subgingival plaque, indicating a positive impact on oral microbiota. The intervention strategies can help patients with AD develop self-care skills, exercise decision-making and problem-solving abilities, and improve social behavior . The findings suggest that oral health interventions can slow cognitive decline in patients with mild AD and improve their cognitive level, self-management ability, and oral health status. These results have implications for

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							the development of low-cost intervention strategies based on self-determination theory, cognitive reserve hypothesis, and neuroinflammation to promote cognitive function in patients with mild AD
Altered Gut Microbiota in Adults with Subjective Cognitive Decline: The SILCODE Study	China, Canada	To characterize the gut microbiota in subjective cognitive decline (SCD)	Gut microbiota of all participants isolated from fecal samples were investigated using 16S ribosomal RNA (rRNA) Illumina Miseq sequencing technique	Multicenter based longitudinal observational study	Total of 105 participants, including 38 normal controls (NC), 53 individuals with SCD, and 14 patients with cognitive impairment (CI)	Gut microbiota compositions were compared among three groups: normal controls (NC), individuals with subjective cognitive decline (SCD), and patients with cognitive impairment (CI). The abundance of phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, and genus Faecalibacterium showed a progressive decline from NC to SCD and CI. Specifically, the abundance of the anti-inflammatory genus Faecalibacterium was	The study suggests that gut microbiota may serve as a susceptibility factor for Alzheimer's disease (AD) and that the alteration of gut microbial compositions may be present in early stages of AD. The findings provide novel insights into the pathophysiological mechanism of AD and highlight the potential role of gut microbiota as a therapeutic target

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	significantly decreased in SCD compared with NC. Altered bacterial taxa among the three groups were associated with cognitive performance. The study also used amyloid positron emission tomography (PET) to validate the alteration of gut microbiota in SCD participants with positive amyloid evidence. The study demonstrated that the anti-inflammatory gut microbiota was significantly altered in SCD and suggested that the alteration of gut microbial compositions may be present in early stages of Alzheimer's disease. The overall structure of gut microbiota was different among the NC, SCD, and CI groups, suggesting distinct gut microbiota at different	for the treatment of AD symptoms. Understanding the relationship between gut microbiota and cognitive decline can help in the development of interventions targeting the gut microbiota to prevent or delay the onset of AD. The study also emphasizes the importance of early detection and intervention in individuals with subjective cognitive decline, as alterations in gut microbiota were observed even at this early stage. Further research is needed to explore the specific mechanisms underlying the association between gut microbiota and

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						stages of Alzheimer's disease	cognitive decline and to develop targeted interventions for AD based on modulating the gut microbiota
Cognitive impairment and CSF proteome modification after oral bacteriotherapy in HIV patients	Italy	To investigate whether a probiotic supplementation to cART patients modifies the cerebrospinal fluid (CSF) proteome and improves neurocognitive impairment	Neurocognitive evaluation and blood sampling at baseline and after 6 months of oral bacteriotherapy	Longitudinal interventional non-randomized study	13 HIV-positive patients [six patients living with HIV (PLHIV) and seven patients with a history of AIDS (PHAIDS)]	Oral bacteriotherapy supplementation to cART patients improved neurocognitive impairment and cognitive test performance in HIV-positive subjects. It also led to a reduction in the percentage of CD4+ CD38+ HLA-DR+ T cells at the peripheral level. The supplementation significantly modified the protein species composition and abundance in the cerebrospinal fluid (CSF), particularly those related to inflammation, such as ß2-microglobulin, haptoglobin, albumin, hemoglobin, immunoglobulin heavy chains constant region, and transthyretin.	Oral bacteriotherapy supplementation in combination with cART could potentially improve neurocognitive impairment in HIV-positive patients, as shown by the improvement in cognitive test performance. This suggests that probiotic supplementation may have a beneficial effect on brain function in HIV patients. The reduction in the percentage of CD4+ CD38+ HLA-DR+ T cells after probiotic intake indicates a potential decrease in immune activation, which

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	Principal component analysis (PCA) showed distinct spatial distribution of CSF samples before and after supplementation, indicating an independent behavior of some samples.	could contribute to the amelioration of inflammation in both peripheral and central nervous system (CNS) levels. The modification of protein species composition and abundance in the cerebrospinal fluid (CSF) after supplementation, particularly those related to inflammation, suggests that oral bacteriotherapy may have a role in reducing inflammation at the CNS level. Further research is needed to understand the specific mechanisms by which probiotic supplementation leads to changes in brain function, such as the impact on gut flora metabolites, gut

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							permeability, and systemic production of proinflammatory cytokines.
Exploration of acupuncture therapy in the treatment of MCI patients with the ApoE ε4 gene based on the brain-gut axis theory	China	To investigate the relationship between ApoE gene polymorphisms and the intestinal microbiome profile in patients with Mild cognitive impairment (MCI)	Intervention group: will receive acupuncture stimulation, exercise and cognitive training Control group: will receive sham acupuncture stimulation, exercise and cognitive training	Randomized assessor-blind controlled study	60 subjects with the ApoE ε4 gene and 60 subjects without the ApoE ε4	The study aims to investigate the improvement in cognitive function of MCI patients with and without the ApoE ε4 gene due to acupuncture and the changes in gut microbiota community composition and abundance in MCI. Enrolment began in March 2021, and the total number of participants at the time of writing is 98 patients. The final results will be published in 2023. The study will provide data on the relationship between the gut microbiota and the effectiveness of acupuncture in patients with MCI from a new angle. It will also provide data on the relationship between	The study explores the relationship between gut microbiota, AD susceptibility genes, and acupuncture in the treatment of MCI patients. The findings of this study may provide evidence for the use of acupuncture as a therapeutic method to improve cognitive function in MCI patients with and without the ApoE ε4 gene. The study also aims to show that acupuncture can regulate the intestinal flora, which may have implications for the management of MCI and AD. Understanding the relationship

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						the gut microbiota and an AD susceptibility gene by integrating microbiologic and molecular approaches. The significance of diversity differences between groups will be evaluated with the Adonis test, with a test level of 0,05. Genus-level differences in faecal microbiota between MCI patients with and without the ApoE ε4 allele will be determined based on linear discriminant analysis (LDA) effect size (log linear LDA score 2,0 and P value 0,01)	between gut microbiota and AD susceptibility genes can contribute to the development of targeted interventions for individuals at risk of developing AD. The integration of microbiologic and molecular approaches in this study may provide valuable insights into the mechanisms underlying the effectiveness of acupuncture and the role of gut microbiota in MCI and AD.
Probiotic intervention benefits multiple neural behaviors in older adults with mild cognitive impairment	China	To explore the effects of probiotic supplementation on multiple neural behaviors in older adults with mild cognitive impairment (MCI)	Probiotic group: consumed 2 g probiotics daily Control group: consumed a 2 g starch capsule placebo daily	Randomized controlled trial	Total: 42 people, divided into a probiotic group (n=21) or a placebo group (n=21)	Probiotic supplementation improved cognitive function and sleep quality in older adults with mild cognitive impairment (MCI) compared to the control group. The improvement was mainly observed in	Probiotic supplementation can be considered as a potential non-pharmacological therapy for older adults with mild cognitive impairment (MCI). The use of probiotics may

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	recall, attention and calculation, visual space, and executive function. The total MoCA score, which reflects cognitive function, was significantly increased in the probiotic group. Probiotic intervention also led to improvements in gastrointestinal symptoms, including upper abdominal pain, acid reflux, constipation, and dry stools. The abundance of certain beneficial bacteria, such as Blautia, Lachnospiraceae, and Ruminococcus, increased after probiotic supplementation. Probiotic supplementation significantly increased serum brain-derived neurotrophic factor (BDNF) levels, which play a role in neuronal nutrition, protection,	help improve cognitive function, sleep quality, and gastrointestinal symptoms in individuals with MCI. Probiotic intervention could potentially reduce the risk of MCI progressing to more severe forms of dementia, such as Alzheimer's disease. The findings suggest that probiotic supplementation could be a simple, effective, and easily acceptable method for early-stage MCI treatment. Healthcare professionals should consider incorporating probiotic supplementation as part of clinical nutritional interventions for MCI patients.

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					learning, and memory formation	The study highlights the importance of maintaining a healthy gut microbiome in older individuals, especially those with MCI, as it plays a role in cognitive function and overall well-being. Further research is needed to explore the specific mechanisms by which probiotics exert their beneficial effects on neural behaviors and cognitive function in MCI patients.
Effectiveness of Yi-Zhi-An-Shen granules (YZASG) on cognition and sleep quality in older adults with amnestic mild cognitive impairment:	To evaluate the efficacy of Yi-Zhi-An-Shen granules (YZASG) in optimizing cognitive performance over time in elderly individuals with amnestic mild cognitive impairment	Intervention group: received YZASG three times a day Control group: received isodose placebo three times a day	Randomized, double-blind, placebo-controlled clinical trial	80 patients	The primary outcome measure of the study is the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Secondary outcome measures include the Mini-Mental State Examination (MMSE), Montreal Cognitive	The study aims to assess the effectiveness of Yi-Zhi-An-Shen granules (YZASG) on cognition and sleep quality in older adults with amnestic mild cognitive impairment (aMCI).

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protocol for a randomized, double-blind, placebo-controlled trial	(aMCI), also to assess whether YZASG can improve sleep quality among aMCI patients, and this herbal formula's safety will also be assessed.			Assessment (MoCA), Pittsburgh Sleep Quality Index (PSQI), serum concentrations of immunological factors and inflammatory cytokines, and fecal microbiota. The study aims to assess the efficacy of Yi-Zhi-An-Shen granules (YZASG) on global cognition in older adults with aMCI and evaluate its safety. The safety of YZASG compared to placebo will be assessed by recording the incidence and severity of treatment-emergent adverse events (TEAEs) and conducting safety assessment tests such as vital signs, weight, clinical laboratory tests, physical and neurological exams, electrocardiography (ECG), and CTMRI scans. The results of this trial will provide insights	If YZASG is found to be effective in improving cognitive function and sleep quality, it could have practical implications for the management of aMCI in older adults. Improved sleep quality has been linked to preserved cognition in the elderly, and sleep complaints are common among those with amnesia. Therefore, interventions that improve sleep may help maintain and improve cognitive capacity in individuals with aMCI. The study also aims to evaluate the potential mechanisms of

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						into the safety and effectiveness of YZASG in intervening aMCI among the elderly and its potential mechanisms via sleep quality, gut microbiota, and serum markers	YZASG, including its effects on gut microbiota and serum markers. Understanding these mechanisms could provide insights into the underlying processes involved in aMCI and potential targets for intervention. The results of this trial will contribute to assessing the safety and effectiveness of YZASG in intervening aMCI among the elderly and determining if it takes effect via the improvement of sleep quality, regulation of gut microbiota, and concentration of certain serum markers
A protocol paper for the MOTION Study—A longitudinal study in a cohort aged 60 years	United Kingdom	To describe and define the composition of the gut microbiome during ageing	Participants will provide biological samples and complete questionnaires and cognitive tests	Longitudinal prospective cohort study	360 participants, including: Cohort 1 (n = 120): no subjective or	The MOTION study is a comprehensive longitudinal cohort study focusing on gut health and cognitive function in individuals	The MOTION study aims to obtain mechanistic knowledge of the role of the gut microbiome during

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and older to obtain mechanistic knowledge of the role of the gut microbiome during normal healthy ageing in order to develop strategies that will improve lifelong health and wellbeing			objective cognitive deficit low dementia risk Cohort 2 (n = 120): subjetive but no objective cognitive deficit medium dementia risk Cohort 3 (n = 120): subjective and objective cognitive high dementia risk	aged 60 years and older. The study aims to determine the association between changes in the gut microbiome and physical and mental capacity in older individuals. The study will collect stool and blood samples, health questionnaires, physical measurements, cognitive tests, and Optical Coherence Tomography scans from participants over a four-year period. The study will also analyze the composition of the gut microbiome and its association with cognitive function, physical function, and other markers of successful aging. Additionally, the study will investigate the mediating effects of	normal healthy aging in order to develop strategies that will improve lifelong health and wellbeing. The study will provide insights into the association between changes in the gut microbiome and physical and mental capacity in older individuals. The findings of the study may help in the development of interventions targeting the gut microbiome to prevent or delay age-related diseases. The study will establish a data and sample repository to facilitate future research into aging and the gut microbiome.

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			the gut microbiome on the relationship between age, lifestyle, and health. The study will establish a data and sample repository to facilitate future research into aging and the gut microbiome. Colonic tissue biopsies and brain imaging data will be collected from a subset of participants to further understand the gut-brain axis and its role in aging. Overall, the results of the paper will provide valuable insights into the role of the gut microbiome in aging, cognitive function, and overall health in older individuals.	The study will also collect colonic tissue biopsies and brain imaging data, which will contribute to a better understanding of the gut-brain axis and its role in aging. The study will provide valuable information on the impact of environmental factors on the structure and function of gut microbes, which can inform strategies for maintaining gut health in older individuals. Overall, the practical implications of this paper include the potential for developing interventions to improve lifelong health and wellbeing, as well

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							as advancing our understanding of the gut microbiome's role in aging and age-related diseases.
In older women, a high-protein diet including animal-sourced foods did not impact serum levels and urinary excretion of trimethylamine-N-oxide	USA, Canada, Taiwan	To determine the association of the relative abundance of the microbial-generated trimethylamine (TMA)-generating taxon, Emergencia timonensis, with serum and urinary trimethylamine-N-oxide (TMAO)	Participants were randomized by Latin-square design to the following: high-protein diet (HPD), HPD + probiotic, HPD + prebiotic, and HPD + synbiotic	Double-blind, placebo controlled, crossover trial	26 participants	The high-protein diet (HPD) increased serum levels of L-carnitine, indoxyl sulfate, and phenylacetylglutamine, but not trimethylamine-N-oxide (TMAO) or p-cresyl sulfate. Urinary excretion of L-carnitine, indoxyl sulfate, phenylacetylglutamine, and trimethylamine (TMA) increased with the HPD, but not TMAO or p-cresyl sulfate. Most participants had undetectable levels of the TMA-generating taxon, Emergencia timonensis, at baseline and only 50 % during the HPD interventions, suggesting other taxa are responsible for the microbial generation of TMA in these individuals.	The study suggests that a high-protein diet, including animal-sourced foods, did not significantly impact serum levels and urinary excretion of trimethylamine-N-oxide (TMAO) in older women. This finding may be reassuring for individuals concerned about the potential cardiovascular and cognitive health risks associated with TMAO. The addition of prebiotic, probiotic, or synbiotic supplementation did not mitigate the effects of the high-protein diet on TMAO levels.

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			The 5-g supplement of prebiotic provided in the study increased total fiber and carbohydrate substrate provision to the microbiota, but a higher dose may be needed to elicit an effect in vivo. Increases in indoxyl sulfate and phenylacetylglutamine were seen in all HPD periods compared to baseline, but no differences were seen for p-cresyl sulfate. When comparing only the four HPD periods, no significant differences were seen for urinary p-cresyl sulfate, but increases were seen for indoxyl sulfate and phenylacetylglutamine	This suggests that these interventions may not be effective in reducing TMAO production in the context of a high-protein diet. The study also found that the microbial taxon Emergencia timonensis was not the primary contributor to TMA production in these individuals, indicating that other microbial taxa may be responsible. Further research is needed to identify these taxa and understand their role in TMA production. The study highlights the importance of considering individual variation in TMAO levels and the need for further

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							investigation into the health impacts of increased proteolytic activity and metabolite production resulting from higher protein intakes.
Oral flora in acute stroke patients: A prospective exploratory observational study	United Kingdom , Australia	To describe the bacterial profile of the oral flora during the first 2 weeks following a stroke, examining changes in the condition of the oral cavity and infections	Fifty participants had a complete set of swabs from four different oral sites and a saliva sample taken at three time points over a 14-day period. Molecular identification of bacteria was performed on the pooled DNA extracted.	prospective exploratory observational study	50 participants	A total of 103 bacterial phylotypes were identified, with 29 not found in the Human Oral Microbiome Database (HOMD). Streptococcus salivarius was the most common bacterial phylotype found in the oral cavity. The condition of the oral cavity worsened during the study period, and 30 % of patients had at least one infection. Gram-negative phylotypes were found in the oral cavity at different time points, with 60,8 % of participants harboring at least one gram-negative phylotype. Streptococcus	The study highlights the huge diversity of bacterial organisms in the oral cavity of stroke patients, with 103 bacterial phylotypes identified, including some not found in the Human Oral Microbiome Database (HOMD). The most common bacterial phylotype found was Streptococcus salivarius, and the presence of gram-negative phylotypes was also observed . The condition of the oral cavity worsened during

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			pneumoniae was the second most common phylotype found, but no association with pneumonia was found in this study.	the study period, and 30 % of patients had at least one infection. The findings suggest that there are no particular patterns linking the presence of specific bacterial phylotypes to infection or the condition of the oral cavity in stroke patients. The study provides valuable data on the changes in oral flora after a stroke, which could support the development of larger observational or interventional studies to explore the impact of interventions on the oral flora and the associated risk of pneumonia. Future research in this area should

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						consider amending protocols to better identify a greater variety of phylotypes and further investigate the role of Streptococcus pneumoniae in the development of pneumonia. Overall, this study emphasizes the importance of oral care and hygiene in stroke patients to prevent infections and maintain good oral health.
The Moo'D Study: protocol for a randomised controlled trial of A2 betacasein only versus conventional dairy products in women with low mood	To advance our understanding of the possible impact of milk proteins on psychological distress in women as well as elucidate mechanisms underpinning any association	Intervention group: A2 beta-casein only dairy products Control group: conventional dairy products	Triple-blinded, randomised controlled trial	45 participants in the intervention group 45 participants in the control group	The study aims to evaluate the comparative effects of consuming dairy products containing A2 beta-casein versus conventional dairy products on symptoms of psychological distress in women with low mood. The primary outcome measure is symptoms of psychological distress, which will be assessed	The findings of this study will contribute to our understanding of the possible impact of milk proteins, specifically A2 beta-casein, on psychological distress in women with low mood. This has potential clinical implications for individuals who

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	using the 21-item Depression, Anxiety and Stress Scale. Secondary outcomes include symptoms of depression, anxiety, and stress, severity of low mood, cognition, gut microbiota composition, gut symptomatology, markers of immune function, gut inflammation, systemic metabolites, endothelial integrity and oxidative stress, body composition, perceived wellbeing, sleep, quality of life, resource use, and cost-effectiveness. The World Health Organization WellBeing Index will be used to assess perceived wellbeing, with participants rating statements on a Likert scale. Adverse events will be monitored and recorded throughout the trial, and any	experience symptoms of psychological distress. The study will also provide insights into the biological effects of A1 and A2 beta-casein consumption in women, expanding our understanding of the differential health effects of these dairy products. The assessment of gut microbiota composition and function may provide valuable information on the potential mechanisms underlying the relationship between dairy consumption and psychological distress. The results may have implications for dietary recommendations

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	unfavourable or unintended medical occurrences will be reported as adverse events. Participants will be randomized to receive either A2 beta-casein only dairy products (intervention) or conventional dairy products containing both A1 and A2 beta-casein proteins (control). The intervention and control products will be prepared and packaged by the a2 Milk Company.	and interventions targeting mental health, particularly in relation to dairy product consumption. The study's findings may also have broader public health implications, considering that dairy products are a significant component of traditional and Western diets. Overall, this research has the potential to inform clinical practice, dietary guidelines, and public health strategies related to the consumption of dairy products and their impact on psychological well-being in women.

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In addition, significant improvements in cognitive function and sleep quality were observed in older adults with mild cognitive impairment after probiotic supplementation. These results suggest that gut microbiota may influence cognitive function and sleep in this population, which is consistent with previous research that has explored the role of probiotics in brain health.[45,46,47,48,49,50,51,52,53,54,55,56,57]

In relation to the study of the high-protein diet and its impact on the gut microbiota, changes in the levels of various metabolites and the composition of the microbiota were observed. These changes could be related to inflammation and other biological processes associated with mental health. However, it was emphasized that more research is needed to fully understand the effects of the high-protein diet on microbiota and mental health.[58,59,60,61,62,63,64,65,66,67,68,69]

CONCLUSIONS

Overall the findings of this review suggest that there is a significant interaction between gut microbiota and mental health, supporting the idea that the gut and brain are connected bidirectionally through the gut-brain axis. However, it is important to note that many of these studies have limitations, such as small sample sizes and varied research designs, making it difficult to draw definitive conclusions. Therefore, more research is needed to fully understand the underlying mechanisms and clinical relevance of these relationships.

This systematic review provides a comprehensive overview of the interaction between gut microbiota and mental health in diverse populations. The findings suggest that gut microbiota may play an important role in mental health, but further studies are required to confirm and better understand these relationships. These results have significant implications for research and the development of interventions targeting the gut microbiota as a potential approach to improve mental health in various conditions.

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CONFLICT OF INTEREST

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