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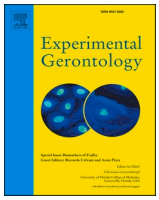

Review article

Influence of human gut microbiome on the healthy and the neurodegenerative aging

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ABSTRACT

The gut microbiome plays a crucial role in host health throughout the lifespan by influencing brain function during aging. The microbial diversity of the human gut microbiome decreases during the aging process and, as a consequence, several mechanisms increase, such as oxidative stress, mitochondrial dysfunction, inflammatory response, and microbial gut dysbiosis. Moreover, evidence indicates that aging and neurodegeneration are closely related; consequently, the gut microbiome may serve as a novel marker of lifespan in the elderly. In this narrative study, we investigated how the changes in the composition of the gut microbiome that occur in aging influence to various neuropathological disorders, such as mild cognitive impairment (MCI), dementia, Alzheimer's disease (AD), and Parkinson's disease (PD); and which are the possible mechanisms that govern the relationship between the gut microbiome and cognitive impairment. In addition, several studies suggest that the gut microbiome may be a potential novel target to improve hallmarks of brain aging and to promote healthy cognition; therefore, current and future therapeutic interventions have been also reviewed.

1. Introduction

The number of people aged 60 and over worldwide is expected to double in the next 35 years, reaching nearly 2.1 billion people (U.N., 2015). Aging is a progressive functional decline of the organism that leads to physiological and functional changes in the brain, including cognitive functioning impairment (Białecka-Dębek et al., 2021; Griñán-Ferré et al., 2021; Sen et al., 2016). Aging also disrupts gastrointestinal functions, including a weakened gut barrier, altered gut neurotransmitters, and modified intestinal immunity (Boehme et al., 2023; Bosco and Noti, 2021). Furthermore, aging is the single most important risk factor for mortality in humans, because of an expected functional decline, an increased frailty, and a higher susceptibility to chronic disease (Blagosklonny, 2022).

The composition of the gut microbiome can be altered by several modifiers throughout life, including lifestyle, age, socio-cultural environment, and individual psychological factors (Nishijima et al., 2016; Salazar et al., 2023a). During aging, the abundance and diversity of the gut microbial composition change, depending on environmental, dietary, and disease exposure factors (Borrego-Ruiz and Borrego, 2024b; García-Peña et al., 2017; Rinninella et al., 2019). This loss of gut homeostasis is called dysbiosis, which provokes chronic inflammation and alterations in the production of microbial metabolites, such as short chain fatty acids (SCFAs), secondary bile acids (BAs) and mucin, which result essential for the regulation of host physiological and immune functions (Blacher et al., 2017; Rampelli et al., 2013). Gut microbiome homeostasis is fundamental to brain health (cognitive function and synaptic plasticity) (Salami, 2021), preventing neuroinflammation and protecting against neurodegenerative disorders in the elderly by maintaining microglial cells in a healthy mature state (Erny et al., 2017; Rothhammer et al., 2016). Microglial cells play essential roles in the central nervous system (CNS), modulating neurogenesis, and maintaining homeostasis and cognition in the brain (Graeber and Streit, 2010). However, microglial hyperactivity increases neuronal damage, CNS neuroinflammation, and cognitive impairment in aging (von Bernhardi et al., 2015).

As a result of the bacterial metabolism, the gut microbiome may modulate the brain function by: (i) the production of neurotransmitters and neutrophil regulators, such as γ-aminobutyric acid (GABA), norepinephrine, dopamine, serotonin, melatonin, histamine and acetylcholine, and through activated-catecholamines action in the gut lumen (Carabotti et al., 2015; Strandwitz, 2018); (ii) the synthesis of

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bioactive metabolites, including SCFAs and BAs, which interact with enteroendocrine and enterochromaffin cells, as well as the mucosal immune system, or cross the intestinal barrier to enter the systemic circulation to reach and cross the blood-brain barrier (BBB) (Osadchiy et al., 2019; Morais et al., 2021; Silva et al., 2020); (iii) the modulation of tryptophan metabolites, serotonin, kynurenic acid, and quinolinic acid (Rothhammer et al., 2018); and (iv) the production of pro-inflammatory or anti-inflammatory cytokines, which may indirectly stimulate the hypothalamic-pituitary-adrenal (HPA) to produce corticotropin-releasing hormone, adrenocorticotropin hormone, and cortisol (Rusch et al., 2023), or directly affect CNS immune activity (Kennedy et al., 2017; Cryan et al., 2019; Morais et al., 2021; Varesi et al., 2022).

Activation of the immune system in the gut and brain by the gut microbiome has been implicated in responses to neuroinflammation, brain injury, and alterations in neurogenesis and neuron plasticity (Salvo-Romero et al., 2020). In addition, the gut microbiome influences in the development and integrity of the BBB to maintain a homeostatic environment for normal brain function (Segarra et al., 2021). Several studies have shown that environmental factors, such as aging, stress, dietary changes and disease, can induce dysfunction of the gut mucosal barrier (König et al., 2016; Salazar et al., 2023b).

In this narrative review, we examined the current knowledge on the relationship between the gut microbiome and the host brain aging, including possible microbial involvement in age-related neurodegenerative diseases such as mild cognitive impairment (MCI), dementia, Alzheimer's disease (AD), and Parkinson's disease (PD). We also reviewed the microbial modulators that improve cognitive function in the elderly, and the potential treatment strategies for intervention in the elderly.

2. Methods

The present work consists of a narrative review aimed at collecting and analyzing the existing literature in order to provide a complete and exhaustive overview of the central topic of the study (Agarwal et al., 2023). Both authors independently conducted a conscientious literature search in the field corresponding to the topic under investigation. For this purpose, PubMed, Scopus and Web of Science were searched between September and October 2023 using different combinations of keywords related to the research topic, such as "human gut microbiome", "gut microbiota", "elderly", "ageing", "aging", "psychiatric diseases", "neurodegenerative ageing", "treatment" or "brain aging". The search strategy also included an examination of the reference list of previous reviews and research papers. Both authors assessed all eligible records separately, considering studies that investigated the consequences of aging on the gut microbiome and its implication in neurodegenerative aging. Each article found was individually assessed for relevance by first screening the title and abstract. Duplicates were removed, and as well the studies that were unlikely to be included in the review due to their subject matter. The full texts of the remaining articles were carefully retrieved, and relevant data were extracted for further analysis. Studies were excluded from the review if they lacked significant information on the relationship between the human gut microbiome and aging.

3. Results

3.1. Healthy aging and gut microbiome

Three predominant hallmarks of aging have been identified: primary, antagonistic, and integrative (Gems and de Magalhães, 2021; Lemoine, 2021). Primary hallmarks included factors detrimental to cellular well-being, such as genome instability, telomere shortening, epigenetic alterations, and loss of proteostasis (López-Otín et al., 2013; Van der Rijt et al., 2020), which contribute to senescence, neoplastic development, and other age-related diseases (Kane and Sinclair, 2019; Metaxakis et al., 2018; Niedernhofer et al., 2018; Zhu et al., 2019). Antagonistic features include dysregulation of metabolic pathways, cellular senescence, and mitochondrial dysfunction (López-Otín et al., 2013, 2016; Podder et al., 2021). Several of these processes increase the production of reactive oxygen species (ROS) and protein glycosylation (Salazar et al., 2023a), leading to alterations in multiple cellular functions, reduced connective tissue elasticity, and activation of inflammatory pathways known to contribute to aging and associated diseases (Chatterjee et al., 2022; Kozakiewicz et al., 2019; Miwa et al., 2022). The integrative hallmarks alter the cellular homeostasis, including stem cell depletion and altered cellular signaling (Carmona and Michan, 2016; López-Otín et al., 2013; Podder et al., 2021). However, diet, physical activity, socio-economic status, smoking or drug use can induce epigenetic changes through endocrine and immune pathways that may have an important impact on longevity (An et al., 2018; de Lucia et al., 2020; Langhammer et al., 2018). More recently, other features have been proposed, including impaired macroautophagy, chronic inflammation, and dysbiosis of the gut microbiome (Guerville et al., 2020; López-Otín et al., 2023; Sharma et al., 2020).

Healthy aging individuals have a different composition and diversity of the gut microbiome compared to young adults (Claesson et al., 2011; Jeffery et al., 2016). Several clinical studies have shown that the Bacillota/Bacteroidota phyla ratio decreases with age, from 10.9 in people aged 25–45 years to 0.6 in people aged over 70 years (Mariat et al., 2009; Ratto et al., 2022; Vemuri et al., 2018). The changes in the gut microbiome that occur with aging are mainly characterized by a decrease in the microbial diversity and in the abundance of beneficial bacteria, and by an increase in the levels of pathobionts (Alsegiani and Shah, 2022). In addition, the reduced production of beneficial metabolites, such as SCFAs, may be related to the pathophysiological processes and cognitive decline associated with aging (Chen et al., 2019; Qian et al., 2022). Some studies in healthy aging individuals have reported a decrease in several bacterial groups compared to the gut microbiome of young adults, including members of the phylum Actinomycetota and the families *Ruminococcaceae, Oscillospiraceae, Lachnospiraceae,* and *Bacteroidaceae*. The major genera detected in these individuals are *Bacteroides*, *Bifidobacterium, Clostridium, Coprococcus, Eubacterium, Faecalibacterium, Lactobacillus, Prevotella,* and *Roseburia*. In contrast, opportunistic pathogenic microorganisms and other commensal bacteria associated with the releasing of pro-inflammatory cytokines are increased with age, including the members of the families *Christensenellaceae, Barnesiellaceae,* and *Enterobacteriaceae*, and the genera *Akkermansia, Alistipes, Anaerotruncus, Bilophila, Butyricicoccus, Butyricimonas, Butyrivibrio, Coprobacillus, Desulfovibrio, Eggerthella, Fusobacterium, Helicobacter, Odoribacter, Parabacteroides, Paraprevotella, Peptoniphilus, Ruminococcus, Staphylooccus,* and *Streptococcus* (Arboleya et al., 2016; Badal et al., 2020; Białecka-Dębek et al., 2021; Claesson et al., 2012; Ghosh et al., 2020a, 2022; Jeffery et al., 2016; Kato et al., 2017; Maffei et al., 2017; Salazar et al., 2023a; Wilmanski et al., 2021).

Although aging is associated with a progressive disruption of the physiological balance between the host and the gut microbiome (Boehme et al., 2023; Kundu et al., 2017), it is not known whether these alterations are due to physiological changes, age-related neuroinflammation (inflammageing), immunosenescence, impaired gut barrier function, diet, medications, or chronic health conditions (Bosco and Noti, 2021; DeJong et al., 2020; Ferrucci and Fabbri, 2018; Ghosh et al., 2022; Thevaranjan et al., 2017). Ghosh et al. (2022) have suggested that the gut microbiome may be a target modulator of aging and have proposed three groups of microorganisms that are altered with age. Group 1 includes the following genera that are lost with aging, and especially with unhealthy aging: *Faecalibacterium, Roseburia, Coprococcus, Eubacterium, Bifidobacterium,* and *Prevotella*. Group 2 consists of pathobionts that increase with age and unhealthy aging, and includes the following genera: *Eggerthella, Bilophila, Desulfovibrio, Fusobacterium, Anaerotruncus, Streptococcus,* and *Escherichia*. Group 3 consists of genera that

are associated with healthy aging, but are lost during unhealthy aging, such as *Akkermansia, Odoribacter, Butyricimonas, Butyrivibrio, Barnesiella,* and *Oscillospira*.

There are controversial results regarding the composition of the gut microbiome in different elderly populations, which can be attributed to dietary, cultural, or environmental differences, as well as to variations in the methodological analysis used (Biagi et al., 2017; Claesson et al., 2012; Odamaki et al., 2016; Park et al., 2015; Salazar et al., 2017; Wilmanski et al., 2021). There are also differences in the composition of the gut microbiome in different geographic regions of the world, which have a wide variety of diets (Białecka-Dębek et al., 2021) or ethnicities (Ang et al., 2021; Gaulke and Sharpton, 2018). For instance, the *Bacteroides* enterotype is most commonly reported in Western countries (with high fat and protein intakes), whereas the *Prevotella* enterotype is common in countries with a high consumption of fiber in their diets. African populations are characterized by higher gut microbiome diversity (abundance of members of the phyla Actinomycetota, Bacteroidota, Bacillota, Pseudomonadota, and Spirochaetota). In the case of East Asian people, Bacillota, Bacteriodota, Pseudomonadota, and Actinomycetota have been reported as the prevalent phyla in their gut microbiome with four enterotypes: *Prevotella, Bacteroides*, *Escherichia,* and another formed by *Ruminococcus, Bifidobacterium*, and *Blautia* (Lu et al., 2021a, 2021b; Therdtatha et al., 2022). The gut microbiomes of Europeans and Americans are enriched in the phyla Bacillota, Actinomycetota, Verrucomicrobiota, and Bacteroidota (Senghor et al., 2018).

Age-related changes in microbiome composition and diversity are closely associated with health outcomes in the elderly, particularly with respect to vulnerability (O'Toole and Jeffery, 2015; Vaiserman et al., 2017; Zapata and Quagliarello, 2015). The gut microbiome of vulnerable elderly people is mainly composed of members of the phylum Bacteroidota, with the genera *Bacteroides*, *Alistipes* and *Parabacteroides* (family *Bacteroidaceae*) being detected at higher levels (Claesson et al., 2011). In general, depending on the quality of life of the elderly, low individual microbial diversity, reduced species richness and increased interindividual variability are associated with aging and disease states (Alsegiani and Shah, 2022; Ticinesi et al., 2019). For example, elderly patients in nursing homes showed an overall reduction in fecal microbial diversity, which was associated with poorer individual health status and social interactions; while the gut microbiome of centenarians (100 years or older) showed higher microbial α-diversity, a greater number of glycolytic and proteolytic microbial taxa (Badal et al., 2020; Biagi et al., 2016, 2017; Bischoff, 2016; Wang et al., 2015; Wu et al., 2019), and amino acid derivatives circulating in the bloodstream (Wilmanski et al., 2021). Gut microbiome diversity is considered an important health indicator (Kong et al., 2019), as reduced gut microbiome diversity is associated with several pathological conditions, including autoimmune diseases, microbial infections, obesity, and metabolic alterations (Santoro et al., 2018).

Table 1 shows the main bacterial genera detected in the gut microbiome of elderly and centenarians, although differences in this composition depend on the culture and region in which the study was performed (Kim et al., 2019; Kong et al., 2016; Odamaki et al., 2016; Tuikhar et al., 2019; Wilmanski et al., 2021). In centenarians, Bacteriodota and Bacillota members dominate the gut microbiome; however, specific changes occur within of these microbial phyla, with a decrease in *Clostridium (C. sphenoides and C. colinum), Eubacterium (E. rectale, E. hallii, and E. ventriosum), Ruminococcus lactaris, Blautia obeum, Roseburia intestinalis, Lachnobacillus bovis, Papillibacter cinnamovorans and Faecalibacterium prausnitzii*, and with an increase in *Bacillus* spp., *Anaerotruncus colihominis, Clostridium (C. leptum and C. orbiscindens), Sporobacter termiditis, Eggerthella lenta, Enterobacter aerogenes, Klebsiella pneumonia, Vibrio* spp. *and Eubacterium limosum* (Biagi et al., 2010). Later, Biagi et al. (2016) reported that members of the family *Christensenellaceae*, and the genera *Akkermansia* and *Bifidobacterium*, were enriched in the gut microbiome of Italian centenarians, suggesting that these may be signatures of longevity and of a healthy microbiome; in contrast, members of the families *Ruminococcaceae*, *Lachnospiraceae* and *Bacteroidaceae* were reduced. On the contrary, Kong et al. (2016) reported an increase in the abundance of *Ruminococcaceae*, *Christensenellaceae, Clostridiaceae* and the genus *Akkermansia* in the gut microbiome of Chinese centenarians. Odamaki et al. (2016) reported a decrease in the members of the family *Lachnospiraceae* and the genera *Faecalibacterium*, *Bifidobacterium*, *Lachnospira* and *Blautia,* and an increase in the members of the families *Enterobacteriaceae, Christensencellaceae and Rikenellaceae*, and the genera *Ruminococcus, Parabacteroides, Oscillospira, Enterococcus, Akkermansia, Desulfovibrio, Odoribacter* and *Klebsiella* in 85- and 98-year-old subjects. In another study in Korean individuals, *Akkermansia*, *Collinsella*, *Clostridium, Escherichia* and *Streptococcus,* as well as the members of the family *Christensenellaceae,* were increased in the fecal microbiome of centenarians, while *Faecalibacterium* and *Prevotella* were decreased (Kim et al., 2019). Kong et al. (2019) found that the diversity of the gut microbiome of Chinese centenarians was greater than that of a young adult control group. The composition of the gut microbiome showed an increase in the abundance of *Escherichia/Shigella* and a decrease in the genus *Faecalibacterium*.

Wu et al. (2019) reported that centenarians in Sardinia (Italy) had a higher diversity of microbiome species and microbial genes compared to younger and older adult individuals. The centenarian microbiome was characterized by a depletion of the genera *Faecalibacterium, Eubacterium, Coprococcus, Dorea* and *Ruminococcus*, and an enrichment of the archaea *Methanobrevibacter* and the bacterial genera *Bifidobacterium, Pyramidobacter, Desulfovibrio, Escherichia,* and *Synergistes.* According to these authors, the microbiota in centenarians had a high capacity to produce SCFAs, but had a reduced expression of carbohydrate degradation genes. SCFAs exert protective functions on the epithelial barrier, supporting the growth of these beneficial bacterial and archaeal species, reducing colonization by opportunistic bacterial pathogens, and regulating the intestinal homeostasis and the immune response. The gut microbiome of Chinese groups aged 90–99 and 100+ years old showed more diversity and richness as compared to the 65–70 old age group (Wang et al., 2019). At the family level, *Prevotellaceae*, *Lachnospiraceae* and *Porphyromonadaceae* were the taxa with higher relative abundance in the longevity group as compared to the 65–70 old age group. Interesting variation in the gut microbiome within the centenarian group was obtained; the 100+ years old age group had a higher relative abundance of *Ruminococcaceae*, *Alistipes,* and *Barnesiella*, but a lower relative abundance of *Lachnospira* and *Prevotella*; while, participants in the 90–99 old age group had a higher relative abundance of *Clostridium*, *Parabacteroides,* and *Streptococcus*, but a lower abundance of *Megamonas*, *Blautia,* and *Coprococcus* as compared to the 65–70 old age group.

Later, Kashtanova et al. (2020), who studied the gut microbiome of Russian centenarians, found that it contained more beneficial bacteria compared to that of the healthy older people, including the families *Ruminococcaceae, Christensenellaceae, and Lactobacillaceae*, and the beneficial genera *Lactobacillus, Christensenella*, and *Roseburia*. In contrast, the centenarians had a lower abundance of the gut microbiome in members of the families *Veillonellaceae, Mogibacteriaceae, Alcaligenaceae, Peptococcaceae*, and *Peptostreptococcaceae*, and of the genera *Dorea, Sutterella, Dialister*, and *Ruminococcus*. In a study conducted in Italy, Rampelli et al. (2020) found that compared to younger individuals, centenarians showed a decrease in the abundance of the genera *Bacteroides*, *Eubacterium*, *Coprococcus,* and *Faecalibacterium*, while showing an increase in *Escherichia*, *Methanobrevibacter*, *Akkermansia,* and *Eggerthella.* Wu et al. (2022) reported that the abundance of Bacteroidota was significantly lower in the Chinese centenarian group than in other younger groups, while the abundance of Pseudomonadota, especially the family *Enterobacteriaceae*, showed a significant increase. In terms of genus dominance, *Akkermansia, Methanobrevibacter*, *Klebsiella*, *Campylobacter, Parabacteroides, Barnesiella, Alistipes, Enterococcus,* and *Fusobacterium* increased in centenarians, while *Anaerostipes, Butyricicoccus*, *Lachnospira, Megamonas, Bifidobacterium, Fusicatenibacter, Paraprevotella,* and *Faecalibacterium* decreased. This change in the gut

Table 1
Main bacterial genera found in the gut microbiome of healthy elderly and centenarians.

Microbiome source	Country	Increased genera	Decreased genera	Reference
Healthy aging	Japan	*Bacteroides* *Eubacterium* *Megamonas* *Peptoniphilus*	*Bifidobacterium*	Odamaki et al. (2016)
	China	*Anaerotruncus* *Parabacteroides* *Paraprevotella*		Wang et al. (2018b)
	Indonesia	*Enterobacteriaceae* *Escherichia* *Lactobacillus*	*Clostridium* *Bifidobacterium* *Prevotella* *Bacteroides* *Streptococcus*	Rahayu et al. (2019)
	Thailand	*Escherichia* *Bacteroides* *Parabacteroides*	*Bifidobacterium* *Dorea*	La-Ongkham et al. (2020)
	Russia	*Dialister* *Dorea* *Ruminococcus*		Kashtanova et al. (2020)
	China, Israel and The Netherlands	*Akkermansia* *Butyrivibrio* *Clostridium* *Coprococcus* *Lactobacillus* *Roseburia* *Subdoligranulum* *Victivallis*	*Bifidobacterium*	Zhang et al. (2021a)
Centenarians	Italy	*Clostridium* spp.[a] *Anaerotruncus* *Sporobacter* *Bacillus* *Eggerthella* *Enterobacter* *Klebsiella* *Vibrio* *Eubacterium* spp.[b]	*Clostridium* spp.[c] *Ruminococcus* *Roseburia* *Lachnobacillus* *Eubacterium* spp.[d] *Papillibacter* *Faecalibacterium*	Biagi et al. (2010)
	Italy	*Akkermansia* *Bifidobacterium* *Oscillospira* *Odoribacter* *Butyricimonas* *Eggerthella* *Anaerotruncus* *Bilophila*	*Coprococcus* *Faecalibacterium* *Roseburia*	Biagi et al. (2016)
	China	*Akkermansia* *Escherichia/Shigella*	*Faecalibacterium*	Kong et al. (2016, 2019)
	Japan	*Ruminococcus* *Parabacteroides* *Oscillospira* *Enterococcus* *Akkermansia* *Desulfovibrio* *Odoribacter* *Klebsiella*	*Faecalibacterium* *Bifidobacterium* *Lachnospira* *Blautia*	Odamaki et al. (2016)
	R. Korea	*Akkermansia* *Collinsella* *Clostridium* *Escherichia* *Streptococcus*	*Faecalibacterium* *Prevotella*	Kim et al. (2019)
	Italy	*Methanobrevibacter* *Bifidobacterium* *Pyramidobacter* *Desulfovibrio* *Escherichia* *Synergistes*	*Faecalibacterium* *Eubacterium* *Coprococcus* *Dorea* *Ruminococcus*	Wu et al. (2019)
	China	*Alistipes* *Barnesiella* *Clostridium* *Parabacteroides* *Streptococcus*	*Lachnospira* *Prevotella* *Megamonas* *Blautia* *Coprococcus*	Wang et al. (2019)
	India	*Eggerthella* *Alistipes* *Akkermansia* *Anaerotruncus* *Odoribacter*	*Faecalibacterium* *Ruminococcus*	Tuikhar et al. (2019)

(*continued on next page*)

Table 1 (*continued*)

Microbiome source	Country	Increased genera	Decreased genera	Reference
		Parabacteroides *Porphyromonas* *Butyricimonas* *Alicyclobacillus*		
	Russia	*Lactobacillus* *Christensenella* *Roseburia*	*Dorea* *Sutterella* *Dialister* *Ruminococcus*	Kashtanova et al. (2020)
	Italy	*Escherichia* *Methanobrevibacter* *Akkermansia* *Eggerthella*	*Bacteroides* *Eubacterium* *Coprococcus* *Faecalibacterium*	Rampelli et al. (2020)
	China	*Akkermansia* *Methanobrevibacter* *Klebsiella* *Parabacteroides* *Barnesiella* *Alistipes* *Campylobacter* *Enterococcus* *Fusobacterium*	*Anaerostipes* *Butyricicoccus* *Lachnospira* *Megamonas* *Bifidobacterium* *Fusicatenibacter* *Paraprevotella* *Faecalibacterium*	Wu et al. (2022)

[a] *C. leptum* and *C. orbiscindens*.
[b] *E. limosum*.
[c] *C. colinum* and *C. sphenoides*.
[d] *E. hallii*, *E. rectale* and *E. ventriosum*.

microbiome was reflected in the plasmatic levels of cytokines in the centenarian group (higher levels of tumor necrosis factor-α [TNF-α], IL-6, and IL-8) due to the increase in members of Pseudomonadota and the genus *Campylobacter*.

Tuikhar et al. (2019) comparatively studied the fecal samples of 125 centenarians from Italy, Japan, and China to identify bacterial species, genes, and pathways that promote the production of secondary BAs, such as lithocholic acid (LCA) and its derivatives, and deoxycholic acid (DCA). The genes encoding these enzymes are found in members of the family *Odoribacteraceae* (Sato et al., 2021), and in *Alistipes* spp., *Bacteroides cellulosilitycus*, *B. intestinalis*, *Parabacteroides merdae*, *P. goldsteinii,* and *Odoribacter laneus* (Salazar et al., 2023a). Isoallo-LCA induces T regulatory cellular function and exerts an antibacterial effect (Sato et al., 2021), while that isoLCA and 3-oxo-LCA suppress Th17 cell activity, protecting the host from immune hyper-responsiveness and contributing to healthy aging (Li et al., 2021). Metagenomic microbiome analysis of centenarians has shown enrichment of some genes associated with nutrient acquisition (Rampelli et al., 2020); however, consumption of a high-fiber diet seems to be the lifestyle factor most frequently associated with extreme longevity and health (Vasto et al., 2012).

Currently, the question of whether differences in microbiome composition contribute to longevity, or whether they are the result of a good lifestyle, remains unanswered. However, Ren et al. (2021) compared the gut microbiota composition from long-lived Chinese families to find a specific bacterial community pattern and signature taxa in long-lived people. The abundance in members of *Lachnospiraceae*, *Roseburia*, and *Blautia* was significantly higher in participants from the long-lived village, but their abundances gradually decreased along with age. The predicted pathways related to metabolism of SCFAs, amino acids, and lipoic acids were significantly higher in the long-lived elderly compared to the control group. The trajectory of gut microbiota composition along with age in participants from long-lived families might reveal potential health-promoting metabolic characteristics, which could play an important role in healthy aging. Later, Pang et al. (2023) conducted a cross-sectional investigation of individuals between 20 and 117 years in Guangxi (China) to characterize the gut microbiome signatures of aging. Compared to their old adult counterparts, centenarians displayed youth-associated features in the gut microbiome characterized by an over-representation of a *Bacteroides*-dominated enterotype and depletion of potential pathobionts. They found that health status stratification in older individuals did not alter the directional trends for these signature comparisons, but revealed more apparent associations in less healthy individuals. The findings revealed that centenarians have unique enterotypes relative to their old adult counterparts, which combine signatures in young and old adult individuals, and exhibit prominent features that show high similarity to young adults in terms of youth-associated microbial hallmarks. Importantly, longitudinal analysis of centenarians across a 1.5-year period indicates that during the aging of the centenarians these features continued to develop and they were either enhanced or conserved. In summary, both studies exclude the influence of lifestyle on the centenarian subjects, providing strong evidence for the conclusion that microbial composition contributes to longevity.

3.2. Gut microbiome dysbiosis and geriatric syndrome

Gut microbial dysbiosis in the elderly may lead to the onset of several age-related diseases, such as gastrointestinal diseases, type 2 diabetes, metabolic syndrome, atherosclerotic diseases, neurodegenerative diseases, cancer, and cachexia (Salazar et al., 2019; Vaiserman et al., 2017). On the other hand, age-related changes in the composition of the gut microbiome may negatively affect musculoskeletal conditions by promoting chronic systemic inflammation, insulin resistance, oxidative stress, and reduced nutrient bioavailability (Ticinesi et al., 2019).

According to the European Working Group on Sarcopenia in Older People (EWGSOP) (Van Ancum et al., 2020), the definition of sarcopenia is based on the decrease in muscle mass and function, and its incidence increases significantly with age (Martone et al., 2020). This systemic musculoskeletal condition increases the risk of falls in the elderly, prolongs hospital stays, and increases costs, morbidity and mortality (Zhao et al., 2021). Skeletal muscle mitochondrial dysfunction appears to be one of the causes of sarcopenia, and the link between the gut microbiome and the skeletal muscle mitochondria is mediated through the production of insulin-like growth factor 1 and urolithin A (Ebner et al., 2019; Franco-Obregón and Gilbert, 2017; Marzetti et al., 2013). In addition, gut microorganisms can utilize amino acids involved in muscle protein synthesis, altering their bioavailability to the host. Clinical studies have shown that the genus *Sutterella*, which is significantly increased in older adults, may play an essential role in muscle mass loss, probably due to decreased levels of vitamin B12 and folic acid (Liu et al.,

2021a; Shen et al., 2018; Xu et al., 2022). Moreover, certain strains of *Lactobacillus* and *Bifidobacterium* have been shown to reverse age-related muscle loss synthesizing SCFA metabolites that inhibit the Atrogin1/MAPK-FoxO3 system involved in skeletal muscle atrophy, and by inhibiting branched-chain amino acid pathways (de Marco Castro et al., 2021). However, the "gut-muscle axis" hypothesis is not supported by sufficient human data to the present date (Alsegiani and Shah, 2022), although these gut microbial alterations are more common in elderly individuals with neurodegenerative diseases and cognitive-motor frailty (Giron et al., 2022). The observation that predictability is associated with both cognitive and motor losses has allowed the introduction of a syndrome, the motor-cognitive risk syndrome, which is a condition of increased risk of dementia and mobility disability (Verghese et al., 2013).

Sarcopenia can be considered as a precursor of frailty. Frailty is a multifactorial geriatric syndrome that represents an increased vulnerability to adverse health outcomes (physical function deficits, decreased muscle strength, fatigue, and unintentional weight loss) and leads to a reduction in quality of life and independence, as well as an increased risk of hospitalization and mortality in older adults (Hoogendijk et al., 2019). The most consistent feature of the gut microbiome in frailty is a decrease in microbial diversity (Jackson et al., 2016), caused by dietary changes, reduced physical activity, long-term care facilities residence, increased exposure to antibiotics and medication changes, increased intestinal permeability, and imbalance in immune function (Claesson et al., 2012; DeJong et al., 2020; Xu et al., 2021). The gut microbiome composition of frail older adults showed a significant reduction in the abundance of the families *Lachnospiraceae, Barnesiellaceae, Gemellaceae, Erysipelotrichaceae* and *Christensenellaceae*, and of the genera *Acidaminococcus, Azospira, Coprococcus, Faecalibacterium, Fusicatenibacter, Gemella, Lachnoclostridium, Lactobacillus, Paraprevotella, Prevotella, Roseburia, Slackia,* and *Sutterella*. On the contrary, the gut microbiome of frail older adults showed increased abundance in the *Enterobacteriaceae, Eubacteriaceae, Bifidobacteriaceae, Atopobiaceae, Mogibacteriaceae, Micrococcaceae, Peptostreptococcaceae, Ruminococcaceae, Veillonellaceae,* and *Coriobacteriaceae* families, and in the genera *Acetanaerobacterium, Actinomyces, Anaerotruncus, Bifidobacterium, Catenibacterium, Clostridium, Coprobacillus, Dialister, Eggerthella, Erwinia, Lachnoanaerobaculum, Megasphaera, Parabacteroides, Pyramidobacter, Rothia, Ruminococcus*, and *Veillonella* compared to people with low frailty scores (Almeida et al., 2022; Haran and McCormick, 2021; Jackson et al., 2016; Jeffery et al., 2016; Kang et al., 2021; Lim et al., 2021; Maffei et al., 2017; Margiotta et al., 2020; Picca et al., 2019; Ponziani et al., 2021; Rampelli et al., 2013; Strasser and Ticinesi, 2023; Ticinesi et al., 2020; Zhang et al., 2020). The relative abundance of the families *Verrucomicrobiaceae, Veillonellaceae, Barnesiellaceae* and *Rikenellaceae*, and of the genera *Bacteroides, Alistipes, Dorea, Eubacterium, Oscillospira,* and *Akkermansia* presented controversial results (Almeida et al., 2022).

Ghosh et al. (2020a) reported that three types of taxonomic groups can be identified in studies related to frailty: Group 1 includes taxa (mainly SCFA-producing bacteria) that are lost during unhealthy aging, including *Blautia, Coprococcus, Dorea, Eubacterium, Faecalibacterium,* and *Roseburia*. Group 2 consists of pathobionts that increase with age, especially with unhealthy aging, such as the families *Enterobacteriaceae* and *Atopobiaceae*, and the genera *Actinomyces, Anaerotruncus, Bacteroides, Bilophila, Campylobacter, Clostridium, Coprobacillus, Corynebacterium, Desulfovibrio, Eggerthella, Enterococcus, Flavonifractor, Fusobacterium, Parvimonas, Porphyromonas, Ruminococcus, Staphylococcus, Streptococcus,* and *Veillonella*. Group 3 is a healthy age-associated gut microbiome that is lost during unhealthy aging and includes the family *Christensenellaceae* and the genera *Akkermansia, Barnesiella, Butyricimonas, Butyrivibrio, Odoribacter*, and *Oscillospira*. In addition, the presence of the *Mogibacteriaceae* family in the gut microbiome was associated with blood C-reactive protein (CRP) levels, which may be related to inflammageing (Margiotta et al., 2020). Members of the family *Barnesiellaceae* have also been associated with increased systemic levels of pro-inflammatory cytokines, such as TNF-α (Margiotta et al., 2021), which induce muscle degradation via the ubiquitin-proteasome pathway, contributing to frailty and sarcopenia (Soysal et al., 2016). The *Bifidobacteriaceae* family regulates intestinal and immune system functions, ameliorating frailty and restoring intestinal homeostasis (Wallen et al., 2020). Interestingly, the relatively high abundance of the genus *Eggerthella* in frail elderly has been reported in several studies (Jackson et al., 2016; Maffei et al., 2017; Margiotta et al., 2020; Picca and Calvani, 2020). Species of this genus utilize threonine, a major component of intestinal mucin, deregulating intestinal epithelial junctions and increasing cellular permeability to endotoxins implicated in some gastrointestinal diseases (Rao, 2008; Thota et al., 2011). Conversely, the lower abundance of the genera *Alistipes*, *Prevotella*, *Fusicatenibacter, Lachnoclostridium*, *Roseburia,* and *Faecalibacterium* in frail and sarcopenic individuals implies lower production of SCFAs (Almeida et al., 2022; Kang et al., 2021; Parker et al., 2020; Ticinesi et al., 2020), which act on muscle cells to improve mitochondrial activity, fatty acid oxidation, protein synthesis, and energy availability (Jackson et al., 2016; Lin et al., 2017; Saint-Georges-Chaumet and Edeas, 2016; Vinolo et al., 2011).

The gut microbiota modulates the process of inflammaging, which contributes to age-related disorders such as neuroinflammation and neurodegeneration (Alsegiani and Shah, 2022). The microbiota has been shown to trigger innate immunity and produces inflammatory responses that include intestinal inflammation and increased circulation of inflammatory cytokines. Gut bacteria can secrete large amounts of other by-products, for example double-stranded RNA, lipoproteins and lipopolysaccharides (LPS), which contribute to the signaling pathways involved in the production of pro-inflammatory cytokines IL-8 and IL-6 (Biagi et al., 2010). Preclinical studies have shown that higher LPS levels correlate with the increased expression of TLR4, myeloid differentiation protein-88, and nuclear translocation of factor κB in both intestinal and brain tissues (Wu et al., 2021b). LPS also induce systemic inflammation, leading to increased permeability of the BBB and disruption of the intestinal epithelial barrier (Choi et al., 2012). Mucosal translocation of bacterial LPS and LPS-binding proteins into the circulation system may also promote the chronic low-grade systemic inflammation, which is particularly prevalent in the elderly, and may initiate CNS inflammation by activating the LPS/TLR4 pathway in brain glial cells (Stehle Jr et al., 2012; Ghosh et al., 2015).

3.3. Neurodegenerative diseases and gut microbiome dysbiosis in aging

Aging is a major risk factor for several neurodegenerative diseases, including subjective cognitive decline (SCD), mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and delirium (Alsegiani and Shah, 2022; Molinero et al., 2023; Sheng et al., 2021; Strasser and Ticinesi, 2023). The gut microbiome has also been implicated in a number of physiological and pathological processes such as satiety, schizophrenia, depression, and stress (Borrego-Ruiz and Borrego, 2024a; Foster and McVey Neufeld, 2013; Liu et al., 2020b; Varesi et al., 2022). In addition, the gut microbiome has been suggested to influence the brain aging process through the initiation and progression of cognitive and neurodegenerative processes. The term "mapranosis" has been proposed to describe microbiota-associated proteopathy, oxidative stress, and neuroinflammation (Friedland and Chapman, 2017). Older adults exhibit significant gut dysbiosis, which in many cases coincides with the development of MCI of the brain functions by initiation (Alsegiani and Shah, 2022; Białecka-Dębek et al., 2021; Fransen et al., 2017). Cognitive deficits between normal aging and dementia disorders are collectively referred to as MCI, often considered an early stage of AD but resulting from a variety of etiologies (Petersen, 2016). Although AD is the most common cause of dementia, there are other forms such as vascular dementia, Pick's disease, or dementia with Lewy bodies, to name a few (Crous-Bou et al., 2017).

3.3.1. Subjective cognitive decline (SCD) and mild cognitive impairment (MCI)

SCD is a self-reported persistent decline in cognitive performance that may be associated with an increased risk of MCI (Jessen et al., 2020; van Harten et al., 2018). Sheng et al. (2021) found a decrease in the abundance of members of the family *Ruminococcaceae* and the genus *Faecalibacterium* in SCD patients; these changes in the gut microbiome were associated with cognitive performance. Duan et al. (2021), who studied patients with SCD and MCI, found that the relative abundance of members of the phylum Bacteroidota was higher in the SCD group, whereas members of the phylum Bacillota were more enriched in the MCI group compared to the SCD group. At the family level, SCD patients had lower abundance of *Christensenellaceae, Ruminococcaceae,* and *Erysipelotrichaceae* compared to the control group, and lower abundance of *Lachnospiraceae* compared to the MCI group. At the genus level, *Fusicatenibacter, Ruminiclostridium,* and *Butyricicoccus* had lower abundance in the SCD group compared to the control group, and *Coprobacter* and *Roseburia* genera decreased compared to the MCI group. In contrast, only members of *Faecalibacterium* showed higher abundance in SCD and MCI groups compared to controls.

MCI is one of the most common diseases of the elderly and can be considered as an intermediate stage between the normal cognitive decline of aging and dementia (Chen et al., 2021). Several studies have reported an association between this neurogenerative disease and gut microbiome dysbiosis. For instance, Manderino et al. (2017) found that subjects with cognitive impairment had an abundance of four bacterial phyla, Bacillota, Bacteroidota, Pseudomonadota and Verrucomicrobia, and reported a significant correlation between cognitive decline and the Verrucomicrobia abundance. In another group of MCI patients, Saji et al. (2019b) reported an increased abundance of *Bacteroides* and *Prevotella* in MCI patients, while the Bacillota/Bacteriodota ratio decreased in these patients. Similar results were found by Nagpal et al. (2019), with a slightly lower abundance of the phylum Bacteroidota in MCI patients compared to controls. The authors also found that members of Pseudomonadota were positively correlated with the amyloid-β-peptide (Aβ) 42/Aβ-40 ratio, while fecal propionate and butyrate were negatively correlated with Aβ-42 in subjects with MCI. Saji et al. (2020) found that fecal ammonia and lactic acid were associated with dementia, independently of the other risk factors for dementia and dysregulation of the gut microbiome.

Interestingly, Khine et al. (2020) found that alterations in several cognitive functions (memory, semantic fluency, recognition, selective attention, or visual spatial skills, to name a few) in elderly MCI patients were consistent with changes in the abundance of *Ruminococcus, Coprococcus, Parabacteroides, Fusobacterium,* and *Phascolarctobacterium*, as well as members of the *Enterobacteriaceae* and *Ruminocococeae* families, considering them as risk indicators for MCI. Later, Pan et al. (2021) reported different gut microbiome profiles between MCI patients and controls, with higher levels of several pathobionts in MCI. Specifically, the major gut microbiome genera correlated with MCI were *Leptotrichia* and *Staphylococcus*, while *Bacteroides* and *Sphingobacterium* were negatively correlated. To determine the associations between diet quality, no-coding microRNA (miRNAs) and risk of MCI in middle-aged and elderly Chinese population, Zhang et al. (2021b) investigated the gut microbiota in MCI patients compared to healthy controls. The results obtained indicated that the α- and β-diversity of the gut microbiome decreased in MCI patients, and they also found lower abundance of members of the families *Rikenellaceae* and *Planococcaceae*, and the genera *Faecalibacterium* and *Alistipes*. In contrast, MCI patients had an increase in the abundance of the families *Rhizobiaceae* and *Enterobacteriaceae*, and the genus *Megasphaera*.

Liu et al. (2021a) reported changes in the gut microbiome of patients associated with amnestic mild cognitive impairment (aMCI). Specifically, aMCI subjects had increased abundance of members of the families *Veillonellaceae* and *Bacteroidaceae*, and the genus *Bacteroides*, while decreased abundance of members of the families *Lachnospiraceae* and *Clostridiaceae*, and the genera *Blautia* and *Ruminococcus*. A microbiome analysis by Aljumaah et al. (2022) identified *Prevotella* and *Bacteroides* species as taxa correlated with MCI, with *Prevotella* spp. being most abundant in MCI subjects compared to cognitively healthy subjects. Asaoka et al. (2022) observed an altered composition in MCI subjects, represented by a lower relative abundance of *Bifidobacterium* and members of the phylum Actinomycetota, and a higher relative abundance of the genera *Prevotella* and *Phascolarctobacterium*, and members of the families *Clostridiaceae* and *Ruminococcaceae*. Li et al. (2023a) found that beta analysis showed that microbial enterotypes were not significantly associated with cognition between individuals with MCI and controls. In addition, they reported differential taxonomic characteristics at the genus level with cognitive status, including positive correlations with *Streptococcus, Hungatella, Holdemania, Fusicatenibacter, Eubacterium, Eggerthella, Clostridium, Citrobacter, Bifidobacterium, Bacteroides,* and *Anaerostipes*. In contrast, negative correlations were found for the genera *Prevotella* and *Dialister*. Table 2 lists several studies conducted in SCD and MCI patients that reported an altered gut microbiome.

3.3.2. Alzheimer's disease (AD)

AD is an irreversible neurodegenerative disease characterized by progressive loss of cognition and memory that accounts for 60–80 % of all cases of dementia in the elderly (75 million people in 2030) and that could lead to the collapse of healthcare systems (Nichols et al., 2019; Wimo et al., 2017). The etiopathogenesis of AD is still not fully understood and it has been described as a multifaceted disease in which aging, environmental and genetic factors are risk factors (Breijyeh and Karaman, 2020; Jagust, 2018). The main characteristic of this pathology is the extracellular accumulation of Aβ, which forms neuritic plaques in the neocortex, as well as by the intracellular aggregation of the hyperphosphorylated tau protein, a process that leads to the development of neurofibrillary tangles (Dujardin et al., 2020; Long and Holtzman, 2019; Perea et al., 2020). Furthermore, neuroinflammation, mitochondrial dysfunction, cerebral hypoperfusion, and impaired calcium balance are factors that have also been implicated in the pathogenesis of AD (Bostancikliоğlu, 2019; Kowalski and Mulak, 2019; Long and Holtzman, 2019).

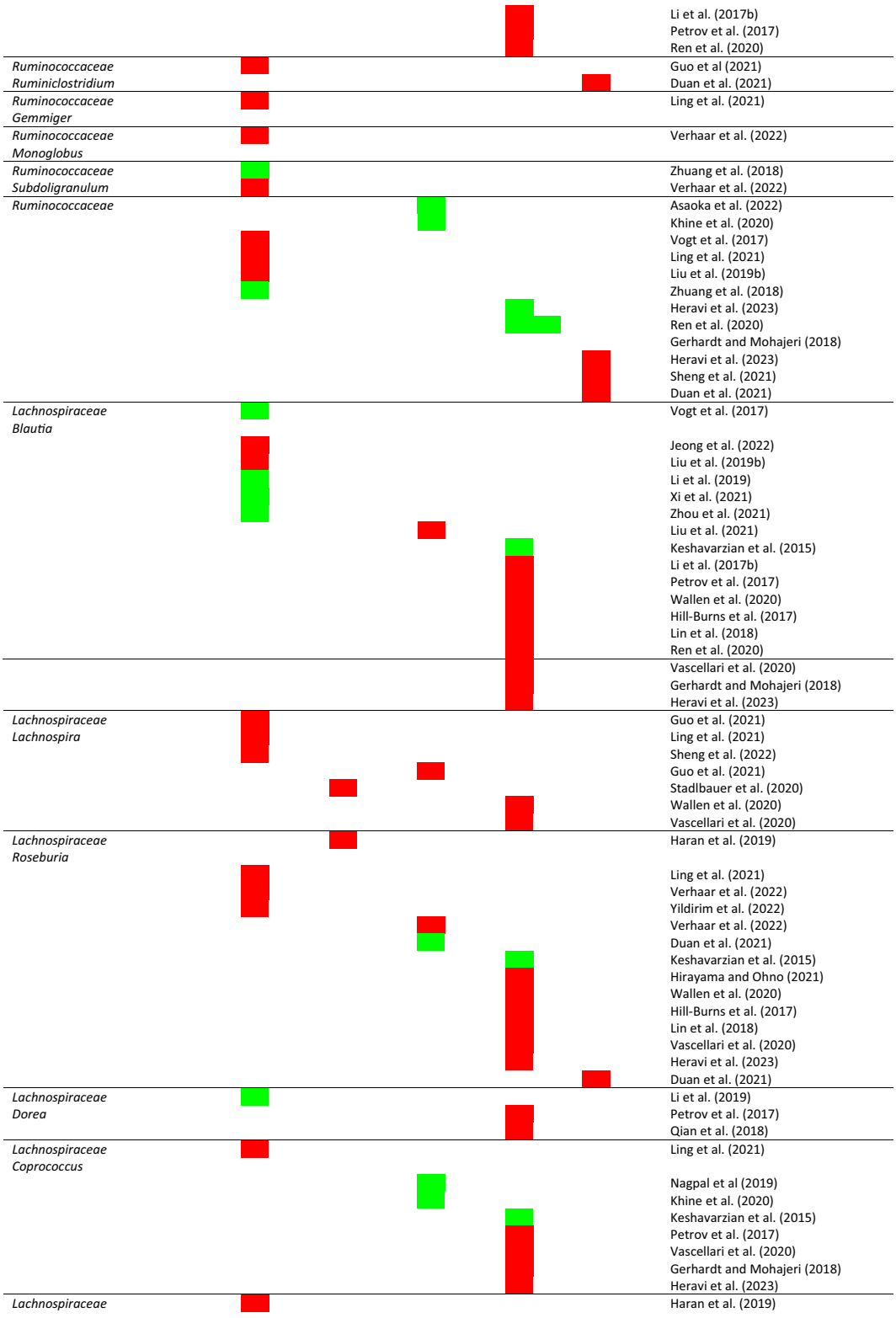
An association of AD with a state of dysbiosis of the gut microbiome has been well established by various authors. According to Bostancikliоğlu (2019), there are three distinct links between the gut microbiome and the pathogenesis of AD: (i) CNS inflammation and cerebrovascular degeneration induced by bacterial metabolites and amyloids; (ii) inhibition of the autophagy-mediated protein clearance process by an impaired gut microbiome; and (iii) alteration of the neurotransmitter levels in the brain through the vagal afferent via caused by the gut microbiome. Some studies have suggested that imbalances in the human microbiome homeostasis may also contribute to tau and Aβ-deposition (Cenit et al., 2017; Sureda et al., 2020; Vogt et al., 2017). Several gut microbiota species have been shown to produce amyloid fibers, including *Escherichia coli, Salmonella enterica, S. typhimurium*, and *Bacillus subtilis* (Friedland and Chapman, 2017; Hufnagel et al., 2013); however, microbial amyloids share only tertiary structural similarities with human CNS amyloids and act as prion-like agents through molecular mimicry, causing the amyloidogenic protein to adopt a pathogenic β-structure (Schwartz and Boles, 2013; Friedland, 2015; Kowalski and Mulak, 2019). In the elderly, these bacterial amyloid fibrils can cross the intestinal and BBB barriers, promote Aβ accumulation in the brain, and enhance the inflammatory response to cerebral amyloids (such as amyloid-β and α-synuclein) (Kowalski and Mulak, 2019; Li et al., 2019).

Bacterial LPS may play a role in AD when they reach brain compartments by crossing the intestinal tract and BBB (Zhao et al., 2017). LPS act on leukocyte and microglial TLR4-CD14/TLR2 receptors and increase Aβ levels (via increased cytokine levels). In addition, Aβ1–42 is an agonist for TLR4 receptors, producing NFκB-mediated increments in

Table 2
Dysbiosis of the gut microbiome in neurodegenerative disorders compared to normal controls.

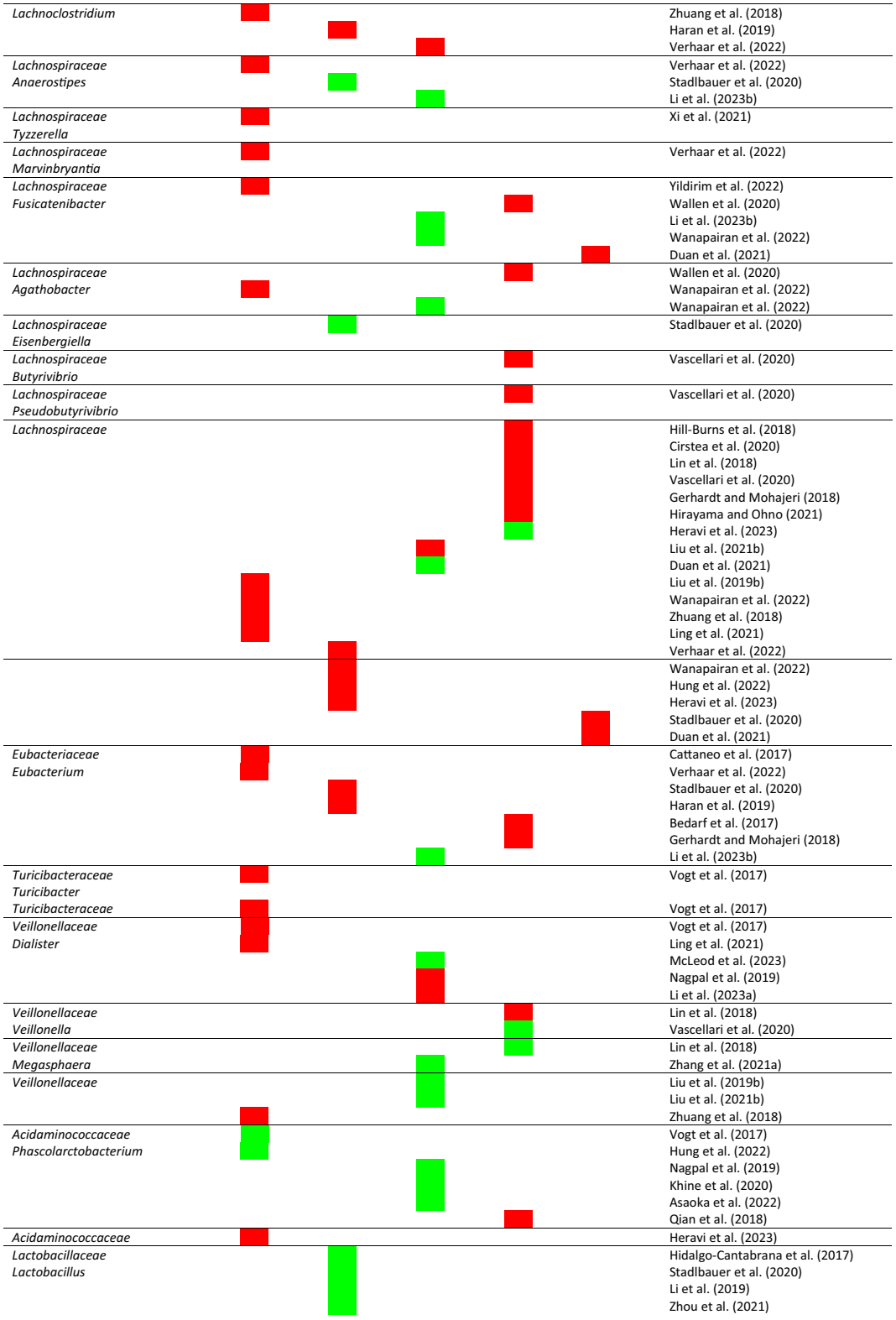
Taxa	AD	D	MCI	PD	SCD	Reference
Phylum Actinomycetota						
Bifidobacteriaceae						Vogt et al. (2017)
Bifidobacterium						Hung et al. (2022)
						Saji et al. (2019a)
						Li et al. (2019)
						Ling et al. (2021)
						Zhou et al. (2021)
						Hill-Burns et al. (2017)
						Wallen et al. (2020)
						Cirstea et al. (2020)
						Petrov et al. (2017)
						Vascellari et al. (2020)
						Gerhardt and Mohajeri (2018)
						Heravi et al. (2023)
						Li et al. (2023b)
						Asaoka et al. (2022)
Bifidobacteriaceae						Lin et al. (2018)
						Vascellari et al. (2020)
						Ling et al. (2021)
Coriobacteriaceae						Vogt et al. (2017)
Adlercreutzia						
Coriobacteriaceae						Haran et al. (2019)
Collinsella						
Coriobacteriaceae						Vascellari et al. (2020)
Slackia						
Coriobacteriaceae						Ling et al. (2021)
Eggerthellaceae						Li et al. (2023b)
Eggerthella						
Eggerthellaceae						Jeong et al. (2022)
Gordonibacter						
Brevibacteriaceae						Vascellari et al. (2020)
Brevibacterium						
Corynebacteriaceae						Wallen et al. (2020)
Corynebacterium						
Corynebacteriaceae						Ling et al. (2021)
						Wallen et al. (2020)
Atopobiaceae						Xi et al. (2021)
Phylum Bacillota						
Clostridiaceae						Vogt et al. (2017)
Clostridium						
						Ling et al. (2021)
						Wanapairan et al. (2022)
						Xi et al. (2021)
						Verhaar et al. (2022)
						Hasegawa et al. (2015)
						Bedarf et al. (2017)
						Gerhardt and Mohajeri (2018)
						Stadlbauer et al. (2020)
						Qian et al. (2018)
						Vascellari et al. (2020)
						Li et al. (2023b)
						Wanapairan et al. (2022)
Clostridiaceae						Li et al. (2023b)
Hungatella						
Clostridiaceae						Vogt et al. (2017)
						Ling et al. (2021)
						Liu et al. (2019b)
						Hung et al. (2022)
						Asaoka et al. (2022)
						Liu et al. (2021b)
						Liu et al. (2019b)
Ruminococcaceae						Li et al. (2019)
Ruminococcus						Liu et al. (2019b)
						Ling et al. (2021)
						Sheng et al. (2022)
						Verhaar et al. (2022)
						Zhuang et al. (2018)
						Xi et al. (2021)
						Khine et al. (2020)
						Liu et al. (2021b)

cytokines that increase Aβ levels, cause injury in the oligodendrocytes, and produce the myelin damage found in AD brain (Zhan et al., 2018). Furthermore, aged-related changes in the microbiota have been shown to lead the entry of glial cells in a reactive state and to induce an inflammation process in the brain (Alsegiani and Shah, 2022). Increased levels of secondary BAs have also been associated with Aβ production and accumulation through disruption of the cholesterol catabolic pathway (Jia et al., 2020). Interestingly, the by-products of gut microbiome dysbiosis may alter the expression of various genes and associated synaptic proteins that promote the accumulation of inflammatory proteins in the brain, as well as the induction of neuroinflammation, astrocyte activation, neuronal apoptosis, and microglial inflammatory response (Alsegiani and Shah, 2022; Perea et al., 2020). Several studies have shown increased peroxidation and decreased levels and activity of

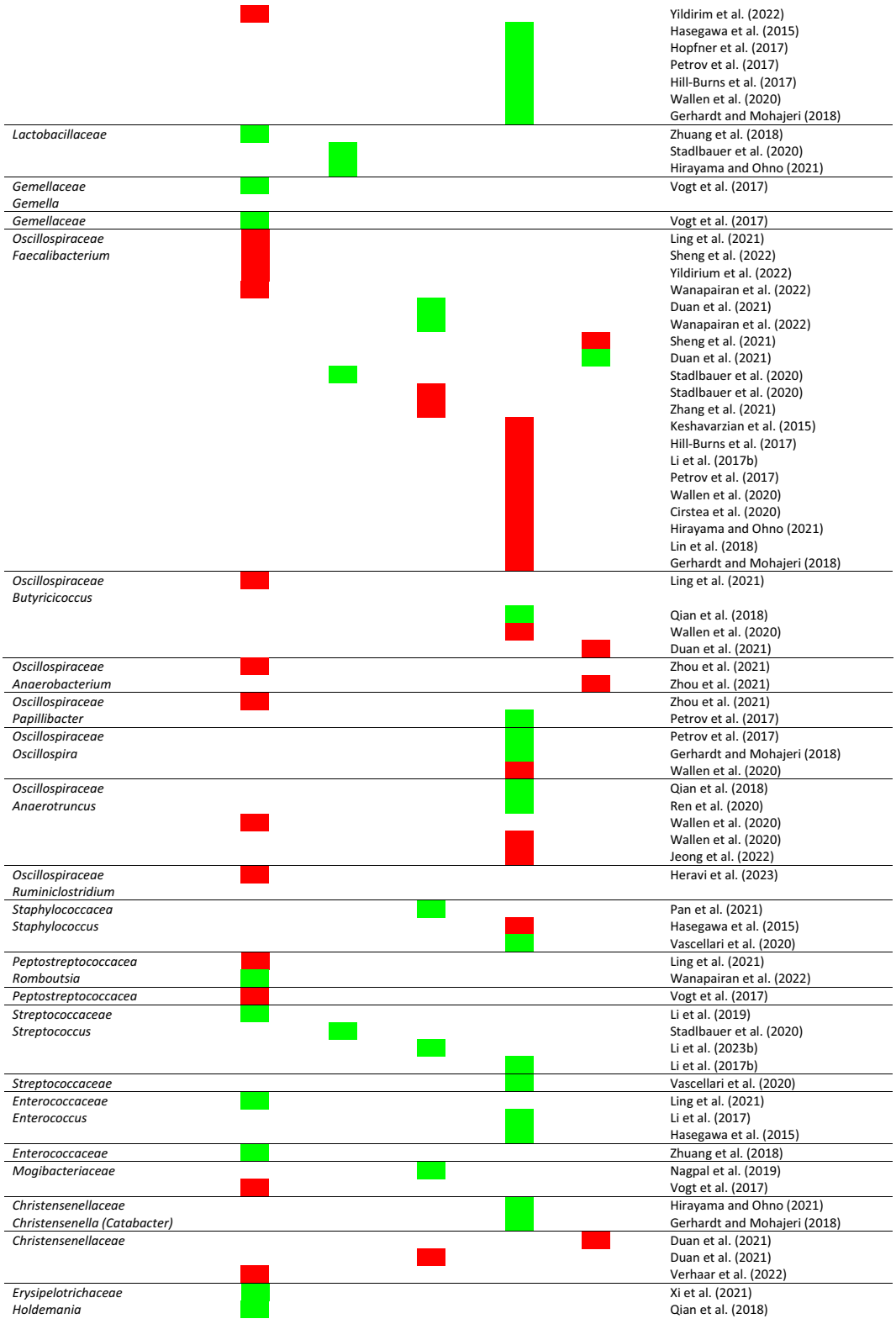


antioxidant molecules in AD patients (Białecka-Dębek et al., 2021; Dumitrescu et al., 2018). Therefore, the role of the gut microbiome in regulating the oxidative state of the CNS is also a factor to consider, as oxidative stress increases Aβ deposition (Huang et al., 2016). This gut microbial regulation occurs through the production of various metabolites and enzymes (SCFAs, polyphenols, vitamins, superoxide dismutase, and catalase) (Sharon et al., 2014).

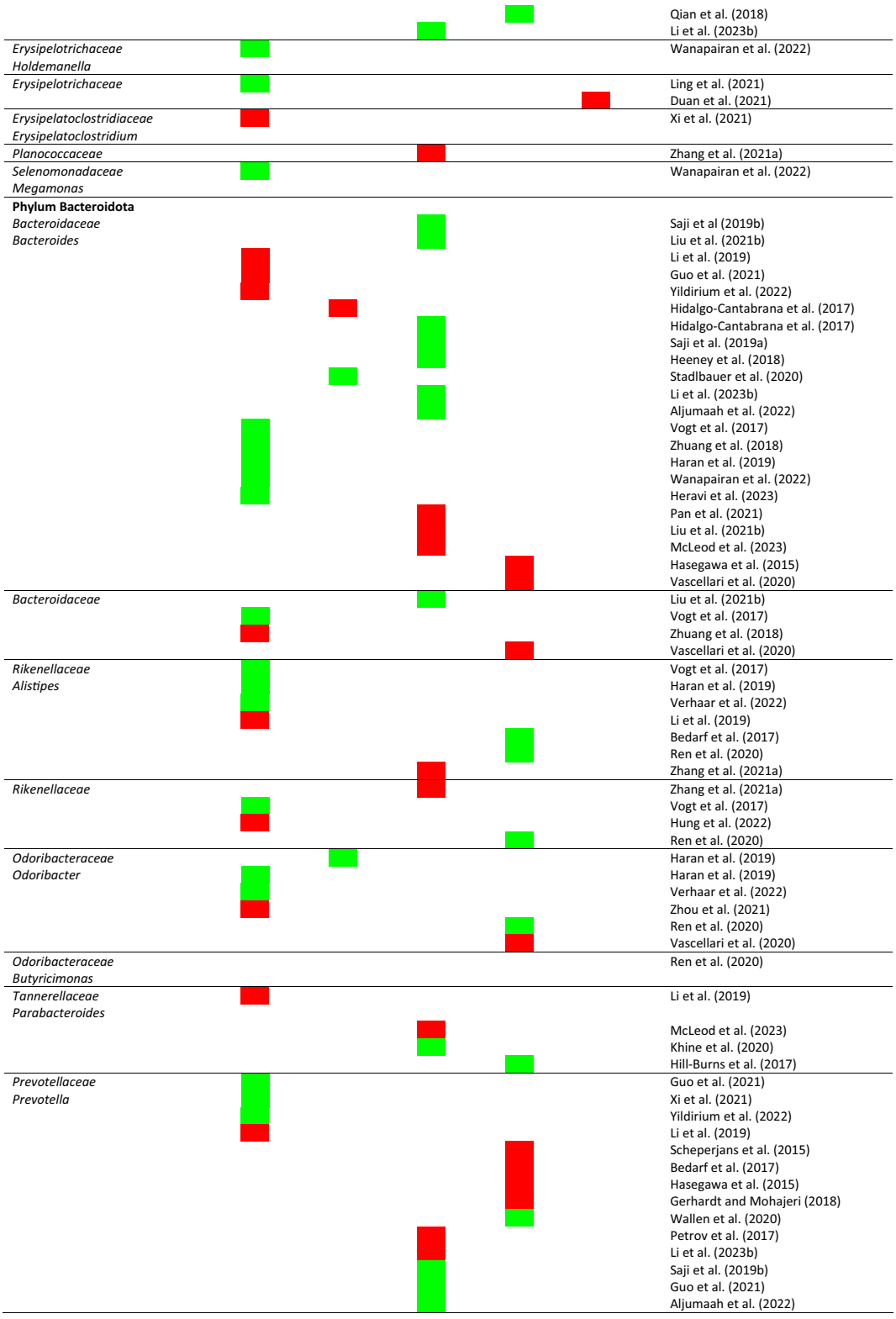
Despite inter- and intra-individual variability and changes associated with gender, diet and geography, nearly 85 % of patients with AD have a different gut microbiome shape compared to healthy individuals of the same age (Morris et al., 2017; Xi et al., 2021). In short, subjects with AD present intestinal dysbiosis, which may play a critical role in modulating



the gut-brain axis, and could actively participate in the pathogenesis of AD (Wu et al., 2021c). Cattaneo et al. (2017) conducted a study to analyze the gut microbiome alterations in AD patients and found higher pro-inflammatory gut microbiota genera *Escherichia/Shigella*, and lower anti-inflammatory species *Eubacterium rectale*, which are associated with peripheral systemic inflammation. The authors reported a significant positive correlation between the pro-inflammatory cytokines IL-1β, NLRP3 and CXCL2 and *Escherichia/Shigella* abundance, and a negative correlation with *E. rectale*. Vogt et al. (2017) reported decreased microbial diversity and altered composition of the AD gut microbiome



group compared to controls, with decreased abundance of members of the phyla Bacillota and Actinomycetota, the families *Ruminococcaceae, Turicibacteraceae, Peptostreptococcaceae, Clostridiaceae* and *Mogibacteriaceae*, and the genera *Bifidobacterium, Adlercreutzia, Dialister, Clostridium, Turicibacter,* and *Bilophila.* On the other hand, increased levels of members of the phylum Bacillota, and the families and genera *Rikenellaceae, Bacteriodaceae, Gemellaceae*, *Alistipes, Gemella, Phascolarctobacterium, Blautia,* and *Bacteroides* were found in AD patients. Zhuang et al. (2018) found that individuals with AD have an alteration in the fecal microbiota composition characterized by a decrease in the



abundance of members of the phylum Actinomycetota and an increase in the phylum Bacteroidota, families *Ruminococcaceae, Enterococcaceae* and *Lactobacillaceae,* and genera *Bacteroides, Subdoligranulum,* and *Ruminococcus.* These authors also reported a decrease in the abundance of *Lachnospiraceae, Bacteroidaceae, Veillonellaceae,* and *Lachnoclostridium*. Later, Saji et al. (2019a) reported a dysregulation of the gut microbiome in a group of patients with dementia, as the Bacillota/Bacteriodota ratio increased in these patients. The number of *Bacteroides* was lower in demented than in non-demented patients, while the abundance of *Bifidobacterium* and members of the order

							Asaoka et al. (2022)
Prevotellaceae *Paraprevotella*							Li et al. (2019)
Prevotellaceae *Alloprevotella*							Li et al. (2019)
Prevotellaceae							Gerhardt and Mohajeri (2018) Heravi et al. (2023)
Barnesiellaceae							Haran et al. (2019)
Barnesiella							Haran et al. (2019) Hopfner et al. (2017) Ren et al. (2020)
Chitinophagaceae							Zhou et al. (2021)
Taibaiella							Zhou et al. (2021)
Porphyromonadaceae *Porphyromonas*							Wallen et al. (2020)
Sphingobacteriaceae *Sphingobacterium*							Pan et al. (2021)
Sphingobacteriaceae							Vascellari et al. (2020)
Phylum Pseudomonadota							
Enterobacteriaceae *Escherichia/Shigella*							Cattaneo et al. (2017) Li et al. (2019) Hou et al. (2021) Yildirium et al. (2022) Nagpal et al. (2019) Scheperjans et al. (2015) Hopfner et al. (2017) Li et al. (2017) Vascellari et al. (2020) Qian et al. (2018)
Enterobacteriaceae *Proteus*							Li et al. (2017)
Enterobacteriaceae *Citrobacter*							Li et al. (2023a)
Enterobacteriaceae *Enterobacter*							Vascellari et al. (2020)
Enterobacteriaceae *Serratia*							Vascellari et al. (2020)
Enterobacteriaceae							Zhang et al. (2021a) Khine et al. (2020) Liu et al. (2019b)
Sutterellaceae *Sutterella*							Li et al. (2019)
Sphingomonadaceae *Sphingomonas*							Zhou et al. (2021) Qian et al. (2018)
Pseudomonadaceae							Xi et al. (2021)
Burkholderiaceae *Ralstonia*							Keshavarzian et al. (2015)
Comamonadaceae *Aquabacterium*							Qian et al. (2018)
Rhizobiaceae							Zhang et al. (2021a)
Phylum Verrucomicrobiota							
Akkermansiaceae *Akkermansia*							Li et al. (2019) Ling et al. (2021) Yildirium et al. (2022) McLeod et al. (2023) Bedarf et al. (2017) Hill-Burns et al. (2018) Cirstea et al. (2020) Hirayama and Ohno (2021) Lin et al. (2018) Vascellari et al. (2020) Gerhardt and Mohajeri (2018) Heravi et al. (2023)
Akkermansiaceae							Hirayama and Ohno (2021)
Verrucomicrobiaceae *Prosthecobacter*							Vascellari et al. (2020)
Verrucomicrobiaceae							Ling et al. (2021) Hopfner et al. (2017) Vascellari et al. (2020) Gerhardt and Mohajeri (2018) Heravi et al. (2023)
Phylum Fusobacteriota							
Fusobacteriaceae *Fusobacterium*							Khine et al. (2020)
Leptotrichiaceae							Pan et al. (2021)
Leptotrichia							
Phylum Synergistota							
Synergistaceae							Xi et al. (2021)
Phylum Thermodesulfobacteriodota							
Desulfovibrionaceae *Bilophila*							Vogt et al. (2017) Sheng et al. (2022) Verhaar et al. (2022)
Phylum Euryarchaeota							
Methanobacteriaeae *Methanobrevibacter*							McLeod et al. (2023)

AD: Alzheimer's Disease; D: Dementia; MCI: Mild Cognitive Impairment; PD: Parkinson's Disease; SCD: Subjective Cognitive Decline

Increase: Decrease:

Additional references cited in Table 2 (Bedarf et al., 2017; Cirstea et al., 2020; Hasegawa et al., 2015; Heeney et al., 2018; Hidalgo-Cantabrana et al., 2017; Hill-Burns et al., 2017; Hopfner et al., 2017; Li et al., 2017b; Lin et al., 2018; Liu et al., 2021b; McLeod et al., 2023; Petrov et al., 2017).

Lactobacillales was slightly higher.

In Austrian patients with different stages of dementia, Stadlbauer et al. (2020) found that members of the genera *Clostridium, Anaerostipes,* and *Bacteroides* were the most frequently associated with dementia, while members of the family *Lachnospiraceae* and the genera *Lachnospira* and *Eubacterium* were associated with health. Moreover, several genera were associated with the severity of cognitive impairment, the genera *Faecalibacterium* with mild dementia, *Lactobacillus* with moderate dementia, and severe dementia was associated with *Clostridium, Eisenbergiella* and *Streptococcus*, and members of the family *Lactobacillaceae*. Ling et al. (2021) reported a remarkable reduction in the bacterial diversity and changes in the composition of the fecal microbiota of Chinese AD patients. The abundance of the butyrate-producing genera *Faecalibacterium, Roseburia, Gemmiger, Coprococcus,* and *Butyricicoccus* decreased significantly, while the abundance of the lactate-producing genus *Bifidobacterium* and propionate-producing genus *Akkermansia* increased. In addition, other genera such as *Clostridium, Dialister,* and *Romboutsia* were found to be decreased in AD patients.

Later, Jeong et al. (2022) identified differentially enriched gut microorganisms and their metabolic pathways in AD patients with dementia compared to MCI subjects. They found significantly increased abundance of Bacillota, but decreased abundance of Bacteroidota at the phylum level in AD compared to controls. In AD patients, cognitive function scores were negatively associated with abundance of the genera *Blautia*, *Anaerotruncus,* and *Gordonibacter*. Hung et al. (2022), in a systematic review, reported that patients with AD showed significantly reduced gut microbiome diversity compared to controls. Based on 11 studies reviewed, the authors concluded that differences in the microbial spectrum of AD were found depending on the geographical area, and the most abundant microorganisms belonged to members of the phylum Pseudomonadota, and the genera *Bifidobacterium* and *Phascolarctobacterium*. In contrast, lower abundance was reported for members of the Bacillota phylum, and the *Clostridiaceae, Lachnospiraceae,* and *Rikenellaceae* families. More recently, Heravi et al. (2023) reported that several studies performed in AD patients showed an altered gut microbiome characterized by the abundance of members of the phyla Acidobacteriota, Actinomycetota, and Bacteriodota, as well as the family *Ruminococcaceae* and the genus *Bacteroides*.

However, some studies have shown conflicting results with no changes in the gut microbiota of AD patients compared to that of controls. For example, Cirstea et al. (2022) reported that the gut microbiota of AD patients was not different from controls, although it showed lower diversity. In addition, other studies have reported that members of the phylum Bacteroidota were present at higher levels in normal controls with Aβ-positive plasma (Sheng et al., 2022) and in AD patients (Haran et al., 2019; Vogt et al., 2017; Zhuang et al., 2018). Hung et al. (2022) and Jemimah et al. (2023) reported that the abundance of *Alistipes* and *Bacteroides* in AD patients was differentially affected by geographic conditions, depending on the diet and lifestyle.

Several clinical studies have focused on the possible relationship between specific gut microbial populations and clinical biomarkers of AD and pathology progression. For instance, Cattaneo et al. (2017) found a possible positive relationship between *Escherichia/Shigella* levels and peripheral inflammation and brain amyloidosis biomarkers. Vogt et al. (2017) obtained correlations between the abundance of certain genera and CSF biomarkers of AD, including Aβ 42/Aβ 40, phosphorylated tau (p-tau), p-tau/Aβ ratio, and chitinase-3-like protein 1. They found a positive correlation between *Blautia* and *Bacteroides* levels and p-tau and p-tau/Aβ42 ratios. Sheng et al. (2022) found a negative correlation between plasma Aβ42 and Aβ42/Aβ40 biomarkers and the levels of the *Desulfovibrionaceae* family, and the genera *Bilophila* and *Faecalibacterium*, suggesting that higher levels of these microbial populations may be associated with lower Aβ brain deposition. Postmortem brain tissue from patients with AD showed that LPS and *E. coli* colocalized with amyloid plaques. Thus, the amyloid pathogenesis of AD would be triggered during MCI by a shift in the gut microbiota (Li et al., 2019).

Various studies have compared the differences in gut microbial profiles between MCI and AD to address whether there is a relationship between these profiles and disease progression. In a clinical study conducted in the United States, Haran et al. (2019) concluded that the composition of the gut microbiome differed depending on the type of dementia. In patients with AD, the genera *Bacteroides, Alistipes, Odoribacter,* and *Barnesiella* increased, and the genus *Lachnoclostridium* decreased. However, in other types of dementia, the authors found increased abundance of *Odoribacter* and *Barnesiella*, and decreased abundance of *Lachnoclostridium, Eubacterium, Roseburia*, and *Collinsella*. Furthermore, Liu et al. (2019) reported that the fecal microbial diversity was decreased in AD patients compared to MCI and control groups. In addition, the microbial composition was different among the three groups. The families *Clostridiaceae* and *Lachnospiraceae* were significantly decreased in AD and MCI groups compared to control, while *Ruminococcaceae, Blautia*, and *Ruminococcus* were decreased in the AD compared to MCI. Members of the family *Enterobacteriaceae* showed a progressive increase from control to AD patients, while this increase was found in MCI vs. control for the family *Veillonellaceae*. Li et al. (2019) found that patients with AD and MCI had decreased microbial diversity, although no difference in microbial communities was found between AD and MCI patients. The authors identified differences between AD and healthy controls in 11 genera from feces and blood, with increases in the genera *Dorea, Lactobacillus, Streptococcus, Bifidobacterium, Blautia,* and *Escherichia*, and decreases in the genera *Alistipes, Bacteroides, Parabacteroides, Sutterella,* and *Paraprevotella*.

Other studies have been conducted to determine the relationship between the differences in gut microbiome profiles and the severity of the disease (Guo et al., 2021; Yıldırım et al., 2022), the presence of neuropsychiatric symptoms (Zhou et al., 2021), or the higher odds of positive amyloid and p-tau status (Verhaar et al., 2022). Interestingly, Guo et al. (2021), comparing the fecal samples from AD and MCI patients and healthy controls, found no difference in the microbial α-diversity among the three groups, although patients with AD or MCI had increased β-diversity. Patients with AD had decreased *Bacteroides*, *Lachnospira* and *Ruminiclostridium*, and increased *Prevotella* compared to healthy controls. Similar changes of these genera were found in MCI patients compared to AD patients. However, *Lachnospira* was the only genus whose abundance was statistically significantly lower in patients with MCI than in healthy controls, and the negative correlation of *Prevotella* with cognitive function remained in patients with MCI. Yıldırım et al. (2022) concluded that patients with AD or MCI have an intestinal dysbiosis consisting of a decrease in protective bacteria, such as *Bacteroides*, and of an increase in pro-inflammatory bacterial genera, such as *Prevotella*. Members of the genera *Roseburia, Lactobacillus, Fusicatenibacter,* and *Faecalibacterium* were underrepresented, while the genera *Escherichia/Shigella* and *Akkermansia* were overrepresented in AD samples. Verhaar et al. (2022) compared patients with AD, MCI, and SCD to find differences in their gut microbiomes; only two genera, *Subdoligranulum* and *Phascolarctobacterium*, had different abundances between groups, but no differences in α- and β-diversity were found. The authors reported that the highest ranked predictors of amyloid and p-tau status belonged to the *Lachnospiraceae* family, including *Roseburia, Ruminococcus, Lachnoclostridium, Monoglobus,* and *Marvinbryantia*. In contrast, higher abundance of *Odoribacter* and *Alistipes* correlated with

more normal levels of AD biomarkers (higher amyloid and lower p-tau CSF levels). In addition, the highest predictors of the amyloid in all subjects included *Eubacterium*, *Subdoligranulum,* and *Anaerostipes*; whereas, the predictors of p-tau included members of *Lachnospiraceae*, *Lachnoclostridium,* and *Blautia*. Wanapaisan et al. (2022) found that there were no significant differences in α- and β-diversity among MCI, AD and control groups in Thai subjects. Regarding the difference in the bacterial abundance between MCI and AD patients, the members of *Lachnospiraceae* and of the genus *Clostridium* were lower compared to the control group. Besides, AD patients showed a higher abundance of *Escherichia/Shigella, Bacteroides, Holdemanella, Romboutsia,* and *Megamonas*, while MCI patients showed an increase in the abundance of *Fusicatenibacter, Agathobacter,* and *Faecalibacterium*. The authors suggested that the decrease in *Clostridium*, *Agathobacter,* and *Faecalibacterium* in AD patients may be positively correlated with the brain volume of the hippocampus and amygdala, which is the first sign of cognitive decline in the elderly (Zanchi et al., 2017). Table 2 lists several studies conducted in AD patients that reported an altered gut microbiome.

3.3.3. Parkinson's disease (PD)

PD is the most common movement disorder characterized by postural instability, gait disturbance, muscle rigidity, bradykinesia, and resting tremor (Hirayama and Ohno, 2021). The hallmark of PD is the aggregation of the presynaptic neuronal protein α-synuclein, which spreads progressively from the ENS to the CNS via the vagus nerve. There is epidemiologic evidence that PD initially begins in the gut and not in the brain, strongly suggesting a role for the vagus nerve in the pathogenesis of PD (Liu et al., 2017; Svensson et al., 2015). In the CNS, α-synuclein aggregates that form Lewy bodies are associated with the presence of dopaminergic neuron loss in the substantia nigra (Lücking and Brice, 2000; Molinero et al., 2023). Irwin et al. (2013) suggested that PD shares similar pathological changes with AD, such as neurofibrillary tangles, Aβ plaques, and tau propagation, which may accelerate the process of cognitive decline in PD. Several disease genes and risk factors have been proposed as modulators of immune function in PD, such as the viral, bacterial, or pesticides exposure. Tansey et al. (2022) hypothesized that gene-environment interactions, combined with an aging immune system, enable the development and progression of PD.

Although several studies have suggested that dysbiosis of the gut microbiome plays an important role in the pathogenesis of more than 80 % of PD patients (Keshavarzian et al., 2015; Molinero et al., 2023; Qian et al., 2018; Scheperjans et al., 2015), the alteration of the fecal microbiota in PD with cognitive impairment has been poorly studied. Gerhardt and Mohajeri (2018) reviewed several studies on neurodegenerative diseases, including PD, and concluded that studies reported an increased abundance of members of the families *Verrumicrobiaceae* and *Ruminococcaceae,* and of the genera *Lactobacillus, Bifidobacterium, Akkermansia, Christensenella,* and *Oscillospira* in PD patients. In contrast, these authors reported a decreased abundance in the families *Prevotellaceae* and *Lachnospiraceae,* and in the genera *Faecalibacterium, Coprococcus, Blautia, Prevotella, Clostridium,* and *Eubacterium*.

Ren et al. (2020) compared the gut microbiota of Chinese PD patients with mild cognitive impairment (PD-MCI), PD patients with normal cognition (PD-NC), and healthy controls. Fecal microbial diversity was increased in patients with PD-MCI and PD-NC compared to controls, and the PD-MCI group had a higher abundance of members of the families *Rikenellaceae* and *Ruminococcaceae,* and members of the genera *Alistipes, Anaerotruncus, Barnesiella, Butyricimonas,* and *Odoribacter*. Moreover, the abundance of the genera *Blautia* and *Ruminococcus* decreased in the PD-MCI group compared to the PD-NC group. Gut microbiota and metabolome changes in Italian PD patients were investigated by Vascellari et al. (2020). The most significant changes within the PD group were a reduction in bacterial taxa, particularly in the families *Lachnospiraceae, Bacteroidaceae, Brevibacteriaceae,* and *Sphingobacteriaceae,* and in the genera *Butyrivibrio, Pseudobutyrivibrio, Coprococcus*, *Blautia*, *Roseburia, Brevibacterium, Bacteroides, Lachnospira, Dolichospermum,* and *Odoribacter*, some of which are producers of SCFAs. In contrast, PD patients had increased abundance of members of the families *Verrumicrobiaceae, Bifidobacteriaceae, Streptococcaceae,* and *Desulfohalobiaceae*, and of the genera *Akkermansia, Escherichia, Bifidobacterium, Streptococcus, Clostridium, Serratia, Veillonella, Prosthecobacter, Enterobacter,* and *Slackia*.

Interestingly, Wallen et al. (2020) identified three clusters of microorganisms associated with PD. Cluster 1 consisted of opportunistic pathogens, all of which were increased in PD; cluster 2 included SCFA-producing bacteria, all of which were decreased in PD; and cluster 3 consisted of carbohydrate-metabolizing probiotics, all of which were increased in PD. At the genus level, they found that *Porphyromonas, Prevotella, Corynebacterium, Bifidobacterium,* and *Lactobacillus* had higher abundance in PD than in controls, while the genera with lower abundance were *Faecalibacterium, Agathobacter, Blautia, Roseburia, Fusicatenibacter, Lachnospira, Butyricicoccus,* and *Oscillospira*. Hirayama and Ohno (2021), in a meta-analysis of PD patients from 5 countries, surprisingly reported that the *Lactobacillaceae* and *Akkermansiaceae* families were dominant in the gut microbiome of PD patients, with *Akkermansia* and *Christensenella* (formerly *Catabacter*) being the predominant genera. In contrast, members of the genera *Roseburia* and *Faecalibacterium*, and the family *Lachnospiraceae*, decreased in PD patients. The decrease in SCFA-producing bacteria and the increase in mucin-degrading bacteria observed in PD suggest that the dysbiosis should increase intestinal permeability, subsequently facilitating exposure of the intestinal neural plexus to toxins such as LPS, which should lead to abnormal aggregation of α-synuclein fibrils. Heravi et al. (2023) reported in a systematic review that the phyla Bacteroidota, Bacillota and Pseudomonadota were the most abundant in the gut microbiome in PD studies. The microbial dysbiosis in PD patients was characterized by a high abundance of members of the families *Verrucomicrobiaceae*, *Lachnospiraceae* and *Ruminococcaceae,* and species of the genera *Akkermansia* and *Bifidobacterium*. Table 2 includes several studies conducted in PD patients that reported an altered gut microbiome.

3.3.4. Other neurodegenerative diseases

Multiple sclerosis (MS) is an autoinmune demyelinating neurodegenerative disease in which aging may play an important role within disease progression due to dysregulation of the adaptive and innate immune systems (Cekanaviciute et al., 2018; Dobson and Giovannoni, 2019). The majority of MS patients develop a relapsing-remitting form of the disease (RRMS), while a smaller proportion of them present a primary progressive form of the disease (PPMS) (Lassmann, 2019). During the course of the disease, many RRMS patients advance to a secondary progressive MS course (SPMS), and aging is one of the greatest risk factors for developing SPMS, adding its associated greater disability and loss of quality of life (Lassmann, 2019). Therefore, it is important to know whether host-microbiome interactions are involved in this aging transition. Chen et al. (2016) reported that MS patients had a distinct microbial profile compared to healthy controls, characterized by increased abundance of the genera *Pseudomonas*, *Mycoplana*, *Haemophilus*, *Blautia,* and *Dorea* in MS patients, whereas the control group showed increased abundance of the genera *Parabacteroides*, *Adlercreutzia,* and *Prevotella*. However, Jangi et al. (2016) found that microbiome changes in MS included increases in the archaea *Methanobrevibacter* and the bacterial genus *Akkermansia,* and decreases in the genus *Butyricimonas*. In addition, treated patients showed increases in the genera *Prevotella* and *Sutterella*, and decreases in the genus *Sarcina*. Patients diagnosed with SPMS showed microbial ß-diversity with increased abundance of *Akkermansia* spp., *Clostridium bolteae* and *Ruthenibacterium lactatiformans*, and decreased abundance of *Blautia wexlerae*, *Dorea formicigenerans,* and members of the family *Erysipelotrichaceae* (Cox et al., 2021). On the contrary, Mirza et al. (2020) conducted a systematic review and concluded that the diversity of the gut microbiota did not differ between MS cases and controls in the majority of studies analyzed, and only two studies reported lower relative

Table 3
Treatments used in human elderly.

Intervention	Components	Outcomes	Reference
Antimicrobials	Rifaximin	Improves working memory and inhibitory control in CI patients.	Ahluwalia et al. (2014)
	Rifaximin	Reduces serum neurofilament-light levels. Does not improve cognition in AD patients.	Suhocki et al. (2022)
Probiotics	*Lactobacillus casei, L. acidophilus, L. fermentum,* and *Bifidobacterium bifidum*	Improves insulin sensitivity and cognitive scores, and reduces CRP levels.	Akbari et al. (2016)
	Several species and strains of *Lactobacillus* and *Bifidobacterium*	No beneficial effects on cognition in AD patients.	Agahi et al. (2018)
	L. casei, L. acidophilus, L. lactis, L. paracasei, L. plantarum, L. salivarius, B. bifidum, and *B. lactis*	No beneficial effects on cognition in AD patients.	Leblhuber et al. (2018)
	L. helveticus	Improves attention and delayed memory in healthy aged adults.	Ohsawa et al. (2018)
	B. longum subsp. *longum, B. longum* subsp. *infantis,* and *B. breve*	Improves mental status, body weight and bowel movement in healthy elderly subjects.	Inoue et al. (2018)
	L. acidophilus, B. bifidum, and *B. longum* + selenium	Improves cognitive function and reduces inflammation and oxidative stress in AD patients.	Tamtaji et al. (2019)
	B. breve	Improves cognitive function in severe MCI subjects.	Kobayashi et al. (2019)
	L. plantarum	Improves attention cognitive scores in MCI subjects.	Hwang et al. (2019)
	L. rhamnosus	Improves cognitive composite score in MCI individuals.	Sanborn et al. (2020)
	B. breve	Improves memory function in subjects with MCI.	Xiao et al. (2020)
	B. bifidum and *B. longum*	Improves cognitive and mental health, and alters microbial gut microbiome composition in healthy adults.	Kim et al. (2021)
	Faecalibacterium prausnitzii	Improves cognitive scores in MCI subjects.	Ueda et al. (2021)
	L. plantarum	Improves motor skills and quality of life in PD patients.	Lu et al. (2021a, 2021b)
	L. rhamnosus	Improves cognitive score in MCI adults.	Aljumaah et al. (2022)
	L. plantarum, L. rhamnosus, L. casei, L. johnsonii, L. paracasei, L. fermentum, L. salivarius, L. acidophilus, L. reuteri, B. lactis, B. animalis, B. infantis, and *Lactococcus lactis*	Improves cognitive function and sleep quality.	Fei et al. (2023)
	B. longum	Improves cognitive function.	Shi et al. (2023)
Prebiotics	Galactooligosaccharides mixture	Improves immune function.	Vulevic et al. (2015)
	Fructooligosaccharides and inulin	Improves exhaustion and handgrip strength. No effect on cognitive behavior or sleep quality.	Buigues et al. (2016)
	Fructooligosaccharides and inulin	Reduces frailty indexes.	Theou et al. (2019)
Synbiotics	Fructooligosaccharides + *B. lactis, L. rhamnosus, L. acidophilus,* and *L. paracasei*	Improves cognition in healthy elderly.	Louzada and Ribeiro (2020)
	Kefir + fermented milk	Improves cognitive deficits in AD patients.	Ton et al. (2020)
	Fructooligosaccharides, inulin and vegetable magnesium stearate + *L. plantarum, L. acidophilus* and *L. reuteri*	Anti-inflammatory effects (reduction in CRP and TFN-α levels).	Cicero et al. (2021)
Postbiotics	Propionic acid	Increases immunoregulatory T cells and reduces brain atrophy.	Duscha et al. (2020)
	Propionic acid	Increases odds of cognitive decline.	Neuffer et al. (2022)
	Heat-inactivated *Lactiplantibacillus plantarum*	Protective effects on memory function in older adults.	Sakurai et al. (2022)
	Bacteriophages	Improves executive function and memory.	Mayneris-Perxachs et al. (2022)

Alzheimer's disease (AD); Cognitive impairment (CI); Mild Cognitive Impairment (MCI); Parkinson's disease (PD); C reactive protein (CRP); Tumor factor necrosis (TFN).

abundance of *Prevotella* spp., *Faecalibacterium prausnitzii*, *Bacteroides coprophilus* and *B. fragilis*, and higher abundance of *Methanobrevibacter* spp. and *Akkermansia muciniphila* in MS patients compared to controls. Therefore, it could be speculated that some microbial species may be protective against MS progression, although further research is needed to verify this hypothesis; in addition, there is no evidence to support the relationship between the age-related changes in the gut microbiome and the MS disease progression.

Post-stroke cognitive impairment (PSCI) is a serious condition that leads to disability after an acute ischemic stroke, which in turn can induce to a state of dementia (Rost et al., 2022). In fact, stroke is increasingly recognized as an important cause of cognitive problems and has been implicated in the development of both AD and vascular dementia in the elderly (Lo Coco et al., 2016). However, the association of PSCI with the gut microbiome has been poorer studied. Singh et al. (2016) found that reduced species diversity and bacterial overgrowth of Bacteriodota members were identified as hallmarks of post-stroke dysbiosis, which was associated with intestinal barrier dysfunction and reduced intestinal motility. Later, Liu et al. (2020b) reported that PSCI patients were characterized by significantly decreased α-diversity, disturbed microbial composition, and corresponding metabolites compared to non-PSCI patients. Increased genera were *Fusobacterium, Bacteroides, Clostridum, Gemella,* and *Flavinofractor*, and decreased abundance of SCFA-producing genera such as *Oscillibacter, Ruminococcus, Gemmiger, Barnesiella,* and *Coprococcus.* Furthermore, patients with post-stroke comorbid cognitive impairment and depression (PSCCID) had increased abundance of members of the phylum Pseudomonadota, particularly members of the family *Enterobacteriaceae*, and decreased abundance of several SCFA-producing bacteria compared to controls (Ling et al., 2020). Zheng et al. (2022) found a high prevalence of gastrointestinal dysfunction and intestinal inflammation with increased gut permeability in cryptogenic stroke (CS) patients compared

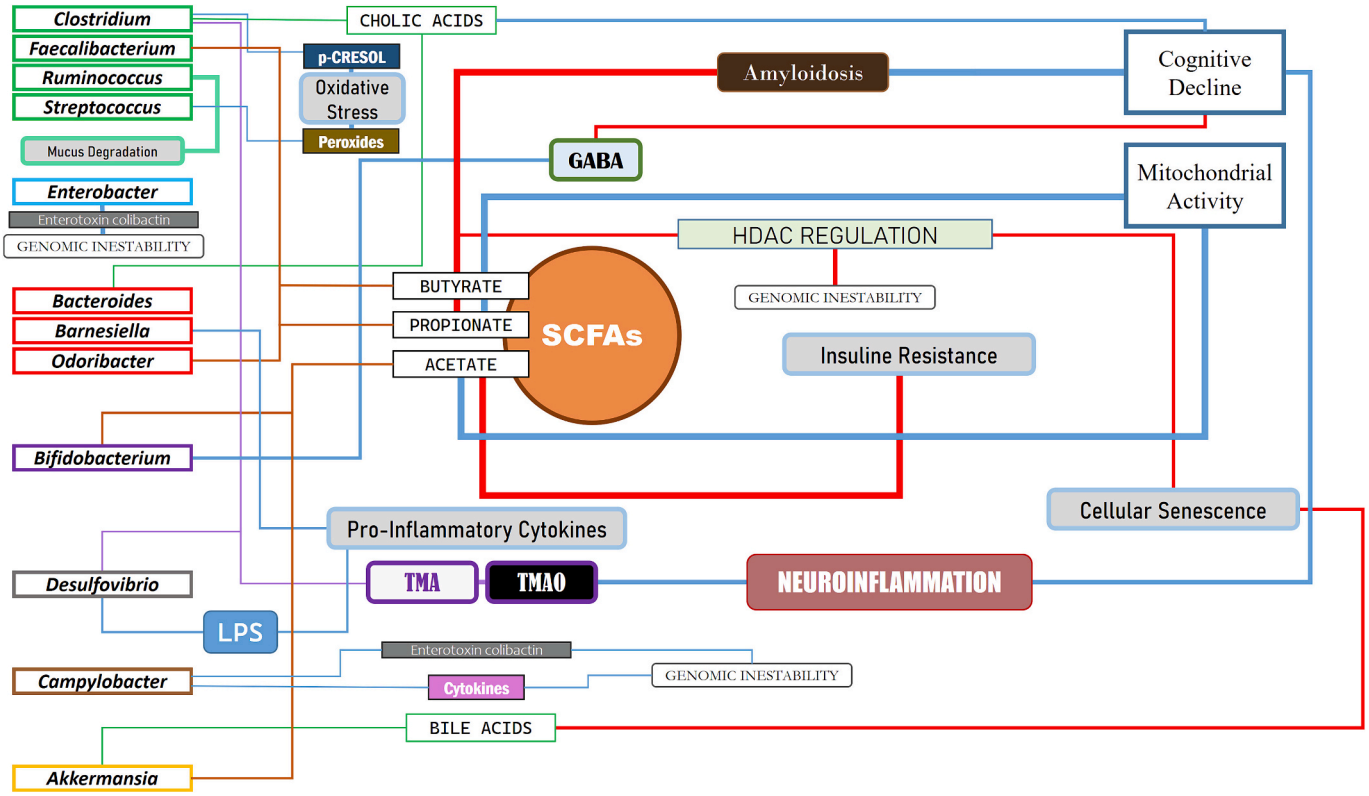


Fig. 1. Relationship between different microbial metabolites and several aged-associated manifestations (according to Ghosh et al., 2020a, 2022; Margiotta et al., 2021; Soysal et al., 2016). Blue lines: positive regulation. Red lines: negative regulation. SCFAs: short-chain fatty acids. GABA: gamma-aminobutyric acid. HDAC: histone deacetylase. LPS: lipopolysaccharide. TMA: trimethylamine. TMAO: trimethylamine N-oxide.

to normal controls. The α-diversity index was significantly higher in CS patients. At the family level, a significantly higher abundance of *Enterobacteriaceae*, *Streptococcaceae* and *Lactobacillaceae*, and a lower abundance of *Veillonellaceae*, were observed in the CS group. At the genus level, there was an increased abundance of *Escherichia/Shigella, Streptococcus, Lactobacillus,* and *Klebsiella* in the CS group, and a decrease in *Faecalibacterium, Dialister,* and *Roseburia.*

Delirium is the most common acute neuropsychiatric complication in hospitalized older adults (Inouye et al., 2014) and is characterized by inattention, disorganized thinking, and altered level of consciousness (Marcantonio, 2017). Curiously, delirium and gut dysbiosis share several characteristics, such as high prevalence in older adults and association with multifactorial conditions, and they are influenced by inflammation, neuroendocrine dysregulation, and oxidative stress (DeJong et al., 2020). Studies in intensive care unit patients have shown that the gut microbiome can be altered during acute illness (Ojima et al., 2016), with lower abundance and diversity of microorganisms (Garcez et al., 2023). In addition, higher inflammatory biomarkers are associated with delirium and gut dysbiosis (DeJong et al., 2020; McNeil et al., 2019), as certain gut bacteria can produce pro-inflammatory cytokines, while other taxa (e.g., *Lactobacillus acidophilus* and *Bifidobacterium breve*) exert anti-inflammatory effects (Thevaranjan et al., 2017). Garcez et al. (2023), investigating the association between gut microbiota and delirium occurrence in acutely ill older adults, found that a higher abundance and richness of microorganisms (α-diversity) was associated with a lower risk of delirium, while bacterial taxa (such as *Enterobacteriaceae*) associated with pro-inflammatory pathways, and increased IL-6 and IL-10, were related with delirium (Garcez et al., 2023; Menezes-Garcia et al., 2020). The enrichment of *Enterococcus* was associated with higher levels of these cytokines, while the archaea *Methanobrevibacter* was associated with lower levels of IL-10. Although IL-10 is thought to be anti-inflammatory, there is evidence for a dual role of this cytokine, with a modulatory effect beginning early in the acute phase response, which explains the elevation of both IL-6 and IL-10 in the delirium group (Saraiva and O'Garra, 2010; Saraiva et al., 2020). Other pathophysiological mechanisms may contribute to this relationship; for example, some bacterial strains can modulate the production of neurotransmitters involved in the onset of delirium (Fond et al., 2015). Strains from the genus *Serratia* have the capability of producing dopamine, while *Bacteroides* and *Parabacteroides* have been associated with GABA modulation (Strandwitz et al., 2019). Thus, the relationship between delirium and gut microbiota is bidirectional: on the one hand, precipitating factors (e.g., infection or metabolic dysfunction) and those related to the pathophysiology of the delirium (e.g., inflammatory biomarkers or neuroendocrine dysregulation) are potential microbiota modifiers. On the other hand, gut bacteria may modulate the onset of delirium by producing cytokines and neurotransmitters.

3.4. *Bacterial metabolomes and neurodegenerative diseases*

Gut bacteria could influence the CNS by secreting specific metabolites that are transported by the adrenal gland or the vagus nerve and cross the BBB, affecting brain cell behavior directly or indirectly by promoting epigenetic changes in chromatin (de Vos et al., 2022; Liu et al., 2020b; Narengaowa et al., 2021; Varesi et al., 2022). In addition, various functional changes induced by microbial metabolites have been reported to be associated with cognitive impairment states (Connell et al., 2022; Duan et al., 2021; Liu et al., 2019; Vogt et al., 2017). Ling et al. (2021) described an increase in functions related to fatty acid and lipoic acid metabolism and folate biosynthesis in AD-associated microbiota, and a decrease in pathways related to bacterial fatty acid biosynthesis. Moreover, it has been reported that gut bacteria from elderly people without dementia present an increase in butyrate-encoding genes involved in butyrate biosynthetic pathways, while

these genes were absent in AD patients (Haran et al., 2019). Wu et al. (2021a) reported several gut metabolomic profiles that distinguished AD and MCI patients from healthy subjects, and found that differences in tryptophan metabolites, SCFAs, and LCA profiles correlated with the microbiome dysbiosis and with the degree of cognitive impairment. Differences in other fecal metabolites, such as organic acids, lipids, benzenoids and piperidine, have been suggested to differentiate AD patients from normal controls (Xi et al., 2021).

SCFAs play important roles in gut microbiome health, such as an energy source for the colonic epithelial cells, as elements that maintain tight junctions to regulate intestinal permeability, as preventive agents in relation to the endotoxin translocation, and they as well have a potential anti-inflammatory effect (Louis and Flint, 2017; Makki et al., 2018; Peng et al., 2009; Vinolo et al., 2011). As mentioned above, SCFAs and BAs cross the intestinal barrier to reach the systemic circulation, and can also cross the BBB to modulate key functions in host health (Monteiro-Cardoso et al., 2021; Mulak, 2021; Silva et al., 2020). Systemic inflammatory responses caused by compounds secreted by bacteria or bacterial structures (LPS) can expand the BBB, by activating the TLR4/IRF-3 signaling pathway in endothelial cells in blood vessels, disrupting the intestinal epithelial barrier (Choi et al., 2012), and promoting CNS inflammation by activating the LPS/TLR4 pathway in brain glial cells (Stehle Jr et al., 2012; Ghosh et al., 2015).

Some of these metabolites are altered in several neurodegenerative diseases: acetate, valerate, and higher serum levels of LPS, have been associated with amyloid deposition in the brain, as well as with pro-inflammatory cytokines in AD patients (Marizzoni et al., 2020); while butyrate, which affects serotonin release and gut hormone release in the enteric nervous system (ENS), can stimulate the vagus nerve and trigger endocrine signaling that affects brain function (Stilling et al., 2016). In addition, AD and cognitive decline have been associated with increased levels of secondary BAs such as DCA, and with decreased serum concentrations of primary BAs such as cholic acid (CA) (MahmoudianDehkordi et al., 2019; Varma et al., 2021). Furthermore, Baloni et al. (2020) reported altered synthesis and metabolism of primary and secondary BAs in postmortem brain samples from AD patients, with higher levels of primary BAs such as taurocholic acid (TCA), and secondary BAs such as DCA, LCA, taurodeoxycholic acid (TDCA), and glycodeoxycholic acid (GDCA), suggesting that these BAs may be associated with cognitive function.

Gut microbiome dysbiosis also alters tryptophan metabolism, resulting in a shift in the balance of the kynurenine pathway (KP), which appears to play a critical role in AD pathology by leading to neuroinflammation (Garcez et al., 2019). Gut bacteria can modulate the circulating concentration of tryptophan, which is mainly metabolized by the KP to produce the neuroprotective kynurenic acid (KYN), the antioxidant 3-hydroxyanthranilic acid (3-HAA), and neurotoxic metabolites such as 3-hydroxykynurenine (3−HK) and quinolinic acid (QUIN) (Garcez et al., 2019; Schwarz et al., 2013). The association between KP and AD includes: (i) decreased tryptophan and 3-HAA concentrations in AD plasma; (ii) increased KYN/tryptophan ratio and 3-HK in serum of AD patients; and (iii) accumulated QUIN in the hippocampus of AD patients (Giil et al., 2017; Guillemin et al., 2003).

Trimethylamine N-oxide (TMAO) has been found at elevated levels in patients with CSF, MCI, PSCI and AD, and can therefore be considered a biomarker of neuronal degeneration (Vogt et al., 2018; Zhu et al., 2020). TMAO, together with LPS, promotes increased permeability of the intestinal barrier and loss of its integrity because of the release of inflammatory cytokines and the unbalanced inflammatory response (Liu et al., 2020a). This enteric inflammation may facilitate the translocation of pathogenic gut bacteria, their dissemination into the CNS, and the passage of pro-inflammatory bacterial neurotoxins, resulting in detrimental effects on neuronal homeostatic function, neuroinflammation, and ultimately the neurodegeneration associated with AD (Emery et al., 2017; Liu et al., 2020a; Rutsch et al., 2020). A novel choroid plexus vascular barrier (PVB) has been described in response to gut inflammation induced by bacterial LPS, suggesting that PVB may be related to mental disorders (Carloni et al., 2021). Additionally, extra-intestinal microbial pathologies have been associated with gut microbiota dysbiosis causing leakage of the gut vascular barrier (GVB), leading to systemic dissemination of microorganisms or microbial-derived molecules to other distant organs (Brescia and Rescigno, 2021).

Higher levels of other gut microbiome metabolites, such as ammonia, formic acid, lactic acid, phenol, and p-cresol, have also been suggested to be associated with the presence of dementia disease, independently of other risk factors for the disease or of the dysregulation of the gut microbiome (Saji et al., 2020).

3.5. Gut microbiome and age-dependent epigenetics changes

In addition to the nuclear chromosome genome, humans possess the mitochondrial and the genome of at least thousands of microorganisms present in various human microbiomes. Epigenetic modifications occur in the human nuclear chromosomes, although methylation can also occur in mitochondrial and microbial DNA (Cheung et al., 2018; Kho and Lal, 2018). Mitochondrial DNA methylation may regulate some functions and may be altered in some cortical neurons with aging, and in some neurodegenerative diseases (Dzitoyeva et al., 2012; Iacobazzi et al., 2013; Sharma et al., 2019).

A number of prominent features, including genetic and epigenetic changes, have emerged during aging. The major age-associated epigenetic changes are derived from DNA methylation, histone modification, chromatin remodeling, non-coding RNA (ncRNA) regulation, and RNA modification (Wang et al., 2022). DNA hypomethylation is associated with aging, but hypermethylation also occurs at selective cytosine-phosphate-guanine (CpG) islands to form 5-methylcytosine (5-mC) (Sailani et al., 2019; Wang et al., 2022), and the levels of CpG methylation are reliable age estimators, called epigenetic clocks, for predicting chronological age (Horvath and Raj, 2018). The second-generation clocks are denominated PhenoAge and GrimAge; the first introduced morbidity and mortality into the model predicting 10- and 20-year old mortality (Levine et al., 2018), and the second is a more predictive element for identifying clinical phenotypes (McCrory et al., 2021). Notably, a recent study constructed a single-cell age clock (scAge) that indicates epigenetic age using single-cell methylation data (Trapp et al., 2021).

DNA methylation is mediated by DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) and their expressions are age-dependent; the expression of DNMT1 decreases with age, resulting in a reduced DNA methylation levels, whereas the expressions of DNMT3A and DNMT3B increase with age and they contribute to de novo methylation of CpG islands in mammalian cells (Yagi et al., 2020). However, DNA methylation at the promoter of a gene can lead to its silencing. In contrast, the methyl group on DNA is removed by ten-eleven translocation (TET) enzymes (Verma et al., 2018). In clinical research, mutations in TET2 or DNMT3A increase the expression of pro-inflammatory cytokines and chronic inflammation in elderly patients, which is associated with conventional cardiovascular disease (Bick et al., 2020).

Post-translational modifications of histones can activate or silence gene expression. The most common modifications found during aging include methylation and acetylation, although phosphorylation, ubiquitination, and ADP ribosylation have also been reported (Wang et al., 2022). In vivo and in vitro studies have reported changes in the levels of H3K9me3 (tri-methylation at the 9th lysine residue of the histone H3 protein subunit), H4K20me3 (tri-methylation at the 20th lysine residue of the histone H4 protein subunit), H3K27me3 (tri-methylation at the 27th lysine residue of the histone H3 protein subunit) (Sidler et al., 2017), and H3K9ac (acetylation at the 9th lysine residue of the histone H3 protein subunit) during aging that show a direct association with longevity (Wang et al., 2022). H3K4me3 (tri-methylation at the 4th lysine residue of the histone H4 protein subunit) plays an important role in determining aging and lifespan by regulating the expression of aging-

related genes, H3K27me3 is associated with gene silencing and compacted heterochromatin, and H3K36me3 (tri-methylation at the 36th lysine residue of the histone H3 protein subunit) and H3K9me3 are associated with a shorter lifespan (Sidler et al., 2017). In addition, RNA modifications and ncRNA regulation have been proposed to be involved in the regulation of aging (Li et al., 2017a).

Bacteria can also influence the epigenetic marks associated with host DNA methylation. Indeed, *Helicobacter pylori* infection promotes DNA methylation in the gastric mucosa, and *Escherichia coli* (uropathogenic UPEC strains) can induce DNA methylation in eukaryotic cells (Muhammad et al., 2019; Russell et al., 2023). Besides, the interaction of bacterial metabolites with human cells can also alter DNA methylation and induce some neurological disorders (Alam et al., 2017; Bulgart et al., 2020; Miro-Blanch and Yanes, 2019). With respect to brain cells, some of the aforementioned age-related changes in DNA methylation have been associated with the risk of various neurological diseases such as AD (Condliffe et al., 2014). A preclinical study, using a mouse model of AD, reported the existence of some punctual changes in DNA methylation (differentially methylated regions or DMRs) associated with specific brain regions (Kundu et al., 2021). Similarly, they reported that 21 gut bacteria significantly predicted some of these DMRs, as well as some behavioral outcomes in mice. The most relevant DMRs were apolipoprotein E, which is associated with the *Muribaculaceae* family, and apolipoprotein C2, which is associated with the *Lachnospiraceae* family. In addition, other DMRs were linked with other AD-associated genes, such as ceramide kinase-like (*Cerkl*) and glucagon-like peptide-2 receptor (*GLp2r*), which have relevant roles in neurite function and spatial cognition, all of which are impaired with aging. These DMRs were positively associated with *Lachnoclostridium* and negatively associated with *Muribaculaceae*, respectively. Interestingly, the results revealed correlations between the presence of the gut microbial family *Lachnospiraceae* and epigenetic changes associated with the hippocampal epigenetic landscape. Xie et al. (2022) found that decreased abundance of bacterial butyrate producers, such as *Roseburia*, *Romboutsia,* and *Prevotella*, was associated with epigenetic changes in leukocytes and neurons from PD patients and with the severity of their depressive symptoms. In short, gut microbiota regulates brain cell activities by modulating DNA methylation and histone modifications, but research on the molecular and signaling pathways underlying this interaction remains limited.

3.6. Microbial therapeutic approaches to improve cognitive functions in elderly

The gut microbiome primarily influences neurological function through the gut-brain axis, by secreting metabolites, limiting pathogens, and maturating the immune system. It provides a route of communication between the SNC and the internal organs, through the nervous system and the production of neuromodulators (Quigley, 2017; Rolhion and Chassaing, 2016). In neurodegenerative diseases, the pathway between gut microbiome dysbiosis and neurodegeneration includes immune activation through a defective gut barrier, induction of a systemic inflammatory response, BBB damage, and neuroinflammation (Konturek et al., 2015).

Although spontaneous reversal of MCI is common, it has never been reported in patients with AD (Fessel, 2023); therefore, there is not a definitive cure for AD, and most of the current drugs approved for clinical use in AD are symptomatic treatments that do not improve the pathological changes of that condition (Li et al., 2023b). However, several preclinical studies have reported success in improving cognition using microbial interventions such as fecal microbiota transplantation (FMT) in the early stages of the disease (Kim et al., 2020; Sun et al., 2019). Several clinical interventions that alter the gut microbiome, such as FMT, probiotics, prebiotics, and antibiotics, as well as lifestyle interventions such as diet and exercise, have been tested to improve the mental health or to reduce the incidence or severity of symptoms of cognitive impairment (Boehme et al., 2023; Hwang et al., 2019; Sorbara and Pamer, 2022) (Table 3).

3.6.1. FMT and antimicrobial treatments

One potential treatment method to restore the composition and function of the dysbiosis of the gut microbiome is the introduction of fecal matter from healthy young subjects into the gastrointestinal tract of elderly people, known as FMT (Alsegiani and Shah, 2022). In addition, the FMT method has been used in clinical trials to treat a variety of pathologies, including functional gastrointestinal disorders, chronic constipation, inflammatory bowel disease, and autoimmune diseases (Choi and Cho, 2016).

Results from clinical trials are limited by small sample sizes, although some have shown that FMT can alleviate symptoms in patients with PD (Kuai et al., 2021; Xue et al., 2020). Furthermore, individual case studies have reported that FMT improved cognitive performance in AD subjects who received FMT to treat *Clostridium difficile* infection (Hazan, 2020; Park et al., 2021, 2022). This evidence suggests that FMT may be a potential treatment to remodel the microbiome-gut-brain axis in patients suffering from age-related neurological diseases. However, the use of FMT is limited due to unknown long-term efficacy and to reported side effects, such as the possibility of transferring bacterial endotoxins and/or infectious agents to the recipient, which could exacerbate the gastrointestinal symptomatology (Alsegiani and Shah, 2022; De Leon et al., 2013; Schwartz et al., 2013). Therefore, the isolation of a defined set of fecal bacteria and their subsequent transplantation into the recipient would be a safer alternative in the FMT method (Buffie et al., 2015).

It has been proposed that antimicrobials with capability to eradicate harmful gut microorganisms may also improve brain health, as some orally administered antimicrobials can escape from the gut and act directly on other organs, including the brain, independently of the microbiota-gut-brain axis. Clinical evidence is largely lacking, but in a pilot study with 10 AD patients it was found that the treatment with rifaximin during 3 months significantly reduced serum neurofilament-light levels, although no improvement in cognition was obtained (Suhocki et al., 2022). Previously, another study that administered rifaximin to patients with cirrhosis and cognitive impairment found that antimicrobial treatment improved working memory and inhibitory control, and enhanced fronto-parietal and subcortical activation and connectivity (Ahluwalia et al., 2014) (Table 3). Nevertheless, antimicrobials are not the best treatment approach for several reasons, including their potential to induce harmful neurotoxic side effects and to deplete symbiotic gut bacteria that may play a beneficial role for the brain during aging. In addition, antimicrobial use has been associated with the onset of delirium in the elderly (Moore and O'Keeffe, 1999), and with a decline in cognitive scores (Mehta et al., 2022). The development of novel antimicrobial strategies, such as the phage therapy, which can specifically eliminate specific pathogenic bacteria, could be valuable in the treatment where specific pathogenic gut microbes are identified.

3.6.2. Probiotics

Probiotics are defined as live microorganisms that provide health benefits to the host (Hill et al., 2014). Several studies have recognized that probiotic modulation of the host microbiome improves cognitive function in aging adults (Eastwood et al., 2021). A large number of randomized and placebo-controlled human trials have shown that probiotics improve cognitive and gastrointestinal symptoms in patients with AD, MCI, and PD, possibly by reducing inflammatory response, by regulating the balance of the gut microbiota (Liu et al., 2022), and by improving lipid metabolism (Xiang et al., 2022).

Supplementation with probiotic milk containing *Lactobacillus acidophilus, L. casei, L. fermentum,* and *Bifidobacterium bifidum* showed improved insulin sensitivity, lower levels of the inflammatory marker CRP, and increased cognitive scores after 12 weeks of supplementation

(Akbari et al., 2016). In contrast, in another Iranian study using a multi-species mixture containing several strains of the genera *Lactobacillus* and *Bifidobacterium* for 12 weeks it was not found a beneficial effect on cognition in patients with severe AD (Agahi et al., 2018). The authors suggested that the stage of the disease and the degree of cognitive impairment may be critical for the efficacy and beneficial outcome of probiotic treatment. Furthermore, another study in a Caucasian population found no benefit on a cognitive score in AD with a multi-species probiotic consisting of *L. acidophilus, L. casei*, *L. lactis*, *L. paracasei, L. plantarum, L. salivarius, B. bifidum,* and *B. lactis* (Leblhuber et al., 2018). The authors reported that probiotic supplementation in AD patients increased the abundance of *F. prausnitzii* and affected the tryptophan metabolism. In addition, supplementation with *L. helveticus*-fermented milk drink for 8 weeks in healthy middle-aged adults improved both attention and delayed memory (Ohsawa et al., 2018). Inoue et al. (2018) showed that supplementation with a probiotic cocktail (*B. longum* subsp. *longum*, *B. longum* subsp. *infantis,* and *B. breve*) and moderate resistance training may improve the mental status, body weight, and bowel movement frequency in healthy elderly subjects.

In a study conducted by Tamtaji et al. (2019), a probiotic mixture (*L. acidophilus, B. bifidum,* and *B. longum*) was combined with selenium to improve AD symptoms. The 12-week intervention improved cognitive function, corrected metabolic dysfunction, and reduced inflammation and oxidative stress. The authors associated this improvement with a significant increase in total antioxidant capacity, and with a decrease in CRP sensitivity in AD patients. Kobayashi et al. (2019) investigated the effects of a strain of *B. breve* on the cognitive function in Japanese older adults, and found that this probiotic induced beneficial effects only in the subpopulation with more severe MCI. In a Korean study, Hwang et al. (2019) supplemented fermented soybean with *L. plantarum* and reported a significantly improvement in attention cognitive scores in MCI subjects. Similar results were obtained by Sanborn et al. (2020) in a Caucasian population, as the use of *L. rhamnosus* showed efficacy in improving a composite cognitive score in elderly subjects with MCI. Den et al. (2020), in a meta-analysis of randomized controlled trials in adults with AD or MCI, reported a significant improvement in cognition with a decrease in the levels of malondialdehyde and of CRP between the probiotic and control groups. Xiao et al. (2020) demonstrated that a strain of *B. breve* was effective in improving memory function in subjects with MCI, showing improvements in various cognitive domains such as immediate, delayed, and visuospatial memory.

Moreover, Kim et al. (2021) found that probiotics (*B. bifidum* and *B. longum*), administered for 12 weeks, improved cognitive and mental health and altered gut microbiota composition in healthy community-dwelling older adults. The authors also reported that probiotic supplementation significantly reduced the abundance of inflammatory microbiota, including *Eubacterium*, *Allisonella,* and *Prevotellaceae*, in healthy older adults. Lv et al. (2021) showed that probiotic supplementation improved cognitive function in human and animal studies, and the effects were greater in cognitively impaired subjects than in healthy subjects. In addition, the authors showed that the duration of less than 12 weeks and the use of a single probiotic strain were more effective in human studies. In a Japanese cohort, Ueda et al. (2021) found that *F. prausnitzii* correlated with cognitive scores and decline in the MCI group compared to the healthy group. Interestingly, the cognitive improvement was also achieved by using inactivated *F. prausnitzii*, suggesting that the postbiotic may also have beneficial effects or may act as immunomodulator. Lu et al. (2021a, 2021b) showed that the supplementation with *L. plantarum* for 12 weeks, along with antiparkinsonian medication, improved motor performance and quality of life in PD patients. The authors suggested that the probiotic could serve as an adjuvant agent in the treatment of PD. Asaoka et al. (2022) investigated the probiotic effect of a *B. breve* strain in improving cognition and preventing brain atrophy in elderly patients with MCI. Probiotic consumption for 24 weeks suppressed the progression of brain atrophy, suggesting that *B. breve* helps to prevent cognitive impairment in MCI subjects. Aljumaah et al. (2022) found that *L. rhamnosus* probiotic supplementation improved cognitive scores in adults with MCI compared to neurologically healthy individuals. They also reported a decrease in the abundance of the genera *Prevotella* and *Dehalobacterium* in response to probiotic supplementation in the MCI group. Fei et al. (2023) investigated the effects of probiotic supplementation on several neural behaviors in older adults with MCI. The probiotic consisted of a cocktail of several strains of *L. plantarum, L. rhamnosus, L. johnsonii, L. paracasei, L. salivarius, L. acidophilus, L. casei, L. reuteri, L. fermentum, B. lactis, B. animalis, B. infantis,* and *Lactococcus lactis*. After 12 weeks of intervention, cognitive function and sleep quality were improved in the probiotic group compared to the control group, and the underlying mechanisms were associated with changes in the gut microbiota. Shi et al. (2023) investigated the effect of *B. longum* on cognitive function in healthy older adults without cognitive impairment. The probiotic significantly improved the cognitive function, particularly in the areas of immediate memory, visuospatial/constructional capacity, attention, and delayed memory. In addition, the bacterial intervention increased the abundance of the beneficial bacteria *Lachnospira, Bifidobacterium, Dorea,* and *Cellulosilyticum*, while decreased the presence of bacteria associated with cognition impairment, such as *Collinsella, Parabacteroides, Tyzzerella, Bilophila*, *Epulopiscium, Porphyromonas,* and *Granulicatella* (Table 3).

Various mechanisms may explain the effects of probiotic supplementation. For example, probiotic supplementation may regulate the relative abundance of the gut microbiome, which plays an important role in maintaining the intestinal barrier. The probiotics may influence the gut microbiome in the production of certain beneficial metabolites and neurotransmitters, such as SCFAs, norepinephrine, 5-hydroxytryptophan, dopamine, noradrenaline, serotonin, GABA, synaptophysin, acetylcholine, and histamine. These beneficial substances, as mentioned above, regulate neuroinflammation and influence the neural behavioral activities of the host (Borodovitsyna et al., 2017; Park et al., 2019; Strandwitz, 2018; Yang, 2019). In addition, probiotic supplementation significantly increased serum levels of brain-derived neurotrophic factor (BDNF) in elderly MCI patients. BDNF plays a key role in neuronal nutrition and protection, in learning, and in memory formation (Fei et al., 2023; Kim et al., 2021). Probiotics have also been used to enhance immune function as measured by improved vaccination responses, reduction of infections, and cardiovascular disease (DeJong et al., 2020; Lei et al., 2017; Wang et al., 2018a).

3.6.3. Prebiotics

Prebiotics are non-digestible and fermented food components that selectively promote the growth and activity of beneficial commensal microbiota (Franco-Robles and López, 2015), as high-fiber diets such as yogurt, fruits, vegetables and grains, and confer health benefit to the host (Gibson et al., 2017). Prebiotic dietary compounds, such as polyphenols, are potent neuroprotectors of brain physiology. These protective effects against neurodegenerative diseases could be attributed to a direct effect on the host response, but also mediated by the conversion of the gut microbiome into bioavailable microbial phenolic metabolites, which, in addition to modulating the growth and activity of SCFA-producing bacteria, also exhibit more protective effects against neuroinflammation than intact polyphenols (Esteban-Fernández et al., 2017; González de Llano et al., 2023).

The role of these dietary compounds in improving brain health in aging is limited. However, Vulevic et al. (2015) analyzed the effect of a galactooligosaccharide mixture on gut microbiota and on immune function in subjects aged 65–80 years, and found a significant increase in *Bacteroides* and Bifidobacteria, and an improvement in immune function (higher IL-10 and IL-8, natural killer cell activity and CRP, and lower IL-1β). There are some evidences showing that a prebiotic mixture containing inulin and fructooligosaccharides may improve frailty, a risk factor for cognitive decline (Kang and Zivkovic, 2021; Long-Smith et al., 2020). In this sense, Buigues et al. (2016) showed that prebiotic

administration (13 weeks) significantly improved two frailty criteria, such as fatigue and handgrip strength, compared to maltodextrin (used as placebo), although no significant effects on cognitive behavior or sleep disturbance were observed. Theou et al. (2019) reported that the prebiotic supplementation for 13 weeks can reduce frailty indices in nursing home residents, particularly in those with higher levels of frailty (Table 3).

3.6.4. Synbiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) updated the definition of a synbiotic to "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that provides a health benefit to the host" (Swanson et al., 2020). Louzada and Ribeiro (2020) used a synbiotic consisting of the combination of the prebiotic fructooligosaccharide with several probiotic bacterial strains (*L. acidophilus, L. paracasei, L. rhamnosus,* and *B. lactis*) to study its effect on the symptoms of brain disorders and inflammation in the elderly. The authors concluded that there were improvement effects on cognition in healthy elderly people. In another studies, synbiotics were shown to increase the bioavailability of microbial antioxidant metabolites, to enhance the activity of antioxidant systems, and to improve cognitive function in patients with AD (Arora et al., 2020; Ton et al., 2020). In contrast, Krüger et al. (2021), who reviewed only three studies involving 161 individuals with AD, concluded that current evidence for the use of probiotics and synbiotics in individuals with dementia is insufficient to support their clinical application. Cicero et al. (2021) applied a randomized treatment with a symbiotic that consisted of *L. plantarum*, *L. acidophilus* and *L. reuteri*, with prebiotics (inulin, fructooligosaccharides and vegetable magnesium stearate), to elderly patients with metabolic syndrome. After 60 days of treatment, an anti-inflammatory effect was observed with a reduction in high-sensitivity CRP and TNF-α levels, indicating a decrease in the prevalence of metabolic syndrome, cardiovascular risks, and insulin resistance in elderly patients. However, Qu et al. (2019) found no statistically significant results regarding inflammatory markers and monocyte chemoattractant protein-1, concluding that the available randomized controlled trials do not suggest a significant benefit of microbiota-directed therapy in reducing the inflammatory responses in the elderly (Table 3).

3.6.5. Postbiotics

Postbiotics include bioactive compounds produced during a microbial process, such as SCFAs, bacterial components, or even inactivated microbial cells (Long-Smith et al., 2020; Malagón-Rojas et al., 2020). Although the exact mechanism of their action is not yet fully understood, their immunomodulatory effects are unquestionable (Akatsu, 2021; Hernández-Granados and Franco-Robles, 2020).

Some preclinical studies have used postbiotics (heat-killed bacteria or SCFAs) as immunoregulators and to improve the neurodegenerative conditions, such as immune system response, modulation of neuroinflammation, and cognitive decline (Govindarajan et al., 2011; Jorjão et al., 2015; Matt et al., 2018), but these findings have not been sufficiently obtained in humans. Duscha et al. (2020) reported that 2 weeks of propionic acid supplementation resulted in a sustained increase in immunoregulatory T (Treg) cells, while prolonging treatment to 3 years reduced the relapse rate associated with brain atrophy. In contrast, in a cohort study conducted in France among community-dwelling individuals older than 65 years old, it was found that elevated serum propionic acid was associated with increased odds of cognitive decline (Neuffer et al., 2022). The authors suggested a metabolic dysregulation as a possible pathway in the relationship between propionic acid and cognitive health. Sakurai et al. (2022) used a heat-inactivated strain of *Lactiplantibacillus plantarum* to test its protective effects on the memory function in older adults. Significant improvements in composite memory and visual memory scores were observed in the elderly group. Interestingly, one study suggests that bacteriophages of the order Caudovirales may improve executive function and memory in both preclinical and human studies (Mayneris-Perxachs et al., 2022). Although this strategy is very attractive, more studies are needed to know the impact of bacteriophages on cognitive health in the elderly (Table 3).

3.6.6. Diets

Diet is a very important factor in shaping the structure of the gut microbiome, influencing its composition and diversity, facilitating the secretion of neurotransmitters and vitamins, and reversing gut dysbiosis linked to increased intestinal permeability and systemic inflammation (Rothschild et al., 2018; Rutsch et al., 2020; Skolnick and Greig, 2019). Moreover, some of the identified mechanisms for gut-brain communication, including microbial metabolite production, and immune, neuronal and metabolic pathways, may be susceptible to dietary modulation (Berding et al., 2021).

Different dietary habits significantly affect the composition of the gut microbiome, which is also a critical factor in maintaining health and in delaying aging (Sandhu et al., 2017). Evidence suggests that the Mediterranean diet, which is mainly composed of cereals, nuts, vegetables and fruits, may be beneficial for the humans (Borrego-Ruiz and Borrego, 2024b; van de Rest et al., 2015) by reducing the incidence of cardiovascular and metabolic diseases, cognitive disorders, and cancers (Wu and Sun, 2017). In particular, the polyphenols present in this diet, which have antioxidant and anti-inflammatory properties, have been proposed as a useful strategy for the prevention of age-related diseases (Yang et al., 2015), based on their capability to reduce oxidative stress and inflammatory processes, to maintain the mitochondrial integrity, and to improve the synaptic plasticity (Caracci et al., 2020; Griñán-Ferré et al., 2021; Petersen and Smith, 2016).

Several lines of evidence have shown that the Mediterranean diet induces changes in the gut microbiome that improve health in the elderly, reducing stroke, and frailty and inflammatory markers, and improving global cognition and episodic memory (Ghosh et al., 2020b; Loughrey et al., 2017; Marseglia et al., 2018; Psaltopoulou et al., 2013; Tsivgoulis et al., 2015). The diet-modulated microbiome alters metabolite profiles with increased production of SCFAs and decreased production of secondary BAs, p-cresol, ethanol, and carbon dioxide (De Filippis et al., 2016; Ghosh et al., 2020b). However, only few studies have examined the relationship between diet, gut microbiome and cognitive function in older adults. For example, studies of adherence to the Mediterranean diet have shown a low progression of MCI and AD (Berti et al., 2018; Ettinger, 2022; Moreno-Arribas et al., 2020; Singh et al., 2014). Furthermore, in a study using a modified Mediterranean-ketogenic diet, Nagpal et al. (2019) found that specific diet could modulate the gut microbiome and metabolites associated with improved AD biomarkers.

More recently, Meng et al. (2023) conducted a dietary intervention in adults of 50 years old and older to investigate the preventing aging effects of a polyphenol-probiotic-enhanced diet (P-diet). P-diet provoked a decrease in levels of interleukins IL-6 and IL-10, and in C-reactive protein. In addition, a significant increase in the abundance of *Lactobacillus* and *Bifidobacterium*, and in butyrate and acetate levels, was reported. At the same time, inflammatory aging potential showed a negative association with *Akkermansia* abundance. Thus, these authors concluded that P-diet may alleviate chronic low-grade inflammation, preventing the progression of inflammatory aging.

On the other hand, vegetarianism is a dietary pattern based on the consumption of foods of plant origin, which is environmentally sustainable and has important ethical implications. Vegetarian diets reduce β bacterial diversity of the gut microbiome, but increase α bacterial diversity, constituting a dietary habit that contributes to a greater diversity in the intestinal microbiome of vegetarians compared to that of omnivores (Borrego-Ruiz and Borrego, 2024b). Likewise, it has been reported that the adoption of a vegetarian diet is related to numerous health indicators, such as anti-inflammatory and antioxidant outcomes,

as well as a lower risk of cardiovascular diseases, type 2 diabetes, certain types of cancer, and obesity (Craig et al., 2021). Additionally, vegetarian diets have been associated with a higher longevity (Norman and Klaus, 2020), which shows the great potential of these dietary patterns to promote health at a general level in older adults.

Conversely, the Western diet, that is high in saturated fat and sugar, may induce cognitive dysfunction in aging (Więckowska-Gacek et al., 2021). Intermittent fasting and caloric restriction may modulate cognitive function in humans in two ways: (i) through metabolic pathways, including ketone bodies synthesis and degradation, butanoate metabolism, pyruvate metabolism, and glycolysis and gluconeogenesis pathways; and (ii) through increased synaptic plasticity and stimulation of neurofacilitating pathways (improved insulin sensitivity and reduced inflammatory activity) in the brain (Ooi et al., 2020; Witte et al., 2009). However, in the absence of long-term human studies, it is not possible to conclude whether prolonged dietary changes can induce permanent alterations in the gut microbiome (Leeming et al., 2019). In summary, dietary adherence has been associated with better cognitive function in older adults, but the integration of the microbiome into clinical nutrition perspectives on brain health has been poorly studied (Ribeiro et al., 2022).

4. Discussion and conclusions

Aging is a gradual and irreversible pathophysiological process associated with a decline in cellular functions and with a significant increase in the risk of several disorders, including neurodegenerative, cardiovascular, metabolic, musculoskeletal, and immune diseases. There are two theories on the origin and development of aging: the programmed or adaptive theory, which states that a "genetic clock" determines the onset of aging in an organism; and the damage or error theory, which explains age-related events as consequences of the lack of natural selection with advancing age (Bektas et al., 2018; Jin, 2010). However, the intrinsic and environmental factors and their mutual interaction as determinants of aging have been proposed as key mechanisms in the elderly (Ogrodnik et al., 2019; Wright et al., 2019). Moreover, there is increasing evidence demonstrating that changes in the epigenome during aging lead to transcriptional alterations and genomic instability, which are major contributors to the development of age-related diseases, such as cancer and neurodegenerative diseases (Sen et al., 2016; Guillaumet-Adkins et al., 2017). Therefore, in our opinion, the current research on the regulation of aging must focus on understanding the role of various endogenous and exogenous stressors, such as genomic instability, epigenetic alterations, autophagy, mitochondrial dysfunction, neuroinflammation, cellular senescence, and altered intercellular communication. Fig. 1 shows the relationship between different microbial metabolites and several age-associated manifestations.

There is a general consensus supporting the hypothesis that the development of human neurodegenerative diseases is strongly linked to the quality of the prenatal lifestyle (Borrego-Ruiz and Borrego, 2024b; Gabbianelli and Damiani, 2018). Recent studies have shown that the gut microbiome is a critical contributor to the host brain aging, including in neurodegenerative diseases, establishing four microbiome-based aging clocks: biodiversity clock, taxonomic clock, functional clock and meta-metabolomic clock (Ratiner et al., 2022). However, an important question is how to define a healthy gut microbiome and whether there is indeed a universal microbiome that is indicative of health during aging (Hill, 2020; Shanahan et al., 2021). The development of technological advances, including next-generation meta-omics analysis and high-throughput sequencing (16S ribosomal RNA microbial profiling, DNA microarrays, metatranscriptomics, metabolomics, and shotgun metagenomics), will allow us to understand the gut environment of cognitively impaired and neurodegenerative patients using functional approaches, and will reveal whether the imbalance of gut microbial communities is involved in the beginning of the pre-onset state of neurodegenerative processes (Satam et al., 2023).

We believe that well-designed, longitudinal, randomized controlled clinical trials will be needed to better understand the potential role of microbial therapeutics in improving brain health in aging. In addition, the elucitation of the factors that drive individual responses and outcomes is critical for the development of personalized microbiome-targeted interventions to improve physiology and brain function in aging. Current clinical trials of dietary interventions and supplementation with probiotics, prebiotics, and synbiotics have shown that they can improve cognitive function. Although the effects of probiotic supplementation seem to be greater in cognitively impaired individuals than in healthy individuals, more studies are needed to draw firm conclusions. Many unknowns remain to be clarified and several parameters need to be controlled from both the probiotic and the host side when planning interventions in elderly patients. (i) Current probiotic approaches are based on bacterial strains that are generally not indigenous to the human gut (Zmora et al., 2018), therefore they do not permanently colonize the gut and exert their beneficial effects through non-specific mechanisms. (ii) The health-promoting effect of a probiotic depends on the strain, dose, and duration of the probiotic treatment (Białecka-Dębek et al., 2021). At present, there is a lack of studies comparing different interventions (e.g., different genus or species and different doses), and it is also unclear whether and for how long the effect persists after the intervention has finished. (iii) Future studies should also consider the baseline of microbiota composition and dietary intake of the intervened older adults. It seems that personalized nutritional strategies will be of particular importance in the future, as evidenced by the growing interest in this area. (iv) Finally, the side effects of probiotic intervention should be considered together with the observed benefits.

Other potential strategies have been proposed, for example: the reintroducing of microbial metabolites derived from indole or its derivatives that are lost during the aging process could be as effective as and safer than the introduction of live bacteria (Sonowal et al., 2017). Boehme et al. (2023) have suggested that elimination of age-related potentially pathogenic microorganisms, through targeted antibiotic use or CRISPR knockout of individual genes or pathogens, may be another potential intervention strategy. However, these strategies are currently limited by a lack of scientific empirical results.

Future researches will be needed to reduce the incidence and development of age-related diseases and to promote a healthy aging by treatments for age-related diseases, for example: depletion of senescent cells, stem cell therapy, antioxidant and anti-inflammatory treatments, hormone replacement therapy, and by novel interventions that promote a healthy aging. More efforts would be necessary in the coming years to improve prevention, early detection, and rationally designed treatment strategies for age-related physiological and neurodegenerative disorders. Thus, the aging population may benefit of the protocols aimed to mitigate the escalating age-related conditions on public health and societal well-being. Moreover, interdisciplinary collaborations among scientists, clinicians, policymakers, and stakeholders will be paramount in advancing our understanding of the underlying mechanisms and risk factors associated with these disorders. Besides, concerted initiatives in research and dissemination will be essential for the development of innovative diagnostic tools and therapeutic interventions customized to individual needs. Embracing emerging technologies holds promise for revolutionizing healthcare delivery and optimizing patient outcomes. Furthermore, a concerted focus on promoting healthy aging and lifestyle interventions, with special emphasis on social development and psychological well-being, can complement medical interventions, potentially delaying the onset or progression of age-related diseases. Ultimately, by prioritizing these efforts, we can aspire to a future in which aging is associated with enhanced wellness and longevity, ushering in a new era of age-related healthspan extension and improved quality of life for individuals across the lifespan.

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We confirm that the manuscript has been read and approved by all named authors.

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Alejandro Borrego-Ruiz: Writing – review & editing, Methodology, Conceptualization. **Juan J. Borrego:** Writing – original draft, Supervision, Resources, Investigation, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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