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How Diet and Lifestyle Can Fine-Tune Gut Microbiomes for Healthy Aging


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Abstract
Many physical, social, and psychological changes occur during aging that raise the risk of developing chronic diseases, frailty, and dependency. These changes adversely affect the gut microbiota, a phenomenon known as microbe-aging. Those microbiota alterations are, in turn, associated with the development of age-related diseases. The gut microbiota is highly responsive to lifestyle and dietary changes, displaying a flexibility that also provides an actionable tool by which healthy aging can be promoted. This review covers, firstly, the main lifestyle and socioeconomic factors that modify the gut microbiota composition and function during healthy or unhealthy aging.
and, secondly, the advances being made in defining and promoting healthy aging, including microbiome-informed artificial intelligence tools, personalized dietary patterns, and food probiotic systems.

1. AGING AND THE ELDERLY

Aging is characterized by progressive physiological and cognitive deterioration, which increases disease risk and negatively affects quality of life and autonomy. Aging inherently implies, on the one hand, a decline in physiological functions, affecting sensorial perception, gastrointestinal motility and permeability, and physical frailty (Norman et al. 2021) and, on the other, impaired psychosocial functions, affecting cognition, behavior, and mood, leading to reduced social interactions and global health. Furthermore, aging has a significant impact on the intestinal microbiota—a phenomenon referred to as microbe-aging—which may contribute to aging in many ways and to a greater susceptibility to aging-related diseases and disabilities.

In high-income countries, the old-age dependency ratio (OADR) hovers at around 25% and is expected to increase considerably in the coming years, reaching about 49% by 2050 (United Nations 2020). Such staggeringly high levels are unsustainable and, therefore, it is imperative to identify interventions that promote healthy aging, which can delay the onset of chronic illness and reduce disability. Increasing empirical evidence shows that the intestinal microbiota influences a host's multiple functional domains, including immunity and inflammation, metabolism, and food preferences as well as cognition and behavior. Accordingly, gut microbiota alterations have been linked to the onset of the main conditions underlying morbidity, disability, and mortality in aged human populations, including type 2 diabetes (T2D), obesity, cardiovascular disease (CVD), cancer, and cognitive and neurological disorders (Cho & Blaser 2012). Besides genetic factors, the composition and function of the gut microbiota are physiologically dependent on multiple lifestyle factors, among which the key elements include demographic and economic factors, physical activity, medication, and dietary habits, from birth to advanced age (Zhernakova et al. 2016). All this together makes the microbiota an accessible modifiable risk factor, especially through dietary changes, and, thus, a promising tool to promote healthy aging and help curb the rise in the OADR. Here, we review the latest evidence on lifestyle–microbiota interactions, with special emphasis on diet as a key accessible modulator. We also present and discuss how advances in microbiota science and big-data analytics can be used to promote healthy aging.

2. NUTRITIONAL AND GUT MICROBIOTA FEATURES DURING AGING

2.1. Influence of Aging on Gut Microbiota Composition and Vice Versa

Gut microbiota colonization starts essentially after birth. The diversity and complexity of the microbiota evolve until the approximate age of three years, then stabilize and remain without noticeable variations during adulthood in healthy subjects, becoming unstable once more in the elderly. Aging is associated with distinctive changes in gut microbiota, especially after the age of 70. Such changes are driven by the accumulation of the effects of multiple stressful events, anatomical and physiological modifications in the gastrointestinal tract, and a general decline in physical and mental functions (immune, metabolic, neural, etc.) along with lifestyle and dietary adaptations (Claesson et al. 2011, 2012; Odamaki et al. 2016). There is still a limited number of studies describing the composition of the microbiota in elderly individuals and even fewer on its
functionality; however, comparisons between adults and the elderly have identified clear differences in the composition and functions of their microbiotas. Nonetheless, there are no consensus microbiome signatures of the elderly to date, which could partly be due to differences in the characteristics of the study populations, as they belong to different cultures and geographical locations, as well as to methodological variations (Cryan et al. 2019).

Age-related changes in the gut microbiota are influenced by both personal and external environmental factors and are, therefore, highly variable. Specifically, one of the age-associated features of the gut microbiota frequently reported is its increased interindividual variability and reduced bacterial alpha diversity. Moreover, shifts in the proportions of different bacterial groups have been documented, in particular a progressive decrease in tentatively anti-inflammatory species and/or producers of short-chain fatty acids (SCFAs), such as Faecalibacterium prausnitzii, Eubacterium spp., Roseburia spp., Ruminococcus spp., and Bifidobacterium spp. Also frequently described in old age are increased proportions of potentially harmful bacteria otherwise found in low abundance, such as members of the families Enterobacteriaceae, Streptococcaceae, and Staphylococcaceae and the species Clostridium difficile (Bárcena et al. 2019, Biagi et al. 2017, Candela et al. 2014, Claesson et al. 2012, O'Toole & Jeffery 2015, Zhang et al. 2021). Despite the above, whether the age-associated microbiota changes underlie healthy or unhealthy trajectories has not been specifically investigated until very recently.

In this respect, Ghosh et al. (2022) compared the microbiota of healthy aging (defined as longevity, high physical activity, healthy diet, low cognitive decline) and unhealthy aging [defined by the presence of frailty, inflammaging (chronic low-grade inflammation due to aging), cognitive disorders, CVD, chronic kidney disease, metabolic syndrome (MetS), obesity, low physical activity, medication, osteoporosis, and/or influenza-like illness susceptibility]. The study included data from 21,000 fecal microbiomes from studies investigating changes in the gut microbiome across the age landscape (18–107 years) and those studying alterations between apparently healthy and unhealthy older individuals, shedding light on age and disease associations (Ghosh et al. 2022). Briefly, gut microbiota diversity and uniqueness correlate with aging but not specifically with healthy aging. Also, an enrichment of disease-associated taxa and a depletion of coabundant subsets of health-associated taxa correlate to aging. Specifically, research has identified three major groups of taxa showing consistent alteration patterns linked to generic aging (increasing or decreasing abundance in older people) and various aspects of healthy or unhealthy aging in humans (increasing or decreasing abundance with unhealthy aging). Group 1 (Faecalibacterium, Roseburia, Coprococcus, Eubacterium rectale, Bifidobacterium, and Prevotella) decreases with age and is associated with healthy aging. Group 2 (Eggerthella, Bilophila, Desulfovibrio, Fusobacterium, Anaerotruncus, Streptococcus, and Escherichia) includes pathobionts that increase with age and are associated with unhealthy aging. Group 3 (Akkermansia, Christensenellaceae, Odoribacter, Butyricimonas, Butyrivibrio, Barnesiella, and Oscillospira) increase with age, whereas their depletion is observed in unhealthy aging. Healthy aging is associated with a progressive, but not severe, loss of some commensals (e.g., Faecalibacterium, Prevotella, and Bifidobacterium), which are often replaced by others such as Odoribacter, the family Christensenellaceae (phylum Bacillota, formerly named Firmicutes) (Oren & Garrity 2021), and Akkermansia (in particular, Akkermansia muciniphila), which are reduced in unhealthy aging (Ghosh et al. 2022). Furthermore, microbiota compositional changes in subjects with unhealthy aging are linked to increased amounts of mildly toxic phenylalanine/tyrosine microbial fermentation products in plasma. By contrast, healthy aging is accompanied by a rise in plasma microbial metabolites, such as indole metabolites (indoleacetate, indolepropionate, indoxyl-sulfate, and indolelactate), which have been shown to increase life span. These findings suggest that information gleaned from the microbiome can help predict a healthy or diseased aging trajectory and determine the host’s longevity (Wilmanski et al. 2021).
Certain taxa of the gut microbiome have been shown to predict exceptional human longevity. Studies of centenarians and especially semisupercentenarians (i.e., people living over 100–110 years) of different ethnicities and living in different geographical locations (different genetics and dietary habits) showed distinct gut microbiotas. Specifically, their microbiotas are characterized by a reorganization of the Bacillota population, associated with health in younger age groups, and an enrichment in Pseudomonadota (formerly named Proteobacteria) (Oren & Garrity 2021), including opportunistic proinflammatory bacteria (pathobionts). Indeed, the gut microbiota of the exceptional survivors presented increased diversity (Kashtanova et al. 2020, Kong et al. 2016, Odamaki et al. 2016, Tuikhar et al. 2019, Wu et al. 2019a) and a higher prevalence of Bifidobacterium as well as higher abundances of health-associated taxa, such as Akkermansia and Christensenellaceae (Bárcena et al. 2019). Besides taxonomical changes, differences in the functional core of the microbiota have been linked to aging. For instance, enrichment in gut microbiota functional genes, as well as in functional genes involved in tryptophan consumption/metabolism, associated with xenobiotic degradation is reported in extreme aging (Rampelli et al. 2020), likely reducing plasma levels in older people, especially centenarians (Collino et al. 2013, Franceschi et al. 2017).

Gut microbiota perturbations occurring during aging can also be causally related to the progression of age-related conditions in older adults (Vaiserman et al. 2017). The continuous stimulation of the immune system causes a functional decline (immunosenescence), along with low-grade chronic inflammation (inflammaging), which leads to a decreased ability to generate protective adaptive immune responses, increasing the risk of both infections (e.g., C. difficile colitis) and noncommunicable diseases (e.g., frailty, atherosclerosis, cachexia, cancer, fatty liver disease, MetS, T2D, neurodegenerative diseases, etc.) (Santoro et al. 2020) (Figure 1). Evidence also suggests that alterations in microbial functionality can impact the gut–brain axis, leading to increased neuroinflammation, chronic oxidative stress, and neurotransmitter dysregulation (Cattaneo et al. 2017), thereby contributing to cognitive and physical decline. Specifically, evidence from animal

![Figure 1](image-url)

Environmental factors associated with the aging process that impact the microbiota and the opportunities that gut microbiota modulation offers to delay the onset of age-related diseases. Abbreviation: SCFAs, short-chain fatty acids.
and human studies indicates that the loss of the adult-associated microbiota and reduced diversity in elderly subjects are associated with frailty (Claesson et al. 2012) and may contribute to the susceptibility and pathogenesis of neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (Cenit et al. 2017, Dinan et al. 2019, Molinero et al. 2023). A few studies show that supplementation with a probiotic bacteria may improve neuromuscular vigor and coordination as well as ameliorate age-related dementia and cognitive decline biomarkers (Cerro et al. 2022, Meng et al. 2022) (Figure 1). Overall, elderly dysbiosis—or microbe-aging—is a multifactorial and dynamic phenomenon that makes the host more susceptible to most chronic diseases found in older people but also represents a modifiable biological layer to rewire aging in the elderly.

2.2. Influence of Nutrient–Microbiota Interactions on Dietary–Health Relationships

Interactions between diet and the gut microbiota have important consequences for human physiology and cognition, which may be particularly relevant throughout the aging process (Cryan et al. 2020, Régnier et al. 2021). On the one hand, the composition and functional capacity of the gut microbiota mirror dietary habits and, therefore, diet may have long-term health consequences. In fact, the idea that the gut microbiota needs to be fueled by our diet is a paradigm shift in the way of thinking about optimal nutrition. Yet, together with other lifestyle and social changes, poor nutrition is common in the elderly and represents an actionable tool for modulating gut microbiota in favor of a health-associated configuration and can thus help prevent the aging-associated decline in health. On the other hand, the gut microbiota influences the health effects of food as it participates in its metabolism.

The gut microbiota, through microbe or host–microbe cometabolic interactions, converts dietary components into metabolites that can modulate body–brain crosstalk and the function of different organs and systems (neuroendocrine or immune systems) (Mittal et al. 2017). Likewise, they can synthesize essential nutrients de novo, such as vitamins, which also have an impact on host nutritional status (Chittim et al. 2018). Furthermore, in the gut ecosystem there are also auxotroph microbes that are consumers of essential nutrients (vitamins, amino acids, etc.), influencing cross-feeding events within the microbial community and the host and ultimately affecting the health trajectory.

Concerning macronutrients, protein consumption has been correlated positively with gut microbiota diversity (Singh et al. 2017). This is possibly due to the role played by microbes in amino acid fermentation; however, the products generated may play many different roles. For example, the metabolic products resulting from the fermentation of leucine, isoleucine, and valine in the gut, such as the branched-chain fatty acids isovaleric and isobutyric acids, may reduce the defensive adaptive immune response, increasing the risk of infection (Lunken et al. 2023). By contrast, some tryptophan metabolites generated by the gut microbiota, such as indoles, play a crucial role in maintaining intestinal immune homeostasis and preventing inflammation (Agus et al. 2018). Proline metabolism and glutamate–GABA conversion driven by intestinal bacteria have been linked to cognitive function and depression in the elderly (Mayneris-Perxachs et al. 2022).

The amount and composition of dietary fat influence the immune response and may impact the aging process in humans. Saturated fatty acids (SFAs) and trans fatty acids are linked to an increased risk of CVD while monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs) are crucial in reducing the risk of chronic diseases. Human studies indicate that intake of dietary fat highly influences the intestinal microbiota, but the effects depend on the quantity and type of fat (Wolters et al. 2019, Yang et al. 2020). Diets rich in SFAs may negatively affect microbiota richness and diversity, whereas PUFAs have no effect on these microbiota metrics.
Specific studies relate high intake of SFAs to increases in *Bacteroides* and *Bilophila* and increased systemic Toll-like receptor activation, white adipose tissue inflammation, and impaired insulin sensitivity. By contrast, other studies relate the intake of PUFAs to the growth of potentially beneficial bacteria, including the taxa *Actinomycetota* (Oren & Garrity 2021), formerly named *Actinobacteria* (*Bifidobacterium* and *Adlercreutzia*), lactic acid bacteria (*Lactobacillus* and *Streptococcus*), and Verrucomicrobiota (Oren & Garrity 2021), formerly named Verrucomicrobia or Verrucomicrobium (*A. muciniphila*) (Caesar et al. 2015). Hence, high-SFA diets exert unfavorable effects on the gut microbiota and are related to an unhealthy metabolic state in which microbiota alterations could be causally involved. By contrast, PUFAs (omega-3 FAs, including eicosapentaenoic acid and docosahexaenoic acid) do not seem to negatively affect the gut microbiota and are related to anti-inflammatory and beneficial metabolic health outcomes, which could also contribute to healthy aging.

Carbohydrates are a very broad group of macronutrients ranging from monosaccharides such as glucose or fructose to disaccharides such as sucrose to polysaccharides. Within the polysaccharides, we can differentiate between those that are absorbable (starch) and those that are not (fiber), which reach the distal part of the intestine where they are utilized by the gut microbiota as energy sources. To a large extent, carbohydrate availability in the gut shapes the microbial communities, but this effect strongly depends on the amount and type of carbohydrate. Some studies show that diets high in simple sugars are associated with a higher abundance of Pseudomonadota and the Bacillota:Bacteroidota (also known as Bacteroidetes) (Oren & Garrity 2021) ratio and reduced numbers of *Lachnobacterium* and *Pediococcus* (Ramne et al. 2021). Fructose intake is correlated with a higher production of microbial enterotoxins and an inflammatory state (Sindhunata et al. 2022). However, not all simple sugars exert deleterious effects. For example, L-arabinose intake is associated with improved lipid and glucose metabolism, reductions in inflammation and the Bacillota:Bacteroidota ratio, and an increased relative abundance of *Parabacteroides gordonii* and *A. muciniphila* (Li et al. 2023). Starch is generally rapidly digested and absorbed into the bloodstream, so it has little impact on the composition of the gut microbiota. However, resistant starches (fiber types) can reach the large intestine and impact positively on microbial diversity (Venkataraman et al. 2016), which is, in turn, generally associated with health and healthier aging.

Fibers (including prebiotics) generally promote the growth or activity of beneficial intestinal bacteria, fostering healthy aging through microbiota-mediated mechanisms. In particular, the main responders to dietary fiber are species belonging to Bacillota and Actinomycetota (formerly named Actinobacteria or *Actinomyces*) (Oren & Garrity 2021), such as *F. prausnitzii*, which has been associated with improvements in intestinal barrier function and anti-inflammatory effects (Makki et al. 2018, Wolters et al. 2019). Fiber consumption also stimulates the production of bioactive metabolites (lactate, SCFAs) with potential protective functions in aging through their anti-inflammatory properties and ability to increase mucus production (Makki et al. 2018).

Other food components, such as phytochemicals (polyphenols, terpenoids, sulfur-containing and nitrogen-containing secondary metabolites), exert effects on the gut microbiota. Such components promote the growth of *Lactobacillus* and *Bifidobacterium* and other bacteria with potential relevance for healthy aging (*Akkermansia*, *Faecalibacterium*) by exerting a prebiotic-like effect (Tomás-Barberán et al. 2016). These food components also have anti-inflammatory and antioxidative properties, which could mitigate the mechanisms underlying aging. For example, polyphenol metabolites, as is the case with urolithins produced from ellagitannins and ellagic acid, reduce systemic inflammation and improve muscular and neuronal function, all of which play a key role during aging (García-Villalba et al. 2023). However, some bioactive products of dietary phytochemicals need to be microbially produced in the gut. Thus, gut bacteria able to produce these bioactive metabolites (Iglesias-Aguirre et al. 2023) should be identified with a view to defining responders.
and nonresponders. In this way, targeted dietary interventions can be designed considering the individual’s microbiota configuration to promote healthy aging (García-Villalba et al. 2023).

3. LIFESTYLE FACTORS AFFECTING MICROBIOTA AND AGING

Beyond diet, many other age-associated changes have been shown to modify the characteristics of the gut microbiota. Some of the major lifestyle factors that impact the gut microbiota in the elderly include medication, physical activity, and socioeconomic status.

3.1. Polypharmacy Associated with Multimorbidities

Chronic diseases and disability in the elderly often require polypharmacy, frequently associated with a high risk of side effects and adverse drug reactions (Greene et al. 2014, Leelakanok et al. 2017, Maher et al. 2014). Drug–microbiota interactions influence both the therapeutic effect of drugs and the composition and metabolic functionality of the microbial ecosystem (Vich Vila et al. 2020, Weersma et al. 2020). Several drug categories frequently prescribed in the elderly, such as proton pump inhibitors, metformin, statins, antidepressants, and laxatives, have lasting effects on the gut microbiota (Zhernakova et al. 2016).

Indeed, the scientific evidence indicates that some of the effects exerted by drugs may be mediated through the microbiota. The most solid evidence has been obtained with the antidiabetic metformin. Metformin has been implicated in maintaining a healthy gut microbiome and reducing age-related degenerative pathologies, like Alzheimer’s, cognitive decline, and most age-related cancers, independent of its antidiabetic effects (Kulkarni et al. 2020). Interestingly, several studies have revealed that the antiaging effect of metformin is mediated by the gut microbiota, mainly through the growth of the genus *A. muciniphila* (Lee et al. 2018). This effect on the microbiota holds clinical relevance, as *A. muciniphila* reduces with age in humans and its administration leads to life-span lengthening in murine models of progeria, which provides a rationale for microbiome-based interventions against age-related diseases (Bárcena et al. 2019).

One of the main causes of morbi-mortality in developed countries is CVD and many elderly people are prescribed drugs to treat this group of diseases. Aspirin, a historical antipyretic and analgesic drug, is also widely used to prevent CVD, with studies showing it can prolong life span (Lushchak et al. 2021) and affect the microbiota composition (Zhao et al. 2020). Specifically, fecal samples from mice fed aspirin were enriched in *Bifidobacterium* (*Bifidobacterium pseudolongum, Bifidobacterium breve, and Bifidobacterium animalis*) and *Lactobacillus* (*Lactobacillus reuteri, Lactobacillus gasseri, and Lactobacillus johnsonii*), which are generally considered beneficial. By contrast, aspirin administration led to reductions in *Alistipes finegoldii* and *Bacteroides fragilis*, which could be considered pathobionts (Zhao et al. 2020). However, research in mice reveals that specific intestinal bacterial species like *Lysinibacillus sphaericus* weaken the potential of aspirin by influencing its bioavailability, hindering its capacity to prevent tumor formation (Zhao et al. 2020). Acenocoumarol, a drug exclusively used as an anticoagulant, can also interact with gut bacteria. For instance, new in vitro studies have concluded that *Bifidobacterium* spp. can modify anticoagulant concentrations, probably due to their ability to enzymatically transform the drug via reductase, esterase, and dehydroxylase activities (Fragomeno et al. 2021). Lastly, statins, which are drugs prescribed to lower cholesterol and prevent heart strokes, seem to restore gut microbiota diversity. This has been proposed as one of the possible mechanisms through which this drug elicits its protective effect against nonalcoholic fatty liver disease (Zhang et al. 2021), although evidence is still limited.

Intestinal alterations, like constipation or excess stomach acidity, frequently appear within aging and are usually treated with drugs that also affect the gut microbiota. Specifically, increases
in *Enterococcus*, *Streptococcus*, *Staphylococcus*, and the potentially pathogenic species *Escherichia coli* were observed in response to proton pump inhibitors (Imhann et al. 2016). Laxatives are the mainstay of constipation management and, for example, polyethylene glycol (one type of osmotic laxative) can cause a long-lasting perturbation to the gut microbiota (Tropini et al. 2018). The interactions between laxatives and the gut microbiota are especially relevant because functional constipation is widespread in the elderly, and the prolonged use of laxatives could impair the beneficial role of commensal bacteria and derived metabolites in regulating gastrointestinal motility and constipation in the long-term (Vriesman et al. 2020).

### 3.2. Socioeconomic Factors and Social Interactions

During aging, numerous socio-economic changes occur, including social isolation and decreased purchasing power, among others (Routasalo et al. 2006). Social status also generates variations in human microbial populations or, vice versa, the microbiota may influence behavior and social relationships, potentially leading to health consequences and unhealthy aging (Cho & Blaser 2012). Nevertheless, our understanding of these interactions is still limited.

There are at least two pathways connecting social networks and the microbiome. The first pathway is a consequence of sharing tastes and preferences for food, similar exposures to environments, and close physical contact with members of a kin group or a household. There is solid empirical evidence supporting the idea that shared ties lead to similar microbiomes (Bennett et al. 2016, Tung et al. 2015). For example, individuals who share households have a skin microbiota that is more similar than those living apart (Lax et al. 2014). The mechanisms may be skin shedding, breathing, and shared surfaces. Furthermore, further research shows that the microbiota of individuals who live together (spouses) is more similar than that of those living apart, even compared to individuals who had shared early living conditions and upbringing (siblings) (Dill-McFarland et al. 2019).

More recently, it has been suggested that just as similar tastes and preferences may shape the microbiomes of members sharing the same social network, so the opposite may occur too. It is conjectured that at least some gut bacteria produce metabolites that play a role in sculpting tastes and preferences for food, social relations, and, more generally, individuals’ behaviors by interacting with the hosts’ central nervous system (Johnson & Foster 2018). Thus, for example, food cravings may be driven by bacterial populations so they can thrive in a chemical environment that favors their fitness. Because tastes, preferences, and behaviors are partially responsible for an individual’s choice of and acceptance into social networks, these connections establish a feedback loop. This could, in turn, influence phenotypes such as obesity and associated chronic conditions, which, at the same time, play a major role in life span and life quality.

All this evidence may have implications for the elderly population. Scientific studies have shown that microbiota diversity is lower in institutionalized individuals over 65 years old, which is associated with frailty and other age-related conditions (Claesson et al. 2012). Therefore, the relationship between bacteria and the human gut may represent a point of entry for potential interventions aiming to modify behaviors, which could in turn help promote general health. This novel information on the mechanisms for transmission of bacterial communities via social contact as well as shared indoor environments should also be investigated further given their potential impact on future intervention measures.

A second pathway connecting social networks and the microbiome is less obvious than the one described above but is equally perplexing. There is robust evidence in population health sciences that loneliness increases mortality, chronic illness, depression, and anxiety (Cacioppo & Cacioppo 2018, Cacioppo et al. 2015, Cacioppo & Patrick 2009). Although we know of no direct evidence of an association between loneliness or isolation and the microbiome, circumstantial evidence
would suggest that such an association may exist. Loneliness is a condition that produces depression, anxiety, and cognitive disorders, much as do other sources of stress, particularly in the aged population (Prince et al. 1997). The pathway that connects exposure to stress and mental health conditions is believed to be related to dysregulation of the hypothalamic–pituitary–adrenocortical axis, inflammation, and metabolic dysfunction, the same pathway that leads from stress to some chronic illnesses. Accordingly, one could expect a relation between isolation and loneliness or, more generally, density of social connections, on the one hand, and microbiota species richness and diversity, on the other. In fact, recent research reveals that depression and anxiety are associated with changes in the microbiota (Radjabzadeh et al. 2022), and other studies in human and animal models provide evidence for the role of psychosocial stress in modulating the microbiota (Bailey et al. 2011, Lach et al. 2018). In mice, for example, exposure to social stressors disrupts intestinal microbiota, which, in turn, affects behavior and immunity. This leads to excessive inflammation and higher risks of infection and depressive and anxious behaviors, which, in turn, cause isolation and loneliness.

A promising new line of research focuses on the relationship between social stress induced by an individual’s position in a social hierarchy, the microbiome, and chronic illness. Just as in the case of loneliness, the mechanism through which social position affects stress is by dysregulating the hypothalamic–pituitary–adrenocortical axis. Considering that responses to stress induce microbiota changes, one could expect that an unfavorable social position in a hierarchy would be a stressful situation, which may also alter the microbiota and have related health consequences.

Finally, the elderly face many economic difficulties. Old-age pensions, retirement, and increased medical expenses bring changes in economic status and purchasing power, which may imply certain lifestyle shifts. In this context, the existence of strong differentials in morbidity and mortality by social class should not come as a surprise. Moreover, recent empirical research identifies a similar pattern of microbiota differentiation with an individual’s social standing and economic resources. Because there are strong social class differentials in some of the determinants that shape the microbiota (diet, physical activities, smoking, alcohol consumption, indoor environments, social contacts, stress exposure), future research should uncover the kind of factors determining microbiota differentiation by social classes (Rook et al. 2014). Of importance are class differentials in psychosocial stress and related markers (C-reactive protein, cortisol), a pathway between economic deprivation, adverse environmental exposure, and isolation, on the one hand, and chronic illnesses and mortality on the other (Rook et al. 2014). These relations may be at the root of class differentials in several modern human conditions that are strongly associated with microbiota and aged-associated conditions, such as obesity and T2D.

3.3. Physical Activity

Regular physical exercise protects against several pathologies associated with aging, such as CVD and other metabolic diseases, and has been frequently considered a “polypill” for chronic disease. Current evidence suggests that physical activity can modulate gut microbiota composition and functionality (Donati Zeppa et al. 2020). In recent years, growing interest has arisen concerning the impact of physical activity on gut microbial communities and the possibility of improving physical performance through changes in the microbiota, which could delay the appearance of chronic diseases associated with aging and thus prolong life span.

The relationship between nutrition, microbiota, and physical exercise has mainly been studied in adults, including professional and nonprofessional athletes. Physical activity may lead to an increase in microbiota diversity (Donati Zeppa et al. 2020), an indicator that is normally related to good health. However, it is difficult to establish an association between increased microbial diversity and the diet of those who practice exercise, as athletes follow remarkably different diets, which
are highly dependent on the particular sport, sex, and sports periodization, from those of the general population (Hughes & Holscher 2021). What has been established is the possible role played by some intestinal bacteria in physical activity. For example, *Prevotella copri* relative abundance was increased in ultraendurance rowers during exercise, with a concomitant increase in gene expression of metabolic pathways involved in L-lysine metabolism, an essential amino acid involved in muscular integrity (Keohane et al. 2019). In another study, Scheiman et al. (2019) showed that *Veillonella atypica* might be increased in marathon runners. *Veillonella* species are able to degrade systemic lactate resulting from muscle activity, thus contributing to muscle recovery after exercise. Recently, a cross-sectional study involving male long-distance runners showed a positive correlation between *Bacteroides uniformis* abundance and enhanced performance in endurance exercise (Morita et al. 2023). All these studies open new applications for probiotics, prebiotics, and symbiotic combinations, focused on improving physical activity through a variety of food supplements (Axelrod et al. 2019, Marttinen et al. 2020).

Studies on how physical activity can shape the microbiota of older individuals and promote healthy aging are still scarce, and the hypotheses raised need more solid experimental validation to reach conclusive results. The current studies dealing with this specific topic point to a modification of the gut microbiota induced by physical activity, but the effects of exercise are usually associated with other healthy habits, which may act as confounding factors. That said, a recent work shows that a one-year lifestyle intervention with an energy-reduced Mediterranean diet and physical activity is associated with a microbiota modulatory effect. The results specifically indicate that calorie restriction along with an increase in physical activity could modulate bile-related bacteria (Muralidharan et al. 2021). The effects of exercise on gut microbiota and CVD risk factors in elderly women were also determined, showing an improvement in physical function and a decrease in the risk of sarcopenic obesity and MetS, as well as an altered alpha diversity of the gut microbiota (Zhong et al. 2022). In a cohort of older Irish adults, moderate to vigorous physical activity was positively associated with the abundance of Lachnospiraceae, and standing time was positively correlated with the abundance of butyrate-producing bacteria, including Ruminococcaceae, Lachnospiraceae, and *Bifidobacterium* (Zhong et al. 2021). Altogether, findings from different studies indicate that exercise could have a beneficial impact on the gut microbiota of the elderly, although certain limitations, such as the few intervention studies available, the small sample size, the confounding factors, the different sampling protocols, and the methodological disparities in analyzing the microbiome, hinders identification of the relevant microbial taxa involved in the observed effects.

### 4. PERSONALIZING DIET AND LIFESTYLE TO PROMOTE HEALTHY AGING

As reviewed above, many lifestyle factors affect our health and the aging process, but diet is undoubtedly one of the most influential (Katz & Meller 2014), and it is the main modulator of the gut microbiota. Suboptimal diets, including overeating and severe dietary restrictions, can lead to malnutrition and/or microbiota alterations. Briefly, some of the physiological changes affecting the nutritional status include mouth dryness, decreased sensitivity of taste and smell, reduced gastrointestinal motility, malabsorption, and changes in nutritional requirements together with microbiota alterations (Lovat 1996). All these factors, together with a social and economic shift, significantly increase the risk of malnutrition, which in turn is associated with higher morbidity and mortality rates.

In this scenario, dietary interventions, including foods such as pre- and probiotics, emerge as part of the most accessible tools to promote healthy aging. Dietary and social interventions have
already been shown to improve health and prevent the onset of chronic diseases in general and in aging populations (Krivanek et al. 2021), but their effectiveness is far from optimal. This is due to the high interindividual variability in the aging process and the environmental and biological factors influencing our biological responses. All this reflects the need to use more accurate deterioration estimators and tools to progress toward personalized and multidisciplinary interventional programs that actively boost healthy and active aging and their integration into the healthcare systems.

Hereafter, we review the most recent tools and approaches being investigated to identify the best measures for preventing the functional and cognitive decline associated with aging. These include the development of artificial intelligence (AI) models, integrating modifiable factors (diet, gut microbiota, and behavior) that mediate or protect against unhealthy aging, the development of more accurate aging estimators and specific probiotics and dietary recommendations meeting aging needs, and application of personalized corrective measures addressing the root of the problem.

4.1. How Artificial Intelligence Might Help Predict an Individual’s Optimal Lifestyle

Machine learning (ML) and deep learning have emerged as key tools to advance microbiome research and inform nutritional and clinical decision-making. Numerous studies have been published in recent years applying AI techniques to human microbiome data that have helped to understand how different microbial communities and their functions affect human health (Bakhir-Gungor et al. 2022, Ghannam & Techtmann 2021, Lo & Marculescu 2019, Marcos-Zambrano et al. 2021, Pasolli et al. 2016, Topcuoğlu et al. 2020, Wassan et al. 2019, Zhu et al. 2020).

In health sciences, state-of-the-art ML algorithms can be classified into supervised learning and unsupervised learning algorithms. In supervised learning, algorithms are trained on labeled data to predict specific outcomes, such as how to determine whether or not a person has a disease from their microbiome data. On the one hand, there are various traditional supervised ML algorithms used to analyze microbiome data. Among the most popular are ensemble methods such as random forest or gradient boosting and others such as support vector machines, elastic networks, and shadow neural networks (Marcos-Zambrano et al. 2021). The availability of larger data sets has facilitated the use of deep learning techniques in microbiome research, such as convolutional neural networks. Unsupervised learning is based on algorithms that are trained on unlabeled data and aim to discover hidden patterns and structures in the data. In microbiome research, unsupervised learning is mainly applied to reduce the high dimensionality of microbiome data. This facilitates the search for biomarkers and clustering techniques that allow the identification of structures leading to a better understanding of the data (Marcos-Zambrano et al. 2021). It is also important to highlight that microbiome data are compositional, sparse, and high dimensional, requiring special treatment and preprocessing before being fed into the ML algorithm (Lin & Peddada 2020).

One of the main applications of ML in human microbiome research is disease prediction and biomarker discovery. The gut microbiome significantly contributes to interindividual variability in health and disease and represents a potentially modifiable factor that can be targeted for personalized therapies (Kashyap et al. 2017). AI methods have demonstrated their ability to successfully identify patients with respect to the controls from gut microbiome data (LaPierre et al. 2019, Oh & Zhang 2020, Pasolli et al. 2016, Zhu et al. 2020). They have also been used to stratify patients and identify microbiome biomarkers that are associated with disease (Wirbel et al. 2019, Yachida et al. 2019). These methods have been particularly successful in diseases such as colorectal cancer, inflammatory bowel disease, and liver cirrhosis. Other diseases, such as T2D and obesity, are more difficult to predict using microbiome data alone (Oh & Zhang 2020).
The collection of additional data, such as human genetics, lifestyle factors (environment and diet), and many others, combined with microbiome information, holds promise for improving the accuracy of disease risk prediction in future ML algorithms. AI could also lead to the development of predictive models for personalized preventive interventions to promote active aging and delay chronic disease onset. Indeed, an ML algorithm has already been developed to predict post-prandial glycemic responses to meals by combining data from blood parameters, dietary habits, anthropometry, physical activity, and gut microbiota (Zeevi et al. 2015).

The development of predictive models for personalized interventions will require a large amount of health and disease-specific microbiome data combined with other data sources. It will also require large-scale longitudinal studies with at-risk individuals over time to monitor the transition between health, subclinical disease, and clinical disease states. New technologies such as wearable devices could help to collect data for longitudinal studies in a dynamic way. Wearables allow for easy monitoring of health data such as heart rate, sleep patterns, physical activity levels, and even nutritional intake and status, all of which can be used to support healthy lifestyle habits adapted to each person. Moreover, recent developments in medical wearables, not yet on the market, include data based on the collection of samples from the skin, sweat, saliva, or stool, which can later be analyzed in an interconnected lab to provide information about the subject's microbiota. This strategy can provide insights into the microbiota configuration associated with the person's health and can be used to identify imbalances linked to deviation from healthy lifestyles and disease. Coupled with appropriate databases and analytical pipelines, still to be fully developed, the above information will be able to provide personalized lifestyle and dietary recommendations for healthy aging.

AI will be crucial here in several ways. Wearable data, including lifestyle and health data, together with biological (genetic, biochemical, immune, microbiota, stress markers), social (wealth, culture, education), and environmental (rural versus urban regions, levels of water and air pollution) information, can be used to train ML models to predict future health outcomes based on past data. These predictions can be used to provide personalized recommendations for lifestyle changes such as diet and exercise choices and for stress management. In other words, predictive modeling can be used to forecast a person’s future health outcomes based on their current lifestyle as well as identify lifestyle changes that can improve those outcomes. At the population level, this effort will generate important information to develop health programs, taking into account the stratification of the population and the multifactorial health trajectories. However, it is important to keep in mind that the algorithms developed will be as good, but also potentially as biased, as the source data used to train them. Therefore, it is essential to maintain constant vigilance and avoid possible biases (ethnic, cultural, gender, etc.). Ethical issues surrounding the use of big data and ML in nutrition and healthcare, such as data privacy and accountability, are also essential. Therefore, it is crucial that these solutions are developed and implemented with appropriate governance and supervision to ensure that they are used in a way that is fair and beneficial to individuals and society.

4.2. Estimating Biological Age

The aging trajectory is sensitive to the individuals’ genetic, social, economic, and lifestyle features, which may accelerate or shield myriad physiological processes that increase the risk of age-related morbidities. This complex constellation of individual interacting variables makes it difficult to define healthy and unhealthy aging as well as identify thresholds from which preventive measures should be recommended. A proxy of deterioration across the life course is chronological age (CA), an easy-to-measure metric that is nearly universally available and highly correlated with the incidence of chronic disease. However, despite noteworthy advantages, CA remains a rather
crude indicator of the latent, unobserved, physiological processes that drive deterioration. Accordingly, recent theoretical and empirical research has been directed to the formulation of an alternative measure, referred to as biological age (BA) (Klemera & Doubal 2006, Nakamura et al. 1988, Voitenko & Tokar 1983).

An ideal estimator of BA should satisfy four main conditions. First, it should be based on accurate information about multiple physiological domains, which, acting separately or with one another, accelerate, slow down, or inhibit the organism’s overall deterioration. Second, an ideal BA should reflect both the state of each domain and the complex interactions and overall state of the organism. Third, it should also be sensitive to both distal exogenous stressors, including socioeconomic and environmental factors, and proximate conditions, such as health-related behaviors, use of medications, and other medical interventions. Fourth, it should be a better predictor than CA of the timing of the onset and seriousness of chronic illness, cognitive decline, emergence of disability, and mortality (Finch 2007, Finch & Kirkwood 2000).

Thus defined, BA is an unobserved quantity reflecting the state and interactions of multiple latent (unobserved) physiological domains defined ex ante by the investigator and disturbed by stochastic noise, mostly independent of each domain. BA need not march in lockstep with CA at all and could be either positively or negatively associated with it within finite segments of an individual’s life span. On this basis, novel nutritional and medical technology can successfully be deployed to prevent and treat chronic conditions among older adults. As a result, physiological functioning may improve, even if it does so transiently, and thereby decelerate biological aging while simultaneously CA preserves the pace at which it increases. In this case, and only in the range of ages within which the interventions operate, there will be a weak association between BA and CA. Conversely, individuals exposed to adverse conditions early in life may experience more rapid deterioration at adult ages and BA will leapfrog CA. Similarly, the adoption of healthy or unhealthy behaviors will decelerate or accelerate damage and intensify the malfunctioning of domains above and beyond what is associated with the routine passage of CA.

As mentioned above, the ideal estimator of BA should be based on joint information about multiple domains. Extant estimators are mostly based on either standard biomarkers of selected physiological states such as blood pressure, glycated hemoglobin, and lipid profiles or, alternatively, a combination of these markers and DNA methylation of multiple tissues. Table 1 summarizes the most commonly employed aging biomarkers classified by classes and the technologies used to identify them. We believe that to make additional progress, researchers should deploy a different strategy, one in which BA is explicitly recognized as a latent construct reflected in well-defined physiological domains. For example, based on information made available from recent surveys of adults, one can bring together classic biomarkers, the assessment of DNA methylation, DNA damage (telomere length), microbiota richness and diversity, and neurodegenerative activity [plasma NfL (neurofilament light), total tau, β-amyloid 1–40 scans]. Estimation of the target quantity should be based on structural equation models that rely on observed indicators of the included domains to define a scale, ordinal BA measure. This can then be paired with selected health outcomes to generate a fully scaled BA indicator. In a second stage, the BA estimator should be tested for its predictive accuracy of individuals’ selected outcomes (presence/absence of chronic illnesses, disability, cognitive decline, mortality). In a third stage, the proposed BA should be utilized as an outcome by itself with the goal of identifying relations with proximate and distal determinants such as health behaviors, early adverse exposures, socioeconomic status, and ethnicity. Only when all these stages are accomplished will we be in a position to employ the BA indicator in clinical settings to predict individuals’ health profiles.

To date, algorithms have been developed to predict a person’s age based on their gut microbiota data (Huang et al. 2020), but such an algorithm should be improved by capturing a more
Table 1  Aging biomarker classes and technologies used to identify them

<table>
<thead>
<tr>
<th>Visible aging features</th>
<th>Physical and molecular readouts of organ function</th>
<th>Cellular and molecular multisignaling hallmarks of aging</th>
<th>Multi-omics technologies to capture individual's physiological status</th>
<th>Factors affecting healthy and unhealthy aging phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision and hearing loss</td>
<td>Pulse and blood pressure</td>
<td>Telomere attrition</td>
<td>Genomics and epigenomics</td>
<td>Intrinsic individual capacity</td>
</tr>
<tr>
<td>Hair greying and loss</td>
<td>Creatinine and albumin AST and ALT</td>
<td>Stem cell exhaustion</td>
<td>Transcriptomics</td>
<td>CNS damage, multimorbidity, medical examinations, and care support</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>CRP and blood count</td>
<td>Loss of proteostasis</td>
<td>Metabolomics and lipidomics</td>
<td>Death, lifestyle and social factors, sleep, and environmental influences, both internal (e.g., hypertension, diabetes, etc.) and external (e.g., place of birth, country of residence, etc.), of early and/or adult life</td>
</tr>
<tr>
<td>Frailty</td>
<td>Glucose, insulin, LDL</td>
<td>Cellular senescence</td>
<td>Proteomics</td>
<td></td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>NfL, total-tau, β-amyloid 1–40 scans</td>
<td>Mitochondrial dysfunction</td>
<td>Glycomics</td>
<td></td>
</tr>
<tr>
<td>Skin wrinkling</td>
<td>Expiratory volume</td>
<td>Genomic instability Mutations DNA methylation</td>
<td>Microbiomes/ microbiome-based biomarkers</td>
<td></td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>Inflamming</td>
<td>Microbe-aging</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CNS, central nervous system; CRP, C-reactive protein; LDL, low-density lipoprotein; NfL, neurofilament light.

4.3. Dietary Patterns for Healthy Microbiota Configurations and Aging

Dietary patterns may better predict health status and disease risk than individual nutrients or foods (Jacobs & Orlich 2014, Solfrizzi et al. 2017). A dietary pattern (all food products a subject habitually eats and drinks) should provide an adequate and balanced amount of macro- and micronutrients to meet the energy and other nutritional needs and, thus, support the physiological body functions of a person. However, personalizing dietary patterns to maximize health benefits, including healthy aging and preventing age-related diseases, is complex and may be considered utopic because of (a) the need to implement parallel healthy lifestyle changes, for example, physical activity and behavioral changes, and (b) the substantial interindividual variability behind dietary health effects due to all the participating actors, i.e., extrinsic (type of diets and food components, food processing and storage affecting specific constituents, culinary methods, etc.) and intrinsic (age, sex, disease status, gut microbiota, genetics, etc.) (Cortés-Martín et al. 2020, Willett et al. 2019). In particular, age-associated microbial alterations may influence nutrient digestion and absorption and could also increase intestinal permeability and contribute to chronic inflammation, which in turn favors translocation of microbial by-products into the circulatory system with subsequent effects on general health (Thevaranjan et al. 2017). A proof-of-concept Mediterranean diet intervention study is reported to help retain microbiota taxa linked to healthy aging (Ghosh et al. 2022); nonetheless, personalized approaches are expected to be more effective given the high interindividual variation of the microbiota and its impact, for example, on the glycemic and lipemic responses to the same food components (Berry et al. 2020, Zeevi et al. 2015).

With a view to adapting dietary patterns to each individual, it is crucial to identify the interactions of different food components (omega-3 fatty acids, polyphenols, and others) (Davinelli &
Scapagnini 2022, Fisette et al. 2022) with the gut microbiota and their consequences on different organ and system functioning. This is especially important because age-related microbiome features are more strongly linked to health or disease in aging than in youth (Ghosh et al. 2022). Current knowledge about the mechanisms underlying an individual’s response to diet is far from complete, but recent evidence supports the idea that the individual’s microbiota is one of the key determinants (Berry et al. 2020). In fact, information on the composition and function of microbiota seems to be a promising tool to identify the best responders to each dietary intervention and personalize the intake of specific foods (including pro- and prebiotics) (Davinelli & Scapagnini 2022, Fisette et al. 2022), which could be applied to target healthy aging.

But currently, to the best of our knowledge, attempts to personalize dietary patterns based on the integration of gut microbiota data and other variables for promoting healthy aging have not been reported. Nonetheless, algorithms integrating multidimensional variables, like the one recently updated by the American Heart Association, have proven useful in quantifying the associations between cardiovascular health and life expectancy in US adults (Ma et al. 2023) as well as for cardiovascular disease prevention in the United Kingdom (Petermann-Rocha et al. 2023). In this example, cardiovascular health was estimated by the Life’s Essential 8 (LE8) score, which integrates each diet component, physical activity, tobacco/nicotine exposure, sleep duration, body mass index, non-high-density lipoprotein cholesterol, blood glucose, and blood pressure. Adhering to LE8, in US adults ($n = 23,000$), a median of 7.8 years of follow-up has been linked to an increase in life expectancy of 8.9 years at the age of 50 years compared with those with a low score (Ma et al. 2023). A targeted intervention also increased LE8 by 10 points among individuals with the lowest initial LE8, which could have prevented 9.2% of major adverse cardiovascular events (Petermann-Rocha et al. 2023). Moreover, the microbiota composition is reported to be predictive for those cardiometabolic blood markers according to a large intervention trial of personalized response to diet (Asnicar et al. 2021). Altogether, this suggests the possibility of using microbiome-informed algorithms to design personalized interventions to reduce risk factors for major morbidity and mortality during aging.

### 4.4. Probiotic Systems for Healthy Aging

Specific probiotics may have various health benefits of interest in managing aging and its related conditions. Concerning pro-longevity effects, several probiotics have shown beneficial effects on the nematode *Caenorhabditis elegans*, whose short half-life facilitates survival rate monitoring. In this experimental animal model, *L. gasseri* SBT2055, but not *L. gasseri* JCM1131T or *Lactobacillus helveticus* JCM1120, was effective in extending life span by strengthening resistance to oxidative stress and stimulating the innate immune response signaling (Nakagawa et al. 2016). Similarly, *Propionibacterium freudenreichii* also successfully extended the life span of *C. elegans* (Kwon et al. 2016). More specifically, the generation of *C. elegans* loss-of-function mutants indicates that *P. freudenreichii* activates pathways related to innate immunity and that this immune activation increases resistance to *Salmonella typhimurium* infection (Kwon et al. 2016). Beyond modulating the immune system, other bacteria, like *Bacillus licheniformis*, which is isolated from traditional Korean foods, enhance the life span of *C. elegans* via different pathways, like host serotonin signaling (Park et al. 2015). More recently, in mouse models of progeria, the administration of *A. muciniphila* caused a modest life-span extension, suggesting a protective role of this microorganism against accelerated aging manifestations (Bárcena et al. 2019).

Apart from increasing longevity, other authors have addressed research to discover whether probiotic administration can counteract some of the features of aging, like age-related bone diseases or neurodegenerative disorders. The following summarizes some of the most recent results obtained in preclinical or clinical intervention studies. First, focusing on osteoporosis, some
studies describe that certain probiotics exert favorable effects by targeting the mechanisms for bone resorption and formation or by modulating immunity (kiousi et al. 2022). for instance, L. reuteri ATCCPTA 6475 was associated with positive outcomes in bone mineral density in a randomized, placebo-controlled intervention study in postmenopausal women (nilsson et al. 2018). Moreover, using fermented dairy products rich in potential probiotic strains to manage osteoporosis has also been considered in a double-blind placebo-controlled trial in osteoporotic patients (tu et al. 2015). The participants receiving the kefir-fermented milk supplement showed a significant improvement in bone mineral density as well as changes in bone-turnover biomarkers, reduction in serum osteocalcin, and an increase in serum parathyroid hormone (tu et al. 2015).

Second, probiotics presenting immunomodulatory responses have been tested for their ability to limit rheumatoid arthritis manifestations, an age-common chronic systemic autoimmune disease. In an intervention study, people with rheumatoid arthritis were randomized to receive a mixture of probiotics (two strains of Bifidobacterium, two of Lactobacillus, and one strain of Lactococcus) or placebo (cannarella et al. 2021). The probiotic group showed a reduction in proinflammatory markers (TNF-α and IL-6) but failed to improve the Disease Activity Score 28 (DAS-28) (cannarella et al. 2021). In contrast, previously, in another placebo-controlled intervention trial, Zamani et al. (2016) had reported that a probiotic supplementation (one strain of Bifidobacterium, two of Lactobacillus) resulted in improved DAS-28 together with a decrease in proinflammatory markers.

Dementia is a broad term that refers to a decline in cognitive functions. Lactobacillus casei LC122 and Bifidobacterium longum BL986 enhanced learning and memory ability in aged mice (ni et al. 2019). AD is the most common cause of dementia and is characterized by the accumulation of β-amyloid protein in the brain, leading to cognitive decline. In a model of AD, rats that received strains of Lactobacillus and Bifidobacterium presented decreased β-amyloid plaque size and improved memory deficit, demonstrating that probiotics can inhibit the pathological mechanisms of AD by modifying microbiota (athari nik azm et al. 2018). However, more promising studies show that probiotics could be used for preventive purposes in animal models of AD. As such, administering B. breve A1 to AD mice prevented cognitive dysfunction (Kobayashi et al. 2017). In humans, Hwang et al. (2019) investigated the impact of probiotic intake on the brain function of AD patients. The researchers discovered that administering L. plantarum C29 to individuals with AD enhanced cognitive performance, especially in the attention domain in a placebo-controlled clinical trial (Hwang et al. 2019). Lastly, probiotics have been studied as a way to improve the quality of life of individuals with Parkinson’s disease, and several placebo-controlled trials have shown a positive impact on gastrointestinal symptoms. Particularly, elderly individuals with Parkinson’s disease who were given a multispecies probiotic containing Lactobacillus, Bifidobacterium, and Streptococcus strains showed improved bowel habits (barichella et al. 2016), stool consistency, and quality of life related to constipation (Tan et al. 2021) and increased intestinal transit time (Ibrahim et al. 2020).

In summary, probiotics have the potential to intercept the paths mediating functional decline during aging, including inflammation, oxidative stress, and neuroendocrine dysfunctions. However, the number and quality of intervention trials are still too limited to provide firm conclusions on efficacy and a consensus on the use of probiotics in nutritional and clinical practice. Our understanding of the biological mechanisms of action of probiotic strains is also too incomplete to support recommendations. Further investigations and advances are expected, however, with the use of throughput multi-omics platforms and AI to scientifically support probiotics’ effects and mode of action and improve their effectiveness by adapting them to target the roots of aging and specific needs of the elderly. Furthermore, the concept of personalized probiotics (and other biotics) intended to repair an individual’s specific microbial loss or modulate particular microbial signatures of health and disease is under development. The new strategies are expected to be based
on not only the potential role of a single bacterium or bacterial cocktails but also ecological concepts encompassing the micro–micro communication network as well. For instance, the vacancy of a microbially mediated metabolic niche (e.g., the amount of lactate or butyrate) may account for the differentiation between responders and nonresponders to different probiotic strains of the genus *Lactobacillus* (Cunningham et al. 2021, Veiga et al. 2020), which are not directly producers of butyrate. This evidence supports the idea that the baseline microbiome and/or metabolome of the individual may indicate its ability to respond to a probiotic-based intervention, which should also be considered in the path toward personalized probiotic systems for promoting healthy aging.

5. CONCLUSIONS AND FUTURE RESEARCH

Age-associated physiological, socioeconomic, and gut microbiota changes seem to contribute to functional decline and onset of chronic diseases in the elderly. Dietary patterns, nutrients, and foods along with social behavior are identified as key drivers of gut microbiota deviations from healthy trajectories in the life course. Therefore, they represent actionable tools to rewire the microaging phenomenon and nourish both the body and the microbial ecosystem in support of healthy aging. The achievement of this promising goal still requires advances to be made in our understanding of the diet–microbe and social–microbe interaction nets and their consequences on health during aging. Attaining this aim also requires advances in AI computational models, aggregating a high-quality lifestyle and microbiota data, to better estimate biological age and predict health outcomes and response to diet and, thus, timely implement more personalized and effective lifestyle and probiotic system-based interventions.

DISCLOSURE STATEMENT

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AUTHOR CONTRIBUTIONS

M.T., M.O., and Y.S. wrote Sections 1, 3.1, 4.4, and 5. P.R.-M. and A.M. wrote Sections 2.2 and 3.3. J.C.E., I.M., and F.A.T.-B. wrote Section 4.3. M.V.M.-A. wrote Sections 2.1 and 4.2 and collaborated in table development. S.C., C.M., and S.O. wrote Section 4.1. H.B.-S. and A.P. wrote Sections 3.2 and 4.2. M.T., M.O., and Y.S. created the figure and merged, completed, and harmonized all the text. All the authors have reviewed and accepted the final version of the manuscript.

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LITERATURE CITED


