REVIEW

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Gut microbiota in relation to frailty and clinical outcomes

Federica D'Amico[a], *Monica Barone*[a], *Patrizia Brigidi*[a] *and Silvia Turroni*[b]

Purpose of review
The gut microbiota is involved in several aspects of host health and disease, but its role is far from fully understood. This review aims to unveil the role of our microbial community in relation to frailty and clinical outcomes.

Recent findings
Ageing, that is the continuous process of physiological changes that begin in early adulthood, is mainly driven by interactions between biotic and environmental factors, also involving the gut microbiota. Indeed, our gut microbial counterpart undergoes considerable compositional and functional changes across the lifespan, and ageing-related processes may be responsible for – and due to – its alterations during elderhood. In particular, a dysbiotic gut microbiota in the elderly population has been associated with the development and progression of several age-related disorders.

Summary
Here, we first provide an overview of the lifespan trajectory of the gut microbiota in both health and disease. Then, we specifically focus on the relationship between gut microbiota and frailty syndrome, that is one of the major age-related burdens. Finally, examples of microbiome-based precision interventions, mainly dietary, prebiotic and probiotic ones, are discussed as tools to ameliorate the symptoms of frailty and its overlapping conditions (e.g. sarcopenia), with the ultimate goal of actually contributing to healthy ageing and hopefully promoting longevity.

Keywords
ageing, dysbiosis, frailty, gut microbiota, microbiome-based interventions

INTRODUCTION

Made up of over 10 trillion bacteria, along with a minority of archaea, fungi and viruses, the human gut microbiota provides a collective genetic capability that significantly enriches the 'superorganism', with activities instrumental in maintaining host health, including the regulation of metabolism, and the modulation of the immune system and the nervous system, just to name a few [1]. The gut microbiota is a stable, yet dynamic ecosystem that adapts its structure in response to a wide variety of endogenous and exogenous stimuli, oscillating between alternative healthy states [2]. Among the main drivers of variation, we can mainly count exposome-related variables such as diet, lifestyle, socioeconomic factors and physical fitness, and only minimally host genetics [3–5]. However, sometimes the persistence and magnitude of these stressors are such that the gut microbiota is pushed towards unstable and unhealthy states, typically termed dysbiotic and usually associated with disease, mostly characterized by loss of diversity and health-associated microbial groups with increased levels of primary or opportunistic pathogens [6▪]. In this context, the debate is still open on whether changes in the gut microbiota profile during ageing (which encompasses the main factors listed earlier) are to be considered dysbiosis or vice versa adaptation to the aged condition, also considering the recent identification of potential longevity signatures in the microbiota of extremely long-lived people [7]. However, it remains a fact that particularly unbalanced gut microbial profiles can be established in the elderly, which have been associated with the

[a]Microbiomics Unit, Department of Medical and Surgical Sciences and [b]Unit of Microbiome Science and Biotechnology, Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy

Correspondence to Patrizia Brigidi, Microbiomics Unit, Department of Medical and Surgical Sciences, University of Bologna, 40138 Bologna, Italy. Tel: +39 0512099727; e-mail: patrizia.brigidi@unibo.it

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KEY POINTS

- The human gut microbiota may contribute to healthy ageing and possibly longevity.
- Gut microbiota dysbiosis occurs in frailty syndrome and overlapping conditions, such as sarcopenia.
- Microbiome-tailored strategies, such as dietary, prebiotic and probiotic interventions, may improve symptoms of frailty and age-related muscle loss.

onset and progression of age-related disorders, one of which is frailty syndrome [8] (Fig. 1).

In this review, we first summarize state of the art on changes in the gut microbiota across ageing and then discuss the potential involvement of the microbiota in age-related frailty syndrome. Finally, particular attention is paid to microbiome-based intervention strategies (such as diet, prebiotics and probiotics) that could improve frailty syndrome and some of its overlapping conditions (e.g. sarcopenia).

GUT MICROBIOTA VARIATIONS ACROSS LIFE: FROM EUBIOSIS TO DYSBIOSIS?

As just mentioned, the gut microbiota is a key element that evolves throughout the lifespan of the host. The processes accompanying this evolution are still mostly unknown and deserve further research, especially regarding the role of age-related dysbiosis in the typical diseases of ageing. This first paragraph summarizes the currently available information on the trajectory of the gut microbiota through life, with particular attention to old age and the eubiotic vs. dysbiotic nature of microbiota changes. See Table 1 for a summary of gut microbiota members associated with age-related health outcomes (and discussed later).

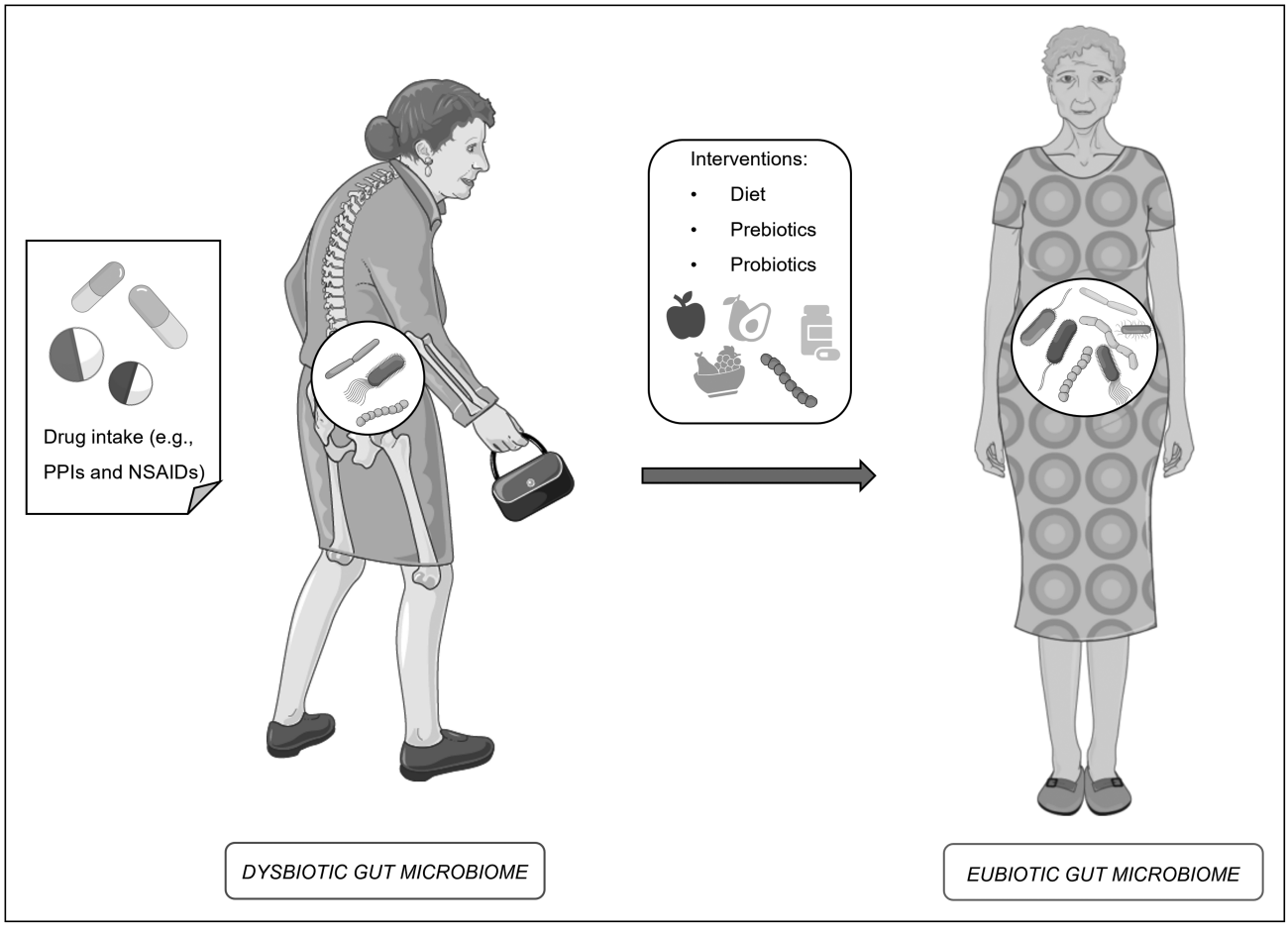

FIGURE 1. The gut microbiota as a novel target to improve frailty syndrome. Alterations (i.e. dysbiosis) of the gut microbial profile have been associated with several age-related disorders, such as frailty syndrome and its overlapping conditions (i.e. sarcopenia). Modulating the gut microbiota towards a eubiotic profile through dietary, prebiotic and probiotic interventions could represent a novel successful strategy for healthy ageing and hopefully the achievement of longevity. PPI, proton pump inhibitor.

Table 1. Association between gut microbiota and frailty and/or other age-related health outcomes

Microbial group	Association with frailty and/or other age-related health outcomes	Ref.
Phyla		
Firmicutes	Decreased in the elderly	[17]
Proteobacteria	Increased in the elderly	[17,18]
Families		
Porphyromonadaceae	Correlated with improved cardiovascular and metabolic health, potential marker of healthy ageing and possibly longevity	[19]
Barnesiellaceae	Decreased in sarcopenic and frail subjects	[37]
Rikenellaceae	Correlated with improved cardiovascular and metabolic health, potential marker of healthy ageing and possibly longevity	[19]
Streptococcaceae	Facilitates the establishment of a pro-inflammatory cycle in the ageing gut; enriched in frail individuals taking proton pump inhibitors	[44]
Christensenellaceae	Correlated with improved cardiovascular and metabolic health, potential marker of healthy ageing and possibly longevity; decreased in sarcopenic and frail subjects	[19]
Enterobacteriaceae	Associated with a high frailty index	[30]
Genera		
Bifidobacterium	Decreased in the elderly and centenarians; recovered after galacto-oligosaccharide supplementation in prefrail elderly	[17,18,51]
Bacteroides	Its high relative abundance in old age is associated with decreased survival over a 4-year follow-up (associated with an increased risk of all-cause mortality)	[10▪,15]
Parabacteroides	Increased in the elderly with antibiotic use	[15]
Alistipes	Increased in the elderly with antibiotic use	[15]
Clostridium	Decreased in the elderly	[17]
Faecalibacterium	Depleted in frail or elderly individuals	[17,18,30]
Oscillospira	Enriched in sarcopenic and frail subjects	[37]
Ruminococcus	Enriched in sarcopenic and frail subjects	[37]
Species		
Eggerthella lenta	Overabundant in frailty, forms a co-abundance pro-inflammatory cluster with *Ruminococcus torques*, *Bacteroides fragilis*, and *Clostridium hathewayi*	[30,33,34,35]
B. fragilis	Overabundant opportunistic pathogen in frail individuals; it forms a co-abundance pro-inflammatory cluster with *E. lenta*, *Ruminococcus torques*, and *C. hathewayi*	[34]
Prevotella copri	Decreased in older adults with sarcopenia	[40]
C. hathewayi	Overabundant opportunistic pathogen in frail individuals; it forms a co-abundance pro-inflammatory cluster with *E. lenta*, *Ruminococcus torques*, and *B. fragilis*	[33,34]
Clostridioides difficile	More than half of patients with *C. difficile* infection suffer from frailty and show poor prognosis with the development of multiple complications	[48]
Ruminococcus torques	Overabundant in frailty, forms a co-abundance pro-inflammatory cluster with *E. lenta*, *B. fragilis* and *C. hathewayi*	[33,35]

For each microbial group (at the phylum, family, genus, and species level), the variation (increase or decrease) in elderly, frail and/or sarcopenic subjects is reported, along with other correlations with health outcomes.

It is known that the human gut microbiome follows distinct ecological dynamics according to age phases, with rapid changes in the first years of life (0–3 years), followed by a long period of relative stability in adult life, ending with gradual compositional and functional shifts that potentially contribute to health decline later in life [9,10▪]. However, despite substantial advances in the field, it is still impossible to say precisely when age-associated changes occur in our lifelong microbial companion and what mechanisms underlie their dynamic influence on host physiology. For example, it is a long way from understanding whether the patterns observed in the gut microbiome of the elderly simply reflect or contribute at least in part to age-related physiological transitions, ultimately influencing survival outcomes. On the other hand, the recent identification of a unique microbial footprint in the gut microbiota of centenarians and semisupercentenarians (i.e. people aged 105 years and older) [7]

seems to suggest that age-related microbiota changes are actually an adaptation to aged conditions rather than a deviation from the eubiotic profile. It goes without saying that identifying ageing patterns of the human gut microbiome could have very relevant clinical implications not only for diagnostic purposes but also for a tailored-modulation of the microbiome towards a profile that is as adapted as possible to each stage of the host's life.

In old age, chronic low-grade inflammation (i.e. inflammageing) [11], impairment of the immune system (immunosenescence), increased permeability of the intestinal epithelium (leaky gut) and alterations in eating habits and gastrointestinal function result in unavoidable changes in gut microbiota composition and function, with a potentially detrimental impact on microbiota-host interactions [12]. Notably, the available studies are quite consistent in emphasizing age-related loss of stability, diversity and core microbes, along with increased proportions of pro-inflammatory proteolytic microbiota members with pathogenic potential [7,13]. It should be noted that these features are particularly evident in the elderly (including the frail) residing in long-term care facilities, have been associated with length of stay and suggested to be driven by poor diet (low-diversity and especially low-fibre) as well as a number of factors related to the pathophysiology of ageing [9,14]. According to the authors, these unbalanced microbiota profiles could feed a pro-inflammatory vicious cycle that in turn could fuel the onset (or worsen the course) of pathological conditions. The most extensively studied elderly cohort to date that also includes gut microbiota data is the ELDERMET cohort, comprising over 750 Irish individuals since 2007, whose faecal samples were collected with the purpose of investigating associations of gut microbiota with health. In particular, within the ELDERMET project, researchers identified a preponderance of the genera *Bacteroides*, *Alistipes* and *Parabacteroides* in individuals aged over 65 years compared to healthy, younger controls [15]. Furthermore, as anticipated earlier, there was a clear separation between the gut microbiota compositions (and metabolomes) of community-dwelling subjects and long-stay home residents [14]. Also, frail individuals from the ELDERMET cohort were characterized by higher levels of lithocholic acid (and derivatives) and deoxycholic acid than nonfrail individuals [16]. By comparing subjects from Ireland, Italy, France, Poland and UK, Ghosh *et al.* [16] demonstrated that elderly individuals older than 60 years showed greater variability in gut microbiota composition than younger individuals (20–60 years), potentially due to increased abundance of pathogens at the expense of health-promoting microbial groups. Indeed, the aged-type gut microbiota is typically depleted in members of the phylum Firmicutes, mainly *Clostridium* and *Faecalibacterium*, as well as *Bifidobacterium*, while enriched in Proteobacteria and *Streptococcaceae*, with a tendency towards exacerbations in the presence of frailty and comorbidities [17,18]. Again, the authors speculated that the overrepresentation of microbiota members with pathogenic potential and the concomitant depletion of immunomodulatory commensals may facilitate the establishment of a pro-inflammatory cycle in the ageing gut, compromising the host–microbiota balance. On the other hand, Tavella *et al.* [19] demonstrated the existence of distinct compositional clusters of the gut microbiota in Italian elderly, some of which (highly diverse and enriched in families *Christensenellaceae*, *Rikenellaceae* and *Porphyromonadaceae*) appeared to be correlated with improved cardiovascular and metabolic health, acting as potential markers of healthy ageing and possibly longevity. In the same year, other authors profiled the gut microbiota of more than 9000 individuals from three study populations aged 18–101 years, demonstrating that maintaining high relative abundances of *Bacteroides* and showing low microbiota uniqueness (i.e. losing one's fingerprint) in individuals approaching extreme ages (above 85 years) were predictive of reduced survival over the next 4 years [10▪].

As a reflection of the compositional shifts observed in the elderly microbiome, its metabolic potential also undergoes physio/pathological adjustments with advancing age. In a pivotal study, Rampelli *et al.* [20] showed an age-related increase in proteolytic potential at the expense of saccharolytic potential, with an underrepresentation of genes dedicated to the production of short-chain fatty acids (SCFAs, known health-related metabolites) while an overrepresentation of genes involved in the metabolism of aromatic amino acids, that is as tryptophan, tyrosine and phenylalanine. In a subsequent study on a larger cohort, in addition to confirming the previous, the researchers also found an age-related increase in genes responsible for the degradation of a range of xenobiotics, such as toluene, ethylbenzene, caprolactam, chlorocyclohexane and chlorobenzene [21]. As discussed in the original article, such a rearrangement could simply mirror long-standing lifestyle habits, such as living in environments under strong anthropic pressure with continuous and consistent exposure to xenobiotics. Similarly, it has been demonstrated that the gut microbiome of elderly people undergoes a progressive increase in resistome (i.e. the collection of both acquired and intrinsic antimicrobial resistance

genes), again following continuous exposure to these substances (for medical reasons, household hygiene and through food chains) [22▪]. In conclusion, the observed changes in the aged-type gut microbiota could the result of an adaptive process, consistent with modifications in human ageing physiology in modern urban societies, but given their prodysbiotic nature; such changes should be carefully monitored over time, especially in precarious health conditions, as in the case of frailty syndrome.

THE RELATIONSHIP BETWEEN GUT MICROBIOTA AND FRAILTY SYNDROME

Frailty is an ageing-related clinical syndrome characterized by the dysregulation of multiple important physiological functions (e.g. reduced strength and endurance), which predisposes patients to adverse health outcomes such as falls, hospitalization, disability and mortality [23–25]. Among community-dwelling older adults, frailty has been estimated to range between 4 and 59% and increases with ageing [26]. As life expectancy increases in industrialized countries, the United States have estimated that the number of people over 60 worldwide will double to 2.1 billion by 2050 [27]. In this scenario, frailty has started to be an urgent concern in a soon-to-be-ageing society. To date, several recent studies have suggested an involvement of the gut microbiota in the pathophysiology of frailty [8,28,29] (see also Table 1). Furthermore, a cross-sectional analysis in a community-dwelling cohort of 728 female twins found that a high frailty index was associated with reduced levels of SCFA-producing microbes with anti-inflammatory properties, such as *Faecalibacterium prausnitzii*, and increased proportions of pro-inflammatory members of the *Enterobacteriaceae* family [30]. Increased lipopolysaccharide synthesis was also found in frail subjects, suggesting an increased local and systemic pro-inflammatory state [31]. As discussed earlier, an elegant study by Claesson *et al*. [14], in Irish elderly showed that long-term stay in a residential facility, which can be considered a proxy for frailty, was associated with a dysbiotic gut microbial profile, reduced levels of microbial metabolites with anti-inflammatory properties (i.e. butyrate), as well as circulating pro-inflammatory markers such as TNF-α, IL-6, IL-8 and C-reactive protein (CRP). Increased levels of IL-6 have also been confirmed in a Chinese cohort of frail individuals [29,32]. Frailty-related overabundance of pro-inflammatory microorganisms has been observed in several studies that also pointed out the potential involvement of *Coriobacteriaceae* members (i.e. *Eggerthella lenta*), which appeared to form a co-abundance pro-inflammatory cluster together with (*Ruminococcus*) *torques* (a mucus degrader), *Bacteroides fragilis* and *Clostridium hathewayi* [30,33–36]. Moreover, dysbiosis of frailty patients has recently been associated with overlapping conditions, such as sarcopenia, that is loss of muscle mass and function. In particular, the gut microbial profile of both sarcopenic and frail subjects was found to be enriched in *Oscillospira* and *Ruminococcus*, with reduction in members of *Barnesiellaceae* and *Christenellaceae* families [37]. These results were confirmed in sarcopenic mouse models, in which butyrate administration contributed to the recovery of lean muscle mass [38,39]. In addition, sarcopenia in old age was associated with lower proportions of *Prevotella copri* [40]. In this context, it has been suggested that an altered gut microbial profile contributes to reduced appetite and therefore protein intake, altered metabolism and bioavailability of proteins and vitamins, and impaired mitochondrial function, thus resulting in reduced antioxidant capacity [41,42].

On the other hand, it is well known that gut microbes can be affected by several types of drugs [43], including proton pump inhibitors (PPIs) [44], whose long-term use in older adults has been associated with an increased rate of fractures [45]. A large study on frail individuals demonstrated that the gut microbiota of those taking PPIs was even less diverse and more depleted in symbiotic microbes, while enriched in pathogenic *Streptococcus* spp. [46]. These findings are of particular clinical significance considering that both ongoing PPI intake and alterations in the gut microbiota are related to the development of *Clostridioides difficile* infection [47] and that more than half of patients with *C. difficile* infection also suffer from frailty and show poor prognosis with the development of multiple complications [48]. Finally, nonsteroidal anti-inflammatory drugs, which are widely prescribed to the frail elderly, may also exacerbate gut microbiota dysbiosis, thus further contributing to health decline [49].

MICROBIOME-BASED INTERVENTION STRATEGIES TO AMELIORATE FRAILTY SYNDROME AND ITS OVERLAPPING CONDITIONS

Based on all the previous evidence, it is not surprising that the gut microbiota is considered a strategic preventive and therapeutic target in the context of age-related disorders [6▪]. Indeed, the development of microbiome-tailored intervention strategies aimed at restoring and maintaining a health-associated layout is gaining increasing attention in the field of healthy ageing (and possibly

longevity), to address the specific needs of the ageing population. In this scenario, some studies have focused on diet, prebiotics or probiotics to reverse gut microbiota imbalances while improving the quality of life of frail or prefrail subjects (see also Fig. 1). Within the NU-AGE project, which involved a 1-year Mediterranean dietary intervention tailored to elderly subjects in five European countries, Ghosh *et al.* [50] demonstrated that adherence to the diet led to an increased abundance of microbial groups positively associated with lower frailty and improved cognitive function, and negatively with inflammatory markers (i.e. CRP and IL-17), along with increased SCFA/branched-chain fatty acid production and lower production of secondary bile acids, p-cresols, ethanol and CO_2. More recently, a randomized controlled cross-over study on 20 prefrail elderly demonstrated recovery of the relative abundance of *Bifidobacterium* spp. after 4 weeks of dietary supplementation with galacto-oligosaccharides, although fecal metabolites and parameters of immune function and oxidative stress remained unaffected [51]. On the other hand, recent data from the US National Health and Nutrition Examination Survey underlined that increasing dietary fibre intake towards recommended levels can be considered a winning strategy to prevent age-associated decline in skeletal muscle mass [52]. In this regard, several clinical trials on sarcopenic individuals are currently underway such as the PROMOTe study, a randomized double-blind trial, which will investigate whether the modulation of the gut microbiota through the administration of a mixture of fructo-oligosaccharides and inulin, in addition to protein supplementation, may help improve muscle strength, compared to protein supplementation alone, in 70 elderly aged at least 60 years [53]. Numerous clinical trials on probiotics in frail individuals with overlapping conditions (i.e. sarcopenia) are also ongoing. Among these, a randomized clinical trial, enrolling 120 participants over the age of 65 with a frailty score greater than three points, will evaluate the efficacy of *Bifidobacterium longum* strains in delaying ageing (clinicaltrial.gov: NCT04911556). With specific regard to sarcopenia, preclinical studies have shown that the intake of *Lacticaseibacillus paracasei* slows age-related muscle loss by ensuring mitochondrial function in the mouse model senescence-accelerated mouse prone 8 [54]. Moreover, increased muscle mass has been observed with *Lactiplantibacillus plantarum* supplementation in both preclinical and clinical studies (but conducted in healthy young adults) [55,56]. In particular, the recent interventional trial conducted by Lee *et al.* [57] showed improvement in hand grip strength and overall functional performance in a cohort of 68 frail elderly people. Furthermore, comparing high and low probiotic dosage up to 18 weeks, the authors suggested a minimum of 6 weeks of continuous *L. plantarum* supplementation to reduce the risk of frailty and sarcopenia in the elderly population, while improving their overall stamina. Finally, although no studies have been conducted on frail or sarcopenic patients to date, it should be remembered that fecal microbiota transplantation is currently a life-saving practice for patients suffering from recurrent *C. difficile* infection, of which one of main risk factors is being over 65 years old [58,59].

CONCLUSION

As evidenced by the abundant literature in the field, the gut microbiota is involved in many different aspects of human life, from health to disease onset and progression, not least healthy ageing. In the course of ageing, the gut microbiota undergoes compositional and functional rearrangements, some of which can lead to dysbiosis, such as that seen in frailty syndrome. In this scenario, the gut microbiota has been identified as a viable option for the development of microbiome-based precision interventions as adjuvants to currently available drug therapies for the elderly. In particular, dietary, prebiotic and probiotic interventions could ameliorate symptoms of frailty and overlapping conditions, such as sarcopenia. However, there are still relatively few studies available in the literature, stressing the need for further research in larger cohorts with a combination of approaches for microbiome profiling, which could actually contribute to healthy ageing and hopefully promote longevity.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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