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**Comparison between frail and non-frail older adults' gut microbiota: A systematic review and meta-analysis.**


## Abstract

### Background

Emerging evidence suggests that the intestinal microbiota (IM) undergoes remodelling as we age, and this impacts the ageing trajectory and mortality in older adults. The aim was to investigate IM diversity differences between frail and non-frail older adults by meta-analysing previous studies.

### Methods

The protocol of this systematic review with meta-analysis was registered on PROSPERO (CRD42021276733). We searched for studies comparing IM diversity of frail and non-frail older adults, indexed on PubMed, Embase, Cochrane and Web of Science, in November, 2021.

### Results

We included 11 studies with 1239 participants, of which 340 were meta-analysed. Frailty was defined by a variety of criteria (i.e. Fried Scale, European Consensus on Sarcopenia). There were no differences in the meta-analyses between the frail and non-frail groups for species richness index (SMD=-0.147; 95% CI -0.394; 0.100, p=0.243) and species diversity index (SMD=-0.033; 95% IC -0.315; 0.250; p=0.820). However, we identified almost 50 differences between frail and non-frail within the relative abundance of bacteria phyla, families, genera, and species in the primary studies.

### Conclusions

The evidence to prove that there are differences between frail and non-frail IM diversity by meta-analysis is still lacking. The present results suggest that further investigation into role of specific bacteria, their function, and their influence on the physiopathology of frailty is needed.



**Keywords:** Frailty; Sarcopenia; Gut microbiome; Microbiota, Ageing.

## 1. Introduction

Although advances in public health and medical care have led to a global expansion of the population aged 65 years and above, the biggest problem is that healthy life expectancy has not kept pace with lifespan extension (House of Lords, 2021). Thus, understanding the potential contributors towards the ageing process is fundamental to bridge the gap between lifespan and health span (Campisi et al., 2019; Kapahi et al., 2010). Frailty is a multifactor geriatric syndrome that is characterized by an increased vulnerability to adverse health outcomes, which include defects in physical functioning, diminished muscle strength, exhaustion and unintentional weight loss, culminating in a reduced quality of life, loss of independence, and increased risk of hospitalisation and mortality in older adults (Fried et al., 2001; Hoogendijk et al., 2019). As a result, it is unsurprising that screening for frailty in older adults using the Fried (Fried et al., 2001) and Rockwood (Rockwood et al., 2005) frailty tools is becoming routine clinical practice (National Health Service, 2019). Moreover, the pathophysiology of frailty is complex and incorporates multiple interconnected pathways that are poorly understood.

In the past decade, we have seen a growing interest in the intestinal microbiome (IM) for its role in regulating multiple aspects of health, including nutrient absorption, carbohydrate fermentation, immune system regulation, central nervous system development, and skeletal muscle metabolism (Bäckhed et al., 2004; Saint-Georges-Chaumet and Edeas, 2016; Sovran et al., 2019; van de Wouw et al., 2017). The human IM remains relatively stable throughout adult life, but the microbiome composition undergoes compositional and functional changes with advancing age. This results in reduced IM biodiversity and a state of microbial dysbiosis (Maffei et al., 2017) that is accompanied by a loss of core commensal bacterial species (*Bacteriodetes, Bifidobacterium*) and an expansion of opportunistic microbes (*Fusobacterium, E.coli*) (Santoro et al., 2018). Microbial dysbiosis with ageing has been associated with a range of age-related conditions, including dementia, autoimmune inflammatory diseases, osteoporosis, increased risk of cardiovascular disease, and physical frailty (Brunt et al., 2019; Calvani et al., 2018; Karlsson et al., 2012; Ohlsson and Sjögren, 2015; Picca and Calvani, 2020). Furthermore, microbial compositional changes are accompanied by a shift in the microbial metabolite profile, namely a decline in short chain fatty acids (SCFAs) which play a key role in regulating host physiological processes (Conway and A Duggal, 2021; Rampelli et al., 2013).

The IM has been shown to impact skeletal muscle metabolism; thus, it makes sense that multiple studies have reported an association between microbial dysbiosis and the loss of muscle mass and function (Poggiogalle et al., 2019; Ticinesi et al., 2019). Claesson *et al*., showed that older adults living in a long-term care centre had a significantly less diverse IM than residents within the community, and the reduction in community-associated biodiversity was correlated with an increase in frailty (Claesson et al., 2012). On the other hand, a study by Milani *et al*., conducted with hospitalized older adults showed a low association between IM diversity and the presence of frailty (Milani et al., 2016). It highlights an urgent need of understanding the underlying pathophysiology driving frailty to elucidate some targetable mechanisms.

Furthermore, age-associated microbial dysbiosis has also been associated with increased intestinal membrane barrier permeability (Tran and Greenwood-Van Meerveld, 2013), resulting in translocation of microbial products and toxins into circulation, which has recently been identified as a contributing factor towards the age-associated increase in basal inflammation in aged individuals, termed inflammageing (Thevaranjan et al., 2017). Pro-inflammatory cytokines have been reported to induce muscle degradation via the ubiquitin proteasome pathway and have been recognised as potential contributors towards frailty (Soysal et al., 2016). Thus, it is safe to hypothesise an involvement of the gut microbiota in driving frailty in older adults, and on these grounds previous studies have confirmed the existence of "gut-muscle axis".

Although a gut-muscle axis might exist, the underlying pathogenesis driving frailty remains incompletely understood in particular the role of the gut microbiome driving the frailty phenotype. We hypothesise that frail older adults will have a lower IM diversity than the non-frail ones in the meta-analyses of previous studies. Furthermore, we expect to see differences in the relative abundance of bacteria.

## 2. Materials and methods

### 2.1 Protocol and registration

This systemic review was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines (Moher et al., 2009). All details of the review protocol can be assessed on PROSPERO (CRD42021276733).

### 2.2 Search strategy and selection criteria

The syntax combined the synonyms for frailty (e.g. “sarcopenia” or “muscular atrophy” or “sarcopenic” or “physical frailty” or “barthel index” or "frailty" or "frailties" or "frailness" or "frailty syndrome") and gut microbiome (e.g. "gastrointestinal microbiome" or "gut microbiome" or "gastrointestinal microbiomes" or "gut microbiota" or "fecal microbiota composition" or "microbiota” or "gut bacteria"), and details of each search can be assessed on PROSPERO (CRD42021276733). The search was conducted on November 2021 on PubMed (MEDLINE), Embase, Cochrane and Web of Science. There was no restriction on the publication’s date, and the terms were searched within all words in titles and abstracts.

Published articles were included in this meta-analysis if they met the following criteria: population older adults (≥ 60 years), both sexes, studies with comparison between two groups frail and non-frail (any validated scale); and the studies that measured diversity IM. The exclusion criteria encompassed non-original studies such as reviews, conference papers, letters and commentaries, non-human studies, non-English language, and studies that did not assess alpha diversity or relative abundance in frail and non-frail groups. Complementarily, papers that evaluated differences in the relative abundance in frail populations regarding the bacteria phyla, families, genera, and species were included in qualitative analysis.

### 2.4 Study selection

The selection of studies based on their abstracts was made on Rayyan (Ouzzani et al., 2016). The studies retrieved after this selection were scrutinized in a spreadsheet and clustered for each of the 3 main analysis. Two authors (HMA and JC) selected the studies independently, and the disagreements were solved with further discussion.

### 2.5 Data extraction

Data extraction was also done independently, and compared to avoid errors. The main IM diversity assessment used in the literature is alpha diversity, which is based on the total number of species, relative abundances of the species, or indices that combine these two dimensions (Lozupone and Knight, 2008). Thus, the two alpha indices, richness index and diversity index, and the relative abundance of bacteria phyla, families, genera, and species were extracted for analysis.

Mean, standard deviation (SD) and sample number (n) between group frail and non-frail for each outcome variable were collected for analysis. Median and interquartile

range (IQR) was replaced by mean and SD (SD=(IQR / 1.35), if SD was not provided in the original study (Hozo et al., 2005). The online software WebPlotDigitizer 4.5 was used to convert pixels to the specific units of measure and used when extraction of data from figures was needed.

Secondary data, such as age of participants, type of frailty criteria applied, frailty effect, method of IM diversity assessment, relative abundance in the frail and non-frail groups and significance level each study, were also collected for descriptive purposes and subgroup analysis.

### 2.6 Assessment of study quality

The quality of the studies was assessed for characterization purposes and was not an exclusion criterion. It was assessed by the Newcastle-Ottawa scale (NOS) (Wells et al., n.d.), which evaluates the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure of interest for case-control and cohort studies, leading to a maximum of 9 points score.

### 2.7 Statistical analyses

The meta-analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3.3.070. We performed two meta-analyses for group comparisons, one for each selected outcome (richness index and diversity index). In these meta-analyses the effect size was calculated based on the standard mean difference (SMD) between frail and non-frail groups. When there was significant heterogeneity ($p \leq 0.05$) we calculated the randomized effect, and when there was no significant heterogeneity ($p > 0.05$) we used fixed effects. Publication bias was analysed by the Egger test and a p-value of $\leq 0.05$ was considered significant.

For species richness index and diversity index, we also ran subgroup analyses, applying the Q test to compare the SMD of studies assessing frailty by different criteria (the ones assessing by frailty criteria and the ones by Sarcopenia criteria), assessing IM diversity by different methods, and the SMD of studies assessing alpha diversity by different indexes.

## 3. Results

### 3.1 Study selection

The flowchart of the study selection is shown in **Figure 1**. One study comparing the IM between frailty and control was excluded due to the inclusion of some frail individuals in the control group (Ntemiri et al., 2017). Studies presenting regression coefficients for comparison between more than two groups (frail and non-frail) were excluded from meta-analysis (Ghosh et al., 2020; Jackson et al., 2016; Maffei et al., 2017), but maintained for the systematic review (Kang et al., 2021; Margiotta et al., 2021, 2020; Picca et al., 2020; Ponziani et al., 2021; Ticinesi et al., 2020, 2017; Zhang et al., 2020). Thus, 11 studies were included in the review and seven in the meta-analyses.

### 3.2 Characteristics of the studies

**Table 1** shows the different methods of frailty assessment in the studies included, such as Fried's Frailty Phenotype score (Fried et al., 2001), Rockwood Clinical Frailty Scale (Rockwood et al., 2005), Rockwood Scale Modified (Joseph et al., 2016) and Groningen Frailty Indicator (GFI) (Steverink et al., 2001), and some sarcopeniaassessments including the operational definition elaborated in the SPRINTT project (Marzetti et al., 2018, 2015), Asian Working Group for Sarcopenia 2019 Consensus Report (Chen et al., 2020), European Consensus on Sarcopenia (Cruz-Jentoft et al., 2010; Janssen et al., 2004), Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (Studenski et al., 2014), European Working Group on Sarcopenia in Older People 2 (Cruz-Jentoft et al., 2019), 34-item frailty index (FI34) (Kim et al., 2013), and Rockwood index (Singh et al., 2012). We meta-analysed 340 (161 frail and 179 non-frail), above 60 years old (range 63-83), including 81.2% woman, 36.4% community dwellers, 45.4% older hospitalized/ nursing homes and 18.8% older adults suffering from chronic diseases, such as chronic kidney disease (CKD). Most of the studies (85.7%) only included participants that did not consume antibiotics in the past one month and belonged to the same demographic location (Italy). Six studies assessed richness index (Kang et al., 2021; Margiotta et al., 2020; Picca et al., 2020; Ponziani et al., 2021; Ticinesi et al., 2020, 2017), three assessed diversity index (Kang et al., 2021; Margiotta et al., 2020; Zhang et al., 2020), and ten assessed the relative abundance of bacteria species (Jackson et al., 2016; Kang et al., 2021; Maffei et al., 2017; Margiotta et al., 2021, 2020; Picca et al., 2020; Ponziani et al., 2021; Ticinesi et al., 2020; van Tongeren et al., 2005; Zhang et al., 2020).

3.3 Risk of bias

The majority of the studies included in the meta-analyses presented a moderate or high-quality score on NOS: four of them scored 6 (Margiotta et al., 2021, 2020; Ticinesi et al., 2017; Zhang et al., 2020) and the other four scored 7 (Kang et al., 2021; Picca et al., 2020; Ponziani et al., 2021; Ticinesi et al., 2020). Within the studies included in the qualitative analysis, two had a moderate quality score of 5 (Jackson et al., 2016; Maffei et al., 2017) and one scored 3 (van Tongeren et al., 2005) due to the lack of clarity on the selection of controlled participants. See details of the NOS assessment in **Supplementary tables 1 and 2.**

3.4 Evidence synthesis

The forest plots (**Figure 2**) showed no significant difference between frail and non-frail groups for any of the alpha diversity indexes: richness index (SMD=-0.147; 95% CI -0.394; 0.100, p=0.243) and diversity index (SMD=-0.033; 95% IC -0.315; 0.250; p=0.820). There was no significant heterogeneity (p >0.05) or inconsistency between studies, and the Egger tests suggested that there were no significant effects for publication bias in these meta-analyses (p >0.05). Complementarily, when the only study assessing kidney patients (Margiotta et al., 2020) was excluded, we confirmed the absence of significance between frail and non-frail groups for richness (SMD=-0.190, 95%CI=−0.467; 0.088, p=0.180) and diversity indexes (SMD=-0.291, 95%CI=−0.784; 0.202, p=0.248). Although, another study assessed cirrhotic patients with sarcopenia (Ponziani et al., 2021), only their control group of healthy participants was included for analysis.

We performed a subgroup analysis on the richness and diversity index, dividing the analysis between studies assessing frailty by conventional scales (i.e. Fried scale, Rockwood score, GFI, modified Rockwood score) and studies assessing frailty by sarcopenia evaluation (i.e. Asian Working Group for Sarcopenia 2019 Guidelines, European Consensus on Sarcopenia, Foundation for the National Institutes of Health sarcopenia project). There was also no difference in the subgroups of frailty assessment between frail and non-frail for the richness index (only frailty criteria SMD=-0.227; 95%IC=-0.578; 0.122; p=0.202; and by sarcopenia criteria SMD=-0.067; 95%IC=-0.416; 0.281; p=0.704, p difference [Q test] =0.525) and the diversity index (only frailty

evaluation SMD=0.017; 95%IC=-0.96; 0.331; p=0.913; and frailty by sarcopenia evaluation (SMD=-0.243; 95%IC=-0.887; 0.400; p=0.459, p difference [Q test] =0.476).

No difference between frail and non-frail was identified within the Chao 1 index (RMD=-17.385, 95%CI=−73.882; 39.113, p=0.546), the Index of species richness (RMD=-3.000, 95%CI=-25.049, 19.049, p=0.790), the Shannon index (RMD=0.075, 95%CI=-0.243; 0.394, p=0.643), the Simpson index (RMD=0.003, 95CI%=-0.009, 0.016; p=0.599), and Species diversity (RDM=-90.909, 95%CI=-331.259; 149.441, p=0.458).

The last subgroup analysis was the comparison between different IM composition assessments of the small ribosomal subunit (16S rRNA) gene, by regions V3-V4, only V3, shotgun metagenomic sequencing and the ones that did not inform the region. There was no difference in the effect of frailty on the diversity index (p=0.443) between the studies assessing 16S rRNA in the regions V3-V4 (SMD=-0.017, 95%CI=-0.433; 0.399, p=0.936) and the studies assessing 16S rRNA with no clear region defined (SMD=-0.358, 95%CI=-1.124; 0.408, p=0.360). There was also no difference in the effect of frailty on the richness index (p=0.391) among studies assessing 16S rRNA in V3 (SMD=-0.401, 95%CI=-0.858; 0.057, p=0.086), assessing 16S rRNA in V3-V4 (SMD=0.001, 95%CI=-0.347; 0.348, p=0.997) and study shotgun metagenomic sequencing (SMD=-0.146, 95%CI=-1.186; 0.902, p=0.790).

We presented in **Table 2** the p-value of the primary studies' comparisons between frail and non-frail, for the relative abundance of bacteria phyla, families, genera, or species. Frail group had a higher *TM7* phylum; *Barnesiellaceae, Bifidobacteriaceae, Coriobacteriaceae, Mogibacteriaceae, Micrococcaceae, Peptostreptococcaceae, Ruminococcaceae families; Actinomyces, Anaerotruncus, Bifidobacterium, Coprobacillus, Dialister, Dorea, Eggerthella, Erwinia, Eubacterium, Faecalibacterium, Lactobacillus, Megasphaera, Oscillospira, Rothia, Ruminococcus, Pyramidobacter Veillonella genera; and Eggerthella lenta, Eubacterium cylindroides, Eubacterium dolichun* species than the non-frail group. The frail group had a lower relative abundance of *Firmicutes and Verrucomicrobia phyla; Erysipelotrichaceae, Gemellaceae* families; *Acidaminococcus, Bacteroides, Prevotella, Fusicatenibacter, Gemella, Paraprevotella, Lachnoclostridium, Roseburia, Slackia, Sutterella* genera; and *Alistipes shahii, Faecalibacterium prausnitzii, Roseburia inulinivorans* species than the non-frail group. The relative abundance of the *Verrucomicrobiaceae, Veillonellaceae and Rikenellaceae*

*families*, and the *Akkermansia genus* presented inconsistent results across the studies, being significantly higher in frail or in non-frail depending on the study that was analysed.

## 4. Discussion

On assessment of alpha diversity, no significant differences were observed between frail and non-frail groups. Diversity and richness index analyses were both consistent and homogeneous, suggesting that there was substantial evidence despite not many studies being included. Our biodiversity analyses were restricted to alpha diversity due to the absence of beta diversity in the studies included. Although there were no differences in IM alpha diversity between the frail and non-frail groups, it is important to highlight that alpha diversity indexes, such as the Chao 1 index (the most commonly used among the studies included), are based on the total number of species within a community. This means that they do not evaluate the dominance and equality of the microorganisms, and are unable to identify differences between species composition (Lozupone and Knight, 2008). With regards to beta diversity, the literature was also inconclusive as one study showed lower beta diversity for frail older adults compared to healthy older adults (Kang et al., 2021), whilst another study investigating IM beta diversity in hospitalized older adults found a higher beta diversity in frail older adults (Zhang et al., 2020). Although it is not expected that frail older adults have a higher beta diversity than non-frail older adults, this contradictory finding could be due to the hospitalization. This also could have been a source of theoretical heterogeneity in our alpha diversity meta-analysis, since the population of the studies included in our review consisted of 57.1% hospitalized older adults and 14.2 % CKD patients. In fact, changes in the composition of the IM of hospitalized patients have been associated with an altered dietary pattern, primarily driven by a low ingestion of dietary fibre, polypharmacy, and slowed transit time (Milani et al., 2016; Roager et al., 2016; Vaziri et al., 2013). Furthermore, studies that have compared alpha diversity in middle-aged community-dwelling adults have found lower diversity in frail adults as expected (Jackson et al., 2016; Maffei et al., 2017).

Among the relative abundances of different phylum between frail and non-frail older adults, *Firmicutes* and *Verrumicrobia* were lower in frail older adults and both phyla are dominant in the healthy human IM (Rinninella et al., 2019). Inversely, the relative abundance of the *TM7* phylum was higher in the frail group, and there is evidence of a correlation between this phylum and inflammatory mucosal diseases which encompasses

inflammatory bowel disease (Brinig et al., 2003; Kuehbacher et al., 2008), this bacterial is possibly involved in the inflammageing potential of the microbiota (Fransen et al., 2017; Jakobsson et al., 2015). In this way, these differences support a shift towards a state of dysbiosis in the IM of frail older adults.

With regards to the relative abundance of families between frail and non-frail, the *Barnesiellaceae, Bifidobacteriaceae, Coriobacteriaceae, Mogibacteriaceae, Ruminococcaceae,* and *Veillonellaceae* are families with higher relative abundance in frail older adults and other studies have shown an association between their abundance and frailty or diseases prevalence (Aho et al., 2019; Claesson et al., 2012; Haran et al., 2018; Li et al., 2021; Lin et al., 2018; Lourençe et al., 2018). The *Mogibacteriaceae* family is commonly associated with inflammation in other niches, such as the periodontal environment (Lourençe et al., 2018). An imbalance in the IM ecosystem of this family is evidently increased in the frail population, and it is positively associated with C-reactive protein levels, further strengthening the hypothesis of a link between microbiome changes, inflammageing and frailty (Margiotta et al., 2020). The *Barnesiellaceae* family has also been associated with increase systemic levels of pro-inflammatory cytokines, such as TNFα (Margiotta et al., 2021). The *Bifidobacteriaceae* family is composed of important probiotic bacteria that regulate intestinal and immune system functions, but since they were improved in the frail group we speculate this could be a potential compensatory mechanism to rebalance gut homeostasis (Wallen et al., 2020). Indeed, another study found higher relative abundance of the *Bifidobacteriaceae* family in patients with Parkinson's disease, who also have other markers of poor IM diversity (Shen et al., 2021).

With respect to the relative abundance of genera, *Actinomyces, Anaerotruncus, Coprobacillus, Dialister, Dorea, Eggerthella,* Eubacterium*, Rothia,* and *Veillonella* were higher in frail than non-frail older adults. Changes in the IM *Actinomyces* species are expected to influence various alimentary tract diseases and inflammation (Li et al., 2018). These diseases cause epithelial atrophy in the intestine, which can induce diminished mucosal resistance. *Anaerotruncus* and *Coprobacillus* have also been associated with inflammation and ageing in prior studies (Candela et al., 2014; Conley et al., 2016). Surprisingly, the *Bifidobacterium, Faecalibacterium, Lactobacillus, Ruminococcus,* and *Oscillospira* genera that are associated with a healthy gut and longevity (Biagi et al., 2016; Wang et al., 2015) were higher in frail older adults. In fact, previous studies have

shown that although Lactobacillus is considered probiotic due to its ability to regulate immune function, produce antioxidants (some species), adhere to the mucus layer in the gut to protect against the invasion of pathogens (Goldstein et al., 2015; Ljungh and Wadström, 2006), some species within this genus can be elevated under specific inflammatory conditions (Liu et al., 2013; Salminen et al., 2006).

An important finding of this review is that the increase in the relative abundance of the *Eggerthella* genus in frail older people was evidenced in four studies within this review (Jackson et al., 2016; Maffei et al., 2017; Margiotta et al., 2020; Picca et al., 2020). Bacteria from this genus use the amino acid threonine, the main component of intestinal mucin, deregulating intestinal epithelial junctions and increasing paracellular permeability to endotoxins (Rao, 2008). Additionally, *Eggerthella lenta*, a key species within the *Eggerthella* genus, was higher in frail older adults in one of the two studies that tested this species (Jackson et al., 2016; Margiotta et al., 2020). Although, *Eggerthella lenta* has been previously considered a commensal bacteria in the gut, it has been associated with gastrointestinal disease (Thota et al., 2011) and strongly correlated with inflammatory diseases (Zhang et al., 2015).

The relative abundance of the *Alistipes shahii, Roseburia inulinivorans,* and *Faecalibacterium prausnitzii* species was lower in frail than in non-frail. Those species are saccharolytic bacteria responsible for short-chain fatty acid (SCFA) generation (Parker et al., 2020). *Faecalibacterium prausnitzii* is considered a key butyrate producer (Sokol et al., 2008), and three studies showed significantly lower relative abundances with frailty. *Prevotella*, *Fusicatenibacter*, Lachnoclostridium, and *Roseburia* genera that are producers of SCFAs were also less abundant in frail older adults. SCFAs play an important role in IM health since butyrate is the main energy source for the colonic epithelial cells (Louis and Flint, 2017) and helps maintain tight junctions to regulate intestinal permeability (Peng et al., 2009), which in turn prevents endotoxin translocation and activation of inflammatory pathways (Vinolo et al., 2011), a potential anti-inflammageing effect. Furthermore, these fatty acids have an effect on muscle cells, improving mitochondrial activity, fatty acid oxidation (Vinolo et al., 2011), protein synthesis (Lin et al., 2017), and energy availability (Jackson et al., 2016; Saint-Georges-Chaumet and Edeas, 2016).

The relative abundance of the *Verrucomicrobiaceae and Veillonellaceae* families and the *Akkermansia* genus was higher in frail older adults in some studies but lower in

frail older adults in other studies. Higher abundances of these families and genus have been associated with a healthy IM diversity, and thus we would expect to see lower abundances in frailty (Margiotta et al., 2021). It is possible that controversial increments in these potential commensal bacteria are an attempt of the IM to compensate intestinal dysfunction and dysbiosis in frail adults.

The findings of this study need to be interpreted with its limitations. Firstly, the small sample size of the studies and the specific ethnic origin (only from Italy, China, Netherlands, UK, USA) require for a cautious interpretation of results and impede generalization of findings older adults from other countries. Given the small number of studies, we could not test the influence of confounding factors such as diet, physical activity, co-morbid conditions, and medications. Polypharmacy and antibiotics, for example, are among the factors that are related to intestinal dysbiosis in older adults (Becattini et al., 2016; Ticinesi et al., 2017), and future studies should explore the interaction between drugs and IM diversity in frail older adults. Another limitation was the inclusion of studies assessing sarcopenia to represent frailty, since frailty is a comprehensive criterion. However, we compared the effect of frailty on IM diversity between these studies and no difference was found, suggesting the IM diversity is not affected by frailty when it is assessed by the validated frailty criteria or only by sarcopenia.

Also, despite the meta-analysis of diversity indexes had sample overlap caused by some studies that evaluated two types of indexes in the same population, we excluded this bias in the further subgroup analysis and confirmed the same results for each index without sample overlapping.

It is noteworthy that contradictory results of relative abundance for some bacteria species in different studies could have been influenced by different methods of IM composition assessments and more studies will be necessary to clarify this influence in future integrative analysis.

## 5. Conclusion

The relationship between microbiota and frailty is complex, and this has been further highlighted in our meta-analyses consistently found no difference in alpha diversity between frail and non-frail, there was some incipient evidence regarding the

different relative abundance of bacteria between frail and non-frail older adults. Future studies need to consider the influence of many covariates, such as diet, location, physical activity level, multimorbidity, and polypharmacy, on the IM composition of frail individuals. The present results reinforce the need for further investigation on the role of specific bacteria and microbial metabolites and their influence on the physiopathology of frailty. Thus, the relationship between IM and frailty in older adults remains a very promising area of research and a target for closing the gap between lifespan and health span.

**Declaration of Conflicts of Interest**

None.

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**References**

Aho, V.T.E., Pereira, P.A.B., Voutilainen, S., Paulin, L., Pekkonen, E., Auvinen, P., Scheperjans, F., 2019. Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression. EBioMedicine 44, 691–707. https://doi.org/10.1016/j.ebiom.2019.05.064

Bäckhed, F., Ding, H., Wang, T., Hooper, L. V, Koh, G.Y., Nagy, A., Semenkovich, C.F., Gordon, J.I., 2004. The gut microbiota as an environmental factor that regulates fat storage. Proc. Natl. Acad. Sci. U. S. A. 101, 15718–15723. https://doi.org/10.1073/pnas.0407076101

Becattini, S., Taur, Y., Pamer, E.G., 2016. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. Trends Mol. Med. 22, 458–478. https://doi.org/10.1016/j.molmed.2016.04.003

Biagi, E., Franceschi, C., Rampelli, S., Severgnini, M., Ostan, R., Turroni, S., Consolandi, C., Quercia, S., Scurti, M., Monti, D., Capri, M., Brigidi, P., Candela, M., 2016. Gut Microbiota and Extreme Longevity. Curr. Biol. 26, 1480–1485. https://doi.org/10.1016/j.cub.2016.04.016

Brinig, M.M., Lepp, P.W., Ouverney, C.C., Armitage, G.C., Relman, D.A., 2003. Prevalence of bacteria of division TM7 in human subgingival plaque and their association with disease. Appl. Environ. Microbiol. 69, 1687–1694. https://doi.org/10.1128/AEM.69.3.1687-1694.2003

Brunt, V.E., Gioscia-Ryan, R.A., Richey, J.J., Zigler, M.C., Cuevas, L.M., Gonzalez, A., Vázquez-Baeza, Y., Battson, M.L., Smithson, A.T., Gilley, A.D., Ackermann, G., Neilson, A.P., Weir, T., Davy, K.P., Knight, R., Seals, D.R., 2019. Suppression of the gut microbiome ameliorates age-related arterial dysfunction and oxidative stress in mice. J. Physiol. 597, 2361–2378. https://doi.org/10.1113/JP277336

Calvani, R., Picca, A., Lo Monaco, M.R., Landi, F., Bernabei, R., Marzetti, E., 2018. Of Microbes and Minds: A Narrative Review on the Second Brain Aging. Front. Med. 5, 53. https://doi.org/10.3389/fmed.2018.00053

Campisi, J., Kapahi, P., Lithgow, G.J., Melov, S., Newman, J.C., Verdin, E., 2019. From discoveries in ageing research to therapeutics for healthy ageing. Nature 571, 183–192. https://doi.org/10.1038/s41586-019-1365-2

Candela, M., Turroni, S., Biagi, E., Carbonero, F., Rampelli, S., Fiorentini, C., Brigidi, P., 2014. Inflammation and colorectal cancer, when microbiota-host mutualism breaks. World J. Gastroenterol. 20, 908–922. https://doi.org/10.3748/wjg.v20.i4.908

Chen, L.-K., Woo, J., Assantachai, P., Auyeung, T.-W., Chou, M.-Y., Iijima, K., Jang, H.C., Kang, L., Kim, M., Kim, S., Kojima, T., Kuzuya, M., Lee, J.S.W., Lee, S.Y., Lee, W.-J., Lee, Y., Liang, C.-K., Lim, J.-Y., Lim, W.S., Peng, L.-N., Sugimoto, K., Tanaka, T., Won, C.W., Yamada, M., Zhang, T., Akishita, M., Arai, H., 2020. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J. Am. Med. Dir. Assoc. 21, 300-307.e2. https://doi.org/10.1016/j.jamda.2019.12.012

Claesson, M.J., Jeffery, I.B., Conde, S., Power, S.E., O'Connor, E.M., Cusack, S., Harris, H.M.B., Coakley, M., Lakshminarayanan, B., O'Sullivan, O., Fitzgerald, G.F., Deane, J., O'Connor, M., Harnedy, N., O'Connor, K., O'Mahony, D., van Sinderen, D., Wallace, M., Brennan, L., Stanton, C., Marchesi, J.R., Fitzgerald, A.P., Shanahan, F., Hill, C., Ross, R.P., O'Toole, P.W., 2012. Gut microbiota

composition correlates with diet and health in the elderly. Nature 488, 178+. https://doi.org/10.1038/nature11319

Conley, M.N., Wong, C.P., Duyck, K.M., Hord, N., Ho, E., Sharpton, T.J., 2016. Aging and serum MCP-1 are associated with gut microbiome composition in a murine model. PeerJ 4, e1854. https://doi.org/10.7717/peerj.1854

Conway, J., A Duggal, N., 2021. Ageing of the gut microbiome: Potential influences on immune senescence and inflammageing. Ageing Res. Rev. 68, 101323. https://doi.org/10.1016/j.arr.2021.101323

Cruz-Jentoft, A.J., Baeyens, J.P., Bauer, J.M., Boirie, Y., Cederholm, T., Landi, F., Martin, F.C., Michel, J.-P., Rolland, Y., Schneider, S.M., Topinková, E., Vandewoude, M., Zamboni, M., 2010. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 39, 412–423. https://doi.org/10.1093/ageing/afq034

Cruz-Jentoft, A.J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A.A., Schneider, S.M., Sieber, C.C., Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., 2019. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48, 16–31. https://doi.org/10.1093/ageing/afy169

Fransen, F., van Beek, A.A., Borghuis, T., Aidy, S. El, Hugenholtz, F., van der Gaast-de Jongh, C., Savelkoul, H.F.J., De Jonge, M.I., Boekschoten, M. V, Smidt, H., Faas, M.M., de Vos, P., 2017. Aged Gut Microbiota Contributes to Systemical Inflammaging after Transfer to Germ-Free Mice. Front. Immunol. 8, 1385. https://doi.org/10.3389/fimmu.2017.01385

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A. Biol. Sci. Med. Sci. 56, M146-56. https://doi.org/10.1093/gerona/56.3.m146

Ghosh, T.S., Das, M., Jeffery, I.B., O'Toole, P.W., 2020. Adjusting for age improves identification of gut microbiome alterations in multiple diseases. Elife 9. https://doi.org/10.7554/eLife.50240

Goldstein, E.J.C., Tyrrell, K.L., Citron, D.M., 2015. Lactobacillus species: taxonomic

complexity and controversial susceptibilities. Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am. 60 Suppl 2, S98-107. https://doi.org/10.1093/cid/civ072

Haran, J.P., Bucci, V., Dutta, P., Ward, D., McCormick, B., 2018. The nursing home elder microbiome stability and associations with age, frailty, nutrition and physical location. J. Med. Microbiol. 67, 40–51. https://doi.org/10.1099/jmm.0.000640

Hoogendijk, E.O., Afilalo, J., Ensrud, K.E., Kowal, P., Onder, G., Fried, L.P., 2019. Frailty: implications for clinical practice and public health. Lancet (London, England) 394, 1365–1375. https://doi.org/10.1016/S0140-6736(19)31786-6

House of Lords, 2021. How can we live longer in better health?

Hozo, S.P., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5, 13. https://doi.org/10.1186/1471-2288-5-13

Jackson, M.A., Jeffery, I.B., Beaumont, M., Bell, J.T., Clark, A.G., Ley, R.E., O'Toole, P.W., Spector, T.D., Steves, C.J., 2016. signatures of early frailty in the gut microbiota (vol 8, 8, 2016). GENOME Med. 8. https://doi.org/10.1186/s13073-016-0275-2

Jakobsson, H.E., Rodríguez-Piñeiro, A.M., Schütte, A., Ermund, A., Boysen, P., Bemark, M., Sommer, F., Bäckhed, F., Hansson, G.C., Johansson, M.E. V, 2015. The composition of the gut microbiota shapes the colon mucus barrier. EMBO Rep. 16, 164–177. https://doi.org/10.15252/embr.201439263

Janssen, I., Baumgartner, R.N., Ross, R., Rosenberg, I.H., Roubenoff, R., 2004. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am. J. Epidemiol. 159, 413–421. https://doi.org/10.1093/aje/kwh058

Joseph, B., Zangbar, B., Pandit, V., Fain, M., Mohler, M.J., Kulvatunyou, N., Jokar, T.O., O'Keeffe, T., Friese, R.S., Rhee, P., 2016. Emergency General Surgery in the Elderly: Too Old or Too Frail? J. Am. Coll. Surg. 222, 805–813. https://doi.org/10.1016/j.jamcollsurg.2016.01.063

Kang, L., Li, P., Wang, D., Wang, T., Hao, D., Qu, X., 2021. Alterations in intestinal microbiota diversity, composition, and function in patients with sarcopenia. Sci. Rep. 11. https://doi.org/10.1038/s41598-021-84031-0

Kapahi, P., Chen, D., Rogers, A.N., Katewa, S.D., Li, P.W.-L., Thomas, E.L., Kockel, L., 2010. With TOR, less is more: a key role for the conserved nutrient-sensing TOR pathway in aging. Cell Metab. 11, 453–465. https://doi.org/10.1016/j.cmet.2010.05.001

Karlsson, F.H., Fåk, F., Nookaew, I., Tremaroli, V., Fagerberg, B., Petranovic, D., Bäckhed, F., Nielsen, J., 2012. Symptomatic atherosclerosis is associated with an altered gut metagenome. Nat. Commun. 3, 1245. https://doi.org/10.1038/ncomms2266

Kim, S., Welsh, D.A., Cherry, K.E., Myers, L., Jazwinski, S.M., 2013. Association of healthy aging with parental longevity. Age (Dordr). 35, 1975–1982. https://doi.org/10.1007/s11357-012-9472-0

Kuehbacher, T., Rehman, A., Lepage, P., Hellmig, S., Fölsch, U.R., Schreiber, S., Ott, S.J., 2008. Intestinal TM7 bacterial phylogenies in active inflammatory bowel disease. J. Med. Microbiol. 57, 1569–1576. https://doi.org/10.1099/jmm.0.47719-0

Li, J., Li, Y., Zhou, Y., Wang, C., Wu, B., Wan, J., 2018. Actinomyces and Alimentary Tract Diseases: A Review of Its Biological Functions and Pathology. Biomed Res. Int. 2018, 3820215. https://doi.org/10.1155/2018/3820215

Li, Zhuo, Lu, G., Li, Zhe, Wu, B., Luo, E., Qiu, X., Guo, J., Xia, Z., Zheng, C., Su, Q., Zeng, Y., Chan, W.Y., Su, X., Cai, Q., Xu, Y., Chen, Y., Wang, M., Poon, W.S., Luo, X., 2021. Altered Actinobacteria and Firmicutes Phylum Associated Epitopes in Patients With Parkinson's Disease. Front. Immunol. 12, 632482. https://doi.org/10.3389/fimmu.2021.632482

Lin, A., Zheng, W., He, Y., Tang, W., Wei, X., He, R., Huang, W., Su, Y., Huang, Y., Zhou, H., Xie, H., 2018. Gut microbiota in patients with Parkinson's disease in southern China. Parkinsonism Relat. Disord. 53, 82–88. https://doi.org/10.1016/j.parkreldis.2018.05.007

Lin, R., Liu, W., Piao, M., Zhu, H., 2017. A review of the relationship between the gut microbiota and amino acid metabolism. Amino Acids 49, 2083–2090. https://doi.org/10.1007/s00726-017-2493-3

Liu, X., Zou, Q., Zeng, B., Fang, Y., Wei, H., 2013. Analysis of fecal Lactobacillus community structure in patients with early rheumatoid arthritis. Curr. Microbiol.

67, 170–176. https://doi.org/10.1007/s00284-013-0338-1

Ljungh, A., Wadström, T., 2006. Lactic acid bacteria as probiotics. Curr. Issues Intest. Microbiol. 7, 73–89.

Louis, P., Flint, H.J., 2017. Formation of propionate and butyrate by the human colonic microbiota. Environ. Microbiol. 19, 29–41. https://doi.org/10.1111/1462-2920.13589

Lourenço, T.G.B., Spencer, S.J., Alm, E.J., Colombo, A.P.V., 2018. Defining the gut microbiota in individuals with periodontal diseases: an exploratory study. J. Oral Microbiol. 10, 1487741. https://doi.org/10.1080/20002297.2018.1487741

Lozupone, C.A., Knight, R., 2008. Species divergence and the measurement of microbial diversity. FEMS Microbiol. Rev. 32, 557–578. https://doi.org/10.1111/j.1574-6976.2008.00111.x

Maffei, V.J., Kim, S., Blanchard, E., Luo, M., Jazwinski, S.M., Taylor, C.M., Welsh, D.A., 2017. Biological Aging and the Human Gut Microbiota. JOURNALS Gerontol. Ser. A-BIOLOGICAL Sci. Med. Sci. 72, 1474–1482. https://doi.org/10.1093/gerona/glx042

Margiotta, E., Caldiroli, L., Callegari, M.L., Miragoli, F., Zanoni, F., Armelloni, S., Rizzo, V., Messa, P., Vettoretti, S., 2021. Association of Sarcopenia and Gut Microbiota Composition in Older Patients with Advanced Chronic Kidney Disease, Investigation of the Interactions with Uremic Toxins, Inflammation and Oxidative Stress. Toxins (Basel). 13. https://doi.org/10.3390/toxins13070472

Margiotta, E., Miragoli, F., Callegari, M.L., Vettoretti, S., Caldiroli, L., Meneghini, M., Zanoni, F., Messa, P., 2020. Gut microbiota composition and frailty in elderly patients with Chronic Kidney Disease. PLoS One 15. https://doi.org/10.1371/journal.pone.0228530

Marzetti, E., Calvani, R., Landi, F., Hoogendijk, E.O., Fougère, B., Vellas, B., Pahor, M., Bernabei, R., Cesari, M., 2015. Innovative Medicines Initiative: The SPRINTT Project. J. frailty aging 4, 207–208.

Marzetti, E., Cesari, M., Calvani, R., Msihid, J., Tosato, M., Rodriguez-Mañas, L., Lattanzio, F., Cherubini, A., Bejuit, R., Di Bari, M., Maggio, M., Vellas, B.,

Dantoine, T., Cruz-Jentoft, A.J., Sieber, C.C., Freiberger, E., Skalska, A., Grodzicki, T., Sinclair, A.J., Topinkova, E., Rýznarová, I., Strandberg, T., Schols, A.M.W.J., Schols, J.M.G.A., Roller-Wirnsberger, R., Jónsson, P. V, Ramel, A., Del Signore, S., Pahor, M., Roubenoff, R., Bernabei, R., Landi, F., 2018. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants. Exp. Gerontol. 113, 48–57. https://doi.org/10.1016/j.exger.2018.09.017

Milani, C., Ticinesi, A., Gerritsen, J., Nouvenne, A., Lugli, G.A., Mancabelli, L., Turroni, F., Duranti, S., Mangifesta, M., Viappiani, A., Ferrario, C., Maggio, M., Lauretani, F., De Vos, W., van Sinderen, D., Meschi, T., Ventura, M., 2016. Gut microbiota composition and Clostridium difficile infection in hospitalized elderly individuals: a metagenomic study. Sci. Rep. 6, 25945. https://doi.org/10.1038/srep25945

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097. https://doi.org/10.1371/journal.pmed.1000097

National Health Service, 2019. Supporting routine frailty identification and frailty through the GP Contract 2017/2018.

Ntemiri, A., Chonchúir, F.N., O'Callaghan, T.F., Stanton, C., Ross, R.P., O'Toole, P.W., 2017. Glycomacropeptide Sustains Microbiota Diversity and Promotes Specific Taxa in an Artificial Colon Model of Elderly Gut Microbiota. J. Agric. Food Chem. 65, 1836–1846. https://doi.org/10.1021/acs.jafc.6b05434

Ohlsson, C., Sjögren, K., 2015. Effects of the gut microbiota on bone mass. Trends Endocrinol. Metab. 26, 69–74. https://doi.org/10.1016/j.tem.2014.11.004

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan---a web and mobile app for systematic reviews. Syst. Rev. 5, 210. https://doi.org/10.1186/s13643-016-0384-4

Parker, B.J., Wearsch, P.A., Veloo, A.C.M., Rodriguez-Palacios, A., 2020. The Genus Alistipes: Gut Bacteria With Emerging Implications to Inflammation, Cancer, and Mental Health. Front. Immunol. 11, 906.

https://doi.org/10.3389/fimmu.2020.00906

Peng, L., Li, Z.-R., Green, R.S., Holzman, I.R., Lin, J., 2009. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J. Nutr. 139, 1619–1625. https://doi.org/10.3945/jn.109.104638

Picca, A., Calvani, R., 2020. Biomarkers of frailty: Moving the field forward. Exp. Gerontol. 133. https://doi.org/10.1016/j.exger.2020.110868 LK - http://bj7rx7bn7b.search.serialssolutions.com?sid=EMBASE&issn=18736815&id=doi:10.1016%2Fj.exger.2020.110868&atitle=Biomarkers+of+frailty%3A+Moving+the+field+forward&stitle=Exp.+Gerontol.&title=Experimental+Gerontology&volume=133&issue=&spage=&epage=&aulast=Picca&aufirst=Anna&auinit=A.&aufull=Picca+A.&coden=EXGEA&isbn=&pages=-&date=2020&auinit1=A&auinitm=

Picca, A., Ponziani, F.R., Calvani, R., Marini, F., Biancolillo, A., Coelho-Junior, H.J., Gervasoni, J., Primiano, A., Putignani, L., Del Chierico, F., Reddel, S., Gasbarrini, A., Landi, F., Bernabei, R., Marzetti, E., 2020. Gut Microbial, Inflammatory and Metabolic Signatures in Older People with Physical Frailty and Sarcopenia: Results from the BIOSPHERE Study. Nutrients 12. https://doi.org/10.3390/nu12010065

Poggiogalle, E., Lubrano, C., Gnessi, L., Mariani, S., Di Martino, M., Catalano, C., Lenzi, A., Donini, L.M., 2019. The decline in muscle strength and muscle quality in relation to metabolic derangements in adult women with obesity. Clin. Nutr. 38, 2430–2435. https://doi.org/10.1016/j.clnu.2019.01.028

Ponziani, F.R., Picca, A., Marzetti, E., Calvani, R., Conta, G., Del Chierico, F., Capuani, G., Faccia, M., Fianchi, F., Funaro, B., Jose Coelho-Junior, H., Petito, V., Rinninella, E., Paroni Sterbini, F., Reddel, S., Vernocchi, P., Cristina Mele, M., Miccheli, A., Putignani, L., Sanguinetti, M., Pompili, M., Gasbarrini, A., study grp, G., 2021. Characterization of the gut-liver-muscle axis in cirrhotic patients with sarcopenia. LIVER Int. 41, 1320–1334. https://doi.org/10.1111/liv.14876

Rampelli, S., Candela, M., Turroni, S., Biagi, E., Collino, S., Franceschi, C., O'Toole, P.W., Brigidi, P., 2013. Functional metagenomic profiling of intestinal microbiome

in extreme ageing. Aging (Albany. NY). 5, 902–912. https://doi.org/10.18632/aging.100623

Rao, R.K., 2008. Acetaldehyde-induced barrier disruption and paracellular permeability in Caco-2 cell monolayer. Methods Mol. Biol. 447, 171–183. https://doi.org/10.1007/978-1-59745-242-7_13

Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G.A.D., Gasbarrini, A., Mele, M.C., 2019. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms 7. https://doi.org/10.3390/microorganisms7010014

Roager, H.M., Hansen, L.B.S., Bahl, M.I., Frandsen, H.L., Carvalho, V., Gøbel, R.J., Dalgaard, M.D., Plichta, D.R., Sparholt, M.H., Vestergaard, H., Hansen, T., Sicheritz-Pontén, T., Nielsen, H.B., Pedersen, O., Lauritzen, L., Kristensen, M., Gupta, R., Licht, T.R., 2016. Colonic transit time is related to bacterial metabolism and mucosal turnover in the gut. Nat. Microbiol. 1, 16093. https://doi.org/10.1038/nmicrobiol.2016.93

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D.B., McDowell, I., Mitnitski, A., 2005. A global clinical measure of fitness and frailty in elderly people. C. Can. Med. Assoc. J. = J. l'Association medicale Can. 173, 489–495. https://doi.org/10.1503/cmaj.050051

Saint-Georges-Chaumet, Y., Edeas, M., 2016. Microbiota-mitochondria inter-talk: consequence for microbiota-host interaction. Pathog. Dis. 74, ftv096. https://doi.org/10.1093/femspd/ftv096

Salminen, M.K., Rautelin, H., Tynkkynen, S., Poussa, T., Saxelin, M., Valtonen, V., Järvinen, A., 2006. Lactobacillus bacteremia, species identification, and antimicrobial susceptibility of 85 blood isolates. Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am. 42, e35-44. https://doi.org/10.1086/500214

Santoro, A., Ostan, R., Candela, M., Biagi, E., Brigidi, P., Capri, M., Franceschi, C., 2018. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell. Mol. Life Sci. 75, 129–148. https://doi.org/10.1007/s00018-017-2674-y

Shen, T., Yue, Y., He, T., Huang, C., Qu, B., Lv, W., Lai, H.-Y., 2021. The Association

Between the Gut Microbiota and Parkinson's Disease, a Meta-Analysis. Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2021.636545

Singh, I., Gallacher, J., Davis, K., Johansen, A., Eeles, E., Hubbard, R.E., 2012. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. Age Ageing 41, 242–246. https://doi.org/10.1093/ageing/afr179

Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermúdez-Humarán, L.G., Gratadoux, J.-J., Blugeon, S., Bridonneau, C., Furet, J.-P., Corthier, G., Grangette, C., Vasquez, N., Pochart, P., Trugnan, G., Thomas, G., Blottière, H.M., Doré, J., Marteau, P., Seksik, P., Langella, P., 2008. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc. Natl. Acad. Sci. U. S. A. 105, 16731–16736. https://doi.org/10.1073/pnas.0804812105

Sovran, B., Hugenholtz, F., Elderman, M., Van Beek, A.A., Graversen, K., Huijskes, M., Boekschoten, M. V, Savelkoul, H.F.J., De Vos, P., Dekker, J., Wells, J.M., 2019. Age-associated Impairment of the Mucus Barrier Function is Associated with Profound Changes in Microbiota and Immunity. Sci. Rep. 9, 1437. https://doi.org/10.1038/s41598-018-35228-3

Soysal, P., Stubbs, B., Lucato, P., Luchini, C., Solmi, M., Peluso, R., Sergi, G., Isik, A.T., Manzato, E., Maggi, S., Maggio, M., Prina, A.M., Cosco, T.D., Wu, Y.-T., Veronese, N., 2016. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Res. Rev. 31, 1–8. https://doi.org/10.1016/j.arr.2016.08.006

Steverink, N., Slaets, J.P.J., Schuurmans, H., Van Lis, M., 2001. Measuring frailty: Developing and testing the GFI (Groningen Frailty Indicator). Gerontologist 41, 236–237.

Studenski, S.A., Peters, K.W., Alley, D.E., Cawthon, P.M., McLean, R.R., Harris, T.B., Ferrucci, L., Guralnik, J.M., Fragala, M.S., Kenny, A.M., Kiel, D.P., Kritchevsky, S.B., Shardell, M.D., Dam, T.-T.L., Vassileva, M.T., 2014. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J. Gerontol. A. Biol. Sci. Med. Sci. 69, 547–558. https://doi.org/10.1093/gerona/glu010

Thevaranjan, N., Puchta, A., Schulz, C., Naidoo, A., Szamosi, J.C., Verschoor, C.P., Loukov, D., Schenck, L.P., Jury, J., Foley, K.P., Schertzer, J.D., Larché, M.J., Davidson, D.J., Verdú, E.F., Surette, M.G., Bowdish, D.M.E., 2017. Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. Cell Host Microbe 21, 455-466.e4. https://doi.org/10.1016/j.chom.2017.03.002

Thota, V.R., Dacha, S., Natarajan, A., Nerad, J., 2011. Eggerthella lenta bacteremia in a Crohn's disease patient after ileocecal resection. Future Microbiol. 6, 595–597. https://doi.org/10.2217/fmb.11.31

Ticinesi, A., Mancabelli, L., Tagliaferri, S., Nouvenne, A., Milani, C., Del Rio, D., Lauretani, F., Maggio, M.G., Ventura, M., Meschi, T., 2020. The Gut-Muscle Axis in Older Subjects with Low Muscle Mass and Performance: A Proof of Concept Study Exploring Fecal Microbiota Composition and Function with Shotgun Metagenomics Sequencing. Int. J. Mol. Sci. 21. https://doi.org/10.3390/ijms21238946

Ticinesi, A., Milani, C., Lauretani, F., Nouvenne, A., Mancabelli, L., Lugli, G.A., Turroni, F., Duranti, S., Mangifesta, M., Viappiani, A., Ferrario, C., Maggio, M., Ventura, M., Meschi, T., 2017. Gut microbiota composition is associated with polypharmacy in elderly hospitalized patients. Sci. Rep. 7. https://doi.org/10.1038/s41598-017-10734-y

Ticinesi, A., Nouvenne, A., Cerundolo, N., Catania, P., Prati, B., Tana, C., Meschi, T., 2019. Gut Microbiota, Muscle Mass and Function in Aging: A Focus on Physical Frailty and Sarcopenia. Nutrients 11. https://doi.org/10.3390/nu11071633

Tran, L., Greenwood-Van Meerveld, B., 2013. Age-associated remodeling of the intestinal epithelial barrier. J. Gerontol. A. Biol. Sci. Med. Sci. 68, 1045–1056. https://doi.org/10.1093/gerona/glt106

van de Wouw, M., Schellekens, H., Dinan, T.G., Cryan, J.F., 2017. Microbiota-Gut-Brain Axis: Modulator of Host Metabolism and Appetite. J. Nutr. 147, 727–745. https://doi.org/10.3945/jn.116.240481

van Tongeren, S.P., Slaets, J.P.J., Harmsen, H.J.M., Welling, G.W., 2005. Fecal microbiota composition and frailty. Appl. Environ. Microbiol. 71, 6438–6442.

https://doi.org/10.1128/AEM.71.10.6438-6442.2005

Vaziri, N.D., Wong, J., Pahl, M., Piceno, Y.M., Yuan, J., DeSantis, T.Z., Ni, Z., Nguyen, T.-H., Andersen, G.L., 2013. Chronic kidney disease alters intestinal microbial flora. Kidney Int. 83, 308–315. https://doi.org/10.1038/ki.2012.345

Vinolo, M.A.R., Rodrigues, H.G., Nachbar, R.T., Curi, R., 2011. Regulation of inflammation by short chain fatty acids. Nutrients 3, 858–876. https://doi.org/10.3390/nu3100858

Wallen, Z.D., Appah, M., Dean, M.N., Sesler, C.L., Factor, S.A., Molho, E., Zabetian, C.P., Standaert, D.G., Payami, H., 2020. Characterizing dysbiosis of gut microbiome in PD: evidence for overabundance of opportunistic pathogens. NPJ Park. Dis. 6, 11. https://doi.org/10.1038/s41531-020-0112-6

Wang, F., Yu, T., Huang, G., Cai, D., Liang, X., Su, H., Zhu, Z., Li, D., Yang, Y., Shen, P., Mao, R., Yu, L., Zhao, M., Li, Q., 2015. Gut Microbiota Community and Its Assembly Associated with Age and Diet in Chinese Centenarians. J. Microbiol. Biotechnol. 25, 1195–1204. https://doi.org/10.4014/jmb.1410.10014

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., n.d. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [WWW Document]. URL http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 8.12.21).

Zhang, L., Liao, J., Chen, Q., Chen, M., Kuang, Y., Chen, L., He, W., 2020. Characterization of the gut microbiota in frail elderly patients. AGING Clin. Exp. Res. 32, 2001–2011. https://doi.org/10.1007/s40520-019-01385-2

Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., Wu, X., Li, Junhua, Tang, L., Li, Yin, Lan, Z., Chen, B., Li, Yanli, Zhong, H., Xie, H., Jie, Z., Chen, Weineng, Tang, S., Xu, Xiaoqiang, Wang, X., Cai, X., Liu, S., Xia, Y., Li, Jiyang, Qiao, X., Al-Aama, J.Y., Chen, H., Wang, L., Wu, Q.-J., Zhang, F., Zheng, W., Li, Yongzhe, Zhang, M., Luo, G., Xue, W., Xiao, L., Li, Jun, Chen, Wanting, Xu, Xun, Yin, Y., Yang, H., Wang, Jian, Kristiansen, K., Liu, L., Li, T., Huang, Q., Li, Yingrui, Wang, Jun, 2015. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat. Med. 21, 895–905. https://doi.org/10.1038/nm.3914

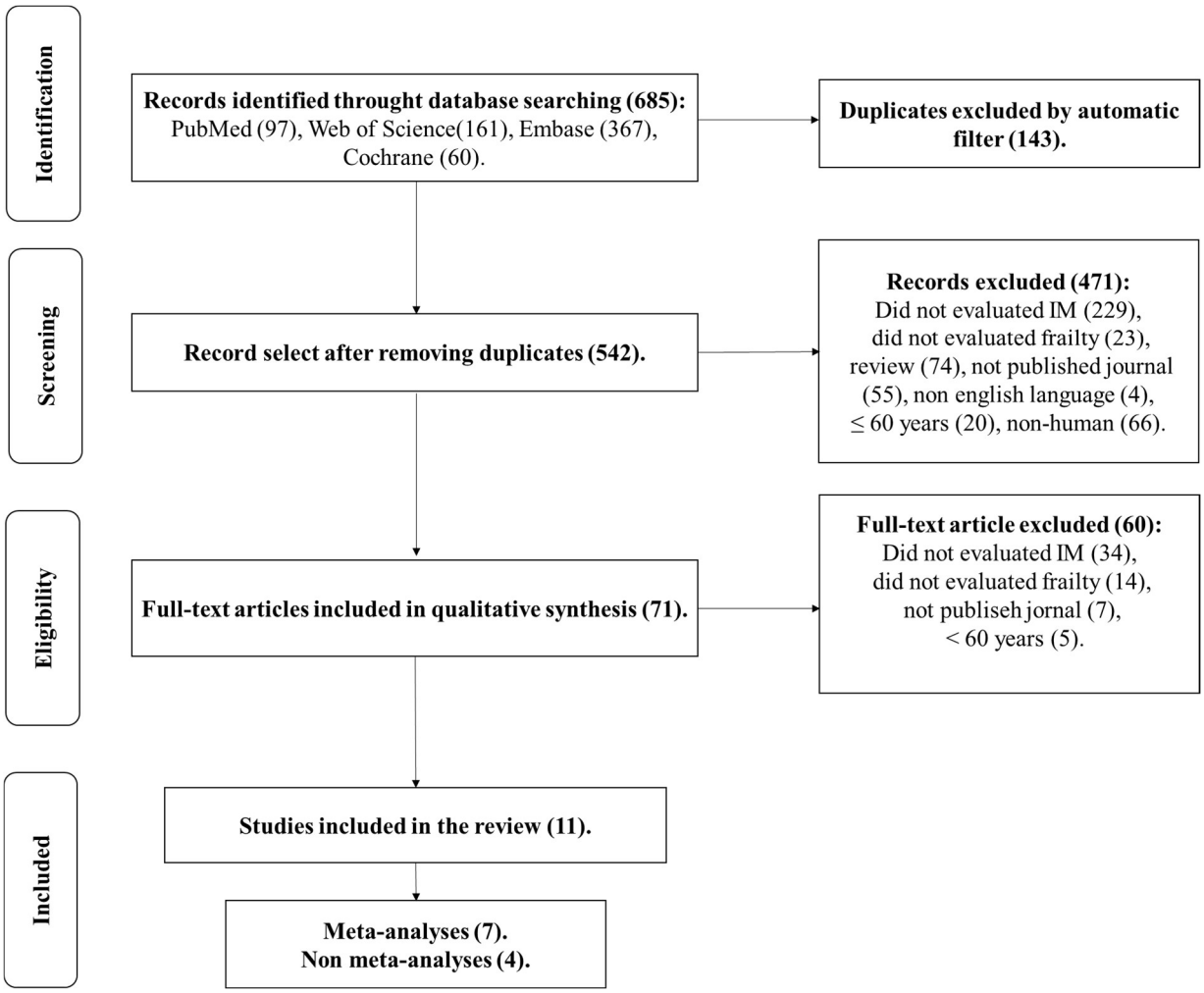



**Figure 1.** Flowchart of the selection of the studies. Text boxes on the left describe the phase of the selection of the studies, while text boxes in the middle describe the studies retained in each phase, and the text boxes on the right describe the studies excluded.

**Table 1.** Characteristics of the studies included.

| First Author, Year | Participants | Age (Mean ± SD) | BMI (Mean ± SD) | Gender | Country | N | Frailty criteria | Cut-off | Methods of IM assessment |
|---|---|---|---|---|---|---|---|---|---|
| Zhang, 2020 | Hospitalized | 81.63 (± 7.90) | F 21.07 (± 4.27) NF 23.83 (± 2.48) | Both | China | 27 | Modified Rockwood scale | F >0.25/ NF ≥ 0.25 | 16S rRNA sequencing without region information, for alpha diversity and relative abundance |
| Margiotta, 2020 | CKD | F 81.8 (± 5.8) NF 79.03 (±6.6) | F 28.77 (± 5.4) NF 27.7 (± 3.4) | Both | Italy | 64 | Fried score | F ≥ 3 / NF < 3 | 16S rRNA sequencing of V3-V4, for alpha diversity and relative abundance |
| Margiotta, 2021 | CKD | S 83.1 (±5.7) NS 79.7 (±6.2) | S 25.5 (±2.6) NS 29.3 (±4.8) | Both | Italy | 63 | EWGSOP2 | S: HS <27 kg M and 16> kg W or 5XSST >15 seconds + ALM <20 kg M and <15 kg W or SMI <7.0 kg/m² M and <5.5 kg/m²+ GS ≤0.8 m/s or SPPB ≤ 8 or TUG ≥20 s or 400WT non-completion or ≥6 min for completion | 16S rRNA sequencing of V3-V4, for relative abundance |
| Picca, 2020 | Community dwellers | FS 75.5 (±3.9) NFS 73.9 (± 3.2) | FS 32.14 (± 6.02) NFS 26.27 (± 2.55) | Both | Italy | 35 | SPRINTT project | FS: 3 ≤ SPPB ≥ 9 + ALM (FNIH) + absence of mobility disability | 16S rRNA sequencing of V3-V4, for alpha diversity and |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | relative abundance |
| Ticinesi, 2020 | Hospitalized | FS 77 (75.5–86)* NFS 71.5 (70–75)* | FS 24.3 (20.9–26.7)* NFS 27.4 (24.5–29.1)* | Both | Italy | 17 | SPPB + Muscle Mass (ECS) | FS: 3/12 and 9/12 SPPB + SMI ECS / NFS: 10/12 and 12/12 SPPB ou ECS | Shotgun metagenomic sequencing, for alpha diversity and relative abundance |
| Kang, 2021 | Hospitalized | S 76.45 (± 8.58) NS 68.38 (± 5.79) | S 20.67 (± 3.27) NS 23.66 (± 2.49) | Both | China | 71 | AWGSG | S: HS <28 kg M and <18 kg W + 6MWT <1.0 m/s, SPPB ≤9, or 5XSST ≥12 seconds + SMI < 7.0 kg/m2 M or < 5.7 kg/m2 W | 16S rRNA sequencing of V3-V4, for alpha diversity and relative abundance |
| Ponziani, 2021 | Community-dwellers | S 75.5 (72-77.25)* NS 72.5 (58.25-75.25)* | S 29.99 (29-31.79)* NS 26.2 (24.39-28.68)* | Both | Italy | 50 | FNIH | ALMBMI < 0.789 M and < 0.512 W; or crude ALM < 19.75 kg M and < 15.02 kg W + HS < 26 kg M or < 16 kg W | 16S rRNA sequencing of V3-V4, for alpha diversity and relative abundance |
| Van Tongeren, 2005 | Nursing homes | 86 (70 - 100)* | ND | Both | Netherlands | 23 | GFI | LF 1 – 4 / HF >5 | Hybridization probes, for relative abundance |
| Ticinesi, 2017 | Hospitalized | 83.3 (± 7.5) | ND | Both | Italy | 76 | Rockwood scale | F ≤ 7/ NF ≥ 4 | 16S rRNA sequencing of V3, for alpha |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | diversity |
| Jackson, 2016 | Community-dwellers | 63 (42 -86) ND | Female | UK | 728 | Rockwood index | LF ≤0.25/ > 0.25 MF ≤ 0.4/ HF >0.4 | 16S rRNA sequencing of V4, for relative abundance |
| Maffei, 2017 | Community-dwellers | 63 (± 6) | Both | USA | 85 | $FI_{34}$ | LF 0–0.083/ MF 0.091–0.137/ HF 0.142–0.365 | 16S rRNA sequencing of V3-V4, for relative abundance |

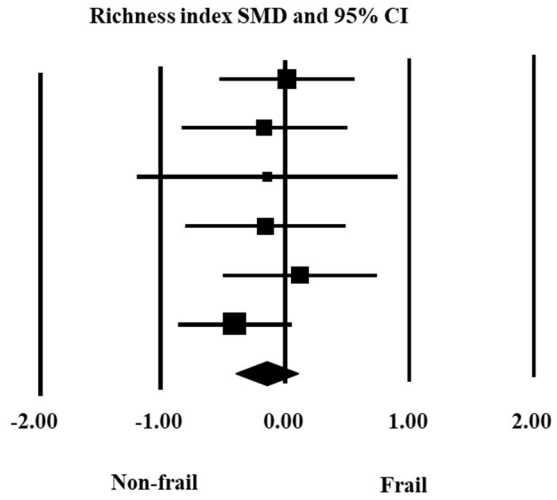
**Legend:** SD: ± standard; F: Frail; NF: Not frail; 16S rRNA: 16S Ribosomal Ribonucleic Acid; V3: region of the 16S rRNA gene; V3-V4: regions of the 16S rRNA gene; V4: regions of the 16S rRNA gene; CKD: Chronic Kidney Disease; S: Sarcopenic; NS: Not sarcopenic; EWGSOP2: European Working Group on Sarcopenia in Older People 2; HS: Handgrip strength; M: Men; W: Women; 5XSST: Five Times Sit to Stand Test; ALM: appendicular lean mass; SMI: Skeletal muscle index; GS: Gait speed; SPPB: Short-Physical Performance Battery; TUG: Timed Up and Go Test; WT: Walk test; FS: Frail and sarcopenic; NFS: Not frail and sarcopenic; +: associated with; FNIH: Foundation for the National Institutes of Health sarcopenia project; ECS: European Consensus on Sarcopenia; 6MWT: 6-minute walk test; AWGSG: Asian Working Group for Sarcopenia 2019 Guidelines; FNIH: Foundation for the National Institutes of Health; ALMBMI: appendicular lean mass to body mass index ratio; ND: No data; GFI: GFI; LF: Low frailty; HF: High frailty; UK: United Kingdom; MF: Middle frailty; USA: United States of America; $FI_{34}$: 34-item frailty index.

**Figure 2.** Forest plots of the richness index (A) and the diversity index (B) showing no differences between frail and non-frail older adults for both indexes.

A

| First author, year | Subgroup | F | NF | SMD [LL; UL] | p-Value |
|---|---|---|---|---|---|
| Margiotta, 2020 | Chao1 index | 37 | 20 | 0.017 [-0.527; 0.561] | 0.951 |
| Picca, 2020 | Chao1 index | 18 | 17 | -0.164 [-0.828; 0.500] | 0.629 |
| Ticinesi, 2020 | ISR | 5 | 12 | -0.142 [-1.186; 0.902] | 0.790 |
| Kang, 2021 | Chao1 index | 11 | 60 | -0.154 [-0.797; 0.490] | 0.640 |
| Ponziani, 2021 | Chao1 index | 14 | 36 | 0.122 [-0.496; 0.740] | 0.699 |
| Ticinesi, 2017 | Chao1 index | 43 | 33 | -0.401 [-0.859; 0.057] | 0.086 |
| **Summarized fixed effects** | | **128** | **178** | **-0.147 [-0.394; 0.100]** | **0.243** |

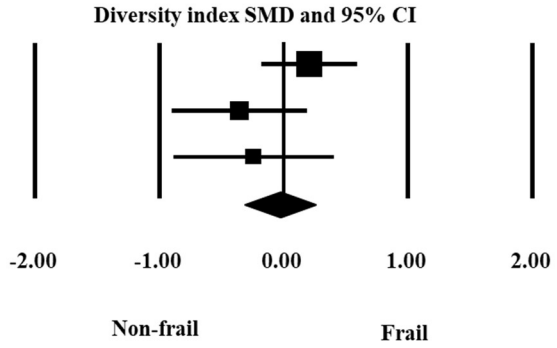
Test for heterogeneity: Q= 2.26; df= 5; p= 0.81; $I^2$= 0.0%; Test for overall effect z= 1.17; (p= 0.24).



B

| Frist author, year | Subgroup | F | NF | SMD [LL;UL] | p-Value |
|---|---|---|---|---|---|
| Margiotta, 2020 | Simpson and Shannon | 74 | 40 | 0.207 [-0.179; 0.592] | 0.293 |
| Zhang, 2020 | Simpson and Shannon | 30 | 24 | -0.356 [ -0.898; 0.185] | 0.197 |
| Kang, 2021 | Species diversity | 11 | 60 | -0.243 [-0.887; 0.401] | 0.459 |
| **Summarized fixed effects** | | **115** | **124** | **-0.033 [-0.315; 0.250]** | **0.820** |

Test for heterogeneity: Q= 3.26; df= 2; p= 0.2; $I^2$= 38.7%; Test for overall effect z=-0.23 (p= 0.82).




**Legend**: F: frail; NF: non-frail; SMD: standard mean difference; LL: low limit; UL: upper limit; CI: confidence interval; ISR: Index of species richness. The text boxes below the forest plot tables detail the heterogeneity analyses and the test of overall hypothesis for each meta-analysis.

**Table 2.** Comparison between F and NF for the relative abundance of bacteria phyla, families, genera, and species.

| Phyla of bacteria | Frailty effect | p-value | Value F vs NF | Sample size F vs NF | Frailty criteria | Ref |
|---|---|---|---|---|---|---|
| Acidobacteria | F < NF | p > 0.05 | 0.2 vs 0.5 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Actinobacteria | F < NF | p > 0.05 | 4.3 vs 4.4 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Actinobacteria | F > NF | p > 0.05 | 0.6*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Actinobacteria | F < NF | p > 0.05 | -0.6*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Bacteroidetes | F > NF | p > 0.05 | 22.8 vs 21.3 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Bacteroidetes | F < NF | p > 0.05 | -0.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Bacteroidetes | F < NF | p > 0.05 | -0.1*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Chloroflexi | F < NF | p > 0.05 | 0.4 vs 0.7 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Cyanobacteria | F > NF | p > 0.05 | 0.8*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Cyanobacteria | F > NF | p > 0.05 | 0.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Epsilonbacteraeota | F < NF | p > 0.05 | 0.4 vs 0.5 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Euryarchaeota | F < NF | p > 0.05 | -2.4*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Firmicutes | F > NF | p > 0.05 | 61 vs 60 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Firmicutes | F > NF | p > 0.05 | 0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Firmicutes** | **F < NF** | **p < 0.05** | **40.4 vs 54.4 (M)** | **11 vs 60** | **Sarcopenia** | **Kang, 2021** |
| Firmicutes | F < NF | p > 0.05 | -0.6*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Fusobacteria | F < NF | p > 0.05 | 0.6 vs 0.7 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Patescibacteria | F > NF | p > 0.05 | 0.2 vs 0.03 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Proteobacteria | F < NF | p > 0.05 | 9.5 vs 10.3 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Proteobacteria | F > NF | p > 0.05 | 1.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Proteobacteria | F > NF | p > 0.05 | 1.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Synergistetes | F > NF | p > 0.05 | 4.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |

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|---|---|---|---|---|---|---|
| TM7 | F > NF | p > 0.05 | 0.8*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| TM7 | F < NF | p > 0.05 | -0.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **TM7** | **F > NF** | **p < 0.05** | **0.04 (FDR)** | **28 vs 30** | **FI34** | **Maffei, 2017** |
| Verrucomicrobia | F < NF | p > 0.05 | 1.0 vs 1.1 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Verrucomicrobia | F < NF | p > 0.05 | -1.1*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Verrucomicrobia** | **F < NF** | **p < 0.05** | **-6.4*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| **Families of bacteria** | **Frailty effect** | **p-value** | **Value F vs NF** | **Sample size F vs NF** | **Frailty criteria** | **Ref** |
| Acidaminobacteraceae | F < NF | p > 0.05 | 0 vs 0.0001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Actinomycetaceae | F > NF | p > 0.05 | 0.1 vs 0.06 | 38 vs 26 | Fried | Margiotta, 2020 |
| Aerococcaceae | F > NF | p > 0.05 | 0.0017 vs 0.0015 | 38 vs 26 | Fried | Margiotta, 2020 |
| Alcaligenaceae | F < NF | p > 0.05 | 0.2 vs 0.3 | 38 vs 26 | Fried | Margiotta, 2020 |
| Alcaligenaceae | F < NF | p > 0.05 | -0.04*(DDA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Anaeroplasmataceae | F < NF | p > 0.05 | 0.001 vs 0.16 | 38 vs 26 | Fried | Margiotta, 2020 |
| Aurantimonadaceae | F < NF | p > 0.05 | 0 vs 0.0009 | 38 vs 26 | Fried | Margiotta, 2020 |
| Bacteroidaceae | F < NF | p > 0.05 | 5.7 vs 6.1 | 38 vs 26 | Fried | Margiotta, 2020 |
| Bacteroidaceae | F < NF | p > 0.05 | -0.17 *(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Bacteroidaceae | F > NF | p > 0.05 | -0.4*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Barnesiellaceae | F < NF | p > 0.05 | 0.4 vs 0.5 | 38 vs 26 | Fried | Margiotta, 2020 |
| Barnesiellaceae | F > NF | p > 0.05 | 0.27 *(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Barnesiellaceae** | **F > NF** | **p < 0.05** | **2.5*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| Bifidobacteriaceae | F > NF | p > 0.05 | 5.7 vs 3.6 | 38 vs 26 | Fried | Margiotta, 2020 |
| Bifidobacteriaceae | F > NF | p > 0.05 | 0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Bifidobacteriaceae** | **F > NF** | **p < 0.05** | **2.1*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| Brevibacteriaceae | F < NF | p > 0.05 | 0.0003 vs 0.001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Brucellaceae | F < NF | p > 0.05 | 0.0003 vs 0.0006 | 38 vs 26 | Fried | Margiotta, 2020 |
| Caldicoprobacteraceae | F < NF | p > 0.05 | 0 vs 0.0008 | 38 vs 26 | Fried | Margiotta, 2020 |

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|---|---|---|---|---|---|---|
| Campylobacteraceae | F > NF | p > 0.05 | 0.003 vs 0.002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Carnobacteriaceae | F < NF | p > 0.05 | 0.01 vs 0.02 | 38 vs 26 | Fried | Margiotta, 2020 |
| Carnobacteriaceae | F < NF | p > 0.05 | -0.05 | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Carnobacteriaceae | F < NF | p > 0.05 | 0.05*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Caulobacteraceae | F < NF | p > 0.05 | 0 vs 0.004 | 38 vs 26 | Fried | Margiotta, 2020 |
| Christensenellaceae | F < NF | p > 0.05 | 0.4 vs 0.9 | 38 vs 26 | Fried | Margiotta, 2020 |
| Christensenellaceae | F < NF | p > 0.05 | -0.17 *(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Christensenellaceae | F < NF | p > 0.05 | -1.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Clostridiaceae | F < NF | p > 0.05 | 3.8 vs 5.5 | 38 vs 26 | Fried | Margiotta, 2020 |
| Clostridiaceae | F > NF | p > 0.05 | 1.4 *(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Clostridiaceae | F < NF | p > 0.05 | -0.05*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Comamonadaceae | F < NF | p > 0.05 | 0.0007 vs 0.01 | 38 vs 26 | Fried | Margiotta, 2020 |
| Coriobacteriaceae | F < NF | p > 0.05 | -0.35 | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Coriobacteriaceae | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Coriobacteriaceae** | **F > NF** | **p < 0.01** | **1.2 ± 0.3 vs 0.8 ± 0.1 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Corynebacteriaceae | F > NF | p > 0.05 | 0.01 vs 0.005 | 38 vs 26 | Fried | Margiotta, 2020 |
| Cytophagaceae | F < NF | p > 0.05 | 0 vs 0.001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Dehalobacteriaceae | F = NF | p > 0.05 | 0.010 vs 0.011 | 38 vs 26 | Fried | Margiotta, 2020 |
| Dehalobacteriaceae | F > NF | p > 0.05 | 0.24*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Dehalobacteriaceae | F < NF | p > 0.05 | -1.1*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Dermabacteraceae | F < NF | p > 0.05 | 0.00004 vs 0.0001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Desulfovibrionaceae | F < NF | p > 0.05 | 0.3 vs 0.4 | 38 vs 26 | Fried | Margiotta, 2020 |
| Desulfovibrionaceae | F > NF | p > 0.05 | 1.8*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Desulfovibrionaceae | F > NF | p > 0.05 | 1.7*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Dethiosulfovibrionaceae | F > NF | p > 0.05 | 0.01 vs 0.002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Dethiosulfovibrionaceae | F > NF | p > 0.05 | 3.8*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Elusimicrobiaceae | F > NF | p > 0.05 | 0.002 vs 0 | 38 vs 26 | Fried | Margiotta, 2020 |
| Enterobacteriaceae | F < NF | p > 0.05 | 0.1 vs 0.6 (MD) | 10 vs 13 | GFI | Van tongeren, 2005 |

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|---|---|---|---|---|---|---|
| Enterobacteriaceae | F > NF | p > 0.05 | 1.1*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Enterobacteriaceae | F < NF | p > 0.05 | 5.3 vs 7.4 | 38 vs 26 | Fried | Margiotta, 2020 |
| Enterobacteriaceae | F > NF | p > 0.05 | 1.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Enterococcaceae | F < NF | p > 0.05 | 0.6 vs 0.7 | 38 vs 26 | Fried | Margiotta, 2020 |
| Enterococcaceae | F > NF | p > 0.05 | 1.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Enterococcaceae | F > NF | p > 0.05 | 1,9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Erysipelotrichaceae | F < NF | p > 0.05 | 3.8 vs 4.4 | 38 vs 26 | Fried | Margiotta, 2020 |
| **Erysipelotrichaceae** | **F < NF** | **p < 0.05** | **-2.4*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| Erysipelotrichaceae | F < NF | p > 0.05 | -0.7*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| EtOH8 | F < NF | p > 0.05 | -0.07*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Eubacteriaceae | F > NF | p > 0.05 | 0.02 vs 0.01 | 38 vs 26 | Fried | Margiotta, 2020 |
| Flavobacteriaceae | F < NF | p > 0.05 | 0.00006 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Fusobacteriaceae | F < NF | p > 0.05 | 0.01 vs 0.09 | 38 vs 26 | Fried | Margiotta, 2020 |
| Gemellaceae | F < NF | p > 0.05 | 0.02 vs 0.03 | 38 vs 26 | Fried | Margiotta, 2020 |
| **Gemellaceae** | **F < NF** | **p < 0.05** | **0.042 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Geodermatophilaceae | F < NF | p > 0.05 | 0 vs 0.0001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Gordoniaceae | F < NF | p > 0.05 | 0 vs 0.0001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Hyphomicrobiaceae | F < NF | p > 0.05 | 0.00006 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Lachnospiraceae | F > NF | p > 0.05 | 22.8 vs 20.8 | 38 vs 26 | Fried | Margiotta, 2020 |
| Lachnospiraceae | F < NF | p > 0.05 | 11.2 vs 11.3 | 15 vs 12 | Rockwood | Zhang, 2020 |
| Lachnospiraceae | F > NF | p > 0.05 | 0.5*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Lachnospiraceae | F > NF | p > 0.05 | 2.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Lactobacillaceae | F > NF | p > 0.05 | 2.3 vs 1.4 | 38 vs 26 | Fried | Margiotta, 2020 |
| Lactobacillaceae | F > NF | p > 0.05 | 1.7*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Lactobacillaceae | F > NF | p > 0.05 | 2.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Leptotrichiaceae | F < NF | p > 0.05 | 0.0006 vs 0.002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Leuconostocaceae | F < NF | p > 0.05 | 0.01 vs 0.02 | 38 vs 26 | Fried | Margiotta, 2020 |
| Methanobacteriaceae | F > NF | p > 0.05 | 0.1 vs 0.08 | 38 vs 26 | Fried | Margiotta, 2020 |

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|---|---|---|---|---|---|---|
| Methanobacteriaceae | F > NF | p > 0.05 | 0.64*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Methanobacteriaceae | F < NF | p > 0.05 | -1.8*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Methylobacteriaceae | F < NF | p > 0.05 | 0.0001 vs 0 | 38 vs 26 | Fried | Margiotta, 2020 |
| Microbacteriaceae | F < NF | p > 0.05 | 0.00007 vs 0.001 | 38 vs 26 | Fried | Margiotta, 2020 |
| Micrococcaceae | F < NF | p > 0.05 | 0.03 vs 0.06 | 38 vs 26 | Fried | Margiotta, 2020 |
| **Micrococcaceae** | **F > NF** | **p < 0.05** | **FDR = 0.012** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Micrococcaceae | F < NF | p > 0.05 | 0.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Mogibacteriaceae | F > NF | p > 0.05 | 0.22 vs 0.19 | 38 vs 26 | Fried | Margiotta, 2020 |
| **Mogibacteriaceae** | **F > NF** | **p < 0.05** | **0.2 ± 0.02 vs 0.02 ± 0.02 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Mogibacteriaceae | F < NF | p > 0.05 | 0.4*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Mogibacteriaceae | F < NF | p > 0.05 | -0.5*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Moraxellaceae | F > NF | p > 0.05 | 0.0005 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Neisseriaceae | F > NF | p > 0.05 | 0.001 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Odoribacteraceae | F > NF | p > 0.05 | 0.4 vs 0.3 | 38 vs 26 | Fried | Margiotta, 2020 |
| Others | F < NF | p > 0.05 | 11 vs 11.2 | 38 vs 26 | Fried | Margiotta, 2020 |
| Oxalobacteraceae | F < NF | p > 0.05 | 0.004 vs 0.01 | 38 vs 26 | Fried | Margiotta, 2020 |
| Paraprevotellaceae | F > NF | p > 0.05 | 0.1 vs 0.06 | 38 vs 26 | Fried | Margiotta, 2020 |
| Paraprevotellaceae | F < NF | p > 0.05 | -1.5*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Paraprevotellaceae | F < NF | p > 0.05 | -1.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Pasteurellaceae | F < NF | p > 0.05 | 0.07 vs 0.3 | 38 vs 26 | Fried | Margiotta, 2020 |
| Pasteurellaceae | F > NF | p > 0.05 | 1.4*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Pasteurellaceae | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Peptococcaceae | F < NF | p > 0.05 | 0.03 vs 0.15 | 38 vs 26 | Fried | Margiotta, 2020 |
| Peptostreptococcaceae | F < NF | p > 0.05 | 0.9 vs 1.3 | 38 vs 26 | Fried | Margiotta, 2020 |
| Peptostreptococcaceae | F > NF | p > 0.05 | 1.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Peptostreptococcaceae** | **F > NF** | **p < 0.05** | **3*(DAA)** | **18 vs 17** | **Fried** | **Picca, 2020** |
| Planococcaceae | F < NF | p > 0.05 | 0.01 vs 0.02 | 38 vs 26 | Fried | Margiotta, 2020 |
| Porphyromonadaceae | F > NF | p > 0.05 | 1 vs 0.8 | 38 vs 26 | Fried | Margiotta, 2020 |

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| Porphyromonadaceae | F > NF | p > 0.05 | 0.17*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Porphyromonadaceae | F < NF | p > 0.05 | -0.5*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Prevotellaceae | F < NF | p > 0.05 | 0.1 vs 0.2 | 38 vs 26 | Fried | Margiotta, 2020 |
| Prevotellaceae | F < NF | p > 0.05 | -1.6*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Prevotellaceae | F < NF | p > 0.05 | -1.4*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Pseudomonadaceae | F < NF | p > 0.05 | 0.002 vs 0.03 | 38 vs 26 | Fried | Margiotta, 2020 |
| Rhizobiaceae | F < NF | p > 0.05 | 0.0001 vs 0.01 | 38 vs 26 | Fried | Margiotta, 2020 |
| Rhodobacteraceae | F > NF | p > 0.05 | 0.0001 vs 0 | 38 vs 26 | Fried | Margiotta, 2020 |
| Rhodocyclaceae | F < NF | p > 0.05 | 0.00003 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Rhodospirillaceae | F < NF | p > 0.05 | 0 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Rikenellaceae | F > NF | p > 0.05 | 2.1 vs 1.4 | 38 vs 26 | Fried | Margiotta, 2020 |
| Rikenellaceae | F > NF | p > 0.05 | 1.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Rikenellaceae** | **F > NF** | **p < 0.05** | **2.2*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| **Rikenellaceae** | **F < NF** | **p < 0.05** | **0.08 (FDR)** | **28 vs 30** | **FI34** | **Maffei, 2017** |
| Ruminococcaceae | F < NF | p > 0.05 | 20 vs 20.4 | 38 vs 26 | Fried | Margiotta, 2020 |
| Ruminococcaceae | F < NF | p > 0.05 | -0.11*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Ruminococcaceae** | **F > NF** | **p < 0.05** | **1.2 *(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| Sphingobacteriaceae | F < NF | p > 0.05 | 0.00009 vs 0.0004 | 38 vs 26 | Fried | Margiotta, 2020 |
| Sphingomonadaceae | F < NF | p > 0.05 | 0.0002 vs 0.0009 | 38 vs 26 | Fried | Margiotta, 2020 |
| Staphylococcaceae | F > NF | p > 0.05 | 0.038 vs 0.036 | 38 vs 26 | Fried | Margiotta, 2020 |
| Streptococcaceae | F < NF | p > 0.05 | 4.9 vs 5.7 | 38 vs 26 | Fried | Margiotta, 2020 |
| Streptococcaceae | F < NF | p > 0.05 | -0.67*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Streptococcaceae | F < NF | p > 0.05 | -0.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Streptomycetaceae | F < NF | p > 0.05 | 0 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Succinivibrionaceae | F < NF | p > 0.05 | 0.0004 vs 0.01 | 38 vs 26 | Fried | Margiotta, 2020 |
| Synergistaceae | F < NF | p > 0.05 | 0.036 vs 0.037 | 38 vs 26 | Fried | Margiotta, 2020 |
| Syntrophomonadaceae | F < NF | p > 0.05 | 0.00006 vs 0.0003 | 38 vs 26 | Fried | Margiotta, 2020 |
| S24-7 | F < NF | p > 0.05 | 1.9*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |

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|---|---|---|---|---|---|---|
| Tissierellaceae | F < NF | p > 0.05 | 0.046 vs 0.048 | 38 vs 26 | Fried | Margiotta, 2020 |
| Turicibacteraceae | F < NF | p > 0.05 | 0.1 vs 0.6 | 38 vs 26 | Fried | Margiotta, 2020 |
| Turicibacteraceae | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Veillonellaceae | F < NF | p > 0.05 | 1.3 vs 1.7 | 38 vs 26 | Fried | Margiotta, 2020 |
| Veillonellaceae | F > NF | p > 0.05 | 0.9*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Veillonellaceae** | **F > NF** | **p < 0.05** | **4.2*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| **Veillonellaceae** | **F < NF** | **p < 0.05** | **0.012 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Verrucomicrobiaceae | F > NF | p > 0.05 | 1.5 vs 0.8 | 38 vs 26 | Fried | Margiotta, 2020 |
| Verrucomicrobiaceae | F < NF | p > 0.05 | -0.73*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Verrucomicrobiaceae** | **F < NF** | **p < 0.05** | **-3.7*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| **Verrucomicrobiaceae** | **F > NF** | **p < 0.05** | **0.012 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Vibrionaceae | F < NF | p > 0.05 | 0.002 vs 0.003 | 38 vs 26 | Fried | Margiotta, 2020 |
| Victivallaceae | F > NF | p > 0.05 | 0.01 vs 0.008 | 38 vs 26 | Fried | Margiotta, 2020 |
| Weeksellaceae | F < NF | p > 0.05 | 0.00009 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Xanthobacteraceae | F < NF | p > 0.05 | 0.00008 vs 0.0002 | 38 vs 26 | Fried | Margiotta, 2020 |
| Xanthomonadaceae | F < NF | p > 0.05 | 0.0001 vs 0.002 | 38 vs 26 | Fried | Margiotta, 2020 |
| **Genera of bacteria** | **Frailty effect** | **p-value** | **Value F vs NF** | **Sample size F vs NF** | **Frailty criteria** | **Ref** |
| **Acidaminococcus** | **F < NF** | **p < 0.05** | **< 0.01 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| **Actinomyces** | **F > NF** | **p < 0.05** | **0.1 ± 0.01 vs 0.05 ± 0.01 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Adlercreutzia | F > NF | p > 0.05 | 0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Adlercreutzia | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Akkermansia | F < NF | p > 0.05 | -1.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Akkermansia** | **F < NF** | **p < 0.05** | **-4.4*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| **Akkermansia** | **F > NF** | **p < 0.05** | **0.008 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Alistipes | F > NF | p > 0.05 | 5.3 vs 5.0 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Alistipes | F > NF | p > 0.05 | 3.2 vs 0.8 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |

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|---|---|---|---|---|---|---|
| Anaerostipes | F < NF | p > 0.05 | -0.04*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Anaerostipes | F < NF | p > 0.05 | -1.1*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Anaerotruncus** | **F > NF** | **p < 0.01** | **0.04 ± 0.01 vs 0.01 ± 0.009 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Anaerotruncus | F < NF | p > 0.05 | -1.0*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Atopobium | F > NF | p > 0.05 | 10.6 vs 3.4 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Atopobium | F > NF | p > 0.05 | 1.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Atopobium | F > NF | p > 0.05 | 0.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Bacteroides | F < NF | p > 0.05 | 35.9 vs 36.3 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Bacteroides | F > NF | p > 0.05 | 38.9 vs 34.7 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Bacteroides | F < NF | p > 0.05 | -0.5*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Bacteroides | F > NF | p > 0.05 | 0.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Bacteroides/Prevotella** | **F < NF** | **p < 0.05** | **9.4 vs 24.2 (MD)** | **10 vs 13** | **GFI** | **Van Tongeren, 2005** |
| Bifidobacterium | F > NF | p > 0.05 | 1.3 vs 0.5 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Bifidobacterium | F < NF | p > 0.05 | 4.6 vs 5.4 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Bifidobacterium | F > NF | p > 0.05 | 7.6 vs 4.1 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| **Bifidobacterium** | **F > NF** | **p < 0.05** | **1.7*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| Bifidobacterium | F > NF | p > 0.05 | 0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Bilophila | F > NF | p > 0.05 | 0.7*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Bilophila | F > NF | p > 0.05 | 2.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Blautia | F > NF | p > 0.05 | 7.9 vs 7.7 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Blautia | F < NF | p > 0.05 | 3.0 vs 6.2 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Blautia | F < NF | p > 0.05 | -0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Blautia | F < NF | p > 0.05 | -1.0*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Catenibacterium | F < NF | p > 0.05 | -4.1*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Christensenella | F < NF | p > 0.05 | -0.4*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Christensenella | F < NF | p > 0.05 | -0.4*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Christensenellaceae_r-7_ | F > NF | NR | 1.7 vs 1.1 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Clostridium | F > NF | p > 0.05 | 0.2 vs 0.02 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |

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|---|---|---|---|---|---|---|
| Collinsella | F > NF | p > 0.05 | 0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Collinsella | F > NF | p > 0.05 | 0.1*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Coprobacillus** | **F > NF** | **p < 0.05** | **0.3 ± 0.1 vs 0.06 ± 0.01** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| **Coprobacillus** | **F > NF** | **p < 0.05** | **0.01 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| **Coprobacillus** | **F > NF** | **p < 0.05** | **0.08 (FDR)** | **28 vs 30** | **FI34** | **Maffei, 2017** |
| Coprococcus | F > NF | p > 0.05 | 0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Coprococcus | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Dehalobacterium | F > NF | p > 0.05 | 3.98E-05*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Dehalobacterium | F < NF | p > 0.05 | -1.6*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Dialister** | **F > NF** | **p < 0.05** | **3,5*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| **Dialister** | **F > NF** | **p < 0.05** | **0.08 (FDR)** | **28 vs 30** | **FI34** | **Maffei, 2017** |
| Dialister | F > NF | p > 0.05 | 2.8*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Dorea** | **F > NF** | **p < 0.05** | **8.9 ± 0.2 vs 8.1 ± 0.2 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Dorea | F < NF | p > 0.05 | -0.7*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Dorea | F > NF | p > 0.05 | 0.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Eggerthella** | **F > NF** | **p < 0.01** | **0.2 ± 0.04 vs 0.08 ± 0.01 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| **Eggerthella** | **F > NF** | **p < 0.05** | **2.0*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| **Eggerthella** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **ND** | **Rockwood** | **Jackson, 2016** |
| **Eggerthella** | **F > NF** | **p < 0.05** | **<0.05 (FDR)** | **ND** | **FI34** | **Maffei, 2017** |
| Eggerthella | F < NF | p > 0.05 | -0.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Enterococcus | F > NF | p > 0.05 | 1.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Enterococcus | F > NF | p > 0.05 | 1.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Erwinia** | **F > NF** | **p < 0.01** | **0.06 ± 0.02 vs 0.006 ± 0.001** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Escherichia -Shigella | F > NF | p > 0.05 | 7.4 vs 3.1 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| **Eubacterium** | **F > NF** | **p < 0.05** | **-3,2*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| Eubacterium | F > NF | p > 0.05 | -2.7*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Eubacterium | F > NF | p > 0.05 | 0.6 (FDR) | ND | Rockwood | Jackson, 2016 |
| Faecalibacterium | F < NF | p > 0.05 | 7.3 vs 8.5 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |

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|---|---|---|---|---|---|---|
| Faecalibacterium | F < NF | p > 0.05 | 5.0 vs 10.4 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Faecalibacterium | F < NF | p > 0.05 | -0.9*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Faecalibacterium | F > NF | p > 0.05 | 1.8*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Faecalibacterium** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **ND** | **Rockwood** | **Jackson, 2016** |
| **Fusicatenibacter** | **F < NF** | **p < 0.05** | **0.5 vs 3.1 (M)** | **11 vs 60** | **Sarcopenia** | **Kang, 2021** |
| **Gemella** | **F < NF** | **p < 0.05** | **0.03 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Granulicatella | F > NF | p > 0.05 | 0.1*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Granulicatella | F < NF | p > 0.05 | -0.8*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Haemophilus | F > NF | p > 0.05 | 1.4*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Haemophilus | F > NF | p > 0.05 | 0.4*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Klebsiella | F < NF | p > 0.05 | -0.9*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Lachnobacterium | F < NF | p > 0.05 | -1.3*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Lachnobacterium | F < NF | p > 0.05 | -2.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Lachnoclostridium | F > NF | p > 0.05 | 8.2 vs 7.0 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| **Lachnoclostridium** | **F < NF** | **p < 0.05** | **1.2 vs 2.2 (M)** | **11 vs 60** | **Sarcopenia** | **Kang, 2021** |
| Lachnospira | F > NF | p > 0.05 | 0.2 vs 0.01 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Lachnospira | F < NF | p > 0.05 | 0.6 vs 2.7 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Lachnospira | F < NF | p > 0.05 | -0.7*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Lachnospira | F < NF | p > 0.05 | -0.6*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Lactobacillus** | **F > NF** | **p < 0.05** | **2.3 ± 0.6 vs 1.3 ± 0.5 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| **Lactobacillus** | **F > NF** | **p < 0.05** | **4.4 vs 0.7 (M)** | **11 vs 60** | **Sarcopenia** | **Kang, 2021** |
| Lactobacillus | F > NF | p > 0.05 | 2.6*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Lactobacillus** | **F > NF** | **p < 0.05** | **4.7*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| **Lactobacillus/Enterococcus** | **F > NF** | **p < 0.01** | **0.3 vs 0.04 (MD)** | **10 vs 13** | **GFI** | **Van Tongeren, 2005** |
| **Megasphaera** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Megamonas | F < NF | p > 0.05 | 1.6 vs 2.9 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Methanobrevibacter | F > NF | p > 0.05 | 1.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Methanobrevibacter | F < NF | p > 0.05 | -1.8*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |

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|---|---|---|---|---|---|---|
| **Oscillospira** | **F > NF** | **p < 0.05** | **0.9 ± 0.06 vs 0.8 ± 0.08 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Oscillospira | F > NF | p > 0.05 | 0.5*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Oscillospira | F > NF | p > 0.05 | 0.6*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Other** | **F > NF** | **p < 0.05** | **3.1*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| Parabacteroides | F > NF | p > 0.05 | 6.3 vs 5.8 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Parabacteroides | F > NF | p > 0.05 | 6.5 vs 2.4 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Parabacteroides | F < NF | p > 0.05 | -0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Parabacteroides | F < NF | p > 0.05 | -0.02*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Paraprevotella | F < NF | p > 0.05 | -1.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Paraprevotella** | **F < NF** | **p < 0.05** | **0.02 (FDR)** | **28 vs 30** | **FI34** | **Maffei, 2017** |
| Paraprevotella | F < NF | p > 0.05 | -0.7*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Phascolarctobacterium | F < NF | p > 0.05 | 0.01 vs 0.04 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Phascolarctobacterium | F < NF | p > 0.05 | 1.1 vs 1.3 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Phascolarctobacterium | F > NF | p > 0.05 | 0.9*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Phascolarctobacterium | F > NF | p > 0.05 | 3.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Prevotella | F < NF | p > 0.05 | -1.6*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Prevotella | F < NF | p > 0.05 | -1.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Prevotella_9 | F < NF | p > 0.05 | 8.3 vs 10.1 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| **Pyramidobacter** | **F > NF** | **p < 0.05** | **4,5*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| Roseburia | F < NF | p > 0.05 | 5.7 vs 7.0 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| **Roseburia** | **F < NF** | **p < 0.05** | **0.8 vs 3.6 (M)** | **11 vs 60** | **Sarcopenia** | **Kang, 2021** |
| Roseburia | F < NF | p > 0.05 | -0.02*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Roseburia | F < NF | p > 0.05 | -0.08*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Rothia | F < NF | p > 0.05 | -0.7*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Rothia** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| Ruminococcaceae_UCG-002 | F > NF | p > 0.05 | 2.4 vs 0.8 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| **Ruminococcus** | **F > NF** | **p < 0.05** | **< 0.05 (FDR)** | **ND** | **FI34** | **Maffei, 2017** |
| Ruminococcus | F < NF | p > 0.05 | 15.2 vs 23.8 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ruminococcus | F > NF | p > 0.05 | 1.8 vs 1.3 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Ruminococcus | F > NF | p > 0.05 | 0.2*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| [Ruminococcus] | F > NF | p > 0.05 | 0.6*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Ruminococcus¬ | F > NF | p > 0.05 | 1.2*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Ruminococcus° | F > NF | p > 0.05 | 0.5*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Slackia** | **F < NF** | **p < 0.05** | **-7.2*(DAA)** | **18 vs 17** | **Sarcopenia** | **Picca, 2020** |
| **Slackia** | **F < NF** | **p < 0.05** | **-9.1*(DAA)** | **14 vs 36** | **Sarcopenia** | **Ponziane, 2021** |
| Streptococcus | F > NF | p > 0.05 | 1.1 vs 0.8 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Streptococcus | F > NF | p > 0.05 | 7.5 vs 5.8 (M) | 15 vs 12 | Rockwood | Zhang, 2020 |
| Streptococcus | F < NF | p > 0.05 | -0.5*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Streptococcus | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Subdoligranulum | F <NF | p > 0.05 | 0.17 ± 0.3 vs 0.21 ± 0.2 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Subdoligranulum | F < NF | p > 0.05 | 2.0 vs 2.6 (M) | 11 vs 60 | Sarcopenia | Kang, 2021 |
| Sutterella | F < NF | p > 0.05 | -0.4*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| **Sutterella** | **F < NF** | **p < 0.05** | **0.08 (FDR)** | **28 vs 30** | **FI34** | **Maffei, 2017** |
| Turicibacter | F < NF | p > 0.05 | -0.3*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| Veillonella | F = NF | p > 0.05 | 0.01 vs 0.01 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Veillonella | F > NF | p > 0.05 | 2.4*(DAA) | 18 vs 17 | Sarcopenia | Picca, 2020 |
| Veillonella | F > NF | p > 0.05 | 3.04*(DAA) | 14 vs 36 | Sarcopenia | Ponziane, 2021 |
| **Veillonella** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **18 vs 45** | **Sarcopenia** | **Margiotta, 2021** |
| **Species of bacteria** | **Frailty effect** | **p-value** | **Value F vs NF** | **Sample size F vs NF** | **Frailty criteria** | **Ref** |
| Akkermansia muciniphila | F = NF | p > 0.05 | 0 ± 6.4 vs 0 ± 0.07 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| **Alistipes shahii** | **F < NF** | **p < 0.05** | **0 ± 0.15 vs 0.9 ± 1.1 (M)** | **5 vs 12** | **Sarcopenia** | **Ticinesi, 2020** |
| Alistipes onderdonkii | F < NF | p > 0.05 | 0.3 ± 9.1 vs 0.6 ± 0.9 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Bacteroides caccae | F < NF | p > 0.05 | 0.4 ± 4.0 vs 1.0 ± 1.7 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Bacteroides dorei | F < NF | p > 0.05 | 0.2 ± 0.5 vs 0.5 ± 1.3 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bacteroides fragilis | F > NF | p > 0.05 | 0.4 ± 8.4 vs 0.3 ± 1.1 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Bacteroides uniformis | F > NF | p > 0.05 | 13.0 ± 10.2 vs 6.3 ± 9.3 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Bacteroides vulgatus | F < NF | p > 0.05 | 1.7 ± 1.6 vs 3.8 ± 5.7 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Barnesiella intestinihominis | F < NF | p > 0.05 | 0.1 ± 2.7 vs 2.4 ± 2.0 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Bifidobacterium longum | F > NF | p > 0.05 | 0.4 ± 0.6 vs 0 ± 0.3 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Eggerthella lenta | F > NF | p > 0.05 | 5.1 ± 0.3 vs 4.0 ± 0.3 (M) | 38 vs 26 | Fried | Margiotta, 2020 |
| **Eggerthella lenta** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **ND** | **Rockwood** | **Jackson, 2016** |
| E. faecium/E. faecalis | F > NF | p > 0.05 | 0.01 vs 0.02 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| E. rectale/C. coccoides | F < NF | p > 0.05 | 13.2 vs 19.7 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| Escherichia coli | F > NF | p > 0.05 | 0.3 ± 2.8 vs 0 ± 0.2 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| **Eubacterium cylindroides** | **F > NF** | **p < 0.05** | **6.0 ± 0.3 vs 5.0 ± 0.2 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| Eubacterium cylindroides | F > NF | p > 0.05 | 1.4 vs 0.9 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| **Eubacterium dolichun** | **F > NF** | **p < 0.05** | **6.5 ± 0.3 vs 5.0 ± 0.4 (M)** | **38 vs 26** | **Fried** | **Margiotta, 2020** |
| **Eubacterium dolichun** | **F > NF** | **p < 0.05** | **< 0.01 (FDR)** | **ND** | **Rockwood** | **Jackson, 2016** |
| Eubacterium hallii | F = NF | p > 0.05 | 0.1 vs 0.1 (MD) | 10 vs 13 | GFI | Van Tongeren, 2005 |
| **Faecalibacterium prausnitzi** | **F < NF** | **p < 0.05** | **0.2 ± 2.8 vs 5.6 ± 6.0 (M)** | **5 vs 12** | **Sarcopenia** | **Ticinesi, 2020** |
| **Faecalibacterium prausnitzi** | **F < NF** | **p < 0.05** | **0.7 vs 3.1 (MD)** | **10 vs 13** | **GFI** | **Van Tongeren, 2005** |
| **Faecalibacterium prausnitzi** | **F < NF** | **p < 0.05** | **< 0.01 (FDR)** | **ND** | **Rockwood** | **Jackson, 2016** |
| Flavonifractor plautii | F > NF | p > 0.05 | 0.9 ± 0.6 vs 0.5 ± 0.5 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Parabacteroides distasonis | F > NF | p > 0.05 | 2.9 ± 12.4 vs 1.0 ± 2.4 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Parabacteroides merdae | F > NF | p > 0.05 | 1.2 ± 2.2 vs 1.1 ± 1.5 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Roseburia intestinalis | F < NF | p > 0.05 | 0.2 ± 0.3 vs 0.3 ± 1.2 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| **Roseburia inulinivorans** | **F < NF** | **p < 0.05** | **0.0 ± 0.0 vs 0.3 ± 0.6 (M)** | **5 vs 12** | **Sarcopenia** | **Ticinesi, 2020** |
| Ruminococcus bromii | F > NF | p > 0.05 | 0.9 ± 1.1 vs 0.3 ±1.0 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Ruminococcus gnavus | F > NF | p > 0.05 | 0.3 ± 2.4 vs 0.1 ± 0.2 (M) | 5 vs 12 | Sarcopenia | Ticinesi, 2020 |
| Ruminococcus torques | F > NF | p > 0.05 | 7.4 ± 0.3 vs 7.3 ± 0.2 (M) | 38 vs 26 | Fried | Margiotta, 2020 |

**Legend:** *: Log2FC; DDA: Differential Abundance Analysis; M: Mean; ±: Standard Deviation; MD: Median; [ ]: Non cited in study; ¬: Firmicutes, Clostridia, Clostridiales, Lachnospiraceae, Ruminococcus; °: Firmicutes, Clostridia, Clostridiales, Ruminococcaceae, Ruminococcus; GFI: Groningen

Frailty Indicator; E. faecium: Enterococcus Faecium; E. faecalis: Enterococcus faecalis; E. rectale: Eubacterium Rectale; C. coccoides: Clostridium Coccoides. Bold lines have a level of significance p< 0.05 or p< 0.01.

**Supplementary table 1.** Newcastle-Ottawa assessment scale case control studies.

| First author, year | Selection | | | | Comparability | Exposure | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Zhang, 2020 | * | - | - | * | ** | * | * | - | 6 |
| Margiotta, 2020 | * | - | - | * | ** | * | * | - | 6 |
| Margiotta, 2021 | * | - | - | * | ** | * | * | - | 6 |
| Picca, 2020 | * | - | * | * | ** | * | * | - | 7 |
| Ticinesi, 2020 | * | - | * | * | ** | * | * | - | 7 |
| Kang, 2021 | * | - | * | * | ** | * | * | - | 7 |
| Ponziani, 2021 | * | - | * | * | ** | * | * | - | 7 |
| Van Tongeren, 2005 | * | - | - | - | - | * | * | - | 3 |
| Ticinesi, 2017 | * | - | - | * | ** | * | * | - | 6 |

Legend: *: one point attributed in the question; **: two points attributed in the question; -: none point attributed in the question; 1: Is the case definition adequate?; 2: Representativeness of the cases; 3: Selection of Controls; 4: Definition of Controls; 5: Comparability of cases and controls on the basis of the design or analysis; 6: Ascertainment of exposure; 7: Same method of ascertainment for cases and controls; 8: Non-Response rate.

**Supplementary table 2.** Newcastle-Ottawa Scale assessment cohort studies scale studies.

| First author, year | Selection | | | | Comparability | Exposure | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Jackson, 2016 | * | * | * | - | * | * | - | - | 5 |
| Maffei, 2017 | * | * | * | - | * | * | - | - | 5 |

**Legend:** *: one point attributed in the question; **: two points attributed in the question; -: none point attributed in the question; 1: Representativeness of the exposed cohort; 2: Selection of the non-exposed cohort; 3: Ascertainment of exposure; 4: Demonstration that outcome of interest was not present at start of study; 5: Comparability of cohorts on the basis of the design or analysis; 6: Assessment of outcome; 7: Was follow-up long enough for outcomes to occur; 8: Adequacy of follow up of cohorts.