The intestinal microbiome and its relevance for functionality in older persons

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Purpose of review
This article summarizes the advances of research on the role of the intestinal microbiota in influencing sarcopenia, frailty, and cognitive dysfunction in older individuals, and thus its relevance for healthy active ageing.

Recent findings
Age-related alterations of intestinal microbiota composition may negatively influence muscle protein synthesis and function by promoting chronic systemic inflammation, insulin resistance, oxidative stress, and reducing nutrient bioavailability. However, this ‘gut-muscle axis’ hypothesis is not supported by human data to date. Some observational studies have instead demonstrated that, in older individuals, frailty and Alzheimer-type dementia are associated with fecal microbiota dysbiosis, that is, reduced biodiversity and overexpression of pathobionts. The main possible mechanisms of the ‘gut-brain axis’ in cognitive function modulation include effects on neurotransmission, neuroinflammation, and amyloid deposition. Conversely, longevity in good health may be associated with the maintenance of a fecal microbiota composition similar to that of healthy young adults. However, the role of gut microbiota as an independent modulator of frailty and cognition still remains uncertain, being influenced by several physiological factors, including diet and exercise.

Summary
The intestinal microbiome composition represents a possible determinant of functional performance in older people, and a promising target for antiaging therapeutic interventions.

Keywords
Cognitive function, frailty, geriatrics, gut microbiota, sarcopenia

INTRODUCTION
Aging is associated with substantial changes in the composition of the gut microbiota, that is, the ensemble of bacteria, protozoa, archaea, viruses, and fungi symbiotically living in the human gastrointestinal tract [1]. Some years ago, the emergence of next-generation sequencing techniques for microbiome analysis, based on 16S rRNA microbial profiling, has allowed the fulfillment of observational studies, demonstrating that older study participants exhibited lower biodiversity and increased interindividual variability of fecal microbiota compared to adults [1]. These alterations were enhanced in those study participants with mobility limitations residing in nursing homes [1].

More recently, microbiome research has been more and more focused on the active involvement of gut bacteria in modulating several aspects of the host physiology and in determining the onset and course of chronic systemic diseases [2]. Thus, gut microbiota may play an important role also in the aging process [3] and in the onset of age-related diseases and syndromes [4], especially when dysbiosis, that is, clinically relevant reduction of gut microbiota biodiversity with overexpression of opportunistic pathogens, arises. Its capacity of modulating inflammation, immune function, and insulin sensitivity may be of utmost importance in this process [3,4].

The translation of these physiopathological concepts and hypotheses into clinical research remains, however, uncertain. The association...
Microbiome and functionality in aging Ticinesi et al.

KEY POINTS

- The intestinal microbiota composition may be directly involved in the physiopathology of age-related sarcopenia, frailty, and cognitive dysfunction.
- Frailty and dementia are associated with reduced microbiota biodiversity, and depletion of taxa with possible beneficial activity on the host metabolism and inflammation.
- A ‘gut-muscle axis’ in the physiopathology of sarcopenia has been demonstrated in animal models, but not yet in human beings.
- Longitudinal studies are needed to better understand the relevance of gut microbiota for the functionality of older persons.
- Gut microbiota represents a promising area for developing novel antiaging interventions.

between gut microbiota and the functionality of older persons represents an area of great interest for identifying novel targets of prevention and treatment of geriatric syndromes leading to disability, such as sarcopenia, physical, and cognitive frailty. However, few data from clinical studies are available, with most literature focused on animal models of aging and age-related conditions. The aim of this study is to review the most recent acquisitions on the role of gut microbiota in the fields of muscle function, frailty, and cognitive function, which are critical for determining functionality of older persons.

MICROBIOTA AND MUSCLE FUNCTION IN AGING

The gut microbiota composition may play a central role in determining the skeletal muscle mass, architecture, and function during aging, and thus be involved in the physiopathology of sarcopenia. In a study on animal models of presarcopenia and sarcopenia, Siddhart et al. [5**] showed that the fecal microbiota of sarcopenic rats was characterized by a distinct composition compared to controls. These changes were accompanied by alterations in the microbiome functional profile, with reduced microbial capacity of contributing to dietary carbohydrate and lipid digestion and reduced vitamin B12 and folate synthesis that prompted altered serum proteomic and lipidomic profiles in the host [5**]. Interestingly, the fecal microbiota representation of several taxa, including the short-chain fatty acid (SCFA) producers Faecalibacterium, Clostridium XIVa, and Butyricicoccus, was positively correlated with muscle mass, suggesting a pro-anabolic action of these bacteria [5**].

Once absorbed into systemic circulation, the microbial metabolites SCFA, and particularly butyrate, may modulate skeletal muscle insulin sensitivity and inflammation. Conversely, in mouse models age-associated intestinal microbiota dysbiosis increases gut permeability, promotes inflammation and macrophage dysfunction, with a possible negative impact on skeletal muscle protein synthesis [6]. Age-associated altered gut microbiota may also promote different expression of host genes pointing toward reduced defenses against infection [7]. Additionally, gut microbiota may mediate the pro-anabolic effects of some nutrients on skeletal muscle cells. In a mouse model of heart failure, resveratrol administration induced gut microbiota modifications (overexpression of Parabacteroides, Bilophila, and Akkermansia, and depletion of Lachnospiraceae) associated with improved skeletal muscle insulin sensitivity, basal metabolic rate, and exercise performance, even without modifications in muscle mass and strength [8].

Some of these mechanisms have been recently confirmed by human studies. Buford et al. [9] performed 16S microbiome analysis on blood samples from healthy young and older adults, showing the presence of microbes derived from gut microbiota as a consequence of increased mucosal permeability (‘leaky gut’). The serum microbiome had different composition in older vs. younger study participants, and the abundance of the Bacteroidetes phylum was positively correlated with the pro-anabolic hormone insulin growth factor-1, and negatively correlated with the inflammatory biomarkers interleukin-6 and tumor necrosis factor-α [9]. Moreover, the administration of a symbiotic containing Lactobacillus rhamnosus CG and soluble corn fiber to healthy older adults resulted in favorable modifications in intestinal microbiota, and reduced chronic inflammation, measured with C-reactive protein levels [10]. Although no outcomes of functional performance or muscle function were measured in these studies, their results support the possible involvement of gut microbiota in the physiopathology of sarcopenia, considering the effects of chronic inflammation on muscle protein synthesis.

Basing on these findings and on previous literature reports, three research groups have independently hypothesized that gut microbiota may contribute to the onset and clinical course of age-related sarcopenia, influencing both muscle mass and muscle function with several mechanisms [11*,12,13]. However, no clinical study has verified this hypothesis to date.

The gut-muscle communication may, however, not simply be one way. Recent human studies have highlighted that exercise training is associated with
favorable fecal microbiota profiles, in terms of biodiversity and production of metabolically active mediators like SCFAs [14,15]. As exercise is the mainstay of sarcopenia prevention and treatment in older individuals, a role of gut microbiota as a mediator of the beneficial effects of exercise on skeletal muscle can be hypothesized. However, in a mouse model of accelerated aging, exercise intervention was not able to modulate the age-related mitochondrial dysfunction, despite increasing gut microbiota biodiversity [16]. Mitochondrial dysfunction is one of the main cellular mechanisms involved in sarcopenia, and these findings need further confirmation in human studies before drawing solid conclusions.

The possible mechanisms linking gut microbiota dysbiosis with the pathogenesis of sarcopenia are summarized in Fig. 1.

**MICROBIOTA, PHYSICAL FUNCTION, AND FRAILTY**

Several preclinical studies have investigated the association between gut microbiota composition and longevity in animal models of aging [17–19]. Specific microbial genes may be involved in extending lifespan in *Caenorhabditis elegans*, through production of polysaccharide mediators such as colonic acid [20]. These studies support the concept that a healthy gut microbiota composition (high biodiversity and representation of bacteria with purported beneficial metabolic activity, low representation of pathobionts) may extend lifespan [21].

Similarly, the elevated gut microbiota biodiversity with high representation of SCFA producers observed in centenarians support an active role of the microbiome in modulating lifespan also in human beings [21]. Recently, Bian *et al.* [22] performed a population-based fecal microbiome analysis of more than 1000 Chinese individuals, including also 198 centenarians with a good performance status. Surprisingly, the fecal microbiota composition of centenarians had an overall composition showing no significant difference from that of study participants aged 30–50 years old, even in the presence of an extreme interindividual variability. The fecal microbiota of centenarians was also particularly enriched of the SCFA producer *Faecalibacterium prausnitzii* [22]. As only the fittest elderly...
Table 1. Summary of the most recent studies (years 2017–2018) exploring the association of gut microbiota composition with frailty or reduced functionality in aging human beings

<table>
<thead>
<tr>
<th>References</th>
<th>Population</th>
<th>Age</th>
<th>Method of frailty or functional performance assessment</th>
<th>Main findings</th>
<th>Main limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>[24]</td>
<td>76 patients hospitalized for acute extraintestinal diseases</td>
<td>83 ± 6</td>
<td>Rockwood Clinical Frailty Scale</td>
<td>Gut microbiota dysbiosis was inversely associated with frailty and polypharmacy and not with age; frailty and predicted long-term mortality. The abundance of seven taxa was significantly and independently associated with frailty</td>
<td>Low sample size, absence of healthy controls, enrolment of patients with acute diseases that may represent a confounder</td>
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<td>[25]</td>
<td>85 community-dwelling healthy volunteers</td>
<td>64 ± 7 (range 43–79)</td>
<td>34-item frailty index</td>
<td>Gut microbiota diversity was inversely associated with frailty index and not with chronological age; high frailty burden was associated with elevated interindividual variability, overexpression of Coprococcus and Dialister, reduced expression of Sutterella and Paraprevotella, and different predicted microbiota functionality</td>
<td>Low sample size, absence of oldest old individuals, functional microbiome profile inferred and not directly assessed</td>
</tr>
<tr>
<td>[26]</td>
<td>22 patients with heart failure (12 young, 10 old), 12 healthy controls</td>
<td>74 ± 3 (old patients), 47 ± 3 (young patients), 41 ± 2 (controls)</td>
<td>New York Heart Association functional class</td>
<td>Heart failure patients had different gut microbiota composition than controls; older heart failure patients had significant depletion of Bacteroidetes and Faecalibacterium prausnitzii and overexpression of Proteobacteria and Lactobacillus compared to young patients with heart failure</td>
<td>Low sample size, absence of healthy controls over 65 years, focus on a single chronic disease without comprehensive functional assessment</td>
</tr>
<tr>
<td>[27]</td>
<td>87 nursing home residents with advanced dementia and severe functional limitations</td>
<td>89 ± 7</td>
<td>Test for Severe Impairment</td>
<td>Extreme gut microbiota dysbiosis and elevated interindividual variability in all participants; overexpression of several taxa, including Akkermansia and Romboutsia, in those colonized by Clostridium difficile</td>
<td>Low sample size, study aimed at identifying factors associated with Clostridium difficile colonization, absence of nondisabled patients</td>
</tr>
<tr>
<td>[28**]</td>
<td>23 nursing home residents</td>
<td>86 ± 8</td>
<td>Rockwood Clinical Frailty Scale</td>
<td>Gut microbiota composition remained stable over time; dysbiosis was associated with the presence of frailty and malnutrition and was influenced by the place of residence; frailty was associated with depletion of beneficial functionalities in gut microbiota, including reduced production of short-chain fatty acids</td>
<td>Low sample size</td>
</tr>
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</table>

In the only recent study with a prospective design (Table 1), Haran et al. [28**] found that the gut microbiota composition of nursing home residents was stable over time and exhibited more pronounced dysbiosis and depletion of SCFA-producing taxa with increasing frailty. Clinical frailty scale score, the presence of malnutrition, and cohabiting with other disabled residents resulted the main factors driving the composition of fecal microbiota, and allowed to identify distinct microbiome clusters. From a functional point of view, aging was associated with a decline in the microbial capacity of metabolizing amino acids and producing vitamin B12.

Additionally, a recent study by Ogawa et al. [29*] analyzed the composition of salivary microbiota, which could influence intestinal microbiota composition, in a group of older frail nursing home residents and healthy-active community dwellers.
They demonstrated a shift toward dysbiosis in nursing home residents, with increased representation of pathobionts including *Streptococcus*, *Veillonella*, and *Haemophilus*. The presence of these bacteria in salivary microbiota may influence intestinal microbiota composition, and represent a risk factor for infections, especially pneumonia.

In general, all the recent studies support the concept that frailty is associated with an altered gut microbiota composition, especially in nursing home residents and in study participants admitted to hospital [24–27,28**,29**]. The contribution of gut microbiota in the physiopathology of frailty is, however, still uncertain. In fact, frailty itself can induce several alterations of the gut physiology, regarding particularly the barrier function of intestinal mucosa [30]. Thus, the observed gut microbiota alterations may simply represent a consequence of the physiopathological mechanisms of frailty, and not a contributing cause. Moreover, frailty is frequently associated with malnutrition and reduced mobility. As gut microbiota is strongly influenced by diet and exercise, the association of gut microbiota dysbiosis with frailty may depend on the changing lifestyle habits rather than on a primary physiopathological process.

Unfortunately, most studies exploring the association between microbiome and frailty were performed in small groups of patients, and often lacked a comprehensive geriatric assessment or a thorough evaluation of possible confounding factors. Population-based microbiome studies, whose feasibility has been recently demonstrated also in older individuals [31], should contribute to clarify these issues in the future.

**MICROBIOTA AND COGNITIVE FUNCTION**

Cognition is a fundamental domain for the functionality of older persons. A large body of literature, reviewed elsewhere [32–35], has recently established a possible connection between gut microbiota composition and cognitive function, hypothesizing a direct involvement of gut microbiota in Alzheimer’s disease pathogenesis. The possible physiopathological mechanisms are summarized in Table 2. However, most of the existing studies on this topic were performed on animal models of dementia, and only few of them report human data. Thus, the translation of physiopathological concepts into clinical practice remains uncertain [32].

In mice genetically prone to dementia, a significant gut microbiota composition alteration was observed [36–42]. The transplantation of fecal microbiota from transgenic mice with dementia to cognitively healthy mice worsened the cognitive performance at behavioral tests, supporting a direct physiopathological involvement of gut microbiota.

### Table 2. Overview of the main mechanisms possibly involved in gut microbiota modulation of cognitive function, according to the most recent scientific literature (years 2017–2018)

<table>
<thead>
<tr>
<th>Intestinal mechanism</th>
<th>Mediators of gut–brain communication</th>
<th>Final mechanism promoting cognitive dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of amyloid proteins by gut bacteria</td>
<td>Neuroinflammation</td>
<td>Increased deposition of amyloid in intestinal and brain tissues</td>
</tr>
<tr>
<td>Production of amyloidogenic bacterial compounds</td>
<td>Molecular mimicry</td>
<td>Increased deposition of brain amyloid</td>
</tr>
<tr>
<td>Alteration of gut mucosa permeability (‘leaky gut’)</td>
<td>Bacterial exotoxins (lipopolysaccharide, saxitoxin, anatoxin)</td>
<td>Activation of neuroinflammation</td>
</tr>
<tr>
<td></td>
<td>Penetration of bacteria into circulation (‘serum microbiota’)</td>
<td>Direct neurodegenerative effect</td>
</tr>
<tr>
<td></td>
<td>Reduced availability of neurotransmitters in the brain</td>
<td>Activation of systemic inflammation and immune response Increased microglial activation and amyloid deposition</td>
</tr>
<tr>
<td>Reduced bacterial synthesis of neurotransmitters (histamine, GABA, serotonin, acetylcholine)</td>
<td>Reduced circulating short-chain fatty acids</td>
<td>Reduced neurotrophism Increased neuronal apoptosis</td>
</tr>
<tr>
<td>Reduced bacterial synthesis of metabolically active mediators</td>
<td>Reduced biotransformation of nutrients (flavonoids)</td>
<td>Increased oxidative stress and apoptosis</td>
</tr>
<tr>
<td></td>
<td>Reduced systemic load of antioxidants of bacterial origin (indole-3-propionic acid)</td>
<td>Increased oxidative stress and apoptosis</td>
</tr>
</tbody>
</table>

GABA, gamma aminobutyric acid.
in cognitive dysfunction [43*]. Gut microbiota may influence the development of dementia inducing increased intestinal mucosa permeability and systemic inflammation [39], favoring the cerebral amyloid deposition [20,33,40], or reducing the production or bioavailability of some nutrients or metabolically active mediators, such as SCFA [41–42]. The fundamental role of altered gut microbiota in activating neural inflammation was also confirmed in Drosophila models of dementia [44] and in studies performed on mouse models of stroke, in which dysbiosis confirmed as a determinant of worsened clinical course and cognitive function after the injury [45,46].

In line with these concepts, manipulation of intestinal microbiota may influence cognitive functions in mouse models of dementia. Dysbiosis induced by total abdominal irradiation resulted in worsened cognitive performance in one study [47], whereas antibiotic administration was associated with improved indexes of neuroinflammation in another one [48]. Conversely, the administration of probiotics or prebiotics improved or prevented decline in spatial learning tasks [49–57]. The probiotics with demonstrated positive effects on mouse cognitive function included bifidobacteria [49,51,54], lactobacilli [50,53,54], and lactic acid bacteria contained in cow milk [52]. The prebiotics, that is, functional foods inducing reproducible modifications in gut microbiota composition, whose administration to mice was associated with improved cognition, were instead tea saponins derived from tea [55], fructo-oligosaccharides from Morinda officinalis [56], and baicalein, a flavonoid from Scutellaria baicalensis roots [57].

Three studies explored the influence of gut microbiota-derived substances on brain function of human beings, without a comprehensive analysis of intestinal microbiota [58–60]. In patients with Alzheimer’s disease, rhamnolipids, Gran-negative bacteria-derived exotoxins, were detected in serum and cerebrospinal fluid samples [58], whereas

<table>
<thead>
<tr>
<th>References</th>
<th>Study design</th>
<th>Number and characteristics of participants</th>
<th>Mean age</th>
<th>Main findings</th>
<th>Comments/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>[61*]</td>
<td>Cross-sectional</td>
<td>40 amyloid-positive patients with dementia</td>
<td>71 ± 7 (Amy+)</td>
<td>Lower abundance of Eubacterium rectale and increased abundance of Escherichia/Shigella, with increased proinflammatory cytokine levels in Amy+</td>
<td>Fecal microbiota analysis performed with quantitative PCR and not next-generation sequencing techniques</td>
</tr>
<tr>
<td>[62**]</td>
<td>Cross-sectional</td>
<td>25 community dwellers with Alzheimer-type dementia</td>
<td>71 ± 7 (cases)</td>
<td>Reduced biodiversity and distinct composition of fecal microbiota in demented patients (overexpression of Bacteroides and Akkotipes, depletion of Bifidobacterium)</td>
<td>Absence of follow-up data and correlation with clinical parameters of cognitive function. No analyses of microbiome function</td>
</tr>
<tr>
<td>[63*]</td>
<td>Cross-sectional</td>
<td>43 patients with dementia</td>
<td>70 ± 9 in both cases and controls</td>
<td>Different composition of fecal microbiota in demented patients, with reduced biodiversity and representation of Lachnospiraceae, Bacteroidaceae, and Veillonellaceae</td>
<td>No analyses of microbiome function. Absence of follow-up data. No microbial profiling at the lowest taxonomic levels</td>
</tr>
<tr>
<td>[64*]</td>
<td>Cross-sectional</td>
<td>43 healthy community dwellers</td>
<td>64 ± 7</td>
<td>Different fecal microbiota composition between participants with and without at least one impairment in neuropsychological tests</td>
<td>No microbial profiling at the lowest taxonomic levels. Absence of follow-up data. No inclusion of study participants with well-established cognitive impairment</td>
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<tr>
<td>[65]</td>
<td>Longitudinal observational (2-year follow-up)</td>
<td>17 obese adult study participants</td>
<td>53 (median obese)</td>
<td>Increased amyloid deposition at follow-up, detected with magnetic resonance, was associated with shifts in gut microbiota composition, and functionality in both groups</td>
<td>No elderly and/or demented study participants enrolled in the study</td>
</tr>
<tr>
<td>[66]</td>
<td>Cross-sectional</td>
<td>37 older community dwellers in good health</td>
<td>65 ± 8</td>
<td>Better sleep quality and cognitive function were associated with fecal microbiota composition (higher proportions of Verrucomicrobia and Lentisphaerae)</td>
<td>No analyses of microbiome function. Absence of follow-up data. No microbial profiling at the lowest taxonomic levels</td>
</tr>
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</table>

Amy, amyloid.
lipopolysaccharide was detected in postmortem hippocampal and temporal cortex extracts [59]. Moreover, fecal samples from demented patients were enriched in bacterial NADH:ubiquinone oxidoreductase, involved in the synthesis of aromatic amino acids that may be involved in neurodegeneration pathways [60].

The fecal microbiota composition was correlated with cognitive function in six human studies [61*,62**,63*,64*,65*,66*], whose findings are summarized in Table 3. In a study performed with quantitative PCR, fecal overexpression of pathobionts, including Escherichia coli, was correlated with systemic inflammation and brain amyloid deposition [61*]. The link between dysbiosis and dementia was later confirmed with next-generation sequencing techniques by Vogt et al. [62**], who also demonstrated significant correlations between cerebrospinal fluid levels of Alzheimer’s disease biomarkers and the relative abundance of some fecal taxa, including positive correlations for Bacteroides and Blautia, and negative correlations for Dialister and Turicibacter. The dementia-associated overexpression of Bacteroides in the intestinal microbiome was also confirmed in the largest-to-date human study by Zhuang et al. [63*] who enrolled 43 study participants with dementia and 43 controls.

Additionally, gut microbiota composition was significantly associated with cognitive performance, particularly in the executive and attention tasks, in healthy older adults [64*] and middle-aged apparently healthy study participants with or without obesity [65]. Dysbiosis was also significantly associated with poorer sleep quality and reduced cognitive flexibility in a small sample of healthy older adults [66].

To date, no prospective studies have assessed the dynamic association between changes in gut microbiota composition and variations of cognitive performance measures in human beings.

Only one intervention study, in which Lactobacillus rhamnosus JB-1 was administered, has evaluated the effects of gut microbiota manipulation on cognitive function in human beings. The authors did not observe any variation in cognitive outcomes after an 8-week treatment, but only healthy young adults with no cognitive complaints were enrolled in the study [67]. Thus, the transferability of these results to older cognitively impaired study participants remains unclear.

CONCLUSION

The current literature state-of-art supports the plausibility of an active involvement of intestinal microbiome in influencing the aging human body functionality at multiple levels.

Frailty is associated with an altered composition of fecal microbiota, especially in those study participants with malnutrition, mobility limitations, acute diseases, or who live in nursing homes. However, the contribution of the microbiome in the physiopathology of frailty is far from understood.

The presence of a ‘gut-muscle axis’ in the pathogenesis of sarcopenia can only be hypothesized at the present moment, as all data on the association between gut microbiota and muscle mass and function come from animal models.

Conversely, the presence of a ‘gut-brain axis’ influencing cognitive function in older individuals is supported by a large body of preclinical literature, and also by some human studies. However, the clinical relevance of this axis remains uncertain, as prospective observational and intervention studies on human beings are lacking.

Still, the intestinal microbiome, and its interactions with diet, represent very interesting areas for ageing research, and a potential target for innovative therapeutic tools.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- - of outstanding interest


Comprehensive analysis of gut microbiota composition and functionality, including its effects on the host proteomics and lipidomics, in rat models of sarcopenia and presarcopenia. This study gives fundamental contribution on the comprehension of mechanisms involved in the ‘gut-muscle axis’ in aging.
Microbiome and functionality in aging Ticienei et al.


Cross-sectional study in which the fecal microbiota was compared among demented patients, either β amyloid-positive or β amyloid-negative, and healthy controls, providing evidence for a possible involvement of fecal microbiota in brain amyloid deposition. Microbiome was analyzed with quantitative PCR and not with metagenomics.


First study in the scientific literature comparing fecal microbiota composition between demented patients and healthy controls using a next-generation sequencing (i.e. metagenomics) approach. It also showed correlations between gut microbiota composition and markers of dementia severity, providing solid bases for a possible involvement of the microbiota in dementia course.


This is the largest study comparing fecal microbiota composition between study participants with Alzheimer’s disease and healthy controls, providing evidence for dementia-related dysbiosis.


Cross-sectional study establishing an association between the composition of the gut microbiota and cognitive performance test in older adults without neurological complaints. The results suggest an influence of the gut microbiota on cognitive function also outside the field of certified dementia.

