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SYSTEMATIC REVIEWS

Gut microbiota changes associated with frailty in older adults: A systematic review of observational studies

Na-Na Wen, Li-Wei Sun, Qian Geng, Guo-Hua Zheng

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Na-Na Wen, Li-Wei Sun, Qian Geng, Guo-Hua Zheng, College of Nursing and Health Management, Shanghai University of Medicine and Health Sciences, Shanghai 201318, China

Na-Na Wen, Graduate School, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

Corresponding author: Guo-Hua Zheng, PhD, Professor, College of Nursing and Health Management, Shanghai University of Medicine and Health Sciences, No. 279 Zhouzhu Road, Pudong New District, Shanghai 201318, China. zhenggh@sumhs.edu.cn

Abstract

BACKGROUND

Frailty is a complex aging-related syndrome characterized by a cumulative loss of physiological reserve and increased vulnerability to adverse clinical outcomes, including falls, disability, incapacity and death. While an increasing number of studies suggest that the gut microbiota may play a key role in the pathophysiology of frailty, direct evaluation of the association between gut microbiome alterations and frailty in older adults remains limited.

AIM

To gain insight into gut dysbiosis in frail older adults.

METHODS

Seven electronic databases (China National Knowledge Infrastructure, VIP, SinoMed, Wanfang, PubMed, Web of Science and EMBASE) were searched for articles published before October 31, 2023 to identify observational studies that compared the microbiomes of older adults with and without frailty. The diversity and composition of the gut microbiota were the main outcomes used to analyze the associations of changes in the gut microbiota with frailty in older adults. The quality of the included studies was assessed *via* the Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality.

RESULTS

Eleven observational studies with 912 older adults were included in this review. Consistent results revealed a significant difference in the gut microbiota composition between frail and non-frail older adults, with a significant decrease in α diversity and a significant increase in β diversity in frail older adults. The pooled results revealed that at the phylum level, four microbiota (*Actinobacteria*, *Proteobacteria*, *Verrucomicrobia* and *Synergistetes*) were significantly enriched, and two

microbiota (*Firmicutes* and *Fusobacteria*) were significantly depleted in frail older adults. At the family level, the results consistently revealed that the abundances of 6 families, most of which belong to the *Actinobacteria* or *Proteobacteria* phylum, were greater in frail than in non-frail older adults. At the genus or species level, consistent results from more than two studies revealed that the abundances of the genera *Prevotella*, *Faecalibacterium,* and *Roseburia* were significantly lower in frail older adults; individual studies revealed that the abundances of some genera or species (*e.g.*, *Megamonas*, *Blautia*, and *Megasphaera*) were significantly lower, whereas those of other genera or species (*e.g.*, *Bifidobacterium*, *Oscillospira*, *Ruminococcus* and *Pyramidobacter*) were significantly greater in frail older adults.

CONCLUSION

This systematic review suggests that changes in the gut microbiota are associated with frailty in older adults, which is commonly reflected by a reduction in beneficial species and an increase in pathogenic species. However, further studies are needed to confirm these findings.

Key Words: Frailty; Gut microbiota; Observational study; Older adults; Systematic review

Core Tip: A growing number of studies have reported changes in the composition and diversity of the gut microbiota between frail and healthy older adults, suggesting that alterations in the gut microbiota may play a key role in the pathophysiology of frailty; however, direct assessment of the associations between changes in the gut microbiome and frailty in older adults remains limited. This review revealed a significant decrease in α diversity and a significant increase in β diversity in frail older adults compared with non-frail older adults, which was commonly reflected by a reduction in beneficial species and an increase in pathogenic species. This study provides a comprehensive overview of the relationship between changes in the gut microbiota and frailty in older adults and suggests a possible role for the gut microbiota in the pathogenesis of frailty.

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INTRODUCTION

Frailty is a complex age-related geriatric syndrome characterized by decreased physiological reserves in the body with decreased anti-stress ability and vulnerability in the face of external stimuli, leading to increased risks of multiple adverse health outcomes, including falls, hospitalization, and even mortality[1,2]. Frailty is common among community-dwelling older adults, with a prevalence ranging from 4% to 59% among those aged 65 years and older and 25% among older adults over 85 years[3]. Current studies have shown that the risk factors associated with frailty in older adults are mainly related to increasing age, lower weight, female sex, living alone, low levels of physical activity, polypharmacy, unhealthy lifestyle, smoking, alcohol consumption, and poor diet. These factors interact and form a cycle to cause chronic malnutrition, inflammation, and disruption of hormone regulation[4-7]. Recently, intestinal dysbacteriosis has been newly identified as a risk factor for frailty in older adults[6,8]. For example, a study of 728 female twins revealed a negative association between gut microbiota α diversity and frailty, with increases in *Eubacterium dolichum* and *Eggerthella lenta* in the frail group[9].

The gut microbiota is a relatively stable community consisting of a large number of bacteria, fungi, and viruses that colonize the human gut. Gut dysbiosis has been shown to contribute to human diseases, including metabolic diseases, neurodegenerative disorders, and chronic inflammatory diseases[10-11]. The pathogenesis of frailty syndrome may involve chronic inflammation, immune activation, and the musculoskeletal system[12]. Many studies have shown that the diversity and composition of the gut microbiota are significantly altered in community-dwelling older adults with frailty, which in turn may play an important role in the development of frailty in community-dwelling older adults. For example, one study suggested that an imbalance in the gut microbiota triggers an inflammatory response, leading to an increase in intestinal permeability and the entry of pathogen-associated antibodies into the circulation[6,13]. However, most of the previous studies on frailty and the gut microbiota have only examined changes in the composition of bacterial species, but the characteristics of the gut microbiota of frail older people are still unclear, although interest in this topic is increasing. Therefore, there is a lack of adequate evidence on changes in the gut microbiota and frailty in older adults. This systematic literature review mainly summarizes the associations between changes in the gut microbiota and frailty in people over 60 years of age.

MATERIALS AND METHODS

Search strategy

Seven databases (PubMed, EMBASE, Web of Science, SinoMed, China National Knowledge Infrastructure, VIP, and Wanfang) were used to search for Chinese and English articles, respectively, using Medical Subject Headings terms or free words (*e.g.*, "gastrointestinal microbiome" or "gut microbiota" or "intestinal microbiomes" or "gastric microbiome" or "enteric bacteria" or "gut microbiome") and ("frailty" or "frailty syndrome" or "frailties" or "frail elder"). The final search began in October 2023, with no publication date restrictions. A summary of the search strategy for the different databases is described in Supplementary Table 1.

Inclusion criteria

Eligible studies were identified according to the following inclusion criteria: (1) Participants were adults over 60 years of age; (2) The profile of the gut microbiota was compared between frail and non-frail older adults; and (3) The primary outcome was the abundance of bacterial phyla, families, genera and species of the human gut microbiota. Studies for which the required data could not be retrieved were excluded.

Study screening, data extraction, and assessment of risk bias

The retrieved records were imported into reference management software (Note Express 3.1) for repeated screening. Two reviewers independently identified the eligibility of the retrieved articles according to the inclusion criteria after the duplicate records were removed. Disagreements were discussed and resolved in consultation with a third reviewer. Data from the eligible studies were extracted by one reviewer *via* prepared data extraction tables and checked by another reviewer. The information extracted included study design, participants, methodological characteristics, sample size, outcomes, and measurement methods. The risk of bias for the eligible studies was assessed *via* the Newcastle-Ottawa Scale (NOS)[14] and the Agency for Healthcare Research and Quality (AHRQ)[15]. Disagreements were resolved by discussion with a third reviewer.

RESULTS

Literature search

A total of 1126 records were found by searching seven electronic databases, and 520 records were deleted because of duplication. A total of 583 studies were excluded based on the title and abstract. The remaining 23 studies were further assessed by reading the full texts. As a result, 12 studies were excluded for various reasons (10 did not match the inclusion criteria, and 2 did not have the full text available). Eleven studies were ultimately included in this review. A detailed flow chart of the literature screening process is shown in Figure 1.

Characteristics of the included studies

Table 1 summarizes the characteristics of the 11 studies included in the systematic review[16-26]. All included studies consisted of 7 cross-sectional studies[16-22], 3 cohort studies[23-25], and 1 case-control study[26], including 912 older adults ranging in age from 65 years to 100 years. Seven studies analyzed the α diversity of the gut microbiota[17-20,22-23,26], whereas seven studies analyzed the β diversity of the gut microbiota[17,19,21-24,26]. For the outcome measures, two studies reported changes in the gut microbiota at the phylum level[17,22], two at the family level[19,22], eight at the genus level[16-22,25], and five at the species level[16,20,23-25]. Among these included studies, seven studies performed genetic analysis of the gut microbiota *via* the 16S rRNA method[17-22,26], three studies used the metagenomic sequencing method[23-25], and one study used the fluorescence in situ hybridization method[16]. The frailty measures used in the included studies varied widely, with the rockwood frailty index[22,25,26], FI[18], Clinical Frailty Scale[23,24], short physical performance battery[19], Groningen Frailty Indicator[16], Fried's definition[17], Fried's Frailty Phenotype[20] and Frailty Phenotype[21] being used. The non-frail controls were mainly healthy older adults.

Quality assessment

Table 2, 3 and 4 summarizes the study quality of the included studies, as assessed by the AHRQ for 7 cross-sectional studies and by the NOS tool for 3 cohort studies and one case-control study[16-21,23-25]. Of the seven cross-sectional studies, six were of moderate quality[16-21], and one was of high quality[22]. All three cohort studies were of moderate quality[23-25], and one case-control study was of high quality [26].

Outcome assessment

Changes in the diversity of the gut microbiota: A total of seven studies analyzed the difference in α diversity of the gut microbiota measured by the Chao index, Simpson index, and Shannon index between frail older adults and non-frail controls[17-20,22,23,26], and two studies reported a significant decrease in frail older adults[18,23]. Seven studies[17,19,21,23,24,26,27] compared the β diversity measured by principal coordinate analysis in frail older adults with that in controls, and two studies reported significantly greater β diversity in frail than non-frail older adults[21,22].

Changes in the gut microbiota composition: Figure 2 summarizes the changes in the gut microbiota composition at each level in frail older adults compared with non-frail older adults. Two studies reported results at the phylum level[17,22],

Table 1 Main characteristics of the included studies in this review

Ref.	Picca *et al*[19], 2020	Van Tongeren *et al*[16], 2005	Xu *et al*[17], 2021	Lim *et al*[18], 2021		Zhang *et al*[22], 2020	Margiotta *et al* [20], 2020	Ticinesi *et al*[26], 2017	Haran *et al* [24], 2018	Haran *et al*[23], 2021	Larson *et al* [25], 2020	Zhang *et al* [21], 2022
Study design	CSS	CSS	CSS	CSS		CSS	CSS	CCS	CHS	CHS	CHS	CSS
Participants	Samples	35	23	94	176	27	64	76	23	166	47	181
	Age (years)	> 70	70-100	80.7 ± 5.7	74.7	81.63 ± 7.90	≥ 65	83.3 ± 7.5	≥ 65	86.2 ± 9.1	> 65	≥ 65
	Male/female	20/15	4/19	44/50	54/122	17/10	43/21	39/37	23	30/136	47	72/109
Genetic analysis	16S rRNA V3-V4	Fluorescence in situ hybridization	16sRNA V3-V4	16S rRNA		16S rRNA	16sRNA V3-V4	16S rRNA	metagenomic sequencing	metagenomic sequencing	metagenomic sequencing	16sRNA V3-V4
Frailty diagnosis	Short physical performance battery	Groningen Frailty Indicator	Fried's definition	Frailty index		Rockwood Frailty Index	Fried's Frailty Phenotype	Rockwood Index	CFS	CFS	Rockwood Index	Frailty Phenotype
Outcome measurement	α-diversity, β-diversity, family level, genus level	Genus level, species level	α-diversity, β-diversity, phylum level, genus level	α-diversity, genus level, dpecies level		α-diversity, β-diversity, phylum level, family level, genus level	α-diversity, phylum level, genus level	α-diversity, β-diversity	β-diversity, species level	α-diversity, β-diversity, species level	Genus level, species level	β-diversity, phylum level, genus level

CSS: Cross-sectional study: CCS: Case-control study; CHS: Cohort study; CFS: Clinical Frailty Scale.

Table 2 The Agency for Healthcare Research and Quality assessment for the cross-sectional study

Ref.	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Scores
Picca *et al*[19], 2020	Yes	Yes		Yes	Yes			Yes		Yes		6
Van Tongeren *et al* [16], 2005	Yes	Yes		Yes	Yes		Yes			Yes		6
Xu *et al*[17], 2021	Yes			Yes	Yes		Yes	Yes		Yes		6
Lim *et al*[18], 2021	Yes	Yes			Yes		Yes	Yes		Yes		6
Zhang *et al*[22], 2020	Yes	Yes		Yes	Yes	Yes	Yes	Yes		Yes		8
Margiotta *et al*[20], 2020	Yes	Yes		Yes	Yes		Yes	Yes		Yes		7
Zhang *et al*[21], 2022	Yes	Yes	Yes		Yes	Yes	Yes	Yes				7

Yes is one point, the total number of stars represents a number of points. Item 1: Define the source of information (survey, record review)? Item 2: Inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications? Item 3: Indicate time period used for identifying patients? Item 4: Indicate whether or not subjects were consecutive if not population-based? Item 5: Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participant? Item 6: Describe any assessments undertaken for quality assurance purposes (*e.g.*, testretest of primary out come measuroments)? Item 7: Explain any patient exclusions from analysis? Item 8: Describe how confounding was assessed and/or controlled? Item 9: If applicable, explain how missing data were handled in the analysis? Item 10: Summarize patient response rates and completeness of data collection? Item 11: Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained?

Table 3 The Newcastle-Ottawa Scale assessment for the cohort studies

Ref.	Selection				Comparability		Exposure			Scores
	Representativeness of selection of the non-exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohort on the basis of the design or analysis	Ascertainment of outcome	Ascertainment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Haran *et al*[24], 2018	Yes	Yes			Yes	Yes, Yes				5
Haran *et al*[23], 2021	Yes	Yes				Yes, Yes		Yes	Yes	6
Larson *et al*[25], 2020	Yes	Yes			Yes	Yes, Yes				5

Yes is one point, the total number of stars represents a number of points.

and all of them reported that frail older adults had a significantly greater relative abundance of the *Actinobacteria* phylum [17,22]. An individual study reported that frail older adults had significantly greater relative abundances of the *Proteobacteria*, *Verrucomicrobia* and *Synergistetes* phyla[17] and significantly lower abundances of the *Firmicutes*[17] and *Fusobacteria* phyla[22].

Two studies reported differences in the gut microbial composition at the family level between frail and non-frail older adults[19,22], with significantly greater abundances of the *Peptostreptococcaceae*[19], *Mogibacteriaceae, Bifidobacteriaceae*[19], *Coriobacteriaceae, Enterobacteriaceae,* and *Moraxellaceae* families[22] in frail older adults.

Eight studies reported changes in gut microbiota composition at the genus level. Three studies reported a significantly lower abundance of the genus *Prevotella* in frail older adults[16-18]; two studies reported that frail older adults presented significantly lower relative abundances of the genera *Faecalibacterium* and *Roseburia*[17,21]. Several individual studies reported that the relative abundances of *Megamonas*, *Blautia*, *Megasphaera*, *Haemophilus*[17], *Adlercreutzia*, *Clostridium*, *Coprococcus*, *Phascolarctobacterium*, *Turicibacter*[21], *Eubacterium*[19], *Gemella, Lachnoanaerobaculum*, *[Eubacterium]_ruminantium_group*, *Tyzzerella*, *Azospira*, *Cloacibacterium and EU455341_g*[22] genera, most of which belong to the

Table 4 The Newcastle-Ottawa Scale assessment for the case-control study

Ref.	Selection				Comparability	Exposure			Scores
	Adequate definition of case	Representativeness of the case	Selection of controls	Definition of controls	Control for important factor	Ascertainment of exposure	Same method of ascertain for cases and controls	Non-responsese rate	
Ticinesi *et al* [26], 2017	Yes	Yes	Yes	Yes	Yes	Yes, Yes		Yes	7

Yes is one point, the total number of stars represents a number of points.

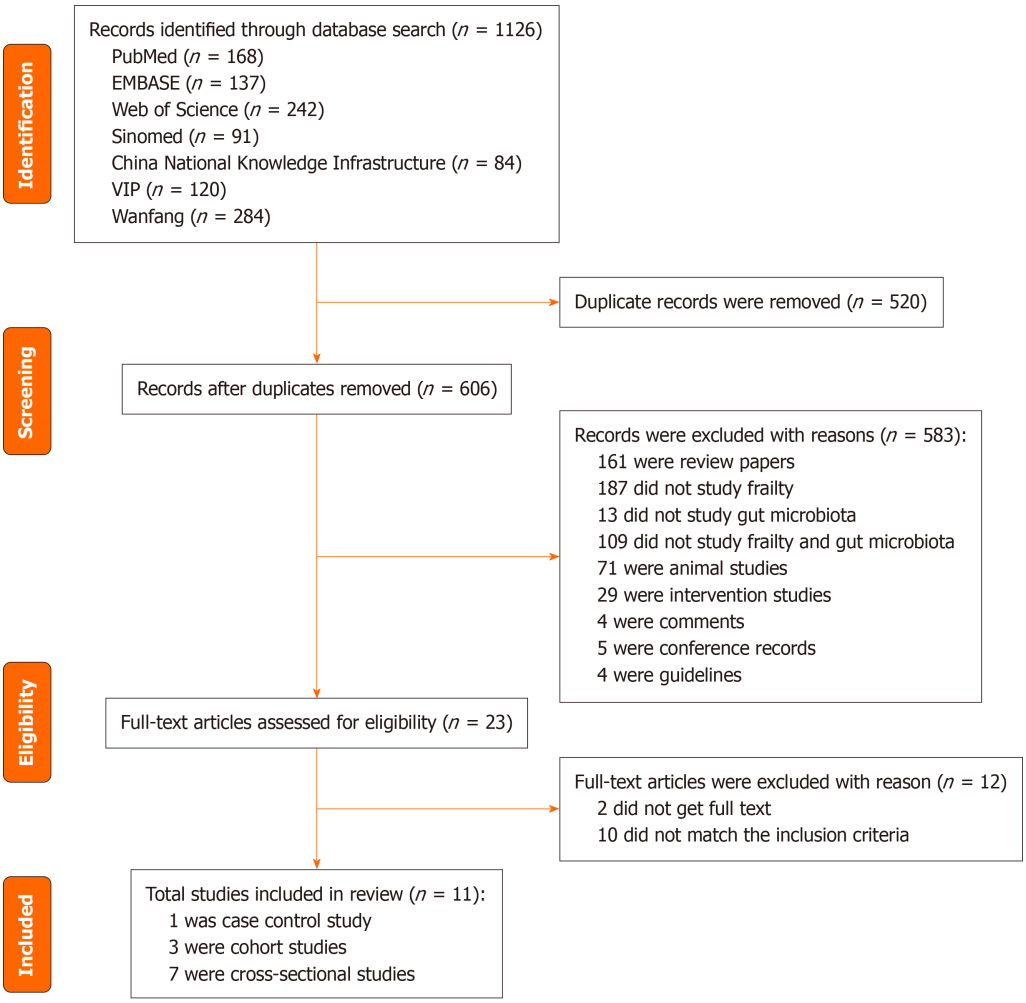

Figure 1 Preferred Items for Systematic Reviews and Meta-Analysis flow diagram of literature search.

Firmicutes phylum, were significantly lower in frail older adults. Moreover, individual studies reported that frail older adults presented increased relative abundances of *Bifidobacterium*[17], *Eggerthella*, *Olsenella*[16], *Atopobium*[22], *Parabacteroides*[17], *Alistipes*[17], *Bacteroides*[18], *Oscillospira*, *Ruminococcus*, *Pyramidobacter* and *Dialister*[19], *Akkermansia* and *Klebsiella*[17], *KF843164_g*, *Pseudoxanthomonas*, *EF434341_g* and *Prevotella_9*[22], and *Oscillospira* and *Coprobacillus*[20]. In addition, the genera of *Lactobacillus* in the included studies were heterogeneous, and three studies[17,20-21] reported a significantly higher relative abundance, but one study[16] reported a significantly lower relative abundance in frail older adults.

At the species level, two studies[16,23] reported that the relative abundance of *Faecalibacterium prausnitzii* was significantly lower in frail than in non-frail older adults. Furthermore, individual studies reported that the abundances of

Figure 2 Changes in the gut microbiota composition in older adults with frailty compared to the controls. Red arrows indicate increasing relative abundance; blue arrows indicate decreasing relative abundance in older adults with frailty compared to the controls; One arrow represents one analyzed study.

the *Prevotella copri*[18], *Coprococcus eutactus*[18], *Bacteroides vulgatus*[23] and *Anaerostipes hadrus* species[23] were significantly lower in frail older adults. However, the abundances of *Bacteroides fragilis*[18], *Clostridium hathewayi*[18], *Eggerthella lenta*[20], *Flavonifractor plautii*[23] and *Ruminococcus gnavus*[24] were significantly increased in frail older adults.

DISCUSSION

This qualitative systematic review, which included 11 eligible studies with 912 older adults over 65 years of age, investigated the relationships between changes in gut microbiota diversity and composition and frailty in older adults. For gut microbiota diversity, the results, which are based on consistent findings reported by more than two eligible studies, revealed a significant decrease in α diversity and a significant increase in β diversity in frail older adults. In terms of the gut microbiota composition, although there was wide variation in the gut microbiota composition reported in the included studies, the consistent results revealed significant differences in the relative abundance of some gut microbiota compositions at different levels, including phylum, family, genus and species, between frail and non-frail older adults. These findings suggest that changes in the gut microbiota may be associated with frailty in older adults.

An increasing number of studies have reported that altered gut microbiota play an important role as a risk factor in the development of many chronic diseases[28-30]. The gut microbiota in healthy individuals maintains a symbiotic relationship with the host but also triggers some pathological processes and causes the evolution of some diseases if potentially pathogenic bacteria overgrow and alter the diversity and abundance of the gut microbiota[31]. The mechanism is related to a deficiency or excess of metabolites resulting from an imbalance in the gut microbiota, which fundamentally affects the physiological status of the host cells and has direct or indirect toxic effects on hormones and the host organism[32]. The gut microbiota is a highly complex and diverse ecosystem of microorganisms living in the digestive tract, and the balance of beneficial and pathogenic bacteria in the gut microbiome is helpful for maintaining host health and homeostasis[33]. However, both environmental factors and host genetics can affect the homeostatic balance of the gut microbiota and lead to a dysbiotic microbiome configuration by altering the diversity and richness of the gut microbiota[34]. Seven studies included in this review compared the differences in gut microbiota diversity between frail and non-frail older adults. Two of the seven studies reported significantly greater β diversity and significantly lower α diversity in frail than non-frail older adults. These findings suggest a possible separation in gut microbiota diversity in older adults with frailty.

The composition of the gut microbiota in older adults can be altered by the constant influence of external environmental factors, such as diet, medication, physical activity, and social environment. Altered gut microbiota composition has also been shown to play an important role in the development of age-related chronic diseases[35]. The gut microbiome can influence host physical function by regulating nutrient absorption, inflammation, oxidative stress, immune function, and anabolic balance and is associated with the progression of aged-physical frailty[35,36]. Among the relative abundances at the phylum level between frail and non-frail older adults, the current review revealed a significant increase in the *Actinobacteria, Proteobacteria, Verrucomicrobia* and *Synergistetes* phyla and a significant decrease in the *Firmicutes* and *Fusobacteria* phyla in frail older adults. These phyla are dominant in healthy humans and are pivotal in the maintenance of gut homeostasis[37,38]. There is evidence of positive associations between increased *Actinobacteria, Proteobacteria, Verrucomicrobia,* and *Synergistetes* phyla and inflammation-related diseases[39,40]. Conversely, the abundance of the *Firmicutes* phylum was negatively associated with inflammatory responses[41].

With respect to the relative abundance of families between frail and non-frail older adults, the current review revealed that the abundances of *Peptostreptococcaceae*, *Bifidobacteriaceae*, *Mogibacteriaceae*, and *Coriobacteriaceae* as well as *Enterobacteriaceae* and *Moraxellaceae* families were greater in frail than in non-frail older adults. Most of them (*Bifidobacteriaceae*, *Mogibacteriaceae, Coriobacteriaceae*, *Enterobacteriaceae X* and *Moraxellaceae*) belong to the *Actinobacteria* or *Proteobacteria* phylum and have previously been implicated in accelerating the aging process through telomere attrition, cellular senescence, inflammasome activation and impaired mitochondrial function, which have been described as correlates of biological aging or are abundant in elderly individuals[42,43]; furthermore, some of them also seem to be positively correlated with various nutritional and physical features[44,45].

With respect to the genera and species levels, more than one study in the current review reported that the abundances of genera (*Roseburia, Faecalibacterium, and Prevotella)* and species *(Faecalibacterium prausnitzii* and *Prevotella copri)* were significantly lower in frail older adults. The *Roseburia* and *Faecalibacterium* genera have anti-inflammatory properties, which are likely mediated by the short-chain fatty acid butyrate[46,47]. *Roseburia* is a anaerobic bacteria that produces butyrate that metabolizes indigestible carbohydrates to produce short-chain fatty acids (particularly high levels of butyric acid), which maintain intestinal function, immune function, and anti-inflammatory properties[47,48]. Furthermore, a lower *Roseburia* level was also found to be associated with inflammation-related diseases such as diabetes, obesity, atherosclerosis, and nonalcoholic liver steatohepatitis[47]. *Faecalibacterium prausnitzii,* which is the only species of the *Faecalibacterium* genus, is a genus of bacteria that produces butyrate and has anti-inflammatory effects[46]. Moreover, the abundance of *Faecalibacterium prausnitzii* is obviously lower in patients with gastrointestinal inflammation and ulcerative colitis (UC)[49]. Hedin *et al*[50] also reported that the abundances of *Faecalibacterium prausnitzii* and *Roseburia* are decreased in patients with the inflammatory Crohn's disease. *Prevotella* and *Prevotella copri*, which belong to the *Prevotellaceae* in this review, were reported to be decreased in frail older adults. *Prevotella* species significantly colonize the human intestine, especially *Prevotella copri,* which is prevalent in populations fed high-fiber diets and is associated with beneficial outcomes, including reduced visceral fat and improved glucose tolerance[51,52]. Studies have shown that *Prevotella copri* transplantation may attenuate oxidative stress and blood-brain barrier damage and alleviate motor and cognitive deficits [53]. In addition, some single studies included in this review reported that the abundances of some genera or species, such as *Eubacterium, Gemella, Lachnoanaerobaculum, Bacteroides vulgatus, Megasphaera, Haemophilus, Adlercreutzia, Clostridium, Coprococcus, and Blautia*, were significantly lower in frail than in non-frail older adults. Most of these microbiomes have been found to be beneficial. For example, several members of the genus *Eubacterium* can produce butyrate, which plays important roles in the immunomodulation and inhibition of inflammation in the gut microbiome[54]. *Eubacterium*, *Gemella*, *Lachnoanaerobaculum* and *Tyzzerella* belong to *Firmicutes,* and an increase in *Firmicutes* is associated with a reduction in inflammatory responses[41]. Moreover, the current review revealed that some genera or species, including *Oscillospira*, *Ruminococcus*, *Alistipes*, *Bacteroides*, *Bacteroides fragilis*, *Pyramidobacter, Eggerthella*, *Olsenella*, *Atopobium, Parabacteroides, etc.,* were more enriched in the frail than the non-frail older adults in the individual included studies; some of these genera or species may be related to the pathological mechanisms of frailty. It has been reported that *Oscillospira* abundance is positively correlated with inflammation in type II diabetes mellitus patients[55] and is associated with a lower body mass index[56]. *Ruminococcus gnavus,* which is a type of Ruminococcus, is enriched in inflammatory diseases, such as inflammatory bowel disease[57]. Treatment of UC patients with fecal microbiome transplants revealed that disease progression was more likely to recrudesce in those who received high concentrations of *Ruminococcus* donors[58]. *Ruminococcus* also aggravated amyotrophic lateral sclerosis in mice, leading to further frailty[59]. *Alistipes, Bacteroides* and *Bacteroides vulgatus* are commonly associated with chronic intestinal inflammation[41,60]. In this review, the results of *Lactobacillus* in the included studies were not consistent, and its relative abundance was greater in the frail older adults in three studies but was lower in the frail older adults in one study. The reason may be related to the different diets of the participants in those studies.

This systematic review provides a comprehensive summary and overview of the current research on the gut microbiota and frailty in adults over 60 years of age. By focusing on older adults over 60 years of age, the frailty states assessed by comprehensive tools, and the non-frail control group consisting mainly of community-dwelling healthy older adults or those with comorbidities, the findings of this review may therefore provide informative guidance for the prevention or rehabilitation of frailty in community-dwelling older adults. However, the following limitations should be acknowledged, as they may affect the interpretation of these findings. First, most of the included studies were cross-sectional in design, which limits the interpretation of the results regarding causality between changes in the gut microbiota and frailty in older adults. Second, the small sample size and insufficient number of studies may hinder the generalization of the findings of this review. The human gut microbiota is complex and may be influenced by internal and external factors. The small number of included studies may limit the ability to observe the influence of confounding factors such as diet, physical activity, comorbid conditions, and medications. In addition, the variation in the measurement of frailty and the gut microbiota across the included studies also makes accurate assessment or analysis of the

associations between the gut microbiota outcomes and frailty difficult.

CONCLUSION

The current review revealed significant changes in the α-diversity and β-diversity and composition of the gut microbiota at the phylum, family, genus, or species level in frail and non-frail older adults aged over 60 years. These changes are commonly reflected by a decrease in the beneficial microbiota (*e.g.*, *Faecalibacterium prausnitzii* at the species level; *Roseburia*, *Eubacterium*, and *Faecalibacterium* at the genus level) and an increase in the pathogenic microbiota (*e.g.*, *Oscillospira*, *Ruminococcus*, *Alistipes*, *Eggerthella*, and *Bacteroides* at the genus level). Future research with large samples and a prospective design is needed to further investigate the impact of specific gut microbiota on frailty in adults over 60 years of age.

FOOTNOTES

Author contributions: Wen NN was responsible for conceptualization, literature screening, data curation, extraction, methodology and writing original draft; Sun LW and Geng Q were responsible for literature screening, data curation, extraction and methodology; Zheng GH was responsible for conceptualization, methodology, project administration, supervision, writing original draft, writing review, and editing; all of the authors read and approved the final version of the manuscript to be published.

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Country of origin: China

ORCID number: Guo-Hua Zheng 0000-0002-4229-7346.

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