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Research Article

Investigating association between gut microbiota and sarcopenia-related traits: a Mendelian randomization study

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Abstract

Background Observational studies have indicated a potential link between gut microbiota and sarcopenia. However, the underlying mechanisms and a causal relationship have not been established. Thus, the objective of this study is to examine the possible causal association between gut microbiota and sarcopenia-related traits, including low hand-grip strength and appendicular lean mass (ALM), to shed light on the gut–muscle axis.

Methods To investigate the potential impact of gut microbiota on low hand-grip strength and ALM, we utilized a two-sample Mendelian randomization (MR) approach. Summary statistics were obtained from genome-wide association studies of gut microbiota, low hand-grip strength, and ALM. The primary MR analysis employed the random-effects inverse-variance weighted (IVW) method. To assess the robustness, we conducted sensitivity analyses using the MR pleiotropy residual sum and outlier (MR-PRESSO) test to detect and correct for horizontal pleiotropy, as well as the MR-Egger intercept test and leave-one-out analysis.

Results *Alcaligenaceae*, *Family XIII*, and *Paraprevotella* were positively associated with the risk of low hand-grip strength (P-values < 0.05). *Streptococcaceae* were negatively associated with low hand-grip strength (P-values < 0.05). Eight bacterial taxa (*Actinomycetales*, *Actinomycetaceae*, *Bacteroidaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Bacteroides*, *Marvinbryantia*, and *Phascolarctobacterium*) were associated with a higher risk of ALM (P-values < 0.05). *Eubacterium fissicatena* group was negatively associated with ALM (P-values < 0.05).

Conclusion We found several gut microbiota components causally associated with sarcopenia-related traits. Our findings provided insights into novel strategies for the prevention and treatment of sarcopenia through the regulation of the gut microbiota, contributing to a better understanding of the gut–muscle axis.

Keywords: gut microbiota, sarcopenia, low hand-grip strength, appendicular lean mass, Mendelian randomization, gut–muscle axis

Introduction

The human intestine harbours a diverse community of gut microbiota that can be influenced by various factors such as diet, environment, and genetics.[1] Previous studies have demonstrated the crucial role of gut microbiota in the development of immune, metabolic, psychiatric, and inflammatory diseases.[2–5] Sarcopenia, characterized by low muscle mass and weak muscle strength, is a common skeletal muscle syndrome that often accompanies ageing and several chronic conditions,[6] which leads to impaired mobility, increased morbidity and mortality,[7–9] and substantially elevated healthcare expenditures for patients.[10] Although the gut–muscle axis, which links gut health to muscle and physical function, has been proposed by several independent research groups,[11–13] the association between gut microbiota and sarcopenia remains debatable. A better understanding of the role of gut microbiota in the management of sarcopenia could pave the way for more viable treatments.

The gut–muscle axis has been shown to play a crucial role in regulating age-related muscle health in animal models and human studies. However, the underlying mechanisms remain poorly understood, and the findings have been inconsistent across studies. Observational studies have reported that gut microbiota can impact muscle mass and function through various factors such as inflammation, immunity, substance metabolism, endocrine function, and insulin sensitivity.[14] By regulating the composition and metabolism of proteins and amino acids, gut microbiota can influence muscle synthesis.[15,16] Tryptophan, for instance, may stimulate the production of insulin-like growth factor-1 in muscle cells, promoting the expression of myofibril-related genes.[17] Conversely, a protein-rich diet has been shown to shift bacterial metabolism to the degradation and fermentation of amino acids.[18] A healthy gut microbiota can improve intestinal barrier function and act as an immunomodulator. However, short-chain fatty acids (SCFAs), which are produced by certain gut microbiota,

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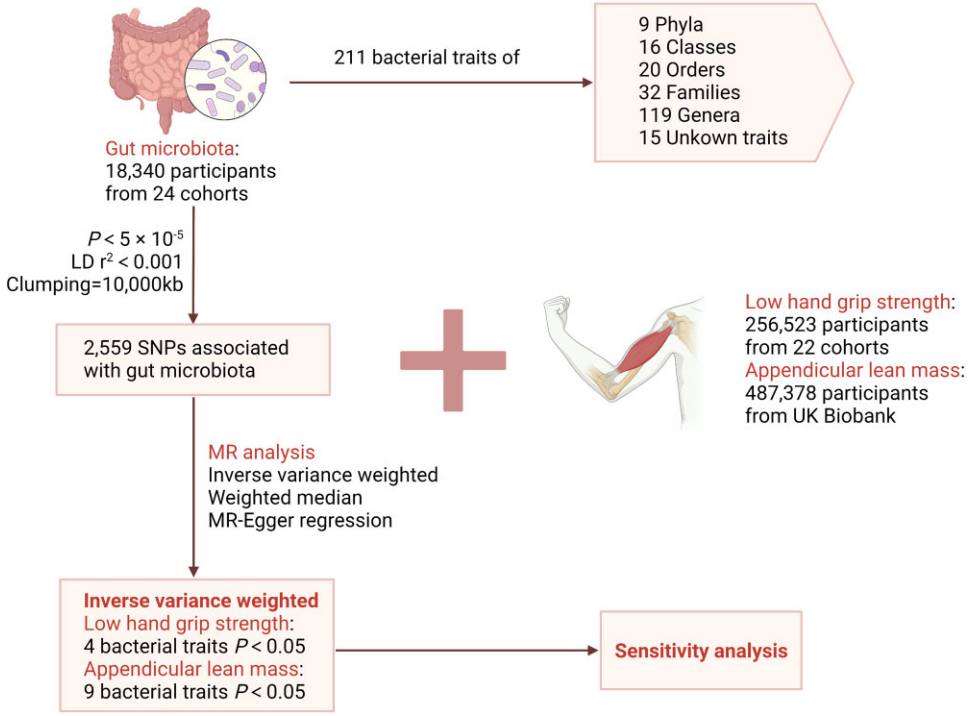

Figure 1. Flowchart for the study of the association between gut microbiota and sarcopenia-related traits. LD: linkage disequilibrium; SNP: single nucleotide polymorphism.

have been linked to increased chronic inflammation, which in turn can lead to sarcopenia.[19] Nonetheless, observational studies are subject to methodological challenges, such as confounding bias and reverse causation, and methods that can infer causation are needed to identify the association between gut microbiota and sarcopenia.

Mendelian randomization (MR) is a valuable approach for establishing potential relationships that overcomes the methodological issues commonly present in observational studies by using genetic variations as instrumental variables (IVs) for exposures.[20] The goal of this study was to uncover the potential causal association between gut microbiota and sarcopenia, which would lead to a better understanding of the gut–muscle axis.

Material and methods

Study design

To establish potential causal relationships between gut microbiota and sarcopenia-related traits, namely low hand-grip strength and appendicular lean mass (ALM), we employed a two-sample MR analysis, which provides stronger associations by minimizing many of the major biases present in traditional epidemiologic observational studies. A flow chart of the study design is shown in Fig. 1.

Data sources and instruments

Gut microbiota

We selected single-nucleotide polymorphisms (SNPs) associated with the gut microbiota as IVs for our study. The summary-level data for these SNPs were obtained from the MiBioGen consortium, which analyzed 16S rRNA gene sequencing data from 18 340 participants of various ethnicities and nationalities (72.3% of the population were European, with the remainder including individuals from Middle-Eastern, East Asian, American Hispanic/Latin, and African American populations).[21]

To select the most appropriate SNPs, we established a *P*-value threshold of $<10^{-5}$.[21,22] All SNPs need to be independently associated with the microbiota (linkage disequilibrium [LD], $r^2 < 0.001$, clumping distance = 10 000 kb). Following the removal of 15 unknown bacterial traits, we identified a total of 2 559 SNPs associated with 196 bacterial traits, including 9 phyla, 16 classes, 20 orders, 32 families, and 119 genera. An overview of genome-wide association studies (GWAS) datasets for gut microbiota is shown in supplementary Table 1, see online supplementary material. IVs are listed in Supplementary Table 2, see online supplementary material. To avoid potential pleiotropy, we also used the PhenoScanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/) to exclude IVs associated with confounding or risk factors for sarcopenia, such as older age, low socioeconomic status, low physical activity, and poor diet.[23] We submitted SNPs strongly linked to gut microbiota for retrieval on the website. SNPs associated with risk factors for sarcopenia, including older age, low socioeconomic status, low physical activity, and poor diet, were excluded (using a *P*-value threshold of $<10^{-5}$). Finally, we discovered no SNPs that were significantly associated with the aforementioned four variables. As a result, 2 559 SNPs were available for further MR analysis. All the confounders and excluded SNPs are listed in supplementary Table 3, see online supplementary material.

Sarcopenia-related traits

For each outcome variable, we have chosen the most recent and largest GWAS studies available. Summary-level data for low hand-grip strength were extracted from a large meta-analysis GWAS including 256 523 participants of European ancestry[24] (ebi-a-GCST90007526). The cutoff level of low hand-grip strength was male <30 kg, female <20 kg. Summary statistics of ALM

were retrieved from a GWAS, in which 450 243 participants of the UK Biobank Study were included[25] (ebi-a-GCST90000025). An overview of GWAS datasets for low hand-grip strength and ALM is shown in supplementary Table 1.

Instrument strength

To rule out the influence of weak IVs bias in association effect estimation, we tested the strength of IVs with an F statistic > 10. The following equation was used to compute the F statistic: $F = (R^2/1-R^2)\ (n-k-1/k)$, where R^2 is the variance interpreted by IVs (per gut microbiota), and n is the sample size.[26] The minor allele frequency (MAF) and effect estimates (β) were used to calculate R^2: $R^2 = 2\text{MAF}\ (1-\text{MAF})\ (\beta/\text{SD})^2$. SD is the standard deviation. The F values of all variables in the present study were >10.

Statistical analysis

Our study utilized two-sample MR analysis as the primary statistical technique to investigate the potential causal association between gut microbiota and low hand-grip strength and ALM. To obtain a robust and reliable result, we combined several statistical methods. The inverse-variance weighted (IVW) method was used as the primary approach, which has stable and balanced pleiotropic effects. In addition, we employed the MR-Egger regression, weighted median, and MR pleiotropy residual sum and outlier (MR-PRESSO) tests as complementary methods to IVW, to estimate the relationship between exposures and outcomes under various conditions.[27,28] When the two-sided P-value was <0.05, statistical significance was considered.

The MR estimates are presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The TwoSampleMR package (version 0.5.6) in R (v4.2.2) was used for the statistical analyses.[29]

Sensitivity analysis

In our study, we utilized several methods to ensure the robustness and reliability of our findings. To detect any potential heterogeneity, we employed Cochran's Q statistic and visualized funnel plots with a significance threshold of P-value < 0.05. Then we utilized the MR-PRESSO test to detect and remove outliers, and retested the results. Additionally, to detect horizontal pleiotropy, we used the MR-Egger intercept test, with a significance threshold of P-value < 0.05. Results are displayed using scatter plots.

We also performed leave-one-out analyzes where we repeated the IVW analysis, removing one exposure-related SNP at a time, to assess the robustness of our findings. By combining these methods, we aimed to ensure the validity and reliability of our findings in determining the potential causal association between gut microbiota and the risk of low hand-grip strength and ALM.

Results

Gut microbiota and low hand-grip strength

Four bacterial taxa were found to be statistically associated with the risk of low hand-grip strength using the IVW method (Fig. 2). *Alcaligenaceae*, *Family XIII*, and *Paraprevotella* were found to have significant positive causal effects on low hand-grip strength (OR: 1.167, 95% CI: 1.051–1.297, $P = 0.004$ for *Alcaligenaceae*; OR: 1.111, 95% CI: 1.022–1.209, $P = 0.013$ for *Family XIII*; OR: 1.088, 95% CI: 1.036–1.142, $P = 0.001$ for *Paraprevotella*; Table 1). *Streptococcaceae* had a negative impact on low hand-grip strength (OR: 0.920, 95% CI: 0.855–0.991, $P = 0.027$). We did not find evidence of heterogeneity or horizontal pleiotropy based on the funnel, scatter, and forest plots (Supplementary Figs. 1–3). Multiple test corrections for the P-values are shown in supplementary Table 4, see online supplementary material.

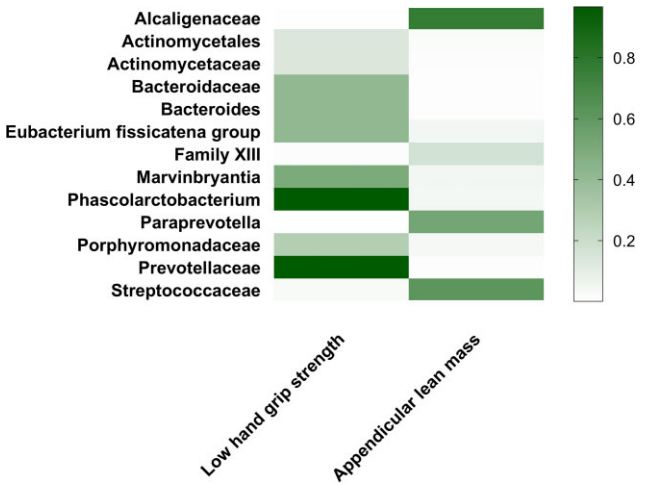

Figure 2. IVW estimates for association between gut microbiota and sarcopenia-related traits. The color of each block represents the IVW-derived P-value for each MR analysis.

Gut microbiota and ALM

There were nine bacterial taxa causally associated with ALM in the IVW method (Fig. 2). *Actinomycetales*, *Actinomycetaceae*, *Bacteroidaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Bacteroides*, *Marvinbryantia*, *Phascolarctobacterium* had positive effects on ALM (OR: 1.029, 95% CI: 1.005–1.053, $P = 0.017$ for *Actinomycetales*; OR: 1.029, 95% CI: 1.005–1.052, $P = 0.016$ for *Actinomycetaceae*; OR: 1.041, 95% CI: 1.010–1.073, $P = 0.008$ for *Bacteroidaceae*; OR: 1.036, 95% CI: 1.002–1.071, $P = 0.037$ for *Porphyromonadaceae*; OR: 1.034, 95% CI: 1.007–1.061, $P = 0.012$ for *Prevotellaceae*; OR: 1.041, 95% CI: 1.010–1.073, $P = 0.008$ for *Bacteroides*; OR: 1.041, 95% CI: 1.000–1.046, $P = 0.045$ for *Marvinbryantia*; OR: 1.027, 95% CI: 1.001–1.054, $P = 0.041$ for *Phascolarctobacterium*). *Eubacterium fissicatena* group had a negative effect on ALM (OR: 0.983, 95% CI: 0.967–1.100, $P = 0.044$) (Table 2). Multiple test corrections for the P-values are shown in supplementary Table 4.

In the sensitivity analysis, only two bacterial taxa, *Prevotellaceae* and *Eubacterium fissicatena* group, showed heterogeneity. We removed the outliers and performed the MR-PRESSO test to correct the heterogeneity. The results showed a significant association (outlier-corrected: $P = 0.034$ for *Prevotellaceae*; $P = 0.039$ for *Eubacterium fissicatena* group). Detailed information is provided in supplementary Table 5, see online supplementary material. We did not find evidence of horizontal pleiotropy based on the funnel, scatter, and forest plots (supplementary Figs. 4–6, see online supplementary material).

Discussion

This study represents the first comprehensive MR analysis investigating the potential causal relationships between gut microbiota and sarcopenia-related traits. Our systematic evaluation of the genetically predicted causal association between gut microbiota and low hand-grip strength and ALM yielded novel findings indicating that different gut microbiota taxa exert different effects on muscle. These findings are consistent with earlier observational studies highlighting the pathophysiological interactions between gut

Table 1. MR estimates of the association between gut microbiota and the risk of low hand-grip strength.

Exposure	Outcome	No. of IVs	Method	OR (95% CI)	P-value[a]	Heterogeneity Cochran's Q (P-value)	MR Egger Intercept (P-value)
Alcaligenaceae	LHGS	18	IVW	1.167 (1.051, 1.297)	**0.004**	18.589 (0.069)	−0.002 (0.922)
			MR Egger	1.197 (0.721, 1.986)	0.502		
			Weighted median	1.194 (1.053, 1.353)	**0.006**		
Family XIII	LHGS	14	IVW	1.111 (1.022, 1.209)	**0.013**	9.990 (0.441)	−0.002 (0.866)
			MR Egger	1.140 (0.846, 1.534)	0.411		
			Weighted median	1.109 (0.990, 1.243)	0.075		
Streptococcaceae	LHGS	17	IVW	0.920 (0.855, 0.991)	**0.027**	9.492 (0.735)	0.003 (0.782)
			MR Egger	0.883 (0.657, 1.186)	0.425		
			Weighted median	0.906 (0.819, 1.002)	0.054		
Paraprevotella	LHGS	13	IVW	1.088 (1.036, 1.142)	**0.001**	9.180 (0.688)	0.009 (0.337)
			MR Egger	1.006 (0.858, 1.180)	0.939		
			Weighted median	1.073 (1.000, 1.151)	**0.049**		

[a]Bold values indicate P-value < 0.05. LHGS, low hand-grip strength.

Table 2. MR estimates of the association between gut microbiota and the risk of ALM.

Exposure	Outcome	No. of IVs	Method	OR (95% CI)	P-value[a]	Heterogeneity Cochran's Q (P-value[a])	MR Egger Intercept (P-value)
Actinomycetales	ALM	5	IVW	1.029 (1.005, 1.053)	**0.017**	5.085 (0.279)	0.003 (0.358)
			MR Egger	0.999 (0.943, 1.058)	0.972		
			Weighted median	1.015 (0.987, 1.044)	0.278		
Actinomycetaceae	ALM	5	IVW	1.029 (1.005, 1.052)	**0.016**	5.064 (0.281)	0.003 (0.361)
			MR Egger	0.999 (0.943, 1.058)	0.978		
			Weighted median	1.015 (0.988, 1.043)	0.275		
Bacteroidaceae	ALM	12	IVW	1.041 (1.010, 1.073)	**0.008**	12.005 (0.151)	0.002 (0.711)
			MR Egger	1.008 (0.852, 1.192)	0.927		
			Weighted median	1.022 (0.987, 1.060)	0.215		
Porphyromonadaceae	ALM	11	IVW	1.036 (1.002, 1.071)	**0.037**	13.816 (0.087)	0.005 (0.232)
			MR Egger	0.951 (0.832, 1.086)	0.481		
			Weighted median	1.047 (1.010, 1.086)	**0.013**		
Prevotellaceae	ALM	18	IVW	1.034 (1.007, 1.061)	**0.012**	38.021 (**0.001**)	0.003 (0.359)
			MR Egger	0.990 (0.902, 1.087)	0.838		
			Weighted median	1.018 (0.994, 1.043)	0.142		
Bacteroides	ALM	12	IVW	1.041 (1.010, 1.073)	**0.008**	12.005 (0.151)	0.002 (0.711)
			MR Egger	1.008 (0.852, 1.192)	0.927		
			Weighted median	1.022 (0.987, 1.060)	0.223		
Eubacterium fissicatena group	ALM	9	IVW	0.983 (0.967, 1.100)	**0.044**	16.317 (**0.038**)	0.004 (0.540)
			MR Egger	0.954 (0.870, 1.047)	0.353		
			Weighted median	0.978 (0.961, 1.995)	**0.010**		
Marvinbryantia	ALM	12	IVW	1.023 (1.000, 1.046)	**0.045**	12.223 (0.201)	−0.001 (0.769)
			MR Egger	1.037 (0.946, 1.137)	0.457		
			Weighted median	1.033 (1.007, 1.059)	**0.013**		
Phascolarctobacterium	ALM	11	IVW	1.027 (1.001, 1.054)	**0.041**	14.772 (0.064)	−0.001 (0.888)
			MR Egger	1.037 (0.909, 1.183)	0.603		
			Weighted median	1.014 (0.984, 1.042)	0.322		

[a]Bold values indicate P-value < 0.05.

microbiota and muscle, commonly referred to as the gut–muscle axis.[11–13]

Our results indicated that *Alcaligenaceae*, *Family XIII*, and *Paraprevotella* had significant positive causal effects on low hand-grip strength, which is negatively correlated with muscle strength. In contrast, *Streptococcaceae* had a significantly negative effect on low hand-grip strength. Previous studies have linked *Paraprevotella* to the onset and progression of irritable bowel syndrome (IBS) and associated chronic intestinal inflammation.[30] Chronic intestinal inflammation and malabsorption of nutrients can lead to decreased muscle function. However, in patients with chronic kidney disease, *Paraprevotella* inversely correlates with the inflammatory factors interleukin 10 (IL-10) and IL-4,[31] which suggests that the association between *Paraprevotella* and muscle function may be modulated by underlying disease states. In a previous study, *Streptococcaceae* dietary supplements were found to help muscles recover from strenuous eccentric exercise, with a corresponding decrease in blood IL-6 levels after 3 weeks of supplementation.[32] Overall, our MR-derived associations between gut microbiota and muscle function are largely consistent with previous observational studies.

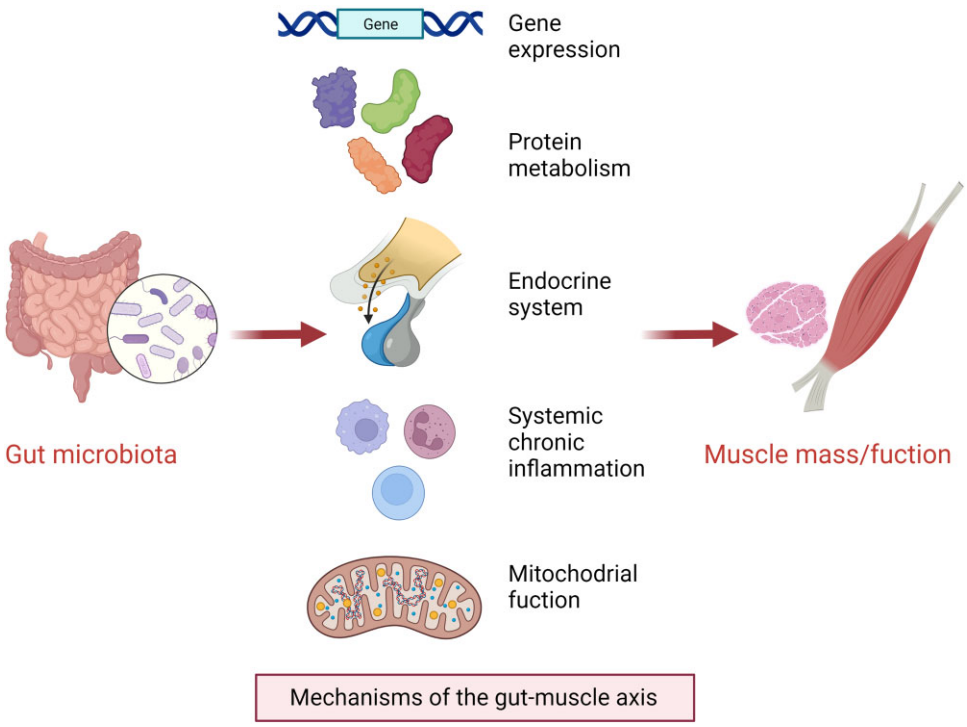

Figure 3. Overview of the gut–muscle axis.

For another sarcopenia-related trait, *Actinomycetales*, *Actinomycetaceae*, *Bacteroidaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Bacteroides*, *Marvinbryantia*, and *Phascolarctobacterium* were found to have significant positive causal effects on ALM, while *Eubacterium fissicatena* group were found to have significant negative causal effects on ALM in the present study. Patients with liver cirrhosis combined with muscle wasting had a higher abundance of *Bacteroides* in their gut than those without muscle wasting.[33] *Bacteroides* can utilize both endogenous and exogenous polysaccharides to create materials that might be advantageous to the host. When substances like cellulose enter the colon, *Bacteroides* ferment and break them down into SCFAs, which are thought to reduce inflammation and aid in the maintenance of skeletal muscle mass. SCFAs appear to improve skeletal muscle function, and some studies suggested that SCFAs supplementation may improve exercise performance or strength.[34,35] Pei *et al.*'s research discovered that Bacteroides could also improve the barrier function of the intestinal mucosa and inhibit the Mystn/ActRIIB/SMAD2 pathway to prevent muscle atrophy.[36] In general, *Bacteroides* can affect muscle function and mass by improving intestinal absorption and energy metabolism. A study transplanted the feces of HF (high-function) and LF (low-function) elderly separately into germ-free mice, and the grip strength of HF-colonized mice increased after a 1-month follow-up, which suggested that these gut microbiota had a beneficial role in maintaining muscle strength in the elderly over 65 years old.[37] The gut microbiota *Prevotellaceae* was present in the HF group in the experiment. Community-dwelling older adults with sarcopenia had a higher concentration of *Phascolarctobacterium* than the control group.[38] Moreover, the reduction of *Phascolarctobacterium* was associated with increased intestinal permeability, inflammation, and nutritional imbalance. Another study found that the body mass index, hand-grip strength, and mid-upper arm muscle circumference were positively correlated with *Phascolarctobacterium*.[39]

However, there were several studies' results inconsistent with the present study. *Eubacterium fissicatena* group was significantly positively correlated with appendicular skeletal mass index and grip strength, and significantly negatively correlated with five-time chair standing test time, indicating that the *Eubacterium fissicatena* group's abundance is positively correlated with muscle mass and muscle function.[40] The inconsistency in the results could be attributed to the observational studies' confounding factors. The positive correlation between *Porphyromonadaceae* and excess visceral adipose tissue (VAT) suggests that it may have an impact on the body's endocrine system.[41] Through the endocrine pathway of adipokines, obesity, especially central obesity with increased VAT, increases the likelihood of sarcopenia.[14] This condition is known as sarcopenic obesity. Further research into whether *Porphyromonadaceae* affects muscle is necessary. There is currently no research on the effects of *Alcaligenaceae* and *Family XIII* on low hand-grip strength, and the effects of *Actinomycetales*, *Actinomycetaceae*, *Prevotellaceae*, and *Marvinbryantia* on ALM need to be further explored. Theoretically, low hand-grip strength and ALM should coexist in most cases of sarcopenia patients. However, the gut microbiota related to these two variables in this study did not overlap. This may be due to several reasons: first, different gut microbiota may affect muscle mass or strength by secreting similar factors. Second, there is a certain threshold range in the study, and gut microbiota that reaches this threshold range is determined to have statistically significant effects. However, if the threshold is relaxed, gut microbiota related to low hand-grip strength and ALM may have further overlap. In general, the relationships discovered in this study between gut microbiota taxa and ALM were partially consistent with previous research findings, but there were still some research findings inconsistent or even contradictory. Future research into the mechanism underlying the relationship between specific gut microbiota taxa and muscle function and muscle mass is needed.

Our finding demonstrates the presence of four gut microbiota associated with reduced hand-grip strength, and nine gut microbiota associated with ALM. It is worth noting that other gut microbiota not covered in this study may also play a role in regulating muscle function and mass. These findings provide valuable insights for potential pharmacological interventions in the treatment of sarcopenia.[42] A study by Eloe-Fadrosh *et al.* found that a supplement of *Lactobacillus* could modify resident microbiota to increase the production of the SCFAs, which could increase the cross-sectional area of muscle fibers and stop intramuscular fat from accumulating.[43] Munukka *et al.* suggested that supplement of *Faecalibacterium prausnitzii* could improve intestinal integrity, reduce inflammatory responses from the body, and improve insulin sensitivity, which will help prevent sarcopenia.[44] Though there have been some human and animal studies about the gut–muscle axis, the mechanism behind it is still unclear. An overview of the gut–muscle axis is shown in Fig. 3.

This study has several strengths. First, it is the largest and most comprehensive MR study of the gut microbiota and sarcopenia-related traits. Second, the GWAS data used in this paper to identify IVs has a large sample size and a high level of accuracy. Third, the UK Biobank undergoes extensive genetic and phenotypic data analysis and is strictly supervised and operated to ensure high quality. Finally, several MR analysis methods were used in this study, which allowed us to estimate the potential causal relationship between the gut microbiota and the two sarcopenia-related variables without interference from residual confounding or reverse causality. However, the study still has certain limitations. First, because of the inherent nature of MR analysis, we cannot be sure that our findings were not influenced by weak IVs, even though all genetic tools were strongly associated with exposure (F value > 10). Second, most of the GWAS data for gut microbiota were from Europeans, whereas all the GWAS data for sarcopenia-related traits were from Europeans, which may contain some bias. Third, the 16S rRNA gene sequencing method only describes the gut microbiota from genus to phylum level. Future metagenomics and multi-omics approaches may be able to describe gut microbiota taxa at a finer level, avoiding species-related bias. In order to provide more theoretical support for the mechanism research of the 'gut–muscle' axis, we will expand the sample size in future studies to investigate the relationship between different gut microbiota taxa and sarcopenia-related traits at the gene level.

With a particular emphasis on the impacts of various gut microbiota taxa on muscle, our findings give researchers a platform to investigate the connection between gut microbiota and sarcopenia-related traits. Future studies should investigate the mechanism by which the gut microbiota and muscle are related, as well as novel therapeutic strategies involving the gut microbiota in the management of sarcopenia.

Supplementary data

Supplementary data is available at *PCMEDI* online.

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Author contributions

J.Z. and J.Y. contributed to the conception of the study; J.Z. and C.W. contributed significantly to analysis and manuscript preparation; J.Z. performed the data analyses and wrote the manuscript; R.L., Q.S., and Shiyu Song helped perform the analysis and contributed to constructive discussions.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Tamburini S, Shen N, Wu HC, *et al.* The microbiome in early life: Implications for health outcomes. *Nat Med* 2016;**22**:713–22. doi:10.1038/nm.4142.
2. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. *Circ Res* 2017;**120**:1183–96. doi:10.1161/CIRCRESAHA.117.309715.
3. Qin J, Li Y, Cai Z, *et al.* A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012;**490**:55–60. doi:10.1038/nature11450.
4. Zhuang Z, Yang R, Wang W, *et al.* Associations between gut microbiota and Alzheimer's disease, major depressive disorder, and schizophrenia. *J Neuroinflammation* 2020;**17**:288. doi:10.1186/s12974-020-01961-8.
5. Ni JJ, Xu Q, Yan SS, *et al.* Gut microbiota and psychiatric disorders: A two-sample mendelian randomization study. *Front Microbiol* 2022;**12**:737197. doi:10.3389/fmicb.2021.737197.
6. Cruz-Jentoft AJ, Bahat G, Bauer J, *et al.* Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* 2019;**48**:16–31. doi:10.1093/ageing/afy169.
7. Sayer AA, Cruz-Jentoft A. Sarcopenia definition, diagnosis and treatment: Consensus is growing. *Age Ageing* 2022;**51**:afac220. doi:10.1093/ageing/afac220.
8. De Buyser SL, Petrovic M, Taes YE, *et al.* Validation of the FNIH sarcopenia criteria and SOF frailty index as predictors of long-term mortality in ambulatory older men. *Age Ageing* 2016;**45**:602–8. doi:10.1093/ageing/afw071.
9. Cawthon PM, Lui LY, Taylor BC, *et al.* Clinical definitions of sarcopenia and risk of hospitalization in community-dwelling older men: The osteoporotic fractures in men study. *J Gerontol A Biol Sci Med Sci* 2017;**72**:1383–9. doi:10.1093/gerona/glw327.
10. Antunes AC, Araujo DA, Verissimo MT, *et al.* Sarcopenia and hospitalisation costs in older adults: A cross-sectional study. *Nutr Diet* 2017;**74**:46–50. doi:10.1111/1747-0080.12287.
11. de Sire R, Rizzatti G, Ingravalle F, *et al.* Skeletal muscle-gut axis: Emerging mechanisms of sarcopenia for intestinal and extra intestinal diseases. *Minerva Gastroenterol Dietol* 2018;**64**:351–62. doi:10.23736/S1121-421X.18.02511-4.
12. Ni LM, Bowyer R, Steves CJ. Dietary protein and muscle in aging people: The potential role of the gut microbiome. *Nutrients* 2018;**10**:929. doi:10.3390/nu10070929.

13. Ticinesi A, Nouvenne A, Cerundolo N, *et al.* Gut microbiota, muscle mass and function in aging: A focus on physical frailty and sarcopenia. *Nutrients* 2019;**11**:1633. doi:10.3390/nu11071633.
14. Zhao J, Huang Y, Yu X. A narrative review of gut-muscle axis and sarcopenia: The potential role of gut microbiota. *Int J Gen Med* 2021;**14**:1263–73. doi:10.2147/IJGM.S301141.
15. Karlund A, Gomez-Gallego C, Turpeinen AM, *et al.* Protein supplements and their relation with nutrition, microbiota composition and health: Is more Protein always better for sportspeople?. *Nutrients* 2019;**11**:829. doi:10.3390/nu11040829.
16. Lin R, Liu W, Piao M, *et al.* A review of the relationship between the gut microbiota and amino acid metabolism. *Amino Acids* 2017;**49**:2083–90. doi:10.1007/s00726-017-2493-3.
17. Dukes A, Davis C, El RM, *et al.* The aromatic amino acid tryptophan stimulates skeletal muscle IGF1/p70s6k/mTor signaling in vivo and the expression of myogenic genes in vitro. *Nutrition* 2015;**31**:1018–24. doi:10.1016/j.nut.2015.02.011.
18. Picca A, Ponziani FR, Calvani R, *et al.* Gut microbial, inflammatory and metabolic signatures in older people with physical frailty and sarcopenia: Results from the BIOSPHERE study. *Nutrients* 2019;**12**:65. doi:10.3390/nu12010065.
19. Ticinesi A, Lauretani F, Tana C, *et al.* Exercise and immune system as modulators of intestinal microbiome: Implications for the gut-muscle axis hypothesis. *Exerc Immunol Rev* 2019;**25**: 84–95.
20. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA* 2017;**318**:1925–6.
21. Liu B, Ye D, Yang H, *et al.* Two-sample mendelian randomization analysis investigates causal associations between gut microbial genera and inflammatory bowel disease, and specificity causal associations in ulcerative colitis or Crohn's disease. *Front Immunol* 2022;**13**:921546. doi:10.3389/fimmu.2022.921546.
22. Lv WQ, Lin X, Shen H, *et al.* Human gut microbiome impacts skeletal muscle mass via gut microbial synthesis of the short-chain fatty acid butyrate among healthy menopausal women. *J Cachexia Sarcopenia Muscle* 2021;**12**:1860–70. doi:10.1002/jcsm.12788.
23. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet* 2019;**393**:2636–46. doi:10.1016/S0140-6736(19)31138-9.
24. Jones G, Trajanoska K, Santanasto AJ, *et al.* Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. *Nat Commun* 2021;**12**:654. doi:10.1038/s41467-021-20918-w.
25. Pei YF, Liu YZ, Yang XL, *et al.* The genetic architecture of appendicular lean mass characterized by association analysis in the UK Biobank study. *Commun Biol* 2020;**3**:608. doi:10.1038/s42003-020-01334-0.
26. Palmer TM, Lawlor DA, Harbord RM, *et al.* Using multiple genetic variants as instrumental variables for modifiable risk factors. *Stat Methods Med Res* 2012;**21**:223–42. doi:10.1177/0962280210394459.
27. Bowden J, Davey SG, Haycock PC, *et al.* Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016;**40**:304–14. doi:10.1002/gepi.21965.
28. Burgess S, Thompson SG. Interpreting findings from mendelian randomization using the MR-Egger method. *Eur J Epidemiol* 2017;**32**:377–89. doi:10.1007/s10654-017-0255-x.
29. Hemani G, Zheng J, Elsworth B, *et al.* The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018;**7**:e34408. doi:10.7554/eLife.34408.
30. Chen YJ, Wu H, Wu SD, *et al.* Parasutterella, in association with irritable bowel syndrome and intestinal chronic inflammation. *J Gastroenterol Hepatol* 2018;**33**:1844–52. doi:10.1111/jgh.14281.
31. Li F, Wang M, Wang J, *et al.* Alterations to the gut microbiota and their correlation with inflammatory factors in chronic kidney disease. *Front Cell Infect Microbiol* 2019;**9**: 206. doi:10.3389/fcimb.2019.00206.
32. Jager R, Purpura M, Stone JD, *et al.* Probiotic Streptococcus thermophilus FP4 and bifidobacterium breve BR03 supplementation attenuates performance and range-of-motion decrements following muscle damaging exercise. *Nutrients* 2016;**8**:642. doi:10.3390/nu8100642.
33. Ren X, Hao S, Yang C, *et al.* Alterations of intestinal microbiota in liver cirrhosis with muscle wasting. *Nutrition* 2021;**83**: 111081. doi:10.1016/j.nut.2020.111081.
34. Okamoto T, Morino K, Ugi S, *et al.* Microbiome potentiates endurance exercise through intestinal acetate production. *Am J Physiol Endocrinol Metab* 2019;**316**:E956–66. doi:10.1152/ajpendo.00510.2018
35. Scheiman J, Luber JM, Chavkin TA, *et al.* Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. *Nat Med* 2019;**25**:1104–9. doi:10.1038/s41591-019-0485-4.
36. Pei T, Zhu D, Yang S, *et al.* Bacteroides plebeius improves muscle wasting in chronic kidney disease by modulating the gut-renal muscle axis. *J Cell Mol Med* 2022;**26**:6066–78. doi:10.1111/jcmm.17626.
37. Fielding RA, Reeves AR, Jasuja R, *et al.* Muscle strength is increased in mice that are colonized with microbiota from high-functioning older adults. *Exp Gerontol* 2019;**127**: 110722. doi:10.1016/j.exger.2019.110722.
38. Lee YA, Song SW, Jung SY, *et al.* Sarcopenia in community-dwelling older adults is associated with the diversity and composition of the gut microbiota. *Exp Gerontol* 2022;**167**: 111927. doi:10.1016/j.exger.2022.111927.
39. Hu J, Zhong X, Liu Y, *et al.* Correlation between intestinal flora disruption and protein-energy wasting in patients with end-stage renal disease. *BMC Nephrol* 2022;**23**:130. doi:10.1186/s12882-022-02762-2.
40. Kang L, Li P, Wang D, *et al.* Alterations in intestinal microbiota diversity, composition, and function in patients with sarcopenia. *Sci Rep* 2021;**11**:4628. doi:10.1038/s41598-021-84031-0.
41. Tavella T, Rampelli S, Guidarelli G, *et al.* Elevated gut microbiome abundance of christensenellaceae, porphyromonadaceae and Rikenellaceae is associated with reduced visceral adipose tissue and healthier metabolic profile in Italian elderly. *Gut Microbes* 2021;**13**:1–19. doi:10.1080/19490976.2021.1880221.
42. Liu X, Yue J. Precision intervention for sarcopenia. *Precis Clin Med* 2022;**5**:c13.
43. Eloe-Fadrosh EA, Brady A, Crabtree J, *et al.* Functional dynamics of the gut microbiome in elderly people during probiotic consumption. *mBio* 2015;**6**:e00231–15. doi:10.1128/mBio.00231-15.
44. Munukka E, Rintala A, Toivonen R, *et al.* Faecalibacterium prausnitzii treatment improves hepatic health and reduces adipose tissue inflammation in high-fat fed mice. *ISME J* 2017;**11**:1667–79. doi:10.1038/ismej.2017.24.

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