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RESEARCH

Association between gut microbiota and sarcopenia in older adults: a cross-sectional analysis from the second wave of the Birjand Longitudinal Aging Study (BLAS)

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Abstract

Introduction Investigating gut microbiota has emerged as a novel approach to exploring the gut-muscle axis and its link to age-related conditions like sarcopenia. While studies suggest gut dysbiosis may promote inflammation and muscle loss, findings vary by region and ethnicity. This study examined the association between gut microbiota and primary sarcopenia in an older adult population in Iran.

Methods This cross-sectional study analyzed 293 community-dwelling participants (aged ≥ 60 years) from the second wave of the Birjand Longitudinal Aging Study in Iran. Fecal samples were collected, and gut microbiota composition was assessed for 12 bacterial genera using quantitative Real-time PCR with genus-specific primers. Sarcopenia was defined according to the 2019 Asian Working Group for Sarcopenia (AWGS) criteria, based on anthropometric measurements, body composition (via bioelectric impedance analysis), handgrip strength, and walking speed. Associations between the abundance of each bacterial genus and sarcopenia, as well as its individual components, were assessed.

Results Out of 293 participants, 38.2% ($n = 112$) were diagnosed with sarcopenia. Participants with sarcopenia were older than those without sarcopenia (mean age 72.99 ± 6.13 vs. 70.20 ± 5.24 years) and had a different sex distribution (55.4% vs. 60.2% women in the sarcopenic and non-sarcopenic groups, respectively). Higher *Akkermansia* abundance was associated with greater odds of sarcopenia and was negatively correlated with handgrip strength, skeletal muscle index (SMI), and gait speed ($p < 0.05$). *Akkermansia* was also associated with low SMI, and low gait speed; each unit increase in *Akkermansia* was associated with 9% higher odds of low SMI and 8% higher odds of low gait speed. Both *Akkermansia* and *Lactobacillus* increased the odds of sarcopenia by 7% and 8%, respectively, whereas *Roseburia* showed an inverse association with sarcopenia and each unit increase in *Roseburia* decreased the odds of sarcopenia by 11.5%. *Roseburia* was also positively correlated with gait speed ($p < 0.05$).

Conclusion This study demonstrates that specific gut microbial profiles are significantly associated with sarcopenia. *Akkermansia* and *Lactobacillus* were associated with sarcopenia, although greater *Roseburia* levels were beneficial. These microbial signatures are associated with sarcopenia and warrant further longitudinal investigation.

Keywords Sarcopenia · Gut microbiota · Aging · Muscle metabolism

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Introduction

Sarcopenia is characterized by a gradual decline in muscle mass, function, and physical performance during aging. This condition is a global concern due to its impact on health outcomes [1]. Sarcopenia is associated with an increased risk of falls and fractures [2]. Globally 10%–16% of the older adults population is affected by sarcopenia; moreover, the incidence of sarcopenia was higher in patients than in the general population [3].

There is evidence that oxidative stress and persistent low-grade inflammation are contributors to sarcopenia [4]. Physical inactivity and poor diet exacerbate these mechanisms, underscoring the importance of exercise and a suitable diet in preventing the adverse effects of sarcopenia [5]. Resistance training is the main non-pharmacological strategy for improving muscle mass and function, while increased protein intake and essential amino acids support muscle health in the older adults [6]. In relation to nutritional status and a variety of disease conditions, the gut microbiota plays a significant role in regulating pro- and anti-inflammatory responses [7].

The gut microbiota metabolizes carbohydrates, proteins, and lipids to produce energy and bioactive compounds that can cross the intestinal barrier or be further metabolized by other organs. These metabolites enter the circulatory system, regulating various tissues beyond the gastrointestinal tract, including muscles [8]. This interaction, known as the “gut-muscle axis,” underscores the microbiota’s role in muscle metabolism, function, and overall health [9, 10].

The gut microbiota in humans consists of different microorganisms, with Bacteroidetes (Bacteroidota) and Firmicutes (Bacillota) being the predominant phyla in adults. This complex ecosystem is essential for the maintenance of health, energy homeostasis, nutritional status, and intestinal immune and endocrine functions [9].

The gut microbiota is increasingly recognized as a critical component in physiological aging and diseases, proposing that gut-muscle axis might connect the microbiota with age-related muscle decline. Nonetheless, direct investigations of microbiota composition in patients with sarcopenia are scarce and frequently lack statistical consistency [10].

Furthermore, few studies specifically investigate the gut microbiota of people with sarcopenia from different ethnic and geographic backgrounds [10], consequently, focusing on the gut-muscle axis may be a novel approach to study age-related muscle dysfunction and atrophy.

Method

Participants

This cross-sectional study was conducted within the framework of second wave of the Birjand Longitudinal Aging Study (BLAS), which was conducted from November 2021 to May 2022 in Birjand, Iran. The BLAS study is a prospective, population-based cohort aiming at determining the prevalence and risk factors of non-communicable diseases (NCD) among an older population ≥ 60 years which were residents in Birjand city. The rational for and methodology was described in detail elsewhere [11]. After an explanation of the study objectives and protocols, written informed consent was obtained from all participants. We carried out a random selection process to choose 300 older adults from participants who were involved in the second wave of the BLAS study and collected their fecal samples. Intake of antibiotics, proton-pump inhibitors (PPIs), prebiotics, probiotics, or synbiotics within the two months prior to sample collection; and history of cancer, autoimmune diseases, Inflammatory Bowel Disease (IBD), or major gastrointestinal surgery were considered as exclusion criteria. All procedures involving human participants in this study were carried out in compliance with the ethical requirements of the Institutional Review Boards of the participating institutions, as well as the 1964 Helsinki Declaration. This study was approved by the Research Ethics Committee of Endocrinology & Metabolism Research Institute (code: IR.TUMS.EMRI.REC.1399.071).

Data collection and group definitions

In this study, covariates including socio-demographic variables, health behaviors, and health status indicators using validated questionnaires. Socio-demographic variables including age, sex, education levels, and marital status had been collected. Health behavior variables included smoking status (smoker vs. non-smoker), total daily energy intake (Kcal/day), and daily intakes of fat, protein, and fiber (g/day). Dietary intake was assessed using a validated Food Frequency Questionnaire (FFQ) [12]. These questionnaires were filled out by trained interviewers. Anthropometric measurements, including height, weight, were assessed. Weight was determined using a calibrated SECA digital scale at the nearest 0.1 kg (SECA, Germany) while wearing the least amount of clothes. Height was measured with participants standing straight, without any shoes, at the nearest 0.1 cm (SECA, Germany). The formula for calculating body mass index (BMI) was weight (kg) divided by the square of height (m^2).

Body composition was measured using a bioelectric impedance analyser (BIA) of eight-point tactile electrodes (TANITA, BC-601-CG, Tokyo, Japan). Using this device fat mass, and muscle mass were measured. Appendicular skeletal muscle mass (ASM) for each participant was derived as the sum of upper and lower limb muscle mass. The skeletal muscle mass index (SMI) was defined as ASM/height^2 (kg/m^2). Muscle strength was measured by handgrip strength, using a digital dynamometer. The measurement was carried out two times for each hand, and maximum grip strength was calculated by taking the average of the highest measurement from both hands. Usual walking speed (m/s) on a 6 m-course was used as an objective measure of physical performance [1].

Fecal DNA collection and extraction

Fecal samples were taken from all participants of the BLAS study once, at the same time that clinical variables were collected. Fresh fecal samples were collected in sterile containers, immediately preserved in ice packs, and transported to the laboratory within 2 h, stored at a temperature of -80 degrees Celsius, to examine the gut microbiota. The collected fecal samples had a volume of 200 milligrams.

DNA was extracted from 200 milligrams of fecal samples using, FavorPrep stool DNA isolation mini kit (Favorgen) with standard protocols, to ensure consistent and reliable DNA yield and purity. The purity of the extracted DNA was determined by measuring the absorbance ratio of A260/A280 using a spectrophotometer. The NanoDrop device (Thermo scientific, US) was used to ascertain the concentration of the extracted DNA. This ensured that only high-quality samples were used for downstream analysis. We quantified selected bacterial genera using quantitative PCR (qPCR) with genus-specific primers. The study utilized genus-specific primer sequences aimed at bacterial 16 S rRNA genes which designed and have been validated and blasted in prior studies. Twelve bacterial genera were selected to compare between sarcopenic and non-sarcopenic individuals based on the prior literature: *Lactobacillus*, *Escherichia*, *Bifidobacterium*, *Bacteroides*, *Roseburia*, *Alistipes*, *Ruminococcus*, *Fecalibacterium*, *Prevotella*, *Dialister*, *Oscillospira*, and *Akkermansia*.

The specificity of the primers was assessed in silico utilizing the nucleotide BLAST in NCBI. The precise sequences of the primers are presented in the Supplementary Table 1. The 12 bacterial genera included in this qPCR project were selected based on existing evidence and their hypothesized potential mechanisms [13].

Assessment of the bacterial load

SYBR Green-based Absolute Real-time PCR was performed using a real-time light cycler 48 device (ABI StepOne, USA). The experiments were performed in duplicate for all samples. Bacterial primers were amplified utilizing the PCR technique with 5 µl of master mix, 1 µl of each primer, and 3 µl of sterile distilled water. According to the appropriate annealing temperature: 1 cycle of 95° for 60 s, followed by 40 cycles of denaturation at 95°for 5 s, primer annealing at 55° for 30 s, and extension at 72° for 30 s. Melting curve analysis was conducted after amplification to control the specificity of PCR reaction, followed by 1 cycle at 95° for 5 s, 60° for 60 s, and 95 °C for 10 s. Finally, melting curve analysis was carried out by gradually cooling the PCRs from 95 °C to 60 °C to verify the specificity of the amplified products. The bacterial concentration in each sample was determined by comparing the measured threshold cycle values with the standard curves established for each experiment, utilizing successive 10-fold dilutions of bacterial genomic DNA from standard genera with known concentration. Subsequently, the bacterial copy numbers of the twelve bacterial genera were quantified in 1 gram of fecal matter. Negative controls in qPCR assays. We used the CT-mean to calculate the number of colony-forming units (CFU) of each bacterium compared to the standard chart and then calculated the logarithm of CFU of each bacterium in one gram of fecal sample.

Definition of terms

In 2019, Asian Working Group for Sarcopenia (AWGS) updated the diagnostic criteria for sarcopenia due to a significant rise in prevalence [1]. Sarcopenia was defined as reduced skeletal muscle mass plus low muscle strength and/or low physical performance based on the (AWGS) 2019 consensus. Low muscle strength was defined as handgrip strength < 28 kg for men and < 18 kg for women and low physical performance was described as walking speed < 1.0 m/s. low muscle mass was defined SMI < 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women by BIA. These variables defined according to the AWGS 2019 cut-offs, and sarcopenia was classified into four stages: severe sarcopenia, sarcopenia, possible sarcopenia, and no sarcopenia [1]. For the main analyses, sarcopenia status was modeled as a binary variable: the sarcopenia group included participants with sarcopenia or severe sarcopenia, and the non-sarcopenia group included participants with no sarcopenia or possible sarcopenia. Subsequently, a sensitivity analysis was also performed in which the outcome was redefined as follows; control group: no sarcopenia; case group: possible sarcopenia, sarcopenia, or severe sarcopenia.

Statistical analysis

The normality of variable distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The bacterial abundance data were log-transformed to normalize the distribution prior to statistical analysis. The data were presented as percentage for categorical variables and mean and standard deviation (SD) for continuous variables and medians and interquartile ranges (IQRs) for non-normal data. A comparison of variables was performed using a Chi-square test or Fisher's exact test for categorical variables and independent t-tests for continuous variables. In instances of non-normality, equivalent non-parametric tests (Wilcoxon Signed-Rank Test and Mann-Whitney U Test) were applied. A Wilcoxon rank-sum test was used to identify differentially abundant bacterial genera in sarcopenia and non-sarcopenia groups. The False Discovery Rate (FDR) method was used to adjust p-values for multiple comparisons, controlling for the increased risk of type I errors. Additionally, Spearman's rank correlation analysis was performed to assess the strength of the relationships between the bacterial genera and the parameters of sarcopenia. Spearman's correlation was chosen due to its non-parametric nature, which is suitable for evaluating monotonic relationships between variables that may not follow a normal distribution. Correlation coefficients were interpreted as very weak ($|r| < 0.20$), weak ($|r| = 0.20–0.39$), moderate ($|r| = 0.40–0.59$), strong ($|r| = 0.60–0.79$), and very strong ($|r| > 0.80$). Linear regression analysis was conducted to assess the associations between sarcopenia-defining parameters and bacterial taxa. Sarcopenia-related continuous variables were used as dependent variables, and bacterial abundances as independent variables. Log transformation was applied to handgrip strength due to its non-normal distribution. Age, sex, education level, marital status, smoking status, BMI, total daily energy intake, and daily intakes of fat, protein, and fiber were adjusted in the model. β coefficients, standard errors (SE), and P-values were reported. To assess the association between the bacterial genera and sarcopenia status, and parameters of sarcopenia, a multivariate logistic regression model was fitted, adjusting for potential confounders, including, age, sex, education levels, marital status, smoking status (smoker/non-smoker), BMI, total daily energy intake (kcal/day), and daily intakes of fat, protein, and fiber (g/day).

To select the best model from all possible subsets and avoid overfitting, best subset method with the Akaike Information Criterion (AIC) and the Bayesian information criterion (BIC) was used. The multi-collinearity between variables was checked and the odds ratio (Adjusted OR) with 95% CI were used as the measure of associations in the final models. Model performance was evaluated using 10-fold cross-validation. Key metrics, including area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, and accuracy, were calculated to assess the models' ability to distinguish between two groups. All statistical analyses were conducted using R version 4.4.1.

Results

After excluding the participants with missing values of bacterial genera or sarcopenia definition, a total of 293 individuals were included in the study. Of these, 92 (31.4%) had severe sarcopenia and 20 (6.8%) had sarcopenia, 80 (27.3%) were classified as having possible sarcopenia, and 101 (34.5%) had no sarcopenia. The demographic and clinical characteristics of the subjects based on sarcopenia status are displayed in Table 1. The mean of age, BMI, and weight were significantly different in individuals with and without sarcopenia. Moreover, all three components of sarcopenia, including handgrip strength, gait speed, and SMI were significantly lower in sarcopenic people ($P < 0.001$). The results also showed significant differences in dietary intake, with the non-sarcopenic group consuming total daily energy (1689.1 kcal, IQR: 1321.4–2327.2) compared to sarcopenic people (1508.9 kcal, IQR: 1203.1–2011.9; $p = 0.0156$) and a higher total daily fat intake (73.9 g, IQR: 56–92.5 vs. 66.1 g, IQR: 50.8–85.4; $p = 0.0436$). Other variables were not statistically significant. A comparative analysis between women and men was also conducted. Regarding all three sarcopenia components, handgrip strength, gait speed, and SMI, women exhibited significantly lower values than men (Supplementary Table 2).

Comparison of bacterial genera frequencies between sarcopenia and non-sarcopenia groups is presented in Table 2. After FDR adjustment of p-values, no significant differences in bacterial genera frequencies were found between the sarcopenia and non-sarcopenia groups. Initial direct comparisons lost significance after correction for multiple comparisons. However, a trend towards a difference in the *Escherichia* genus was observed (FDR-adjusted p-value = 0.16).

To assess the association between gut bacterial genera and sarcopenia, a multivariate logistic regression model was used in which potential confounding effects of demographic and dietary factors were also included. As shown in Table 3, *Roseburia* was inversely associated with sarcopenia (OR = 0.89, 95% CI: 0.80–0.97, P value = 0.011). For each unit increase in *Roseburia* levels, the odds of sarcopenia decreased by approximately 11.5%. By contrast, *Akkermansia* showed a positive association with sarcopenia (OR = 1.07, 95% CI: 1.02–1.12, P value = 0.004). Each

Table 1 Demographic data and basic clinical characteristics of the studied population

Variable	Non-sarcopenic group (*n* = 181)	Sarcopenic group (*n* = 112)	*P*-value
Age, years	70.20 ± 5.24	72.99 ± 6.13	< 0.001
Sex, n (%)			0.41
Men	72 (39.8%)	50 (44.6%)	
Women	109 (60.2%)	62 (55.4%)	
Education level, n (%)			0.052
<12 years	140 (77.3%)	94 (83.9)	
≥12 years	41 (22.7%)	18 (16.1%)	
Marital status, n (%)			0.54
Married	149 (82.3%)	89 (79.5%)	
Not Married	32 (17.7%)	23 (20.5%)	
Current smoking, n (%)			0.68
Smoker	10 (5.5%)	5 (4.5%)	
Nonsmoker	171 (94.5%)	107 (95.5%)	
Weight, kg	77.12 ± 13.01	64.41 ± 9.46)	< 0.001
Body mass index (BMI), kg/m^2	30.68 ± 4.84	26.52 ± 4.02	< 0.001
Handgrip strength, kg	20.2 (14.7–30.4)	14.9 (11.8–22.6)	< 0.001
Gait speed, m/s	0.81 ± 0.24	0.75 ± 0.25	0.03
Skeletal muscle mass index (SMI)	6.41 ± 0.72	5.69 ± 0.69	< 0.001
Total daily energy, kcal	1689.1 (1321.4–2327.2)	1508.9 (1203.1–2011.9)	0.01
Total daily fat, g	73.9 (56–92.5)	66.1 (50.8–85.4)	0.04
Total daily protein, g	52.9 (40.4–79.7)	49.7 (36.7–68.2)	0.10
Total daily fiber, g	23.7 (17.3–40.5)	20.5 (14.5–34.2)	0.07

Data are presented as mean± standard deviation, median (Interquartile range), or number(percent)

The sarcopenic group included participants with sarcopenia or severe sarcopenia, and the non-sarcopenic group included participants with no sarcopenia or possible sarcopenia

Table 3 Association between gut bacterial genera and sarcopenia in a multivariate logistic regression model

Variables	Estimate (β)	OR (95% CI)	*P*-value
Roseburia, log CFU/g	-0.122	0.89 (0.80–0.97)	0.011
Akkermansia, log CFU/g	0.065	1.07 (1.02–1.12)	0.004
Lactobacillus, log CFU/g	0.079	1.08 (1.00–1.17)	0.049
Escherichia, log CFU/g	0.074	1.08(0.99–1.16)	0.054
Age, years	0.073	1.08 (1.02–1.13)	0.004
BMI, kg/m^2	-0.247	0.78 (0.72–0.84)	< 0.001
Total daily energy, kcal	-0.002	0.99 (0.99–0.99)	0.006
Total daily protein, g	0.021	1.02 (0.99–1.05)	0.096
Total daily fiber, g	0.023	1.02 (0.99–1.05)	0.107
Sex	-0.412	0.66 (0.35–1.23)	0.195

OR: odds ratio; CI: confidence interval; BMI: body mass index

unit increase in *Akkermansia* levels corresponded to a 7% increase in the odds of sarcopenia. *Lactobacillus* was also positively associated with sarcopenia (OR = 1.08, 95% CI: 1.00- 1.17, P value = 0.049), with an 8% increase in the odds for each unit increase in *Lactobacillus* levels. In addition, *Escherichia* had a positive association with sarcopenia; however, this relationship was only marginally significant. Age, BMI, and total daily energy intake were other factors significantly associated with sarcopenia.

We conducted a sensitivity analysis in which we redefined the groups as follows: control group (no sarcopenia; *n* = 101) versus case group (possible sarcopenia, sarcopenia, or severe sarcopenia; *n* = 192) (Supplementary Table 3); And refitted the logistic regression including all covariates and bacterial genera, using backward selection. All variables were initially entered into the model; In the final model, only four bacterial genera and four confounding variables remained. Age, sex, and *Roseburia* significantly associated with this broader sarcopenia outcome. Higher *Roseburia* abundance remained protective. Other genera such as *Ruminococcus*, *Akkermansia*, and *Escherichia*

Table 2 Comparison of bacterial genera frequencies between sarcopenia and non-sarcopenia groups using Wilcoxon rank-sum test

Bacterial genera	Non-sarcopenia		Sarcopenia		*P*-value	FDR-adjusted *p*-value
	Mean	SD	Mean	SD		
Akkermansia	7.23318	6.517730	8.97964	7.046902	0.05	0.27
Alistipes	18.77717	2.257652	18.80167	2.363268	0.97	0.98
Bacteroides	15.36746	4.711247	15.62481	5.413527	0.69	0.98
Bifidobacterium	13.65364	5.265565	14.20042	6.943850	0.43	0.98
Dialister	12.45615	4.438076	12.05045	4.516272	0.32	0.98
Escherichia	11.31945	3.869063	12.52995	4.120464	0.01	0.16
Faecalibacterium	15.8558	4.84687	16.2039	5.89278	0.98	0.98
Lactobacillus	10.94890	4.133047	10.98100	4.133093	0.86	0.98
Oscillospira	13.36283	4.304314	13.85236	4.811689	0.74	0.98
Prevotella	9.03126	6.187818	9.00820	6.752581	0.79	0.98
Roseburia	12.39290	3.557072	12.11371	3.523217	0.42	0.98
Rumminococcus	14.82581	4.209821	15.32955	4.571980	0.51	0.98

Bacterial Genera are presented as log CFU/g of stool

FDR; False Discovery Rate

showed similar directional trends to the primary analysis but did not reach statistical significance when possible sarcopenia was included in the sarcopenia group. Therefore, including “possible sarcopenia” in the sarcopenia group did not change our main microbiota patterns, and the protective association of *Roseburia* with sarcopenia status appears robust (Supplementary Table 3).

Figure 1 shows that the correlation between 12 bacterial genera and three sarcopenia-related components: handgrip strength, gait speed, and SMI. We observed weak correlations between several bacterial genera and the sarcopenia components ($p<0.05$). *Akkermansia* was significantly negatively correlated with handgrip strength (ρ = -0.19, $p=0.001$), SMI (ρ = -0.16, $p=0.005$), and gait speed (ρ = -0.12, $p=0.042$). *Roseburia* showed a significant positive correlation with gait speed (ρ=0.17, $p=0.003$). No other significant correlations were found between the bacteria and handgrip strength, gait speed, or SMI. Further details on all relationships between bacteria are highlighted in Fig. 1.

The associations between sarcopenia-defining parameters and bacterial taxa were assessed using linear regression analyses. For handgrip strength, a significant negative association was observed with *Ruminococcus* ($p=0.04$), while *Akkermansia* showed a borderline negative association ($p=0.08$) and *Lactobacillus* demonstrated a borderline positive association ($p=0.09$). For gait speed, *Akkermansia* exhibited a borderline negative association ($p=0.06$). Regarding SMI, significant negative associations were identified with *Bacteroides* ($p=0.04$) and *Akkermansia* ($p=0.003$), whereas *Escherichia* and *Lactobacillus* showed borderline negative associations ($p=0.08$ and $p=0.05$, respectively) (Supplementary Table 4).

The association between gut bacterial genera and parameters of sarcopenia is shown in Table 4. *Akkermansia* was positively associated with low muscle mass (OR=1.09, 95% CI: 1.03–1.15, P-value=0.002). For each unit increase in *Akkermansia*, the odds of low muscle mass increased by approximately 9%. BMI was significantly inversely associated with low muscle mass (OR=0.58, 95% CI: 0.51–0.66, P-value<0.001). Education level showed a significant association in which individuals with a higher level of education had lower odds of muscle mass loss (OR=0.47, 95% CI: 0.23–0.93, P-value=0.034). Other variables, such as age, sex, and *Alistipes*, did not have a relationship with low muscle mass index. not statistically significant.

Roseburia was inversely and significantly associated with low handgrip strength, with a higher presence of *Roseburia* decreasing the odds of low grip strength (OR=0.89, 95% CI: 0.81–0.97, P-value=0.010). *Akkermansia* showed a marginally significant association (OR=1.04, 95% CI: 0.99–1.09, P-value=0.055), indicating a potential positive association with low grip strength. Age and sex had

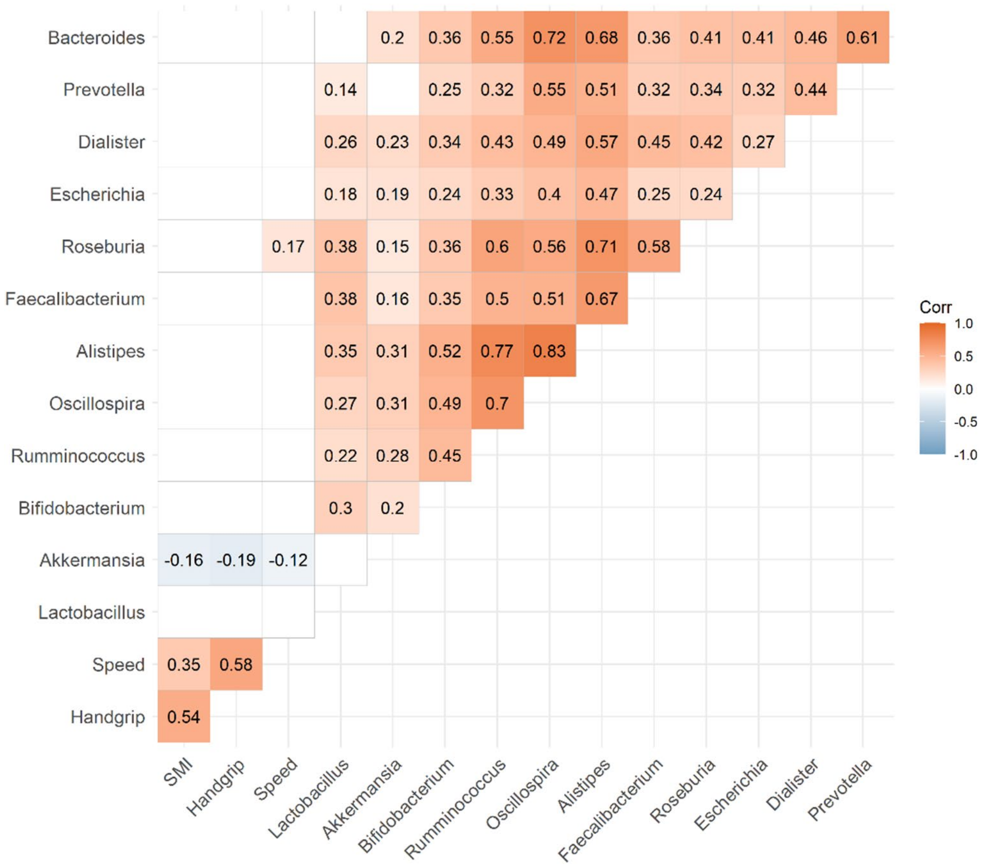

Fig. 1 Spearman correlation heatmap. Significant correlations ($p<0.05$), between bacterial genera and the components of sarcopenia are illustrated, while non-significant correlations are represented by blank white squares. (Fig. 1, SMI; Skeletal Muscle Mass Index)

Table 4 Relationship between parameters of sarcopenia and gut bacterial genera in a multivariate logistic regression model

Variables	Estimate (β)	OR (95% CI)	*P*-value
low skeletal muscle index			
Alistipes, log CFU/g	-0.13	0.88 (0.75–1.01)	0.083
Akkermansia, log CFU/g	0.086	1.09 (1.03–1.15)	0.002
Age, years	0.053	1.05 (0.99–1.13)	0.123
BMI, kg/m^2	-0.537	0.58 (0.51–0.66)	<0.001
Education			
≥12 years	-0.764	0.47 (0.23–0.93)	0.034
Sex	0.13	1.14 (0.53–2.42)	0.736
low muscle strength			
Roseburia, log CFU/g	-0.121	0.89 (0.81–0.97)	0.010
Rumminococcus, log CFU/g	0.072	1.07 (0.99–1.17)	0.087
Akkermansia, log CFU/g	0.042	1.04 (0.99–1.09)	0.055
Escherichia, log CFU/g	0.061	1.06 (0.99–1.14)	0.099
Sex	-0.958	0.38 (0.22–0.66)	<0.001
Age, years	0.078	1.08 (1.03–1.14)	0.002
Total daily energy, Kcal	-0.001	0.99 (0.99–0.99)	0.022
Total daily protein, g	0.022	1.02 (0.99–1.05)	0.067
Total daily fiber, g	-0.002	0.99 (0.97–1.02)	0.885
low physical performance (Low gait speed)			
Faecalibacterium, log CFU/g	-0.055	0.95(0.89–1.01)	0.103
Akkermansia, log CFU/g	0.074	1.08 (1.02–1.14)	0.011
Lactobacillus, log CFU/g	-0.065	0.94 (0.86–1.02)	0.147
Sex	-2.256	0.10 (0.04–0.23)	<0.001
Age, years	0.124	1.13 (1.06–1.22)	<0.001
BMI, kg/m^2	0.082	1.09 (1.01–1.18)	0.039
Education			
≥12 years	-0.395	0.67 (0.37–1.21)	0.187

OR: odds ratio; CI: confidence interval; BMI: body mass index

Low muscle strength: handgrip strength < 28 kg for men and < 18 kg for women. Low physical performance: walking speed < 1.0 m/s. Low SMI: bioimpedance < 7.0 kg/m2 in men and < 5.7 kg/m2 in women

a strong association with low muscle strength, Total daily energy intake was negatively associated with low handgrip strength, with higher energy intake reducing the odds of low grip strength.

Akkermansia was significantly associated with lower physical performance (OR = 1.08, 95% CI: 1.02–1.14, $p = 0.011$). A one-unit increase in *Akkermansia* was associated with a 8% higher odds of low gait speed. Sex and age were strongly associated with gait speed and BMI also showed a positive association with low physical performance (OR = 1.09, 95% CI: 1.01–1.18, $p = 0.039$). Other variables, such as *Faecalibacterium* ($p = 0.103$) and *Lactobacillus* ($p = 0.147$), were not statistically significant.

The performance of the logistic regression models was assessed using 10-fold cross-validation, and the evaluation metrics, including AUC, sensitivity, specificity, and accuracy, were calculated for each model. For the model predicting sarcopenia, the AUC was found to be 0.796, with a sensitivity of 81%, specificity of 61%, and an accuracy of 73%. For low skeletal muscle mass, the model demonstrated an AUC of 0.899, sensitivity of 81%, specificity of 82%, and an accuracy of 82%. Similarly, the model for low physical performance (low gait speed) showed an AUC of 0.841 with a sensitivity of 43%, specificity of 92%, and an accuracy of 82%. Thus, the models for sarcopenia and low skeletal muscle mass correctly identified most affected individuals (high sensitivity), whereas the low gait speed model favored high specificity at the expense of sensitivity. Finally, the model predicting low handgrip strength yielded a sensitivity of 35%, specificity of 87%, accuracy of 69%, and an AUC of 0.698. This model demonstrated a specificity of 87%, indicating a low false positive rate (13%), which suggests it is reliable for correctly identifying healthy subjects. However, the sensitivity of 35% implies a high false negative rate (65%), meaning the model misses a significant proportion of true positive cases, reflecting a high specificity but limited screening performance for this outcome. ROC curves for each model are provided in Fig. 2, demonstrating the discriminative ability of the models.

Discussion

Present study investigated the association between gut microbiota and sarcopenia, along with its components, in an older adult's population in Iran. Among the twelve gut microbiota types examined, our findings demonstrated a significant association between *Akkermansia* and sarcopenia. *Akkermansia* exhibited negative associations with hand grip strength, gait speed, and SMI. The risk of developing sarcopenia increased by 7% for every unit rise in *Akkermansia* levels. We also explored the association of *Akkermansia* with low gait speed, and low SMI, finding a significant correlation with these components of sarcopenia. A single unit increase in *Akkermansia* was related with an 8% increase in the risk of low gait speed and a 9% increase in the likelihood of low SMI. Moreover, in the linear regression analysis, *Akkermansia* showed consistent negative associations with SMI, along with borderline negative associations with handgrip strength and gait speed; Although *Akkermansia* has demonstrated an age-related rise in previous investigations [14], this pattern was not consistently observed across all studies [10]. In line with our findings, a study demonstrated that *Akkermansia* is more prevalent in sarcopenic patients compared to non-sarcopenic individuals [15], and exhibits a negative correlation with BMI. This inverse correlation may partially elucidate the relationship between sarcopenia and BMI [16]. *Akkermansia* is regarded as a beneficial bacteria owing to its anti-inflammatory characteristics; it has been negatively associated with inflammatory bowel

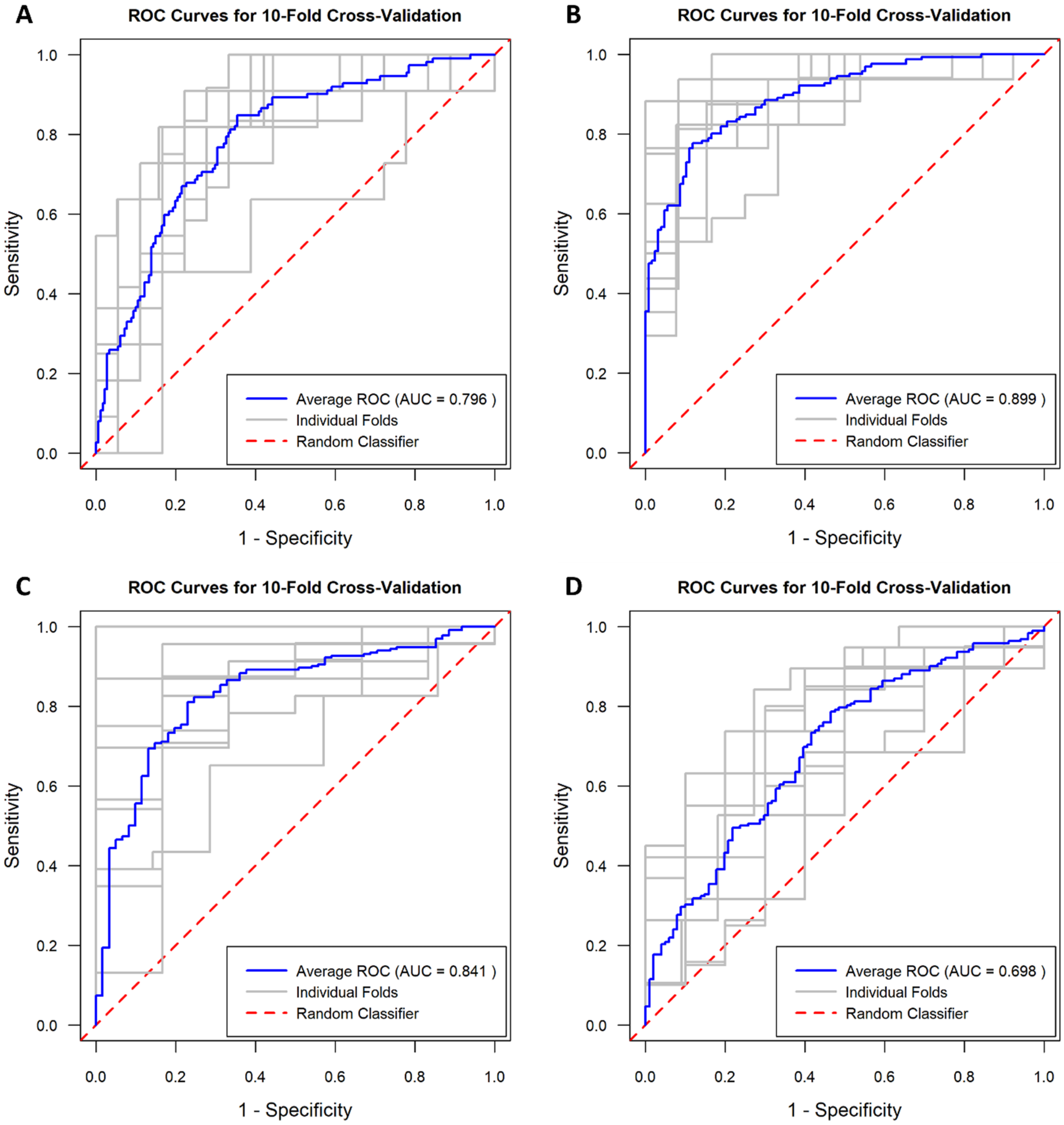

Fig. 2 ROC curves obtained from a 10-fold cross-validation of multivariate logistic regression models for predicting (**A**) sarcopenia (**B**) low muscle mass (**C**) low physical performance (gait speed) (**D**) low handgrip strength. (Fig. 2, ROC; receiver operating characteristic curve)

disease [17], BMI and obesity, while exhibiting a favorable association with weight reduction [18]. *Akkermansia* has been extensively studied in animal models and in patients with colorectal carcinomas and multiple sclerosis; It can exacerbate intestinal inflammation generated by *Salmonella typhimurium* due to its capacity to disrupt host mucus homeostasis [19, 20]. These results point to a complicated function for *Akkermansia* in sarcopenia, suggesting that its higher prevalence in sarcopenic people may affect the onset of sarcopenia, possibly via pro-inflammatory pathways.

Additionally, our research indicates a significant correlation between the *Lactobacillus genus* and sarcopenia. Notably, *Lactobacillus*, a common component of probiotic formulations, has been identified as a potential biomarker for individuals with pre-sarcopenia; Research indicated that people with sarcopenia exhibit reduced gut microbiota diversity, characterized by elevated levels of *Lactobacillus* and decreased levels of *Lachnospira*, *Fusicatenibacter*, *Roseburia*, *Eubacterium*, and *Lachnoclostridium* [10].

Multiple studies have revealed a correlation between tryptophan-metabolizing gut bacteria and the levels of uremic toxins, such as indoxyl sulfate (IS) and p-cresyl sulphate (PCs). Both toxins are produced from the metabolism of dietary tryptophan and contribute to muscle atrophy through a variety of mechanisms [21]. Indoxyl sulfate is produced in the gut when gut microbiota, particularly *Lactobacillus* and *Bifidobacterium longum* convert tryptophan into indole. This indole is then absorbed into the bloodstream and metabolized by the liver into IS [15, 22]. Elevated levels of IS promote the production of reactive oxygen species, leading to muscle degradation. In dialysis patients with end-stage renal disease, higher plasma IS levels are significantly associated with lower skeletal muscle mass [21]. Moreover, previous studies have shown that patients with CKD have a greater abundance of *Lactobacillus* compared to healthy individuals, underscoring its potential importance for overall systemic health [23]. Nevertheless, *Lactobacillus* genus may alleviate chronic inflammation through various mechanisms; for instance, *Lactobacillus* strains have been shown to lower levels of lipopolysaccharide (a bacterial-derived endotoxin), and related inflammatory markers that are linked to muscular degeneration [24]. Given that chronic inflammation is a key factor in the development of sarcopenia, the overrepresentation of *Lactobacillus* in pre-sarcopenic individuals suggests that a reduction in these beneficial, inflammation-modulating bacteria could accelerate sarcopenia progression [4, 10] and supplementation with *Lactobacillus* and *Bifidobacterium* significantly improved muscular mass, strength, and endurance capacity in aged mice [25]. *Lactobacillus* appears to play a dual role in sarcopenia, acting as both a biomarker and a potential contributor to muscle atrophy through inflammatory pathways and uremic toxins, while also providing anti-inflammatory benefits that may mitigate disease progression.

The main bacteria implicated in protein metabolism in small intestine include *Escherichia*, *Klebsiella spp*., *Succinivibrio dextrinosolvens*, *Streptococcus spp.*, *Mitsuokella spp.*, *and Anaerovibrio lipolytica*. These bacteria release proteases and peptidases that affect protein metabolism and, ultimately influencing skeletal muscle [26]. Nevertheless, we identified a weak connection between sarcopenia and *Escherichia*. The positive correlation between *Escherichia* and sarcopenia is particularly noteworthy, as certain strains of *Escherichia* are associated with gut inflammation and infection. An increase in *Escherichia* may indicate a transition towards dysbiosis in gut environment, which can compromise gut integrity, promote systemic inflammation, and impair nutrient absorption. Inflammation and malabsorption could directly impact muscle maintenance [27].

The findings of the current study reveal that *Roseburia* is positively correlated with gait speed and inversely related to sarcopenia, suggesting it may have a protective function against muscle degeneration. *Roseburia* is recognized for its production of short-chain fatty acids (SCFAs), particularly butyrate, which have anti-inflammatory and metabolic benefits [28]. Likewise, prior studies have shown a decrease in the prevalence of butyrate-producing genera in individuals with sarcopenia [10]. These genera, which include *Lachnospira*, *Roseburia*, and *Eubacterium*, all have the potential to produce SCFAs, which include butyrate, a crucial chemical by which microbiota impact host physiology [29]. Indeed, in our study the risk of developing sarcopenia dropped by around 11.5% for every unit rise in *Roseburia* levels. In the current study *Roseburia* was inversely associated with low hand grip strength, and also *Roseburia* correlated significantly with physical performance or gait speed. These findings imply that there might be a relationship between the progression of sarcopenia and the loss of these butyrate-producing bacteria. An important microbial source of SCFAs such as butyrate is *Roseburia* [29]. *Roseburia* previously has been associated with an increased SMI [30], and was shown to be less abundant in individuals with sarcopenia [10]. Additionally, prior research on humans and animals has demonstrated the anti-inflammatory qualities of *Roseburia* [31], and it might have a role in the metabolism of skeletal muscle.

There is mounting evidence that both SCFAs and SCFA-producing bacteria are beneficial for the health of skeletal muscles. For instance, mice that were germ-free and were supplied with a combination of SCFAs (acetate, propionate, and butyrate) exhibited an increase in muscle mass when compared with mice that were fed a control diet [32]. Consistent with our findings, certain gut bacteria associated with SCFA production significantly affect sarcopenia; for example, a research revealed that *Alloprevotella* exhibited reduced abundance in sarcopenic patients compared to healthy controls [33].

Skeletal muscle metabolism and function are sensitive to alterations in the gut microbiota; this relationship seems to be partially mediated by the production of SCFAs. Importantly, SCFAs are gut microbiota compounds through the fermentation of undigested carbohydrates and dietary fiber [34]; And they are believed to reduce inflammation and support the preservation of skeletal muscle mass and function [32]. Research have shown that taking SCFAs supplements improves exercise capacity or strength [32]. SCFAs have been demonstrated to affect the metabolism and function of skeletal muscle, through regulating the metabolism of carbohydrates, lipids, and proteins in skeletal muscle tissues in both in vitro and in vivo [8].

Chronic low-grade inflammation is a primary pathological mechanism behind sarcopenia, characterized by decreased muscle mass [4]. According to reports, butyrate, one of the most important SCFAs, has the potential to provide a beneficial outcome by anti-inflammatory properties through downregulation of NF-κB and STAT2 activity [28]. Simultaneously, SCFAs mitigate systemic inflammation by binding to G-protein receptors on cell surfaces and increase myocardial energy metabolism, so serving a cardioprotective function [35]. Although, a research found no significant variation in fecal SCFAs between sarcopenic and non-sarcopenic groups [34], positive relationships have been discovered between SCFA levels and SCFA-producing bacteria [36], and an elevated abundance of *Verrucomicrobia* was seen in mice consuming a diet enriched with butyrate and SCFAs, therefore reinforcing the metabolic significance of SCFAs in muscle health [37].

Sarcopenia is an age-related condition, and the present study found a substantial association between age and sarcopenia, our findings further indicated that aging is significantly correlated with lower hand grip strength and gait speed. Although overall microbiome processes are modified in both aging and sarcopenia, the differing results indicate that some enriched or decreased taxa may be specific to each different process. Microbial diversity typically diminishes with age [38], but this drop is particularly significant in sarcopenic individuals [10]. Age-related changes in the gut microbiota might promote systemic immune-mediated chronic inflammation and hinder nutrient absorption, ultimately affecting muscle protein synthesis and, subsequently, skeletal muscle [4, 38]. These findings indicate that the aging process may affect microbiota and impair gut-muscle axis balance. Moreover, research has demonstrated a significant relationship between frailty, sarcopenia, and decreased microbial diversity; And lower microbial diversity is associated with elevated frailty scores. The decline in microbial diversity is influenced by a variety of factors, including increased medication use, dietary alterations, hospitalization, chronic diseases, and low-grade inflammation [39]. These factors also correlate with risk factors for sarcopenia, such as chronic illness, malnutrition, and sedentary lifestyles sarcopenia [5].

A comprehensive population-based investigation revealed a strong association between gut microbiota and skeletal muscle mass in middle-aged males. The study indicated that, decreased gut microbial diversity was independently associated with a diminished SMI despite adjusting for age, sex, BMI, and physical activity [30]. And another research also detected alterations in gut microbiota composition in older persons exhibiting physical frailty and sarcopenia [33].

From a clinical perspective, the models predicting sarcopenia and, in particular, low skeletal muscle mass showed good discriminative ability, with relatively high AUCs and balanced sensitivity and specificity, suggesting that gut microbiota profiles may help identify individuals at risk of sarcopenia-related muscle loss. Although, the models for low handgrip strength and low gait speed showed lower sensitivity (35% and 43%, respectively), despite high specificity. This pattern indicates a substantial proportion of false negatives, therefore, while this model is effective as a screening tool to rule out healthy individuals, it should be used with caution as a standalone diagnostic test due to the risk of missing actual positive cases.

Strengths and limitation

Our findings should be acknowledged as early evidence indicating a function for the microbiome in sarcopenia. Investigating the gut microbiota composition in people with sarcopenia may enhance our comprehension of its association with this illness and facilitate the development of diagnostic tools derived from gut microbiota studies for early identification and intervention. This strategy might improve overall health outcomes and result in more specialized therapies for sarcopenia patients across different groups. Nevertheless, this study has several limitations. First, it was conducted in Birjand, Iran, where gut microbiota composition may differ from other populations due to cultural, dietary, and geographic factors; therefore, caution is needed when generalizing these findings. Second, we quantified only 12 preselected bacterial genera using targeted real-time qPCR with specific primer sets rather than sequencing-based approaches, which prevented us from characterizing the full taxonomic diversity or functional capacity of the gut microbiota and from computing standard alpha- and beta-diversity indices. Although the targeted qPCR method provides high sensitivity and precise quantification of key bacterial groups, it cannot capture broader community or functional profiles. Third, the lack of an independent replication cohort and preclinical validation, together with the cross-sectional design, means that we cannot determine whether the observed microbiota differences are a cause or a consequence of sarcopenia. Fourth, despite adjustment for several demographic and dietary factors, residual confounding is possible because we did not have information on all medication, comorbidities, stool moisture or consistency, or gastrointestinal transit time. Physical activity and exercise characteristics may also have been imperfectly captured, and future studies should consider objective measures such as accelerometers. In addition, dietary intake was assessed using a food frequency questionnaire, which is prone to recall and social desirability bias, and skeletal muscle mass was estimated using BIA, which, although practical in large studies, is not the gold standard compared with DXA or MRI. Future research should incorporate longitudinal studies to establish the causal link between gut microbiota, their metabolites, and sarcopenia development. Advanced techniques such as shotgun metagenomics or whole-genome sequencing are needed to explore microbiome functional changes related to aging and muscle loss. Additionally, larger studies with participants from diverse geographical and cultural backgrounds will enhance the generalizability of findings.

Conclusion

This study offers a novel, early insight into specific microbial signatures associated with sarcopenia in Iranian older adults. Notably, elevated levels of *Akkermansia*, might be associated to an increased risk of sarcopenia and its components. *Lactobacillus* also was associated with sarcopenia, while higher *Roseburia* levels appeared protective. It seems that targeting the gut microbiota may present a unique diagnostic and therapeutic strategy for preventing or mitigating muscle loss in aging populations. Further research is essential to uncover causal links and ascertain whether probiotic supplementation may offer protection against sarcopenia and physical frailty.

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Author contributions HSE, MK and GS Came with the idea of this study and MHN, and ES designed the study. FS did the search strategy and MM and MK participated in the data gathering. FR, FS, RH, and FEM analyzed the data. FR, SN, MST and FSH drafted the main manuscript, and HSE, GS and FR revised the main manuscript. All of the authors read and approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval This study was approved by the Research Ethical Committee of Endocrinology Metabolism Research Institute of Tehran University of Medical Sciences (code: IR.TUMS.EMRI.REC.1399.071).

Statement of human and animal rights All procedures involving human participants in this study were carried out in compliance with the ethical requirements of the Institutional Review Boards of the participating institutions, as well as the 1964 Helsinki Declaration and its later revisions or comparable ethical standards.

Informed consent Written informed consent was obtained from all participants prior to participation.

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