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Review

Disease-Associated and Shared Gut Microbes of Sarcopenia and Osteoporosis: A Systematic Review and Meta-Analys

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ABSTRACT: Age-related declines in muscle and bone mass increase the risk of sarcopenia and osteoporosis. Both conditions contribute to morbidity and mortality in older adults and frequently coexist as osteosarcopenia. Gut microbiota play a crucial role in maintaining muscle and bone homeostasis, and dysbiosis may accelerate the onset and progression of these conditions. We therefore performed a systematic review and meta-analysis of observational studies published up to May 6, 2025. We identified 45 eligible studies including 6,751 participants. Patients with sarcopenia showed significant reductions in α-diversity indices compared with controls, including Chao1 (SMD=-0.28, 95% CI=-0.44, -0.11), observed species (SMD=-0.52, 95% CI=-0.79, -0.25), and ACE (SMD=-0.24, 95% CI=-0.48, -0.01), whereas patients with osteoporosis exhibited no significant differences. Distinct clustering of β-diversity was observed in twelve of eighteen sarcopenia studies (66.7%) and twelve of twenty-one osteoporosis studies (57.1%). This suggests that microbial community structures are altered in both conditions. Moreover, sarcopenia and osteoporosis shared consistent microbial alterations, with enrichment of the genus *Eggerthella* and depletion of the family Lachnospiraceae and the genus *Blautia*. A qualitative summary of functional pathway analyses suggests potential enrichment of purine, pyrimidine, cysteine and methionine metabolism, implying common metabolic disruptions. These findings highlight overlapping microbial signatures in sarcopenia and osteoporosis and support a role for gut dysbiosis in musculoskeletal decline. They also provide mechanistic clues that may help guide future preventive and therapeutic strategies for osteosarcopenia.

Keywords: sarcopenia; osteoporosis; gut microbiota; meta-analysis

INTRODUCTION

Muscle and bone mass progressively decline with aging, increasing the risk of sarcopenia (SP) and osteoporosis (OP) in later life [1]. SP is a multifactorial skeletal muscle disorder characterized by a gradual, generalized decline in muscle mass and function [2]. OP, the most prevalent metabolic bone disorder among the elderly, involves a

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reduction in bone mass and deterioration of bone microarchitecture [3]. Both of these conditions are associated with increased morbidity and mortality [4]. Previous studies have highlighted a mechanistic correlation between muscle and bone, with patients affected by SP being at a higher risk of developing OP, and vice versa [5, 6]. This results in a more severe co-morbid condition known as osteosarcopenia, which affects an estimated 5% to 37% of community-dwelling older adults [7]. However, the biological underpinnings of these diseases, particularly the mechanisms they share, remain poorly understood, hindering the development of effective therapeutic strategies for SP, OP, and osteosarcopenia.

Gut microbiota constitutes a complex community that interacts both internally and with the host to modulate biological processes essential for health.[8]. Micronutrients and metabolites produced by the gut microbiota have been shown to influence both muscle and bone [9, 10]. Previous studies have separately characterized the gut microbiota in SP and OP, suggesting its potential role in the onset and progression of these diseases [11, 12]. However, the findings of these studies vary significantly, making it difficult to fully understand the relationship between gut microbiota alterations and SP or OP. Moreover, shared microbial features between the two conditions have not been clearly identified. Clarifying these overlapping microbial signatures may help guide more targeted interventions to prevent or treat osteosarcopenia.

Combining meta-analysis with systematic review enables researchers to identify consistent findings across studies while minimizing false positives and negatives that may obscure true biological patterns. Therefore, in this study, we synthesized the evidence on the gut microbiota and associated metabolic pathways in SP and OP. These findings could serve as potential targets for the development of advanced treatment strategies for patients with these conditions.

METHODS

Protocol

This review was registered in PROSPERO (CRD420 22320590), and it was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Search details

A comprehensive search of PubMed, Embase, and the Cochrane Library was independently performed by two reviewers (C.L. and H.W.). The search covered all records from database inception to May 6, 2025. The detailed search strategy is provided in Supplementary Appendix 1. No language or publication restrictions were applied, and non-English studies were translated into English for inclusion.

Selection criteria

Study selection was independently conducted by two reviewers (C.L. and H.W.). Titles and abstracts were first screened, followed by a full-text review of studies meeting the initial criteria. Discrepancies were resolved through discussion with a third investigator (J.Z.). Studies were included if they met the following criteria: (1) used a case-control, cross-sectional, or cohort design; (2) analyzed gut microbiota and reported indices of diversity or abundance; and (3) involved participants diagnosed with SP or OP.

Data extraction

Data extraction was performed independently by two authors (J.Z. and W.R.) using a standardized form and all entries were cross-verified. Extracted data included community-level indices of gut microbiota composition (α-diversity and β-diversity), taxonomic results across phylum, family, genus and species levels (relative abundance), and predicted metabolic pathways based on the Kyoto Encyclopedia of Genes and Genomes (KEGG). α-diversity summarizes microbial richness and evenness within individual samples and allows comparisons between groups. β-diversity reflects differences in community structure and phylogenetic composition between samples. Additional data such as publication characteristics, participant demographics, and methodological details were also collected. When bone mineral density was reported at multiple skeletal sites (e.g., femoral neck and spine), values from the femoral neck were prioritized for analysis due to its stronger predictive value for fracture risk [14].

Quality assessment

The methodological quality of all included studies was independently evaluated by two reviewers (C.L. and H.W.) using the Newcastle-Ottawa Scale (NOS). Any discrepancies in scoring were resolved through discussion and consensus. The NOS assesses the quality of observational research based on three domains, including selection, comparability and outcome [15]. It is a well-established tool recommended by the Cochrane Collaboration for assessing study quality and risk of bias in systematic reviews and meta-analyses. A study was considered low quality with a score of ≤5 points on the

NOS, moderate quality with a score of 6-7 points, and high quality with a score of ≥8 points [16].

Quantitative synthesis

Meta-analysis was conducted to evaluate differences in α-diversity indices, including Chao1, observed species, abundance coverage estimator (ACE), Shannon, and Simpson, between SP or OP groups and their respective controls [17]. For each index, pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using a random-effects model. When studies reported medians and interquartile ranges, these values were converted to means and standard deviations [18]. Numerical data presented only in graphical form were digitized using WebPlotDigitizer (version 4.42). Between-study heterogeneity was quantified using the DerSimonian-Laird method and summarized with the I^2 statistic. Heterogeneity was considered substantial when I^2 exceeded 50% [15]. Funnel plots and Egger's regression test were applied to assess potential publication bias. Sensitivity analyses were additionally conducted by excluding studies with low methodological quality. Subgroup analyses were performed by region, population age, sequencing type and additionally by diagnostic criteria in studies evaluating SP. All statistical analyses were performed in Review Manager version 5.2 (RevMan 5.2, The Cochrane Collaboration, Oxford, UK), with $P<0.05$ considered statistically significant.

Qualitative synthesis

To determine disease-specific and shared microbial and metabolic pathway alterations, we first synthesized within-disease findings for microbes that were reported in at least two independent studies [17]. Taxonomic results were compiled across the phylum, family, and genus levels. Microbes were then classified according to the following criteria [17]: (1) categorized as increased, decreased, or "inconsistent" relative to control groups; (2) results with <75% agreement across studies were defined as "inconsistent"; (3) findings replicated in three or more studies were considered disease-associated, while those confirmed by two studies were noted for further validation; (4) microbes showing consistent directional changes were regarded as candidates for disease-related alterations; and (5) alterations replicated in both SP and OP were defined as shared features. For genera consistently identified as disease-associated, species-level information was further explored where available. A similar classification approach was applied for functional analyses, focusing on KEGG level 3 pathways.

Table 1. Characteristics of the included studies.

Disorder	Study	Country	Controls	Cases	Mean age	Female ratio (%)	Sequencing	Diagnostic criteria
SP	Aliwa 2023	Austria	38	78	P: 64.0 C: 62.0	P: 17.9 C: 42.1	16S rDNA V1-2	EWGSOP
	Efremova 2024	Russia	22	18	51.0	55.0	16S rRNA V3-4	SMI <50 cm^2/m^2 in males and <39 cm^2/m^2 in females
	He 2023	China	31	32	P: 75.2 C: 68.8	P: 75.0 C: 61.3	Metagenomics	AWGS 2019
	Kang 2021	China	60	27	P: 76.5 C: 68.4	P: 63.6 C: 55.0	16S rRNA V3-V4	AWGS 2019
	Lee 2022	Korea	33	27	P: 66.5 C: 64.8	P: 81.5 C: 69.7	16S rRNA V3-V4	AWGS 2019
	Liu 2023	China	142	141	P: 69.1 C: 64.1	P: 63.8 C: 73.9	Metagenomics	AWGS 2014
	Liu 2024	China	23	28	P: 71.0 C: 69.0	P: 25.0 C: 73.9	16S rDNA V3-4	AWGS 2019
	Lou 2024	China	98	108	P: 72.5 C: 71.6	P: 38.89 C: 37.76	16S rRNA V3-4	AWGS 2019
	Margiotta 2021	Italy	45	18	P: 83.1 C: 79.7	P: 11.1 C: 37.8	16S rRNA V3-V4	EWGSOP 2
	Peng 2023	China	33	29	P: 75.1 C: 71.8	P: 55.2 C: 17.3	16S rRNA V3-V4	SMI <7.26 kg/m^2 in males and <5.45 kg/m^2 in females
	Picca 2019	Italy	17	18	P: 75.5 C: 73.9	P: 55.6 C: 29.4	16S rRNA V3-V4	FNIH criteria
	Ponziani 2021	Rome	67	33	P: 72.3 C: 69.5	P: 39.4 C: 34.3	16S rRNA V3-V4	FNIH criteria
	Shan 2024	China	40	40	P: 76.5 C: 74.2	P: 37.5 C: 37.5	16S rDNA V3-4	AWGS 2019
	Ticinesi 2020	Italy	12	5	P: 77.0 C: 71.5	P: 80.0 C: 83.3	Metagenomics	EWGSOP
	Wang 2022a	China	1,276	141	P: 72.2 C: 62.3	P: 48.2 C: 60.1	Metagenomics	AWGS 2019

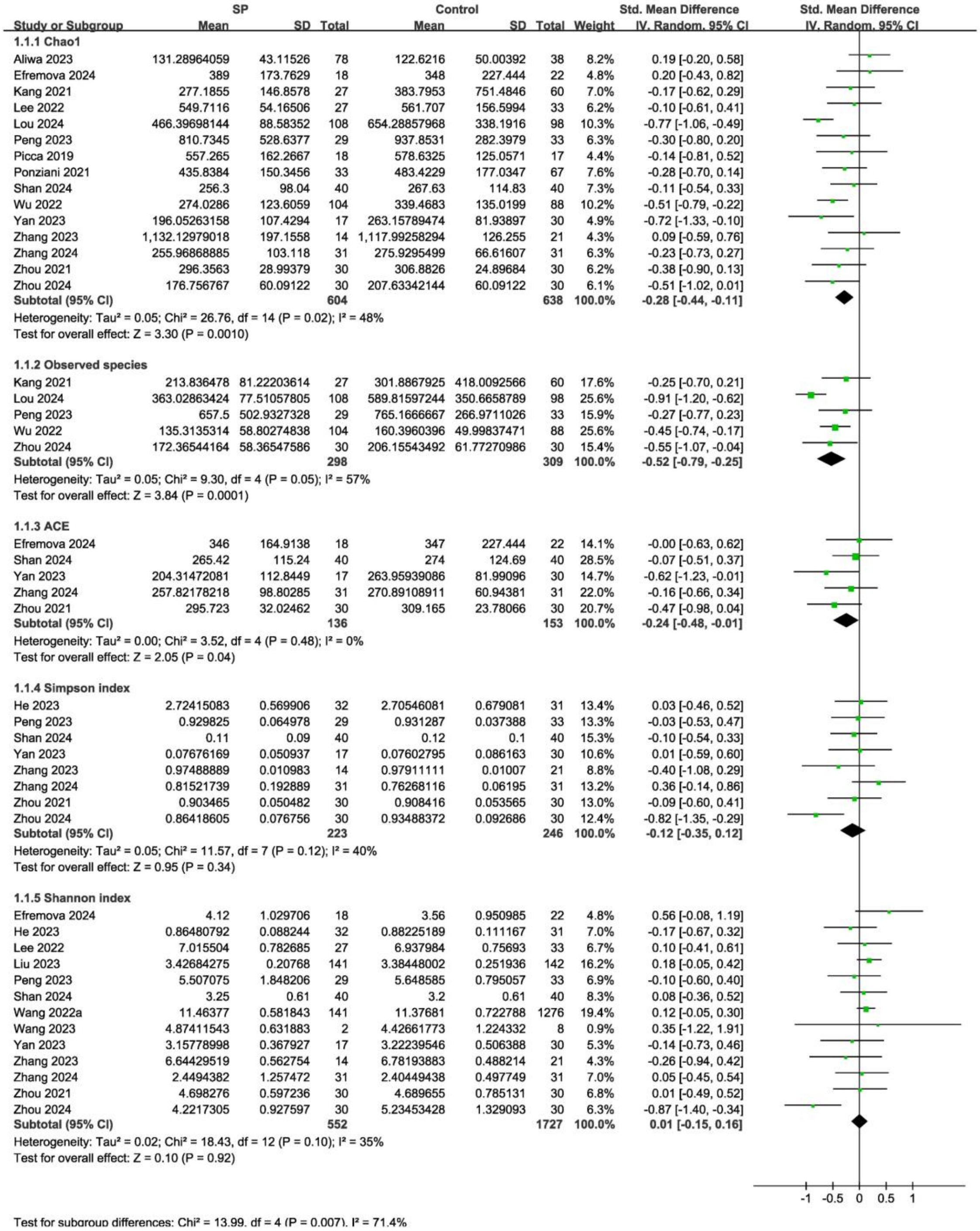
	Wang 2023	China	8	2	43.50	49.1	16S rRNA V1-9	AWGS 2019
	Wu 2022	China	88	104	P: 77.0 C: 70.0	P: 53.0 C: 52.0	16S rRNA V3-V4	EWGSOP 2
	Yan 2024	China	30	17	P: 75.26 C: 70.26	P: 100.0 C: 100.0	16S rRNA V3-4	AWGS 2019
	Zhang 2023	China	21	14	P: 71.21 C: 71.00	P: 50.0 C: 85.7	16S rRNA V3-4	AWGS 2019
	Zhang 2024	China	31	31	P: 55.39 C: 49.81	P: 51.61 C: 51.61	16S rRNA V3-4	AWGS 2019
	Zhou 2021	China	30	30	P: 49.9 C: 45.9	P: 43.3 C: 43.3	16S rRNA V3-V4	AWGS 2019
	Zhou 2024	China	30	30	P: 91.0 C: 71.0	P: 40.0 C: 30.0	16S rDNA V3-4	AWGS 2019
OP	Chen 2020	China	5	10	P: 88.5 C: 90.1	NA	16S rRNA V3-V4	T-scores ≤−2.5
	Das 2019	Ireland	60	60	P: 65.1 C: 63.6	P: 81.7 C: 78.3	16S rRNA V3-V4	T-scores ≤−2.5
	Di 2021	China	172	228	P: 67.4 C: 66.4	P: 100.0 C: 100.0	16S rRNA V3-4	T-scores ≤−2.5
	Gao 2024	China	241	94	P: 60.4 C: 59.8	P: 90.4 C: 32.8	Metagenomics	T-scores ≤−2.5
	He 2020	China	31	42	P: 59.7 C: 57.4	P: 100.0 C: 100.0	16S rRNA	T-scores ≤−2.5
	Huang 2023	China	34	58	P: 59.1 C: 56.9	P: 100.0 C: 100.0	16S rRNA V3-V4	T-scores ≤−2.5
	Ji 2024	China	483	266	P: 61.7 C: 57.8	P: 100.0 C: 100.0	16S rRNA V3-4	T-scores ≤−2.5
	Kuo 2023	America	8	21	P: 53.5 C: 56.0	P: 100.0 C: 100.0	16S rRNA V3-V4	T-scores ≤−2.5
	Lai 2024	China	64	44	Total: 20.2	P: 61.29 C: 62.50	16S rRNA V3-4	T-scores ≤−2.5
	Liang 2023	China	48	48	P: 68.2 C: 65.0	P: 100.0 C: 100.0	16S rRNA V3-4	T-scores ≤−2.5
	Ling 2021	China	483	266	P: 64.5 C: 64.6	P: 88.3 C: 55.8	16S rRNA V3-4	T-scores ≤−2.5
	Lyu 2021	China	9	24	P: 61.0 C: 55. 3	P: 100.0 C: 100.0	16S rRNA V3-V4	T-scores ≤−2.5
	Rettedal 2021	New Zealand	26	18	P: 64.6 C: 62.5	P: 100.0 C: 100.0	Metagenomics	T-scores ≤−2.5
	Sun 2024	China	24	43	P: 66.93 C: 64.04	P: 100.0 C: 100.0	16S rDNA V3-4	T-scores ≤−2.5
	Ul-Haq 2022	Korea	60	31	P: 66.3 C: 59.1	NA	16S rRNA V4	T-scores ≤−2.5
	Wang 2017	China	23	27	P: 70.0 C: 64.8	P: 83.3 C: 83.3	16S rRNA V3-V4	T-scores ≤−2.5
	Wang 2021	China	8	31	NA	P: 100.0 C: 100.0	Metagenomics	T-scores ≤−2.5
	Wang 2022b	China	16	49	P: 61.0 C: 58.6	P: 100.0 C: 100.0	16S rRNA V4	T-scores ≤−2.5
	Wang 2024	China	58	40	P: 59.69 C: 57.35	P: 100.0 C: 100.0	16S rRNA V3-4	T-scores ≤−2.5
	Wei 2021	China	64	44	P: 69.7 C: 67.8	P: 79.5 C: 50.0	16S rRNA V3-V4	T-scores ≤−2.5
	Xu 2020	China	48	48	P: 57.5 C: 60.2	P: 60.4 C: 62.5	16S rRNA V3-V4	T-scores ≤−2.5
	Yan 2023	China	38	25	P: 75.3 C: 70.3	P: 100.0 C: 100.0	16S rRNA V3-V4	T-scores ≤−2.5
	Yang 2022	China	51	34	P: 57.5 C: 56.0	P: 100.0 C: 100.0	16S rRNA V3-V4	T-scores ≤−2.5

AWGS, Asian Working Group for Sarcopenia; C, control group; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health Sarcopenia Project; NA, not available; P, patient group; SMI, skeletal muscle index; SP, sarcopenia; OP, osteoporosis.

RESULTS

Characteristics of included studies

We initially identified 5,364 records. Of these, 45 studies involving a total of 6,751 participants met the inclusion criteria and were included in the analysis (Supplementary Fig. 1). Among them, 22 studies with 3,146 participants compared gut microbiota profiles between patients with SP and controls, while 23 with 3,605 participants examined differences between participants with and without OP. A detailed summary of study characteristics is presented in Table 1. The majority of studies (33, 73.3%) employed 16S rRNA sequencing, whereas 7 (15.6%) used shotgun metagenomics and 5 (11.1%) adopted 16S rDNA sequencing. Details of stool sample processing are provided in Supplementary Table 1. Methodological quality, assessed by the NOS, ranged from 4 to 7 (Supplementary Table 2). No study was excluded because of inadequate quality.



	SP			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.1.1 Chao1								
Aliwa 2023	131.28964059	43.11526	78	122.6216	50.00392	38	8.2%	0.19 [-0.20, 0.58]
Efremova 2024	389	173.7629	18	348	227.444	22	4.8%	0.20 [-0.43, 0.82]
Kang 2021	277.1855	146.8578	27	383.7953	751.4846	60	7.0%	-0.17 [-0.62, 0.29]
Lee 2022	549.7116	54.16506	27	561.707	156.5994	33	6.2%	-0.10 [-0.61, 0.41]
Lou 2024	466.39698144	88.58352	108	654.28857968	338.1916	98	10.3%	-0.77 [-1.06, -0.49]
Peng 2023	810.7345	528.6377	29	937.8531	282.3979	33	6.3%	-0.30 [-0.80, 0.20]
Picca 2019	557.265	162.2667	18	578.6325	125.0571	17	4.4%	-0.14 [-0.81, 0.52]
Ponziani 2021	435.8384	150.3456	33	483.4229	177.0347	67	7.6%	-0.28 [-0.70, 0.14]
Shan 2024	256.3	98.04	40	267.63	114.83	40	7.3%	-0.11 [-0.54, 0.33]
Wu 2022	274.0286	123.6059	104	339.4683	135.0199	88	10.2%	-0.51 [-0.79, -0.22]
Yan 2023	196.05263158	107.4294	17	263.15789474	81.93897	30	4.9%	-0.72 [-1.33, -0.10]
Zhang 2023	1,132.12979018	197.1558	14	1,117.99258294	126.255	21	4.3%	0.09 [-0.59, 0.76]
Zhang 2024	255.96868885	103.118	31	275.9295499	66.61607	31	6.3%	-0.23 [-0.73, 0.27]
Zhou 2021	296.3563	28.99379	30	306.8826	24.89684	30	6.2%	-0.38 [-0.90, 0.13]
Zhou 2024	176.756767	60.09122	30	207.63342144	60.09122	30	6.1%	-0.51 [-1.02, 0.01]
Subtotal (95% CI)			**604**			**638**	**100.0%**	**-0.28 [-0.44, -0.11]**
Heterogeneity: Tau² = 0.05; Chi² = 26.76, df = 14 (P = 0.02); I² = 48%								
Test for overall effect: Z = 3.30 (P = 0.0010)								
1.1.2 Observed species								
Kang 2021	213.836478	81.22203614	27	301.8867925	418.0092566	60	17.6%	-0.25 [-0.70, 0.21]
Lou 2024	363.02863424	77.51057805	108	589.81597244	350.6658789	98	25.6%	-0.91 [-1.20, -0.62]
Peng 2023	657.5	502.9327328	29	765.1666667	266.9711026	33	15.9%	-0.27 [-0.77, 0.23]
Wu 2022	135.3135314	58.80274838	104	160.3960396	49.99837471	88	25.6%	-0.45 [-0.74, -0.17]
Zhou 2024	172.36544164	58.36547586	30	206.15543492	61.77270986	30	15.4%	-0.55 [-1.07, -0.04]
Subtotal (95% CI)			**298**			**309**	**100.0%**	**-0.52 [-0.79, -0.25]**
Heterogeneity: Tau² = 0.05; Chi² = 9.30, df = 4 (P = 0.05); I² = 57%								
Test for overall effect: Z = 3.84 (P = 0.0001)								
1.1.3 ACE								
Efremova 2024	346	164.9138	18	347	227.444	22	14.1%	-0.00 [-0.63, 0.62]
Shan 2024	265.42	115.24	40	274	124.69	40	28.5%	-0.07 [-0.51, 0.37]
Yan 2023	204.31472081	112.8449	17	263.95939086	81.99096	30	14.7%	-0.62 [-1.23, -0.01]
Zhang 2024	257.82178218	98.80285	31	270.89108911	60.94381	31	22.0%	-0.16 [-0.66, 0.34]
Zhou 2021	295.723	32.02462	30	309.165	23.78066	30	20.7%	-0.47 [-0.98, 0.04]
Subtotal (95% CI)			**136**			**153**	**100.0%**	**-0.24 [-0.48, -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 3.52, df = 4 (P = 0.48); I² = 0%								
Test for overall effect: Z = 2.05 (P = 0.04)								
1.1.4 Simpson index								
He 2023	2.72415083	0.569906	32	2.70546081	0.679081	31	13.4%	0.03 [-0.46, 0.52]
Peng 2023	0.929825	0.064978	29	0.931287	0.037388	33	13.3%	-0.03 [-0.53, 0.47]
Shan 2024	0.11	0.09	40	0.12	0.1	40	15.3%	-0.10 [-0.54, 0.33]
Yan 2023	0.07676169	0.050937	17	0.07602795	0.086163	30	10.6%	0.01 [-0.59, 0.60]
Zhang 2023	0.97488889	0.010983	14	0.97911111	0.01007	21	8.8%	-0.40 [-1.08, 0.29]
Zhang 2024	0.81521739	0.192889	31	0.76268116	0.06195	31	13.2%	0.36 [-0.14, 0.86]
Zhou 2021	0.903465	0.050482	30	0.908416	0.053565	30	13.0%	-0.09 [-0.60, 0.41]
Zhou 2024	0.86418605	0.076756	30	0.93488372	0.092686	30	12.4%	-0.82 [-1.35, -0.29]
Subtotal (95% CI)			**223**			**246**	**100.0%**	**-0.12 [-0.35, 0.12]**
Heterogeneity: Tau² = 0.05; Chi² = 11.57, df = 7 (P = 0.12); I² = 40%								
Test for overall effect: Z = 0.95 (P = 0.34)								
1.1.5 Shannon index								
Efremova 2024	4.12	1.029706	18	3.56	0.950985	22	4.8%	0.56 [-0.08, 1.19]
He 2023	0.86480792	0.088244	32	0.88225189	0.111167	31	7.0%	-0.17 [-0.67, 0.32]
Lee 2022	7.015504	0.782685	27	6.937984	0.75693	33	6.7%	0.10 [-0.41, 0.61]
Liu 2023	3.42684275	0.20768	141	3.38448002	0.251936	142	16.2%	0.18 [-0.05, 0.42]
Peng 2023	5.507075	1.848206	29	5.648585	0.795057	33	6.9%	-0.10 [-0.60, 0.40]
Shan 2024	3.25	0.61	40	3.2	0.61	40	8.3%	0.08 [-0.36, 0.52]
Wang 2022a	11.46377	0.581843	141	11.37681	0.722788	1276	19.4%	0.12 [-0.05, 0.30]
Wang 2023	4.87411543	0.631883	2	4.42661773	1.224332	8	0.9%	0.35 [-1.22, 1.91]
Yan 2023	3.15778998	0.367927	17	3.22239546	0.506388	30	5.3%	-0.14 [-0.73, 0.46]
Zhang 2023	6.64429519	0.562754	14	6.78193883	0.488214	21	4.3%	-0.26 [-0.94, 0.42]
Zhang 2024	2.4494382	1.257472	31	2.40449438	0.497749	31	7.0%	0.05 [-0.45, 0.54]
Zhou 2021	4.698276	0.597236	30	4.689655	0.785131	30	6.8%	0.01 [-0.49, 0.52]
Zhou 2024	4.2217305	0.927597	30	5.23453428	1.329093	30	6.3%	-0.87 [-1.40, -0.34]
Subtotal (95% CI)			**552**			**1727**	**100.0%**	**0.01 [-0.15, 0.16]**
Heterogeneity: Tau² = 0.02; Chi² = 18.43, df = 12 (P = 0.10); I² = 35%								
Test for overall effect: Z = 0.10 (P = 0.92)								
Test for subgroup differences: Chi² = 13.99, df = 4 (P = 0.007), I² = 71.4%								

Figure 1. Forest plots of α-diversity estimators in the gut microbiota of SP group compared with the control group. CI, confidence interval; SP, sarcopenia; SD, standard deviation.

α-diversity

Thirty-six studies reported α-diversity data, including 19 that compared patients with SP (n=920) and controls (n=2,095), and 18 that examined OP (n=1,113) versus control groups (n=1,592). Five α-diversity indices were analyzed to assess microbial richness (Chao1, observed species, ACE) and richness/evenness (Simpson, Shannon). Funnel plots assessing publication bias demonstrated a generally symmetrical distribution in the SP analysis, indicating no obvious publication bias. The OP funnel plot displayed clear asymmetry, suggesting potential publication bias (Supplementary Fig. 2).

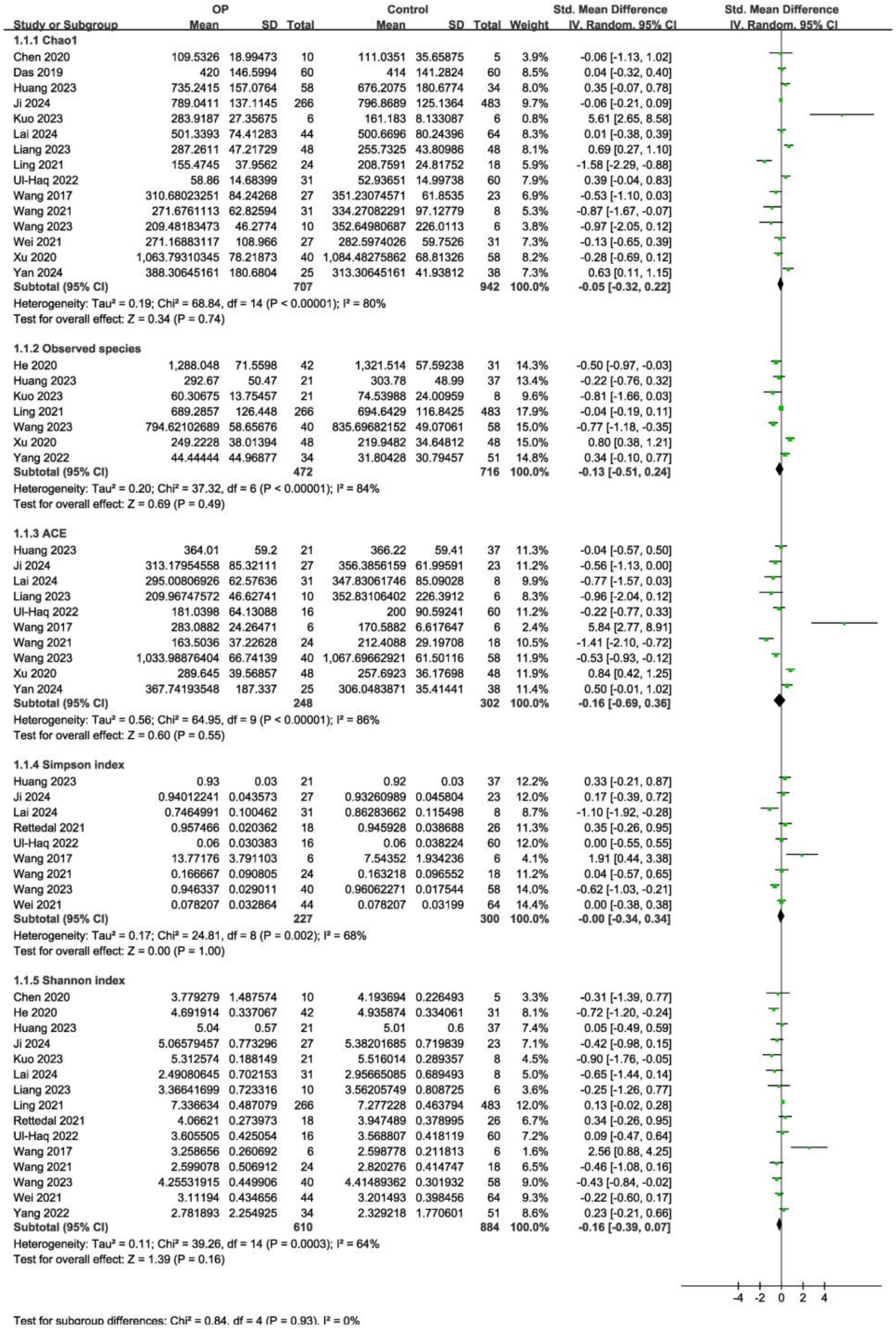


Figure 2. Forest plots of α-diversity estimators in the gut microbiota of OP group compared with the control group. CI, confidence interval; OP, osteoporosis; SD, standard deviation.

In terms of richness, all indices demonstrated a significant reduction in gut microbial richness among patients with SP compared with controls (Chao1: SMD=-0.28, 95% CI=-0.44, -0.11, P=0.001, I^2=48%; observed species: SMD=-0.52, 95% CI=-0.79, -0.25, P<0.001, I^2=57%; ACE: SMD=-0.24, 95% CI=-0.48, -0.01, P=0.04, I^2=0%) (Fig. 1). In contrast, richness-related α-diversity indices did not differ significantly between OP and control participants (Chao1: SMD=-0.05, 95% CI=-0.32, 0.22, P=0.74, I^2=80%; observed species: SMD=-0.13, 95% CI=-0.51, 0.24, P=0.49, I^2=84%; ACE: SMD=-0.16, 95% CI=-0.69, 0.36, P=0.55, I^2=86%) (Fig. 2). Regarding indices reflecting both richness and evenness, no significant differences were found for SP (Simpson: SMD=-0.12, 95% CI=-0.35, 0.12, P=0.34, I^2=40%; Shannon: SMD=0.01, 95% CI=-0.15, 0.16, P=0.92, I^2=35%) or for OP (Simpson: SMD=-0.00, 95% CI=-0.34, 0.34, P=1.00, I^2=68%; Shannon: SMD=-0.16, 95% CI=-0.39, 0.07, P=0.16, I^2=64%). Sensitivity analyses excluding low-quality studies showed similar trends. For SP, Chao1 remained significantly reduced with an SMD of -0.38 (95% CI=-0.58, -0.17), and the Simpson and Shannon indices showed no significant changes. For OP, all indices continued to show non-significant differences (Supplementary Table 3). Subgroup analyses showed that the overall trends were consistent with the main results (Supplementary Table 4 and 5). α-diversity indices, including Chao1, observed species and ACE, were significantly decreased in patients with SP from Eastern countries, with SMDs ranging from -0.52 to -0.28. Stratification by age revealed a notable reduction in Chao1 among individuals aged 60 years and older (SMD=-0.30, 95% CI=-0.49, -0.11). Similarly, studies employing 16S rRNA sequencing or defining SP according to the Asian Working Group for Sarcopenia 2019 diagnostic criteria consistently showed significant decreases in Chao1, observed species and ACE, with SMDs ranging from -0.60 to -0.28. No significant differences were observed in other subgroups. In patients with OP, a significant decrease in the Shannon index was observed in those younger than 60 years (SMD=-0.36, 95% CI=-0.63 to -0.09).

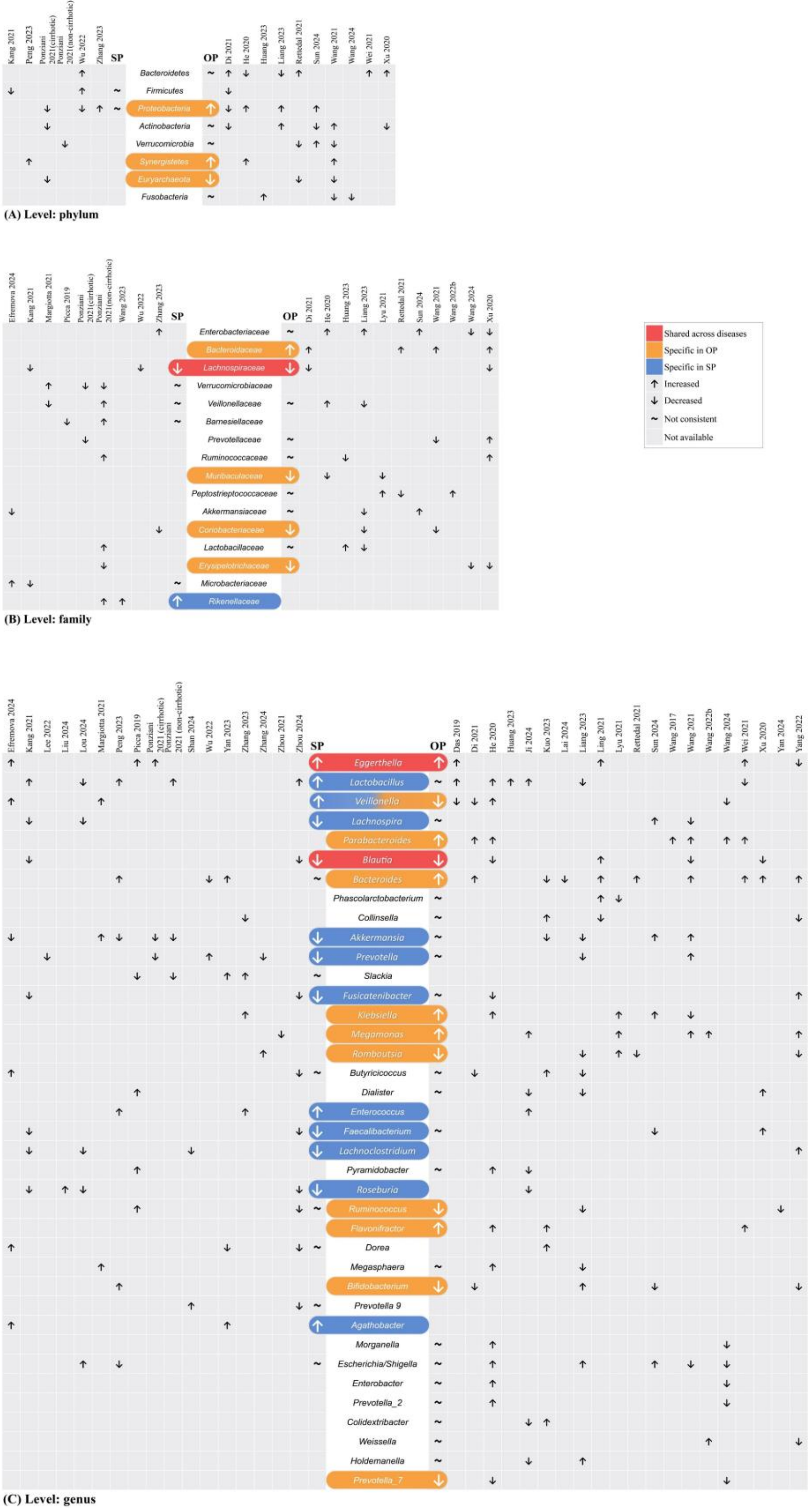
β-diversity

Eighteen studies evaluated β-diversity for the SP and control groups (Supplementary Table 6), while twenty-one studies examined these differences for OP (Supplementary Table 7). Among these studies, twelve of eighteen studies (66.7%) reported significant β-diversity differences in SP, and twelve of twenty-one (57.1%) reported such differences in OP. This suggests altered microbial community composition in both conditions.

Disease-associated and shared microbes and metabolic pathway

Nineteen studies compared the relative abundance of gut microbes between SP and control groups. For SP, differences involved 8 phyla, 30 families, and 80 genera, whereas OP-related differences covered 17 phyla, 35 families, and 103 genera. In SP, enrichment was observed for the family Rikenellaceae and the genera *Eggerthella*, *Lactobacillus*, *Veillonella*, *Enterococcus* and *Agathobacter*, alongside depletion of the family Lachnospiraceae and the genera *Lachnospira*, *Blautia*, *Akkermansia*, *Prevotella*, *Fusicatenibacter*, *Faecalibacterium*, *Lachnoclostridium* and *Roseburia*. Conversely, OP was characterized by enrichment of the phyla Proteobacteria and Synergistetes, the family Bacteroidaceae, and the genera *Eggerthella*, *Parabacteroides*, *Bacteroides*, *Klebsiella*, *Megamonas* and *Flavonifractor*. Depletion was noted for the phylum Euryarchaeota; the families Lachnospiraceae, Muribaculaceae, Coriobacteriaceae and Erysipelotrichaceae; and the genera *Veillonella*, *Blautia*, *Romboutsia*, *Ruminococcus*, *Bifidobacterium* and *Prevotella_7*. As for shared alterations, both SP and OP showed an enrichment of genus *Eggerthella*, while the family Lachnospiraceae and the genus *Blautia* were consistently depleted. Figure 3 and Supplementary Table 8 summarize microbial alterations in SP and OP, categorized by phylum, family and species level, for microbes reported by two or more studies. A network diagram summarizing shared and unique bacterial taxa in SP and OP is provided in Supplementary Figure 3. Detailed study-specific data are provided in Supplementary Figure 4 and Supplementary Figure 5. Further species-level analysis was conducted across all disease-associated genera, and *Bacteroides vulgatus* was identified as significantly increased in patients with OP (Supplementary Table 9).

Functional predictions of gut microbial metabolism were summarized qualitatively from seven studies involving SP and twelve involving OP. In the SP group, five pathways showed potential enrichment, whereas nucleotide metabolism appeared to be relatively decreased. In the OP group, seventeen pathways were predicted to be enriched, while two, glycerolipid metabolism and chloroalkane/chloroalkene degradation, showed possible depletion. Across both conditions, purine, pyrimidine, and cysteine-methionine metabolism pathways were consistently enriched, suggesting shared functional alterations in microbial activity. Figure 4 and Supplementary Table 10 present KEGG-predicted functional pathway alterations in SP and OP for pathways reported by two or more studies. Supplementary Figure **6** illustrates the predicted metabolic pathways in SP and OP through a network diagram.



Kang 2021	Peng 2023	Ponziani 2021(cirrhotic)	Ponziani 2021(non-cirrhotic)	Wu 2022	Zhang 2023	SP		OP	Di 2021	He 2020	Huang 2023	Liang 2023	Rettedal 2021	Sun 2024	Wang 2021	Wang 2024	Wei 2021	Xu 2020
				↑			Bacteroidetes	~	↑	↓		↓	↑				↑	↑
↓				↑		~	Firmicutes		↓									
		↓		↓	↑	~	🟧 Proteobacteria	↑	↓	↑		↑		↑				
		↓					Actinobacteria	~	↓			↑		↓	↑			↓
			↓				Verrucomicrobia	~					↓	↑	↓			
	↑						🟧 Synergistetes	↑		↑					↑			
		↓					🟧 Euryarchaeota	↓					↓		↓			
							Fusobacteria	~			↑				↓	↓		

(A) Level: phylum

Efremova 2024	Kang 2021	Margiotta 2021	Picca 2019	Ponziani 2021(cirrhotic)	Ponziani 2021(non-cirrhotic)	Wang 2023	Wu 2022	Zhang 2023	SP		OP	Di 2021	He 2020	Huang 2023	Liang 2023	Lyu 2021	Rettedal 2021	Sun 2024	Wang 2021	Wang 2022b	Wang 2024	Xu 2020
								↑		Enterobacteriaceae	~		↑		↑			↑			↓	↓
										🟧 Bacteroidaceae	↑	↑					↑		↑			↑
	↓						↓		↓	🟥 Lachnospiraceae	↓	↓										↓
		↑		↓	↓				~	Verrucomicrobiaceae												
		↓			↑				~	Veillonellaceae	~		↑		↓							
			↓		↑				~	Barnesiellaceae												
				↓						Prevotellaceae	~								↓			↑
					↑					Ruminococcaceae	~			↓								↑
										🟧 Muribaculaceae	↓		↓			↓						
										Peptostrieptococcaceae	~					↑	↓			↑		
↓										Akkermansiaceae	~				↓			↑				
								↓		🟧 Coriobacteriaceae	↓				↓				↓			
					↑					Lactobacillaceae	~			↑	↓							
					↓					🟧 Erysipelotrichaceae	↓										↓	↓
↑	↓								~	Microbacteriaceae												
					↑	↑			↑	🟦 Rikenellaceae												

(B) Level: family

Efremova 2024	Kang 2021	Lee 2022	Liu 2024	Lou 2024	Margiotta 2021	Peng 2023	Picca 2019	Ponziani 2021 (cirrhotic)	Ponziani 2021 (non-cirrhotic)	Shan 2024	Wu 2022	Yan 2023	Zhang 2023	Zhang 2024	Zhou 2021	Zhou 2024	SP		OP	Das 2019	Di 2021	He 2020	Huang 2023	Ji 2024	Kuo 2023	Lai 2024	Liang 2023	Ling 2021	Lyu 2021	Rettedal 2021	Sun 2024	Wang 2017	Wang 2021	Wang 2022b	Wang 2024	Wei 2021	Xu 2020	Yan 2024	Yang 2022
↑							↑	↑									↑	🟥 Eggerthella	↑	↑								↑								↑			↓
	↑			↓		↑			↑							↑	↑	🟦 Lactobacillus	~	↑		↑	↑	↑			↓									↓			
↑					↑												↑	🟦🟧 Veillonella	↓	↓	↓	↑													↓				
	↓			↓													↓	🟦 Lachnospira	~												↑		↓						
																		🟧 Parabacteroides	↑		↑	↑										↑	↑		↑	↑			
	↓															↓	↓	🟥 Blautia	↓			↓						↑					↓				↓		
						↑					↓	↑					~	🟧 Bacteroides	↑		↑				↓	↓		↑		↑			↑			↑	↑		↑
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	↓			↓						↓							↓	🟦 Lachnoclostridium																					↑
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																		Enterobacter	~			↑													↓				
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																		Colidextribacter	~					↓	↑														
																		Weissella	~															↑					↓
																		Holdemanella	~					↓			↑												
																		🟧 Prevotella_7	↓			↓													↓				

(C) Level: genus

🟥 Shared across diseases
🟧 Specific in OP
🟦 Specific in SP
↑ Increased
↓ Decreased
~ Not consistent
⬜ Not available

Figure 3. Changes of microbes were reported by at least two studies. OP, osteoporosis; SP, sarcopenia.

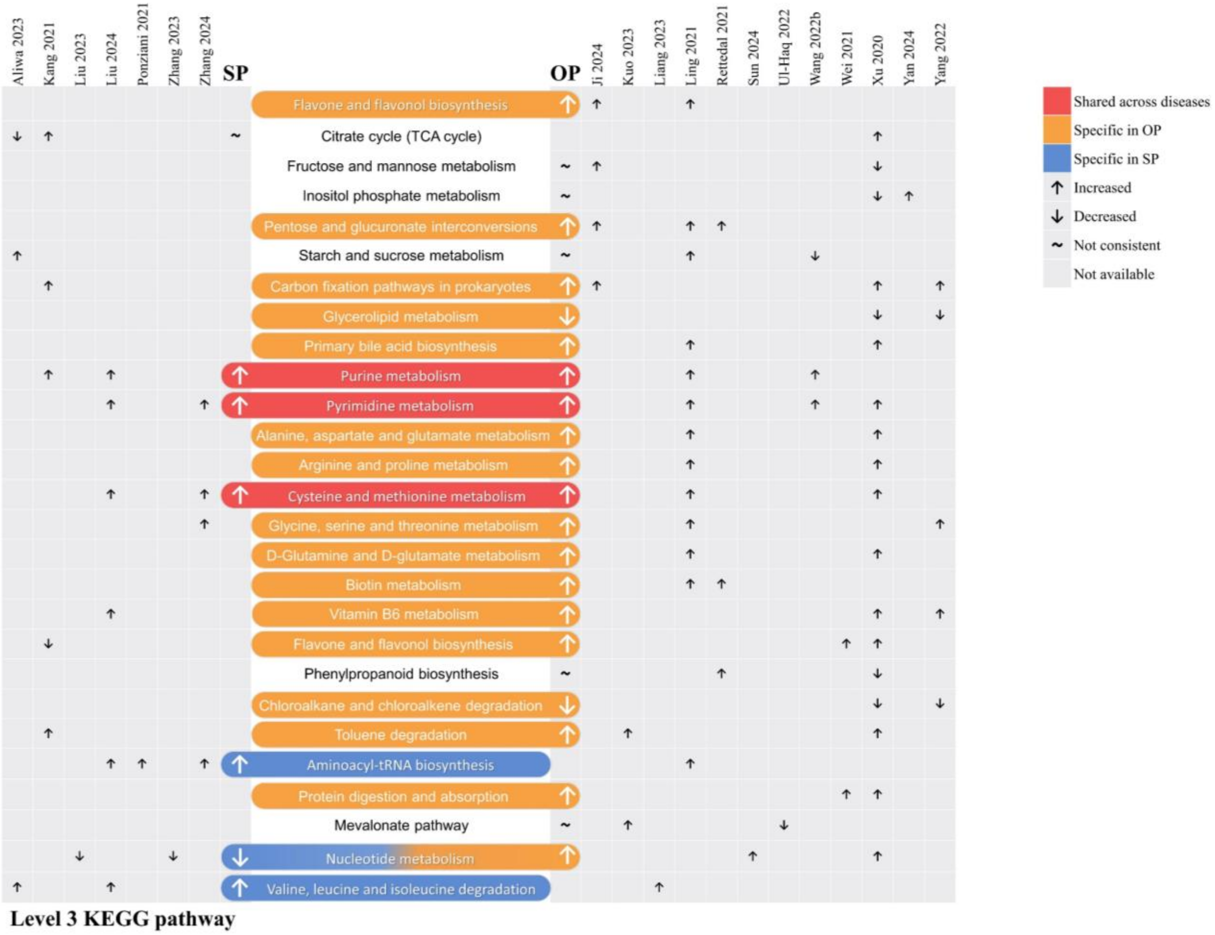

Figure 4. Changes of metabolic pathway were reported by at least two studies. KEGG, Kyoto Encyclopedia of Genes and Genomes; OP, osteoporosis; SP, sarcopenia; TCA, tricarboxylic acid; tRNA, transfer ribonucleic acid.

DISCUSSION

This study assessed gut microbiota changes in SP and OP through a systematic review and meta-analysis. α-diversity indices showed a significant decrease of gut microbiome richness in SP, but not in OP. Although β-diversity comparisons were not entirely consistent, significant differences were observed in more than half of the studies on SP and OP. Both conditions exhibit similar changes in gut microbiota, such as the increase in *Eggerthella* and the decrease in Lachnospiraceae and *Blautia*. A qualitative summary of functional pathway analyses suggests potential enrichment of purine, pyrimidine, and cysteine and methionine metabolism in both conditions, implying common metabolic disruptions. These findings provide valuable insights into the gut microbiota changes associated with these conditions.

Comparison with previous studies

A previous systematic review and meta-analysis examined the relationship between the gut microbiota and OP using 16S rRNA sequencing [19]. It found no significant differences in Chao1 and Shannon indices between patients with OP and healthy controls. The study observed that the genus *Bacteroides* was significantly increased in the OP group, whereas *Turicibacter* and *Collinsella* were more abundant in healthy controls. Another systematic review has examined gut microbiota in relation to muscle phenotypes, including muscle mass and function [20]. This review highlighted that gut microbiota dysbiosis is related to lower muscle mass and poor physical function. It also reported that improvements in function after exercise are linked to changes in the gut microbiome. However, this review did not assess the consistency of reported gut microbiome changes across studies. In our study, we included 45 observational studies spanning SP and OP. By including a broader range of studies, we conducted a qualitative evaluation of the association between gut microbiota and both conditions. Furthermore, by comparing gut microbiota profiles between SP and OP, we identified shared microbial signatures and related metabolic pathways that may underlie their coexistence.

Possible explanations

Analyses of α-diversity showed that gut microbial diversity was reduced in SP, whereas no overall differences were observed in OP. To explore potential sources of variation across studies, we further conducted subgroup analyses. For SP, the significant reductions in Chao1 did not remain statistically significant in several subgroups, including Western populations, participants aged <60 or ≥60 years, studies using 16S rDNA sequencing, and those applying the Foundation for the National Institutes of Health Sarcopenia criteria or skeletal muscle index. The decrease in observed species did not reach statistical significance in studies using 16S rRNA sequencing. In general, although the trend in within-study diversity was consistently downward, each subgroup included only two to four studies, which likely limited statistical power. For OP, the age-stratified analysis showed a significant reduction in the Shannon index among participants younger than 60 years. This suggests that age may be an important source of variation in OP-related microbiota findings. Gut microbial diversity often increases with age, and can also change with illness or medication use [21]. Older people usually have more health problems and take more drugs than younger people [22], which can further modify the microbiota. Future studies should consider these factors when exploring how the microbiota affects disease.

The shared gut microbiota changes across SP and OP identified in this study may provide insights into the pathogenesis of both diseases and their comorbid condition. Lachnospiraceae, a key butyrate-producing family in the human gut, plays a key role in preserving intestinal barrier integrity and maintaining immune equilibrium [23]. Reduced Lachnospiraceae abundance can compromise gut permeability, trigger systemic inflammation, and decrease short-chain fatty acid synthesis. These changes may ultimately contribute to muscle and bone deterioration [24]. Likewise, the genus *Blautia* may exert beneficial effects through its anti-inflammatory roles and metabolic regulation [25]. Its consistent depletion in both SP and OP further supports a potential link between reduced *Blautia* abundance and impaired musculoskeletal health. Conversely, the genus *Eggerthella* may promote systemic inflammatory responses [26]. Increased *Eggerthella* abundance has also been associated with reduced intestinal vitamin D receptor expression, potentially impairing bone formation and promoting muscle wasting [27]. To refine our understanding of microbial contributions to pathogenesis, we further examined species-level alterations. In this study, *Bacteroides vulgatus* was identified as significantly enriched in OP. This finding suggests a potential pathogenic role in bone metabolism. Previous studies have shown that *Bacteroides vulgatus* reduces gut-derived valeric acid production, increases inflammation, and disrupts bone remodeling, thereby contributing to bone loss [28]. In addition, key genera like *Bacteroides* contain both commensal and pathogenic species, such as *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, and *Bacteroides acidifaciens* [29]. *Bacteroides fragilis* can regulate intestinal immune activity in opposite directions: non-toxigenic strains help maintain immune balance, whereas enterotoxigenic strains increase inflammation and damage the intestinal barrier [30, 31]. *Bacteroides thetaiotaomicron* supports mucosal nutrition and barrier function, contributing to a more stable local inflammatory environment [32]. *Bacteroides acidifaciens* could impair the intestinal barrier and is associated with increased gut inflammation [33]. However, these species changes were not consistently observed here due to limited species-level data.

The functional pathways that were similarly altered in SP and OP may offer additional understanding of their shared pathophysiological mechanisms. Purine metabolism is a key regulator of aging-related biological processes and affects multiple tissues and organ systems [34]. Disturbances in this pathway can promote musculoskeletal deterioration by disrupting immune regulation, and may also enhance uric acid-related inflammatory signaling, thereby contributing to chronic low-grade inflammation [34]. Likewise, pyrimidine metabolism, which regulates the synthesis, turnover, and recycling of nucleotides such as cytosine, thymine, and uracil, is essential for preserving nucleotide homeostasis and sustaining cellular energy balance [33, 35]. Interference with this pathway can restrict nucleotide availability, impair osteoblast activity, and limit muscle repair, ultimately promoting both bone loss and muscle decline [35]. Furthermore, imbalances in cysteine and methionine metabolism have been associated with excessive reactive oxygen species production, which increases oxidative stress, impairs physiological performance, and accelerates tissue degeneration [36, 37].

Strengths and limitations

We conducted a comprehensive search based on predefined inclusion criteria and identified 45 observational studies including 6,751 participants. This allowed us to systematically assess gut microbiota alterations in SP and OP and to summarize the available evidence. This study provides an integrated summary of existing evidence on microbial diversity and on disease-specific and overlapping alterations in gut microbiota. Moreover, as all included studies were based on human observational data, the findings may hold direct clinical significance. Nevertheless, several limitations should be noted. First, substantial heterogeneity was observed in the meta-analysis. Unlike randomized controlled trials, meta-analyses of observational studies are more prone to variability that cannot be fully controlled. Differences in methods, such as DNA extraction procedures, sequencing platforms and depth, and the reference databases used, are likely to have contributed to the inconsistencies across studies. Second, many of the included studies had relatively small sample sizes, which may have limited the overall statistical power of our analyses and highlight the need for confirmation in larger populations. Third, the observed alterations in bacterial taxa and predicted functional pathways were mainly derived from 16S rRNA sequencing data and from functional prediction tools, including PICRUSt, PICRUSt2, and Tax4Fun2. Given the limited validation using metagenomic or metabolomic analyses, these findings should be interpreted with caution and require further validation in future studies. Fourth, our findings may be influenced by dietary factors owing to the insufficient adjustment for dietary confounders in the primary studies. Future research should systematically incorporate and adjust for detailed dietary data to enable a more comprehensive evaluation of gut microbiota alterations in relation to disease. Fifth, the multiple subgroup analyses conducted in this study may increase the risk of type I error, and the related findings should therefore be interpreted with caution. Sixth, potential publication bias in the OP analysis may introduce uncertainty into the pooled estimates. However, its overall impact is likely limited given the generally consistent findings across studies.

Clinical and research implications

Reduced microbial diversity may favor the emergence of pathogenic microbes. These microbes can disrupt the intestinal barrier and stimulate the production of inflammatory mediators by mucosal cells in the lamina propria and mesenteric lymph nodes [38]. In our study, we observed a significant decrease in diversity metrics of richness among patients with SP. This finding may help generate hypotheses and guide future research on SP with a focus on the gut microbiota. Conversely, as previously reported, OP showed no significant association with α-diversity. This suggests that microbial diversity may be largely preserved in these patients. Importantly, we identified specific microbial alterations that were consistently enriched or depleted in both SP and OP, with shared changes observed in Lachnospiraceae, *Blautia*, and *Eggerthella* across both conditions. We also summarized KEGG pathway findings from previous studies to describe reported specific and shared metabolic alterations in SP and OP. In particular, disruptions in purine, pyrimidine, and cysteine-methionine metabolism could be common in both SP and OP. Such metabolic disturbances may help explain overlapping biological mechanisms and support the view of osteosarcopenia as a combined phenotype. These findings suggest several ways in which changes in the gut microbiome may contribute to musculoskeletal decline, including increased inflammation, poorer bone-muscle healing, and reduced ability to build protein. In addition, these metabolic pathways present clear and testable targets for future mechanistic and translational studies.

Recent studies have highlighted the potential of targeting the gut microbiota for the screening, intervention, and treatment of age-related diseases such as diabetes and metabolic syndrome [39-41]. Meanwhile, several interventional studies have demonstrated that modulating the gut microbiota can enhance musculoskeletal health in older adults. Probiotic supplementation has been found to improve muscle strength and slow bone loss among elderly individuals, likely through anti-inflammatory and metabolic mechanisms [42,43]. Similarly, prebiotic supplementation has been associated with increased muscle strength, supporting its role in maintaining musculoskeletal function [44]. Collectively, our findings provide a foundation for future microbiota-targeted interventions focusing on specific genera or species relevant to musculoskeletal decline. However, the widespread use of gut microbiota profiling in geriatric clinics or disease screening programs is still limited by the lack of standardized detection methods and by high costs [45]. Further research is needed to validate these associations and translate microbiome-based strategies into feasible clinical applications.

CONCLUSION

This systematic review and meta-analysis provide compelling evidence of a strong association between gut microbiota dysbiosis and both SP and OP. This study further provides insight into the shared microbial alterations and metabolic pathways between these two distinct yet closely related diseases and suggests potential interventions that may be effective against osteosarcopenia.

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Author Contributions

Ning Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read, provided critical feedback on intellectual content, and approved the final manuscript. Concept and design: Ning Wang. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Cong Lu, Haochen Wang and Ning Wang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Jie Wei. Obtained funding: Ning Wang, Chao Zeng, and Guanghua Lei. Administrative, technical, or material support: Chao Zeng and Guanghua Lei. Supervision: Ning Wang.

Conflict of Interest

No conflict of interest for any of the authors.

Ethical approval

Since no private or confidential patient data will be contained in the reporting, approval from an ethics committee is not required.

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Supplementary Materials

The Supplementary data can be found online at:
www.aginganddisease.org/EN/10.14336/AD.2025.1116.

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