Table S1 Characteristics of Observational Studies in the Systematic Review on the Relationship between Gut Microbiota and Osteoporosis

Study	Country	Population	Study design	Mean Age (SD)		Sex (%female)		Outcomes	Genetic analysis
				Trial group	Control group	Trial group	Control group		
Mrinmoy Das 2019	Ireland	OP (N=60) HC (N=60)	Case-control study	65.07±5.58	63.57±5.73	Female: 81.6% Male: 18.3%	Female: 78.3% Male: 21.7%	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq sequences Region: V3-V5 Pipeline analysis: QIIME Database: RDP
Lishan Li 2019	China	OP (N=12) HC (N=17)	Case-control study	64.00±10.94	50.17±9.02	Female: 58.3% Male: 41.7%	Female: 17.6% Male: 82.4%	Fecal microbiota THl7 / Treg cell ratio	16S rRNA gene sequencing using Illumina MiSeq sequences Region: V4 Pipeline analysis: QIIME Database: unspecified
C. Li 2019	China	Low-BMD (N=51) Control group HC (N=51)	Case-control study	65.5±6.00	66.6±6.00	Female: 80.4% Male: 19.6%	Female: 37.3% Male: 62.7%	Fecal microbiota	16S rRNA gene sequencing using Illumina MiSeq sequences Region: V3-V4 Pipeline analysis: Mothur Database: RDP
Palacios-González B 2020	Mexico	Low-BMD (N=58) Normal-BMD (N=34)	Cross-sectional	68.00±6.00	60.50±5.00	Female: 100%	Female: 100%	Fecal microbiota BCAAs AAAs	16S rRNA gene sequencing using Illumina MiSeq 2 × 250 platform Region: V4 Pipeline analysis: QIIME Database: Greengenes
Jianquan He 2020	China	OP (N=42) HC (N=31)	Cross-sectional	59.69±5.51	57.35±3.98	Female: 100%	Female: 100%	Fecal microbiota	Gene sequencing platform: Illumina MiSeq HiSeq 2500 sequences Sequencing Region: V3-V4 Data analysis pipeline: QIIME Database: SILVA
Zhiming Xu 2020	China	OP (N=48) HC (N=48)	Prospective study	57.50±10.15	60.23±11.43	Female: 60.42% Male: 39.58%	Female: 37.5% Male:62.5%	Fecal microbiota	Gene sequencing platform:Ion S5TMXL sequences Sequencing Region: V3-V4 Data analysis pipeline: unstated Database: SILVA132 SSUrRNA
Muhong Wei 2021	China	OP (N=74) HC (N=101)	Case-control study	68.59±5.36	67.06±5.00	Female: 77.1% Male: 22.9%	Female: 47.5% Male: 52.5%	Fecal microbiota	Gene sequencing platform: Illumina MiSeq sequences Sequencing Region: V3-V4 Data analysis pipeline: unstated Database: RDP
Jing Lyu 2021ab	China	OP (N=24) HC (N=9)	Cross-sectional	61.00±6.60	55.30±3.60	Female: 100%	Female: 100%	Fecal microbiota	Gene sequencing platform: Illumina NovaSeq 6000 sequences Sequencing Region: V3-V4 Data analysis pipeline: QIIME Database: NCBI NR database

Table S1 Continued

Study	Country	Population	Study design	Mean Age (SD)		Sex (%female)		Outcomes	Genetic analysis
				Trial group	Control group	Trial group	Control group		
Jing Lyu 2021a	China	OP (N=14) HC (N=21)	Cross-sectional	61.20±7.70	60.00±8.00	Male: 100%	Male: 100%	Fecal microbiota ALP P1NP β-CTX	Gene sequencing platform: Illumina MiSeq sequences Sequencing Region: V3-V4 Data analysis pipeline: QIIME Database: unstated
Elizabeth A Rettedal 2021	New Zealand	OP (N=18) HC (N=26)	Cross-sectional	64.6±5.66	62.5±4.54	Female: 100%	Female: 100%	Fecal microbiota	Gene sequencing platform: Illumina MiSeq HiSeq 2500 sequences Sequencing Region: unstated Data analysis pipeline: unstated Database: NCBI NR database
Zhongxiang Wang 2021	China	OP (N=24) HC (N=18)	Case-control study	60.25±4.51	61.56±4.03	Female: 100%	Female: 100%	Fecal microbiota	Gene sequencing platform: Illumina MiSeq 250 Sequence Sequencing Region: V4-V5 Data analysis pipeline: Mothur Database: RDP
Chu-Wen Ling 2021	China	OP (N=179#) HC (N=1013#)	Cross-sectional	64.5±6.0	64.6±5.9	Female: 88.3% Male: 11.7%	Female: 55.8% Male: 44.2%	Fecal microbiota	Gene sequencing platform: Illumina MiSeq sequences Sequencing Region: V3-V4 Data analysis pipeline: QIIME Database: unstated

OP, Osteoporosis; HC, Healthy Control; SD, standard deviation; RDP, Ribosomal Database Project; QIIME, Quantitative Insights into Microbial Ecology; BCAAs, Branched amino acid; AAAs, leucine and valine Aromatic Amino Acids. # Only included the sample size data measured by lumbar bone mineral density.

Table S2 Quality Assessment of 12 Studies on the Newcastle-Ottawa Scale

Study	Selection				Comparability Control for important factor	Exposure			Score
	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	
Mrinmoy Das 2019	★	★	☆	★	★☆	★	★	★	7
Lishan Li 2019	★	★	☆	★	☆☆	★	★	★	6
C. Li 2019	★	★	★	★	★☆	★	★	★	8
Palacios-González B 2020	★	★	★	★	★★	★	★	★	9
Jianquan He 2020	★	★	★	★	★★	★	★	★	9
Zhiming Xu 2020	★	★	☆	★	★★	★	★	★	8
Muhong Wei 2021	★	★	☆	★	★★	★	★	★	8
Jing Lyu 2021a	★	★	☆	★	★★	★	☆	★	7
Jing Lyu 2021b	★	★	☆	★	★★	★	☆	★	7
Elizabeth A Rettedal 2021	★	★	★	★	★☆	★	★	★	8
Zhongxiang Wang 2021	★	★	☆	★	★★	★	★	★	8
Chu-Wen Ling 2021	★	★	★	★	★☆	★	☆	★	7

A maximum of two stars can be allotted in this category, one for gender, and one for another controlled factor.
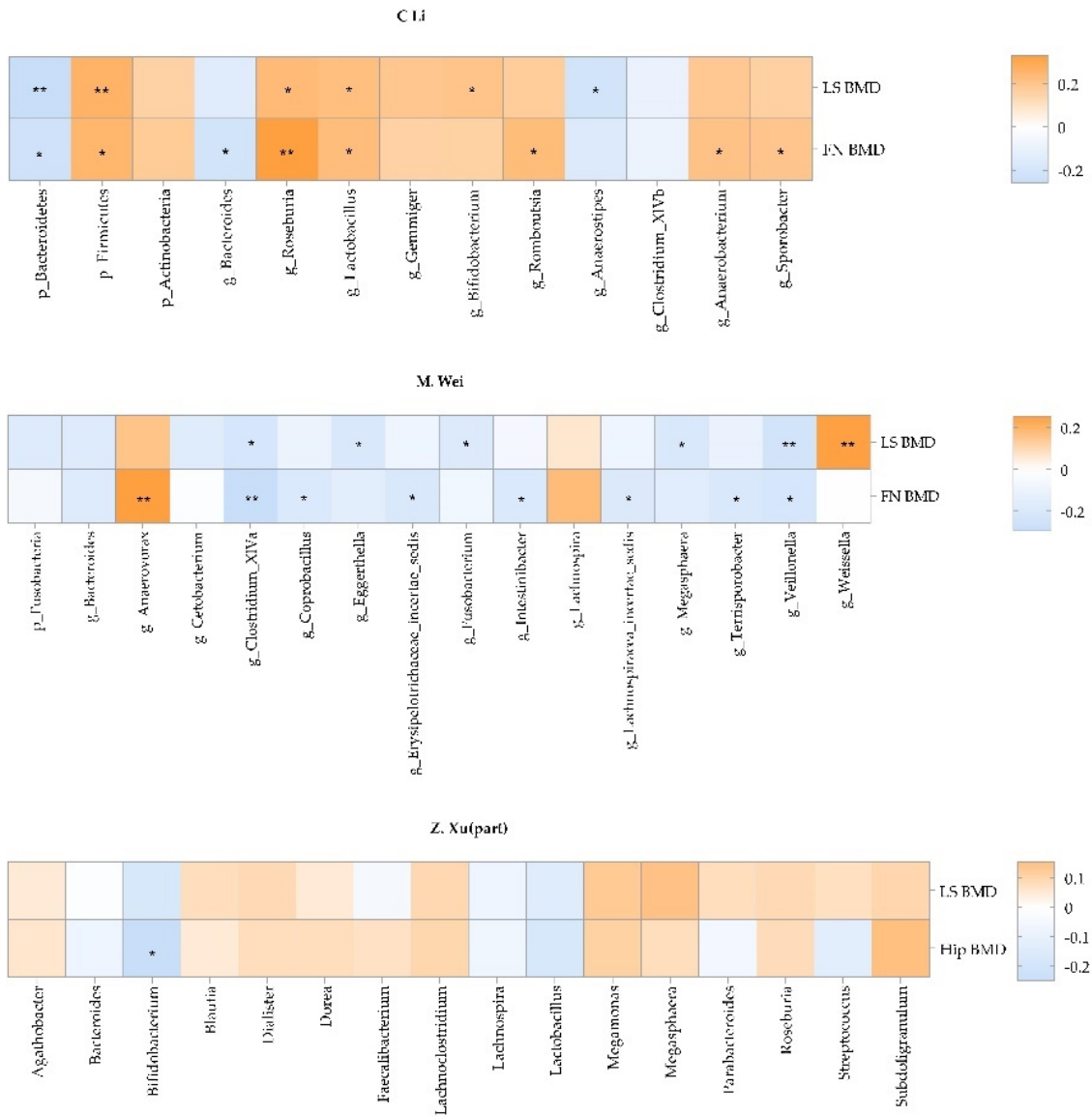
Fig. S1 Spearman's correlation. Each cell in the heatmap corresponds to a Spearman's correlation coefficient. The orange color represents positive correlation between the strain and bone mineral density measurement, and the blue color represents negative correlation between the strain and bone mineral density. This map represents the strain transversely, and it represents the lumbar bone mineral density group (LS BMD) or the femoral and neck bone mineral density group (FN BMD) longitudinally. * *P*<0.05, ** *P*<0.01. p, phylum, g, genus.

(a) Chao

Funnel plot with pseudo 95% confidence limits

(b) Shannon

Funnel plot with pseudo 95% confidence limits

(c) F/B

Funnel plot with pseudo 95% confidence limits
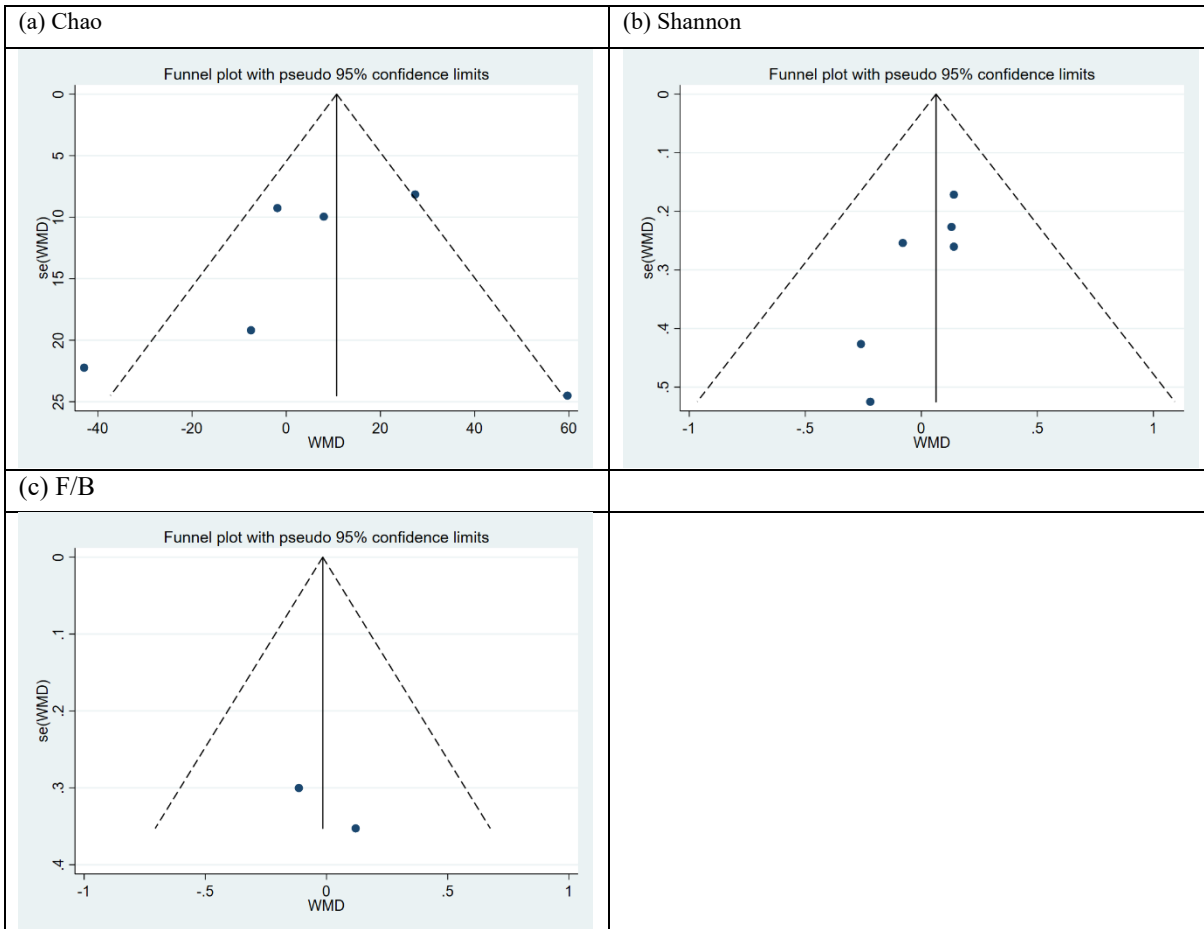
Fig. S2 Funnel plots of gut microbiota analysis results, estimating potential publication bias of the included studies for each study. SE, standard error; WMD, weighted mean difference.

1. Materials and methods

1.1 Inclusion criteria

If the published papers met the following criteria, they were included in this meta-analysis:
(1) Prospective or retrospective, case-control or cohort studies conducted on the population.
(2) Articles published between January 1, 2000 and Aug 1, 2022.
(3) Studies involving 16s rRNA sequencing techniques.
(4) Studies providing GM profiles and GM data for a case group and a control group.
The exclusion criteria for this meta-analysis were as follows:
(1) Articles that do not meet the inclusion criteria.
(2) Studies that do not correspond to the published types, including animal studies, reviews, case reports, systematic reviews, etc.
(3) Studies that do not provide sufficient data or those with incomplete data.
(4) Studies with fewer than 10 participants.

1.2 Literature search

The present review was conducted by following PRISMA guidelines and was prospectively registered at the PROSPERO International Prospective Register of Systematic Reviews (CRD42022314704). According to the Population, Intervention, Comparison, Outcome, and Study design (PICOS) principle and the combination of subject words and free words, we thoroughly searched the databases of PubMed, Web of Science, Cochrane Library, Embase, and CNKI for articles published between January 2000 and Aug 2022, combined with literature tracking and manual search when necessary. The specific retrieval strategy was listed in Table S3.

Table S3 Search strategies

PubMed *(from inception to 1 August 2022)*

Search	Query	Results
#4	Search: ((("Osteoporosis"[Mesh]) OR ((((((((((((((((((((((Osteoporoses[Title/Abstract]) OR (Osteoporosis, Post-Traumatic[Title/Abstract])) OR (Osteoporosis, Post Traumatic[Title/Abstract])) OR (Post-Traumatic Osteoporoses[Title/Abstract])) OR (Post-Traumatic Osteoporosis[Title/Abstract])) OR (Osteoporosis, Senile[Title/Abstract])) OR (Osteoporoses, Senile[Title/Abstract])) OR (Senile Osteoporoses[Title/Abstract])) OR (Osteoporosis, Involutional[Title/Abstract])) OR (Senile Osteoporosis[Title/Abstract])) OR (Osteoporosis, Age-Related[Title/Abstract])) OR (Osteoporosis, Age Related[Title/Abstract])) OR (Bone Loss, Age-Related[Title/Abstract])) OR (Age-Related Bone Loss[Title/Abstract])) OR (Age-Related Bone Losses[Title/Abstract])) OR (Bone Loss, Age Related[Title/Abstract])) OR (Bone Losses, Age-Related[Title/Abstract])) OR (Age-Related Osteoporosis[Title/Abstract])) OR (Age Related Osteoporosis[Title/Abstract])) OR (Age-Related Osteoporoses[Title/Abstract])) OR (Osteoporoses, Age-Related[Title/Abstract])) OR (Osteoporosis, Postmenopausal[Title/Abstract])) OR (Perimenopausal Bone Loss[Title/Abstract]))) AND (("RNA, Ribosomal, 16S"[Mesh]) OR ((((rRNA, 16S[Title/Abstract]) OR (16S Ribosomal RNA[Title/Abstract])) OR (RNA, 16S Ribosomal[Title/Abstract])) OR (Ribosomal RNA, 16S[Title/Abstract])))) AND (("Gastrointestinal Microbiome"[Mesh]) OR ((((((((((((((((((((((((((((((Gastrointestinal Microbiomes[Title/Abstract]) OR (Microbiome, Gastrointestinal[Title/Abstract])) OR (Gut Microbiome[Title/Abstract])) OR (Gut Microbiomes[Title/Abstract])) OR (Microbiome, Gut[Title/Abstract])) OR (Gut Microflora[Title/Abstract])) OR (Microflora, Gut[Title/Abstract])) OR (Gut Microbiota[Title/Abstract])) OR (Gut Microbiotas[Title/Abstract])) OR (Microbiota, Gut[Title/Abstract])) OR (Gastrointestinal Flora[Title/Abstract])) OR (Flora, Gastrointestinal[Title/Abstract])) OR (Flora, Gut[Title/Abstract])) OR (Gastrointestinal Microbiota[Title/Abstract])) OR (Gastrointestinal Microbiotas[Title/Abstract])) OR (Microbiota, Gastrointestinal[Title/Abstract])) OR (Gastrointestinal Microbial Community[Title/Abstract])) OR (Gastrointestinal Microbial Communities[Title/Abstract])) OR (Microbial Community, Gastrointestinal[Title/Abstract])) OR (Gastrointestinal Microflora[Title/Abstract])) OR (Microflora, Gastrointestinal[Title/Abstract])) OR (Gastric Microbiome[Title/Abstract])) OR (Microbiome, Gastric[Title/Abstract])) OR (Intestinal Microbiome[Title/Abstract])) OR (Intestinal Microbiomes[Title/Abstract])) OR (Microbiome, Intestinal[Title/Abstract])) OR (Intestinal Microbiota[Title/Abstract])) OR (Intestinal Microbiotas[Title/Abstract])) OR (Microbiota, Intestinal[Title/Abstract])) OR (Intestinal Microflora[Title/Abstract])) OR (Microflora, Intestinal[Title/Abstract])) OR (Intestinal Flora[Title/Abstract])) OR (Flora, Intestinal[Title/Abstract])) OR (Enteric Bacteria[Title/Abstract])) OR (Bacteria, Enteric[Title/Abstract])))	14
#3	Search: ("Gastrointestinal Microbiome"[Mesh]) OR ((((((((((((((((((((((((((((((Gastrointestinal Microbiomes[Title/Abstract]) OR (Microbiome, Gastrointestinal[Title/Abstract])) OR (Gut Microbiome[Title/Abstract])) OR (Gut Microbiomes[Title/Abstract])) OR (Microbiome, Gut[Title/Abstract])) OR (Gut Microflora[Title/Abstract])) OR (Microflora, Gut[Title/Abstract])) OR (Gut Microbiota[Title/Abstract])) OR (Gut Microbiotas[Title/Abstract])) OR (Microbiota, Gut[Title/Abstract])) OR (Gastrointestinal Flora[Title/Abstract])) OR (Flora, Gastrointestinal[Title/Abstract])) OR (Gut Flora[Title/Abstract])) OR (Flora, Gut[Title/Abstract])) OR	68,799

	(Gastrointestinal Microbiota[Title/Abstract])) OR (Gastrointestinal Microbiotas[Title/Abstract])) OR (Microbiota, Gastrointestinal[Title/Abstract])) OR (Gastrointestinal Microbial Community[Title/Abstract])) OR (Gastrointestinal Microbial Communities[Title/Abstract])) OR (Microbial Community, Gastrointestinal[Title/Abstract])) OR (Gastrointestinal Microflora[Title/Abstract])) OR (Microflora, Gastrointestinal[Title/Abstract])) OR (Gastric Microbiome[Title/Abstract])) OR (Gastric Microbiomes[Title/Abstract])) OR (Microbiome, Gastric[Title/Abstract])) OR (Intestinal Microbiome[Title/Abstract])) OR (Intestinal Microbiomes[Title/Abstract])) OR (Microbiome, Intestinal[Title/Abstract])) OR (Intestinal Microbiota[Title/Abstract])) OR (Intestinal Microbiotas[Title/Abstract])) OR (Microbiota, Intestinal[Title/Abstract])) OR (Intestinal Microflora[Title/Abstract])) OR (Microflora, Intestinal[Title/Abstract])) OR (Intestinal Flora[Title/Abstract])) OR (Flora, Intestinal[Title/Abstract])) OR (Enteric Bacteria[Title/Abstract])) OR (Bacteria, Enteric[Title/Abstract]))	
#2	Search: ("RNA, Ribosomal, 16S"[Mesh]) OR ((((rRNA, 16S[Title/Abstract]) OR (16S Ribosomal RNA[Title/Abstract])) OR (RNA, 16S Ribosomal[Title/Abstract])) OR (Ribosomal RNA, 16S[Title/Abstract]))	62,658
#1	Search: ("Osteoporosis"[Mesh]) OR (((((((((((((((((((((Osteoporoses[Title/Abstract]) OR (Osteoporosis, Post-Traumatic[Title/Abstract]) OR (Osteoporosis, Post Traumatic[Title/Abstract])) OR (Post-Traumatic Osteoporoses[Title/Abstract])) OR (Post-Traumatic Osteoporosis[Title/Abstract])) OR (Osteoporosis, Senile[Title/Abstract])) OR (Osteoporoses, Senile[Title/Abstract]) OR (Senile Osteoporoses[Title/Abstract])) OR (Osteoporosis, Involutional[Title/Abstract])) OR (Senile Osteoporosis[Title/Abstract])) OR (Osteoporosis, Age-Related[Title/Abstract])) OR (Osteoporosis, Age Related[Title/Abstract])) OR (Bone Loss, Age-Related[Title/Abstract])) OR (Age-Related Bone Loss[Title/Abstract])) OR (Age-Related Bone Losses[Title/Abstract])) OR (Bone Loss, Age Related[Title/Abstract])) OR (Bone Losses, Age-Related[Title/Abstract])) OR (Age-Related Osteoporosis[Title/Abstract])) OR (Age Related Osteoporosis[Title/Abstract])) OR (Age-Related Osteoporoses[Title/Abstract])) OR (Osteoporoses, Age-Related[Title/Abstract])) OR (Osteoporosis, Postmenopausal[Title/Abstract])) OR (Perimenopausal Bone Loss[Title/Abstract]))	61,751

Embase *via Ovid (from inception to 1 March 2022)*

Search	Query	Results
#1	'osteoporosis':ab,ti 'osteoporosis, post-traumatic':ab,ti 'osteoporosis, post traumatic':ab,ti 'post-traumatic osteoporoses':ab,ti OR 'post-traumatic osteoporosis':ab,ti OR 'osteoporosis, senile':ab,ti OR 'osteoporoses, senile':ab,ti OR 'senile osteoporoses':ab,ti OR 'osteoporosis, involutional':ab,ti OR 'senile osteoporosis':ab,ti OR 'osteoporosis, age-related':ab,ti OR 'osteoporosis, age related':ab,ti OR 'bone loss, age-related':ab,ti OR 'age-related bone loss':ab,ti OR 'age-related bone losses':ab,ti OR 'bone loss, age related':ab,ti OR 'bone losses, age-related':ab,ti OR 'age-related osteoporosis':ab,ti OR 'age related osteoporosis':ab,ti OR 'osteoporoses, age-related':ab,ti OR 'osteoporosis, postmenopausal':ab,ti OR 'perimenopausal bone loss':ab,ti	115449
#2	'RNA, Ribosomal, 16S':ab,ti OR '16s rrna':ab,ti OR 'rrna, 16s':ab,ti OR '16s ribosomal rna':ab,ti OR 'rna, 16s ribosomal':ab,ti OR 'ribosomal rna, 16s':ab,ti	69824
#3	'gastrointestinal microbiomes':ab,ti OR 'gastrointestinal microbiomes':ab,ti OR 'microbiome, gastrointestinal':ab,ti OR 'gut microbiome':ab,ti OR 'gut microbiomes':ab,ti OR 'microbiome, gut':ab,ti OR 'gut microflora':ab,ti OR 'microflora, gut':ab,ti OR 'gut microbiota':ab,ti OR 'gut microbiotas':ab,ti OR 'microbiota, gut':ab,ti OR 'gastrointestinal flora':ab,ti OR 'flora, gastrointestinal':ab,ti OR 'gut flora':ab,ti OR 'flora, gut':ab,ti OR 'gastrointestinal microbiota':ab,ti OR 'gastrointestinal microbiotas':ab,ti OR 'microbiota, gastrointestinal':ab,ti OR 'gastrointestinal microbial community':ab,ti OR 'gastrointestinal microbial communities':ab,ti OR 'microbial community, gastrointestinal':ab,ti OR 'gastrointestinal microflora':ab,ti OR 'microflora, gastrointestinal':ab,ti OR 'gastric microbiome':ab,ti OR 'gastric microbiomes':ab,ti OR 'microbiome, gastric':ab,ti OR 'intestinal microbiome':ab,ti OR 'intestinal microbiomes':ab,ti OR 'microbiome, intestinal':ab,ti OR 'intestinal microbiota':ab,ti OR 'intestinal microbiotas':ab,ti OR 'microbiota, intestinal':ab,ti OR 'intestinal microflora':ab,ti OR 'microflora, intestinal':ab,ti OR 'intestinal flora':ab,ti OR 'flora, intestinal':ab,ti OR 'enteric bacteria':ab,ti OR 'bacteria, enteric':ab,ti	71319
#4	1 and 2 and 3	28

Web of Science *via Ovid (from inception to 1 March 2022)*

Search	Query	Results
#1	TS=(Osteoporosis OR Osteoporoses OR Osteoporosis, Post-Traumatic OR Osteoporosis, Post Traumatic OR Post-Traumatic Osteoporoses OR Post-Traumatic Osteoporosis OR Osteoporosis, Senile OR Osteoporoses, Senile OR Senile Osteoporoses OR Osteoporosis, Involutional OR Senile Osteoporosis OR Osteoporosis, Age-Related OR Osteoporosis, Age Related OR Bone Loss, Age-Related OR Age-Related Bone Loss OR Age-Related Bone Losses OR Bone Loss, Age Related OR Bone Losses, Age-Related OR Age-Related Osteoporosis OR Age Related Osteoporosis OR Age-Related Osteoporoses OR Osteoporoses, Age-Related OR Osteoporosis, Postmenopausal OR Perimenopausal Bone Loss)	106,742
#2	TS=(RNA, Ribosomal, 16S OR 16S rRNA OR rRNA, 16S OR 16S Ribosomal RNA OR RNA, 16S Ribosomal OR Ribosomal RNA, 16S)	86,835
#3	TS=(Gastrointestinal Microbiome OR Gastrointestinal Microbiomes OR Microbiome, Gastrointestinal OR Gut Microbiome OR Gut Microbiomes OR Microbiome, Gut OR Gut Microflora OR Microflora, Gut OR Gut Microbiota OR Gut Microbiotas OR Microbiota, Gut OR Gastrointestinal Flora OR Flora, Gastrointestinal OR Gut Flora OR Flora, Gut OR Gastrointestinal Microbiota OR Gastrointestinal Microbiotas OR Microbiota, Gastrointestinal OR Gastrointestinal Microbial Community OR Gastrointestinal Microbial Communities OR Microbial Community, Gastrointestinal OR Gastrointestinal Microflora OR Microflora, Gastrointestinal OR Gastric Microbiome OR Gastric Microbiomes OR Microbiome, Gastric OR Intestinal Microbiome OR Intestinal Microbiomes OR Microbiome, Intestinal OR Intestinal Microbiota OR Intestinal Microbiotas OR Microbiota, Intestinal OR Intestinal Microflora OR Microflora, Intestinal OR Intestinal Flora OR Flora, Intestinal OR Enteric Bacteria)	103755
#4	1 and 2 and 3	40

1.3 Study Selection and Data Extraction

Two researchers (HR and SYP) independently read the titles and abstracts, evaluated and classified them, and then cross-examined their results. In the event of a disagreement, a third reviewer (LP) was involved to determine if the paper should be included. We extracted the following information from the original report: first author's name, year of publication, region, sex, age, the sample size of the case group and control group, data of fecal microbiota, and LDA score in the Lefse analysis. When extracting relevant information from the included studies and their attachments, we tried to contact the authors to obtain or verify the data if necessary. If we did not receive a response, we used Borenstein or Luo et al.'s transformation equation to estimate the effect variable (Luo et al., 2018; Borenstein et al., 2021).

1.4 Quality Assessment

The included studies were evaluated using the Newcastle-Ottawa scale (NOS), which is a non-randomized systematic evaluation tool, with a total score of nine, divided into three categories: selection, comparability, and exposure. The highest scores were 4, 2, and 3, respectively (Margulis et al., 2014). Literatures with final scores <6 were considered low-quality and those ≥6 were regarded as high-quality. Any differences between the two researchers in the quality assessment process were resolved through consultation with a third reviewer (LP).

1.5 Statistical analysis

All statistical analyses in this study were performed using R language version 4.0.3 (the meta and metafor packages) and Stata software version 15.1 (Stata Corp LLC, College Station, TX, USA). The analysis results of the effect index were expressed by weight mean difference (WMD) and 95% confidence interval (CI). Taking $\alpha = 0.05$ as the test standard, a forest map was drawn to describe the statistical results. The heterogeneity between the results was evaluated using I^2 statistics (Rhodes et al., 2016). If the heterogeneity was low ($I^2 < 50\%$), the fixed-effect model was used for analysis. If the heterogeneity was high ($I^2 > 50\%$), the random effect model was adopted, the sensitivity was analyzed, and the source of the heterogeneity was discussed. Publication bias was evaluated using funnel charts, Egger's test and Begg's test. If the funnel chart was asymmetrical, there was publication bias, which could be quantified by Egger's and Begg's test. When the Egger's or Begg's test value is greater than 0.05, we considered that there was no publication bias (Table S4) (Egger et al., 1997).

Table S4 *P* value for Egger's and Begg's tests for publication bias

	P for Egger's test	*P* for Begg's test
Chao	0.642	0.573
Shannon	0.109	0.348
F/B	-	0.317

No significant publication bias is present when *P*>0.05.

References

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