European Spine Journal (2023) 32:149–166
https://doi.org/10.1007/s00586-022-07463-w

REVIEW ARTICLE

Bone mineral density in children and young adults with idiopathic scoliosis: a systematic review and meta-analysis

Yuqi Yang[1] · Xiaoli Han[2] · Zhengquan Chen[3] · Xin Li[3] · Xiaoqing Zhu[3] · Haiyan Yuan[4] · Zefan Huang[3] · Xuan Zhou[3] · Qing Du[3,4]

Received: 23 May 2022 / Accepted: 8 November 2022 / Published online: 1 December 2022

Abstract

Purpose Osteoporosis is a risk factor for idiopathic scoliosis (IS) progression, but it is still unclear whether IS patients have bone mineral density (BMD) loss and a higher risk of osteoporosis than asymptomatic people. This systematic review aims to explore the differences in BMD and prevalence of osteoporosis between the IS group and the control group.

Methods We searched 5 health science-related databases. Studies that were published up to February 2022 and written in English and Chinese languages were included. The primary outcome measures consisted of BMD *z* score, the prevalence of osteoporosis and osteopenia, and areal and volumetric BMD. Bone morphometry, trabecular microarchitecture, and quantitative ultrasound measures were included in the secondary outcome measures. The odds ratio (OR) and the weighted mean difference (WMD) with a 95% confidence interval (CI) were used to pool the data.

Results A total of 32 case–control studies were included. The pooled analysis revealed significant differences between the IS group and the control group in BMD *z* score (WMD −1.191; 95% CI −1.651 to −0.732, $p < 0.001$). Subgroup analysis showed significance in both female (WMD −1.031; 95% CI −1.496 to −0.566, $p < 0.001$) and male participants (WMD −1.516; 95% CI −2.401 to −0.632, $p = 0.001$). The prevalence of osteoporosis and osteopenia in the group with IS was significantly higher than in the control group (OR = 6.813, 95% CI 2.815–16.489, $p < 0.001$; OR 1.879; 95% CI 1.548–2.281, $p < 0.000$). BMD measures by dual-energy X-ray absorptiometry and peripheral quantitative computed tomography showed a significant decrease in the IS group (all $p < 0.05$), but no significant difference was found in the speed of sound measured by quantitative ultrasound between the two groups ($p > 0.05$).

Conclusion Both the male and female IS patients had a generalized lower BMD and an increased prevalence of osteopenia and osteoporosis than the control group. Future research should focus on the validity of quantitative ultrasound in BMD screening. To control the risk of progression in IS patients, regular BMD scans and targeted intervention are necessary for IS patients during clinical practice.

Keywords Bone density · Idiopathic scoliosis · X-ray absorptiometry · Computed tomography · Meta-analysis

Abbreviations

IS	Idiopathic scoliosis
BMD	Bone mineral density
WOS	Web of Science
CINAHL	Cumulative Index of Nursing and Allied Health Literature
aBMD	Areal bone mineral density
DEXA	Dual-energy X-ray absorptiometry
vBMD	Volume bone mineral density
pQCT	Peripheral quantitative computed tomography
SOS	Speed of sound

Yuqi Yang, Xiaoli Han and Zhengquan Chen contributed equally to this study.

✉ Xuan Zhou
zhouxuan@xinhuamed.com.cn

✉ Qing Du
duqing@xinhuamed.com.cn

[1] College of Global Public Health, New York University, New York, USA

[2] Centers for Disease Control and Prevention of Chongming, Shanghai, China

[3] Department of Rehabilitation, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

[4] Chongming Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, China

BUA	Broadband ultrasonic attenuation
SI	Stiffness index
NOS	Newcastle–Ottawa scale
GRADE	Grading of recommendation assessment, development, and evaluation
OR	Odds ratio
CI	Confidence interval
WMD	Weighted mean difference
BMI	Body mass index
ROI	Region of interest
LSBMD	Lumbar spine BMD
FNBMD	Femoral neck BMD
BV/TV	Trabecular bone volume to tissue volume ratio

Introduction

Idiopathic scoliosis (IS) is a three-dimensional deformity of the spine that can be diagnosed with a Cobb angle ≥10° and unknown causes [1]. The progression of IS is a thorny problem faced by the clinic. With the rapid growth phase, this change in bone metabolism leads to greater deformability of the bone, especially the vertebrae, which exacerbates the abnormal alignment of the vertebrae in all planes [2]. The deformities of the spine may deteriorate rapidly if no intervention to slow the progression of IS, which leads to a higher frequency of musculoskeletal complications such as pelvic tilt, asymmetries of lower extremities, decreased muscular endurance, and severe back pain [3].

Osteopenia refers to bone mineral density (BMD) below the normal reference value [4]. If low BMD continues to progress, osteoporosis may be diagnosed, which indicates a high tendency for fracture and structural deformity. The prevalence of osteoporosis is around 18.3% worldwide, which is more common in females, and the prevalence of females is 4 times that of males [5, 6]. About 27–38% of adolescent IS patients suffer from osteopenia [7]. Osteopenia and osteoporosis are recognized as the key factors associated with the progression of IS [7, 8]. Moreover, low BMD may prolong the duration of brace intervention and reduce the correction effect on the spinal curve, especially for IS patients with osteoporosis [9, 10].

However, it remains unsolved whether osteoporosis or osteopenia is an individual characteristic or a general phenomenon in IS patients. Some studies showed that the low BMD in IS patients was associated with congenital genetic factors, such as defects in the RANK/RANKL, or Runx2 signal pathway, which are associated with osteopenia and osteoporosis [11, 12]. Osteopenia is present in IS individuals with an abnormal RANKL/OPG ratio, but this genetic susceptibility is not common in the IS population [11]. Some studies have noted a reduction in BMD, but this reduction is limited and does not meet the criteria for osteopenia or osteoporosis. The results of these studies suggest that there is only a weak correlation between osteopenia and IS [13].

In contrast, some studies showed that through screening for BMD, osteopenia or osteoporosis was a systematic issue in IS patients [14], and IS patients generally had low bone density and bone mass throughout their bodies [15]. A high level of bone turnover markers was also found in IS patients [16], suggesting the impairment in the bone microstructure and a decrease in BMD. A link between scoliosis and osteopenia was found, which suggested that IS patients had abnormal bone mass profiles, such as altered cortical thickness and disordered trabecular bone structures [17–19].

The purpose of this systematic review is to clarify whether IS patients have less BMD and a higher prevalence of osteoporosis, compared to age and gender-matched asymptomatic controls. We hypothesized that the BMD of IS patients may be significantly lower than that in healthy controls and a higher prevalence of osteopenia and osteoporosis may be figured out in IS patients than in healthy controls.

Methods

The protocol of this systematic review was developed and registered in PROSPERO, with the registration number CRD42022309629. Q. D. and X. Z. contributed to the study's concept and design.

Search strategy

This review was conducted following the PRISMA guidelines [20]. We searched five databases on health science, including PubMed, the Cochrane Library, Embase, Web of Science (WOS), and the Cumulative Index of Nursing and Allied Health Literature (CINAHL). Terms, such as "Scoliosis", "Children", "Osteoporosis", and "Bone Density", were used in studies retrieval (detailed in Table 1). We also wrote to corresponding authors for unpublished results related to this topic. The search was restricted to human studies that were published in Chinese and English. Two reviewers (Y. Y. and X. H.) worked separately on study retrieval and title/abstract screening.

Eligibility criteria

After screening, the retained studies were further reviewed whether they fulfilled the eligibility criteria. Participants in the case group should be children and young adults diagnosed with IS. IS is defined as an abnormal spine curve with a Cobb angle greater than 10° and without specific causes [1, 21]. The control group should include age and gender-matched participants without IS. Participants should

Table 1 Search strategy

Bone Mineral Density in Idiopathic Scoliosis Search Strategy
#1 Scoliosis OR Scoliotic OR "Spine Curve" OR "Spinal Curve" OR "Spine Curvature" OR "Spinal Curvature" OR "Spine Deformit*" OR "Spinal Deformit*" OR "Vertebral Curve" OR "Vertebral Deformit*" OR Kyphoscoliosis
#2 Osteoporosis OR "Bone Density" OR Osteopenia OR Fracture OR "Bone Loss" OR "Bone Mineral Density" OR "Bone Mineral Content" OR "Bone Mass Density" OR "Bone Mass Content" OR BMD OR "Dual-energy X-ray Absorptiometry" OR DEXA OR DXA
#3 Children OR Child OR Adolescent OR Adolescence OR Pediatric OR Teenager OR Youth OR Infant
#4 Case–Control OR "Case Control" OR Retrospective OR "Observational Study"
#5 #1 AND #2 AND #3 AND #4
#6 Animals NOT Humans
#7 #5 NOT #6

*The truncation wildcard, represents any characters

be excluded from both the IS group and control group if they (1) had any medical issues that may affect bone metabolisms, such as renal disease, rickets, thyroid disease, or osteosarcoma, or (2) previously received any interventions that may affect bone metabolisms, such as additional calcium intake, calcitriol, or therapeutic exercise (Table S1).

The primary outcome measures were (1) BMD z score; (2) osteoporotic prevalence; (3) osteopenia prevalence; (4) areal bone mineral density (aBMD) measured by dual-energy X-ray absorptiometry (DEXA); (5) volume bone mineral density (vBMD) measured by peripheral quantitative computed tomography (pQCT); and (6) speed of sound (SOS), broadband ultrasonic attenuation (BUA), and stiffness index (SI) measured by quantitative ultrasound. Bone morphometry and trabecular bone microarchitecture measures from pQCT were collected as the secondary outcome measures.

Data extraction and management

Two reviewers (Z. C and X. L.) independently extracted the data using a self-designed form that followed the Cochrane Collaboration's data extraction criteria [22]. The basic information, the severity of scoliosis, interventions, outcome measurements related to bone density and bone metabolism, and the main results were among the data that were extracted. Articles from the same author or institution were re-evaluated and compared, carefully scrutinized for duplication of participants. For articles that do not provide participant enrollment time, we sent emails to inquire about the specific situation. Any missing data were inquired through the contact information of the corresponding author provided in the included articles. In order to include as many relevant studies as possible, we contacted the authors of the published conference abstracts to confirm the completeness of the data presented in the abstracts. All conference abstracts with complete data were then included. Disagreements would be discussed and settled by a third reviewer (Q. D.).

Quality assessment and certainty of evidence

The Newcastle–Ottawa scale (NOS) for case–control studies was utilized [23] for quality assessment. Y. Y. and H. Y. independently assessed the potential of bias in the collected articles, and any disagreements were settled by Q. D.

We applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to categorize the certainty of the results into high, moderate, low, or very low quality [24].

Data synthesis

STATA 16.0 (StataCorp, College Station, TX, USA) was used. The odds ratio (OR) with a 95% confidence interval (CI) was used to assess discontinuous outcomes, while the weighted mean difference (WMD) with 95% CI was used to synthesize quantitative data. The chi-squared test with I^2 was used to examine statistical heterogeneity between study results. The random-effects model was applied to calculate the effect size. Subgroup analysis was performed between different gender (males + females vs. females only). The magnitude of publication bias was estimated by Begg's test.

Results

Study characteristics

The analysis was comprised of 32 case–control studies [2, 11–13, 15–19, 25–47], and 27 studies were entered into the meta-analysis [11–13, 15–19, 26–31, 33, 34, 36–43, 45–47]

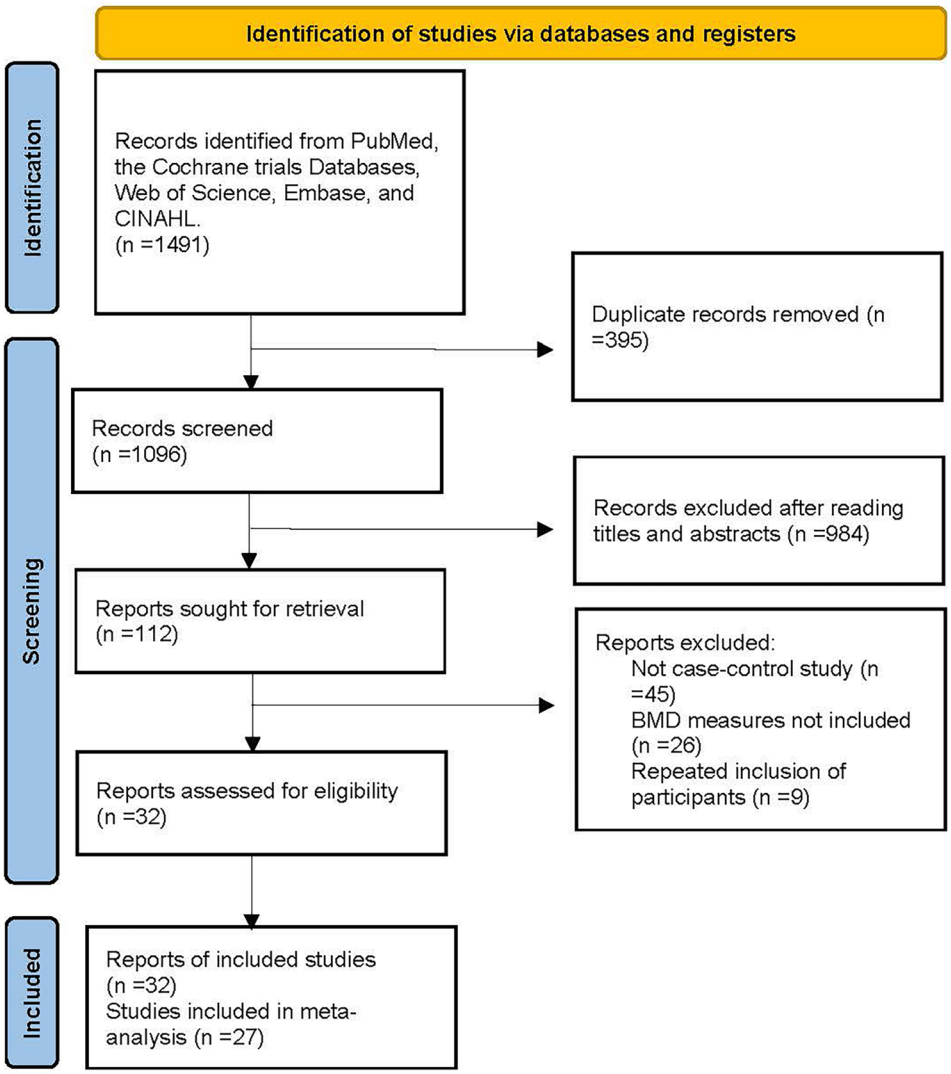


Fig. 1 PRISMA flow diagram of studies in this review

(Fig. 1). The regions of the articles included Asia (28 articles), Europe (3 articles), and North America (1 article).

The demographic variables, outcome measures, and main results of the included studies are shown in Table 2. Eleven case–control studies [11, 12, 17, 28, 30, 36, 41, 42, 44, 46, 47] recruited 469 males. The body mass index (BMI) in the IS group was generally lower than that in the control group. Most studies included patients with mild to moderate scoliosis (Cobb's angle 10–40°), while two studies focused on patients with severe scoliosis who needed surgical intervention [16, 17].

The NOS for case–control studies was used in the methodological quality assessment and 7 studies scored 9 points. The results of the risk of bias assessment are shown in Table S2. Table S3 shows the results of evidence quality assessment using the GRADE methodology.

Primary outcomes

BMD *z* score

The BMD z score is the standardized value calculated by comparison with BMD of the same age, gender, and ethnic group [29]. The BMD z score was reported in 12 case–control studies 11, 12, 15, 16, 18, 19, 27, 29, 38, 42, 45, 47, and the pooled analysis revealed significant differences (WMD −1.191; 95% CI −1.651 to −0.732, $p < 0.001$; $I^2 = 96.9\%$, $p < 0.001$). Evidence of publication bias was observed with Begg's test in the BMD z score ($z = -2.06$, Pr>|z| = 0.040).

The inclusion of the subgroup analysis was based on the gender of the participants. Eight case–control studies [15, 16, 18, 19, 27, 29, 38, 45] that exclusively included female participants showed significant differences between the IS group and control group (WMD −1.031; 95% CI −1.496 to −0.566, $p < 0.001$; $I^2 = 96.4\%$, $p < 0.001$). Significant differences were also observed in the other four case–control

Table 2 Characteristics of included studies

	Author, Year	No. of participants (% Men)	Age(y), range/ mean(SD)	Mean weight (kg)/ height (cm)/BMI (kg/ m^2)	Severity of AIS	Interventions	Outcome measures	Significant results
1	Avram 2010 [25]	T:60 A:30 C:30	–	–	–	–	BMD: DEXA	BMD: A group < C group
2	Catan 2020 [15]	T:64 (0) A:32 (0) C:32 (0)	A:14.75 (1.34) C:14.75 (1.34)	BMI: A:18.3 (2.99) C:BMI:19.26 (1.3)	Cobb angle: median 31 (Quartile 27–38)	–	1. BMD: DEXA 2. Laboratory tests: 25OHD, Ca	25OHD, Ca, & BMD: A group < C group
3	Chen 2019 [17]	T: 33 (18.2) A:20 (15) C:13 (23.1)	A:14.3 (2.20) C:16.5 (4.79)	BMI: A:18.4(2.40) C:20.1(5.09)	Cobb angle: mean 55.66 (SD 10.61°)	Posterior spinal fusion	1. BMD: DEXA 2. Bone histomorphometry 3. Confocal imaging and quantitative analysis 4. Energy-dispersive X-ray spectrometry 5. Bone turnover markers	A group: 1. Ultrastructural change in bone tissue 2. Serum osteocalcin level negatively associated with Cobb angle
4	Cheng 2000 [13]	T: 169 (0) A:75 (0) C:94 (0)	12:T36, A14, C22 13:T77, A26, C51 14:T56, A35, C21	BMI: A:17.2 (15.7–18.8) C:17.9 (16.3–19.7)	–	None	BMD: DEXA, pQCT	Areal and volumetric BMD: A group < C group
5	Cheuk 2016 [26]	T:321 (0) A:132 (0) C:189 (0)	12–16	–	–	–	1. Bone quality: pQCT 2. BMD: DEXA	Severe micro-architectural decay in A group Osteopenia incidence: A group > C group
6	Cheuk 2015 [27]	T:192 (0) A:95 (0) C:97 (0)	A:13.01 (0.72) C:13.08 (0.57)	BMI: A:17.64 (2.56) C:18.70 (2.70)	Cobb angle mean 21.2(SD 5.9)	None	1. BMD: DEXA 2. Bone quality: HRpQCT 3. Calcium intake and physical activity	Areal BMD: A group < C group

Table 2 (continued)

	Author, Year	No. of participants (% Men)	Age(y), range/ mean(SD)	Mean weight (kg)/ height (cm)/BMI (kg/ m^2)	Severity of AIS	Interventions	Outcome measures	Significant results
7	Cheung 2006 [2]	T:921 (0) A:621 (0) C:300 (0)	A:13.3 (1.2) C:13.3 (1.2)	A: ≤12: W37.8 (32.9–42.6),H150.4 (7.3) 13: W40.9 (37.6–45.6),H155.2 (5.8) 14: W42.7 (39.5–46.7),H157.5 (5.5) ≥15: W44.5 (40.0–48.9),H159.9 (5.8) C: ≤12: W39.4 (35.5–45.8),H151.3 (6.7) 13: W42.9 (38.3–49.3),H154.8 (5.5) 14: W44.2 (40.8–48.5),H156.3 (4.6) ≥15: W45.3 (41.7–52.3),H158.0 (5.4)	Cobb angle mean 26.3(SD 7.9)	None	1. BMD: DEXA 2. Bone turnover markers: alkaline phosphatase, deoxypyridinoline)	1. BMD: A group < C group 2. Bone turnover: A group > Cgroup
8	Diarbakerli 2020 [28]	T:130 (26.2) A:78 (26.9) C:52 (25)	A:13.7 (8.5–19.6) C:13.8 (9.1–17.6)	BMI: A:18.9 (3.2) C:19.6 (3.9)	Cobb angle mean 29° (SD 11°; Range 12–58°)	Braced and untreated	1. BMD: DEXA 2. Bone quality: pQCT	Volume BMD & pQCT: A group < C group
9	Du 2015 [29]	T:136 (0) A:78 (0) C:58 (0)	T:10–16 A: 12.3 (1.6) C:12.6 (1.9)	BMI: A:16.7 (2.0) C:19.0 (3.5)	Cobb angle mean 27.4° (SD 10.4°)	None	BMD: Quantitative ultrasound (*z*-score, SOS)	BMD: A group < C group
10	Gao 2018 [30]	T: 392 (32.7) A:182 (28.6) C:210 (36.2)	T:10–16 A: 13.13 (1.99) C: 13.11 (1.88)	BMI: A:19.4 (4.9) C:19.3 (4.9)	Cobb angle mean 27.9° (SD 5.7°)	Brace	BMD: DEXA Bone turnover markers: serum IL-6, bone Gla protein, tartrate resistant acid phosphatase 5b,TRACP-5b level, Ca, Cr	BMD: A group < C group
11	Hung 2006 [31]	T:60 (0) A:32 (0) C:28 (0)	T: 11–16 A: 13.0 (1.2) C: 12.7 (1.1)	–	Cobb angle mean 31° (SD 12°)	–	BMD: Quantitative ultrasound, DEXA	None
12	Lam 2015 [32]	T:186 (0) A:104 (0) C:82 (0)	12–14	–	–	–	Bone quality: HR-pQCT Serum total leptin and sOB-R levels	Decreased bone strength in A group

Table 2 (continued)

	Author, Year	No. of participants (% Men)	Age(y), range/ mean(SD)	Mean weight (kg)/ height (cm)/BMI (kg/ m^2)	Severity of AIS	Interventions	Outcome measures	Significant results
13	Lam 2011 [18]	T:904 (0) A:635 (0) C:269 (0)	A:13.3 (1.2) C13.3 (1.4)	BMI: A:16.7 (2.9) C:18.0 (3.7)	Cobb angle mean 27.8° (SD 10.7°)	–	BMD: Quantitative ultrasound, DXEA	BMD: A group < C group
14	Lam 2015 [33]	T:395 (0) A:212 (0) C:183 (0)	A: 12.9 (0.6) C: 12.9 (0.5)	–	–	–	1.BMD: DEXA 2.Serum 25(OH)Vit-D	None
15	Lee 2010 [34]	T: 318 (0) A:198 (0) C:120 (0)	A: 12.5 (11.1–13.9) C: 12.7 (11.0–13.9)	BMI: A:18.0 (15.0–23.9) C:18.2 (14.7–29.3)	Cobb angle mean 24.8° (Range 16–69°)	None	1. BMD: DEXA 2. Bone turnover markers: Serum alkaline phosphatase, Serum 25(OH)D3 and 1,25(OH)2D3 levels	BMD: A group < C group
16	Lee 2003 [35]	T:788 (0) A:582 (0) C:206 (0)	T:11–16 A: 13.3 (1.3) C:13.3 (1.3)	BMI: A:17.3 (2.4) C:18.4 (2.9)	–	None	1. BMD: DEXA 2. Bone quality: HR-pQCT	BMD: A group < C group
17	Moon 2013 [36]	T:103 (33) A:68 (33) C:35 (34)	A:14.7 (5.0) C:13.4 (3.1)	BMI: A:19.2 (2.4) C:20.1 (3.5)	Cobb angle mean (SD) < 40°: 25.8 (7.6) > 40°: 58.8 (21.0)	None	1. BMD: DEXA 2. Bone turnover markers: serum Osteocalcin, CTX, ALP, 25(OH)D3 levels 3. Gene analysis through SNP	25(OH)D3: A group < C group
18	Park 2009[37]	T:35 (0) A:19 (0) C:16 (0)	A:13.5 (0.88) C:13.1 (0.8)	BMI: A:17.4 (1.5) C:18.3 (2.7)	–	–	BMD: DEXA MSC differentiation: Doubling time, Alkaline phosphatase activity, Osteogenic differentiation (%)	BMD & MSC differentiation: A group < C group
19	Sadat-Ali 2008 [38]	T:59 (0) A:32 (0) C:27 (0)	A:18.42 (5.71) C:17.65 (4.5)	BMI A:17.7 (0.69) C:19.84 (0.6)	–	–	BMD: DEXA	BMD: A group < C group
20	Suh 2010 [39]	T:318 (0) A:198 (0) C:120 (0)	A:12.5 (0.8) C:12.7 (1.0)	BMI: A:18.0 (1.6) C:18.2 (2.3)	–	None	1. BMD: DEXA 2.Bone turnover markers: serum Osteocalcin, ALP, 25(OH)D3 3.Gene analysis through SNP	BMD: A group < C group

Table 2 (continued)

	Author, Year	No. of participants (% Men)	Age(y), range/ mean(SD)	Mean weight (kg)/ height (cm)/BMI (kg/ m^2)	Severity of AIS	Interventions	Outcome measures	Significant results
21	Suh 2007 [40]	T:136 (0) A:72 (0) C:64 (0)	A:11 to 14	BMI: A:17.5 (1.6) C:18.7 (2.6)	–	–	BMD: DEXA Bone turnover markers: OPG and RANKL	BMD: A group < C group RANKL & RANKL/ OPG ratio: A group > C group
22	Szalay 2008 [41]	T:89 (12.4) A:49 (12.2) C:40 (12.5)	A:14.1 (11–20) C:13.7 (10–17)	BMI A:19.9 (13.5–34.3) C:20.9 (15.5–44.7)	Cobb angle mean 51° (Range 19°-96°)	–	BMD: DEXA	Incidence of osteoporosis: A group > C group
23	Tahvildari 2014 [42]	T:100 (25) A:46 (19.6) C:54 (29.6)	A:17.8 (4.9) C:16.6 (3.9)	BMI: A:18.59 C:21.34	–	Without barce:29 With brace:17	BMD: DEXA	BMD: A group < C group
24	Tam 2014 [43]	T:181 (0) A:94 (0) C:87 (0)	A:13.05 (0.52) C:12.93 (0.43)	BMI: A:17.91 (2.20) C:18.64 (2.15)	Cobb angle mean 25.6° (SD 6.7°)	None	Bone quality: HR-pQCT Leptin: Soluble leptin receptor, Leptin receptor, Free leptin, Bound leptin, Serum total leptin, Leptin bioavailability	vBMD: A group < C group
25	Wang 2016 [44]	T:87 (100) A:47 (100) C:40 (100)	A:15.3 (2.2) C:15.3 (1.8)	BMI: A:18.5 (2.6) C:21.3 (4.3)	Cobb angle mean 52.7° (SD 8.0°)	None	Body composition: body fat mass, lean mass, BMC, BMD	BMC & BMD: A group < C group
26	Wang 2017 [45]	T:444 (0) A:257 (0) C:187 (0)	A:12.7 (0.8) C:12.9 (0.5)	BMI: A:18.1 (2.6) C:19.6 (3.1)	Cobb angle mean 22.3° (SD 7.8°)	None	1. BMD: DEXA 2. Bone quality: HR-pQCT (bone geometry, vBMD, trabecular bone micro-architecture)	BMD & Bone quality: A group < C group Incidence of osteopenia: A group > C group
27	Wu 2005 [46]	T:72 (18.1) A:36 (16.7) C:36 (19.4)	A:14.94 (1.57) C:15.56 (1.03)	–	Cobb angle mean 53° (SD 17°)	None	1.BMD: DEXA 2.Serum IL-6	BMD: A group < C group
28	Xiao 2021 [47]	T:28 (42.9) A:16 (37.5) C:12 (50)	A:15.12 (1.7) C:16.41 (3.2)	BMI: A:17.39 (2.73) C:25.36 (5.41)	Cobb angle mean 45.56° (SD 12.78°)	None	.BMD: lumbar spine and femoral neck Serum ions: Ca, Mg, P Plasma metabolite	BMD & Phosphate: A group < C group

Table 2 (continued)

	Author, Year	No. of participants (% Men)	Age(y), range/ mean(SD)	Mean weight (kg)/ height (cm)/BMI (kg/ m^2)	Severity of AIS	Interventions	Outcome measures	Significant results
29	Xiao 2020 [11]	T:127 (37.8) A:83 (35) C:44 (43.1)	A:14.52 (2.24) C:14.23 (2.04)	BMI: A:17.76 (2.60) C:20.87 (4.54)	Cobb angle Osteopenia: mean 30.2 (SD 7.3) Normal bone mass: mean 24.8 (SD 8.1)	None	BMD: DEXA(lumbar spine and femoral neck) Serum ghrelin through ELISA Gene analysis through SNP	BMD: A group < C group Dysregulation of the ghrelin/RANKL/OPG pathway in A group
30	Yu 2014 [19]	T:401 (0) A:214 (0) C:187 (0)	A:12.9 (0.6) C:12.9 (0.5)	BMI: A:18.2 (2.6) C:19.5 (3.0)	Cobb angle mean 22.0° (SD 8.5°, Range 10°-35°)	None	1. BMD: DEXA 2. Bone quality: HR-pQCT (bone geometry, vBMD, Trabecular bone micro-architecture) 3. Dietary calcium intake and physical activity level	BMD & Bone quality: A group < C group Incidence of osteopenia: A group > C group
31	Zhang 2019 [12]	T:127 (58.3) A:92 (51.1) C:35 (68.6)	A:13.85 (2.22) C:14.31 (2.04)	BMI: A:17.30 (1.14) C:18.76 (1.24)	Cobb angle mean 22.8° (SD 6.98°)	–	1. BMC & BMD: DEXA 2. Serum Adiponectin	BMC & BMD: A group < C group Adiponectin: A group > C group
32	Zhang 2021 [16]	T:322 (0) A:161 (0) C:161 (0)	A:13.9 (12.8–15.0) C:13.8 (12.9–15.1)	Height: A:155.1 (6.1) C:156.4 (6.6) Weight: A:42.7 (6.3) C:48.2 (6.7)	Cobb angle: median 27°(Quartile 19–39)	Brace:104 Observation:30 Surgery:27	1. BMD: DEXA 2. Bone quality: HR-pQCT (bone geometry, vBMD, Trabecular bone micro-architecture) 3.Bone turnover markers: serum CTX and p1NP	BMD: A group < C Bone turnover markers level & bone remodeling: A group > C group

AIS Adolescent idiopathic scoliosis; *T* Total; *A* Adolescent idiopathic scoliosis; *C* Control; *W* Weight; *H* Height; *BMI* Body mass index; *BMD* Bone mineral density; *SD* Standard deviation; *DEXA* Dual-energy X-ray absorptiometry; *MSC* Mesenchymal stem cells; *25OHD or 25(OH)Vit-D* 25-Hydroxy vitamin D test; *Ca* Calcium; *Cr* Chromium; *Mg* Magnesium; *P* phosphorus; *pQCT* peripheral quantitative computed tomography; *HR-pQCT* High-resolution quantitative computed tomography; *sOB-R levels* soluble Leptin receptor levels; *ALP* Alkaline Phosphatase; *CTX* Carboxy-terminal collagen crosslinks; *SNP* Single nucleotide polymorphism; *MSC differentiation* Mesenchymal stem cell differentiation; *OPG* Osteoprotegerin; *RANKL* Receptor activator of nuclear factor Kappa-B ligand; *BV/TV* Bone volume fraction; *Tb.N* trabecular number; *Tb.Th* trabecular thickness; *Tb.Sp* trabecular separation; *SMI* structure model index; *Conn.D* connectivity density; *BS/BV* specific bone surface; *vBMD* average volumetric bone mineral density; *mBMD* material bone tissue mineral density; *ELISA* Enzyme-linked immunosorbent assay; *p1NP* Procollagen Type I Intact N-terminal Propeptide

studies that recruited both males and females [11, 12, 42, 47] (WMD −1.516; 95% CI −2.401 to −0.632, $p = 0.001$; $I^2 = 93.9\%$, $p < 0.001$) (Fig. 2).

Osteoporotic prevalence

Osteoporosis prevalence was reported by five case–control studies [13, 29, 38, 41, 42]. The pooled analysis is shown in Fig. 3, which indicated that the prevalence of osteoporosis in the IS group was estimated to be 6.813 times higher than that in the control group (OR 6.813; 95% CI 2.815–16.489, $p < 0.000$; $I^2 = 18.3\%$, $p = 0.298$).

In the subgroup analysis, the pooled results of three case–control studies [13, 29, 38] with only female participants showed that the prevalence of osteoporosis in the IS group was significantly higher than that in the control group (OR 10.219; 95% CI 3.024–34.536, $p < 0.001$; $I^2 = 50.9\%$, $p = 0.131$). Although there was no significant heterogeneity in the two case–control studies that recruited both males and females [41, 42], the synthesized results also showed no significant differences between the two groups (OR 3.559; 95% CI 0.935–13.547, $p = 0.063$; $I^2 = 0.0\%$, $p = 0.575$).

Osteopenia prevalence

Osteopenia is a lack of bone mass between healthy bone and osteoporotic bone. Clinically, osteopenia can be diagnosed when the BMD z score is less than –1.0 [2]. Eight case–control studies [13, 18, 19, 26, 27, 38, 42, 45] reported osteopenia prevalence, and the pooled analysis showed that the IS group had a significantly higher prevalence of osteopenia than control group (OR 1.879; 95% CI 1.548–2.281, $p < 0.000$; $I^2 = 69.4\%$, $p = 0.002$).

The gender subgroup analysis is shown in Fig. 4. When we pooled the data from studies that only included female participants [13, 18, 19, 26, 27, 38, 45], the results showed that the prevalence of osteopenia was estimated to be 1.818 times higher in the IS group than in the control group (OR 1.818; 95% CI 1.489–2.219, $p < 0.000$; $I^2 = 70.9\%$, $p = 0.002$). However, the OR increased when both males and females were enrolled in the study for the subgroup analysis (OR 3.380; 95% CI 1.469–7.777, $p = 0.004$) [42].

Areal bone mineral density

The measurement of aBMD is based on two-dimensional imaging techniques, such as dual-energy X-ray absorptiometry [13] aBMD equals bone mineral content divided by the area of the region of interest (ROI). The lumbar spine and the nondominant side femoral neck are two frequently selected ROIs in clinical practice [11–13, 19, 28, 30, 34, 36–40, 42, 46, 48].

Lumbar spine BMD (LSBMD)

LSBMD was reported in 14 case–control studies [11–13, 19, 28, 30, 34, 36–40, 42, 46]. In the pooled analysis, significant differences were found between the two groups (WMD

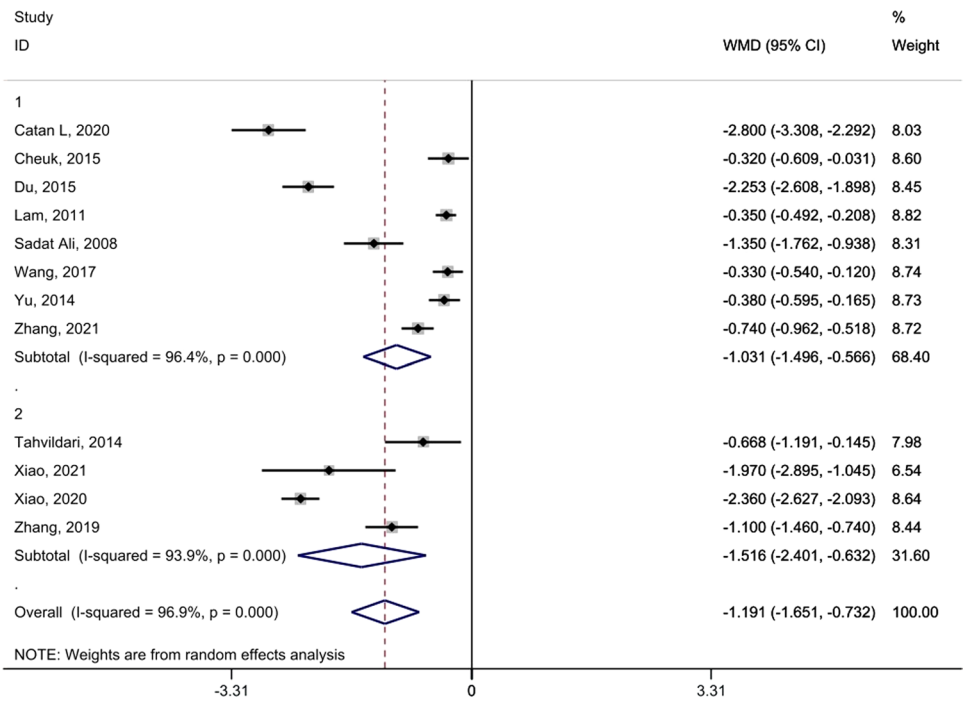


Fig. 2 Forest plot of bone mineral density z score

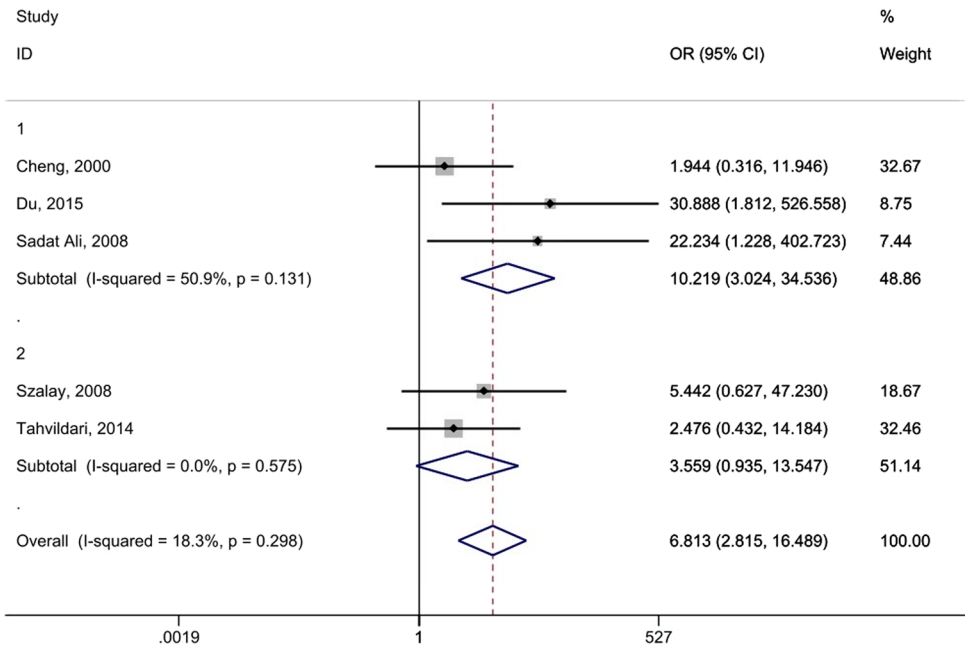


Fig. 3 Forest plot of osteoporotic prevalence

−0.096; 95% CI −0.129 to −0.062, $p < 0.001$; $I^2 = 94.6\%$, $p < 0.001$). Evidence of publication bias in LSBMD was observed with Begg's test ($z = -2.68$, Pr>|z| = 0.007).

In the gender subgroup analysis, significant differences between the IS group and control group were discovered in seven included studies [13, 19, 34, 37–40] that only enrolled female participants (WMD −0.058; 95% CI −0.090 to −0.027, $p < 0.001$; $I^2 = 91.3\%$, $p < 0.001$). The synthesized results from seven case–control studies with male and female participants [11, 12, 28, 30, 36, 42, 46] also showed significant differences between two groups (WMD −0.126; 95% CI −0.199 to −0.052, $p = 0.001$; $I^2 = 95.1\%$, $p < 0.001$) (Fig. 5a).

Femoral neck BMD (FNBMD)

Nineteen studies reported FNBMD of the nondominant side in the outcome measures [11–13, 17–19, 27, 28, 30, 33, 34, 36–40, 42, 45, 46]. There was a significant difference between the IS and control groups in FNBMD (WMD −0.061; 95% CI −0.078 to −0.044, $p < 0.001$; $I^2 = 86.6\%$, $p < 0.001$). The Begg's test revealed evidence of publication bias in FNBMD ($z = -2.97$, Pr>|z| = 0.003).

Significant differences were observed in the subgroup of 7 studies [13, 18, 19, 27, 33, 34, 37–40, 45] with all female participants (WMD −0.043; 95% CI −0.061 to −0.025, $p < 0.001$; $I^2 = 86.5\%$, $p < 0.001$). The pooled results from the studies [11, 12, 17, 28, 30, 36, 42, 46] including both male and female participants showed significant differences between IS group and control group as well (WMD −0.090; 95% CI −0.126 to −0.055, $p < 0.001$; $I^2 = 80.6\%$, $p < 0.001$) (Fig. 5b).

Volumetric bone mineral density

Compared to DEXA, pQCT is a three-dimensional imaging tool that can reveal vBMD through the modeling of ROIs [43]. The distal radius is usually selected as the ROI during clinical practice [16].

Total vBMD The total vBMD was presented as an outcome measure in 6 studies [13, 16, 19, 28, 43, 45]. Significant differences were found between the two groups when the results were pooled (Fig. 6a) (WMD −17.770; 95% CI −25.998 to −9.543, $p < 0.001$; $I^2 = 47.1\%$, $p = 0.093$).

The pooled data from five studies [13, 16, 19, 43, 45] with female participants disclosed significant differences between the IS group and control group (WMD −17.538; 95% CI −27.125 to −7.950, $p < 0.001$; $I^2 = 56.8\%$, $p = 0.055$). In a study with both genders [28], the BMD in the IS group was also significantly lower than that in the control group (WMD −20.500; 95% CI −39.504 to −1.496, $p = 0.034$).

Cortical vBMD Four studies included cortical vBMD [16, 19, 43, 45] and significant differences were found when the data were synthesized (Fig. 6b) (WMD −28.903; 95% CI −39.992 to −17.814, $p < 0.001$; $I^2 = 35.4\%$, $p = 0.200$).

Trabecular vBMD Trabecular vBMD was examined in 6 studies [13, 16, 19, 28, 43, 45]. Figure 6c shows that there were significant differences between the two groups (WMD −6.341; 95% CI −10.178 to −2.504, $p = 0.001$; $I^2 = 37.9\%$, $p = 0.153$).

After subgrouping, the IS group had significantly less trabecular vBMD than the control group, with no significant

heterogeneity (WMD −5.680; 95% CI −9.340 to −2.020, $p=0.002$; $I^2 = 34.1\%$, $p=0.194$) according to the pooled results from [13, 16, 19, 43, 45] with all female participants.

Secondary outcomes

Bone morphometry and trabecular microarchitecture

Peripheral quantitative computed tomography can provide bone morphometry and trabecular microarchitecture measurements via high-precision imaging and software-aided analysis. The data from 4 case–control studies with 1348 participants were pooled [16, 19, 43, 45].

Regarding bone morphometry (Figure S1), the results showed that compared with the control group, the IS group had a significantly smaller cortical area (WMD −4.521; 95% CI −7.219 to −1.824, $p=0.001$; $I^2 = 71.6\%$, $p=0.014$) and cortical thickness (WMD −0.109; 95% CI −0.166 to −0.051, $p<0.001$; $I^2 = 77.5\%$, $p=0.004$). However, the cortical perimeter in the group with scoliosis was significantly larger than that in the control group (WMD 0.419; 95% CI −0.100 to 0.938, $p=0.114$; $I^2 = 18.9\%$, $p=0.296$).

For the measurements regarding trabecular microarchitecture (Figure S2), the IS group had a significantly smaller trabecular number (WMD −0.057; 95% CI −0.084 to −0.030, $p<0.001$; $I^2 = 14.6\%$, $p=0.319$) and trabecular bone volume to tissue volume ratio (BV/TV, WMD −0.005; 95% CI −0.008 to −0.002, $p=0.003$; $I^2 = 36.8\%$, $p=0.191$) than the control group. Meanwhile, the trabecular area in the IS group was significantly larger than that in the control group (WMD 3.861; 95% CI 0.811–6.910, $p=0.013$; $I^2 = 0.0\%$, $p=0.519$). No significant differences were found between the two groups in trabecular separation (WMD 0.022; 95% CI −0.012 to 0.056, $p=0.213$; $I^2 = 91.3\%$, $p<0.000$) or trabecular thickness (WMD −0.000; 95% CI −0.001 to 0.001, $p=0.759$; $I^2 = 0.0\%$, $p=0.895$).

Only two studies included the total area of the ROI [16, 28], and no significant difference was shown (WMD −0.514; 95% CI −5.743 to 6.772, $p=0.872$; $I^2 = 0.0\%$, $p=0.514$) (Figure S3).

Quantitative ultrasound

QUS is an effective and radiation-free method to measure bone mineral status in specific peripheral bones. One study [29] chose the distal radius as the measurement area of the ultrasound probe, while the calcaneus was selected as the measurement target in two studies [18, 31].

The SOS was reported in three studies [18, 29, 31], and there was no significant difference in the SOS between the IS group and the control group. (WMD −83.462; 95% CI −163.946 to 1.023, $p=0.053$; $I^2 = 98.1\%$, $p=0.000$). Two studies reported BUA and SI [18, 31] and significance was shown in BUA (WMD −5.610; 95% CI −9.001 to −2.219, $p=0.001$; $I^2 = 35.4\%$, $p=0.213$) and SI (WMD −25.401; 95% CI −30.984 to −19.818, $p<0.001$; $I^2 = 0.0\%$, $p=0.828$), respectively (Figure S4).

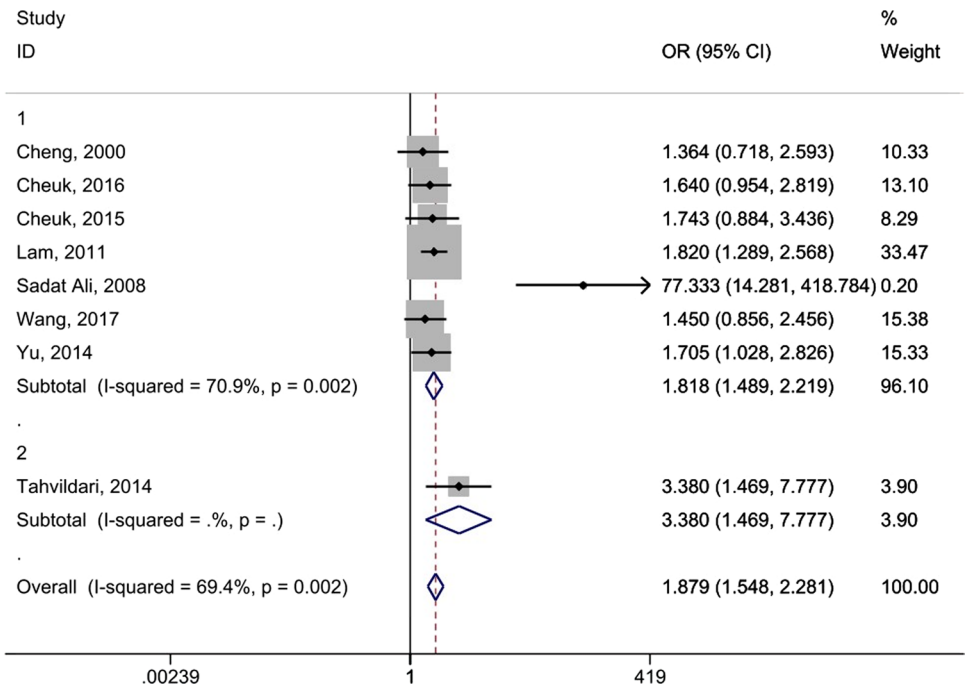
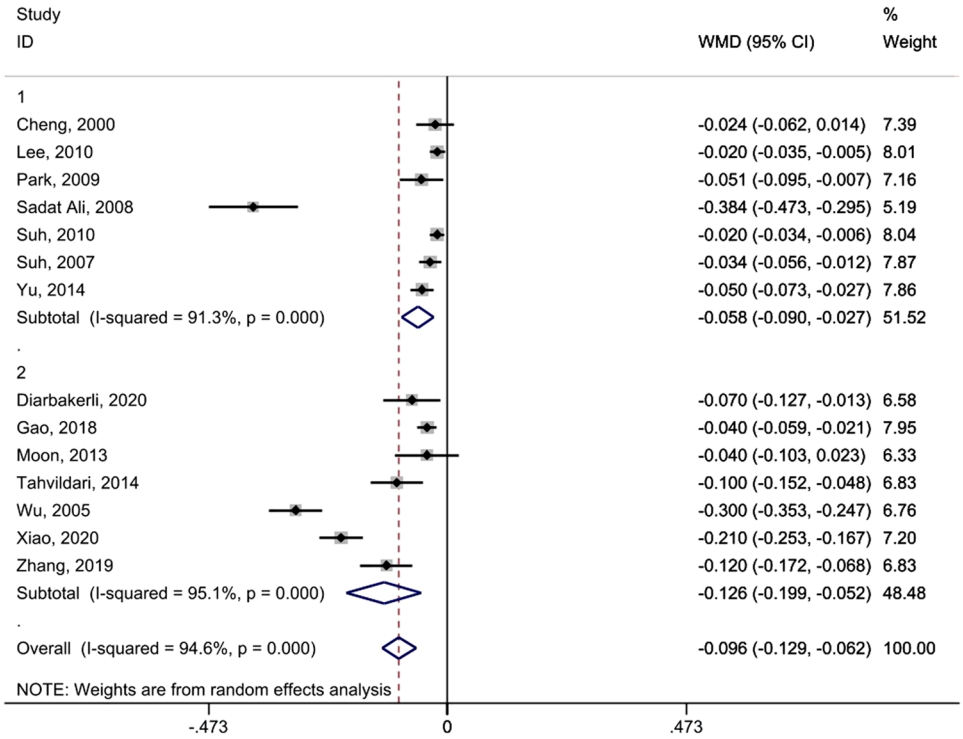
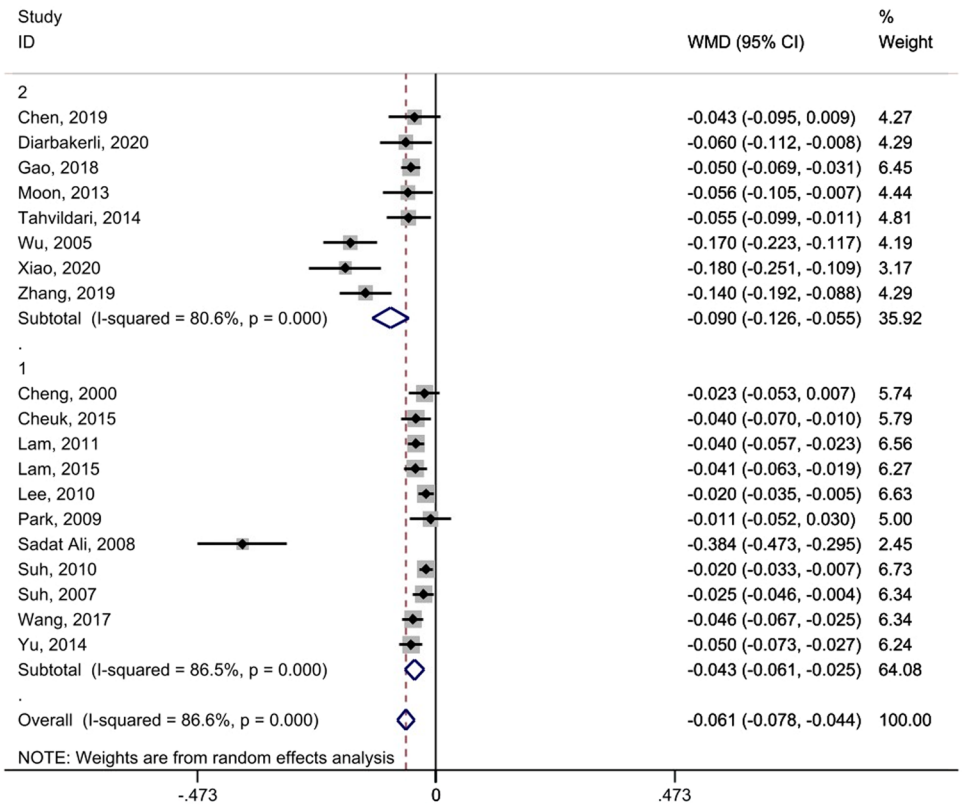


Fig. 4 Forest plot of osteopenic prevalence



(a) Lumbar spine bone mineral density (LSBMD)



(b) Femoral neck bone mineral density (FNBMD)

Fig. 5 Forest plots of areal bone mineral density. **a** Lumbar spine bone mineral density (LSBMD) and **b** Femoral neck bone mineral density (FNBMD)

Discussion

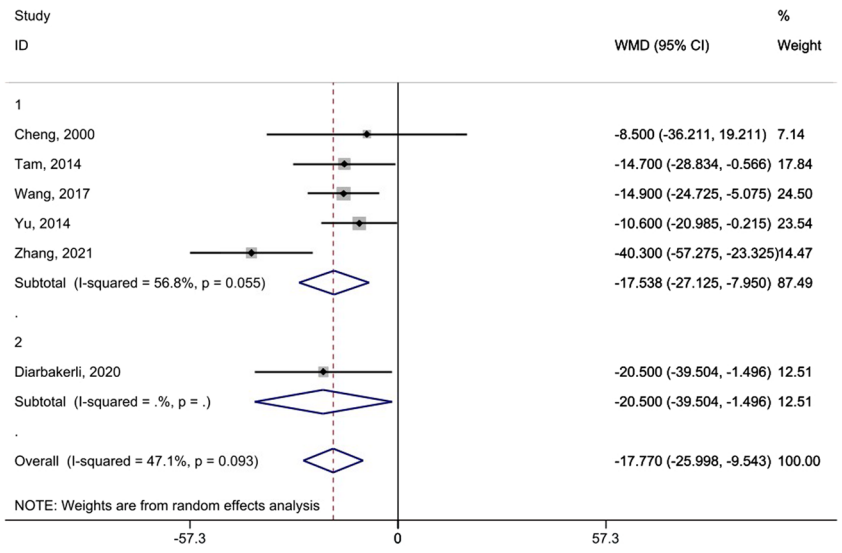
This review aimed to explore the bone status of IS patients. Overall, the BMD *z* score of the IS patients was smaller than that of the control group. The prevalence of osteoporosis and osteopenia significantly increased in the IS group. The results of DEXA and pQCT measures showed a significant decrease in BMD throughout the limbs and trunk, and in both cortical and cancellous bone. The SOS measured by quantitative ultrasound did not show significant differences between the two groups. Bone morphometry and microarchitecture were also altered in the scoliosis group.

Noticeably, high heterogeneity was found in the BMD *z* score, and aBMD measures. Some studies have found that there was no significant difference in the prevalence of osteoporosis between IS patients and the control group [47, 49]. However, this heterogeneity was caused by the characteristics of the control group, as the participants in the control group had a history of fractures, which suggested that they may have potentially low BMD [50]. Although gender may be a source of heterogeneity [51], the results of the subgroup analysis revealed that gender disparities might not be linked to heterogeneity. Another source of heterogeneity may be the diversity of measurement methods (DEXA, CT, or QUS). For example, Hung et al. [31] found only moderate correlations (3.4 < correlation coefficient < 4.5) between QUS and DEXA indicators. when interpreting the results of this review, the above possible sources of heterogeneity should be noticed. DEXA is the gold standard technology for measuring BMD as it is recommended by some guidelines, because of the low radiation, short time required, and affordable [52]. There is also methodological heterogeneity associated with BMD measurements of different body sites in IS patients. Because DEXA uses two-dimensional imaging to measure BMD, three-dimensional spinal deformity may overlap in DEXA imaging, leading to the underestimation of BMD [53]. Studies have shown that LSBMD measured by DEXA may be underestimated by 11.5–17.5%, because of axial rotation and anteroposterior curvatures in IS patients [54]. Results of our systematic review also showed the trend that the effect size of the differences in LSBMD between IS and control groups was higher than that of FNBMD ($WMD_{LSBMD} = -0.096$ vs. $WMD_{FNBMD} = -0.061$). It should be noted that because of the underestimation effect of DEXA, the significant decrease of LSBMD in IS patients should be interpreted carefully.

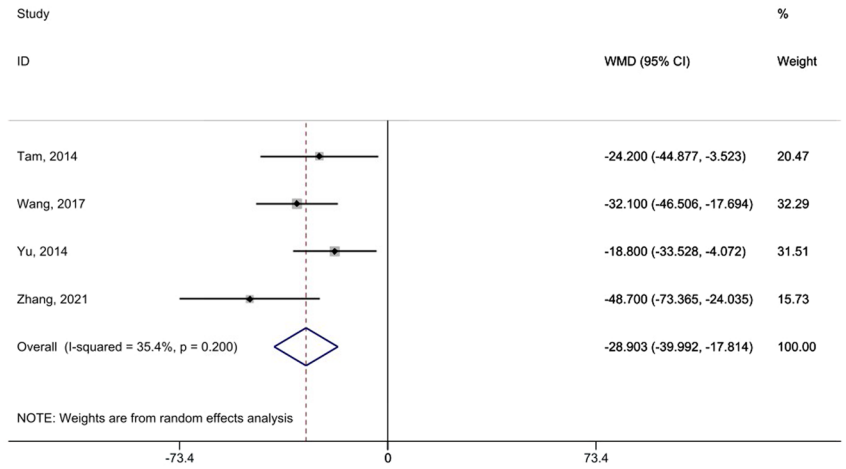
Our results also suggested a significant increase in the prevalence of osteoporosis and osteopenia in the IS group (OR 6.813 and 1.879). However, the diagnostic criteria for osteoporosis have not yet reached a consensus because of the differences in age, gender, and race [55]. For example, the WHO recommends people with a BMD *z* score less than −2.5 SD would be diagnosed with osteoporosis, but this diagnostic criterion is based on Caucasian postmenopausal women [55]. Because adolescents have not yet reached the peak bone mass, the *z* score should be used as a reference for the diagnosis of adolescent osteoporosis, rather than the *T*-value that reflects the absolute bone mass [42]. Three included studies in this systematic review used BMD less than −2.0 SD as the diagnostic criterion for osteoporosis [13, 29, 41], while another 2 included studies used a threshold of less than −2.5 SD [38, 42]. However, a BMD *z* score of −2.0 SD standard is recommended for adolescent IS patients [56], since osteoporosis can be diagnosed and treated early, compared to the criterion of less than −2.5 SD.

With regard to the pathogenesis of osteoporosis in IS patients, our study shows that IS patients have higher rates of osteopenia (OR = 1.879) and osteoporosis (OR = 6.813), suggesting that osteoporosis may not be an occasional symptom but comorbidity in IS patients. This condition may be associated with genetic susceptibility to osteoporosis in IS patients. Compared with normal people, IS patients have higher osteoprotegerin (OPG) and lower RANKL, disrupting the balance of RANKL/RANK and OPG. So the number of osteoclasts increases excessively, which enhances bone resorption, and leads to a decrease in BMD [11]. On the other hand, some studies have suggested the importance of lifestyle factors. Szalay et al. suggested that the main cause of osteopenia in IS patients is low body mass index, which is an outcome measure that is related to lifestyle [41]. Some studies showed that sufficient vitamin D intake may increase calcium absorption by approximately 40% during puberty maturation [57], while adolescents with vitamin D deficiency may not achieve peak bone mass [58]. Physical activity is another important factor related to BMD. Weight-bearing activities, such as running and climbing, can significantly improve lumbar spine BMD in adolescents [59].

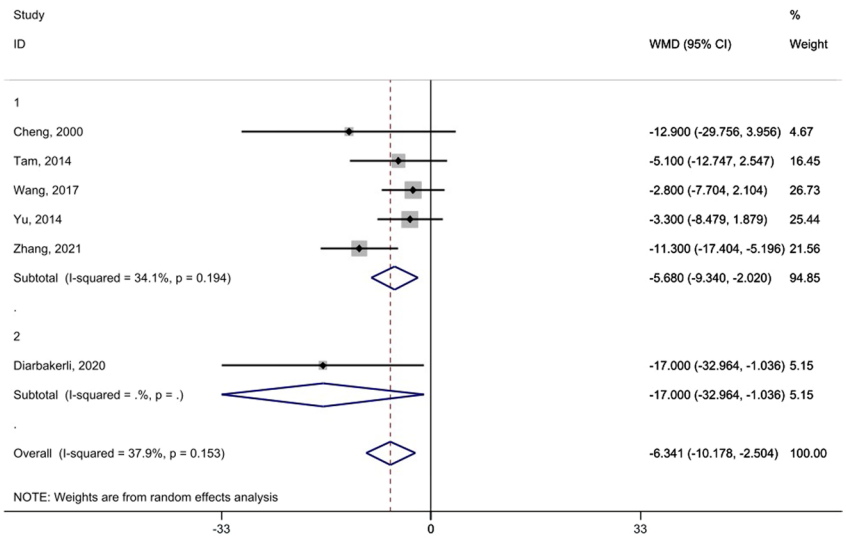
Subgroup analyses showed that male IS patients might have lower BMD and a higher prevalence of osteopenia than female IS patients, which was inconsistent with previous findings that low BMD is more common in females than in males [6]. It might be explained that internal (such as genetic factors) or external factors (such as daily habits) may be associated with low BMD in male IS patients. Studies have shown that BMD increased significantly in males between the ages of 15–18, and the BMD of males may not catch up to that of females until eighteen [60]. This suggested that male adolescents may have less BMD than females before the age of 15. In the prevalence of osteoporosis, subgroup analysis showed that only the female IS patients showed a significantly higher prevalence of osteoporosis, suggesting that female IS patients may have a poor prognosis. In contrast, male IS patients may have osteopenia but have not reached the degree of osteoporosis. The results also



(a) Total vBMD



(b) Cortical vBMD



(c) Trabecular vBMD

Fig. 6 Forest plots of volumetric bone mass density (vBMD). **a** Total vBMD. **b** Cortical vBMD. **c** Trabecular vBMD

indicated that BMD in both male and female patients should be carefully concerned and evaluated.

Regular BMD screening can help detect bone problems early and avoid the negative impact of osteopenia on IS progression. Our results suggested that DEXA and pQCT might be two effective instruments for BMD screening. Although nonradiative quantitative ultrasound may be more acceptable to patients and their parents, our results showed that the validity of SOS may need to be further verified, including discriminant validity between IS group and control group and the association between SOS and BMD measured by DEXA and pQCT. Early intervention can be used to counter the effect of osteopenia on the progression of IS.

Due to the generally low BMD of IS patients, bone improvement should be included in their comprehensive interventions. In terms of pathogenesis, since many factors of daily life are associated with osteoporosis, the economical and efficient intervention may include increased physical activity and calcium and vitamin intake [61, 62]. In the future, more clinical evidence can be provided by promoting research on the effect of these osteoporotic interventions in improving IS patients.

Limitations

There were several limitations to our systematic review. Although IS patients showed lower BMD z scores and aBMD and a higher prevalence of osteopenia, the heterogeneity arising from the methodology needs attention, such as the differences in the measurements of BMD and diagnostic criteria of osteoporosis. It is necessary to establish a standardized BMD measurement scheme and unified diagnostic criteria to reduce methodological heterogeneity among studies. In addition, this systematic review only included case–control studies that compared BMD between the IS group and the control group, which could not provide direct evidence for the pathogenesis of osteoporosis or clinical intervention in IS patients. In the future, well-designed RCT studies on potential intervention protocols for BMD improvement will be needed, and long-term cohort studies will also be required to clarify low BMD in the pathogenesis of IS.

Conclusion

In this systematic review and meta-analysis, the BMD of both male and female IS patients was generally decreased, with an increase in the prevalence of osteopenia and osteoporosis. It is necessary to regularly monitor BMD through DEXA or pQCT while the employ of quantitative ultrasound in BMD screening should be further validated. Targeted interventions are necessary for IS patients during clinical practice. Future research should focus on the etiology of osteoporosis in individuals with scoliosis to determine the intervention target.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00586-022-07463-w.

Author contributions The study's concept and design were contributed to by QD and XZ. Material preparation, data collection and analysis were performed by YY, XH, ZC and XL. YY and HY assessed the bias in articles, and disagreements were settled by QD. All the authors contributed to the draft of the manuscript.

Funding This work was supported by the General Program of National Natural Science Foundation of China (81972030), Clinical Research Plan of SHDC (SHDC2020CR3041B), and Action Plan for Sustainable Development of Science and Technology Innovation in Chongming District, Shanghai (CKY2021-50).

Declarations

Conflict of interests The authors have no competing interests to declare that are relevant to the content of this article.

Ethical standards This is a systematic review and meta-analysis, we only include published literature, ethics approval, and patient informed consent are not required.

References

1. Negrini S, Donzelli S, Aulisa AG, Czaprowski D, Schreiber S, de Mauroy JC, Diers H, Grivas TB, Knott P, Kotwicki T, Lebel A, Marti C, Maruyama T, O'Brien J, Price N, Parent E, Rigo M, Romano M, Stikeleather L, Wynne J, Zaina F (2018) 2016 SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth. Scoliosis Spinal Disord 13:1–48. https://doi.org/10.1186/s13013-017-0145-8
2. Cheung CS, Lee WT, Tse YK, Lee KM, Guo X, Qin L, Cheng JC (2006) Generalized osteopenia in adolescent idiopathic scoliosis–association with abnormal pubertal growth, bone turnover, and calcium intake? Spine 31:330–338. https://doi.org/10.1097/01.brs.0000197410.92525.10
3. Cheng JC, Castelein RM, Chu WC, Danielsson AJ, Dobbs MB, Grivas TB, Gurnett CA, Luk KD, Moreau A, Newton PO, Stokes IA, Weinstein SL, Burwell RG (2015) Adolescent idiopathic scoliosis. Nat Rev Dis Primers 1:1–21. https://doi.org/10.1038/nrdp.2015.30
4. Karaguzel G, Holick MF (2010) Diagnosis and treatment of osteopenia. Rev Endocr Metab Disord 11:237–251. https://doi.org/10.1007/s11154-010-9154-0
5. Salari N, Ghasemi H, Mohammadi L, Rabieenia E, Shohaimi S, Mohammadi M (2021) The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. J Orthop Surg Res 16:1–20. https://doi.org/10.1186/s13018-021-02772-0
6. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, Cui L, Zhao N, Lin Q, Chen L (2021) Prevalence of osteoporosis and fracture in China: the China osteoporosis prevalence study. JAMA Netw Open 4:e2121106–e2121106. https://doi.org/10.1001/jamanetworkopen.2021.21106

7. Hung VWY, Qin L, Cheung CSK, Lam TP, Ng BKW, Tse YK, Guo X, Lee KM, Cheng JCY (2005) Osteopenia: a new prognostic factor of curve progression in adolescent idiopathic scoliosis. J Bone Jt Surg 87:2709–2716. https://doi.org/10.2106/jbjs.D.02782
8. Lee WT, Cheung CS, Tse YK, Guo X, Qin L, Lam TP, Ng BK, Cheng JC (2005) Association of osteopenia with curve severity in adolescent idiopathic scoliosis: a study of 919 girls. Osteoporos Int 16:1924–1932. https://doi.org/10.1007/s00198-005-1964-7
9. Sun X, Wu T, Liu Z, Zhu Z, Qian B, Zhu F, Ma W, Yu Y, Wang B, Qiu Y (2013) Osteopenia predicts curve progression of adolescent idiopathic scoliosis in girls treated with brace treatment. J Pediatr Orthop 33:366–371. https://doi.org/10.1097/BPO.0b013e31827b7b5f
10. El Hawary R, Zaaroor-Regev D, Floman Y, Lonner BS, Alkhalife YI, Betz RR (2019) Brace treatment in adolescent idiopathic scoliosis: risk factors for failure: a literature review. Spine J 19:1917–1925. https://doi.org/10.1016/j.spinee.2019.07.008
11. Xiao L, Zhang H, Wang Y, Li J, Yang G, Wang L, Liang Z (2020) Dysregulation of the ghrelin/RANKL/OPG pathway in bone mass is related to AIS osteopenia. Bone. https://doi.org/10.1016/j.bone.2020.115291
12. Zhang HQ, Wang LJ, Liu SH, Li J, Xiao LG, Yang GT (2019) Adiponectin regulates bone mass in AIS osteopenia via RANKL/OPG and IL6 pathway. J Transl Med 17:1–15. https://doi.org/10.1186/s12967-019-1805-7
13. Cheng JC, Qin L, Cheung CS, Sher AH, Lee KM, Ng SW, Guo X (2000) Generalized low areal and volumetric bone mineral density in adolescent idiopathic scoliosis. J Bone Miner Res 15:1587–1595. https://doi.org/10.1359/jbmr.2000.15.8.1587
14. Li XF, Li H, Liu ZD, Dai LY (2008) Low bone mineral status in adolescent idiopathic scoliosis. Eur Spine J 17:1431–1440. https://doi.org/10.1007/s00586-008-0757-z
15. Catan L, Cerbu S, Amaricai E, Suciu O, Horhat DI, Popoiu CM, Adam O, Boia E (2020) Assessment of static plantar pressure, stabilometry, vitamin D and bone mineral density in female adolescents with moderate idiopathic scoliosis. Int J Environ Res Public Health 17:2167. https://doi.org/10.3390/ijerph17062167
16. Zhang J, Wang Y, Cheng KL, Cheuk K, Lam TP, Hung ALH, Cheng JCY, Qiu Y, Müller R, Christen P, Lee WYW (2021) Association of higher bone turnover with risk of curve progression in adolescent idiopathic scoliosis. Bone. https://doi.org/10.1016/j.bone.2020.115655
17. Chen H, Zhang J, Wang Y, Cheuk KY, Hung ALH, Lam TP, Qiu Y, Feng JQ, Lee WYW, Cheng JCY (2019) Abnormal lacunocanalicular network and negative correlation between serum osteocalcin and Cobb angle indicate abnormal osteocyte function in adolescent idiopathic scoliosis. FASEB J 33:13882–13892. https://doi.org/10.1096/fj.201901227R
18. Lam TP, Hung VW, Yeung HY, Tse YK, Chu WC, Ng BK, Lee KM, Qin L, Cheng JC (2011) Abnormal bone quality in adolescent idiopathic scoliosis: a case-control study on 635 subjects and 269 normal controls with bone densitometry and quantitative ultrasound. Spine 36:1211–1217. https://doi.org/10.1097/BRS.0b013e3181ebab39
19. Yu WS, Chan KY, Yu FW, Ng BK, Lee KM, Qin L, Lam TP, Cheng JC (2014) Bone structural and mechanical indices in adolescent Idiopathic Scoliosis evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT). Bone 61:109–115. https://doi.org/10.1016/j.bone.2013.12.033
20. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1–9. https://doi.org/10.1186/2046-4053-4-1
21. Horne JP, Flannery R, Usman S (2014) Adolescent idiopathic scoliosis: diagnosis and management. Am Fam Phys 89:193–198
22. Stern C, Jordan Z, McArthur A (2014) Developing the review question and inclusion criteria. Am J Nurs 114:53–56. https://doi.org/10.1097/01.naj.0000445689.67800.86
23. Luchini C, Stubbs B, Solmi M, Veronese N (2017) Assessing the quality of studies in meta-analyses: advantages and limitations of the newcastle ottawa scale. World J Meta-Anal 5:80–84. https://doi.org/10.13105/wjma.v5.i4.80
24. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, Morgan RL, Gartlehner G, Kunz R, Katikireddi SV (2019) GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol 111:105–114. https://doi.org/10.1016/j.jclinepi.2018.01.012
25. Avram CM, Cioara F, Mihailov M (2010) Study of aspects of bone mineral density in children with scoliosis. Osteoporos Int 21:S40–S41. https://doi.org/10.1007/s00198-010-1247-9
26. Cheuk KY, Wang J, Yu FWP, Lee WYW, Lam TP, Edward Guo X, Cheng JCY (2016) Abnormal trabecular plate and rod structure in adolescent idiopathic scoliosis: a study with individual trabecula segmentation (ITS). J Orthop Res. https://doi.org/10.1002/jor.23247
27. Cheuk KY, Zhu TY, Yu FW, Hung VW, Lee KM, Qin L, Cheng JC, Lam TP (2015) Abnormal bone mechanical and structural properties in adolescent idiopathic scoliosis: a study with finite element analysis and structural model index. Calcif Tissue Int 97:343–352. https://doi.org/10.1007/s00223-015-0025-2
28. Diarbakerli E, Savvides P, Wihlborg A, Abbott A, Bergström I, Gerdhem P (2020) Bone health in adolescents with idiopathic scoliosis. Bone Jt J 102:268–272. https://doi.org/10.1302/0301-620X.102B2.BJJ-2019-1016.R1
29. Du Q, Zhou X, Li JA, He XH, Liang JP, Zhao L, Yang XY, Chen N, Zhang SX, Chen PJ (2015) Quantitative ultrasound measurements of bone quality in female adolescents with idiopathic scoliosis compared to normal controls. J Manipulative Physiol Ther 38:434–441. https://doi.org/10.1016/j.jmpt.2015.06.009
30. Gao J, Zhang L, Liu Z, Yao S, Gao S (2018) Correlation analysis between interleukin 6 polymorphism and adolescent idiopathic scoliosis susceptibility and bracing effectiveness. Chin J Repar Reconstr Surg 32:678–684. https://doi.org/10.7507/1002-1892.201710054
31. Hung VWY, Yeung HY, Qin L, Lee KM, Ng BKW, Cheng JCY (2006) Assessment of low bone mass in adolescent idiopathic scoliosis: a correlation study of DXA and quantitative ultrasound. Osteoporos Int 17:S284–S285
32. Lam EMS, Lee W, Cheuk KY, Lam TP, Ng BKW, Lee SKM, Qiu Y, Cheng JCY (2015) Morphological and bone strength indices in girls with adolescent idiopathic scoliosis and their correlations with leptin and soluble leptin receptor. Scoliosis 10:1–2. https://doi.org/10.1186/1748-7161-10-S1-O13
33. Lam TP, Wah Ng BK, Lee KM, Hung ALH, Tam EMS, Cheung FTF, Tsang EKL, Cheng JCY (2015) Serum 25(OH)vitamin D level and its correlation with bone mineral density in girls with adolescent idiopathic scoliosis (AIS). Scoliosis 10:1–1. https://doi.org/10.1186/1748-7161-10-S1-O7
34. Lee JS, Suh KT, Eun IS (2010) Polymorphism in interleukin-6 gene is associated with bone mineral density in patients with adolescent idiopathic scoliosis. J Bone Jt Surg 92:1118–1122. https://doi.org/10.1302/0301-620X.92B8.23676
35. Lee WT, Cheng JC, Cheung CS, Guo X (2003) Inadequate calcium intake is a significant determinant on generalised osteopenia in Hong Kong Chinese adolescents with idiopathic scoliosis. J Hyg Res 32:568–572
36. Moon ES, Kim HS, Sharma V, Park JO, Lee HM, Moon SH, Chong HS (2013) Analysis of single nucleotide polymorphism in adolescent idiopathic scoliosis in Korea: for personalized

treatment. Yonsei Med J 54:500–509. https://doi.org/10.3349/ymj.2013.54.2.500
37. Park WW, Suh KT, Kim JI, Kim SJ, Lee JS (2009) Decreased osteogenic differentiation of mesenchymal stem cells and reduced bone mineral density in patients with adolescent idiopathic scoliosis. Eur Spine J 18:1920–1926. https://doi.org/10.1007/s00586-009-1129-z
38. Sadat-Ali M, Al-Othman A, Bubshait D, Al-Dakheel D (2008) Does scoliosis causes low bone mass? A comparative study between siblings. Eur Spine J 17:944–947. https://doi.org/10.1007/s00586-008-0671-4
39. Suh KT, Eun IS, Lee JS (2010) Polymorphism in vitamin D receptor is associated with bone mineral density in patients with adolescent idiopathic scoliosis. Eur Spine J 19:1545–1550. https://doi.org/10.1007/s00586-010-1385-y
40. Suh KT, Lee SS, Hwang SH, Kim SJ, Lee JS (2007) Elevated soluble receptor activator of nuclear factor-kappa B ligand and reduced bone mineral density in patients with adolescent idiopathic scoliosis. Eur Spine J 16:1563–1569. https://doi.org/10.1007/s00586-007-0390-2
41. Szalay EA, Bosch P, Schwend RM, Buggie B, Tandberg D, Sherman F (2008) Adolescents with idiopathic scoliosis are not osteoporotic. Spine 33:802–806. https://doi.org/10.1097/brs.0b013e318169578f
42. Tahvildari BP, Erfani MA, Nouraei H, Sadeghian M (2014) Evaluation of bone mineral status in adolescent idiopathic scoliosis. Clin Orthop Surg 6:180–184. https://doi.org/10.4055/cios.2014.6.2.180
43. Tam EM, Yu FW, Hung VW, Liu Z, Liu KL, Ng BK, Lee SK, Qiu Y, Cheng JC, Lam TP (2014) Are volumetric bone mineral density and bone micro-architecture associated with leptin and soluble leptin receptor levels in adolescent idiopathic scoliosis?: a case-control study. PLoS ONE 9:e87939. https://doi.org/10.1371/journal.pone.0087939
44. Wang W, Wang Z, Zhu Z, Zhu F, Qiu Y (2016) Body composition in males with adolescent idiopathic scoliosis: a case-control study with dual-energy X-ray absorptiometry. BMC Musculoskelet Disord 17:1–6. https://doi.org/10.1186/s12891-016-0968-0
45. Wang ZW, Lee WY, Lam TP, Yip BH, Yu FW, Yu WS, Zhu F, Ng BK, Qiu Y, Cheng JC (2017) Defining the bone morphometry, micro-architecture and volumetric density profile in osteopenic versus non-osteopenic adolescent idiopathic scoliosis. Eur Spine J 26:1586–1594. https://doi.org/10.1007/s00586-016-4422-7
46. Wu J, Qiu Y, Zhang L, Sun YF, Chen X (2005) Changes of bone mineral density in association with serum interleukin-6 in adolescent idiopathic scoliosis. Chin J Clin Rehab 9:223–225. https://doi.org/10.3321/j.issn:1673-8225.2005.10.056
47. Xiao L, Yang G, Zhang H, Liu J, Guo C, Sun Y (2021) Non-targeted metabolomic analysis of plasma metabolite changes in patients with adolescent idiopathic scoliosis. Mediat Inflamm. https://doi.org/10.1155/2021/5537811
48. Yu WS, Chan KY, Yu FW, Yeung HY, Ng BK, Lee KM, Lam TP, Cheng JC (2013) Abnormal bone quality versus low bone mineral density in adolescent idiopathic scoliosis: a case-control study with in vivo high-resolution peripheral quantitative computed tomography. Spine J 13:1493–1499. https://doi.org/10.1016/j.spinee.2013.05.018
49. Wang Z, Chen H, Yu YE, Zhang J, Cheuk KY, Ng BK, Qiu Y, Guo XE, Cheng JC, Lee WY (2017) Unique local bone tissue characteristics in iliac crest bone biopsy from adolescent idiopathic scoliosis with severe spinal deformity. Sci Rep 7:1–10. https://doi.org/10.1038/srep40265
50. Martins A, Monjardino T, Nogueira L, Canhão H, Lucas R (2017) Do bone mineral content and density determine fracture in children? A possible threshold for physical activity. Pediatr Res 82:396–404. https://doi.org/10.1038/pr.2017.113
51. Wu XP, Yang YH, Zhang H, Yuan LQ, Luo XH, Cao XZ, Liao EY (2005) Gender differences in bone density at different skeletal sites of acquisition with age in Chinese children and adolescents. J Bone Miner Metab 23:253–260. https://doi.org/10.1007/s00774-004-0592-1
52. Blake GM, Fogelman I (2007) The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgrad Med J 83:509–517. https://doi.org/10.1136/pgmj.2007.057505
53. Garg M, Kharb S (2013) Dual energy X-ray absorptiometry: pitfalls in measurement and interpretation of bone mineral density. Indian J Endocrinol Metab 17:203. https://doi.org/10.4103/2230-8210.109659
54. Izadyar S, Golbarg S, Takavar A, Zakariaee SS (2016) The effect of the lumbar vertebral malpositioning on bone mineral density measurements of the lumbar spine by dual-energy X-ray absorptiometry. J Clin Densitom 19:277–281. https://doi.org/10.1016/j.jocd.2015.12.001
55. Dimai HP (2017) Use of dual-energy X-ray absorptiometry (DXA) for diagnosis and fracture risk assessment; WHO-criteria, T-and Z-score, and reference databases. Bone 104:39–43. https://doi.org/10.1016/j.bone.2016.12.016
56. Kung AW, Wu C-H, Itabashi A, Lee JK, Park HM, Zhao Y, Chan WP, Kendler DL, Leib ES, Lewiecki EM (2010) International society for clinical densitometry official positions: Asia-pacific region consensus. J Clin Densitom 13:346–351. https://doi.org/10.1016/j.jocd.2010.05.006
57. Saggese G, Baroncelli GI, Bertelloni S (2002) Puberty and bone development. Best Pract Res Clin Endocrinol Metab 16:53–64. https://doi.org/10.1053/beem.2001.0180
58. Lehtonen-Veromaa MK, Möttönen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS (2002) Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. Am J Clin Nutr 76:1446–1453. https://doi.org/10.1093/ajcn/76.6.1446
59. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, O'Karma M, Wallace TC, Zemel BS (2016) The national osteoporosis foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int 27:1281–1386. https://doi.org/10.1007/s00198-015-3440-3
60. Bonjour J-P, Theintz G, Buchs B, Slosman D, Rizzoli R (1991) Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab 73:555–563. https://doi.org/10.1210/jcem-73-3-555
61. Ferrari S, Bianchi ML, Eisman JA, Foldes AJ, Adami S, Wahl DA, Stepan JJ, de Vernejoul MC, Kaufman JM (2012) Osteoporosis in young adults: pathophysiology, diagnosis, and management. Osteoporos Int : A J Establ Result Coop Between Eur Found Osteoporos Natl Osteoporos Found USA 23:2735–2748. https://doi.org/10.1007/s00198-012-2030-x
62. Gómez-Bruton A, Matute-Llorente Á, González-Agüero A, Casajús JA, Vicente-Rodríguez G (2017) Plyometric exercise and bone health in children and adolescents: a systematic review. World J Pediatr 13:112–121. https://doi.org/10.1007/s12519-016-0076-0