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REVIEW

# Bone density and fracture risk factors in ankylosing spondylitis: a meta-analysis

**Fei Yan[1] · Linfeng Wu[1] · Juan Lang[1] · Zongju Huang[1]**

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## Abstract

**Summary** We included 39 studies in our meta-analysis, finding that patients with ankylosing spondylitis (AS) exhibit decreased bone mineral density (BMD) and an elevated risk of fractures. Additionally, we analyzed the risk factors associated with fractures in these patients.

**Introduction** AS is a chronic inflammatory disease primarily affecting the spine and sacroiliac joints, with reduced BMD, osteoporosis, and fractures being common complications. This study aims to systematically consolidate and conduct a meta-analysis of existing research to comprehensively understand decreased bone mineral density, osteoporosis, and fracture risks at various anatomical sites in AS patients. The objective is to provide reliable information for the management of AS patients and to inform clinical decision making.

**Methods** We conducted a thorough search in various databases including Embase, PubMed, Cochrane Library, and Web of Science. These studies focused on the risk of and risk factors for decreased BMD, osteopenia, osteoporosis, and fractures at different sites among AS patients such as the lumbar spine and femoral neck. The quality of eligible studies was evaluated. Sensitivity analysis was performed to assess the reliability of our analysis results and understand the effects of individual studies on the heterogeneity across studies.

**Results** A total of 39 studies were included. Our meta-analysis results revealed significant differences between AS patients and healthy controls. AS patients had significantly lower BMDs at the femoral neck, hip, lumbar vertebra 2 (L2), lumbar vertebra 3 (L3), and lumbar vertebra 4 (L4), but higher BMDs at 1/3 distal radius and ultra distal radius. Risk factors for fractures among AS patients included old age, long course of disease, and low BMD at the lumbar spine. In contrast, factors such as erythrocyte sedimentation rate (ESR), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, gender, and body mass index (BMI) were not risk factors for fractures in AS patients.

**Conclusion** Our study highlights that BMD at the femoral neck is more effective for evaluating AS patients compared with the BMD at the lumbar spine. Additionally, the risk of osteoporosis and fractures in AS patients is higher in younger patients and those at the early stage of this disease.

**Keywords** Ankylosing Spondylitis · BMD (bone mineral density) · Fractures · Meta-analysis

## Introduction

Ankylosing spondylitis (AS) is a chronic and progressive inflammatory disease that primarily affects the spine and sacroiliac joints [1]. Its prevalence varies globally due to regional and ethnic differences. According to a study [2], the average incidence of AS per 10,000 people is 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America, and 7.4 in Africa.

Despite differences in prevalence, AS poses a significant global public health challenge, potentially leading to joint pain, restricted flexibility, and physical deformities. Unfortunately, there is currently no cure for AS, and available treatments focus on pain relief, inflammation management, and addressing related complications [3]. Common complications include reduced bone mineral density (BMD), osteoporosis, and fractures [4] that undermine patients' quality

✉ Zongju Huang
hzj9488@163.com

[1] Department of Acupuncture and Moxibustion, Jiangbei District Hospital of Traditional Chinese Medicine, No.35, No.1 Village, Jianxin East Road, Jiangbei District, Chongqing 400021, China

of life and impose tremendous psychological and medical burdens [5–7].

Some studies have demonstrated decreased BMD in AS patients, with systematic reviews indicating a higher risk of low BMD and osteoporosis during the early stages of the disease [8]. However, these reviews only analyzed a limited number of studies, without conducting comprehensive meta-analyses, and only BMDs at the femoral neck and lumbar spine were investigated. Another meta-analysis targeted the risk of fractures and risk factors affecting fractures among AS patients [9]. However, the significant heterogeneity among the included studies and their publication date call for updated and more comprehensive meta-analyses.

Therefore, our study aimed to systematically integrate and evaluate existing studies through meta-analysis to gain deeper insights into the risk of decreased BMD, osteoporosis, and fractures at various body sites, as well as related risk factors in AS patients in the hope of producing more reliable and valuable analysis results to aid in the management of AS patients and inform clinical decision-making.

## Materials and methods

The current study adheres to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. It has been registered on the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42023412441.

### Literature search strategy

A comprehensive and systematic search was conducted in multiple databases, namely PubMed, Cochrane Library, Embase, and Web of Science as of February 2023.

Two researchers independently carried out the search using a combination of specified and broad terms based on a pre-established search strategy. Specified terms included "Spondylitis, Ankylosing" [Mesh], "Osteoporosis" [Mesh], "Bone Density" [Mesh], and "Fractures, Bone" [Mesh]. More details on the search strategy can be found in the Supplementary Materials.

### Literature screening

Two researchers independently screened articles retrieved from databases. Duplicate publications were first removed, and then the titles and abstracts of the remaining articles were reviewed, where studies that did not meet the eligibility criteria were excluded. Then, candidate studies underwent full-text review, resulting in the selection of 39 studies that were eligible for inclusion in the meta-analysis. To ensure the reliability of the screening results, cross-checking was done by two researchers. In cases where discrepancies arose, a third researcher was consulted to make the final decision.

The inclusion criteria were as follows:

Study type: case–control studies, cohort studies, and cross-sectional studies.

Participants: patients with a clear diagnosis of AS. No restrictions were imposed on gender, age, ethnicity, or disease progression.

Outcome measures: the number of participants experiencing fractures, cases of reduced bone mass, osteoporosis, and bone mineral density (BMD) at different sites, among other relevant factors.

Language: no restriction was placed on the language of the publication.

The exclusion criteria were as follows:

Initial trials without clear diagnostic criteria or those with unclear or unacceptable diagnostic criteria were excluded.

Duplicate publications were excluded.

Studies that did not meet the inclusion criteria in terms of study type, such as case reports, literature research, literature reviews, and conference proceedings, were excluded.

Original trials with obvious flaws, such as errors in the data or data processing that did not follow statistical principles, were excluded.

Studies whose full texts or outcome measurement methods were unavailable were excluded.

### Data extraction

Two researchers independently extracted information from 39 studies, including (1) basic study information, such as title, the first author, and year of publication; (2) baseline information of participants, such as sample size in treatment and control groups, age, gender, course of disease, body mass index (BMI), erythrocyte sedimentation rate (ESR), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, the Bath Ankylosing Spondylitis Functional Index (BASFI) score, the Bath Ankylosing Spondylitis Metrology Index (BASMI) score, etc. (3) outcome measures: BMDs at various sites, osteopenia, osteoporosis, and fractures. After data extraction, both researchers cross-checked their results and corrected any mistakes.

### Study quality assessment

The Newcastle Ottawa Scale (NOS) was utilized to evaluate the quality of the included studies. The NOS is usually used for assessing the quality of case–control studies and cohort studies, and can also be used for cross-sectional studies [10].

This scale measures the quality of studies based on three parameters: selection, comparability, and outcome. Under the Selection category, studies can earn a maximum of four points, assessing the selection and definition of study subjects, including exposure definition, representativeness

of the exposed cohort, and selection of the non-exposed cohort. The Comparability parameter allows for a maximum of two points, where the comparability of cohorts was investigated. In the present study, particular attention was given to whether confounding factors were considered and controlled in the included studies. The Outcome category permits a maximum of three points. We evaluated included studies regarding outcome assessment, follow-up duration, and degree of follow-up completeness.

After reaching a consensus, the two researchers scored each study on a scale of 1 to 9 based on the abovementioned categories. Studies were rated as having low quality (1–3 points), moderate quality (4–6 points), and high quality (7–9 points) [11].

### Statistical analysis

Statistical analyses were conducted using the software Stata 17.0. Binary variables were expressed as odds ratio (OR) and continuous variables as weighted mean difference (WMD) or standardized mean difference (SMD). The 95% confidence interval (CI) was calculated for each effect size. The $I^2$ statistic was used to measure the heterogeneity across studies, where $I^2 \geq 50\%$, $P < 0.05$ indicates significant heterogeneity, and thus a random-effects model will be used for meta-analysis. Otherwise, a fixed-effects model will be utilized. Sensitivity analysis was performed for examining the sources of heterogeneity in meta-analyses. Publication bias was assessed through Egger's test and Begg's test. If at least 10 studies of interest were included, a funnel plot was generated for visual presentation of publication bias, where the trim-and-fill method would be used to further detect publication bias in case of the asymmetric distribution indicated by the funnel plot.

## Results

### Literature search

A total of 8423 articles were retrieved from databases. Among them, 1854 were removed for duplicate publication, and 1128 were excluded for irrelevant study types such as reviews, animal experiments, and letters. After reviewing the titles and abstracts of the remaining articles, 5117 were removed. Subsequently, 32 articles were excluded due to a lack of full text, and the remaining 292 full-text articles underwent review. Finally, 39 studies were determined to be eligible for meta-analysis after excluding 238 that did not investigate relevant outcome measures and 15 that were not relevant in terms of study design. The literature screening process is presented in Fig. 1.

### Study baseline characteristics and quality assessment

A total of 39 studies [12–50] were included in the meta-analysis. These studies spanned from 1990 to 2023 and were conducted across 20 regions or countries, with the majority originating conducted in China and Turkey (5 studies each). Overall, the quality of the studies was relatively high, with 36 of them scoring over 7 and 3 studies scoring 6, as shown in Table 1.

### Meta-analysis results

Out of the 39 studies, 32 focused on measuring bone density, with the results consistently expressed in the unified unit of g/cm$^2$. These measurements were conducted using instruments from 6 different companies, as presented in Table S1. In terms of the measurement methods, only the study by Cai et al. employed quantitative computed tomography (QCT) for assessing bone density; the remaining studies used dual-energy X-ray absorptiometry (DEXA) [39]. For the specific BMD measurements from Cai et al. (at the femoral neck**,** femur trochanter, intertrochanter area, and hip), we utilized the standardized mean difference (SMD) as the effect size for the meta-analysis [39].

#### BMD at the lumbar spine

BMDs at the lumbar spine among AS patients and healthy controls were reported in 19 studies. Meta-analysis showed that the BMD at the lumbar spine in AS patients was lower than that in healthy controls [WMD = −0.07, 95% CI (−0.11, −0.03), $I^2 = 89.1\%$], $P_{\text{heterogeneity}} < 0.001$].

A subgroup analysis based on age was performed. AS patients were divided into two subgroups: the young age (< 40) group and the old age (≥ 40) group, involving 11 and 8 studies, respectively. The analysis revealed that in the young age group, the BMD at the lumbar spine was lower in AS patients than in healthy controls [WMD = −0.10, 95% CI (−0.15, −0.05), $I^2 = 91\%$, $P_{\text{heterogeneity}} < 0.001$], while in the old age group, no significant difference was found in the BMD at the lumbar spine between AS patients and healthy controls [WMD = −0.01, 95% CI (−0.05, 0.02), $I^2 = 37.8\%$, $P_{\text{heterogeneity}} = 0.128$], as shown in Fig. 2 A.

Among the 19 studies, 16 provided information about the disease course of AS. Therefore, AS patients were split into two subgroups based on the length of the disease course for subgroup analysis: a short-course group (< 10 years) and a long-course group (≥ 10 years). The meta-analysis for the short-course group (involving 8 studies) indicated a significantly lower BMD at the lumbar spine in AS patients compared with healthy controls [WMD = −0.11, 95% CI (−0.17, −0.05), $I^2 = 89.9\%$, $P_{\text{heterogeneity}} < 0.001$]. However, for the long-course group (involving 8 studies), no statistically significant difference in BMD was observed between

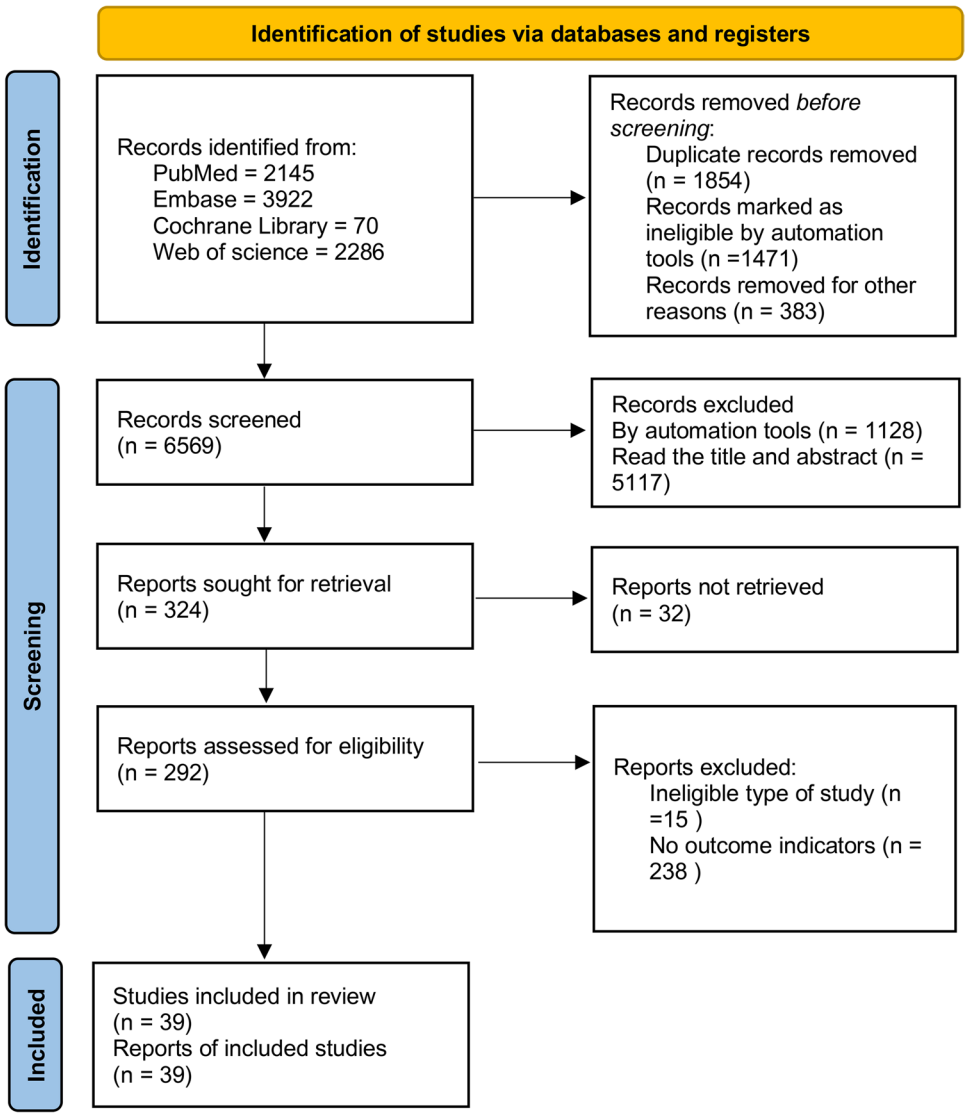


**Fig. 1** Literature selection process

AS patients and healthy controls [WMD = −0.02, (95% CI (−0.05, 0.01), $I^2$ = 24.7%, $P_{heterogeneity}$ = 0.232], as presented in Fig. 2 B.

### Lumbar spine T-score

T-scores at the lumbar spine were reported in 9 studies. The overall analysis indicated that the T-score at the lumbar spine was lower in AS patients than in healthy controls [WMD = −0.78, 95% CI (1.18, −0.38), $I^2$ = 83.8%, $P_{heterogeneity}$ < 0.001].

The subgroup analysis based on age was performed. AS patients were divided into two subgroups: the young age (< 40) group and the old age (≥ 40) group, involving 5 and 4 studies, respectively. Analysis results demonstrated that in the young age group, the T-score at the lumbar spine in AS patients was lower than that in healthy controls [WMD = −1.08, 95% CI (−1.44, −0.73), $I^2$ = 62.3%, $P_{heterogeneity}$ = 0.031], while in the old age group, no significant difference was observed in the T-score at the lumbar spine between AS patients and healthy controls [WMD = −0.32, 95% CI (−0.70, 0.06), $I^2$ = 53.0%, $P_{heterogeneity}$ = 0.094]. See more details in Fig. 2 C.

Additionally, among the 9 studies reporting T-scores, 7 provided data on the course of disease for AS patients. Therefore, AS patients were split into short-course (< 10 years) and long-course (≥ 10 years) groups for subgroup analysis. A total of five and two studies respectively provided data on short and long courses of AS, and the results of meta-analyses on them demonstrated no significant differences between AS patients and healthy controls, regardless of the length of disease course. See more details in Fig. 2 D.

### BMD at the femoral neck

A total of 24 studies examined BMD at the femoral neck. The overall analysis indicated that BMD at the femoral neck was lower in AS patients than in healthy controls [SMD = −0.61,

**Table 1** The characteristics and NOS scores of the included studies

| Author | Country | Year | Study design | Diagnosis of AS | Age (M ± SD) | Disease duration (M ± SD) | observation group (M/F) | control group (M/F) | NOS scores |
|---|---|---|---|---|---|---|---|---|---|
| Muntean | Romania | 2016 | Cross-sectional study | MNY | 40.6 ± 10.1 | 13.21 ± 9.45 | 23/6 | 22/7 | 9 |
| Haroon | Canada | 2015 | Cross-sectional study | MNY | 44 ± 12 | 17 ± 5 | 29 /24 | 25/60 | 9 |
| Gamez-Nava | Mexico | 2016 | Cross-sectional study | MNY | 46.06 ± 9.77 | 9 ± 6.75 | 50/28 | 35/23 | 9 |
| Klingberg | Sweden | 2013 | Case–control study | MNY | 49 ± 15 | 23 ± 14 | 8/0 | 16/0 | 6 |
| Feki | Tunisia | 2019 | Cross-sectional study | MNY | 43.8 ± 13.4 | 15 ± 10.9 | 35/12 | 35/12 | 8 |
| Wang | China | 2015 | Cross-sectional study | MNY | 35.5 ± 2.9 | 5.6 ± 1.43 | 102/0 | 102/0 | 8 |
| Vasdev | India | 2010 | Prospective cohort study | MNY | 34.96 ± 8.30 | 8.15 ± 5.82 | 80/0 | 160/0 | 8 |
| Mehmet | Turkey | 2012 | Cross-sectional study | MNY | 34.53 ± 8.95 | 4.84 ± 4.83 | 69/17 | 35/15 | 9 |
| Sayed | Egypt | 2014 | Cross-sectional study | MNY | 32.97 ± 8.7 | 5.6 ± 7.5 | 42/2 | 20* | 8 |
| Selda | Turkey | 2007 | Cross-sectional study | MNY | 44.31 ± 10.87 | ND | 21/5 | 20/13 | 7 |
| Muntean | Romania | 2011 | Cross-sectional study | MNY | 41 ± 10.2 | 13.3 ± 8.9 | 44/0 | 39/0 | 8 |
| Bedriye | Turkey | 2009 | Cross-sectional study | MNY | 39.9 ± 10.9 | 10.5 ± 7.84 | 75/25 | 46/12 | 9 |
| Hatinder | India | 2013 | Case–control study | MNY | 35.19 ± 8.23 | ND | 100* | 150* | 6 |
| Anupam | India | 2020 | Cross-sectional study | ASAS | 38 ± 10 | 9 ± 6 | 46/4 | 46/4 | 9 |
| Wei | China | 2009 | Cross-sectional study | MNY | 30 ± 8 | 7.4 ± 3.7 | 65/0 | 62/0 | 8 |
| Ulu | America | 2014 | Cross-sectional study | MNY | 34.3 ± 9.4 | 4.5 ± 4.3 | 50/9 | 28/12 | 9 |
| Wu | China | 2021 | Cross-sectional study | MNY | 32.6 ± 8.3 | ND | 158/35 | 42/13 | 8 |
| Sharif | Israel | 2022 | Cohort study | ICD-9 codes | 48.1 ± 16.8 | ND | 3625/1851 | 18,129/9528 | 8 |
| Fakhreldin | Egypt | 2020 | Cross-sectional study | MNY | 27.9 ± 6.2 | 4.2 ± 3.6 | 30/0 | 30/0 | 8 |
| D.Wang | China | 2015 | Prospective cohort study | MNY | 29.1 ± 10.7 | 7.7 ± 6.4 | 417/87 | 87/19 | 9 |
| Deborah | England | 2023 | Cross-sectional study | MNY | 43.4 ± 10.6 | 21.1 ± 5.3 | 0/66 | 0/132 | 8 |
| Altindag | Turkey | 2008 | Cross-sectional study | MNY | 33.4 ± 7.5 | 5.7 ± 4.2 | 36/26 | 20/16 | 9 |
| Jun | Korea | 2006 | Cross-sectional study | MNY | 30.7 ± 6.5 | 7.16 ± 5.42 | 68/0 | 91/0 | 8 |
| Bronson | America | 1997 | Cross-sectional study | MNY | 50.5 ± 14.5 | 25.2 ± 13.4 | 19/0 | 19/0 | 8 |
| Santos | France | 2023 | Cohort study | MNY | 37.6 ± 9.1 | 8.4 ± 6.3 | 39/0 | 39/0 | 8 |
| Franck | Germany | 2004 | Cross-sectional study | MNY | 50.4 ± 10.4 | ND | 190/74 | 182/58 | 8 |
| Tsur | Israel | 2022 | Cohort study | ICD-9 codes | 49 ± 17 | ND | 3762/2147 | 18,223/10448 | 8 |
| Cai | China | 2019 | Case–control study | MNY | 32.5 ± 10.3 | ND | 41/19 | 45/15 | 8 |

**Table 1** (continued)

| Author | Country | Year | Study design | Diagnosis of AS | Age (M ± SD) | Disease duration (M ± SD) | observation group (M/F) | control group (M/F) | NOS scores |
|---|---|---|---|---|---|---|---|---|---|
| Faten | Egypt | 2020 | Case–control study | MNY | 31.7 ± 9.1 | 7.8 ± 4.4 | 46/14 | 46/14 | 9 |
| Vosse | Netherlands | 2008 | Case–control study | ICD-9 codes | ND | ND | 238/178 | 204/138 | 6 |
| Ghozlani | Morocco | 2008 | Cross-sectional study | MNY | 38.9 ± 11.8 | 10.8 ± 6.6 | 34* | 46* | 8 |
| Feldtkeller | Netherlands and Belgium | 2005 | Cross-sectional study | ND | 49.8 ± 12.1 | 24.6 ± 12.3 | 43/18 | 636/1374 | 9 |
| Kang | Korea | 2014 | Cross-sectional study | MNY | 33.9 ± 10.9 | 3.8 ± 5.1 | 4/22 | 215/61 | 9 |
| Klingberg | Sweden | 2012 | Cross-sectional study | MNY | 50 ± 13 | 15 ± 11 | 24* | 180* | 8 |
| Maas | Netherlands | 2016 | Cohort study | ASAS | 42.8 ± 12.5 | 6 ± 11.11 | 47/12 | 158/75 | 9 |
| Ayla | Turkey | 2007 | Prospective controlled study | MNY | 36.8 | 7.6 ± 6.8 | 38/0 | 30/0 | 8 |
| Ralston | England | 1990 | Case–control study | MNY | 48 ± 11.85 | 18 ± 14.07 | 13/2 | 26/4 | 9 |
| Arends | America and Netherlands | 2010 | Cross-sectional study | MNY | 41.0 ± 11.1 | 14 ± 13 | 50* | 78* | 8 |
| Montala | Spain | 2011 | Cross-sectional study | MNY | 48.6 ± 13.1 | 22.5 ± 12.6 | 52/5 | 86/33 | 9 |

*MNY* Modified New York Criteria, *ASAS* Assessment of SpondyloArthritis International Society, *ND* no data

*Only the total number is reported with no specific number of males and females

95% CI (−0.77, −0.45), $I^2 = 78.8\%$, $P_{\text{heterogeneity}} < 0.001$]. This trend was consistent in subgroup analyses based on age, disease course, and gender, all showing statistically significant differences. See more details in Fig. 3 A.

Furthermore, after excluding the study by Cai et al., we conducted a meta-analysis using the WMD as the effect size, and the results remained unchanged [WMD = −0.09, 95% CI (−0.11, −0.07), $I^2 = 76.7\%$, $P_{\text{heterogeneity}} < 0.001$] [39].

### Femoral neck T-score

A total of 10 studies reported T-scores at the femoral neck. In general, meta-analysis results demonstrated lower T-scores at the femoral neck in AS patients, compared with healthy controls [WMD = −1.14, 95% CI (−1.53, −0.76), $I^2 = 88\%$, $P_{\text{heterogeneity}} < 0.001$]. The same trend was found in the subgroup analysis based on age, disease course, or gender, with statistically significant differences. See more details in Fig. 3 B.

### T-scores and BMDs at other sites

T-scores and BMDs at other sites between AS patients and controls were compared, including the T-score at the hip and BMDs at the hip, lumbar vertebra 2 (L2), lumbar vertebra 3 (L3), lumbar vertebra 4 (L4), femur total, femur trochanter, intertrochanter area, 1/3 distal radius, and ultra distal radius. Meta-analysis results revealed that the T-score at the hip and the abovementioned BMDs at different sites were lower in AS patients than in healthy controls, with a statistically significant difference, as shown in Table 2. Subgroup analyses of hip BMD, femur total BMD, and femur trochanter BMD were performed based on age, disease course, and gender, and the results showed that these BMDs were still significantly lower in AS patients than healthy controls.

### Risk of osteopenia

Five studies reported the number of participants experiencing osteopenia. In general, meta-analysis results demonstrated that the risk of osteopenia in AS patients was 3.13 times higher than that in healthy controls [OR = 3.13, 95% CI (1.29, 7.60), $I^2 = 84.3\%$, $P_{\text{heterogeneity}} < 0.001$]. A subgroup analysis based on age was performed. AS patients were divided into two subgroups: the young age (< 40) group and the old age (≥ 40) group, involving 3 and 2 studies, respectively. Analysis results showed that in the young age group, the risk of osteopenia in AS patients was 4.77 times higher than that in healthy controls [OR = 4.77, 95% CI (1.78, 12.75), $I^2 = 77.0\%$, $P_{\text{heterogeneity}} = 0.013$], while

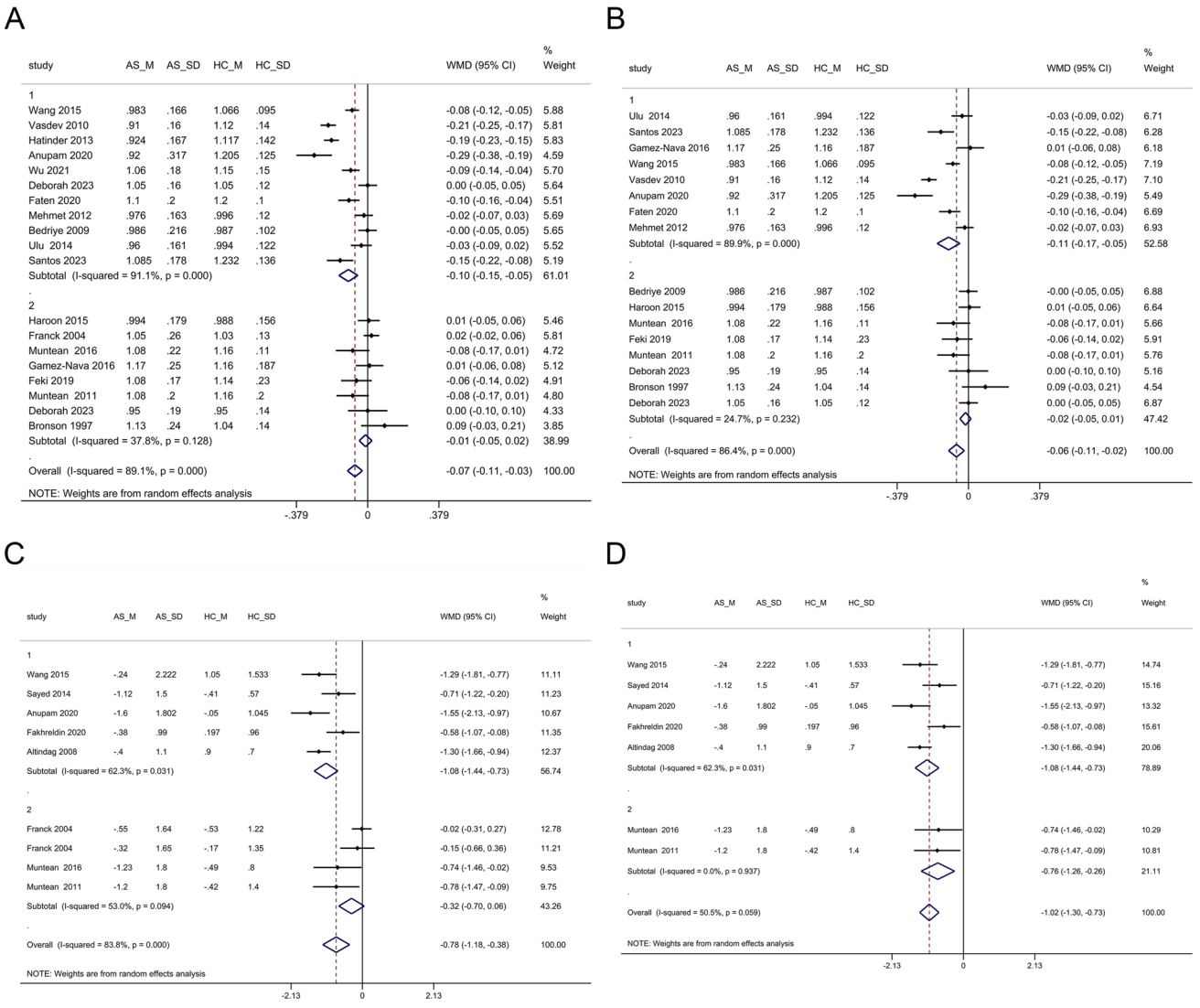


**Fig. 2** **A** Lumbar spine BMD age subgroup forest plot; **B** lumbar spine bone density disease course subgroup forest map; **C** lumbar spine T-score by age forest chart; **D** lumbar T-score disease course subgroup forest map

in the old age group, no statistically significant difference was found regarding the risk of osteopenia between AS patients and healthy controls [OR = 1.65, 95% CI (0.27, 10.19), $I^2 = 89.4\%$, $P_{heterogeneity} = 0.002$]. See more details in Fig. 4 A.

### Risk of osteoporosis

Seven studies reported the number of participants who experienced osteoporosis. There was significant heterogeneity between these studies ($I^2 = 80.0\%$, $P_{heterogeneity} < 0.001$). The meta-regression analysis indicated that age may be the source of heterogeneity. Therefore, AS patients were divided into two groups based on age for subgroup analysis: the young age (< 40) group and the old age (≥ 40) group, involving 3 and 4 studies, respectively. The results illustrated that in the young age group, the risk of osteoporosis in AS patients was 26.11 times higher than that in healthy controls [OR = 26.11, 95% CI (9.09, 75.01), $I^2 = 0$, $P_{heterogeneity} = 0.812$], and in the old age group, it was 1.83 times higher than that in healthy controls [OR = 1.83, 95% CI (1.68, 2.00), $I^2 = 0$, $P_{heterogeneity} = 0.633$], as shown in Fig. 4 B.

## Risk of fractures among AS patients

Of the reviewed studies, ten of them reported the occurrence of fractures among participants, with eight studies focusing on vertebral fractures. Out of these eight studies, five utilized

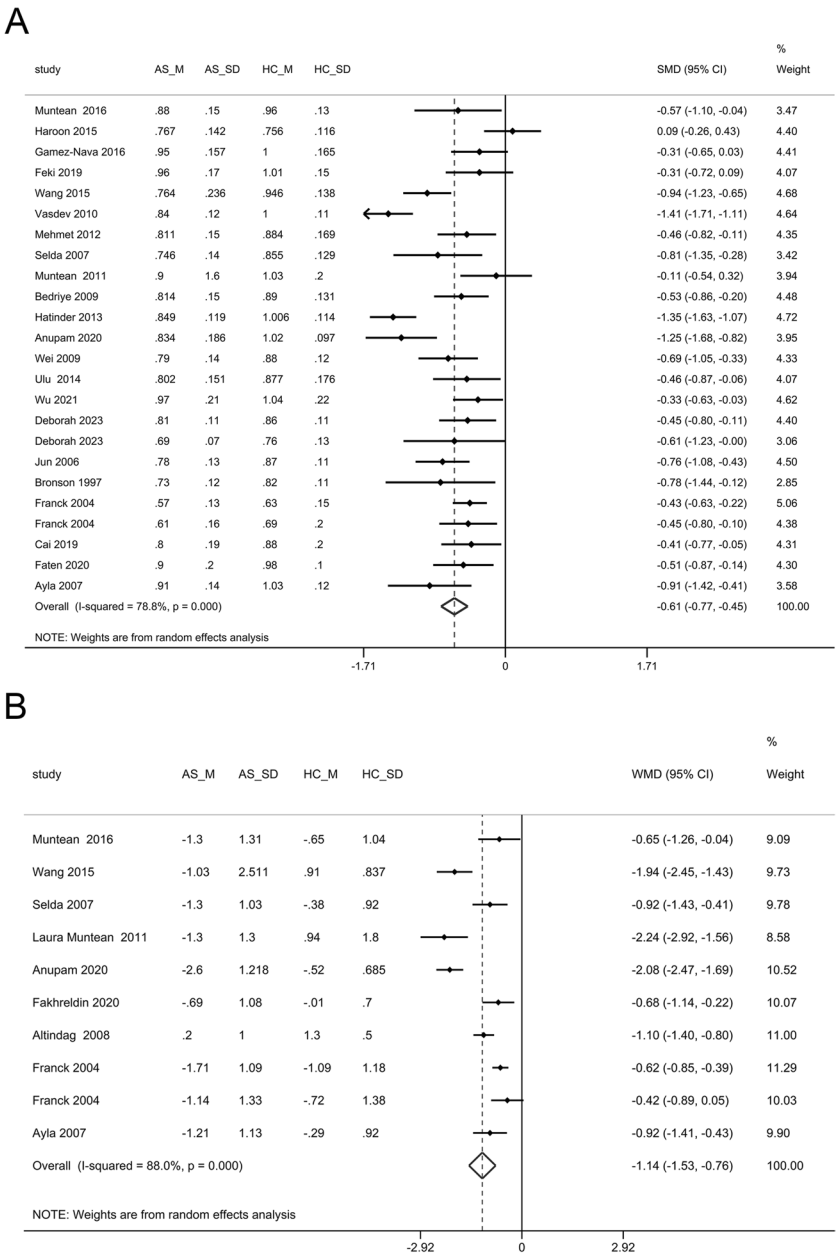


**Fig. 3** **A** Femoral neck BMD forest plot; **B** femoral neck T-score forest plot

a consistent diagnostic standard for vertebral fractures, defined by a reduction of over 20% in the anterior, middle, and/or posterior height. However, the remaining three studies did not provide specific details on how vertebral fractures were diagnosed. Furthermore, one study reported hip fractures, while another reported fragility fractures without specifying the exact location. Analyzing the collected data revealed moderate heterogeneity ($I^2 = 60.5\%$, $P_{\text{heterogeneity}} = 0.007$). Meta-regression analysis suggested that the sources of heterogeneity might be linked to factors such as fracture location, participants' age, and the duration of disease.

To gain more insights, we conducted a subgroup analysis based on the fracture location, categorizing them into vertebral fractures and fractures occurring in other locations). The results indicated that the risk of vertebral fractures in patients with AS was found to be 13.98 times higher than that in non-AS patients [OR = 13.98, 95% CI (4.84, 40.40), $I^2 = 0.0\%$, Pheterogeneity = 0.844]. Additionally, the risk of fractures in other locations among AS patients was 1.49 times higher compared to non-AS patients [OR: 1.49, 95% CI (1.21, 1.84), $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.894$]. These findings are illustrated in Fig. 5.

Based on their age, AS patients were divided into the young age group (< 40) and the old age group (≥ 40). Six studies investigated the young age group and the meta-analysis of them revealed that the risk of fractures in AS patients was 19.82 times higher than that in healthy

**Table 2** BMD and T-score at other sites

| Sites | Number of studies | WMD or SMD (95%CI) | $I^2$, $P_{heterogeneity}$ | Test of WMD or SMD = 0 |
|---|---|---|---|---|
| Hip BMD | 7 | −0.06(95% CI −0.08, −0.05) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.626 | $z$ = 7.40, p = 0.000 |
| Hip T-score | 4 | −0.66(95% CI −0.82, −0.51) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.617 | $z$ = 8.37, p = 0.000 |
| L2 BMD | 3 | −0.07(95% CI −0.09, −0.04) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.831 | $z$ = 5.24, p = 0.000 |
| L3 BMD | 3 | −0.08 (95% CI −0.11, −0.05) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.588 | $z$ = 5.86, p = 0.000 |
| L4 BMD | 3 | −0.07 (95% CI −0.09, −0.04) | $I^2$ = 14.4%, $P_{heterogeneity}$ = 0.311 | $z$ = 5.28, p = 0.000 |
| Femur Total BMD | 6 | −0.09 (95% CI −0.12, −0.07) | $I^2$ = 91.2%, $P_{heterogeneity}$ < 0.001 | $z$ = 7.20, p = 0.000 |
| Femur trochanter BMD* | 6 | −0.91 (95% CI −1.13, −0.68) | $I^2$ = 59.2%, $P_{heterogeneity}$ = 0.031 | $z$ = 7.91, p = 0.000 |
| Intertrochanter area BMD* | 3 | −1.09 (95% CI −1.74, −0.43) | $I^2$ = 89.4%, $P_{heterogeneity}$ = 0.000 | z = 3.26, p = 0.001 |
| 1/3 distal radius BMD | 2 | 0.09 (95% CI 0.05, 0.14) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.645 | $z$ = 3.75, p = 0.000 |
| Ultra distal radius BMD | 2 | 0.04 (95% CI 0.004, 0.08) | $I^2$ = 51.5%, $P_{heterogeneity}$ = 0.151 | $z$ = 2.15, p = 0.032 |

*Using the standardized mean difference (SMD) as the effect size

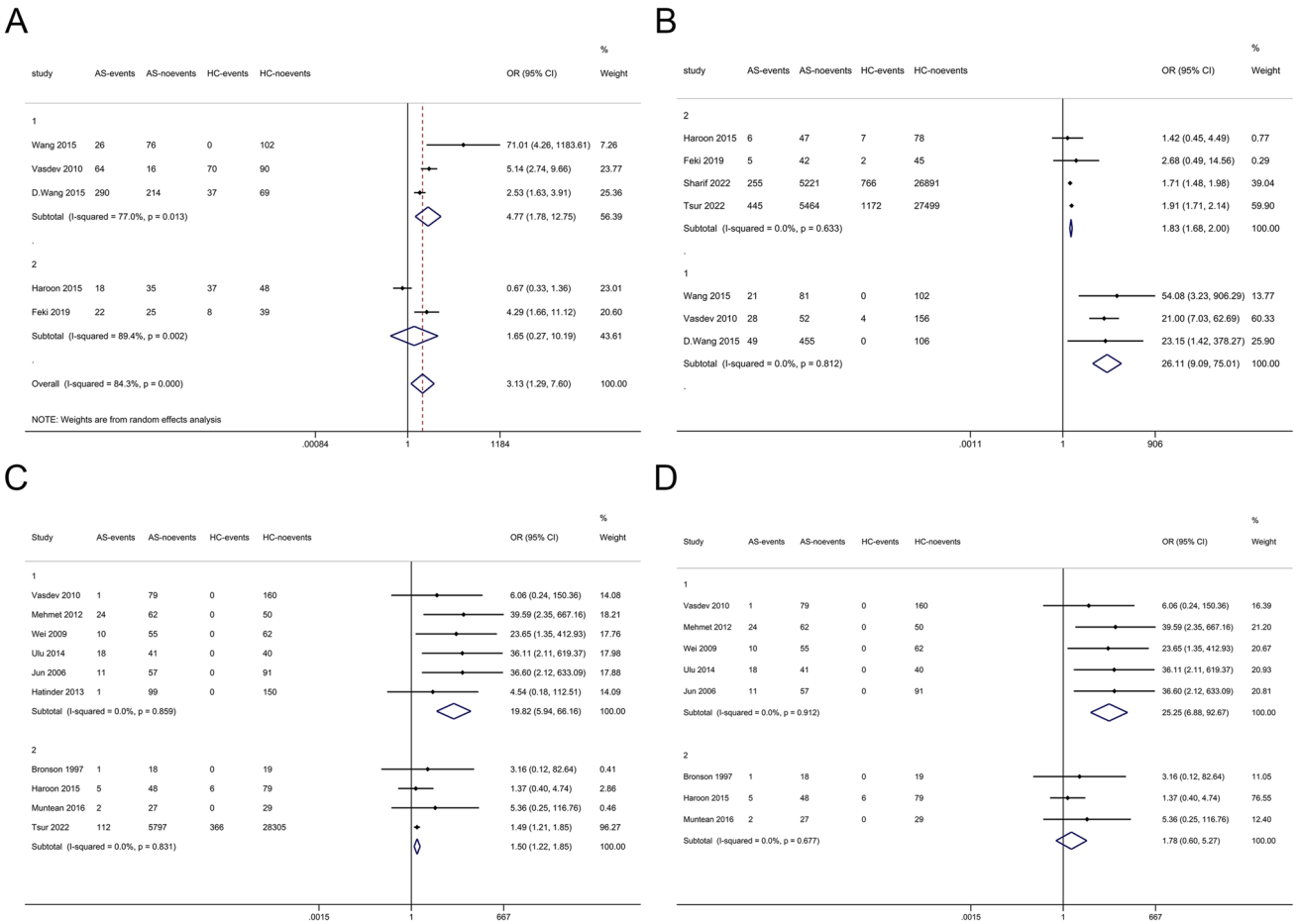


**Fig. 4** **A** Bone loss age subgroup forest plot; **B** osteoporosis risk forest plot; **C** fracture by age forest plot; **D** fracture by course forest plot

controls [OR = 19.82, 95% CI (5.94, 66.16), $I^2$ = 0, $P_{heterogeneity}$ = 0.859]. Four studies investigated the old age group and the meta-analysis of them demonstrated that the risk of fractures in AS patients was 1.50 times higher than that in healthy controls [OR = 1.50, 95% CI (1.22, 1.85), $I^2$ = 0, $P_{heterogeneity}$ = 0.831]. See more details in Fig. 4 C.

Among the ten studies, eight reported disease courses for AS patients who were split into two subgroups: the

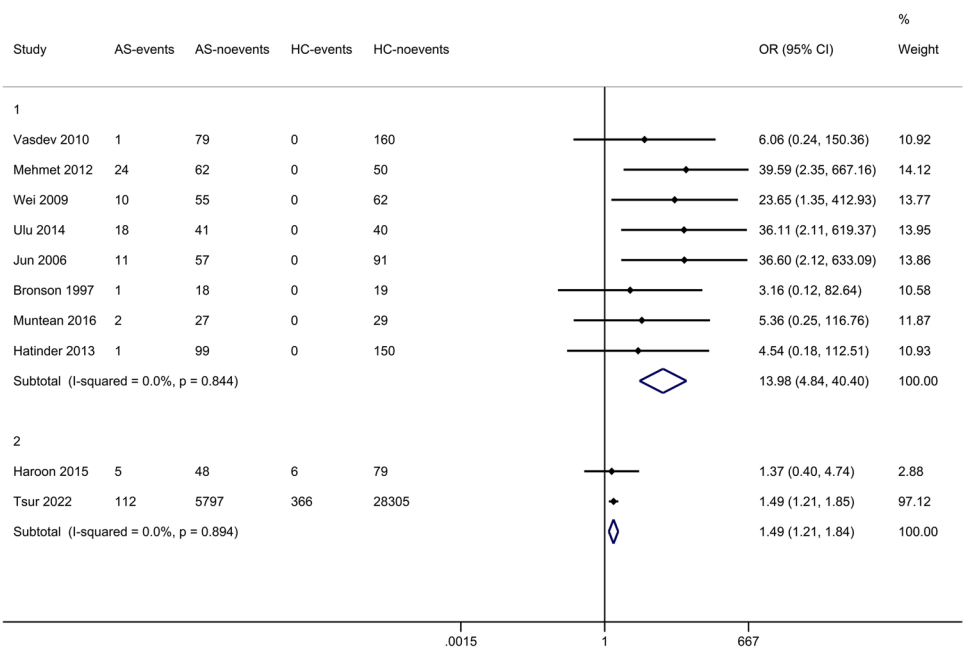


**Fig. 5** Forest plot of fracture site

short-course group (< 10 years) and the long-course group (≥ 10 years). In total, there were 5 short-course groups and 3 long-course groups. It should be noted that all 5 studies that reported the short disease course investigated AS patients aged under 40 (in the young age group). That is, among the 6 studies that investigated AS patients aged under 40, only one study did not report the courses of disease for AS patients. On the other hand, all 5 studies that reported the short disease course investigated AS patients aged under 40 (in the young age group). That is, among the 6 studies that investigated AS patients aged under 40, only one study (Hatinder 2013) did not report the courses of disease for AS patients. On the other hand, 3 studies that reported the long disease course investigated AS patients aged at least 40 (in the old age group). That is, among the 6 studies that investigated AS patients no less than 40, only one study (Tsur 2022) did not report the courses of disease for AS patients.

The meta-analysis of 5 studies that reported short courses of disease showed that the risk of fractures in AS patients was 25.25 times higher than that in healthy controls [OR = 25.25, 95% CI (6.88, 92.67), $I^2 = 0$, $P_{\text{heterogeneity}} = 0.912$]. The meta-analysis of 3 studies that reported long courses of disease showed no significant difference in the risk of fractures between AS patients and healthy controls [OR = 1.78, 95% CI (0.60, 5.27), $I^2 = 0$, $P_{\text{heterogeneity}} = 0.677$]. See more details in Fig. 4 D.

## Risk factors behind fractures among AS patients

Sixteen studies compared AS patients with or without fractures, based on multiple factors such as age, course of disease, gender, and so on. Through meta-analysis, it was found that there was no statistically significant difference between AS patients with or without fractures in terms of gender, ESR (mm/h), BASDAI score, BMI, history of peripheral arthritis, human leukocyte antigen B27 (HLA-B27) positive, lumbar spine (L1-L4) T-score, oral sulfasalazine, and oral non-steroidal anti-inflammatory drugs (NSAIDs), as shown in Table 3. However, significant differences were found between AS patients with or without fractures regarding patient age, course of disease, lumbar BMD, femoral neck BMD, C-reactive protein (CRP) level, BASFI score, chest expansion, occiput-wall distance, onset time, the Bath Ankylosing Spondylitis Radiology Index (BASRI) score, and so on, as shown in Table 4.

## Sensitivity analysis

The sensitivity analysis conducted for each group of meta-analyses revealed a high level of stability and reliability of analysis results which remained largely unchanged after the removal of any individual studies. This finding indicates that no single study significantly contributed to the observed heterogeneity in the meta-analysis results.

## Publication bias

A funnel plot was drawn for lumbar spine BMD, femoral neck BMD, femoral neck T-score, and the risk of fractures in AS patients, as well as patient age and course of disease. The funnel plots demonstrated symmetrical distributions concerning BMD at the lumbar spine (Egger's test, $P = 0.497 > 0.05$), BMD at the femoral neck (Egger's test,

**Table 3** No difference in risk factors for fracture

| Factors | Number | OR/WMD(95%CI) | $I^2$, $P_{heterogeneity}$ | Test of OR = 1/ Test of WMD = 0 |
|---|---|---|---|---|
| NSAIDs | 3 | 1.19 (0.71, 1.98) | $I^2$ = 52.6%, $P_{heterogeneity}$ = 0.121 | $z$ = 0.65 $p$ = 0.514 |
| Salazosulfapyridine | 3 | 1.26 (0.76, 2.08) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.728 | $z$ = 0.89 $p$ = 0.374 |
| LS (L1–L4), T-score | 3 | 0.09 (−0.31, 0.48) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.542 | $z$ = 0.43 $p$ = 0.667 |
| B27positive | 4 | 1.37 (0.91, 2.06) | $I^2$ = 48.0%, $P_{heterogeneity}$ = 0.123 | $z$ = 1.51 $p$ = 0.131 |
| History of peripheral arthritis | 4 | 0.74 (0.39, 1.40) | $I^2$ = 54.1%, $P_{heterogeneity}$ = 0.088 | $z$ = 0.93 $p$ = 0.355 |
| BMI | 6 | −0.58 (−1.36, 0.20) | $I^2$ = 18.9%, $P_{heterogeneity}$ = 0.294 | $z$ = 1.45 $p$ = 0.146 |
| Gender | 7 | 0.84 (0.67, 1.05) | $I^2$ = 47.4%, $P_{heterogeneity}$ = 0.076 | $z$ = 1.55 $p$ = 0.121 |
| BASDAI | 7 | −0.16 (−0.51, 0.19) | $I^2$ = 45.6%, $P_{heterogeneity}$ = 0.118 | $z$ = 0.89 $p$ = 0.371 |
| ESR (mm/h) | 8 | 0.14 (−4.40, 4.69) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.800 | $z$ = 0.06 $p$ = 0.951 |

**Table 4** There are differences in fracture risk factors

| Factors | Number | OR/WMD (95%CI) | $I^2$, $P_{heterogeneity}$ | Test of OR = 1/ test of WMD = 0 |
|---|---|---|---|---|
| Inflammatory bowel disease | 3 | 0.46 (0.29, 0.74) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.753 | $z$ = 3.23 $p$ = 0.001 |
| BASMI | 3 | −1.10 (−1.67, −0.53) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.360 | $z$ = 3.78 $p$ = 0.000 |
| Finger-to-ground distance(cm) | 3 | −9.58 (−15.46, −3.70) | $I^2$ = 56.7%, $P_{heterogeneity}$ = 0.100 | $z$ = 3.19 $p$ = 0.001 |
| Total hip BMD (g/cm$^2$) | 3 | 0.11 (0.08, 0.15) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.494 | $z$ = 6.72 $p$ = 0.000 |
| total hip T-score | 3 | 0.82 (0.52, 1.12) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.602 | $z$ = 5.30 $p$ = 0.000 |
| BASRI | 4 | −2.04 (−2.53, −1.54) | $I^2$ = 7.3%, $P_{heterogeneity}$ = 0.357 | $z$ = 8.02 $p$ = 0.000 |
| Time of disease onset, year | 4 | −3.08 (−5.33, −0.84) | $I^2$ = 25.5%, $P_{heterogeneity}$ = 0.261 | $z$ = 2.70 $p$ = 0.007 |
| Pillow wall distance, cm | 4 | −4.35 (−8.27, −0.43) | $I^2$ = 91.1%, $P_{heterogeneity}$ = 0.000 | $z$ = 2.17 $p$ = 0.030 |
| Chest expansion, cm | 4 | 0.73 (0.38, 1.07) | $I^2$ = 44.6%, $P_{heterogeneity}$ = 0.144 | $z$ = 4.13 $p$ = 0.000 |
| Femoral neck BMD (g/cm$^2$) | 5 | 0.09 (0.06, 0.12) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.666 | $z$ = 6.09 $p$ = 0.000 |
| BASFI | 6 | −0.78 (−1.24, −0.33) | $I^2$ = 0.0%, $P_{heterogeneity}$ = 0.479 | $z$ = 3.36 $p$ = 0.001 |
| CRP(mg/L) | 6 | 0.73 (0.17, 1.29) | $I^2$ = 46.6%, $P_{heterogeneity}$ = 0.095 | $z$ = 2.55 $p$ = 0.011 |
| Lumbar vertebra BMD (g/cm$^2$) | 7 | 0.04 (0.02, 0.06) | $I^2$ = 25.8%, $P_{heterogeneity}$ = 0.232 | $z$ = 3.68 $p$ = 0.000 |
| Course of disease,year | 10 | −2.75 (−4.69, −0.82) | $I^2$ = 70.7%, $P_{heterogeneity}$ = 0.000 | $z$ = 2.79 $p$ = 0.005 |
| Age, year | 11 | −4.42 (−5.78, −3.07) | $I^2$ = 10.7%, $P_{heterogeneity}$ = 0.343 | $z$ = 6.40 $p$ = 0.000 |

$P = 0\,494 > 0.05$), T-score at the femoral neck (Egger's test, $P = 0.303 > 0.05$), age as a risk factor for fractures (Egger's test, $P = 0.647 > 0.05$), and course of disease (Egger's test, $P = 0.372 > 0.05$) suggested no publication bias.

However, the asymmetrical distribution as shown in the funnel plot for the risk of fractures among AS patients (Egger's test, $P = 0.003 < 0.05$) indicated the presence of publication bias. The trim-and-fill method indicated that five missing studies needed to be filled in the funnel plot. Initially, the funnel plot was plotted using 10 studies [log0R = 0.484, 95% CI (0.277, 0.690)] (Fig. 6). After adding the five missing studies were filled, there was a slight decrease in the logOR value [log0R = 0.413, 95% CI (0.209, 0.617)]. Given the slight change in the overall effect size when potential publication bias was taken into account, it could be considered that the results of the meta-analysis of the 10 studies still had statistical significance.

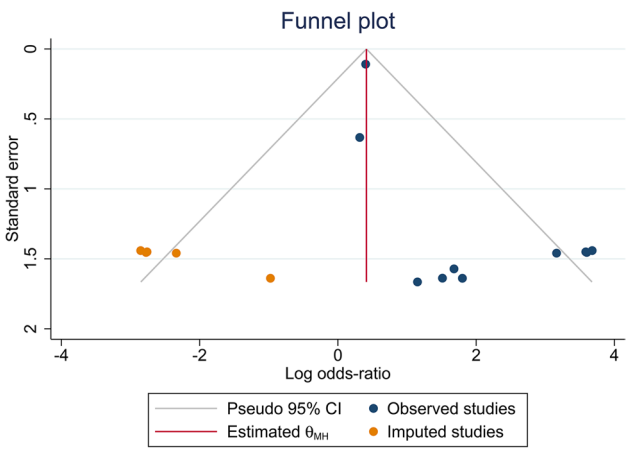


**Fig. 6** Fracture risk clipping and patching method funnel diagram

As for the remaining meta-analyses involving at least three effect sizes, Egger's test and Begg's test were utilized to assess publication bias. The analysis of risk factors for fractures demonstrated that BASRI score, occiput-wall distance, and Schober's index had $P < 0.05$ (0.036, 0.017, and 0.003, respectively) in the Egger's test, whereas they had $P > 0.05$ (0.308, 0.296, and 0.089, respectively) in the Begg's test. Since only three or four studies contributed to the analysis of these three outcome measures, funnel plots cannot be drawn for publication bias assessment. Nevertheless, sensitivity analysis was performed and indicated stable meta-analysis results for the three outcome measures. This implies that although there may be publication bias, its impact on meta-analysis results is likely limited.

## Discussion

This meta-analysis provides valuable insights into BMD and fracture risk in AS patients compared to healthy controls. The results indicated that AS patients had lower BMDs at various sites, including the femoral neck, hip, lumbar spine (L2, L3, L4), femur total, Ward's triangle, femur trochanter, and intertrochanter area, while they had higher BMDs at 1/3 distal radius and ultra distal radius, as well as the risk of fractures. Subgroup analysis based on age revealed that AS patients under the age of 40 had lower BMDs at the lumbar spine, lower T-scores at the lumbar spine, and a higher risk of osteopenia, compared to healthy controls. However, there was no significant difference between AS patients aged 40 or older and healthy controls regarding the abovementioned three aspects. The risk of fractures among AS patients with a disease course of less than 10 years was higher compared to healthy controls, while no significant difference was found between AS patients with a disease course of 10 years or more and healthy controls regarding the risk of fractures. The meta-analysis also identified various risk factors associated with fracture risk among AS patients, including old age, long disease course, low BMD at the lumbar spine and femoral neck, low CRP levels, high BASFI score, reduced thoracic range of motion, increased occiput-wall distance, longer onset time, higher BASRI score, lower BMD at the hip, lower T-score at the hip, increased finger-to-floor distance, higher BASMI score, and inflammatory bowel disease. However, factors such as ESR, BASDAI, gender, BMI, history of peripheral arthritis, HLA-B27 positive, lumbar spine T-score, sulfasalazine, and the administration of NSAIDs were not identified as risk factors for fractures in AS patients.

### About BMD

The decrease in BMD in AS patients can be primarily attributed to the inflammatory response caused by the disease itself and the long-term use of medications [51]. Inflammatory reactions lead to increased bone resorption and reduced bone formation, thereby reducing bone density [52]. Additionally, disease progression and limited range of motion due to spinal and joint damage, stiffness, and deformity may further contribute to reduced bone density as the load that can stimulate bone growth is reduced [42]. On the other hand, long-term use of medications by AS patients, such as glucocorticoids, can affect bone metabolism and bone morphology development, leading to decreased bone mass and osteoporosis, although the drugs are effective in combating inflammation [8]. As a result, it is not surprising that even young AS patients were found to have lower BMD at most sites of the body compared to healthy controls, although their forearm BMDs were higher. However, since only two studies of interest were included in the present meta-analysis, the results need to be interpreted with caution.

Regarding BMD measurement, it was found that BMD at the femoral neck is relatively more reliable compared to BMD at the lumbar spine, which may be affected by factors such as ligament ossification and excessive ossification [53]. This is consistent with the results of the present meta-analysis, as we found that there was no significant difference in the lumbar spine BMD between the old age group or the long-course group of AS patients and healthy controls, and the same trend was also found when comparing the old age group of AS patients and healthy controls in terms of lumbar spine T-score. Although the meta-analysis results suggested that the lumbar spine T-scores among AS patients with long courses of disease were lower than that among healthy controls, the results should be interpreted with caution, considering that only two studies of interest were available for meta-analysis.

However, according to the standards set by the World Health Organization (WHO) [54], the z-score is recommended for diagnosing osteoporosis in males under 50 years of age and premenopausal females, while the T-score is advised for males over 50 years of age and postmenopausal females. However, in this meta-analysis, the T-score was evaluated without considering age due to two reasons:

First, the original studies included in the analysis reported the T-score for patients regardless of age but did not provide data on the Z-score. Despite attempts to contact authors and other methods, relevant data were not obtained.

Second, although the utilization of the T-score for diagnosing osteoporosis or reduced bone mass in males under 50 and premenopausal females may not be accurate, it still reflects the difference in bone density between individuals within a specific group (e.g., same race, same gender young adults). This compensates, to some extent, for variations in bone mass among different races when conducting a meta-analysis based on direct bone density measurements ($g/cm^2$).

Therefore, using the T-score in the meta-analysis for males under 50 and premenopausal females may remain

meaningful in assessing the bone density differences between patients with AS and non-AS patients.

According to the findings of this meta-analysis, age stratification does not seem to influence the risk of osteoporosis in patients with AS. This observation may be attributed to the consistently lower bone density in the femoral neck of AS patients compared to the healthy control group, a trend that holds across different age categories. However, given the lack of difference in the risk of reduced bone mass in the older age group compared to the healthy control group, analysis results may be interpreted with caution. This finding might be influenced by the limited inclusion of only two studies in the analysis, both exhibiting significant heterogeneity, which potentially affected the outcome.

## About the risk of fractures

The risk of fractures was found to be significantly higher in patients with AS compared to non-AS patients, particularly with a notable increase in vertebral fractures in AS patients. However, the limited number of studies reporting non-vertebral fractures introduces some constraints on the meta-analysis results concerning the risk of such fractures. Furthermore, the absence of a standardized diagnostic method for vertebral fractures in some of the included studies may also have influenced the meta-analysis outcomes. In younger patients and those with a shorter duration of the disease, the meta-analysis suggests a heightened fracture risk among AS patients. As patients' age and disease duration increase, the risk of fractures among AS patients seems to decrease. Nevertheless, our meta-analysis examining the risk factors for fractures among AS patients reveals a positive correlation between the course of AS or patient age and the risk of fractures, aligning with the results of a previous meta-analysis [9]. This apparent discrepancy in findings may be explained by the increase in the risk of fractures among healthy controls with advancing age, which to some extent affects the OR value.

## Risk factors behind fractures

Previous meta-analyses have revealed that being male, instead of having low BMD at the lumbar spine, is a risk factor for fractures in AS patients. However, our meta-analysis demonstrated that gender was not a risk factor for fractures in AS patients, while low BMD at the lumbar spine was, which is consistent with the results of other meta-analyses such as the one by Pray 2017 [9]. Additionally, our analysis identified new risk factors while excluding some previously considered factors.

## Heterogeneity and publication bias

Despite conducting subgroup analysis based on age and disease course to explore potential sources of heterogeneity, there were still unexplained variations in our analysis results. Heterogeneity may be influenced by differences in research locations and study populations, as genetic backgrounds, lifestyles, and dietary habits of AS patients in different regions can impact fracture risk and bone density loss.

## Clinical significance of meta-analysis results

The implications of our meta-analysis hold great importance for clinical practice. First, it underscores the need to monitor BMD in AS patients to maintain healthy bones. Our analysis results reveal that patients with AS generally have lower bone density and a higher risk of fractures. Second, regular assessments of bone mass and fracture risk are required for timely interventions in lifestyle and treatments for AS patients, thus aiding in fracture prevention and management. Third, our meta-analysis results several potential risk factors for fractures such as age, course of disease, lumbar spine BMD, and so on. Healthcare professionals can use these factors to evaluate AS patient conditions and tailor appropriate treatment plans. Moreover, our study emphasizes the importance of early intervention in preventing fractures among AS patients. For young AS patients, active intervention may have a positive effect on preventing the risk of fractures in the later stage. Corresponding measures can be implemented to mitigate future fracture risks for this group, such as medication treatment, lifestyle interventions, and regular tests to measure bone density.

In summary, the findings of this meta-analysis have significant implications for guiding the management of AS patients, helping to improve their quality of life and reduce the risk of complications. However, further research is required to delve deeper into bone density and the risk of fracture in AS patients, necessitating more robust clinical studies with large sample sizes to further explore the impact of interventions on bone density and fracture risks in this population.

## Limitations

There are some limitations in this study. Firstly, variations in the quality and sample size between the included studies possibly affected the data analysis results. Besides, some studies had methodological shortcomings, potentially introducing bias. Secondly, significant heterogeneity emerged in certain meta-analysis results. Although the sources of heterogeneity were explored through subgroup analysis and meta-regression, the presence of heterogeneity could not be fully explained. Moreover, some funnel plots suggested possible publication bias, which may affect the accuracy of our analysis results. Additionally, differences

in study design, patient characteristics, course of disease, and treatment options among the included studies could affect the objectivity and comparability of our findings. Notably, we couldn't investigate all potential risk factors for fractures in AS patients comprehensively, limiting a holistic assessment of fracture risk. Finally, patient follow-up in the included studies was not long enough to provide sufficient data on clinical outcomes, possibly restricting our in-depth evaluation of fracture risk in AS patients over time.

## Strengths

On the other hand, our research exhibits several strengths. Firstly, BMDs at different sites were investigated in this meta-analysis, confirming previous studies' findings that BMD at the lumbar spine is unreliable for measuring bone density in AS patients. Through subgroup analyses, we identified age and disease course as critical factors leading to the unreliability of lumbar spine BMD measurements in AS patients. Secondly, our meta-analysis included 39 studies with large sample sizes, enhancing the reliability and testing effectiveness of our analysis. Although previous meta-analyses focused on the risk of fractures and related risk factors among AS patients, our study provides crucial evidence on the association between fracture risk and age and disease course, shedding light on fracture prevention in young AS patients and those at the early stage of AS. Lastly, our study validates some prior conclusions while updating and presenting new findings.

According to the results of this meta-analysis, BMD at the femoral neck is more effective in measuring bone density in AS patients. Moreover, young AS patients and patients in the early stages of this disease face a higher risk of osteoporosis and fractures. Therefore, early bone density testing and fracture screening are recommended for individuals diagnosed with AS.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00198-023-06925-1.

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**Author contribution** Conceptualization: Fei Yan, Zongju Huang. Data curation: Fei Yan, Zongju Huang. Formal analysis: Fei Yan, Zongju Huang. Funding acquisition: Fei Yan, Zongju Huang. Investigation: Fei Yan, Zongju Huang. Methodology: Linfeng Wu, Juan Lang. Project administration: Linfeng Wu, Juan Lang. Resources: Linfeng Wu. Software: Linfeng Wu. Supervision: Juan Lang, Fei Yan. Validation: Juan Lang, Linfeng Wu. Visualization: Juan Lang. Writing -original draft: Fei Yan, Linfeng Wu, Juan Lang, Zongju Huang. Writing-review & editing: Fei Yan, Linfeng Wu, Juan Lang, Zongju Huang.

**Data availability** The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.

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