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Ankylosing spondylitis disease activity and serum vitamin D levels

A systematic review and meta-analysis

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Abstract

Background: To prove that serum vitamin D (VD) levels are strongly associated with ankylosing spondylitis (AS) disease activity, the association between serum VD levels and key monitoring indicators of AS disease activity has been analyzed, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Methods: Studies published in PubMed, Cochrane Library, EMBASE, and China National Knowledge Infrastructure by August 30, 2022 were searched, and 6 studies finally met the selection criteria. Serum 25-hydroxyvitamin D (25(OH)D), ESR, CRP levels, and correlation coefficients between serum VD and BASDAI, ESR, CRP in AS, and control in these studies were extracted for the meta-analysis.

Results: When compared to controls, patients with AS had considerably lower blood 25(OH)D levels (MD = –7.53 ng/mL, 95% CI, –9.78 to –5.28, $P < .001$) and significantly higher ESR and CRP levels (ESR: MD = 11.75 mm/h, 95% CI, 4.20 to 19.31, $P = .002$; CRP: MD = 15.36 mg/L, 95% CI, 4.95 to 25.77, $P = .004$). Additionally, a negative correlation was discovered between serum VD levels and BASDAI, ESR, and CRP (Fisher' Z = –0.34, –0.38, –0.35, respectively).

Conclusion: The findings of our meta-analysis demonstrated a negative correlation between serum VD levels and the main monitoring indices of disease activity in patients with AS and verified that the differences in the continent and ethnicity may be one of the major contributors to this finding.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D, AHRQ = Agency for Healthcare Research and Quality, AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, CI = confidence intervals, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, INPLASY = International Platform of Registered Systematic Review and Meta-analysis Protocols, MD = mean differences, NOS = Newcastle-Ottawa Scale, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, VD = vitamin D.

Keywords: Vitamin D level, ankylosing spondylitis, disease activity, osteoporosis

1. Introduction

Ankylosing spondylitis (AS) affects the spine joints, sacroiliac joints, and hip joints and is a chronic inflammatory rheumatic illness that falls under the category of spondyloarthritis. Osteophytes, thoracolumbar kyphosis, osteophytes, and inflammatory back pain are the major clinical symptoms of AS.[1,2] A major impact on the patients' quality of life is caused by the advanced stage of AS, which can also present as trouble sitting up straight, lying flat and looking straight ahead, and limitation of everyday activities.[3] Arthritic complex formation and cortical bone erosion are the 2 main pathological manifestations of AS.[4] The Bass Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are 3 indicators that are often used clinically to evaluate and track disease activity in AS.[5,6] As a result, postponing bone loss and lowering disease activity are the top priorities for enhancing AS patients' quality of life.

In addition to aiding in calcium homeostasis and bone metabolism, vitamin D (VD), as a fat-soluble vitamin, lowers the body's levels of pro-inflammatory cytokines, which helps to lessen inflammatory reactions.[7] It has been demonstrated that AS is connected with vitamin D-related gene polymorphisms.

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The datasets generated during and/or analyzed during the current study are publicly available.

This manuscript is a systematic evaluation and meta-analysis article. The Ethics Committee of the Guizhou University of Traditional Chinese Medicine confirmed that no ethical approval was required.

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A study by Zhang et al revealed that long noncoding RNA (lncRNA) H19, which has been demonstrated to be considerably overexpressed in individuals with AS, has been found to compete with the vitamin D receptor for binding and to promote the production of IL-17A and IL-23 cytokines. As opposed to this, VD can bind to the vitamin D receptor in vivo and lower levels of pro-inflammatory IL-17A and IL-23, which benefits AS sufferers.[8] Additionally, it has been demonstrated that VD can control the cellular regulation of cytokines to control the activity of the innate and adaptive immune systems.[9,10] Despite the fact that no pertinent experiments have been able to confirm that VD interferes with the targets and pathways of AS, several studies have evaluated and analyzed the relationship between VD and rheumatic disease activity and found that VD can regulate the function of Th17-related cytokines to prevent the persistence of inflammation in several rheumatic diseases.[11] Additionally, clinical research has demonstrated that slowing VD metabolism and increasing bone resorption can both worsen AS.[12,13] Therefore, we assume that better outcomes in AS are related with greater in vivo VD level.

The primary marker used to assess the body's vitamin D levels is serum 25-hydroxyvitamin D (25(OH)D).[14] Previous clinical investigations have demonstrated that individuals with AS had lower blood levels of 25(OH)D relative to controls, and that this is related with a higher risk of all-cause death in these patients.[15–17] However, according to several other research, there is no connection between VD levels and AS.[18] In order to confirm the effect of high and low VD levels on the treatment of illness in AS patients, we conducted this meta-analysis to further evaluate the link between serum VD levels and the main monitoring indicators of AS disease activity, including BASDAI, CRP, and ESR.

2. Materials and methods

2.1. Search strategy

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement served as the reporting guidelines for this systematic review (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/H920, Supplementary Content, which describes the PRISMA checklist), which was registered beforehand in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) with the ID INPLASY202290030 (see Protocol S1, Supplemental Digital Content, http://links.lww.com/MD/H921, Supplemental Content, describing the protocol registered in advance with the INPLASY).[19]

In order to include as much research on the connection between VD and AS as feasible, 2 of our writers (CML and CYH) did a literature search of PubMed, the Cochrane Library, EMBASE, and the China National Knowledge Infrastructure. A random combination of the following search terms was used to conduct the literature review: "vitamin D" or "vitamin D levels" or "25-hydroxyvitamin D" or "25-hydroxyvitamin D levels" or "25 (OH) D" or "25 (OH) D levels" and "ankylosing spondylitis" or "ankylosing spondyloarthritis" or "Bechterew's disease," with a time frame limited to August 2022 following a third reviewer arbitrated any disputes between the 2 writers (LW). To ensure that no potentially pertinent researches were overlooked, references to the primary article and associated reviews were thoroughly examined as well.

2.2. Literature selection

The following criteria had to be met for inclusion: studies had to be case-control, cohort, or cross-sectional studies; healthy people had to make up the control group; neither patients nor controls were taking VD supplements; data at 25 (OH) D levels in patients and controls; and data on the correlation index between serum VD levels and BASDAI, correlation index with ESR, or correlation index with CRP in patients and controls.

Exclusion criteria include the following: the type of literature was a review, systematic evaluation, meta-analysis, case report, animal study, in vitro study, and editorial article; the control group population was not healthy; patients or controls were taking VD supplements; and patients' or controls' 25 (OH) D levels were not available.

2.3. Risk of bias assessment

The effectiveness of the included studies was evaluated separately by 2 reviewers (CML and CYH). Cross-sectional studies were evaluated using the Agency for Healthcare Research and Quality (AHRQ), whereas cohort and case-control studies were evaluated using the Newcastle-Ottawa Scale (NOS).[19] Finally, for statistical analysis, we chose case–control studies with NOS scores 7 or cross-sectional studies with AHRQ ratings 4.

2.4. Data extraction

The following data was taken from the included studies by 2 separate authors: the first author's name and the year the study was published, the nation, the subjects' basic characteristics, such as the study category, sample size, mean age, mean BMI, and mean disease duration, the levels of serum 25 (OH) D and/or ESR and CRP in patients and controls, and the correlation coefficients between serum VD and BASDAI, ESR, and CRP in patients and controls. We followed the procedure outlined in other research[20,21] for converting Spearman correlation coefficients to Pearson correlation coefficients for inclusion in the paper.

2.5. Statistical analysis methods

All extracted data were evaluated using Review Manager software version 5.4 for data analysis. Serum 25(OH)D, ESR, and CRP levels, as well as correlations between serum VD levels and significant indicators of AS disease activity, were investigated between AS patients and controls using mean differences (MD) and 95% confidence intervals (CI). In cases where homogeneity was suboptimal ($I^2 \leq 50\%$), a fixed-effects model was applied. Otherwise, a random-effects model was used. Differences were considered statistically significant when $P < .05$. Subgroup analyses were done based on the continents where the article studies were completed. Sensitivity analyses were performed by eliminating each study one at a time to examine the impact of each study on the overall meta-analysis.

3. Results

3.1. Literature search result

We discovered 709 records after evaluating the literature, including those from PubMed (n = 98), EMBASE (n = 470), the Cochrane Library (n = 10), and China National Knowledge Infrastructure (n = 131). After the software had removed 413 duplicate entries, we went through the titles and abstracts of the remaining studies, discarding 267 articles from noncase–control, cohort, and cross-sectional studies. Then, after carefully reading the entirety of each research to evaluate eligibility, we rejected 23 of them in accordance with the inclusion and exclusion criteria we had already established. Finally, 6 papers[13,16,22,23,24] and [25] were incorporated into our meta-analysis. Figure 1 shows the literature screening procedure.

3.2. Characteristics of the studies

In the end, 6 studies totaling 503 AS patients and 398 healthy volunteers were included in our meta-analysis. 3 of these investigations were conducted in Turkey, while the other 3 were conducted in Germany, Morocco, and China. One cross-sectional study and 5 case–control studies made up the total. Table 1 displays the fundamental features of the collected studies.

3.3. Literature quality assessment

The inclusion studies' methodological quality was evaluated using NOS and AHRQ. Four of the 6 studies received 7, one received 8, and one received a 9. Overall, all included studies had moderate to high methodological quality.

3.4. Meta-analysis of the differences in serum 25(OH)D levels between AS patients and controls

The results of the meta-analysis and subgroup analysis are summarized in Tables 2 and 3, respectively. Among the included studies, 6 studies provided data on the serum 25(OH)D levels of 503 AS patients and 398 controls. Figure 2 illustrates the statistical findings that 25(OH)D levels in AS patients were substantially lower than in controls (MD = −7.53 ng/mL, 95% CI: −9.78 to −5.28, $P < .001$). We ran a series of subgroup analyses based on the various continents where the studies were done in order to identify possible influencing factors after high statistical heterogeneity was identified ($I^2 = 67\%$, $P = .009$). As shown in Figure 3, notably, statistical heterogeneity was significantly lower in the Asian subgroup ($I^2 = 50\%$, $P = .11$), and statistical results remained statistically different in the European and African subgroups. Furthermore, the stability of the pooled results was further supported by the results of the sensitivity analysis (Table 4).

3.5. Meta-analysis of the differences in ERS levels between AS patients and controls

Three studies out of the total of the included studies reported serum ERS levels for 226 AS patients and 150 controls. Figure 4 demonstrates that ERS levels were significantly higher in patients with AS compared to controls (MD = 11.75 mm/h, 95% CI: 4.20–19.31, $P = .002$), and significant statistical heterogeneity was found ($I^2 = 94\%$, $P < .001$); however, subgroup analyses were not carried out because these studies did not cover all continents involved in the studies. Notably, the sensitivity analysis's findings did not support the stability of the pooled results because statistical shifts occurred when one study was excluded at a time (Table 4).

3.6. Meta-analysis of the differences in CRP levels between AS patients and controls

Serum CRP levels were measured in 238 individuals with AS and 232 controls across 3 investigations. Figure 5 demonstrates that CRP levels in AS patients were significantly higher than in controls (MD = 15.36 mg/l, 95% CI: 4.95–25.77, $P = .004$). High statistical heterogeneity was also noted ($I^2 = 96\%$, $P < .001$), but subgroup analyses were not carried out because these studies did not cover all of the involved continents. Additionally, due to statistical variance after excluding one research at a time, sensitivity analysis could not support the stability of the pooled results (Table 4).

3.7. Meta-analysis of the relationship between serum VD levels and BASDAI in AS patients

Five of the 6 studies that were included in the analysis looked at the link between AS patients' BASDAI and blood VD levels and produced Pearson's or Spearman's correlation coefficients. To run a pooled analysis to ascertain the link between VD levels

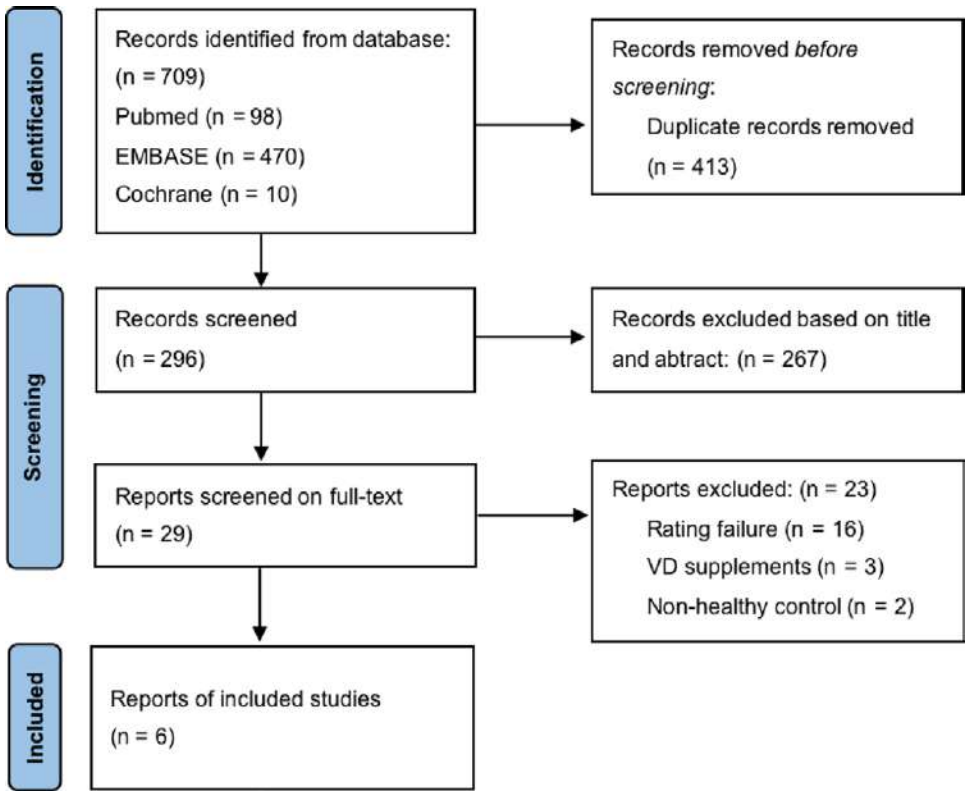

Figure 1. The procedure for screening literature.

Table 1

The basic characteristics of the included studies.

Study	Country	Study design	Sample size (AS/control)	Mean age (AS/control)	Mean BMI (kg/cm²) (AS/control)	Mean disease duration (year)	Outcomes	Statistical methods	NOS/AHRQ
Bedriye 2009	Turkey	Case–control	100/58	39.9/38.1	26.05/25.9	10.5	Serum 25(OH)D ESR CRP COR of VD and BASDAI COR of VD and ESR COR of VD and CRP	Student's *t* test Mann–Whitney *U* test Pearson correlation test Spearman correlation test	7
Burhan 2018	Turkey	Case–control	68/34	41.51/39.11	27.2/26.11	N	Serum 25(OH)D ESR CRP COR of VD and BASDAI COR of VD and ESR COR of VD and CRP	Chi-square test independent sample *t* test Mann–Whitney *U* test Spearman's rho test	9
Durmus 2012	Turkey	Cross-sectional	99/42	36.8/36.1	N/N	10.48	Serum 25(OH)D COR of VD and BASDAI COR of VD and ESR COR of VD and CRP	Shapiro–Wilk test Pearson correlation one-way analysis of variance HOC Tukey's test Chi-square test	7
Hmamouchi 2013	Morocco	Case–control	70/140	40/42	23.1/24.8	12.1	Serum 25(OH)D CRP COR of VD and BASDAI	Kolmogorov Smirnov test Student's *t* test chi-squared test Fisher's exact test Pearson correlation test	7
Lange 2001	Germany	Case–control	70/45	38.4/N	N/N	N	Serum 25(OH)D ESR COR of VD and BASDAI COR of VD and ESR COR of VD and CRP	Spearman's correlation test Mann–Whitney *U* test	7
Mu 2014	China	Case–control	108/66	40/41	N/N	N	Serum 25(OH)D COR of VD and ESR	*t* test Pearson correlation test	8

25(OH)D = serum 25-hydroxyvitamin D, AHRQ = Agency for Healthcare Research and Quality, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NOS = Newcastle-Ottawa Scale, VD = vitamin D.

Table 2

Results of meta-analysis of the associations of serum 25(OH)D, ESR, and CRP between AS patients and controls, and the relationships between serum VD levels and BASDAI, ESR, and CRP in AS patients.

Outcomes	Eligible studies	Sample size (AS/Control)	MD (95% CI)	*P* value	Heterogeneity test
25(OH)D	6	503/398	-7.53 (-9.78, -5.28)	<0.001	I^2 = 67%, *P* = .009
ESR	3	226/150	11.75 (4.20, 19.31)	0.002	I^2 = 94%, *P* < .001
CRP	3	238/232	15.36 (4.95, 25.77)	0.004	I^2 = 96%, *P* < .001
VD and BASDAI	5	395	-0.34 (-0.50, -0.18)	0.001	I^2 = 59%, *P* = .04
VD and ESR	5	433	-0.38 (-0.61, -0.16)	< 0.001	I^2 = 81%, *P* < .001
VD and CRP	4	325	-0.35 (-0.69, -0.01)	= 0.04	I^2 = 89%, *P* < .001

25(OH)D = serum 25-hydroxyvitamin D, AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, VD = vitamin D.

and BASDAI in AS patients, these Pearson's or Spearman's correlation coefficients were changed to Fisher's Z values. We did a number of subgroup analyses based on the various continents where the study was done because, as shown in Figure 6, the meta-analysis produced a Fisher's Z value of –0.34 (95% CI, –0.50 to –0.18, $P < .001$), but there was significant statistical heterogeneity ($I^2 = 59\%$, $P = .04$). As shown in Fig. 7, statistical heterogeneity was significantly lower in the Asian subgroup ($I^2 = 11\%$, $P = .33$), while statistical results remained significant in the European and African subgroups, which indicated that serum VD levels were negatively correlated with BASDAI in all subgroups. The stability of the pooled results was further supported by the results of the sensitivity analysis, which showed that the results remained stable even when one study was excluded at a time (Table 5).

3.8. Meta-analysis of the relationship between serum VD levels and ESR in AS patients

Five of the included studies looked at the connection between AS patients' blood VD levels and ESR. Figure 8 illustrates the statistical results, which produced a Fisher's Z value of –0.38 (95% CI: –0.61 to –0.16, $P < .001$), despite the fact that there was significant statistical heterogeneity ($I^2 = 81\%$, $P < .001$) and that subgroup analyses were not conducted. Notably, the

Table 3

Results of subgroup analysis of the association of serum 25(OH)D between AS patients and controls, and the relationship between serum VD levels and BASDAI in AS patients.

Outcomes	Subgroup	Eligible studies	Sample size (AS/control)	MD/Fisher'Z (95% CI)	*P* value	Heterogeneity test
25(OH)D	Asian	4	375/200	−7.77 (−10.38, −5.16)	<.001	I^2 = 50%, *P* = .11
	European	1	58/58	−9.95 (−12.39, −7.51)	<.001	None
	African	1	70/140	−4.40 (−7.01, −1.79)	<.001	None
VD and BASDAI	Asian	3	267	−0.34 (−0.50, −0.18)	.001	I^2 = 11%, *P* = .33
	European	1	58	−0.67 (−0.93, −0.41)	<.001	None
	African	1	70	−0.33 (−0.57, −0.09)	.007	None

25(OH)D = serum 25-hydroxyvitamin D, AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, ESR = erythrocyte sedimentation rate, VD = vitamin D.

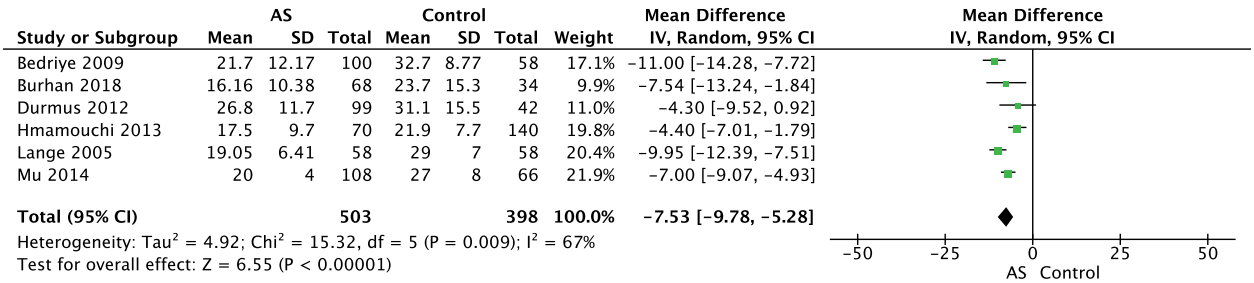

Figure 2. Forest plot of differences in serum 25(OH)D levels between AS patients and controls. AS = ankylosing spondylitis, 25(OH)D = serum 25-hydroxyvitamin D.

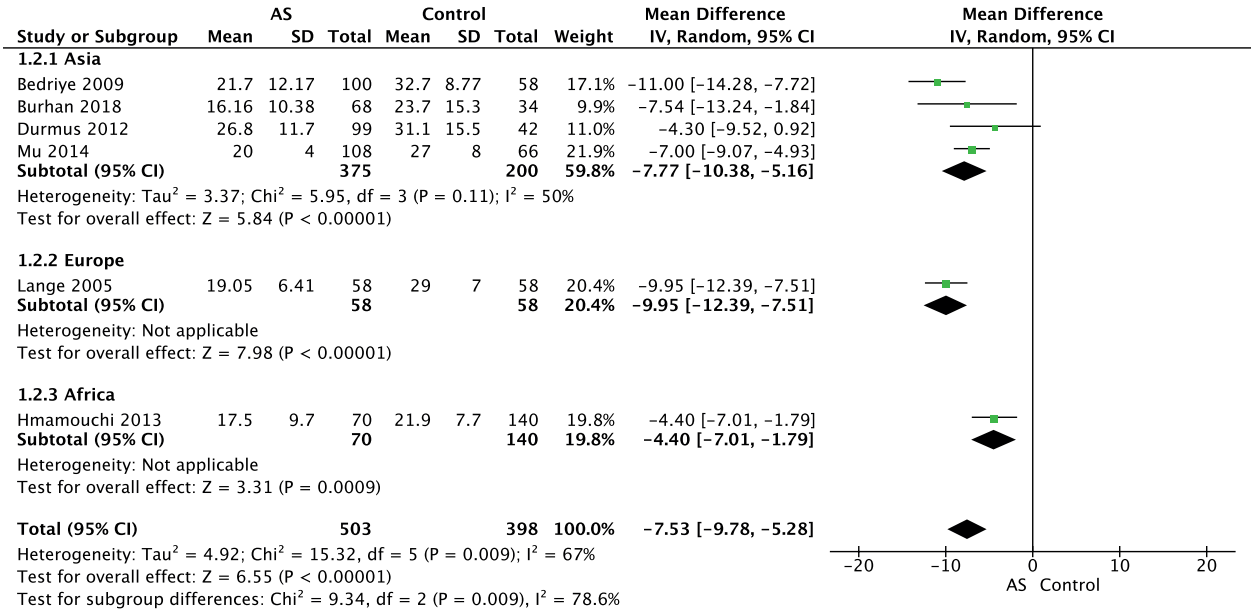

Figure 3. Forest plot of subgroup analysis of differences in serum 25(OH)D levels between AS patients and controls. AS = ankylosing spondylitis, 25(OH)D = serum 25-hydroxyvitamin D.

sensitivity analysis findings supported the reliability of the combined results (Table 5).

3.9. Meta-analysis of the relationship between serum VD levels and BASDAI, ESR as well as CRP in AS patients

Among the included studies, 5 studies examined the relationship between serum VD levels and CRP in patients with AS. As shown in Fig. 9, the statistical results yielded a Fisher's Z value of −0.35 (95% CI: −0.69 to −0.01, *P* = .04), while high statistical heterogeneity was detected (I^2 = 89%, *P* < .001), but no subgroup analysis was performed. However, the results of the sensitivity analysis did not confirm the stability of the pooled results (Table 5).

4. Discussion

AS is a lifelong condition with a prevalence of 0.2% to 1% in adults, and men are 2 to 3 times more likely than women to develop the disease.[26,27] There is no cure for AS, and available treatments can only delay the process of spinal stiffness and fusion as much as possible, maximize physical function and long-term quality of life, and reduce patient symptoms.[28,29] Current clinical recommendations advocate nonsteroidal

Table 4

Sensitivity analysis of the differences in serum 25(OH)D, ERS and CRP levels between AS patients and controls.

Omitted studies	Estimation		95% CI	*I2(P)*
Serum 25(OH)D				
Bedriye 2009	−6.84	−9.12	−4.56	62% (0.03)
Burhan 2018	−7.52	−10.03	−5	74% (0.004)
Durmus 2012	−7.93	−10.34	−5.52	71% (0.008)
Hmamouchi 2013	−8.37	−10.48	−6.26	51% (0.09)
Lange 2005	−6.91	−9.36	−4.46	62% (0.03)
Mu 2014	−7.62	−10.65	−4.6	73% (0.005)
Combine	−7.53	−9.78	−5.28	67% (0.009)
ESR				
Bedriye 2009	8.43	−1.4	18.27	96% (<0.001)
Burhan 2018	15.69	10.4	20.98	81% (0.02)
Lange 2005	10.99	−4.19	26.17	97% (<0.001)
Combine	11.75	4.2	19.31	94% (<0.001)
CRP				
Cervellati 2016	14.19	−1.86	30.24	97% (<0.001)
Liu 2010	20.02	15.48	24.56	56% (0.13)
Zuo 2016	11.89	0.38	23.39	96% (<0.001)
Combine	15.36	4.95	25.77	96% (<0.001)

25(OH)D = serum 25-hydroxyvitamin D, AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, VD = vitamin D.

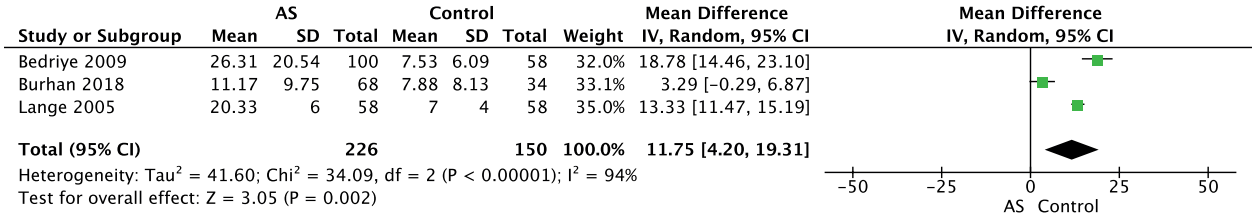

Figure 4. Forest plot of differences in ESR levels between AS patients and controls. AS = ankylosing spondylitis, ESR = erythrocyte sedimentation rate.

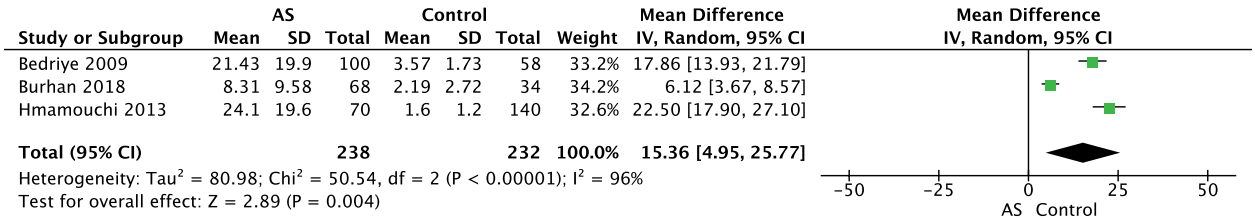

Figure 5. Forest plot of differences in CRP levels between AS patients and control. AS = ankylosing spondylitis, CRP = C-reactive protein.

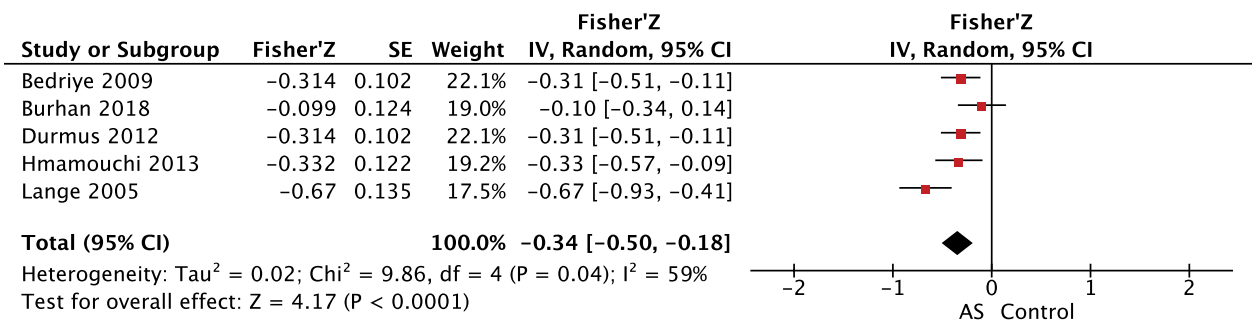

Figure 6. Forest plot of the correlation between serum VD levels and BASDAI in AS patients. AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, VD = vitamin D.

anti-inflammatory medicines as the first-line treatment. Additionally, interleukin (IL)-17 inhibitors and antitumor necrosis factor medications, which are newer treatments for AS, can also significantly reduce AS symptoms.[30–32] When AS is not adequately treated, one of its complications, osteoporosis, frequently causes pathological fractures,[33] which can easily happen in the intervertebral space or vertebral body and are also known as Andersson's lesions, which are closely related to bone

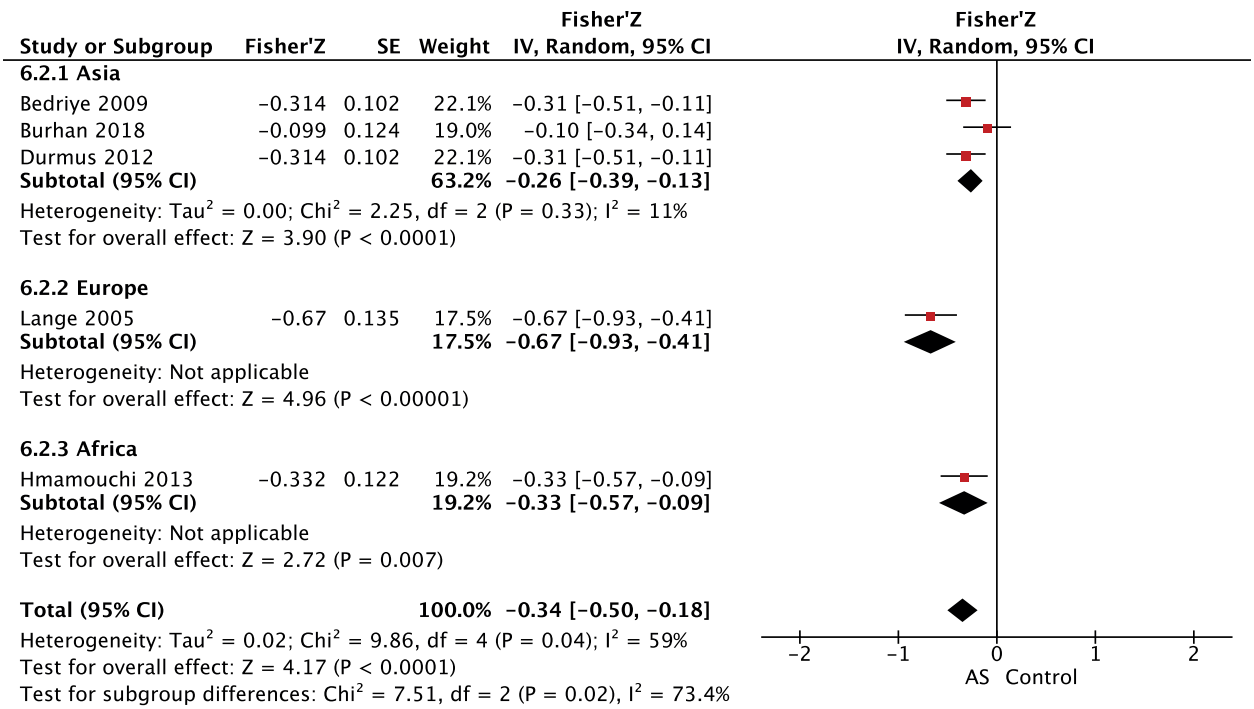

Figure 7. Forest plot of subgroup analysis of correlation between serum VD levels and BASDAI in AS patients. AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, ESR = erythrocyte sedimentation rate, VD = vitamin D.

Table 5

Sensitivity analysis of the correlation between serum VD levels and BASDAI, ESR as well as CRP in AS patients.

Omitted studies	Estimation		95% CI	I^2 (*P*)
Serum 25(OH)D				
Bedriye 2009	−0.35	−0.56	−0.14	69% (0.02)
Burhan 2018	−0.39	−0.54	−0.24	46% (0.13)
Durmus 2012	−0.35	−0.56	−0.14	69% (0.02)
Hmamouchi 2013	−0.34	−0.55	−0.14	70% (0.02)
Mu 2014	−0.27	−0.38	−0.17	0% (0.47)
Combine	−0.34	−0.5	−0.18	59% (0.04)
ESR				
Bedriye 2009	−0.43	−0.69	−0.17	82% (<0.001)
Burhan 2018	−0.46	−0.68	−0.24	77% (0.005)
Durmus 2012	−0.38	−0.68	−0.08	86% (<0.001)
Lange 2005	−0.31	−0.56	−0.07	81% (0.001)
Mu 2014	−0.32	−0.56	−0.08	78% (0.003)
Combine	−0.38	−0.61	−0.16	81% (<0.001)
CRP				
Bedriye 2009	−0.44	−0.88	0	90% (<0.001)
Burhan 2018	−0.44	−0.87	−0.02	91% (<0.001)
Durmus 2012	**−0.35**	**−0.85**	**0.15**	**93% (<0.001)**
Lange 2005	−0.18	−0.37	0	55% (0.11)
Combine	−0.35	−0.69	−0.01	89% (<0.001)

25(OH)D = serum 25-hydroxyvitamin D, AS = ankylosing spondylitis, BASDAI = Bass Ankylosing Spondylitis Disease Activity Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, VD = vitamin D.

resorption and decreased bone density in advanced AS.[34] The surgical management of AS fractures is likewise fraught with risks, including as surgical site infection, nonbacterial pneumonia, implant failure, and mortality.[35] As a result, bone preservation and fracture prevention for AS patients are crucial since they are strongly tied to disease management and AS patients' quality of life.

It is well known that VD is a significant steroid hormone in the body, with its major roles being to increase intestine synthesis for calcium and phosphate absorption as well as to regulate bone metabolism. But recent research has demonstrated that VD also plays a key role in autoimmune and rheumatic illnesses.[36,37] In order to undertake this meta-analysis, we statistically evaluated the findings from 6 research that looked at the relationship between VD and AS. The results of our meta-analysis showed that serum 25(OH)D levels were generally lower in AS patients than in controls, and the overall results were confirmed by our subgroup analysis. We hypothesized that low serum 25(OH)D levels in AS patients are closely related to the continent and ethnicity of the subjects, but since fewer studies were included in Europe and Africa, more case-control trials are required to further confirm these findings.

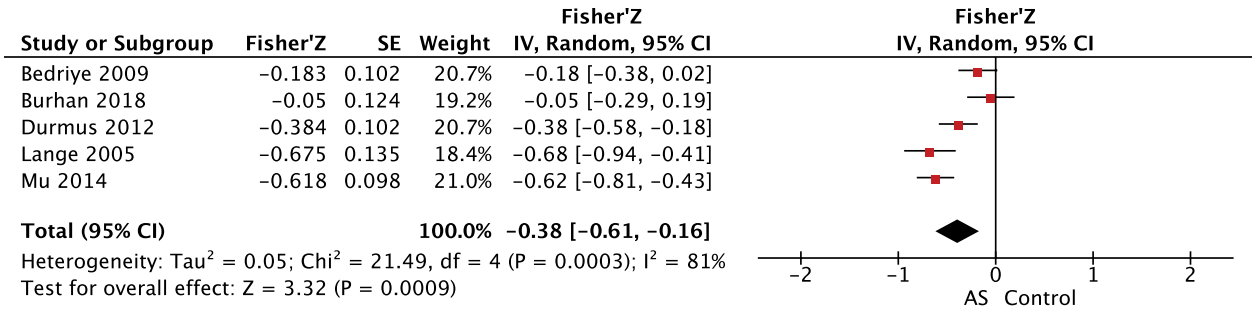

Figure 8. Forest plot of the correlation between serum VD levels and ESR in AS patients. AS = ankylosing spondylitis, ESR = erythrocyte sedimentation rate, VD = vitamin D.

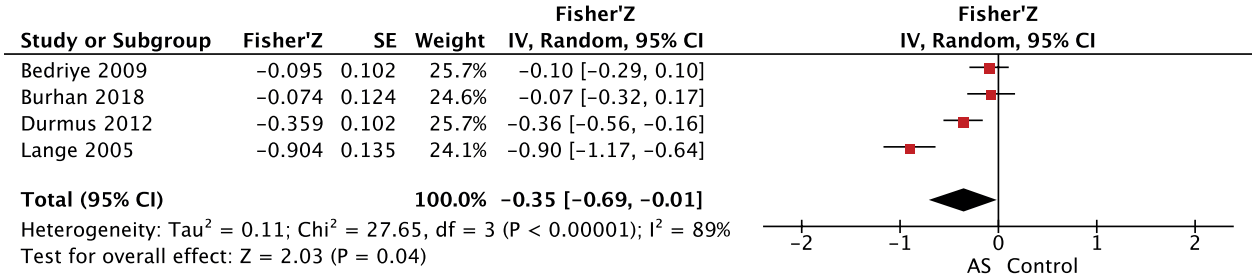

Figure 9. Forest plot of the correlation between serum VD levels and CRP in AS patients. AS = ankylosing spondylitis, CRP = C-reactive protein, VD = vitamin D.

A meta-analysis was carried out to look at the connection between serum VD levels and BASDAI, ESR, and CRP in order to further highlight the association between serum VD levels and AS disease activity. The BASDAI is a score derived from a patient-self-administered questionnaire that is used to quantify disease activity in AS patients. A cutoff of BASDAI ≥ 4 is used to indicate a high level of disease activity.[5,38] Our subgroup analysis supported the negative correlation between serum VD levels and BASDAI that was identified by the findings of our meta-analysis. According to this, it can be evidenced that higher serum VD levels are closely linked to better disease management and quality of life in AS patients. It also supports the idea that continental and ethnic differences may significantly affect the negative correlation between serum VD levels and BASDAI. Additionally, research has shown that regular exposure to sunshine greatly increases the blood levels of VD in people.[39,40] As a result, individuals with AS may see an improvement in their quality of life if they receive an acceptable amount of sun exposure. Meanwhile, it has been demonstrated that lower VD levels are linked to higher all-cause mortality in AS patients, and it has been proposed that VD supplementation, used as a secondary prevention measure in cases of VD deficiency or insufficiency, may lessen AS patients' disease activity and comorbidity.[15,41]

ESR and CRP are nonspecific inflammatory biomarkers that are frequently used to monitor AS disease activity and assess whether patients' symptoms improve while receiving therapy.[42,43] As a result, using meta-analysis, we looked at the variations in ESP and CRP levels between AS patients and controls as well as the relationship between serum VD levels and ESR and CRP levels in AS patients. The findings demonstrated that serum VD levels in AS patients had a negative correlation with total ESR and CRP levels, which were also considerably higher in AS patients compared to controls.

While the stability of the pooled results was not supported by the results of all sensitivity analyses, it is noteworthy that our meta-analysis of ESR and CRP levels and their correlation with serum VD levels revealed a significant overall heterogeneity ($I^2 \geq 89\%$), indicating that a number of unidentified factors contributed to the heterogeneity of these data sets' results. These factors may include the mean BASDAI score and mean disease duration of the subjects, but we did not perform further subgroup.

Our meta-analysis has several advantages: first, our meta-analysis focused on the relationship between serum VD levels and 3 key markers of AS disease activity, including BASDAI, ESR, and CRP; second, we divided studies of serum 25(OH)D levels in AS patients and controls, as well as the relationship between serum VD levels and BASDAI, according to ethnicity; and thirdly, despite the large heterogeneity in the results of a subset of our studies, the quality of the included studies was moderately high.

There are certain nonnegligible restrictions despite the fact that our investigation produced some fresh findings. We first conducted a thorough search for clinical studies pertaining to AS and VD, but due to our stringent inclusion and exclusion criteria, we were only able to find 6 that met our standards. These studies were primarily focused on Asia, with few studies in Europe and Africa, and there is a lack of information from studies on other continents, so the results of our analysis should be interpreted with caution for populations on other continents. Second, the Ankylosing Spondylitis Disease Activity Score[44] is the primary index for tracking and assessing AS disease activity in addition to BASDAI, ESR, and CRP; however, since only one of our included studies[16] recorded the correlation coefficient between VD levels and Ankylosing Spondylitis Disease Activity Score, we did not examine it separately. Third, despite our best efforts to account for confounding influences, some unidentified factors continued to contribute to the high heterogeneity of some of our findings, which had an impact on the overall conclusions. Fourth, despite the fact that several of our results had a high degree of heterogeneity, which may greatly reduce their validity, our sensitivity analysis supported the stability of some findings.

5. Conclusion

In conclusion, our findings revealed a negative correlation between serum VD levels and the primary monitoring markers of disease activity in AS patients, including BASDAI, ESR, and CRP levels. This finding suggests that higher serum VD levels are strongly linked to both disease control and an improved

quality of life for AS patients. Additionally, we confirmed that the total serum 25(OH)D levels and the inverse relationship between serum VD levels and BASDAI in AS patients may be significantly influenced by continental and ethnic variations. Therefore, patients with AS are advised to supplement VD by sun exposure or supplements in order to lessen clinical symptoms and enhance quality of life. ESR and CRP levels were examined in our meta-analysis in relation to the occurrence of AS, but their correlation with serum VD levels was based on less conclusive evidence. Therefore, more clinical high-quality studies in these areas should be conducted in the future to further validate our results.

Author contributions

Menglu Chen participated in the design of the study and was involved in data extraction and completed the manuscript writing.
Wen Li participated in the design of the study.
Lailai Li edited the manuscript.
Yihui Chai participated in the data extraction.
Yuqi Yang performed the statistical of the collected data.
Xiang Pu revised and reviewed the manuscript.
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Formal analysis: Menglu Chen, Yuqi Yang.
Funding acquisition: Xiang Pu.
Investigation: Yihui Chai.
Methodology: Wen Li, Lailai Li.
Project administration: Xiang Pu.
Software: Menglu Chen.
Visualization: Yuqi Yang.
Writing—original draft: Menglu Chen.
Writing—review and editing: Wen Li, Lailai Li, Xiang Pu.

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