

Serum vitamin D and fracture risk in children and adolescents: A systematic review and meta-analysis highlighting age and altitude as key moderators

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Abstract. The present systematic review and meta-analysis aimed to synthesize current comparative evidence to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and fracture risk in children and adolescents. Observational studies comparing serum 25(OH)D levels between pediatric fracture and non-fracture groups were systematically searched in PubMed, Embase and Cochrane databases up to October 1, 2025. Data were pooled using random-effects models. The primary outcomes were the mean difference (MD) in 25(OH)D levels and the odds ratio (OR) for fracture risk associated with vitamin D deficiency (≤ 20 ng/ml). Subgroup and meta-regression analyses were performed to investigate heterogeneity. A total of 28 studies involving 10,479 participants were included. Meta-analysis revealed significantly lower 25-hydroxyvitamin D (25(OH)D) levels in the fracture group [MD: -1.94 ng/ml; 95% confidence interval (CI): -2.89 to -0.99 ; $P < 0.00001$]. Vitamin D deficiency was associated with a 71% increased odds of fracture (OR: 1.71; 95% CI: 1.29-2.27; $P < 0.0001$), which remained significant after adjustment for confounders (adjusted OR: 2.41; 95% CI: 1.74-3.34). Meta-regression identified specific age (8.3-9.5 years) and altitude residence (≥ 600 m) as core moderators explaining the heterogeneity. Vitamin D deficiency is markedly associated with an elevated fracture risk in children and adolescents, with the association being particularly pronounced in early adolescence and at ≥ 600 m altitudes. These findings highlighted the need for targeted screening and preventive nutritional strategies in these high-risk subgroups.

Introduction

Fractures constitute a major public health concern in pediatrics, with 30-50% of children experiencing at least one fracture before adulthood, imposing significant clinical and economic burdens (1,2). Vitamin D is fundamental for skeletal integrity, primarily by regulating calcium and phosphate homeostasis to facilitate bone mineralization (3). Its classic deficiency leads to rickets and osteomalacia. Mounting evidence indicates that suboptimal vitamin D status, often defined as serum 25-hydroxyvitamin D [25(OH)D] < 50 nmol/l (20 ng/ml), is highly prevalent globally among youth, even in sun-rich regions, with puberty being a period of heightened physiological demand (4-6).

Despite a plausible biological mechanism, the epidemiological link between vitamin D status and fracture risk in children and adolescents remains inconsistent. Recent case-control studies report conflicting findings, from a strong association to null results, potentially due to variations in study design, population characteristics [such as body mass index (BMI) or puberty], geography, and definitions of deficiency (7-9). A previous meta-analysis by Yang *et al* (10) synthesized evidence up to mid-2020, confirming an association but with substantial heterogeneity ($I^2 = 73.9\%$), partially attributed to latitude and season. Another relevant systematic review and meta-analysis published by Zheng *et al* (11) yielded consistent positive associations based on an updated body of literature. Since then, several new, methodologically robust studies have emerged, including investigations into specific subgroups and diverse geographical settings, which were not comprehensively addressed previously (8,9,12).

Therefore, an updated and comprehensive meta-analysis is warranted. The present study aimed to synthesize the most current evidence to: i) Re-evaluate the association between serum 25(OH)D levels and fracture risk in children and adolescents; ii) quantify the pooled odds ratio for fractures comparing individuals with vitamin D deficiency/insufficiency to those with sufficient levels using standardized thresholds; and iii) systematically explore potential sources of heterogeneity, including latitude, season, trauma energy, and age group. By incorporating recent studies and conducting thorough subgroup and meta-regression analyses, this meta-analysis

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provided a more precise and contemporary estimate of this association, offering crucial insights for clinical practice regarding screening and nutritional interventions in at-risk pediatric populations.

Materials and methods

Search strategies. According to PRISMA statement (13), two review authors independently conducted a systematic electronic and manual search in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Cochrane (<https://www.cochranelibrary.com/>) and Embase (<https://www.embase.com/>) databases to identify observational studies that had compared the serum vitamin D levels in a population of children and adolescents with and without fracture. All the available literature without language restrictions was retrieved, with the last search made on October 1, 2025. Search terms included ‘vitamin D’, ‘25-hydroxyvitamin D2’, ‘children’ and ‘fractures’. A combination search using the subject terms (Medical Subject Heading, MeSH) and free terms was carried out. The references of these full-text assessed articles were also reviewed.

A combination search in PubMed revealed the following: (‘vitamin D’ [Title/Abstract] OR ‘vitamin D’ [MeSH Terms] OR ‘cholecalciferol’ [Title/Abstract] OR ‘hydroxycholecalciferols’ [Title/Abstract] OR ‘25 hydroxyvitamin D2’ [Title/Abstract] OR ‘dihydrotachysterol’ [Title/Abstract]) AND (‘fractures, bone’ [MeSH Terms] OR ‘fractures bone’ [Title/Abstract]) AND (‘adolescent’ [MeSH Terms] OR ‘adolescents’ [Title/Abstract] OR ‘adolescence’ [Title/Abstract] OR ‘youth’ [Title/Abstract] OR ‘youths’ [Title/Abstract] OR ‘teens’ [Title/Abstract] OR ‘teen’ [Title/Abstract] OR ‘teenagers’ [Title/Abstract] OR ‘teenager’ [Title/Abstract] OR ‘pediatric’ [Title/Abstract] OR ‘child’ [MeSH Terms] OR ‘child’ [Title/Abstract] OR ‘children’ [Title/Abstract]). Corresponding search strategies adapted for Embase (Emtree thesaurus, :ti,ab field labels) and Cochrane Library (MeSH terminology, :ti,ab field labels) were developed with identical core search concepts, free-text synonyms and Boolean logic to the PubMed search string. The full search formulas for Embase and Cochrane Library are presented in Table SI.

Grey literature including clinical trial registry records, conference abstracts, dissertations and unpublished research reports was not retrieved in this meta-analysis. Most grey literature lacked complete standardized data of serum 25(OH) D and fracture outcomes and their inconsistent methodological quality would introduce substantial heterogeneity to pooled analyses and reduce the reliability of synthetic results.

The eligibility criteria. Studies were included if they met the following strict criteria: i) Compared the vitamin D level between fracture and non-fracture groups; ii) involved only children and adolescents population.

Study design. Prospective or retrospective case-control studies, cross-sectional studies.

Data extraction. For each study, two independent reviewers (BT and JM) extracted the following information: Surname of the first author, publication year, country where the study was conducted, design of the study, sample size, latitude,

altitude, season, ethnicity, fracture site, trauma energy and Newcastle-Ottawa Scale (NOS).

Statistical analysis. Review Manager statistical software (version RevMan 5.4; <https://revman.cochrane.org/>) and R software (version 4.4.3; <https://www.r-project.org/>) were used to analyze all the datasets. The mean difference (MD) was used to compare measurement data. The odds ratio (OR) was calculated for counting data. Cochran's Q χ^2 test was employed to assess statistical heterogeneity across studies. In accordance with the Cochrane Handbook, the selection between fixed-effect and random-effects models should not be guided by the results of statistical heterogeneity tests. The present study therefore employed the random-effects model consistently across all analyses. The heterogeneous studies were analyzed, univariate and further multivariate meta-regression analysis was performed to isolate the possible factors causing heterogeneity. For the subgroup analyses, if a study exhibited marked clinical heterogeneity (such as markedly different baseline characteristics) compared with the other studies within the same stratum, it was manually excluded from the pooled subgroup estimates to avoid misleading results. These excluded studies are clearly marked as having zero weight or labelled as ‘Not estimable’ in the corresponding forest plots, ensuring the clinical homogeneity of the specific subgroup analyses. If heterogeneity between the 2 groups was still significant, descriptive statistics were employed. All the statistical tests were two-sided. $P < 0.05$ was considered to indicate a statistically significant difference.

Publications assessment. The methodological quality of the included studies was assessed using the NOS (14). This tool employs a ‘star system’ to appraise studies across three domains: i) The selection of study groups, ii) the comparability of groups and iii) the ascertainment of exposure (for case-control studies) or outcome (for cohort studies). Based on the total star score, studies were categorized as high quality (≥ 7 stars), moderate quality (5-6 stars), or low quality (≤ 4 stars). Two review authors independently performed the assessments, with any discrepancies resolved through discussion until consensus was reached.

Results

Selection of publications. In total, 4,987 literature sources were retrieved from PubMed, Cochrane and Embase Databases. A total of 3,046 literature articles were left for further evaluation after the removal of duplicates. 124 literatures were screened out through title and abstract evaluation, and 28 studies were finally included according to the inclusion criteria (7-9,12,15-38) (Fig. 1).

This systematic review and meta-analysis included a total of 28 observational studies, comprising five cross-sectional and 23 case-control designs. The pooled analysis encompassed 4,135 pediatric and adolescent patients with fractures and 6,344 age- and sex-matched controls. The included studies were conducted across diverse geographical regions: Nine from the United States, three from Türkiye, two from Lebanon, two from Poland and one each from Romania, Ireland, New Zealand, China, Iran, Canada, Egypt, Jordan, Greece, Finland, Switzerland and Saudi Arabia (Table I).

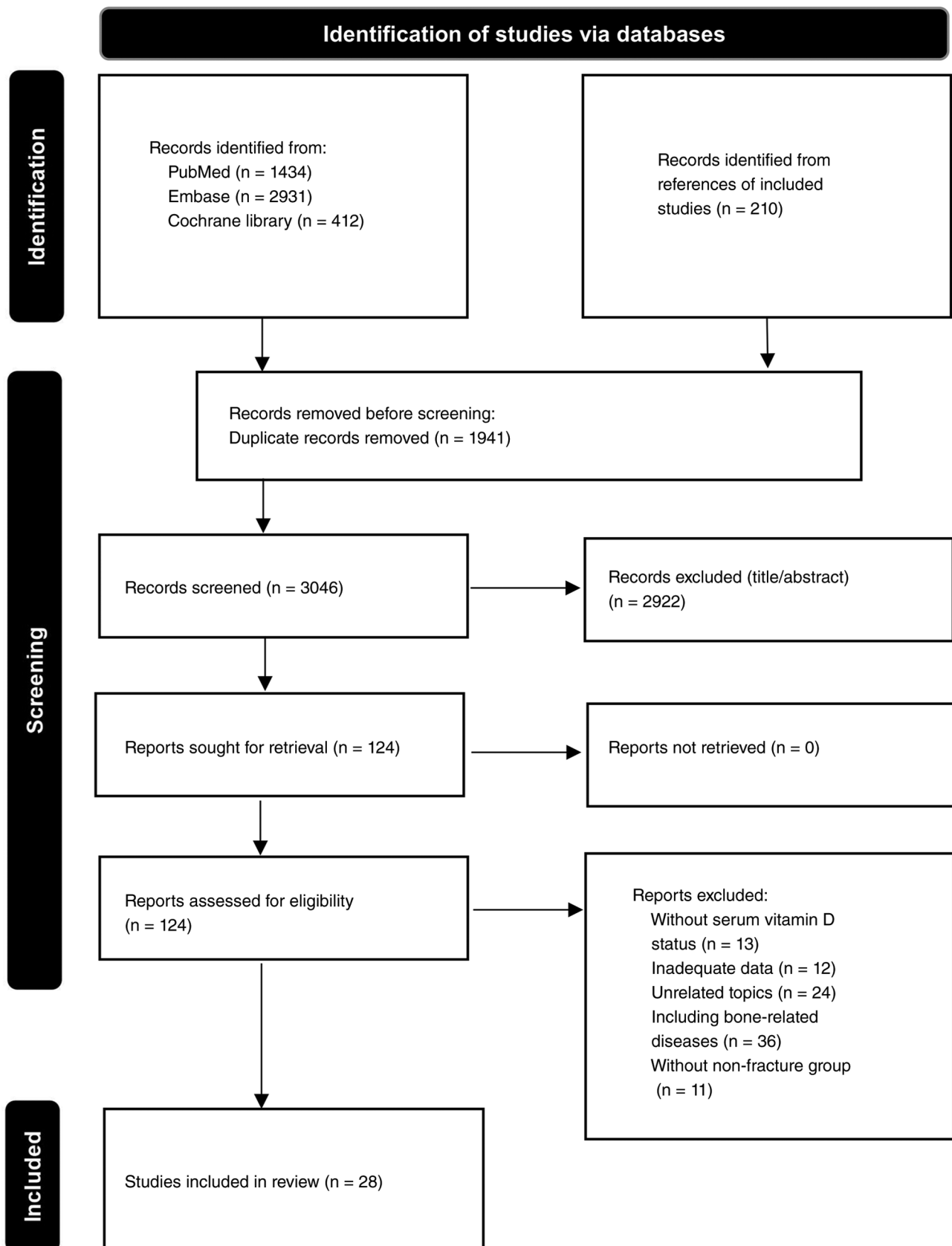


Figure 1. The flowchart of literature inclusion and exclusion.

Quality assessment of included studies. Based on the NOS 'star system', the 28 included studies were predominantly moderate in methodological quality. Specifically, two studies

achieved a rating of seven stars, six received six stars, nine were assessed as five stars, another nine as four stars, while one study was rated three stars and one two stars. Notably, a

Table I. Basic characteristics of included studies.

First author/s, year	Design	City	Country	Latitude	Altitude, m	Season	Sample size (n)	Age, years	Sex (M/F)	Ethnicity	Fracture site	Trauma energy	NOS	(Refs.)
Assaf <i>et al</i> , 2024	Case-con	Byblos	Lebanon	34° N	20	May to October	107	Trial: 7.4±3.7 Con: 7.8±4.6	Trial: 30/7 Con: 42/28	Unclear	Upper and lower limb	Low	6	(7)
Segal <i>et al</i> , 2023	Retros case-con	Cincinnati	USA	39° N	150	All	103	15.9±2.2	48/55	Mixed	Mixed	Low or middle	7	(9)
Matcovic <i>et al</i> , 2023	Pros case-con	Columbus	USA	40° N	275	All	856	Trial: 6-17 Con: 6.7-17.6	Unclear	Mainly White	Distal forearm	Low or middle	7	(8)
Herdea <i>et al</i> , 2023	Pros case-con	Bucharest	Romania	44° N	70	All	1577	2-17	Trial: 399/289 Con: 439/450	Unclear	Upper limb	Low	6	(12)
Varkal <i>et al</i> , 2022	Pros Case-con	Istanbul	Turkiye	41° N	40	All	Trial: 76 Con: 50	9.2±4.1 (2-18)	Trial: 4 8/28 Con: 24/26	Unclear	Mixed	Low	6	(38)
Moore <i>et al</i> , 2022	Pros case-con	Dublin	Ireland	53° N	20	All	Trial: 58 Con: 58	Trial: 8.0±4.2 Con: 8.9±4.4	Trial: 39/19 Con: 31/27	Mainly White	Mixed	Mixed	6	(37)
Talmac <i>et al</i> , 2021	Pros case-con	Istanbul	Turkiye	41° N	40	Feb to May	Trial: 50 Con: 50	Trial: 8.3±2.8 (5-15) Con: 7.9 ± 3.4 (5-15)	Trial: 32/18 Con: 34/16	Unclear	Distal radius	Low	5	(36)
Delshad <i>et al</i> , 2020	Cross-sectional	Auckland	New Zealand	36° S	200	Aug	647	9.8±0.7 (8-12)	293/354	Mixed	Mixed	Mainly low or middle	4	(35)
Liu <i>et al</i> , 2019	Case-con	Shen yang	China	41° N	55	All	Trial: 695 Con: 224	Trial: 7.1±2.8 (1-15) Con: 7.8±3.4 (1-15)	Trial: 448/247 Con: 113/111	Chinese	Upper limb	Low or middle	5	(34)
Younes <i>et al</i> , 2019	Cross-sectional	GB and ML	Lebanon	34° N	50-2000	May to October	Trial: 165 Con: 809	13.37±2.92 (8-18)	508/466	Lebanese	Mixed	Unclear	5	(33)
Popko <i>et al</i> , 2018	Case-con	Bialystok	Poland	53° N	120	May to Aug	Trial: 20 Con: 19	Trial: 12 (5-15) Con: 13.5 (7-17)	Trial: 14/6 Con: 9/10	unclear	unclear	Low	6	(32)
Ramirez <i>et al</i> , 2018	Case-con	Mayaguez	USA	18° N	7	Jan to Jul	Trial: 107 Con: 94	8.6±4.0 (1-18)	Trial: 64/43 Con: 48/46	Hispanic	Upper and lower limb	Low	4	(31)
Saglam <i>et al</i> , 2017	Case-con	Istanbul	Turkiye	41° N	40	Jun to Aug	60	Trial: 8.2±2.6 Con: 7.7±2.1	Trial: 18/12 Con: 14/16	Unclear	Forearm	Unclear	3	(30)
Minkowitz <i>et al</i> , 2017	Case-con	Morristown	USA	40° N	110	Unclear	Trial: 369 Con: 662	Trial: 10.7±4.1 Con: 12.2±4.8	530/486	Mainly White	Mixed	Mixed	4	(29)
Thompson <i>et al</i> , 2017	Pros case-con	Chicago	USA	42° N	179	All	120	Trial: 5.8±2.8 Con: 7.5±4.4	Trial: 33/27 Con: 25/35	Mixed	Mainly long bone	Low	5	(28)
Jeddi <i>et al</i> , 2017	Cross-sectional	Kawar	Iran	30° N	1600	Unclear	478	13.7±2.6	241/237	Iranian	Mixed	Mixed	4	(27)
Karpinski <i>et al</i> , 2017	Case-con	Bialystok	Poland	53° N	120	Apr to Sep	227	11.6±3.7 (3-18)	161/66	unclear	Unclear	Low	5	(26)
Andersan <i>et al</i> , 2017	Case-con	Toronto	Canada	43° N	76	All	549	3.5±1.5 (<6)	307/242	Mainly White	Upper and lower limb	Low	5	(25)
El-Sakka <i>et al</i> , 2016	Pros case-con	Cairo	Egypt	30° N	23	Dec to Jun	Trial: 23 Con: 23	Trial: 6.7±2.3 Con: 7.7±1.7	Trial: 14/9 Con: 14/9	Egyptian	Forearm	Unclear	5	(24)

Table I. Continued.

First author/s, year	Design	City	Country	Latitude	Altitude, m	Season	Sample size (n)	Age, years	Sex (M/F)	Ethnicity	Fracture site	Trauma energy	NOS	(Refs.)
Jahmani <i>et al</i> , 2017	Case-con	Ar-Ramtha	Jordan	32° N	525	Unclear	119	6.5±4.6	70/49	Unclear	Mixed	Unclear	2	(23)
AL-Daghri <i>et al</i> , 2016	Cross-sectional	Riyadh	Saudi Arabia	25° N	600	All	Trial: 234 Con: 1022	Trial: 14.07±1.39 Con: 14.03±1.81	Trial: 148/86 Con: 476/546	Saudi Arab	Mixed	Low or middle	4	(22)
Contreras <i>et al</i> , 2014	Pros case-con	Winston-Salem	USA	36° N	300	Oct to Jan	Trial: 100 Con: 100	Trial: 10.1 (9.2-11) Con: 11 (10.0-11.9)	Trial: 70/30 Con: 50/50	Mixed	Mixed	Low	4	(21)
Papaefthymiou <i>et al</i> , 2014	Case-con	Athens	Greece	38° N	70	All	Trial: 21 Con: 42	Trial: 14.10±2.15 Con: 13.47±2.12	All male	Greek	Mixed	Traumatic	4	(20)
Mäyränpää <i>et al</i> , 2012	Pros case-con	Helsinki	Finland	60° N	10	All	Trial: 66 Con: 64	Trial: 10.7 (4.4-16.8) Con: 11.2	Trial: 44/22 Con: 43/21	Mainly Finnish	Mixed	Low	6	(19)
Ryan <i>et al</i> , 2012	Case-con	Washington DC	USA	39° N	125	All	Trial: 70 Con: 71	Trial: 6.9±1.4 Con: 7.0±1.5	Trial: 44/32 Con: 40/34	African American	Forearm	Low	5	(18)
Ceroni <i>et al</i> , 2012	Pros cross-sectional	Geneva	Switzerland	46° N	375	Unclear	Trial1: 50 Trial2: 50 Con: 50	Trial1: 12.9±1.7 Trial2: 3.0±1.7 Con: 12.7±2.3	Unclear	Swiss Caucasian	Appendicular	Low or middle	5	(17)
Olney <i>et al</i> , 2008	Case-con	Jacksonville	USA	40° N	5	Unclear	Trial: 68 Con: 57	Trial: 12.0±3.0 Con: 11.1±3.2	Trial: 48/20 Con: 34/23	Mainly White	Mixed	Low	4	(16)
Chan <i>et al</i> , 1984	Case-con	SLC	USA	30° N	1300	Unclear	Trial: 17 Con: 17	Trial: 6.4±0.8 Con: 6.4±0.8	Trial: 9/8 Con: 9/8	Unclear	limb	Accidental	4	(15)

pros, prospective; retros, retrospective; con, control; NOS, Newcastle-Ottawa Scale; SLC, Salt Lake City; GB, Great Beirut; ML, Mount Lebanon.

primary factor contributing to the relatively lower NOS scores in certain studies was insufficient documentation of seasonal factors, particularly the unclear comparability of vitamin D blood sampling seasons between the fracture and non-fracture groups. This methodological limitation consequently diminished the overall methodological rigor and the reliability of their respective findings.

Egger test and funnel plot for publication bias. The results of Egger's linear regression test indicated that the intercept term was not statistically significant ($P=0.53$; 95% CI: -2.16 to 1.08), suggesting no significant asymmetry in the funnel plot and thus no evidence of substantial publication bias. Through a combination of funnel plot visualization and Egger's test, the present study did not detect significant publication bias, indicating a low risk of bias among the included studies and supporting the reliability of the pooled effect estimate (Fig. 2).

Sensitivity analysis. The sensitivity analysis results of the present study demonstrated that upon the sequential removal of any single study, the direction and statistical significance of the pooled effect size remained unchanged, with minimal fluctuation in heterogeneity ($<5\%$; Fig. 3). Leave-one-out sensitivity analysis included low-quality studies rated two or three stars; sequential individual omission of each low-quality study did not materially change the pooled effect estimate or its statistical significance. This indicates that the core conclusion of the present study, that adolescents in the fracture group have significantly lower vitamin D levels than those in the control group (pooled MD ~ -1.95), exhibits good robustness and is not unduly influenced by individual studies. Even after excluding the studies with the largest sample sizes [such as Herdea 2023 (12), Matcovic 2023 (8)], the pooled effect size remained stable (MD = -1.78 to -1.94), indicating that large-sample studies did not disproportionately influence the overall results. This minimized the risk of 'weight bias' interfering with the conclusions. In summary, the findings of this meta-analysis were robust and reliable. The core conclusions possess strong external validity and can provide stable evidence to support clinical practice and public health decision-making.

Comparison of serum vitamin D levels between the fracture and the non-fracture groups. A total of 27 studies involving 10,433 adolescent participants were included, comprising 4,112 in the fracture group and 6,321 in the non-fracture group. The mean vitamin D levels ranged from 12.28-35.4 ng/ml in the fracture group and from 15.08-36.64 ng/ml in the non-fracture group. Considerable variation in sample sizes was observed across studies, with the smallest study including 34 participants [Chan 1984 (15)] and the largest including 1,577 [Herdea 2023 (12)]. Study weights were evenly distributed (range: 3.1-5.0%), indicating that no single study unduly influenced the pooled results. Three studies [Contreras 2014 (21), Younes 2019 (33), Segal 2023 (9)] reported slightly higher vitamin D levels in the fracture group compared to the non-fracture group. However, the effect sizes were small (MD = 0.10-2.72), and only the result from Younes 2019 reached statistical significance (MD = 1.29; 95% CI: 0.15-2.43). The overall effect of these studies on the pooled results was limited. Meta-analysis revealed that the mean vitamin D level was significantly

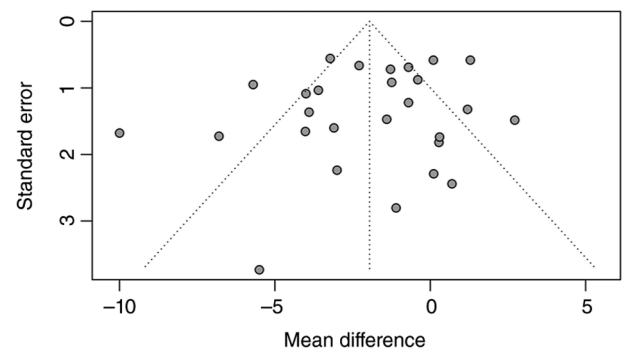


Figure 2. Funnel plot for publication bias.

lower in the fracture group than in the non-fracture group (MD = -1.94 [-2.89 -0.99]; $P < 0.00001$; $I^2 = 80\%$). However, this finding requires cautious interpretation due to significant heterogeneity (Fig. 4).

Comparison of risk of serum vitamin D deficiency between the fracture and the non-fracture groups. A total of 17 studies, comprising 5,473 adolescent participants (2,488 in the fracture group and 2,985 in the non-fracture group), were included in this analysis on the correlation of vitamin D deficiency (vitamin D level ≤ 20 ng/ml) with fracture (Fig. 5). Within these studies, vitamin D deficiency was reported in 1,620 participants from the fracture group and 1,894 from the non-fracture group. The distribution of study weights varied, with the highest weight assigned to Herdea 2023 (12) (34.9%) and the lowest to Saglam 2017 (30) (0.5%). Importantly, no single study contributed $>50\%$ of the total weight, thus mitigating the risk of any individual study exerting undue influence on the pooled result. Of the 17 studies, 13 reported a positive association between vitamin D deficiency and fracture risk in adolescents ($OR > 1$), with eight reaching statistical significance, the strongest effect was observed in the study by Saglam *et al* (30) ($OR = 13.14$; 95% CI: 3.84-45.02), indicating a 13.14-fold higher fracture risk among adolescents with vitamin D deficiency in that study. The studies with the highest statistical weights, Herdea 2023 (12) ($OR = 2.42$; 95% CI: 1.94-3.01) and Liu 2019 (34) ($OR = 1.78$; 95% CI: 1.30-2.45); both supported the conclusion that vitamin D deficiency increases fracture risk, further validating the robustness of the pooled result.

The pooled analysis revealed that adolescents with vitamin D deficiency (vitamin D level ≤ 20 ng/ml) had a significantly higher risk of fracture compared to those with sufficient vitamin D levels ($OR = 1.71$ [1.29-2.27]; $P < 0.0001$; $I^2 = 65\%$). This result indicates that vitamin D deficiency is associated with a 71% increased risk of fracture in adolescents, confirming a significant positive association between vitamin D deficiency and fracture risk in this population. Similarly, this result should be interpreted with caution owing to substantial heterogeneity (Fig. 5).

Building upon the previous unadjusted analyses, the present study further incorporated studies that explicitly reported adjusted ORs to focus on the independent association between vitamin D deficiency and fracture risk in adolescents. Statistical analysis was performed using the metafor package in R software version 4.4.3 (<https://www.r-project.org/>).

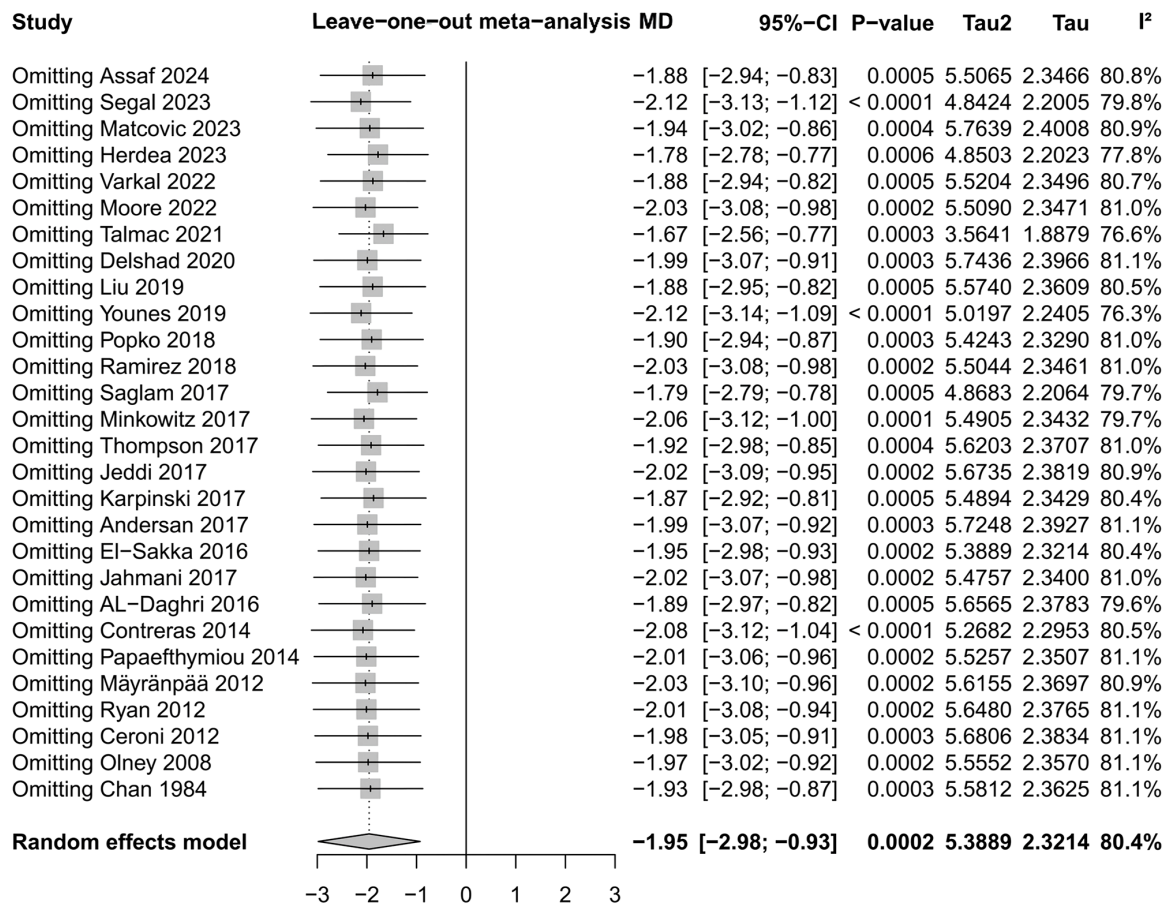


Figure 3. Leave-one-out meta-analysis for sensitivity analysis. MD, mean difference; CI, confidence interval; Tau², Tau-squared; I², I-squared.

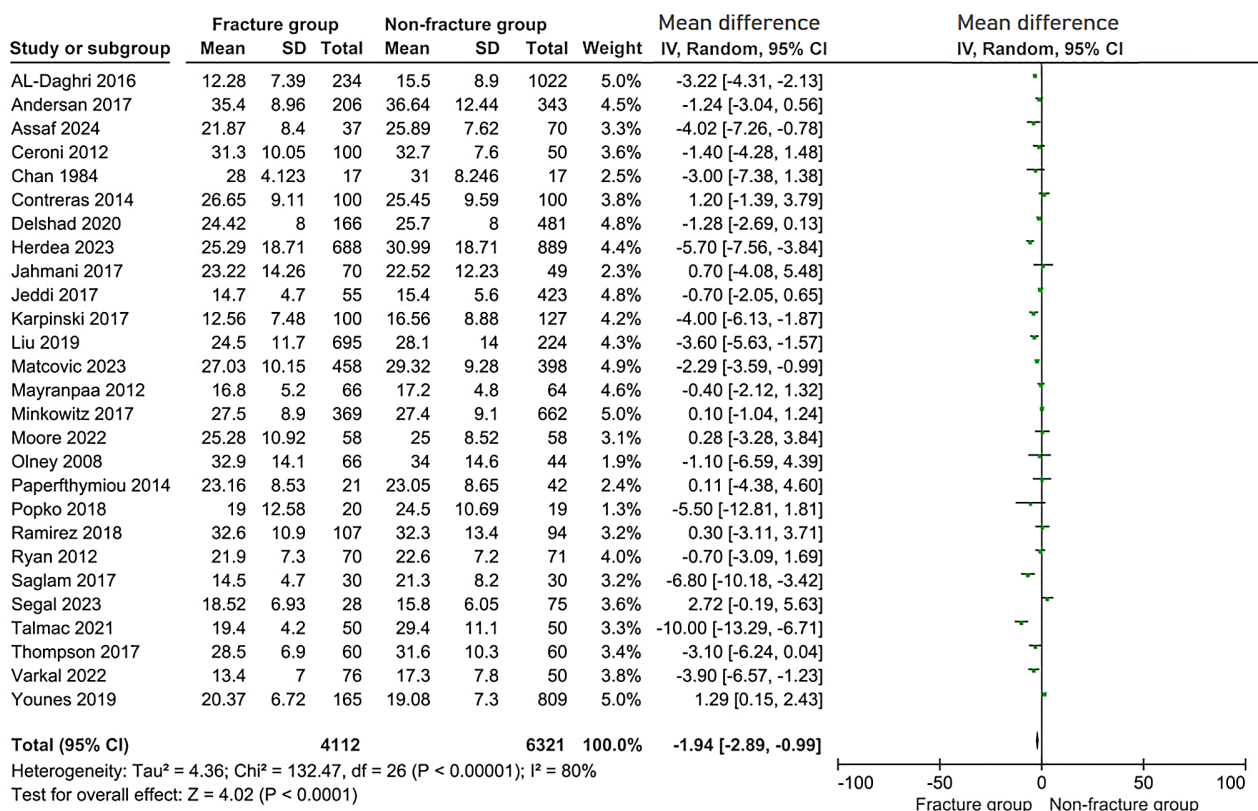


Figure 4. Pooled results of serum vitamin D levels between the fracture and the non-fracture groups. SD, standard deviation; IV, inverse variance; CI, confidence interval.

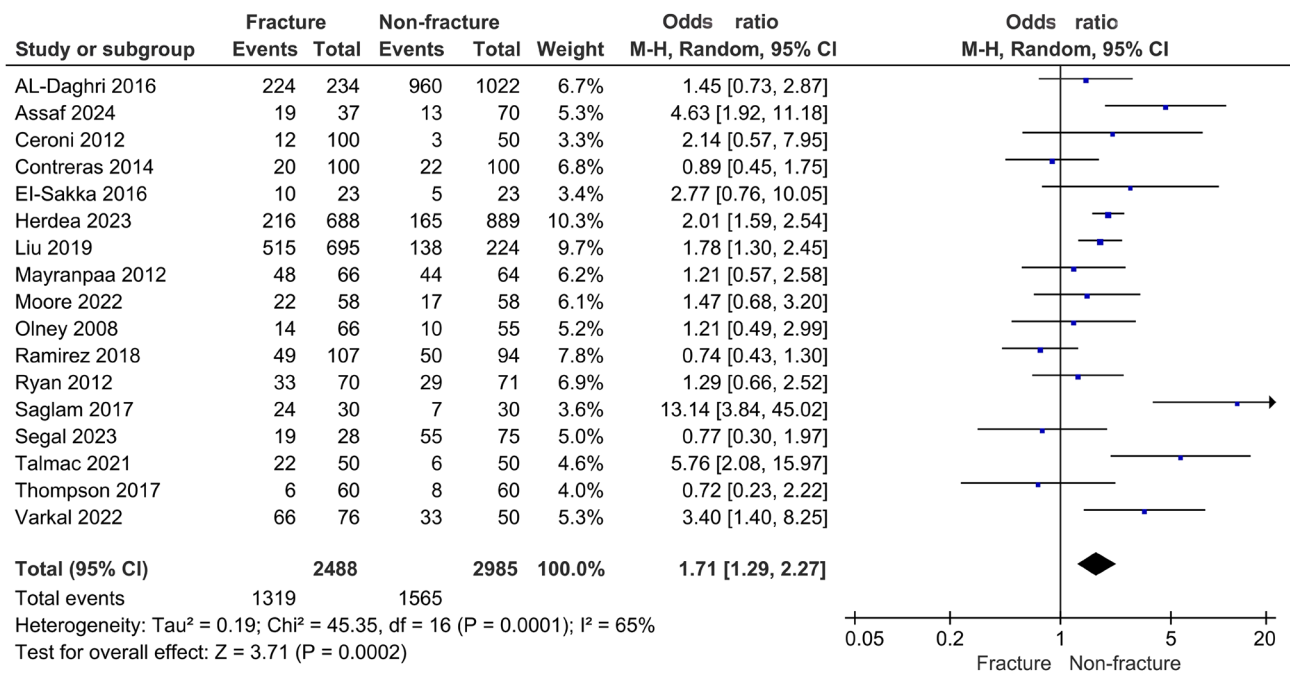


Figure 5. Pooled OR for fracture risk in vitamin D deficiency (vitamin D level ≤ 20 ng/ml). OR, odds ratio; M-H, Mantel-Haenszel; CI, confidence interval; τ^2 , Tau-squared; χ^2 , Chi-squared; df , degrees of freedom; I^2 , I-squared; Z , Z-statistic.

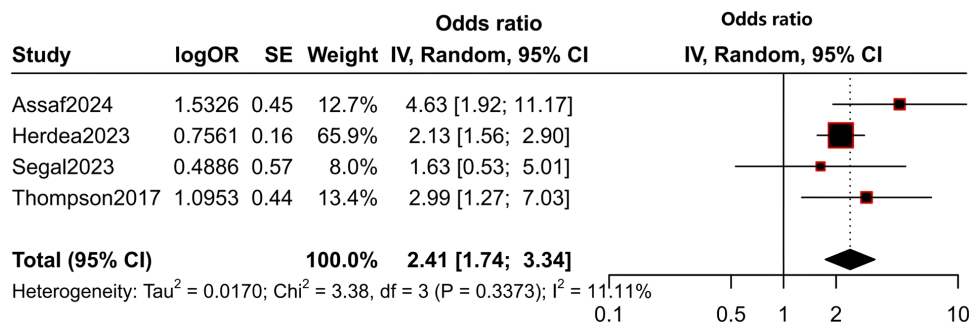


Figure 6. Pooled adjusted OR for fracture risk in vitamin D deficiency (vitamin D level ≤ 20 ng/ml). SE, standard error; IV, inverse variance; CI, confidence interval; τ^2 , Tau-squared; χ^2 , Chi-squared; df , degrees of freedom; I^2 , I-squared.

Adjusted ORs with their corresponding 95% CI served as the core effect measure to evaluate the strength of the independent association. The pooled analysis demonstrated that, even after adjusting for potential confounders, vitamin D deficiency remained significantly associated with an increased risk of fracture [OR=2.41 (95% CI: 1.74-3.34); $P < 0.0001$; $I^2 = 11.11\%$; $P = 0.3373$; Fig. 6]. This result suggested that, independent of confounding factors such as age and altitude, adolescents with vitamin D deficiency face a 2.41 times higher risk of fracture compared to those with sufficient levels, further confirming the independence and robustness of this association.

Univariate and multi-variate meta-regression analysis on the heterogeneity. Given the considerable number of original studies, the present study further conducted meta-regression to explore sources of heterogeneity. Metafor package in R software was mainly employed to perform the univariate regression analysis, the results demonstrated that age, altitude, latitude, and season could markedly explain the heterogeneity (Table II). Subsequent multivariate meta-regression indicated

that a model combining age and altitude sufficiently accounted for the heterogeneity, while latitude and season also contributed partially to explaining its sources (Table III). The two variables with the strongest explanatory power in the univariate analysis (age and altitude, both accounting for 100% of the heterogeneity) remained capable of fully explaining the heterogeneity within the multivariate core model, confirming their central moderating roles. Variables with weaker explanatory power in the univariate analysis (such as Study design and Trauma energy) were not included in the multivariate model. Since the core model already explained 100% of the heterogeneity, the addition of Latitude and Season did not alter the model's explanatory power or the AIC value, indicating that these variables are either collinear with the core variables (age/altitude) or that their moderating effects are encompassed by the core variables.

The multivariate regression model further delineated the specific moderating effects of age and altitude, the age groups of 8.3 and 9.5 years were identified as high-risk periods for fracture ($\beta = -6.1$; $P = 0.0048$; and $\beta = -5.81$, $P = 0.0191$, respectively),

Table II. Univariate meta-regression analysis on the heterogeneity.

Variable/subgroup	Coefficient (β)	Explained heterogeneity, %	Standard error	Q-Model test P-value
Age, years				
8.3	-6.10	100	2.16	0.0048
9.5	-5.81	100	2.49	0.0191
13.37	2.23	100	0.64	0.0005
15.9	3.66	100	1.51	0.0151
Altitude, m				
≥600	-2.28	100	0.61	0.0002
120	-3.18	100	1.07	0.0031
40	-2.96	100	1.39	0.0329
Latitude, °N				
>40	-5.18	94.18	1.94	0.0076
≤40	-1.41	94.18	1.34	0.2930
Season				
May-Oct	-15.25	64.84	2.85	0.0001
Dec-Mar	1.59	64.84	3.95	0.6880
Study design				
Case-control	0.32	26.42	0.49	0.5140
Cross-sectional	-0.18	26.42	0.53	0.7330
Trauma energy low	-0.45	31.93	0.38	0.2370
Newcastle-Ottawa Scale	-0.02	0.31	0.07	0.7891
Fracture site: Upper limb	-0.57	29.07	0.41	0.1640

Age and altitude subgroups were defined based on the values reported in the original studies, grouped by similar ranges: Age subgroups-8.3 years (≤ 9 years), 9.5 years (9-11 years), 13.37 years (12-14 years) and 15.9 years (≥ 15 years); altitude subgroups-40 m (≤ 76 m), 120 m (110-200 m) and ≥ 600 m (≥ 275 m).

Table III. Multi-variate meta-regression analysis on the heterogeneity.

Model	Heterogeneity explained, %	Number of studies	Residual heterogeneity, %	Q-Model test P-value	Akaike Information Criterion value
Core model (age + altitude)	100	27	0	<0.0001	105.6369
Core + latitude model	100	27	0	<0.0001	105.6369
Core + latitude + season model	100	27	0	<0.0001	105.6369

indicating that the association between vitamin D deficiency and fracture risk is significantly stronger in these age groups compared to others. For ≥ 600 m altitude regions, the regression coefficient was $\beta = -2.28$ ($P = 0.0002$), indicating a stronger correlational pattern linking vitamin D deficiency and fracture risk among adolescents living aforementioned 600 m, alongside observations of higher fracture prevalence in this subgroup.

Subgroup analyses. To explore potential sources of heterogeneity, the present study conducted prespecified subgroup analyses using random-effects models, stratified by latitude, season/month, trauma energy and study design (Figs. S1-S4). All forest plots present subgroup analyses performed using a random-effects model. Studies exhibiting substantial clinical heterogeneity within the same stratum were manually

excluded from the pooled estimates; these excluded studies are displayed with zero weight or labelled as 'not estimable' in the respective plots.

In the latitude-based analysis, studies at $\leq 40^\circ\text{N}$ showed no significant fracture benefit from vitamin D after excluding Al-Daghri 2016 (22) (unique Saudi ethnicity) and Matcovic 2023 (8) (distal forearm fractures only), with heterogeneity dropping from 74-44% ($P = 0.73$). Conversely, among studies at $> 40^\circ\text{N}$, excluding Herdea 2023 (12) (pandemic period), Mäyränpää 2012 (19) (60°N ; low winter sunlight) and Talmac 2021 (36) (February-May) reduced heterogeneity from 78-47%, and revealed a significant protective effect of vitamin D on fractures ($P < 0.00001$).

In the seasonal subgroup analysis (18 of 27 studies with clear seasonal data), studies conducted from May to October

showed a significant fracture benefit after excluding Delshad 2020 (Southern Hemisphere) and Younes 2019 (wide altitude range), with heterogeneity falling from 87-0% ($P<0.00001$). In the December-April subgroup, after removing Talmac 2021 (36) (late winter/early spring, lowest solar radiation) and extreme exposure conditions, heterogeneity decreased from 93-0%, with no significant fracture benefit ($P=0.41$). In the full-year subgroup, excluding Herdea 2023 (12) (pandemic) and Segal 2023 (9) (age up to 15.9 years) reduced heterogeneity from 61-46% and showed a significant effect ($P<0.00001$).

In the trauma energy stratification (24 studies with clear energy data), the low-energy subgroup showed reduced heterogeneity from 79-38% after excluding seasonally or temporally conflicting studies ($P=0.01$). The low-or-moderate subgroup exhibited a marked fracture benefit, with heterogeneity dropping from 72-0% ($P<0.00001$). The mixed-energy subgroup (three studies) showed 0% heterogeneity and no significant benefit ($P=0.57$), and the unintentional injury subgroup (two studies) also showed 0% heterogeneity and no significant benefit ($P=0.35$).

In the study design analysis, cross-sectional studies demonstrated significant fracture risk reduction after excluding the two largest studies, which were the primary sources of heterogeneity; heterogeneity decreased from 87-0% ($P=0.03$).

Discussion

The main finding of the present systematic review and meta-analysis was that children aged 8.3-9.5 or those residing at altitudes (≥ 600 m) were at higher fracture risk. Univariate regression results indicated that age and altitude are complete explanatory factors for heterogeneity, capable of eliminating all heterogeneity independently. This finding was strongly supported by recent large-scale epidemiological studies and aligns with the physiology of skeletal development and geographical influences on vitamin D synthesis. Adolescents aged 8.3-9.5 years are in a peak period of bone growth, where the skeletal demand for vitamin D increases sharply. Vitamin D deficiency during this stage directly impairs calcium absorption and bone mineralization, leading to reduced bone strength and consequently amplifying fracture risk. Therefore, the strong negative moderating effect observed for specific ages ~ 9 years likely captures the beginning of this critical high-risk window. Although the absolute between-group disparities in serum 25(OH)D levels identified in this meta-analysis appear modest, with a pooled weighted mean difference of -1.94 ng/ml (95% CI: -2.89 to -0.99), such minor differences carry clear clinical relevance for pediatric and adolescent populations experiencing rapid bone turnover. Small shifts in circulating 25(OH)D can shift the overall population distribution of vitamin D status, raising the share of youth meeting clinical thresholds for insufficiency or deficiency. Within the growing skeleton, sustained subtle deficits in vitamin D correlate with gradual reductions in calcium absorption efficiency and slowed bone mineral accrual over childhood and adolescence. For the high-risk subgroups highlighted in the present study, children aged 8.3-9.5 years and adolescents living at altitudes ≥ 600 m, these modest disparities collectively correspond to altered fracture risk patterns at a population level, reinforcing the clinical value of targeted vitamin D monitoring and preventive supplementation

for these vulnerable groups. A large Brazilian study involving $>413,000$ children and adolescents demonstrated a clear inverse relationship between age and vitamin D status. The prevalence of deficiency [25(OH)D <20 ng/ml] was lowest in children <2 years (4.5%) and increased progressively with age, peaking at 18.4% in adolescents (11-18 years). Notably, among female adolescents, the deficiency rate reached 20.1%, and in a high-risk subset (southern region, winter months), it soared to 36%, with 5% experiencing severe deficiency (<12 ng/ml) (39). This pattern is corroborated by the study by Yang *et al* (40), which found that children aged 6-8 years had the highest vitamin D levels and sufficiency rates, while levels markedly declined in older age groups.

Girls may experience an earlier onset of the pubertal growth spurt, a period of rapid bone elongation where mineralization may lag behind, temporarily increasing bone fragility. Concurrently, lifestyle factors such as greater use of sunscreen, more indoor-oriented activities, and potentially lower dietary calcium intake may exacerbate vitamin D deficiency. However, the association between vitamin D status and fracture risk among female adolescents has shown considerable heterogeneity across studies. The study by Delshad *et al* (35) provided more detailed insights, indicating that while high sugar-sweetened beverage intake and family history of osteoporosis were the primary predictors of fractures in girls, the association between vitamin D levels and fracture history did not reach statistical significance in this population. By contrast, the aforementioned two studies reported a higher risk profile among females (39,40). This may be explained by the fact that the direct link with fracture risk is modulated by other factors, such as calcium intake and consumption of sugar-sweetened beverages. In the present meta-analysis, due to the limited availability of stratified data reporting vitamin D levels and fracture risk by sex, it was not possible to conduct a corresponding pooled analysis to further investigate whether adolescent females indeed face a higher fracture risk compared to males.

The univariate meta-regression analysis identifies altitude (≥ 600 m) as a significant and independent explanatory factor for heterogeneity, accounting for 100% of the variance with a strong negative coefficient ($\beta=-2.28$; $P=0.0002$). The persistent vitamin D deficiency observed at high altitudes, despite increased ultraviolet B radiation, can be attributed to several interconnected factors. Studies in high-altitude populations, such as those in Saudi Arabia and the Andes, demonstrate that local environmental and lifestyle factors offset the potential benefits of elevated ultraviolet radiation, alongside a high prevalence of vitamin D deficiency in these groups (41,42). When combined with age in the multivariate model, altitude remains a core determinant, explaining all residual heterogeneity. This suggests that high-altitude residence exhibits a profound, consistent correlational link with altered vitamin D status, alongside parallel correlations with modified bone metabolism and elevated fracture risk among adolescents living in such regions. Thus, altitude should be considered a critical, independent variable in assessing vitamin D status and its health consequences in youth. The present subgroup analyses revealed that the protective association of vitamin D with fracture risk was not consistent across all strata, but was conditional on several factors, including geographic latitude,

season and trauma energy. Significant effects were detected in high-latitude regions, during the May-October period, and among low to moderate-energy fractures. The observation that a significant association also emerged during sunnier months is noteworthy, as it implies that seasonal sunlight exposure alone may not fully compensate for suboptimal vitamin D status in fracture-prone populations. Michaëlsson *et al* (43) also supports this view, finding that individuals with insufficient accumulation of vitamin D reserves during the summer may remain deficient throughout the year, thereby increasing fracture risk. These findings support a targeted rather than universal approach to vitamin D supplementation, with consideration of latitude, season, and injury mechanism.

Notwithstanding the strong explanatory power of age and altitude in the regression models of the present study, it is acknowledged that residual unmeasured heterogeneity and multiple unadjusted confounding factors may still constrain the generalizability of the findings. First, heterogeneity originating from disparate 25(OH)D testing assays [immunoassay vs. liquid chromatography-tandem mass spectrometry (LC-MS/MS)], inconsistent trauma energy classification standards and absent stratification by fracture site could not be fully captured by the regression covariates. Second, key confounders including long-term calcium intake, daily outdoor activity volume and sugar-sweetened beverage consumption were incompletely reported and rarely uniformly adjusted across primary studies; these unbalanced covariates may interfere with the true magnitude of the vitamin D-fracture association. Additionally, insufficient sex-stratified data restricted the ability to parse sex-specific effect differences, which represents another source of residual variation that could not be eliminated in the current pooled analysis.

In summary, the present meta-analysis advanced prior syntheses by systematically identifying both age and altitude residence as core, independent moderators explaining heterogeneity in the vitamin D-fracture association among adolescents. While previous reviews have noted age or latitude as factors, the present study uniquely integrates altitude, a significant yet often neglected environmental determinant, and pinpoints a critical high-risk window (ages 8.3-9.5 years). This dual identification enables more precise risk stratification, moving beyond broad geographic generalizations. The findings underscored the necessity of context-specific public health strategies, advocating for targeted vitamin D screening and supplementation prioritization for young children and residents of high-altitude regions to mitigate fracture risk.

Several limitations of the present meta-analysis warrant consideration. The evidence primarily derived from observational, predominantly case-control studies, which are susceptible to selection bias, residual confounding and cannot establish causality. The overall quality of included studies, as assessed by the NOS, was moderate, indicating potential methodological weaknesses. Notably, substantial between-study heterogeneity existed in multiple aspects. First, 25(OH)D was measured using different laboratory assays across studies, including immunoassay and LC-MS/MS, which may introduce measurement discrepancies. Second, studies varied in the classification of trauma energy, as well as the adjustment for key confounders such as precise sunlight exposure, dietary intake and physical activity. Beyond these factors, BMI,

calcium intake, outdoor activity and skin pigmentation were also insufficiently adjusted in most primary studies. Third, the majority of original studies failed to perform stratified analyses according to fracture site and trauma energy. All the aforementioned issues may have influenced the accuracy of pooled estimates. Future prospective cohort studies or well-designed trials are required to confirm the associations observed in this analysis.

In conclusion, the present meta-analysis confirmed and extended prior evidence by demonstrating a significant positive association between vitamin D deficiency and fracture risk in children and adolescents. The identification of specific age windows (8.3-9.5 years) and altitude residence (≥ 600 m) as key effect modifiers provides a novel framework for clinical and public health risk stratification. Despite limitations inherent to observational data, such as potential residual confounding and the inability to establish causality, these findings strongly advocated for targeted public health strategies. These include prioritized screening for vitamin D status and consideration of supplementation programs for children in early adolescence and those living in high-altitude regions. Future research should focus on prospective cohort studies to clarify causal relationships and on intervention trials to assess the efficacy of targeted vitamin D supplementation in reducing fracture incidence in these identified high-risk subgroups.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZCD was responsible for the conception and design of the study. BT and JHM independently reviewed the full-text versions of all the articles retrieved from the literature and were responsible for the data analysis and drafting of the manuscript. ZJZ was responsible for constructing the comprehensive search strategy, performing the Newcastle-Ottawa Scale quality assessment and providing statistical support for the meta-regression analysis. JHM and ZJZ were involved in revising the manuscript critically for important intellectual content. JHM and ZJZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and informed consent

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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