J Musculoskelet Neuronal Interact 2026; 26(3):482-495

Journal of Musculoskeletal and Neuronal Interactions JMNI

Review Article

Vitamin D Status and Supplementation in Lumbar Spinal Fusion: A Systematic Review and Meta-Analysis of Radiographic and Clinical Outcomes

Stylianos Kapetanakis[1,2], Michael Patrianakos[1], Mikail Chatzivasiliadis[1], Panagiotis Konstantinou[2], Lazaros Kostretzis[2], Konstantinos Ditsios[2]

[1]Spine Department and Deformities, Interbalkan European Medical Center, Thessaloniki, Greece;
[2]2nd Orthopaedic Department, Aristotle University of Thessaloniki, G. Genimmatas Hospital, Thessaloniki, Greece

Abstract

This systematic review and meta-analysis evaluated the association between vitamin D status or vitamin D–related interventions and outcomes following lumbar spinal fusion. PubMed/MEDLINE, Scopus, and Web of Science were searched from inception to January 2026 in accordance with PRISMA guidelines. Studies including adult patients undergoing lumbar fusion with assessment of vitamin D status or supplementation and a comparator group were eligible. Random-effects models were used as the primary analyses. Nine studies were included. Five studies (n = 351) assessed radiographic fusion success, demonstrating a significantly higher likelihood of fusion in patients with better vitamin D status or supplementation (RR 1.25, 95% CI 1.13–1.38; I^2 = 0%). Six studies (n = 3,081) evaluated fusion failure, showing a significantly lower risk in vitamin D–exposed groups (RR 0.45, 95% CI 0.27–0.76; I^2 = 34.8%). Sensitivity analyses indicated that heterogeneity was partly related to differences in outcome definitions and study design. Patient-reported outcomes showed inconsistent results, with no significant effects in random-effects analyses and changes below minimal clinically important differences. Vitamin D exposure was associated with improved radiographic outcomes; however, findings should be interpreted cautiously due to clinical and methodological heterogeneity. Further prospective studies are required.

Keywords: Bone Healing, Lumbar Spinal Fusion, Pseudarthrosis, Systematic Review, Vitamin D

Introduction

Lumbar spinal fusion is one of the most commonly performed procedures for degenerative spine disorders, and its utilization continues to increase[1]. In the United States, elective lumbar fusion volume rose by 62% between 2004 and 2015, while more recent national data demonstrate that the proportion of patients treated with fusion for degenerative spondylolisthesis nearly doubled from 30.9% in 2010 to 54.8% in 2021[2,3]. Despite advances in surgical technique and instrumentation, the primary goal of achieving solid arthrodesis remains biologically challenging. Pseudarthrosis at the lumbosacral junction has been reported in approximately 10% of single-level L5–S1 fusions and up to 20% of two-level constructs[4].

Given the growing surgical volume and the clinical consequences of nonunion, increasing attention has been directed toward optimization of patient-related biological factors that influence bone healing. Among these, vitamin D plays a central role in calcium homeostasis, bone mineralization, and osteoblastic activity[5,6]. Vitamin D deficiency is highly prevalent among patients undergoing elective spine surgery, with approximately 30% demonstrating deficiency and an additional 38.9% showing insufficiency[7]. These findings suggest that vitamin D status may represent a modifiable perioperative risk factor.

Despite the biological rationale and increasing clinical

The authors have no conflict of interest.

Corresponding author: Mikail Chatzivasiliadis, Spine Department and Deformities, Interbalkan European Medical Center, Thessaloniki, Greece
E-mail: mikail@chatzi.com
ORCID iD: 0009-0003-8677-4153

Edited by: G. Lyritis
Accepted 10 May 2026

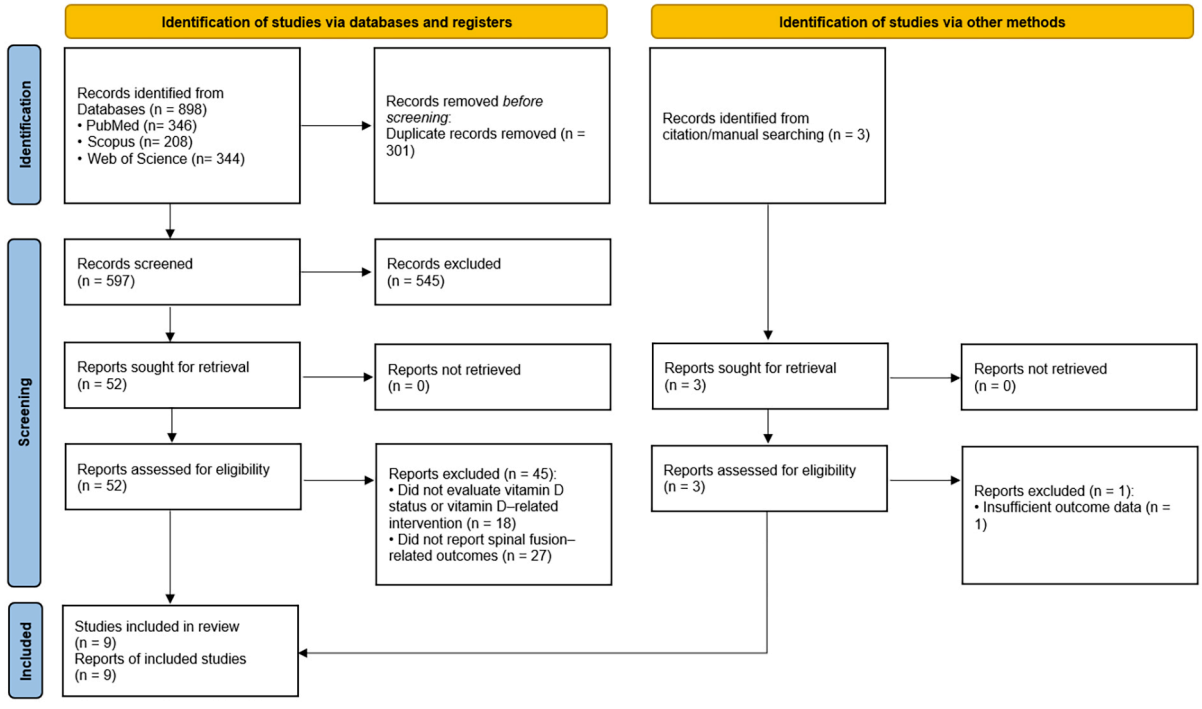

Figure 1. PRISMA flow diagram of the study selection process.

interest in perioperative optimization, the impact of vitamin D status on spinal fusion outcomes remains unclear. Individual clinical studies have reported conflicting results regarding the association between vitamin D and fusion rates, risk of pseudarthrosis, and patient-reported outcomes. In addition, interpretation of these findings is limited by small sample sizes, heterogeneous study designs, and variability in the definitions of vitamin D exposure and outcome assessment. Accordingly, an updated synthesis of the available evidence is warranted.

The aim of this systematic review and meta-analysis was to evaluate the association of vitamin D status and vitamin D-related interventions with outcomes following lumbar spinal fusion, including radiographic fusion success, fusion failure, and patient-reported measures of pain and functional disability.

Materials and Methods

This systematic review and meta-analysis was conducted to evaluate the association between vitamin D status or vitamin D–related interventions and outcomes following spinal fusion surgery. The study was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8]. All methodological steps, including eligibility criteria, literature search, study selection, data extraction, and statistical analyses, were predefined to ensure methodological consistency and reproducibility.

Search Strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, and Web of Science from database inception to January 2026. The search strategy was designed to identify clinical studies evaluating the relationship between vitamin D status or vitamin D supplementation and outcomes after spinal fusion surgery. These databases were selected to provide broad coverage of biomedical and clinical literature; Embase and CENTRAL were not searched.

Search terms included free-text keywords and database-specific search terms related to vitamin D (e.g., “vitamin D,” “25-hydroxyvitamin D,” “vitamin D deficiency,” “cholecalciferol,” “calcitriol,” “vitamin D supplementation”) and spinal fusion procedures (e.g., “spinal fusion,” “lumbar fusion,” “arthrodesis,” “instrumented fusion”). No language restrictions were applied during the search; however, only studies with sufficient data available in English were included for analysis. The review was not prospectively registered.

The reference lists of all included studies and relevant

review articles were manually screened to identify additional eligible publications. The complete electronic search strategy is provided in Supplementary File 1.

Study Selection

All records identified through the database searches were imported into a reference management software and duplicates were removed. Two reviewers independently screened titles and abstracts to identify potentially eligible studies. Full-text articles were subsequently reviewed for eligibility according to the predefined inclusion and exclusion criteria. Disagreements at any stage of the screening process were resolved through discussion and consensus. The study selection process is summarized using a PRISMA flow diagram (Figure 1).

Eligibility Criteria

Studies were eligible for inclusion if they involved adult patients undergoing primarily lumbar spinal fusion surgery. Studies including mixed spinal cohorts (e.g., cervical, thoracic, and lumbar) were considered eligible only if lumbar procedures constituted the majority of the study population or if lumbar-specific outcomes could not be separately extracted; such studies were retained for completeness and evaluated through sensitivity analyses.

Eligible studies evaluated vitamin D status, such as deficiency versus sufficiency, or examined the administration of vitamin D–related interventions. To account for clinical heterogeneity, exposures were conceptually categorized a priori into: (1) observational studies assessing baseline vitamin D deficiency or sufficiency, (2) interventional studies evaluating perioperative vitamin D supplementation (e.g., cholecalciferol), and (3) studies involving active vitamin D analogues or combination regimens (e.g., vitamin D with calcium or vitamin K2), which were analyzed separately or considered exploratory where appropriate.

Included studies were required to incorporate a comparator group consisting of patients without vitamin D deficiency or without vitamin D supplementation. Eligible study designs included observational cohort studies, case–control studies, randomized controlled trials, and population-based database studies.

Studies were excluded if they were non-clinical in nature, including animal, cadaveric, or in vitro investigations, as well as case reports, small case series, review articles, editorials, or conference abstracts without sufficient extractable data. Studies without a comparator group, without extractable outcome data, or involving overlapping patient populations were also excluded.

Data Extraction

Data extraction was performed independently by two reviewers using a predefined data extraction framework. Extracted data included study characteristics (study design, country, sample size), patient demographics, spinal fusion technique and level, vitamin D definition or supplementation regimen, comparator characteristics, outcome definitions, and follow-up duration.

For studies included in quantitative synthesis, outcome data were extracted separately for each comparison group. When studies reported outcomes at multiple follow-up timepoints, data were extracted for each eligible timepoint. In cases of overlapping cohorts, the most comprehensive or recent dataset was prioritized. Any discrepancies in data extraction were resolved by consensus.

Outcomes

The primary outcome of interest was radiographic fusion success, as defined by the original studies using explicit radiographic criteria, including plain radiography and/or computed tomography (CT), as reported by each study.

The secondary outcome was fusion failure, defined according to study-specific criteria. For radiographic studies, fusion failure included radiographic nonunion, pseudarthrosis, or incomplete fusion as defined by the original authors. For the administrative database study by Garcia et al., the pooled endpoint was EHR-coded pseudoarthrosis at 1-year follow-up. Given variability in outcome ascertainment methods, particularly imaging-based assessment versus administrative coding, these endpoints were analyzed collectively, with predefined sensitivity analyses performed to account for differences in definition and data source.

Tertiary outcomes included patient-reported outcome measures, specifically pain assessed using the Visual Analog Scale (VAS) and functional disability assessed using the Oswestry Disability Index (ODI), with outcomes extracted at all reported follow-up timepoints and analyzed separately by timepoint.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers using validated tools according to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool[9]. Assessments were performed at the domain level, including bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result.

Non-randomized and observational studies were assessed using the Newcastle–Ottawa Scale (NOS)[10]. For studies assessed with the NOS, overall study quality was categorized based on total score, with higher scores indicating lower risk of bias. In addition to overall scores, individual NOS domains (selection, comparability, and outcome) were recorded to allow a more detailed evaluation of methodological quality.

Table 1. Baseline characteristics of included studies. Studies evaluated vitamin D status or supplementation in patients undergoing lumbar spinal fusion. Vitamin D exposure was defined by serum levels or postoperative supplementation. Fusion techniques, levels fused, and imaging modalities are reported as described in the original studies. Database studies lacked radiographic fusion assessment. Abbreviations: TLIF, transforaminal lumbar interbody fusion; PLIF, posterior lumbar interbody fusion; PLF, posterolateral fusion; RCT, randomized controlled trial; CT, computed tomography; MRI, magnetic resonance imaging; DDD, degenerative disc disease; ELIF, endoscopic lumbar interbody fusion; DS, degenerative spondylolisthesis.

Study	Country	Design	N	Population	Fusion Type	Levels Fused	Vitamin D Exposure	Comparison	Imaging for Fusion	Vit D Measurement
Ravindra (2015)[13]	USA	Prospective cohort	133	Mixed spine (C 49%, L 47%, T 4%)	Mixed approaches, instrumented	Mean 2 (1–16)	Deficient <20 ng/mL	Deficient vs non-deficient	X-ray + CT	Serum 25-OH-D
Xu 2014[14]	China	Retrospective cohort	44	Osteoporosis + lumbar DDD	TLIF	N/A	$1,25(OH)_2D_3$ supplementation	Vit D vs none	X-ray + CT (Brantigan)	N/A
Xu 2020[15]	China	Retrospective cohort	360	Lumbar DDD	PLIF / PLF	Mean 1.5 (1–2)	Deficient <20 ng/mL	Deficient vs non-deficient	X-ray (no formal fusion imaging)	Serum 25-OH-D
Hu 2022[16]	Taiwan	RCT	34	Lumbar stenosis / DS	TLIF	Mean 2.5 (2–3)	Vit D + calcium	Ca vs Ca+Vit D	X-ray + CT	Serum 25-OH-D
Haddadi 2022[17]	Iran	RCT	81	Women, lumbar DDD	Posterior lumbar fusion	Predominantly 4	Vit D vs alendronate vs control	Multi-arm	MRI used for Modic changes	Serum 25-OH-D
Krasowska 2019[18]	Poland	RCT	39	Lumbar DDD	PLIF	N/A	Vit D supplementation	Vit D vs placebo	N/A	Serum 25-OH-D
Garcia 2025[19]	USA	Propensity-matched cohort	2,730	Single-level lumbar DDD	Posterior lumbar fusion	Single	Deficient <20 ng/mL	Deficient vs non-deficient	N/A (EHR)	Serum 25-OH-D
Wang 2025[20]	China	Prospective nonrandomized controlled trial	71	Single-level lumbar DDD	ELIF	Single	Vit D_3 + Vit K_2	Vit D_3 + K_2 vs Vit D_3 alone	X-ray + CT	Serum 25-OH-D
Zhang 2022[21]	China	Prospective nonrandomized controlled trial	78	Lumbar DDD	TLIF / PLIF	Mean 1.58 (1–2)	VK2 + VD3 (+ calcium)	VD3 (+ calcium)	X-ray + CT + MRI	N/A

Any discrepancies between reviewers were resolved through discussion and consensus.

Statistical Analysis

For binary outcomes (fusion success and fusion failure), risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Effect direction was standardized such that RRs <1 indicated a lower risk of adverse outcomes in the better vitamin D status or vitamin D-treated group, whereas RRs >1 indicated a higher likelihood of favorable outcomes (fusion success). For continuous outcomes (VAS and ODI), mean differences (MDs) with 95% CIs were calculated as intervention minus control, with negative values indicating clinical improvement.

Random-effects meta-analyses were performed and considered the primary analyses to account for anticipated clinical and methodological heterogeneity. Fixed-effect models were calculated as secondary analyses and interpreted cautiously.

Statistical heterogeneity was assessed using Cochran's Q test, the I^2 statistic, and τ^2, with I^2 >50% indicating substantial heterogeneity. Predefined subgroup analyses were performed based on follow-up duration and exposure type (deficiency/sufficiency, supplementation, and combination or analogue regimens).

Table 2. Baseline patient characteristics of included studies. Values are reported at the study level as mean ± SD or percentage where available. Follow-up duration is expressed in months. C = control/comparator group; E = experimental/intervention group. Baseline characteristics are reported separately when study-level aggregate data were unavailable.

Study	N	Age, mean SD (range)	Female (%)	BMI, mean ± SD	Levels fused, mean ± SD	Follow-up, mean (months)
Ravindra 2015[13]	133	57.6 ± 12.7	43.6	29.5 ± 6.0	2.14 ± 1.9	16.0
Xu 2014[14]	44	N/A	N/A	N/A	N/A	14.5
Xu 2020[15]	360	C: 63.22 ± 11.23 (24–90)	C: 45.5	C: 23.26 ± 2.77	1.54 ± 0.50	3
		E: 61.45 ± 12.22 (24–90)	E: 71.0	E: 24.02 ± 2.67		
Hu 2022[16]	34	C: 56.1 ± 15.0	C: 53.8	C: 28.0 ± 6.9	C: 2.8 ± 1.0	12
		E: 64.0 ± 11.1	E: 81.0	E: 23.9 ± 3.5	E: 2.3 ± 0.5	
Haddadi 2022[17]	81	51.3 ± 8.6 (20–65)	100	29.7 ± 3.5	3.7 ± N/A	6
Krasowska 2019[18]	39	C: 47.3 ± 2.15	C: 57.1	28.14 ± 0.51	N/A	3.5
		E: 41.9 ± 2.97	E: 50.0	E: 29.15 ± 1.15		
Garcia 2025[19]	2,730	C: 57.1 ± 14.3	C: 55	N/A	1.0	12
		E: 56.8 ± 13.5	E: 54.7		1.0	
Zhang 2022[21]	78	C: 56.0 ± 8.3	C: 53.8	C: 24.5 ± 1.8	C: 1.51	6
		E: 53.1 ± 12.5	E: 69.2	E: 25.9 ± 2.1	E: 1.64	
Wang 2025[20]	71	C: 54.7 ± 8.2 (50–72)	C: 69.4	C: 25.37 ± 4.19	C: 1.0	6
		E: 55.2 ± 9.4 (50–74)	E: 65.7	E: 26.04 ± 4.52	E: 1.0	

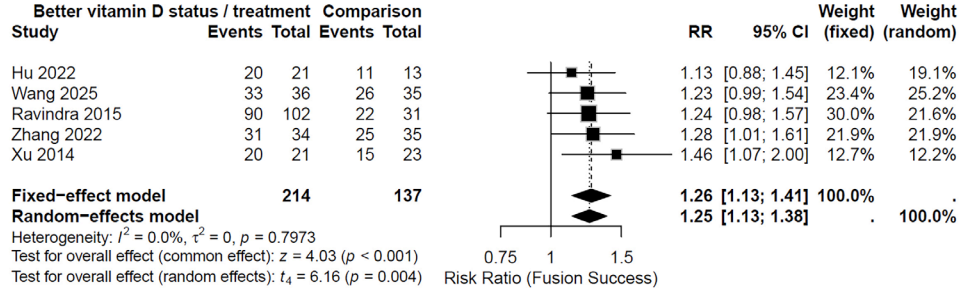

Figure 2. Forest plot of radiographic fusion success. Random-effects meta-analysis demonstrating a higher likelihood of fusion in the better vitamin D status or vitamin D–treated group compared with controls.

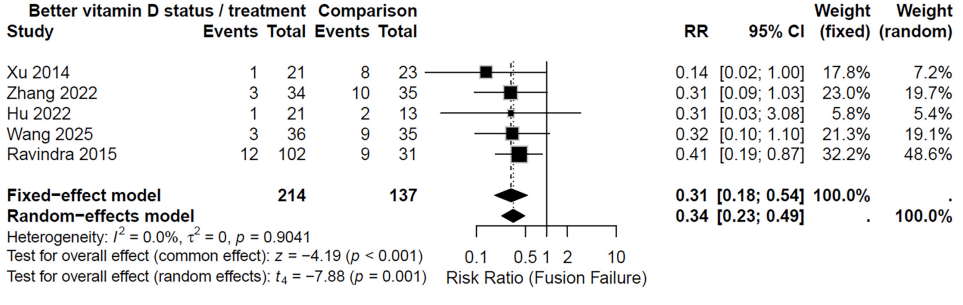

Figure 3. Forest plot of fusion failure. Random-effects meta-analysis demonstrating a lower risk of fusion failure in the better vitamin D status or vitamin D–treated group compared with controls.

Table 3. Outcome Definitions and Contributions to Meta-analysis. Summarizes the specific outcomes contributed by each included study, along with study-level definitions of radiographic fusion success and fusion failure, imaging modalities used for outcome assessment, and the follow-up timepoints included in the quantitative synthesis. For Garcia et al., the endpoint included in the fusion-failure meta-analysis was EHR-coded pseudoarthrosis at 1-year follow-up.

Study	Outcome(s) included	Fusion definition	Failure definition	Imaging modality	Timepoint(s) used
Ravindra 2015[13]	Radiographic fusion success; fusion failure (nonunion/ pseudarthrosis); time to fusion	Presence of bone trabeculation with no motion between graft and instrumentation and no hardware loosening or breakage	Nonunion/ pseudarthrosis (absence of radiographic fusion at 12 months)	Primarily dynamic radiographs (flexion/extension); CT used selectively if radiographs were inconclusive	6 weeks, 3 months, 6 months, and 12 months
Xu 2014[14]	Radiographic fusion success; ODI	Brantigan assessment system based on radiographic criteria	Not explicitly defined; inferred as absence of radiographic fusion (nonunion)	X-ray and thin-section CT reconstruction	6 months and final follow-up
Xu 2020[15]	VAS, ODI, JOA (patient-reported outcomes); postoperative complications	N/A	N/A	N/A	3 months postoperative (primary); final follow-up
Hu 2022[16]	Radiographic fusion rate, time to fusion, VAS, ODI	Bridging callus formation without radiolucent line, <5° motion between fused vertebrae, and no implant loosening/failure	Implicit (absence of fusion criteria / pseudarthrosis not separately defined)	X-ray + CT	Fusion: 12 months Time to fusion: serial (1, 2, 3, 6, 12 months) VAS/ODI: 3 and 6 months
Haddadi 2022[17]	VAS, ODI, Modic changes	N/A	N/A	MRI (Modic changes)	6 months
Krasowska 2019[18]	VAS pain only; inflammatory markers were reported but not included in the meta-analysis	N/A	N/A	N/A	VAS extracted after rehabilitation/ final reported postoperative assessment
Garcia 2025[19]	Fusion failure: EHR-coded pseudoarthrosis	N/A	EHR-coded pseudoarthrosis	Not applicable (administrative EHR database)	1 year
Wang 2025[20]	Fusion rate; ODI; JOA-BPEQ; BMD; bone markers (P1NP, β-CTX)	Bridwell-based CT grading + <5° motion on dynamic X-ray = complete fusion	Incomplete bridging (CT grade II/III or motion ≥5°)	CT + dynamic X-ray	3 months, 6 months
Zhang 2022[21]	Fusion rate; VAS; JOA-BPEQ; BMD; bone markers (P1NP, β-CTX)	CT-based grading (Grade I = complete fusion; total score = 2)	Grade II–III (partial/no fusion; score ≥3)	CT	3 months, 6 months

Sensitivity analyses included exclusion of large database studies and studies with differing outcome ascertainment or non-lumbar populations. The minimal clinically important difference (MCID) was interpreted using commonly reported thresholds in lumbar spine surgery populations, with approximate reference values of 1.5–2.0 points for VAS and 10–15 points for ODI[11,12].

For multi-arm studies, relevant groups were combined or selected to avoid double-counting. Outcomes reported at multiple timepoints were analyzed separately, with each participant contributing only once per analysis. Continuous outcomes were extracted as final values, and mixing of change scores and final values was avoided.

Studies not suitable for quantitative synthesis were summarized narratively. All analyses were performed using R (version 4.5.1) with the *meta* package. Statistical

significance was set at $p < 0.05$. Publication bias was not assessed due to the small number of included studies.

Results

The systematic literature search identified 597 records after removal of duplicates. Following title and abstract screening and full-text assessment, 9 studies met the predefined eligibility criteria and were included in the qualitative synthesis. All studies contributed data to at least one quantitative meta-analysis, including radiographic fusion outcomes and/or patient-reported outcome measures. The baseline characteristics of the included studies and patient populations are summarized in Table 1 and Table 2[13-21]. Detailed definitions of radiographic fusion outcomes, imaging modalities, and follow-up timepoints across studies are summarized in Table 3.

Radiographic Fusion Success

Five studies involving 351 patients (214 in better vitamin D status or vitamin D-treated groups and 137 controls) were included in the meta-analysis of radiographic fusion success.

In the random-effects analysis, better vitamin D status or vitamin D-based treatment was associated with a significantly greater likelihood of radiographic fusion success (RR 1.25, 95% CI 1.13–1.38; Figure 2). No heterogeneity was observed among included studies ($I^2 = 0\%$). The corresponding fixed-effect model yielded similar findings (RR 1.26, 95% CI 1.13–1.41; $p < 0.001$). Individual study estimates consistently favored better vitamin D status or vitamin D-based treatment, although the magnitude of effect varied across studies.

Because one included study by Ravindra et al. involved a mixed-spine cohort that included cervical and thoracic procedures, and lumbar-specific outcomes could not be separately extracted, this study was retained under the predefined mixed-cohort eligibility criterion. A lumbar-only sensitivity analysis excluding this study was performed. The association remained statistically significant after exclusion of the mixed-spine cohort (RR 1.25, 95% CI 1.08–1.45; $p = 0.018$), with no heterogeneity ($I^2 = 0\%$), suggesting that inclusion of non-lumbar cases did not materially influence the pooled estimate.

Exploratory analyses were also performed according to exposure type. Studies evaluating baseline vitamin D deficiency or sufficiency alone demonstrated a trend toward improved fusion success that did not reach statistical significance (RR 1.24, 95% CI 0.98–1.57; $p = 0.071$). In contrast, studies evaluating perioperative supplementation strategies demonstrated a significant association with improved radiographic fusion success (RR 1.25, 95% CI 1.08–1.45; $p = 0.018$), with no observed heterogeneity ($I^2 = 0\%$).

Additional sensitivity analyses suggested that the overall signal was not materially altered by exclusion of the active vitamin D analogue study, as the pooled estimate remained significant after excluding Xu et al (RR 1.22, 95% CI 1.04–1.42; $p = 0.032$). However, exclusion of combination-regimen studies, particularly those involving vitamin D3 plus vitamin K2, attenuated the observed association and rendered the pooled estimate non-significant (RR 1.24, 95% CI 0.92–1.68; $p = 0.087$). This suggests that combination-regimen studies may have contributed substantially to the observed fusion-related benefit.

Fusion Failure

Six studies comprising 3,081 patients were included in the meta-analysis of fusion failure.

In the random-effects analysis, better vitamin D status or vitamin D-based treatment was associated with a significantly lower risk of fusion failure (RR 0.45, 95% CI 0.27–0.76; $p = 0.011$). Low-to-moderate heterogeneity was observed among included studies ($I^2 = 34.8\%$). The corresponding fixed-effect model also demonstrated a significant reduction in fusion failure risk (RR 0.65, 95% CI 0.55–0.76; $p < 0.001$).

Because one large study by Garcia et al. contributed EHR-coded pseudoarthrosis at 1-year follow-up rather than direct radiographic assessment of fusion status, a sensitivity analysis excluding this study was performed. After exclusion, five studies with a total of 351 patients remained. In this restricted analysis, the association became stronger, with a random-effects RR of 0.34 (95% CI 0.23–0.49; Figure 3), and no residual heterogeneity was observed ($I^2 = 0\%$). This suggests that inclusion of the Garcia study introduced heterogeneity because of differences in endpoint definition and administrative outcome ascertainment.

Because Ravindra et al. included a mixed-spine cohort and lumbar-specific fusion-failure outcomes could not be separately extracted, its influence was also assessed through a lumbar-only sensitivity analysis. Excluding this study demonstrated similar findings, with a persistent reduction in fusion failure risk (RR 0.44, 95% CI 0.21–0.90; $p = 0.033$; $I^2 = 34.4\%$), indicating that inclusion of non-lumbar cases did not materially alter the overall estimate.

Exploratory analyses according to exposure type showed that studies evaluating baseline vitamin D deficiency or sufficiency alone did not demonstrate a significant association with fusion failure (RR 0.61, 95% CI 0.03–13.05; $p = 0.288$). In contrast, supplementation-based studies demonstrated a significant reduction in fusion failure risk (RR 0.28, 95% CI 0.16–0.48; $p = 0.0047$), with no heterogeneity ($I^2 = 0\%$).

Exclusion of the active vitamin D analogue study did not materially change the findings, as the association remained significant after excluding Xu et al (RR 0.32, 95% CI 0.29–0.34; $p < 0.001$). However, exclusion of combination-regimen studies, particularly those involving

Table 4. Risk of bias assessment for randomized controlled trials (RoB 2). Each domain was rated as "low risk," "some concerns," or "high risk," and an overall risk of bias judgment was assigned for each study according to RoB 2 guidance. Domain-level assessments are presented to provide transparency regarding potential sources of bias within individual trials.

Study	Randomization	Deviations	Missing data	Outcome measurement	Reporting	Overall
Hu 2022[16]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Haddadi 2022[17]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Krasowska 2019[18]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

Table 5. Newcastle–Ottawa Scale (NOS) assessment for observational studies. Higher scores indicate lower risk of bias. Study quality was categorized as low (≤4), moderate (5–6), moderate-high (7), or high (≥8). Individual domain scores are presented to provide detailed insight into study-level methodological strengths and limitations.

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total (9)	Quality
Ravindra 2015[13]	4	2	2	8	High
Xu 2014[14]	3	1	2	6	Moderate
Xu 2020[15]	4	1	1	6	Moderate
Garcia 2025[19]	3	2	2	7	Moderate-High
Wang 2025[20]	4	1	2	7	Moderate-High
Zhang 2022[21]	4	1	2	7	Moderate-High

vitamin D3 plus vitamin K2, attenuated the association and rendered it non-significant (RR 0.50, 95% CI 0.21–1.19; p = 0.084). These findings suggest that the apparent benefit on fusion failure may be driven predominantly by perioperative supplementation strategies and may also be influenced by combination-regimen studies rather than vitamin D alone.

Visual Analog Scale (VAS)

Nine comparisons from five studies were included in the quantitative synthesis of patient-reported pain outcomes. At early follow-up (≤3.5 months), the random-effects model did not demonstrate a significant reduction in pain scores associated with better vitamin D status or vitamin D-based treatment (MD -0.48, 95% CI -4.98 to 4.01; p = 0.403), although the corresponding fixed-effect model showed a modest but statistically significant reduction in VAS scores (MD -0.27, 95% CI -0.43 to -0.10; p = 0.0017). Moderate heterogeneity was observed (I^2 = 61.0%).

At 6 months, the random-effects model again showed no significant difference in VAS scores between groups (MD -0.51, 95% CI -15.76 to 14.73; p = 0.742), whereas the fixed-effect model demonstrated a significant reduction favoring better vitamin D status or vitamin D-based treatment (MD -0.75, 95% CI -1.29 to -0.22; p = 0.006). Heterogeneity remained very high at this timepoint (I^2 = 94.5%), limiting confidence in the pooled estimate.

Exploratory exposure-type analyses suggested that supplementation-based studies demonstrated a significant short-term reduction in pain at 3 months (MD -1.00, 95% CI -1.91 to -0.09; p = 0.032), whereas deficiency-only studies demonstrated a smaller but statistically significant reduction (MD -0.24, 95% CI -0.41 to -0.07; p = 0.005). However, these findings were based on a small number of studies and should be interpreted cautiously.

Oswestry Disability Index (ODI)

At 3 months, the random-effects model demonstrated a borderline but non-significant reduction in disability scores favoring better vitamin D status or vitamin D-based treatment (MD -0.75, 95% CI -1.59 to 0.09; p = 0.061), with moderate heterogeneity (I^2 = 44.7%). The corresponding fixed-effect model demonstrated a statistically significant reduction in ODI scores (MD -0.75, 95% CI -1.03 to -0.47; p < 0.001).

At 6 months, the random-effects model showed no significant difference in ODI scores between groups (MD -2.17, 95% CI -10.75 to 6.41; p = 0.390), whereas

the fixed-effect model showed a modest but statistically significant reduction favoring better vitamin D status or vitamin D-based treatment (MD -1.55, 95% CI -2.66 to -0.45; p = 0.006). Heterogeneity at 6 months was very high (I^2 = 90.6%), suggesting substantial between-study variability and limiting confidence in the pooled estimate.

Overall, patient-reported outcome measures demonstrated less consistent effects than radiographic fusion outcomes, with most random-effects analyses remaining non-significant and substantial heterogeneity observed across studies, particularly at later follow-up timepoints.

Risk of Bias Assessment

Overall, the included studies demonstrated predominantly moderate methodological quality and risk of bias (Tables 4 and 5).

Among randomized controlled trials (Table 4), most studies demonstrated some concerns, primarily related to limited reporting of allocation concealment, blinding procedures, and outcome assessment methodology. No randomized study was judged to be at high risk of bias.

Observational studies (Table 5) were generally of moderate methodological quality (NOS scores 5–8). While cohort selection and exposure assessment were generally adequate, comparability was often limited because of insufficient adjustment for key confounders. Outcome assessment was considered acceptable in studies using radiographic or CT-based criteria, whereas database studies carried a higher risk of misclassification bias due to reliance on administrative coding and non-radiographic outcome ascertainment.

Residual confounding, variability in exposure definitions, and heterogeneity in outcome assessment methods should be considered when interpreting the pooled findings.

Discussion

In this systematic review and meta-analysis of nine studies, better vitamin D status or vitamin D–related interventions were associated with statistically significant improvements in radiographic fusion outcomes in pooled analyses. However, these effects were modest, derived from a limited number of heterogeneous studies, and their clinical significance remains uncertain. Sensitivity analyses demonstrated that the observed associations were influenced by study characteristics, including outcome definitions and the inclusion of large database cohorts, highlighting the potential instability of pooled estimates.

Patient-reported outcomes demonstrated modest early improvements in pain and disability in some analyses; however, these effects were not consistently observed across random-effects models and were accompanied by moderate to high heterogeneity. The magnitude of improvement observed in VAS and ODI was small and below commonly accepted minimal clinically important differences, suggesting limited clinical relevance. Overall, while pooled estimates suggest a potential beneficial association between vitamin D exposure and structural outcomes, the findings remain inconsistent across analytical approaches and are characterized by substantial clinical and methodological variability.

Previous systematic reviews have explored the relationship between vitamin D status and outcomes following spinal fusion, but the available evidence has been limited and heterogeneous. Kerezoudis et al. reported a high prevalence of vitamin D deficiency among spine surgery patients and suggested a potential association between hypovitaminosis D and less favorable postoperative outcomes, although the conclusions were constrained by the small number of available studies and variability in study design[22]. More recently, Khalooeifard et al. conducted a systematic review and meta-analysis focusing primarily on patient-reported outcomes and demonstrated modest improvements in early postoperative pain and disability with vitamin D supplementation, but found no consistent or statistically significant effect on radiographic fusion[23].

In contrast to these prior reviews, the current analysis places primary emphasis on structural endpoints, including both radiographic fusion success and fusion failure, the principal measures of arthrodesis. In addition, multiple exposure frameworks were evaluated, including baseline vitamin D deficiency, standard supplementation, active vitamin D analogues, and combination regimens, reflecting the variability encountered in clinical practice. Importantly, these exposure types represent distinct clinical constructs (risk factor versus intervention), and the pooled estimates should therefore be interpreted as an aggregate signal rather than a single unified effect of vitamin D. By applying random-effects modeling with sensitivity and stratified analyses, the present study offers a more conservative and robust assessment of the available evidence.

In addition, the present study incorporates recently published large-scale administrative database analyses and evaluates their impact on pooled estimates through predefined sensitivity analyses, demonstrating the potential for disproportionate weighting to influence overall conclusions. Stratified analyses based on follow-up duration further suggest a temporal pattern, with early signals favoring vitamin D exposure that are not sustained at longer-term assessment. These findings help explain inconsistencies across the literature and highlight the influence of study size, exposure definition, and outcome timing as key sources of heterogeneity. Together, these findings complement prior work and contribute to a more complete understanding of the current evidence base, representing an incremental step toward clarifying the clinical role of vitamin D optimization in patients undergoing lumbar fusion.

Since these earlier syntheses, the evidence base has

expanded with the addition of randomized controlled trials and large observational studies evaluating both vitamin D supplementation and baseline deficiency[16,17,19,24]. Recent randomized trials have reported improvements in early postoperative pain and functional outcomes with vitamin D supplementation, but have not demonstrated consistent differences in radiographic fusion at 12 months[16,17]. In parallel, large administrative database analyses have suggested an association between vitamin D deficiency and increased mechanical complications. A national claims study of more than 108,000 lumbar fusion patients reported higher rates of hardware failure and revision surgery among patients with preoperative vitamin D deficiency, and a large propensity-matched cohort including over 40,000 patients found vitamin D deficiency to be associated with an increased risk of postoperative complications[19,24]. More recent prospective data have further suggested that lower vitamin D levels may be associated with delayed early clinical recovery, without significant differences in outcomes among patients undergoing fusion[25]. Collectively, these studies have increased sample size and methodological diversity, but have also contributed to persistent variability in reported effects across structural and clinical endpoints.

The inconsistent findings observed for radiographic fusion may reflect the complex and multifactorial nature of spinal arthrodesis[26,27]. Fusion represents a continuous biological process of bone remodeling and maturation, yet it is commonly reported as a binary outcome, which may obscure differences in the rate or timing of healing[28]. In addition, substantial variability exists across studies in the methods used to assess fusion, including differences in imaging modality (plain radiographs versus computed tomography), grading systems, and criteria used to define nonunion[27,29]. These factors can all influence reported fusion rates and interobserver reliability. The timing of assessment further contributes to heterogeneity, as radiographic consolidation may continue for 12–24 months after surgery and early differences in healing may diminish over time[30]. Such methodological and temporal variability reduces comparability between studies and contributes to wider confidence intervals and attenuation of pooled effects in random-effects models, even when point estimates consistently favor vitamin D exposure.

The inconsistent results observed for fusion failure in the current study appear to be largely related to differences in study size, endpoint definition, outcome ascertainment, and study design. The significant association observed in the common-effect model was heavily influenced by the large administrative database study by Garcia et al., which contributed 2,730 of the 3,081 patients (approximately 89%) included in the fusion failure analysis[19]. In this study, the endpoint pooled in the present meta-analysis was EHR-coded pseudoarthrosis at 1-year follow-up, rather than direct radiographic assessment of fusion status. However, sensitivity analysis excluding this study demonstrated that the association remained statistically significant under random-effects modeling (RR 0.34, 95% CI 0.23–0.49), with no residual heterogeneity (I^2 = 0%). These findings suggest that the Garcia study contributed substantially to between-study heterogeneity, likely because of differences in endpoint definition and administrative outcome ascertainment compared with radiographically assessed fusion outcomes.

While administrative claims studies provide substantial statistical power, they rely on coding-based outcome definitions and often lack important clinical variables such as bone density, smoking status, and adherence to supplementation, all of which are known to influence fusion outcomes[31]. The need for sensitivity analyses further indicates meaningful differences in patient populations, exposure definitions, and outcome ascertainment across studies. Although heterogeneity was eliminated after exclusion of the Garcia et al. database study, variability in endpoint definitions and data sources supports cautious interpretation of the pooled fusion-failure estimate. Taken together, these findings suggest that the association between vitamin D status and fusion failure remains uncertain and should be interpreted cautiously in the context of heterogeneous clinical evidence.

However, a biologically plausible link between vitamin D status and lumbar fusion outcomes remains. Vitamin D signaling through the vitamin D receptor (VDR) regulates osteoblast proliferation and differentiation, expression of bone-matrix proteins, and mineralization, which are processes central to graft incorporation and maturation of arthrodesis[32,33]. In addition, vitamin D is also implicated in bone repair biology (hard callus formation and remodeling), even though clinical evidence in fracture-healing populations still remains mixed. This ultimately suggests that any effect may be context-dependent and modest rather than uniformly detectable across heterogeneous cohorts[34,35]. Beyond osseous biology, vitamin D/VDR pathways have been linked to modulation of nociceptive and inflammatory signaling, which gives a plausible explanation for why some studies observe early improvements in pain and disability without a durable radiographic fusion signal[36]. Importantly, any potential effect of vitamin D is likely to be influenced by stronger and well-established predictors of fusion such as smoking, advanced age, and the number or complexity of fused levels. Recent evidence continues to highlight these factors as major determinants of pseudarthrosis, which may overshadow more modest metabolic effects of vitamin D in heterogeneous clinical populations[37].

Vitamin D status may be particularly relevant in patients with osteoporosis or impaired bone quality, in whom reduced bone mineral density, altered remodeling capacity, and compromised implant-bone interface mechanics may increase the risk of delayed fusion, subsidence, screw loosening, and pseudarthrosis. Recent translational work has emphasized the broader musculoskeletal consequences of vitamin D deficiency, while emerging mechanistic evidence suggests that

vitamin D signaling may interact with pathways regulating bone metabolism and osteoporosis, including the Sirt1/PGC1α axis[38]. However, the included studies inconsistently reported bone mineral density, osteoporosis treatment, calcium supplementation, bisphosphonate use, and other bone-active medications, limiting the ability to determine whether vitamin D effects differ in osteoporotic subgroups.

In addition, variability in the definition of vitamin D deficiency across studies should be considered when interpreting these findings. There is no universal consensus regarding optimal serum 25-hydroxyvitamin D [25(OH)D] thresholds, and guideline recommendations differ substantially[39-42]. For example, the Institute of Medicine and European Food Safety Authority consider levels of approximately ≥20 ng/mL (50 nmol/L) sufficient for bone health, whereas the Endocrine Society has historically defined sufficiency as ≥30 ng/mL[39,40]. In contrast, the Scientific Advisory Committee on Nutrition emphasizes avoidance of severe deficiency, with thresholds closer to 10 ng/mL (25 nmol/L)[41]. This heterogeneity in definitions may have led to inconsistencies in exposure classification across included studies and may represent an additional source of between-study variability.

Several limitations should be considered when interpreting the findings of this review. First, the overall evidence base was limited, with only nine studies included and relatively small sample sizes for several outcomes. For example, analyses of radiographic fusion success and sensitivity analyses for fusion failure were based on only 351 patients. In addition, most included studies were observational in design, introducing the potential for residual confounding despite generally moderate methodological quality. Second, substantial clinical heterogeneity was present across studies, including differences in patient populations, surgical techniques, number of fused levels, and follow-up duration. Third, considerable variability existed in the definition and measurement of vitamin D exposure, with studies evaluating baseline deficiency, standard supplementation, active vitamin D analogues, or combination regimens, limiting the ability to draw formulation-specific conclusions. Importantly, studies evaluating baseline vitamin D deficiency and those assessing supplementation represent distinct clinical frameworks (risk factor versus intervention), which may have further contributed to heterogeneity and influenced pooled estimates. Fourth, outcome assessment was not standardized, with differences in imaging modality, fusion criteria, and timing of evaluation, as well as variation in the reporting of patient-reported outcomes. Finally, several analyses were influenced by statistical limitations, including high between-study heterogeneity, limited power for subgroup analyses, and the disproportionate impact of large database studies, which may obscure smaller clinical effects.

Future research should focus on well-designed prospective studies with standardized assessment of vitamin D status and clearly defined supplementation protocols. Randomized controlled trials with adequate sample sizes and long-term follow-up are needed to determine whether correction of vitamin D deficiency influences radiographic fusion and reduces the risk of pseudarthrosis. In addition, future studies should incorporate multivariable analyses to account for established risk factors such as bone density, smoking, metabolic comorbidities, and construct characteristics, and should employ uniform radiographic criteria to improve comparability across studies.

Conclusion

This systematic review and meta-analysis suggests that better vitamin D status or vitamin D–related interventions may be associated with improved radiographic fusion outcomes; however, these effects were modest and influenced by heterogeneity in study design, exposure definitions, and outcome ascertainment. Patient-reported outcomes showed inconsistent and clinically limited improvements, with most random-effects analyses remaining non-significant and substantial heterogeneity observed across studies. Given the biological plausibility and high prevalence of hypovitaminosis D, optimization of vitamin D status may remain reasonable in selected patients. However, current evidence does not establish a clear, independent, and clinically meaningful effect of vitamin D on fusion outcomes. Further high-quality prospective studies are required to clarify the role of vitamin D optimization in perioperative risk stratification and outcome improvement in lumbar fusion surgery.

Authors' Contributions

Stylianos Kapetanakis: Conceptualization, methodology, supervision, critical revision of the manuscript for intellectual content, and project oversight. Mikail Chatzivasiliadis: Conceptualization, methodology, data curation, formal analysis, data interpretation, and original draft preparation. The primary author and guarantor of the study and responsible for the integrity of the data analysis. Michael Patrianakos: Data acquisition, literature screening, manuscript revision, and validation. Panagiotis Konstantinou: Data extraction, risk-of-bias assessment, and manuscript revision. Lazaros Kostretzis: Data acquisition and quality control. Konstantinos Ditsios: Supervision, manuscript review, and intellectual oversight. All authors meet the ICMJE authorship criteria, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Supplemetary Table 1. Search Strings.

PubMed (346 results): ("vitamin D"[Title/Abstract] OR "25-hydroxyvitamin D"[Title/Abstract] OR "25(OH)D"[Title/Abstract] OR cholecalciferol[Title/Abstract] OR calcitriol[Title/Abstract]) AND (spine[Title/Abstract] OR spinal[Title/Abstract] OR lumbar[Title/Abstract]) AND (fusion[Title/Abstract] OR arthrodesis[Title/Abstract] OR surgery[Title/Abstract] OR operative[Title/Abstract] OR instrumented[Title/Abstract] OR instrumentation[Title/Abstract] OR interbody[Title/Abstract] OR decompression[Title/Abstract])
Scopus (208 results): TITLE-ABS-KEY ("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR cholecalciferol OR calcitriol) AND TITLE-ABS-KEY ("spinal fusion" OR "lumbar fusion" OR "interbody fusion" OR "posterolateral fusion" OR arthrodesis OR PLIF OR TLIF OR ALIF)
Web of Science (344 results): TS=("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR cholecalciferol OR calcitriol) AND TS=(spinal OR lumbar) AND TS=(fusion OR arthrodesis OR interbody OR surgery)