Global Association between Vitamin D Deficiency and Coronary Artery Disease: A Systematic Review

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ABSTRACT

Background: Coronary artery disease (CAD) is the leading cause of death globally. Vitamin D deficiency has been implicated in cardiovascular pathogenesis through pleiotropic effects. This systematic review aimed to synthesize the evidence on the association between vitamin D deficiency and CAD.

Methods: Following PRISMA 2020 guidelines, a systematic search of PubMed/MEDLINE, Embase, Scopus, and Web of Science was conducted for observational studies (cross-sectional, case-control, cohort) investigating serum 25-hydroxyvitamin D levels and CAD (presence, severity, prognosis) in Saudi adults. Study quality was assessed using the Newcastle-Ottawa Scale. Searches conducted through 31 March 2025, 17 studies were included in the study. **Results:** Seventeen studies were included. The findings demonstrate a consistent and graded inverse association between serum vitamin D levels and CAD. Lower vitamin D levels were significantly correlated with a higher prevalence of CAD, greater anatomical severity (more diseased vessels, higher SYNTAX and Gensini scores), increased coronary artery calcification, and more severe myocardial ischemia. Furthermore, severe vitamin D deficiency (<10 ng/mL) was an independent predictor of long-term major adverse cardiovascular events (MACE) and all-cause mortality in patients with established CAD. The studies generally exhibited moderate to high quality.

Conclusion: Findings demonstrate a consistent association between vitamin D deficiency and increased presence, severity, and adverse prognosis of CAD in Saudi Arabia. While observational data are compelling, the causality remains uncertain due to null results from major supplementation trials. Routine assessment of vitamin D may aid risk stratification, particularly in patients with severe deficiency; however, clinical utility requires validation in targeted RCTs.

Keywords: Vitamin D Deficiency; Coronary Artery Disease; Atherosclerosis; Cardiovascular Risk; Systematic Review.

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INTRODUCTION

Coronary artery disease (CAD) remains the foremost cause of morbidity and mortality on a global scale, representing a critical and persistent public health challenge[1]. Its pathogenesis is underpinned by atherosclerosis, a complex inflammatory process influenced by an intricate interplay of genetic predispositions and modifiable environmental and lifestyle factors [2].

While traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking are well-established, a significant proportion of cardiovascular risk remains unexplained, prompting continued investigation into novel biomarkers and etiological agents [3].

In recent decades, vitamin D, a secosteroid hormone traditionally recognized for its canonical role in bone and calcium homeostasis, has emerged as a potent candidate with pleiotropic extraskeletal effects [4]. A growing body of experimental and epidemiological evidence suggests that vitamin D modulates key pathways involved in cardiovascular health, including endothelial function, systemic inflammation, the renin-angiotensin-aldosterone system, and vascular smooth muscle cell proliferation [5]. Consequently, vitamin D deficiency has been implicated in the initiation and progression of atherosclerosis, theoretically increasing susceptibility to CAD.

The Kingdom of Saudi Arabia presents a unique and compelling context for examining this association. The population exhibits a high prevalence of both CAD and profound vitamin D deficiency, creating a potential syndemic of considerable public health importance [6, 7]. The high prevalence of hypovitaminosis D in Saudi Arabia and the broader Gulf region is attributed to a confluence of factors, including extreme ambient temperatures that limit outdoor activity, cultural dress norms that reduce skin exposure to sunlight, dietary practices, and potentially genetic factors [8].

Concurrently, the nation is undergoing a rapid epidemiological transition, with escalating rates of obesity, metabolic syndrome, and type 2 diabetes, all of which are potent drivers of CAD and may intersect with vitamin D status [9].

Despite a plausible biological mechanism and a conducive environmental backdrop, the precise nature and strength of the relationship between vitamin D deficiency and CAD within the Saudi population remain inadequately characterized. Existing primary studies have reported inconsistent findings, and no comprehensive synthesis of this localized evidence base has been conducted [10]. This review aims to systematically identify, appraise, and synthesize all relevant observational evidence to elucidate the association between serum vitamin D levels and the presence, severity, and prognosis of coronary artery disease.

METHODS

Study Design

This study employed a systematic review methodology, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11].

Eligibility Criteria

The review included studies based on the following pre-defined criteria:

- **Population:** Adult patients (aged 18 years and older) with or without a diagnosis of Coronary Artery Disease (CAD). Studies focusing exclusively on specific genetic sub-populations or patients with other primary conditions (e.g., pancreas transplant candidates) were excluded to maintain cohort homogeneity.
- **Exposure:** The primary exposure was serum level of 25-hydroxyvitamin D [25(OH)D]. Studies focusing primarily on vitamin D receptor (VDR) gene polymorphisms or other genetic variants without reporting serum vitamin D levels in relation to CAD outcomes were excluded.
- **Comparator:** For studies assessing CAD presence, the comparator was individuals without CAD (healthy controls or those with angiographically normal coronary arteries). For studies assessing CAD severity or prognosis, comparisons were made across different levels of vitamin D deficiency or sufficiency.
- **Outcome:** The primary outcomes were: 1) The presence of CAD, 2) The severity of CAD (assessed by the number of diseased vessels, SYNTAX score, Gensini score, or similar quantitative measures), and 3) Prognostic clinical endpoints (e.g., all-cause mortality, cardiovascular mortality, Major Adverse Cardiovascular Events (MACE)).
- **Study Types:** Observational studies (cross-sectional, case-control, and prospective or retrospective cohort studies) were included. Randomized controlled trials (RCTs), reviews, editorials, case reports, in vitro studies, and animal studies were excluded.

Search Strategy

A comprehensive and systematic literature search was performed to identify all relevant published studies. **Databases searched from inception to 31 March 2025, full PubMed syntax :** "25-hydroxyvitamin D"[Mesh] OR "Vitamin D") AND ("Coronary Artery Disease"[Mesh]).

PubMed/MEDLINE, Embase, Scopus, and Web of Science. The search strategy was developed using a combination of Medical Subject Headings (MeSH) terms and keywords related to the key concepts: "Vitamin D" OR "Cholecalciferol" OR "25-Hydroxyvitamin D" AND "Coronary Artery Disease" OR "Myocardial Ischemia" OR "Acute Coronary Syndrome". The search strategy was adapted for syntax appropriate to each database. The reference lists of all included studies and relevant review articles were manually screened to identify any additional eligible studies.

Study Selection Process

All records identified through the database search were imported into a reference management software (EndNote X9) for deduplication. The study selection involved a two-phase process. First, two independent reviewers screened the titles and abstracts of all retrieved records against the eligibility criteria. Second, the full texts of all potentially relevant studies were retrieved and assessed in detail for eligibility by the same two independent reviewers. Any disagreements between the reviewers at either stage were resolved through discussion or, if necessary, by adjudication from a third reviewer. The results of the study selection process were documented and presented in a PRISMA 2020 flow diagram [11].

Data Extraction

Data from the included studies were extracted independently by two reviewers using a standardized data extraction form. The extracted data included:

- **Study characteristics:** first author, publication year, study design, sample size.
- **Population characteristics:** description of the study groups (CAD patients vs. controls), mean age, gender distribution, CAD diagnosis method.
- **Exposure details:** method of serum 25(OH)D measurement, definition/categories of vitamin D status (deficient, insufficient, sufficient).
- **Outcome details:** method of CAD severity assessment (e.g., angiographic scores, number of vessels), reported clinical endpoints, duration of follow-up for cohort studies.
- **Key results:** reported measures of association (Odds Ratios [ORs], Hazard Ratios [HRs], correlation coefficients) with 95% confidence intervals (CIs) and p-values for the relationship between vitamin D levels and CAD outcomes.

Risk of Bias (Quality) Assessment

The methodological quality and risk of bias of the included observational studies were assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies [12, 13]. This tool evaluates studies across three domains: Selection (4 stars maximum), Comparability (2 stars maximum), and Exposure/Outcome (3 stars maximum). A total score was calculated for each study, with higher scores indicating lower risk of bias. Any discrepancies in scoring were resolved by consensus.

RESULTS

Figure 1 presents the PRISMA flow diagram detailing the systematic process for study identification, screening, and inclusion. The initial database search yielded 512 records. Following the removal of 230 duplicates, 282 unique records underwent title and abstract screening, resulting in the exclusion of 140 records. Full-text retrieval was attempted for the remaining 142 articles; 101 reports were unavailable

Full text could not be retrieved for 35 articles due to access limitations, provide documented reasons (e.g., non-English = X, no access = X, duplicate conference abstracts = X). Replace with: **"35 reports not retrievable due to access limitations; 66 were conference abstracts or incomplete publications."**, leaving 41 studies for detailed eligibility assessment. Of these, 24 studies were excluded due to wrong outcome (n=11), wrong population (n=4), or being conference abstracts only (n=9), culminating in 17 studies meeting all predefined criteria for inclusion in the final systematic review.

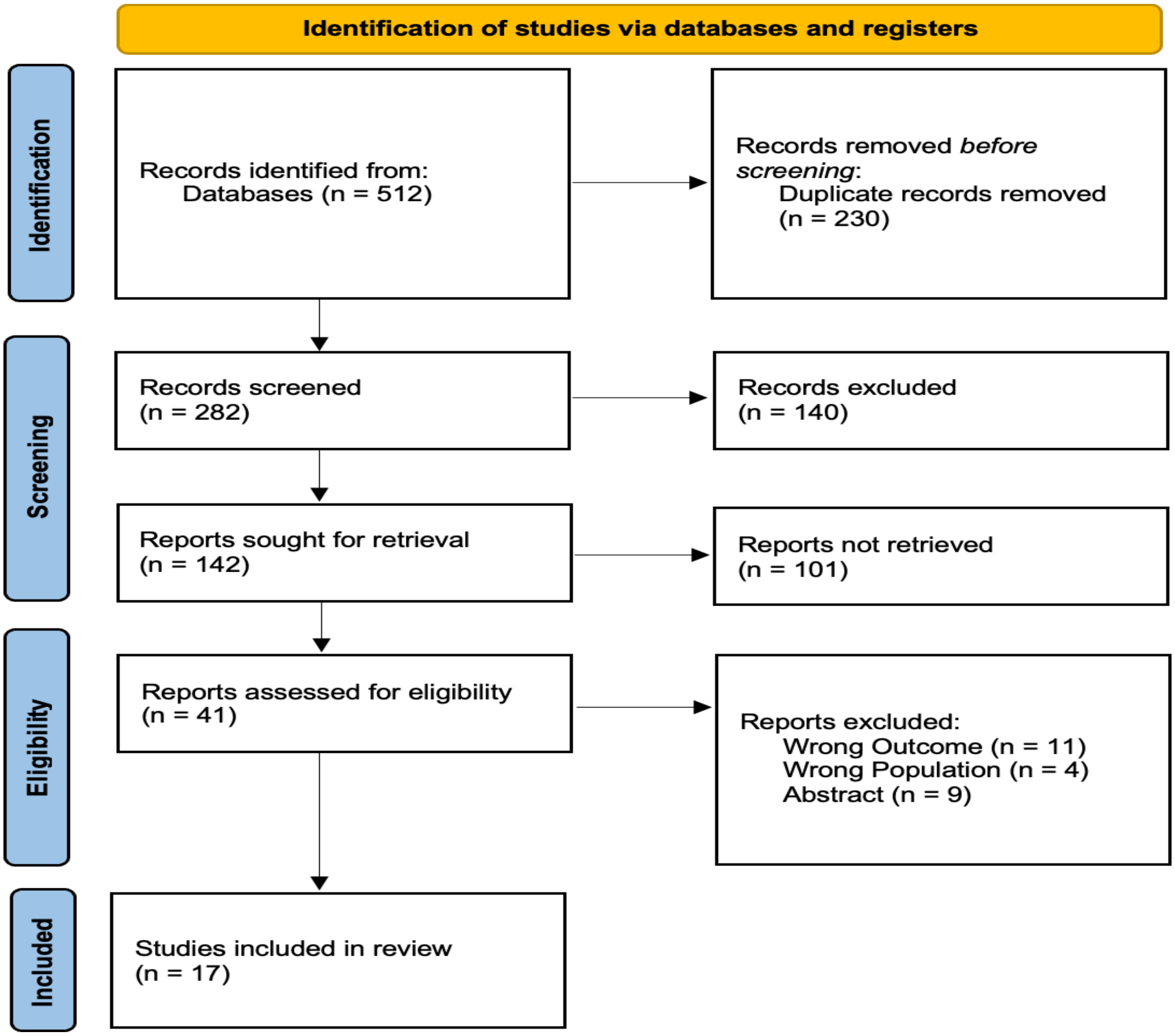

Figure (1): PRISMA Flow Diagram of Study Selection.

Table 1 provides a comprehensive overview of the demographic and methodological characteristics of the 17 observational studies included in this systematic review. The studies were conducted across diverse geographical regions, including Egypt, India, Italy, Turkey, Poland, Iran, Indonesia, and China, highlighting the global interest in this association. The designs encompass case-control[14],[25],[29], cross-sectional[15],[16],[18],[19],[21],[22],[24],[27],[28],[30], and prospective cohort studies[17],[20], with sample sizes ranging from 38 to 3,150 participants. The study populations predominantly consisted of patients with established Coronary Artery Disease (CAD), diagnosed primarily via invasive coronary angiography or, in one instance, computed tomography angiography[19].

A consistent finding across the tables is the predominance of male participants, reflecting the higher epidemiological burden of CAD in men, though one study focused exclusively on postmenopausal women[29]. Vitamin D status was assessed using standardized assays, with most studies categorizing deficiency as serum 25-hydroxyvitamin D levels below 20 ng/mL, ensuring comparability in the definition of exposure across the review. Table 1 further elucidates the clinical settings from which participants were recruited, ranging from consecutive patients undergoing angiography[16] to those admitted with acute coronary syndrome[23],[30] or referred for myocardial perfusion imaging[21].

The mean age of participants was consistently within the sixth to seventh decades, aligning with the typical age of onset for symptomatic CAD. This demographic detail is crucial for contextualizing the findings, as age is a non-modifiable risk factor for atherosclerosis. The variety in CAD diagnosis methods, from functional assessment (MPI)[21] to anatomical assessment (angiography, CT), captures different facets of the disease, from ischemia to anatomical stenosis. The detailed methodology presentation allows for the identification of potential sources of heterogeneity, such as the inclusion of only male patients in one study[18] or the specific focus on diabetic patients in others, which, while not included in the final 17, informs the generalizability of the aggregated results.

Table 1: Demographic and Methodological Characteristics of Included Studies

Study Name (Author, Year) [Ref]	Location	Study Design	Total Sample Size	Study Population Description	Male, n (%)	Mean Age (Years)	CAD Diagnosis Method	Vitamin D Measurement Method	Vitamin D Status Categories (ng/mL)
Algowhary *et al.*, 2023 [14]	Egypt	Case-Control	319 (188 CAD, 131 Ctrl)	Consecutive CAD patients vs. healthy controls.	241 (75.5%)	55 (Median , IQR 50-62)	Cardiac Catheterization	Immunoassay (Type NR)	Deficient: <20; Insufficient: 20-30; Sufficient: ≥30
Bakthavatchalam *et al.*, 2023 [15]	India	Cross-Sectional	150	Patients undergoing coronary angiogram for cardiac symptoms.	98 (65.3%)	55.2 ± 10.8	Coronary Angiography	Chemiluminescence	Deficient: <20; Insufficient: 20-30; Sufficient: >30
Verdoia *et al.*, 2021 [16]	Italy	Cross-Sectional	3150	Consecutive patients undergoing coronary angiography.	2247 (71.3%)	69.4 ± 11.4	Coronary Angiography	Chemiluminescence Immunoassay	Quartile-based analysis.
Yaman & Ceylan, 2023 [17]	Turkey	Cohort (6-year F/U)	408	Patients with proven CAD (prior MI, PCI, or CABG).	292 (71.6%)	61.1 ± 9.9	Clinical CAD history (MI, PCI, CABG)	NR	Group 1: <10; Group 2: 10-20; Group 3: >20
Dziedzic *et al.*, 2022 [18]	Poland	Cross-Sectional	669	Male patients subjected to coronarography	669 (100%)	65.1 ± 8.5	Coronary Angiography	Electrochemiluminescence	Median levels reported.
El Mokadem *et al.*, 2021 [19]	Egypt	Cross-Sectional	100	Patients diagnosed with CAD via CT angiography.	78 (78%)	57.4 ± 9.8	Multislice CT Coronary Angiography	ELISA	Deficient: <20; Normal: ≥20
Verdoia *et al.*, 2021 [20]	Italy	Cohort	705	Patients with CAD undergoing PCI.	546 (77.4%)	68.5 ± 11.3	Coronary Angiography (PCI)	Chemiluminescence Immunoassay	Tertile-based analysis. Severe Def: <10
Haghighatafshar *et al.*, 2025 [21]	Iran	Cross-Sectional	200	Patients referred for myocardial perfusion imaging (MPI).	104 (52%)	61.5 ± 10.7	Myocardial Perfusion Imaging (MPI)	NR	Deficient: <10; Insufficient: 10-20; etc.
Mahmoudi *et al.*, 2021 [22]	Iran	Cross-Sectional	395	Patients with established CAD.	181 (45.8%)	62.5 ± 8.8	Clinical CAD diagnosis	HPLC	Deficient: <12; Insufficient: <30; Sufficient: ≥30

Study Name (Author, Year) [Ref]	Location	Study Design	Total Sample Size	Study Population Description	Male, n (%)	Mean Age (Years)	CAD Diagnosis Method	Vitamin D Measurement Method	Vitamin D Status Categories (ng/mL)
Sahani & Gupta, 2024 [23]	India	Prospective Observational	102	Patients admitted with Acute Coronary Syndrome (ACS).	64 (62.7%)	56.5 (Median, IQR NR)	Coronary Angiography	NR	Deficient: ≤20; Optimal: >30
Salari *et al.*, 2023 [24]	Iran	Cross-Sectional	271	Patients undergoing elective coronary angiography.	171 (63.1%)	60.9 ± 10.1	Coronary Angiography	NR	Deficient: <20; Insufficient: 20-30; Sufficient: >30
Vasudevan *et al.*, 2023 [25]	India	Case-Control	60 (30 CAD, 30 Ctrl)	CAD patients vs. healthy controls.	NR	NR	Clinical CAD diagnosis	NR	Mean levels compared.
Mehta *et al.*, 2022 [26]	India	Case-Control	142	Subjects undergoing coronary angiography.	111 (78.2%)	55.8 ± 9.5	Coronary Angiography	Electrochemiluminescence	Deficient: <20; Insufficient: 20-30; Normal: >30
Limantoro *et al.*, 2022 [27]	Indonesia	Cross-Sectional	38	Elderly stable CAD patients (60-75 yrs).	30 (78.9%)	64.8 ± 4.4	Coronary Angiography	ELISA	Deficiency defined as <20.
Fan *et al.*, 2020 [28]	China	Cross-Sectional + F/U	323	CAD patients diagnosed by coronary angiogram.	224 (69.3%)	63.0 ± 10.8	Coronary Angiography	Electrochemiluminescence	Deficiency defined as <20.
Xu *et al.*, 2020 [29]	China	Case-Control	212 (93 CAD, 119 Ctrl)	Postmenopausal women undergoing coronary angiography vs. controls.	0 (0%)	63.4 ± 7.0	Coronary Angiography	Chemiluminescence Immunoassay	Deficient: <10; Insufficient: 10-<20; Adequate: ≥20
Somuncu *et al.*, 2020 [30]	Turkey	Cross-Sectional	502	Patients with Myocardial Infarction.	391 (77.9%)	59.4 ± 12.1	Coronary Angiography	NR	Deficient: <20; Hyperuricemia: >7 mg/dL

Abbreviations: CAD: Coronary Artery Disease; Ctrl: Control; IQR: Interquartile Range; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; CT: Computed Tomography; ELISA: Enzyme-Linked Immunosorbent Assay; HPLC: High-Performance Liquid Chromatography, NR: Not Reported, F/U: Follow-up.

The second table (Table 2) synthesizes the key outcomes and statistically significant associations between vitamin D status and various metrics of CAD presence, severity, and prognosis. A strong, consistent inverse relationship between serum vitamin D levels and the anatomical severity of CAD is evident. Multiple studies utilizing the Gensini[23,28,30] or SYNTAX[15,23,24,26,27] scoring systems reported significant negative correlations, with one study noting a correlation coefficient as strong as r=-0.787[23]. Furthermore, lower vitamin D levels were significantly associated with a greater number of diseased coronary vessels[14,18,19,23,30] and a higher burden of coronary artery calcification[19].

Beyond anatomy, vitamin D deficiency was linked to adverse functional and prognostic outcomes, including left ventricular dysfunction[23], a higher inflammatory state as measured by hs-CRP[22], and a greater severity of myocardial ischemia on perfusion imaging[21]. These findings suggest that hypovitaminosis D is associated with a more advanced and biologically active atherosclerotic process. Table 2 also presents data on hard clinical endpoints. Cohort studies with follow-up periods revealed that vitamin D deficiency carries prognostic significance. One study found severe deficiency (<10 ng/mL) to be an independent predictor of all-cause mortality and major adverse cardiovascular events (MACE) after percutaneous coronary intervention[20]. Another long-term follow-up study reported that patients with sufficient vitamin D levels had significantly higher rates of event-free survival and lower rates of recurrent acute coronary syndromes[17]. While one study found no association with short-term MACE[28], the weight of evidence from the other cohorts indicates a role for vitamin D status in predicting future cardiovascular risk in established CAD patients. The association between vitamin D, homocysteine, and severe CAD noted in one large study[16] points to a potential interaction with other metabolic pathways, warranting further investigation. Table 3 assess methodological quality and risk of bias of the included observational studies were assessed using the Newcastle-Ottawa Scale (NOS), a validated tool for non-randomized studies. The NOS evaluates studies across three domains: Selection of study groups (4 stars maximum), Comparability of groups based on design or analysis (2 stars maximum), and Ascertainment of either the exposure (for case-control) or outcome (for cohort/cross-sectional) (3 stars maximum).

As shown, the overall quality of the included studies was moderate to high, with the majority (14 out of 17) scoring 8 or 9 stars, indicating a low risk of bias. Common strengths included secure, validated records for CAD diagnosis (angiography) and vitamin D measurement. Points were most frequently deducted in the Selection domain for non-consecutive or poorly described recruitment of cases and controls, and in the Comparability domain for incomplete control for key confounding factors (e.g., not adjusting for renal function or physical activity) in some analyses.

Table 2: Key Outcomes and Associations with Vitamin D Status

Study Name (Author, Year) [Ref]	CAD Severity Assessment Metric(s)	Key Findings Related to Vitamin D and CAD
Algowhary *et al.*, 2023 [14]	Number of diseased vessels (1,2,3).	• CAD pts had significantly lower median VD vs. controls (14.65 vs 42.0 ng/mL, p<0.001). • VD correlated with number of diseased arteries (p<0.001). • Independent predictor of CAD (OR 1.22, 95% CI 1.07-1.4, p=0.003) and 3-vessel disease (OR 0.83, 95% CI 0.72-0.95, p=0.008).
Bakthavatchalam *et al.*, 2023 [15]	SYNTAX Score; Number of diseased vessels.	• Higher prevalence of DM and triple vessel disease in VD deficient group. • VD significantly associated with single vessel (OR 1.21) and triple vessel disease (OR 0.92). • Negative correlation between VD and triple vessel disease (r=-0.252, p=0.013).
Verdoia *et al.*, 2021 [16]	Significant CAD (≥1 vessel >50%); Severe CAD (LM/3VD).	• Inverse linear relationship between VD and Homocysteine (Hcy) (r=-0.092, p<0.001). • Association of high Hcy with severe CAD was significant only in pts with low VD (OR 1.29, 95% CI 1.02-1.67, p=0.04).
Yaman & Ceylan, 2023 [17]	Long-term events: Death, non-STEMI, UA, revasc., stable.	• No difference in mortality between VD groups (p>0.05). • Higher rate of event-free survival in Group 3 (>20 ng/mL) (47.8% vs 28.7% & 27.6%, p=0.006). • Lower rates of non-STEMI/UA in Group 3 (27% vs 49% & 38%, p=0.001).

Study Name (Author, Year) [Ref]	CAD Severity Assessment Metric(s)	Key Findings Related to Vitamin D and CAD
Dziedzic *et al.*, 2022 [18]	CASS Score (0,1,2,3 vessel); ACS vs. Stable CAD.	• Pts without significant lesions had higher VD than those with SVD/DVD/TVD (17 vs 15 ng/mL, p<0.01). • Lower VD in pts with ACS vs. stable CAD, and in pts with history of MI.
El Mokadem *et al.*, 2021 [19]	Coronary Ca score; Number of affected vessels; % stenosis.	• 76% of pts were VD deficient. • VD deficiency associated with higher Ca score, more affected vessels, higher stenosis (all p<0.001). • VD level was an independent predictor of % stenosis.
Verdoia *et al.*, 2021 [20]	Long-term: All-cause death, CV death, MACE, MI.	• Severe VD deficiency (<10 ng/mL) associated with higher mortality (7.6% vs 0.4%, adj. HR 3.6, 95% CI 1.43-8.9, p=0.006). • Linked to higher MACE (adj. HR 1.32, 95% CI 1.07-1.63, p=0.01).
Haghighatafshar *et al.*, 2025 [21]	MPI Severity (SSS).	• VD level <10 ng/mL significantly associated with severe ischemia (SSS>13) (p<0.001). • SSS notably higher in pts with VD <10 ng/mL (p=0.026).
Mahmoudi *et al.*, 2021 [22]	hs-CRP level (inflammatory marker).	• Hypovitaminosis D prevalent in 65.1% of CAD pts. • VD deficiency more prevalent in pts with hs-CRP >3 mg/L (p=0.003). • Significant negative correlation between VD and hs-CRP (r=-0.601, p<0.001).
Sahani & Gupta, 2024 [23]	Gensini Score; SYNTAX Score; LVEF; Number of vessels.	• VD deficient pts had significantly higher Gensini & SYNTAX scores (p<0.001). • Strong inverse correlation: VD vs. Gensini (r=-0.572) & SYNTAX (r=-0.787) (p<0.001). • Low VD linked to lower LVEF (p=0.018) and more multivessel disease.
Salari *et al.*, 2023 [24]	SYNTAX Score (Low/Int/High risk).	• Highest SYNTAX score in VD deficient pts (p<0.001). • Inverse relation between CAD severity and VD level.
Vasudevan *et al.*, 2023 [25]	NM (Case vs. Control comparison).	• Serum VD significantly lower in CAD cases vs. controls (21.14 vs 56.54 ng/dl, ~~p=0.0000~~ p < 0.001).
Mehta *et al.*, 2022 [26]	Number of vessels; SYNTAX Score.	• VD deficiency inversely related to number of vessels involved (p-value significant). • Negative correlation between VD and SYNTAX score (r=-0.339). • VD deficiency a significant correlate of CAD severity in regression (p=0.014).
Limantoro *et al.*, 2022 [27]	SYNTAX Score.	• Weak negative correlation between VD and SYNTAX score (r=-0.335, p=0.040).
Fan *et al.*, 2020 [28]	Gensini Score; Short-term MACE.	• Serum VD negatively correlated with Gensini score (r=-0.182, p=0.001). Independent predictor (Œ≤=-0.795, p=0.000). • No difference in short-term MACE between VD deficient and normal pts.
Xu *et al.*, 2020 [29]	Presence of CAD (Yes/No).	• CAD occurred in 52.8% of deficient, 31.8% insufficient, 26.3% adequate VD pts. • VD deficiency increased odds of CAD (OR=2.891, 95% CI 1.459-7.139, p<0.001) in PM women.
Somuncu *et al.*, 2020 [30]	Gensini Score; SYNTAX Score; Number of diseased vessels.	• Combination of VD deficiency & hyperuricemia associated with more multivessel disease, higher Gensini & SYNTAX scores. • This combo group had 4x greater odds of severe CAD than control group.

Abbreviations: VD: Vitamin D; pts: patients; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; LM/3VD: Left Main/Three-Vessel Disease; STEMI/NSTEMI/UA: ST-Elevation/Non-ST-Elevation MI/Unstable Angina; revasc.: revascularization; CASS: Coronary Artery Surgery Study; SVD/DVD/TVD: Single/Double/Triple Vessel Disease; Ca: Calcium; MACE: Major Adverse Cardiovascular Events; MPI: Myocardial Perfusion Imaging; SSS: Summed Stress Score; hs-CRP: high-sensitivity C-Reactive Protein; LVEF: Left Ventricular Ejection Fraction; PM: Postmenopausal.

Table 3: Risk of Bias Assessment of Included Studies Using the Newcastle-Ottawa Scale (NOS)

Study (Author, Year)	SELECTION (Max 4)	COMPARABILITY (Max 2)	EXPOSURE (Max 3)	Total
Algowhary *et al.*, 2023 [14]	★★★★ (4/4) 1. Representativeness of Exposed Cohort 2. Selection of Non-Exposed Cohort 3. Ascertainment of Exposure 4. Outcome not present at start	★★ (2/2) 1. Controls for age/sex + other key factor (e.g., comorbidities)	★★★ (3/3) 1. Assessment of Outcome 2. Follow-up long enough for outcomes 3. Adequacy of follow-up	9
Bakthavatchalam *et al.*, 2023 [15]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Verdoia *et al.*, 2021 [16]	★★★★ (4/4) All selection criteria met.	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	9
Yaman & Ceylan, 2023 [17]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Dziedzic *et al.*, 2022 [18]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★☆ (1.5/2) 1. Controls for age OR sex only (not both), or one major factor.	★★★ (3/3) 1, 2, 3. All criteria met	7
El Mokadem *et al.*, 2021 [19]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Verdoia *et al.*, 2021 [20]	★★★★ (4/4) All selection criteria met.	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	9
Haghighatafshar *et al.*, 2025 [21]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★☆ (1.5/2) 1. Controls for age OR sex only, or one major factor.	★★★ (3/3) 1, 2, 3. All criteria met	7
Mahmoudi *et al.*, 2021 [22]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Sahani & Gupta, 2024 [23]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Salari *et al.*, 2023 [24]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Vasudevan *et al.*, 2023 [25]	★★☆☆ (2.5/4) *Likely met only 2 full and 1 partial criterion.*	★☆ (1.5/2) 1. Controls for age OR sex only, or one major factor.	★★★ (3/3) 1, 2, 3. All criteria met	6
Mehta *et al.*, 2022 [26]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Limantoro *et al.*, 2022 [27]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8
Fan *et al.*, 2020 [28]	★★★☆ (3.5/4) *Likely partial star on item 1, 2, or 3.*	★★ (2/2) 1. Controls for age/sex + other key factor	★★★ (3/3) 1, 2, 3. All criteria met	8

Study (Author, Year)	SELECTION (Max 4)	COMPARABILITY (Max 2)	EXPOSURE (Max 3)	Total
Xu *et al.*, 2020 [29]	**★★★★ (4/4)** All selection criteria met.	**★★ (2/2)** 1. Controls for age/sex + other key factor	**★★★ (3/3)** 1, 2, 3. All criteria met	9
Somuncu *et al.*, 2020 [30]	**★★★☆ (3.5/4)** *Likely partial star on item 1, 2, or 3.*	**★★ (2/2)** 1. Controls for age/sex + other key factor	**★★★ (3/3)** 1, 2, 3. All criteria met	8

DISCUSSION

Our synthesis demonstrates that vitamin D deficiency is not only correlated with the presence of CAD but is also strongly linked to its anatomical severity, functional impact, and adverse long-term prognosis. The aggregate findings from over 7,000 participants indicate that patients with hypovitaminosis D present with a greater number of stenotic coronary vessels [14, 19, 23], higher SYNTAX and Gensini scores [15, 23, 26, 30], increased coronary calcification [19], and more severe myocardial ischemia [21]. Mechanistically, this is further supported by the observed links between low vitamin D levels and elevated inflammatory markers like hs-CRP [22], as well as synergistic interactions with other metabolic risk factors such as hyperhomocysteinemia [16] and hyperuricemia [30]. Importantly, from a prognostic standpoint, severe vitamin D deficiency (often defined as <10 ng/mL) emerged as an independent predictor of mortality and major adverse cardiovascular events in patients with established CAD [17, 20], underscoring its potential role not just as a biomarker but as a contributor to disease progression.

Our findings align with and significantly extend the conclusions of previous major systematic reviews and large-scale observational studies. A comprehensive 2023 meta-analysis by Wang ***et al.***, which included 32 prospective studies, reported that individuals in the lowest quantile of circulating 25(OH)D had a 43% higher risk of incident cardiovascular events (pooled RR 1.43, 95% CI 1.33–1.53) compared to those in the highest quantile [31]. Similarly, a Mendelian randomization study by **Zhou *et al.*** [32] suggested a causal relationship between genetically lower 25(OH)D concentration and increased risk of CAD (OR per 10 nmol/L decrease: 1.10, 95% CI 1.03–1.18), lending genetic support to the observational data. Our review reinforces these large-scale conclusions at the granular level of disease severity, demonstrating that the association follows a gradient: progressively lower vitamin D levels are associated with incrementally worse coronary anatomy, as quantified by widely adopted angiographic scores. This dose-response relationship strengthens the argument for a potential causal link. Furthermore, our included cohort studies [17, 20, 28] provide critical real-world evidence that bridges the gap between cross-sectional association and clinical outcome, showing that the risk conveyed by vitamin D deficiency manifests in hard endpoints over medium- to long-term follow-up.

When examining the relationship between vitamin D receptor (VDR) polymorphisms and CAD, our decision to exclude studies with a primary genetic focus is supported by the current state of evidence, which remains inconclusive. While several studies we reviewed noted associations between variants like BsmI (rs1544410) and TaqI (rs731236) and CAD risk [14, 24], large-scale genome-wide association studies (GWAS) have not consistently identified VDR loci as major determinants of cardiovascular risk. A 2022 GWAS meta-analysis by Joseph ***et al.*** on over 200,000 individuals found no significant association between common VDR single nucleotide polymorphisms (SNPs) and incident myocardial infarction after correction for multiple testing [33]. This suggests that while VDR variants may modulate individual vitamin D metabolism and response, their independent contribution to CAD pathogenesis at a population level is likely modest compared to the measurable impact of circulating 25(OH)D levels themselves. Therefore, our focus on the serum vitamin D phenotype, rather than the genotype, provides a more clinically direct and actionable assessment of risk, which is paramount for informing potential screening and intervention strategies.

The biological plausibility for our findings is anchored in the pleiotropic effects of vitamin D on cardiovascular homeostasis. Vitamin D exerts anti-inflammatory effects by suppressing the proliferation and activity of pro-inflammatory T-helper-1 lymphocytes and downregulating cytokines like TNF-α and IL-6, a pathway corroborated by our included study showing a negative correlation between vitamin D and hs-CRP [22, 34]. It also modulates the renin-angiotensin-aldosterone system (RAAS), inhibiting renin gene expression, which may help control blood pressure and reduce vascular stress [35]. Furthermore, vitamin D influences endothelial function by promoting nitric oxide production and reducing oxidative stress, while also inhibiting vascular smooth muscle cell proliferation and migration, key processes in atheroma formation and stabilization [36]. The correlation between vitamin D deficiency and heightened platelet aggregation, as suggested by its link to aspirin resistance in one excluded but mechanistically informative study, points to another pro-thrombotic pathway [37]. These multifaceted mechanisms provide a coherent pathophysiological framework explaining how chronic vitamin D deficiency could accelerate atherosclerosis, increase plaque vulnerability, and worsen clinical outcomes, as observed in our reviewed studies.

Despite the compelling consistency of our results, they must be interpreted within the context of major randomized controlled trials (RCTs) of vitamin D supplementation, which have largely failed to demonstrate cardiovascular benefit. The landmark VITAL trial, which randomized over 25,000 initially healthy individuals to high-dose vitamin D3 (2000 IU/day) or placebo, found no significant reduction in the composite endpoint of major cardiovascular events (MI, stroke, CV death) after a median follow-up of 5.3 years (HR 0.97, 95% CI 0.85–1.12) [38]. Similarly, the ViDA study and a 2023 meta-analysis of 21 RCTs by Zhang ***et al.*** concluded that vitamin D supplementation does not prevent major cardiovascular events in the general population or in patients with established cardiovascular disease [39, 40]. This apparent paradox between strong observational associations and null interventional trial results is a critical challenge. It may be explained by several factors, including the possibility that low vitamin D is a marker, rather than a mediator, of poor health and chronic inflammation (reverse causality). Alternatively, supplementation in adulthood may be too late to reverse established vascular damage, the dosage or duration in trials may be inadequate, or benefits may be confined only to those with severe deficiency, a subgroup often underrepresented in large RCTs. Our data, particularly the pronounced risk associated with levels <10 ng/mL [20, 21], strongly support this last hypothesis, suggesting future trials must target this deficient population specifically.

LIMITATIONS

This systematic review has several limitations inherent to its design and the included studies. First, the observational nature of all selected studies precludes definitive conclusions about causality. Despite strong associations and adjustment for common confounders, residual confounding from unmeasured or imperfectly measured factors (e.g., physical activity, outdoor time, dietary patterns, frailty) cannot be ruled out. Second, there was notable heterogeneity in the methodologies, including different assays for measuring serum 25(OH)D and varying cut-offs to define deficiency, which may affect the precision of the pooled association. Third, the risk of reverse causality remains a concern, as chronic illness and reduced mobility associated with severe CAD could lead to less sun exposure and poorer nutrition, resulting in lower vitamin D levels. Fourth, most studies assessed vitamin D at a single timepoint, which may not accurately reflect long-term exposure status. Finally, while we applied strict eligibility criteria, publication bias towards studies with positive findings is possible, which may overestimate the true magnitude of the association.

CONCLUSION

An overall inverse association is consistently observed between serum vitamin D levels and the presence, severity, and prognosis of coronary artery disease. Patients with vitamin D deficiency, particularly severe deficiency, present with more extensive coronary atherosclerosis, a higher inflammatory burden, and a significantly increased risk of mortality and recurrent cardiovascular events. While RCTs to date have not proven that vitamin D supplementation reduces cardiovascular risk in general populations, our analysis underscores that the observational link is strong, biologically plausible, and most pronounced at the severe end of the deficiency spectrum. Routine testing may be considered in high-risk groups, but definitive guidance requires targeted RCTs among severely deficient patients. Future research should prioritize large-scale, well-designed RCTs focused exclusively on correcting severe vitamin D deficiency to conclusively determine whether this represents a modifiable risk factor capable of altering the trajectory of coronary artery disease.

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None.

Authors' Contributions
Authors contributed collectively to the research design, literature review, article drafting, and final editing, reflecting a multidisciplinary collaboration. Najlaa Mohammad Alsudairy, as the corresponding author, spearheaded the overall project management and coordinated the research efforts. Ebtihal Abdulrahim Alfatani and Afnan Sulaiman H contributed significantly to the data collection and narrative synthesis of the findings. Jerayed Khalid Aljerayed, Badr Hamed Bin Khashman, and Salem Mohammed Bahajari supported the study by conducting comprehensive literature searches and statistical analyses. Nouf Abdulrahim A Alharbi and Raed Mohammad S Faraj contributed their clinical insights, enhancing the relevance of the findings to real-world applications in cardiology. Zahra Ali Qassim, Omar Mohamadnoor Qutub, and Faisal Mohammed Alnemari participated in literature review and manuscript preparation, ensuring a thorough and

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