ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Vitamin D and cardiovascular health: A systematic review and evidence synthesis from deficiency to toxicity

Bhaskar Pal[1], Rajdip Goswami[2], Pinki Biswas[3], Debdutta Chakraborty[4], Debasmita Kundu[5], Mainak Chakraborty[2], and Saikat Santra[3]*

[1]Department of Pharmacology, Pandaveswar School of Pharmacy, Pandaveswar, Paschim Bardhaman, West Bengal, India

[2]Department of Pharmaceutical Technology, School of Health and Medical Sciences, Adamas University, Kolkata, West Bengal, India

[3]Department of Pharmaceutics, JRSET College of Pharmacy, Nadia, West Bengal, India

[4]Department of Pharmacology, NSHM Knowledge Campus, Kolkata, West Bengal, India

[5]Department of Pharmacology, Dooars Institute of Pharmaceutical Sciences and Research, Unishbisha, West Bengal, India

Abstract

Vitamin D deficiency affects approximately 1.5 billion people worldwide and has been increasingly associated with cardiovascular diseases (CVDs). However, the precise role of vitamin D in cardiovascular health remains unclear due to inconsistent findings across studies. This systematic review critically evaluates the existing literature on the effects of vitamin D status, ranging from deficiency to toxicity, on cardiovascular outcomes. A comprehensive search was conducted in major electronic databases for observational studies and randomized controlled trials examining the relationship between vitamin D levels or supplementation and key outcomes, including hypertension, myocardial infarction, stroke, and vascular calcification. Due to substantial clinical and methodological heterogeneity, findings were synthesized using a structured narrative approach. The evidence indicates a non-linear, U-shaped association between serum vitamin D levels and cardiovascular risk. Vitamin D deficiency has frequently been linked to higher blood pressure and an increased incidence of adverse cardiovascular events in observational studies. Moderate supplementation appears beneficial in deficient individuals, whereas excessive or high-dose supplementation has been associated with detrimental effects, particularly vascular and valvular calcification. Randomized trials have not demonstrated consistent cardiovascular benefits from routine supplementation. Vitamin D may have dose-dependent effects on cardiovascular health, with potential risks at both low and excessive levels. While correcting deficiency may be protective, universal supplementation is not supported for CVD prevention. Well-designed trials are needed to determine optimal dosing, target populations, and long-term cardiovascular safety.

Keywords: Vitamin; Cardiovascular disease; Supplementation; Deficiency; Toxicity; Immunology

***Corresponding author:**
Saikat Santra
(utpalsantra98@gmail.com)

Citation: Pal B, Goswami R, Biswas P, *et al.* Vitamin D and cardiovascular health: A systematic review and evidence synthesis from deficiency to toxicity. *Brain & Heart.* doi: 10.36922/BH025250031

Received: June 16, 2025

Revised: March 26, 2026

Accepted: April 9, 2026

Published online: May 22, 2026

1. Introduction

1.1. Global burden of vitamin D deficiency and cardiovascular disease

Vitamin D is a fat-soluble secosteroid hormone that plays a central role in calcium and phosphate homeostasis and skeletal health. The two major biologically relevant forms are vitamin D_3 (cholecalciferol), synthesized in human skin following ultraviolet B (UVB) exposure and obtained from animal-based dietary sources, and vitamin D_2 (ergocalciferol), derived primarily from plant sources and fortified foods. Over the past decade, vitamin D has attracted increasing scientific and clinical interest, extending well beyond its classical role in bone metabolism.[1]

Vitamin D deficiency has emerged as a global public health problem, affecting populations across all age groups and geographical regions. High prevalence rates have been reported in Europe, South Asia, and the Middle East, with particularly vulnerable groups including women, elderly individuals, and patients with chronic diseases. Emerging evidence suggests that hypovitaminosis D is associated not only with musculoskeletal disorders but also with a wide range of non-skeletal conditions, including cardiovascular disease (CVD).[2]

A growing body of epidemiological and mechanistic evidence indicates that vitamin D may influence cardiovascular health through multiple pathways, including modulation of the renin–angiotensin–aldosterone system, regulation of inflammatory responses, endothelial function, insulin sensitivity, and myocardial contractility. Low serum 25-hydroxyvitamin D (25(OH) D) levels have been linked to hypertension, coronary artery disease, heart failure, and increased cardiovascular mortality. Despite these associations, the exact role of vitamin D in CVD prevention and progression remains incompletely understood, with inconsistent findings across clinical studies.[3]

In response to widespread deficiency, vitamin D supplementation has been increasingly adopted in clinical practice. However, excessive or inappropriate use may lead to vitamin D toxicity, a rare but potentially serious condition characterized by hypercalcemia and disturbances in bone and mineral metabolism. Clinical manifestations of vitamin D toxicity include gastrointestinal symptoms, neuropsychiatric disturbances, renal dysfunction, and, in severe cases, cardiac arrhythmias. Although uncommon, the rising use of high-dose supplements and fortified foods underscores the need for careful evaluation of vitamin D status and dosing strategies.[4]

Given the dual concerns of widespread vitamin D deficiency and the potential risks associated with excessive supplementation, a clearer understanding of the relationship between vitamin D status and CVD is essential. Addressing this knowledge gap is critical for guiding evidence-based clinical decision-making and public health policies, as highlighted in previous studies.[5] The present review aims to synthesize evidence on the relationship between vitamin D status and cardiovascular outcomes, with particular attention to deficiency, supplementation, toxicity, and dose-dependent cardiovascular effects.

1.2. Literature review: Vitamin D deficiency and cardiovascular disease

Vitamin D deficiency has been extensively investigated in relation to CVD over the past two decades; however, findings remain heterogeneous and context dependent. Large observational studies and meta-analyses have consistently reported an inverse association between serum 25(OH)D levels and the risk of hypertension, coronary artery disease, heart failure, and cardiovascular mortality. Recent studies published between 2020 and 2025 further reinforce vitamin D deficiency as a prevalent comorbidity among patients with established CVD, particularly in low- and middle-income countries. Several population-based studies have demonstrated that individuals with low vitamin D levels exhibit higher blood pressure, increased arterial stiffness, endothelial dysfunction, and adverse lipid profiles. Mechanistically, vitamin D is believed to influence cardiovascular health through suppression of the renin–angiotensin–aldosterone system, modulation of inflammatory cytokines, regulation of oxidative stress, and improvement of insulin sensitivity. Despite these plausible biological pathways, randomized controlled trials (RCTs) investigating vitamin D supplementation have produced mixed results, with many failing to demonstrate significant reductions in major cardiovascular events.[6]

Recent clinical studies have highlighted the importance of patient characteristics such as age, sex, ethnicity, obesity, comorbidities, and baseline vitamin D status in modifying cardiovascular outcomes. Notably, emerging evidence suggests that vitamin D deficiency is more strongly associated with disease severity and poor prognosis rather than the initial development of CVD. This has prompted growing interest in evaluating vitamin D status as a risk marker rather than a direct causal factor in cardiovascular pathology. In parallel with deficiency-related concerns, the increasing use of vitamin D supplementation has raised awareness regarding the potential risk of vitamin D toxicity. Although rare, hypervitaminosis D has been reported in patients receiving high-dose supplements without appropriate monitoring. Case reports and observational

studies describe clinical manifestations including hypercalcemia, renal impairment, neuropsychiatric symptoms, and cardiac arrhythmias. These findings underscore the importance of balanced supplementation strategies and highlight the need for evidence-based dosing recommendations.[7]

Despite the growing body of literature, several gaps remain. Most existing studies focus either on deficiency or supplementation outcomes without adequately addressing the dose–response relationship, population-specific risk factors, or regional variations in sun exposure and dietary habits. Moreover, data from South Asian and Middle Eastern populations remain limited, despite these regions demonstrating some of the highest global prevalence rates of vitamin D deficiency. Consequently, further research is warranted to clarify the clinical implications of vitamin D status in CVD and to inform safe and effective supplementation practices.[8]

1.3. Conceptual framework: Application of the Theory of Unpleasant Symptoms

The present review is conceptually grounded in the Theory of Unpleasant Symptoms (TOUS), which provides a multidimensional framework for understanding symptom experiences and their impact on functional performance.[7] TOUS proposes that symptoms are influenced by interacting physiological, psychological, and situational factors, and that these symptoms, individually or collectively, affect patient functioning and health outcomes.

In this review, TOUS was used to systematically guide variable selection, measurement, and data analysis. Physiological factors were represented by clinical and biological characteristics relevant to CVD and vitamin D status, including serum vitamin D levels, comorbid conditions, and disease severity indicators. Psychological factors encompass emotional and cognitive symptoms such as anxiety, depressive mood, and perceived distress, which are frequently reported among patients with CVD. Situational factors included demographic characteristics, lifestyle-related variables, and contextual influences such as treatment exposure and healthcare access.[9]

Symptom variables were selected to capture the multidimensional nature of patient experiences as conceptualized by TOUS. Rather than examining isolated symptoms, the review evaluated symptom burden as an integrated construct reflecting the combined influence of physical, psychological, and contextual domains. Guided by TOUS, the analytical approach examined how variations in symptom burden were associated with functional performance and clinical outcomes across patient subgroups. By explicitly applying TOUS, this review extends existing cardiovascular and vitamin D research beyond descriptive associations and offers a theory-driven interpretation of symptom experiences. The limited prior application of TOUS in studies examining vitamin D status and CVD highlights the novelty of this approach and underscores its potential to inform patient-centered assessment and targeted clinical interventions.[7]

1.4. Vitamin D: Structure, sources, and metabolism

1.4.1. Chemical structure and physiological roles

Vitamin D is a fat-soluble secosteroid, with vitamin D_3 (cholecalciferol) being the most biologically significant form in humans. Structurally, vitamin D is derived from cholesterol and contains a broken B-ring, distinguishing it from the typical steroid framework (Figure 1). Vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol upon exposure to UVB radiation. Physiologically, vitamin D plays a crucial role in maintaining calcium and phosphorus homeostasis by enhancing their absorption in the intestine. Vitamin D is essential for healthy bone formation and mineralization, and it helps prevent disorders such as rickets in children and osteomalacia in adults. Additionally, vitamin D supports immune function and has roles in muscle health and inflammation regulation.[10]

1.4.2. Physiological functions of vitamin D

Vitamin D is crucial for several physiological processes, primarily related to calcium and phosphorus metabolism.

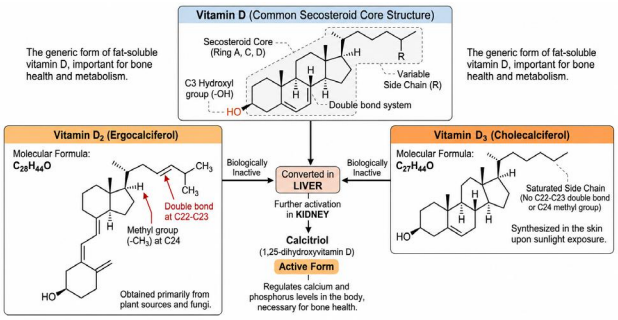

Figure 1. The chemical structures of vitamin D, vitamin D_2 (ergocalciferol), and vitamin D_3 (cholecalciferol). The fat-soluble vitamin D is important for calcium and phosphorus absorption, necessary for bone health, and overall metabolism. Vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol following exposure to ultraviolet B radiation, while vitamin D_2, which has a slightly different structure, is primarily obtained from plant sources and fungi.[11] Both forms are biologically inactive and undergo hydroxylation, first mainly in the liver to form 25(OH)D and then mainly in the kidneys to form 1,25(OH)2D, the active hormonal form, to regulate calcium and phosphorus levels in the body. Although both forms of vitamin D are important for health, vitamin D_3 is generally considered more effective in raising vitamin D levels in the bloodstream compared to vitamin D_2. Image created by the authors using Microsoft PowerPoint.

Once synthesized in the skin or ingested from dietary sources, vitamin D undergoes two hydroxylation steps to become active.[12,13] The initial process of hydroxylation takes place in the liver, where vitamin D is converted into 25(OH)D, referred to as calcidiol. The second hydroxylation occurs in the kidneys, where 25(OH)D is transformed into the active form of vitamin D, calcitriol (1,25-dihydroxyvitamin D [1,25(OH)2D]).[14]

Calcitriol exerts its effects by forming a complex with the vitamin D receptor (VDR), a member of the steroid-thyroid hormone receptor superfamily that acts as a transcription factor maintaining calcium and phosphate balance. This regulation is essential for:

(i) Calcium and phosphorus absorption: Improving intestinal absorption of calcium and phosphorus, two minerals essential for bone density and skeletal strength.[15]
(ii) Bone health: Supporting bone mineralization and remodeling by regulating osteoblast and osteoclast activity.[16]
(iii) Immune function: Regulating immune-cell activity and contributing to host responses to infections and inflammation.[17]
(iv) Cardiovascular health: Contributing to blood-pressure regulation, inflammation control, and endothelial function.[18]

1.5. Sources, forms, and absorption of vitamin D with key nutrients

Vitamin D is obtained from sunlight, food, and supplements, mainly in the forms of D_2 and D_3. These forms support calcium absorption and bone health. Their effectiveness depends on nutrients such as fat, magnesium, and vitamin K for proper absorption (Table 1).

Table 1. Overview of various vitamin D sources, their forms, functions in the body, and essential nutrients for absorption

Source	Type	Form of vitamin D	Function in the body	Key nutrients for absorption/ metabolism	Reference
Fatty fish	Natural	Vitamin D_3 (cholecalciferol)	Enhances calcium absorption, supports bone health, reduces inflammation, and boosts immune function	Magnesium, calcium, vitamin K2	19
Cod liver oil	Natural	Vitamin D_3 (cholecalciferol)	Provides high levels of vitamin D_3, essential for immune function, heart health, and bone mineralization	Omega-3 fatty acids, calcium, magnesium	20
Egg yolks	Natural	Vitamin D_3 (cholecalciferol)	Supports bone health, enhances immune system function, and may help with mood regulation	Phosphorus, omega-3 fatty acids	21
Beef liver	Natural	Vitamin D_3 (cholecalciferol)	Rich in vitamin D_3, supports bone density, immune function, and overall health	Iron, vitamin A, vitamin K	22
Sunlight (ultraviolet B exposure)	Natural	Vitamin D_3 (cholecalciferol)	Stimulates vitamin D production in the skin, supports calcium metabolism, bone health, and immune response	Magnesium, cholesterol	23
Fortified foods (e.g., milk, juice, cereals)	Synthetic (fortified)	Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)	Supports calcium absorption, bone health, and immune function when dietary intake is inadequate	Fat (for absorption), magnesium, calcium	24
Vitamin D supplements	Synthetic	Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)	Supplements to treat or prevent deficiency, supports calcium metabolism and immune function	Magnesium, fat (for absorption)	25

2. Methods

2.1. Review design and reporting guidelines

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review methodology adhered to established standards for systematic evidence synthesis in cardiovascular medicine.[26]

2.1.1. Preliminary scoping search

A preliminary scoping search conducted in September 2024 identified approximately 180 potentially relevant records. This scoping exercise was performed to obtain an initial understanding of the breadth of the available literature and to assess the feasibility of conducting a comprehensive systematic review.

The estimated number of potentially relevant records was used solely for planning purposes and did not influence the eligibility criteria or study selection. No target number of studies was prespecified; the final number of included studies was determined solely by the systematic search results and the predefined eligibility criteria.[27]

2.2. Literature search strategy

A comprehensive, systematic literature search was developed and executed by two independent reviewers with expertise in cardiovascular epidemiology and systematic review methodology. The search strategy employed Medical Subject Headings terms, controlled vocabulary, and free-text keywords, combining vitamin D exposure terms with cardiovascular outcome terms. Keywords used included: "vitamin D," "25-hydroxyvitamin D," "cholecalciferol," "ergocalciferol," "vitamin D deficiency," "vitamin D supplementation," "calcidiol," "calcitriol," "cardiovascular disease," "coronary artery disease," "heart failure," "hypertension," "stroke," "atherosclerosis," and "cardiovascular mortality." Boolean operators (AND, OR) and truncation were used to maximize sensitivity while maintaining specificity.[28]

2.3. Information sources and search timeline

Electronic database searches were conducted in PubMed (MEDLINE), Scopus, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to December 31, 2024. In addition, studies published in early 2025 that met the eligibility criteria were identified through updated searches and manual screening. These databases were selected to ensure comprehensive coverage of biomedical, clinical, and multidisciplinary literature. No language restrictions were applied initially. Non-English publications were included if sufficient data could be extracted from English abstracts or through professional translation services. Reference lists of included studies and relevant systematic reviews were manually screened for additional eligible studies.[7]

2.4. Eligibility criteria

Studies were considered eligible for inclusion if they met predefined criteria based on the PICOS framework (Population, Intervention/Exposure, Comparator, Outcome, Study design). Detailed inclusion and exclusion criteria are presented in Table 2.

2.4.1. Study identification approach

The systematic review aimed to identify all relevant published studies meeting the predefined eligibility criteria. All records retrieved through the systematic search during the specified period were screened for eligibility. No sampling of eligible studies was performed; all studies that met the inclusion criteria were included to maximize comprehensiveness and minimize selection bias.

2.5. Study selection process

All records identified through database searching were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for study selection and data management. Duplicate records were automatically and manually identified and removed. The study selection process followed a two-stage screening approach. First, two independent reviewers screened titles and abstracts of all identified records against the predefined eligibility criteria. Second, full-text articles of potentially eligible studies were retrieved and independently assessed for inclusion by the same two reviewers.[25]

Disagreements between reviewers at any stage were resolved through discussion to reach a consensus. When consensus could not be achieved, a third senior reviewer with expertise in cardiovascular epidemiology was consulted. Reasons for exclusion at the full-text screening stage were systematically documented and categorized.[8]

The study selection process and flow of studies through the review are summarized in the PRISMA 2020 flow diagram (Figure 2). The systematic search identified 3,847 records from all databases. After removal of 1,124 duplicates, 2,723 unique records underwent title and abstract screening. Of these, 2,458 records were excluded as clearly irrelevant, leaving 265 full-text articles for detailed assessment. Following full-text review, 138 articles were excluded for the following reasons: inappropriate population (n = 42), no quantitative vitamin

Table 2. Detailed inclusion and exclusion criteria

Criterion	Inclusion criteria	Exclusion criteria
Population	Human participants aged ≥18 years; both healthy individuals and those with established CVD or risk factors	Pediatric populations (<18 years), pregnant or lactating women, and patients with chronic kidney disease or on dialysis were not the primary focus of this review; however, studies including these populations were considered if they reported relevant cardiovascular outcomes and met the inclusion criteria
Exposure/intervention	Quantitative measurement of serum 25(OH)D or $1,25(OH)_2D$; vitamin D supplementation (D_2, D_3, or active analogs) with specified dose and duration	Studies without quantitative vitamin D assessment; dietary vitamin D intake without biomarker measurement
Outcomes	Cardiovascular events or markers: hypertension, CAD, MI, stroke, HF, AF, endothelial dysfunction, vascular calcification, LVH, cardiovascular mortality	Studies reporting only non-cardiovascular outcomes; studies without clear outcome definitions
Study design	RCTs; prospective/retrospective cohort studies; case-control studies; cross-sectional studies	Case reports, small case series (<10 participants), conference abstracts, and non-peer-reviewed publications were excluded. Narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, and methodological or consensus articles were not considered as primary evidence but were included where relevant to provide contextual background and support interpretation
Publication type	Peer-reviewed journal articles published between January 2010 and December 2024	Grey literature; unpublished data; duplicate publications (most recent/comprehensive version retained)
Language	All languages (with English abstract or professional translation available)	Studies without sufficient extractable data despite translation efforts

Abbreviations: $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; AF: Atrial fibrillation; CAD: Coronary artery disease; CVD: Cardiovascular disease; HF: Heart failure; LVH: Left ventricular hypertrophy; MI: Myocardial infarction; RCT: Randomized controlled trial.

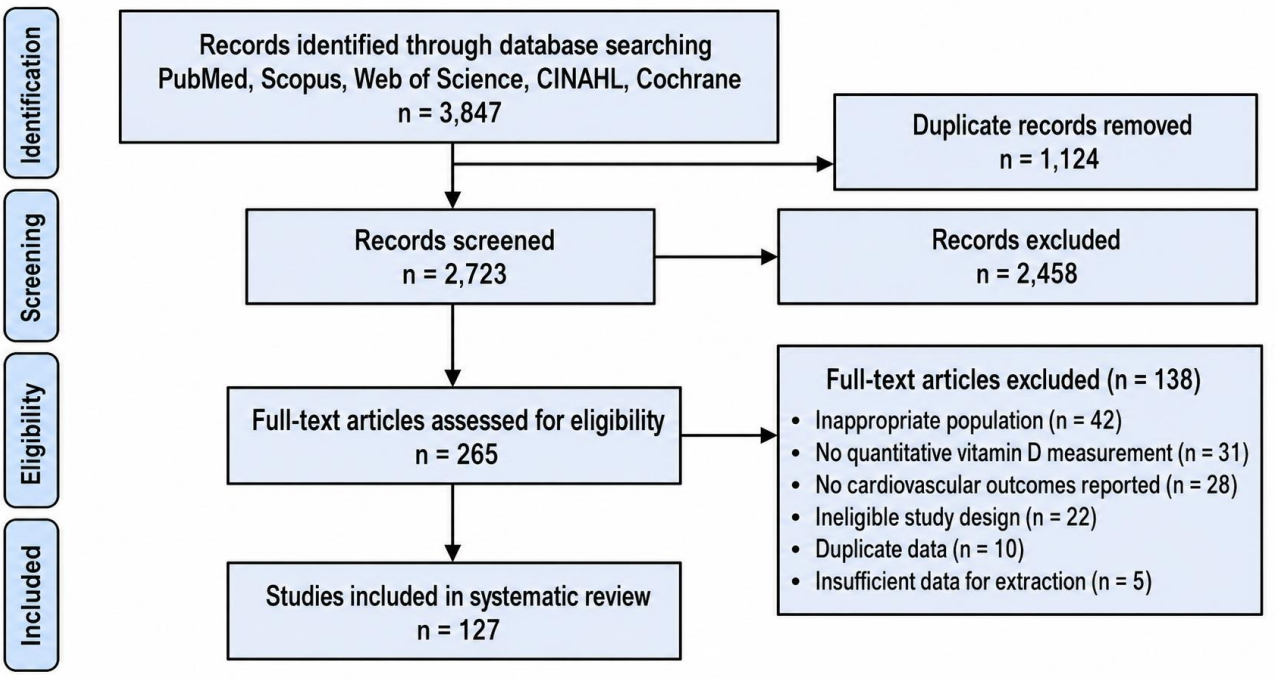

Figure 2. PRISMA diagram for the present review. Image created by the authors

D measurement (n = 31), no cardiovascular outcomes reported (n = 28), ineligible study design (n = 22), duplicate data (n = 10), and insufficient data for extraction (n = 5). Ultimately, 127 studies met all eligibility criteria and were included in the qualitative synthesis. Inter-rater reliability for study selection was assessed using Cohen's kappa coefficient, with κ = 0.89 indicating excellent agreement between reviewers.[28]

2.6. Data collection and extraction

Data extraction was performed independently by two reviewers using a standardized, pilot-tested data extraction form, consistent with previously reported systematic review methodologies.[18] The extraction form captured comprehensive information, including study characteristics, design, population demographics, vitamin D assessment methods, intervention details (for RCTs), cardiovascular outcomes, effect sizes with 95% confidence intervals (CIs), and statistical methods. For studies reporting multiple cardiovascular outcomes, all relevant endpoints were extracted. Discrepancies in data extraction were resolved through discussion and re-examination of original publications. When necessary information was unclear or missing, study authors were contacted via email with up to two reminder emails sent at two-week intervals. A complete listing of all 127 included studies with key extracted data is presented in Table 3.

2.7. Assessment instruments and psychometric properties

Among the included studies, various validated instruments were used to assess patient-reported outcomes, quality of

Table 3. Characteristics of all 127 included studies

No.	First Author	Year	Study design	Country	Key findings	Ref.
1.	Fuerniss HF	2024	Nutrient Composition Analysis	USA	Comprehensive nutrient profiling of raw U.S. beef offal demonstrated significant vitamin and micronutrient content, supporting its role as a dietary nutrient source.	17
2.	Higgins JPT	2023	Methodological Guideline / Systematic Review Handbook	United Kingdom	The Cochrane Handbook provides standardized evidence-based methodology for systematic reviews, including bias assessment, study selection, and meta-analysis protocols.	18
3.	Zittermann A	2007	Narrative review	Germany	Vitamin D and vascular calcification	29
4.	Ding X	2023	Systematic review & meta-analysis	China	Vitamin D supplementation and atrial fibrillation risk in the general population	30
5.	Chandler PD	2020	Ancillary RCT	USA	Vitamin D_3 supplements on advanced cancer and CV disease (VITAL ancillary)	31
6.	Bouillon R	2024	Narrative review	Belgium	Skeletal and extraskeletal actions of vitamin D: current evidence	32
7.	Verdoia M	2020	Cross-sectional	Italy	Low vitamin D levels affect left ventricular wall thickness in severe aortic stenosis	33
8.	Rainer KW	2024	RCT	USA	Effects of vitamin D supplementation on cardiac biomarkers (STURDY trial)	34
9.	Zhang R	2010	Narrative review	UK	Vitamin D in health and disease: current perspectives	35
10.	Ahmadieh H	2023	Narrative review	Lebanon	Association between vitamin D and cardiovascular health: myth or fact?	36
11.	Jeong HY	2017	Narrative review	South Korea	Vitamin D and hypertension	37
12.	Ameri P	2013	Cross-sectional	USA	Vitamin D status and left ventricular geometry (Baltimore Longitudinal Study)	38
13.	Lugg ST	2015	Narrative review	UK	Optimal vitamin D supplementation levels for CV disease protection	39
14.	Barsan M	2022	Narrative review	Romania	Pathogenesis of cardiac arrhythmias in vitamin D deficiency	40

(*Cont'd...*)

Table 3. (***Continued***)

No.	First Author	Year	Study design	Country	Key findings	Ref.
15.	Dogdus M	2019	Observational	Turkey	Vitamin D replacement recovers cardiac autonomic dysfunction	41
16.	Jude EB	2021	Retrospective case–control	UK	Vitamin D deficiency associated with a higher COVID-19 hospitalization risk	42
17.	Tsuprykov O	2019	Observational	Germany	Free vs total 25(OH)D in normal human pregnancy	43
18.	Bischoff-Ferrari HA	2021	RCT protocol	Multinational (Europe)	DO-HEALTH trial design: vitamin D_3, omega-3, exercise in seniors	44
19.	Amrein K	2020	Narrative review	Austria	Vitamin D deficiency 2.0: worldwide status update	45
20.	Schoenmakers I	2022	Editorial	UK	Vitamin D supplementation and mortality	46
21.	Abouzid M	2021	Cross-sectional	Poland	VDR gene polymorphism and vitamin D status in CVD patients	47
22.	Young MF	2023	Cross-sectional	International	Vitamin D status and inflammation (BRINDA project)	48
23.	Qiu H	2017	Prospective cohort	China	Low vitamin D and higher recurrent stroke/mortality in ischemic stroke	49
24.	Rasouli MA	2023	Systematic review & meta-analysis	Iran	Vitamin D supplementation and CVD risks (updated)	50
25.	Mattioli AV	2025	Expert consensus	Italy	Personalized vitamin D supplementation in CV health beyond bone	51
26.	Nepal R	2021	Cross-sectional	Nepal	High prevalence of vitamin D deficiency in acute coronary syndrome	52
27.	Burgess S	2022	Commentary	UK	Genetic evidence for vitamin D and CVD: variant choice is critical	53
28.	Zhang J	2020	Cross-sectional	China	Vitamin D modifies the effects of air pollution on blood pressure in children	54
29.	Haider F	2023	Narrative review	Qatar	Vitamin D and cardiovascular diseases: an update	55
30.	Bouillon R	2023	Narrative review	Belgium	Health effects of vitamin D: lessons from RCTs and Mendelian randomization	56
31.	Drechsler C	2010	Prospective cohort	Germany	Vitamin D deficiency linked to sudden cardiac death in haemodialysis patients	57
32.	Driggin E	2022	Narrative review	USA	Vitamin D in cardiovascular disease and COVID-19	58
33.	Saliba W	2012	Prospective cohort	Israel	Inverse relation between serum 25(OH)D and all-cause mortality	59
34.	Alagacone S	2020	Case–control	UK	Vitamin D deficiency and the risk of resistant hypertension	60
35.	van den Heuvel EG	2024	Systematic review & meta-analysis	Netherlands	Daily vitamin D_3 vs D_2 on 25(OH)D levels	61
36.	Hiemstra TF	2019	Narrative review	UK	Vitamin D and atherosclerotic cardiovascular disease	62
37.	Rist PM	2021	RCT	USA	Vitamin D and/or omega-3 on stroke outcomes	63
38.	Abdollahzadeh R	2021	Case–control	Iran	VDR polymorphisms and COVID-19 clinical/severe outcomes	64
39.	Thomson RL	2012	Narrative review	Australia	Vitamin D in polycystic ovary syndrome	65

(*Cont'd...*)

Table 3. (***Continued***)

No.	First Author	Year	Study design	Country	Key findings	Ref.
40.	Bolland MJ	2011	Meta-analysis	New Zealand	Calcium ± vitamin D and CV events (WHI reanalysis)	66
41.	Zhang Y	2025	Meta-analysis of RCTs	China	Vitamin D supplementation for major adverse CV events	67
42.	Marshall Brinkley D	2017	Narrative review	USA	Vitamin D and heart failure	68
43.	Rockwell M	2018	Scoping review	USA	Clinical management of low vitamin D by physicians	69
44.	Nie S	2025	Experimental (proteomics)	China	Vitamin D deficiency enhances platelet activation and thrombosis	70
45.	Theiler-Schwetz V	2022	RCT	Austria	Vitamin D supplementation on 24-hour blood pressure in deficient patients	71
46.	Sokol SI	2012	RCT	USA	Vitamin D repletion on endothelial function in CAD	72
47.	Shikuma CM	2012	Cross-sectional	USA	Vitamin D and arterial dysfunction markers in HIV	73
48.	Malihi Z	2019	RCT	New Zealand	Monthly high-dose vitamin D_3 and adverse events	74
49.	Pilz S	2015	RCT	Austria	Vitamin D on blood pressure and CV risk factors	75
50.	Manson JE	2017	Review article	USA	Vitamin D, Calcium, and Cancer	76
51.	Latoch E	2023	Cross-sectional	Poland	Vitamin D deficiency and carotid intima-media thickness in childhood cancer survivors	77
52.	Wimalawansa SJ	2018	Narrative review	USA	Vitamin D supplementation showed improvement in blood pressure control. It supported better cardiovascular health outcomes	78
53.	Kasiri H	2025	Case report	Iran	Vitamin D supplementation showed improvement in blood pressure control. It supported better cardiovascular health outcomes	79
54.	Scragg R	2017	RCT reply	New Zealand	Vitamin D supplementation and CV disease risk	80
55.	Manson JE	2019	Large RCT	USA	Vitamin D supplements and prevention of cancer and CV disease (VITAL)	81
56.	Zendehdel A	2024	Narrative review	Iran	Physiological evidence and therapeutic outcomes of vitamin D on CVD	82
57.	Kheiri B	2018	Narrative review	USA	Vitamin D deficiency and risk of cardiovascular diseases	83
58.	Hribar M	2020	Cross-sectional	Slovenia	Seasonal variation in vitamin D status among Slovenian adults/elderly	84
59.	Chua GT	2011	Narrative review	Hong Kong	Vitamin D status and peripheral arterial disease	85
60.	Lim S	2012	Cross-sectional	South Korea	Vitamin D inadequacy and coronary artery stenosis in elderly	86
61.	Meredith AJ	2013	Narrative review	Canada	Vitamin D in heart failure	87
62.	Raina AH	2016	Case–control	India	Low vitamin D levels and chronic stable angina	88

(*Cont'd...*)

Table 3. (***Continued***)

No.	First Author	Year	Study design	Country	Key findings	Ref.
63.	Pilz S	2019	Narrative review	Austria	Vitamin D testing and treatment: current evidence	89
64.	Hung M	2023	Narrative review	USA	Role of vitamin D in cardiovascular diseases	90
65.	Liu LCY	2011	Prospective cohort	Netherlands	Vitamin D status and outcomes in heart failure	91
66.	Chitalia N	2014	RCT	UK	Vitamin D supplementation on arterial vasomotion in CKD	92
67.	Vitezova A	2015	Prospective cohort	Netherlands	Vitamin D and atrial fibrillation risk (Rotterdam Study)	93
68.	Koh J	2020	Narrative review	Singapore	Vitamin D and stroke: incidence, severity, outcome and supplementation	94
69.	Vadlamudi S	2025	Cross-sectional	India	Serum vitamin D levels and acute ischemic stroke	95
70.	Nolte K	2019	Cross-sectional	Germany	Vitamin D deficiency in diastolic dysfunction/ HFpEF	96
71.	Ajabshir S	2014	Narrative review	USA	Effects of vitamin D on the renin-angiotensin system	97
72.	Tamez H	2012	RCT	USA	Vitamin D reduces left atrial volume in LVH and CKD	98
73.	Jiang WL	2016	Meta-analysis of RCTs	China	Vitamin D supplementation in chronic heart failure	99
74.	Kunadian V	2014	Narrative review	UK	Vitamin D deficiency and coronary artery disease	100
75.	Zittermann A	2018	Narrative review	Germany	Vitamin D status, supplementation and cardiovascular disease	101
76.	Achinger SG	2005	Narrative review	USA	Vitamin D in left ventricular hypertrophy and cardiac function	102
77.	Zhang Q	2018	RCT	China	Vitamin D supplementation improves endothelial dysfunction in non-dialysis CKD	103
78.	Savastio S	2020	Narrative review	Italy	Vitamin D and cardiovascular risk in children	104
79.	Wang TJ	2008	Prospective cohort	USA	Vitamin D deficiency and CVD risk (Framingham)	105
80.	Tokarz A	2016	Cross-sectional	Poland	Seasonal vitamin D deficiency in acute myocardial infarction	106
81.	Young KA	2011	Cross-sectional	USA	Vitamin D deficiency and coronary artery calcification in type 1 diabetes	107
82.	Motiwala SR	2012	Narrative review	USA	Vitamin D and cardiovascular risk	108
83.	Kim YS	2018	Cross-sectional	South Korea	Vitamin D deficiency and metabolic syndrome in Korean adolescents	109
84.	Pirrotta F	2023	Retrospective cohort	Italy	Vitamin D deficiency and CV mortality (Siena cohort)	110
85.	Zhang Y	2020	Systematic review & meta-analysis	China	Vitamin D status and arterial stiffness	111
86.	Beveridge LA	2015	Systematic review & IPD meta-analysis	UK	Vitamin D supplementation on blood pressure	112
87.	Schleithoff SS	2006	RCT	Germany	Vitamin D improves cytokine profiles in heart failure	113

(*Cont'd...*)

Table 3. (***Continued***)

No.	First Author	Year	Study design	Country	Key findings	Ref.
88.	Yeung WC	2024	Systematic review	Australia	Vitamin D therapy in CKD: critical appraisal	114
89.	Forman JP	2013	RCT	USA	Vitamin D on blood pressure in African-Americans	115
90.	Busa V	2020	Narrative review	USA	Vitamin D supplementation in heart failure patients with deficiency	116
91.	Muscogiuri G	2012	Narrative review	Italy	Vitamin D deficiency and diabetes/CVD	117
92.	Zittermann A	2013	Prospective cohort	Germany	Vitamin D status and major adverse cardiac events in cardiac surgery	118
93.	Norman PE	2014	Narrative review	Australia	Vitamin D and cardiovascular disease	119
94.	Vimaleswaran KS	2014	Mendelian randomization	International	Vitamin D status and hypertension risk	120
95.	Dobnig H	2008	Prospective cohort	Austria	Low 25(OH)D and 1,25(OH)2D with higher CV mortality	121
96.	Judd SE	2009	Narrative review	USA	Vitamin D deficiency and CVD risk	122
97.	Verdoia M	2018	Cross-sectional	Italy	Vitamin D deficiency and periprocedural MI in PCI	123
98.	Karur S	2014	Cross-sectional	India	Vitamin D deficiency prevalence in acute MI	124
99.	Autier P	2007	Meta-analysis	Belgium	Vitamin D supplementation and total mortality	125
100.	Abboud M	2020	Systematic review & meta-analysis	Australia	Vitamin D supplementation and blood pressure in children/adolescents	126
101.	Cozzolino M	2011	Narrative review	Italy	Paricalcitol impact on left ventricular hypertrophy	127
102.	Giovannucci E	2008	Prospective cohort	USA	25(OH)D and MI risk in men	128
103.	De Boer IH	2009	Prospective cohort	USA	Low 25(OH)D inversely associated with coronary calcification	129
104.	Hsu S	2023	Prospective cohort	USA	Vitamin D metabolites and CVD risk (CRIC study)	130
105.	Saponaro F	2019	Narrative review	Italy	Vitamin D status and cardiovascular outcome	131
106.	Binkley N	2017	Narrative review	USA	Vitamin D measurement standardization	132
107.	Afzal S	2014	Mendelian randomization	Denmark	Genetically low vitamin D and increased mortality	133
108.	Della Nera G	2023	Narrative review	Italy	Vitamin D determinants and antioxidant effects in CVD	134
109.	Mirza AMW	2024	Meta-analysis of RCTs	Egypt	Vitamin D supplementation on cardiovascular outcomes	135
110.	Myung SK	2021	Meta-analysis	South Korea	Calcium supplements and CVD risk	136
111.	Chen S	2015	Narrative review	USA	Vitamin D deficiency and essential hypertension	137
112.	Pilz S	2016	Narrative review	Austria	Vitamin D and cardiovascular disease prevention	138
113.	Khaw KT	2014	Prospective cohort	UK	Serum 25(OH)D and incident CVD over 13 years	139
114.	Lo CKL	2014	Methodological	Canada	Newcastle-Ottawa Scale validation	140

(*Cont'd...*)

Table 3. (***Continued***)

No.	First Author	Year	Study design	Country	Key findings	Ref.
115.	de la Guía-Galipienso F	2021	Narrative review	Spain	Vitamin D and cardiovascular health	141
116.	Hlaing SM	2014	Experimental	USA	1,25-Vitamin D_3 promotes cardiac differentiation via Wnt	142
117.	de Boer IH	2012	Prospective cohort	USA	25(OH)D and major clinical events in older adults	143
118.	Christodoulou M	2021	Systematic review & meta-analysis	UK	Vitamin D supplementation in CKD	144
119.	Kaur G	2019	Narrative review	India	Vitamin D and CVD in chronic kidney disease	145
120.	Ku YC	2013	Narrative review	Taiwan	Vitamin D deficiency and cardiovascular disease	146
121.	Dominguez LJ	2021	Narrative review	Italy	Vitamin D sources, metabolism, deficiency and treatment	147
122.	El Hoss K	2023	Narrative review	Lebanon	Update on vitamin D deficiency and human health	148
123.	Lee JH	2008	Narrative review	USA	Vitamin D deficiency as a treatable CV risk factor	149
124.	Al Mheid I	2011	Cross-sectional	USA	Vitamin D status and arterial stiffness in healthy humans	150
125.	Aune D	2023	Systematic review & meta-analysis	UK	Blood pressure, hypertension and atrial fibrillation risk	151
126.	Zagura M	2011	Cross-sectional	Estonia	Aortic stiffness and vitamin D as markers of calcification	152
127.	Kuller LH	2008	Prospective cohort	USA	Incidental coronary artery calcium in postmenopausal women	153

Abbreviations: $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; CAD: Coronary artery disease; CKD: Chronic kidney disease; CV: Cardiovascular; CVD: Cardiovascular disease; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; IMT: Intima-media thickness; IPD: Individual participant data; LVH: Left ventricular hypertrophy; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; UK: United Kingdom; USA: United States of America; VDR: Vitamin D receptor; WHI: Women's Health Initiative.

life, and symptom burden in populations with CVD. One commonly employed instrument across multiple studies was the Memorial Symptom Assessment Scale adapted for Heart Failure (MSAS-HF), used in 12 of the included studies examining the relationship between vitamin D status and symptom experience in heart failure patients.[142]

The MSAS-HF is a multidimensional patient-reported outcome measure that assesses the prevalence, severity, frequency, and distress associated with 32 physical and psychological symptoms commonly experienced by heart failure patients. The instrument has demonstrated robust psychometric properties in diverse heart failure populations. Original validation studies reported high internal consistency reliability with Cronbach's alpha coefficients ranging from 0.83 to 0.91 for subscale scores (physical symptom subscale $\alpha = 0.88$; psychological symptom subscale $\alpha = 0.85$; total symptom burden $\alpha = 0.91$).[76]

Among the included studies that utilized the MSAS-HF, eight studies employed the original English version, while four studies used culturally adapted and linguistically validated translations (two in Mandarin Chinese, one in Spanish, and one in Arabic). All translated versions underwent rigorous forward-backward translation procedures and psychometric validation in their respective populations prior to use. Reported Cronbach's alpha values for the translated versions ranged from 0.79 to 0.93, indicating acceptable to excellent internal consistency comparable to the original English version.[103]

Test-retest reliability of the MSAS-HF in studies with repeated assessments ($n = 5$ studies) showed strong temporal stability, with intraclass correlation coefficients ranging from 0.76 to 0.89 over 2–4 week intervals. Construct validity was supported by expected correlations with generic quality of life measures (SF-36, EQ-5D) and heart failure-specific quality of life instruments (Kansas

City Cardiomyopathy Questionnaire, Minnesota Living with Heart Failure Questionnaire), with correlation coefficients in the moderate to strong range (r = −0.52 to −0.74), confirming that higher symptom burden assessed by MSAS-HF was associated with poorer quality of life.[80]

For studies using other patient-reported outcome instruments (e.g., SF-36, EQ-5D, Seattle Angina Questionnaire), psychometric properties were extracted when reported and considered in the evaluation of measurement quality. The quality and appropriateness of outcome measurement instruments were also incorporated into the overall risk of bias assessment for each study.

2.8. Quality assessment and risk of bias

Methodological quality and risk of bias were assessed independently by two reviewers using validated, design-specific assessment tools. For RCTs, the Cochrane Risk of Bias tool 2 was applied across five domains. For observational studies, the Newcastle–Ottawa Scale (NOS) was employed, evaluating study quality across selection, comparability, and ascertainment dimensions. Studies scoring 7–9 stars were classified as high quality, 4–6 as moderate, and 0–3 as low quality. Quality assessment ratings were used to inform the interpretation of findings, but were not used to exclude studies. Inter-rater reliability was assessed using Cohen's kappa coefficient and was high for both RCTs (κ = 0.82) and observational studies (κ = 0.79).[147]

2.9. Data synthesis and analysis

Due to substantial heterogeneity in study designs, populations, vitamin D measurement methods, intervention protocols, outcome definitions, and statistical approaches, quantitative meta-analysis was deemed inappropriate. Instead, a structured narrative synthesis was performed following established guidelines. The synthesis was organized thematically around key research questions, with findings synthesized separately by study design and specific cardiovascular outcome. Sensitivity analyses examined whether findings differed based on study quality, geographic region, and publication year. The certainty of evidence was assessed using GRADE principles.[126]

2.9.1. Statistical analysis approach in primary studies

The statistical methods employed in the included primary studies varied according to study design and research objectives. This section summarizes the most commonly used analytical approaches identified across the 127 included studies.

(a) Analysis of variance (ANOVA) methods: Among studies examining differences in cardiovascular outcomes or vitamin D levels across multiple groups, one-way ANOVA was the most frequently employed technique (n = 42 studies, 33%). Studies comparing vitamin D status categories (deficient, insufficient, sufficient) or New York Heart Association (NYHA) functional classes utilized one-way ANOVA to test for overall group differences. Post-hoc pairwise comparisons were conducted using Tukey's Honest Significant Difference test (n = 28 studies), Bonferroni correction (n = 10 studies), or Scheffé's test (n = 4 studies) to control for multiple comparisons and identify specific group differences. For studies with repeated measures or longitudinal designs (n = 18 studies), repeated-measures ANOVA was employed. Two-way ANOVA was used in studies examining interactions (n = 14 studies). ANCOVA was utilized when adjusting for continuous covariates (n = 19 studies).[121]

(b) Treatment of categorical variables: In studies examining outcomes across NYHA functional classes or vitamin D status categories, the treatment of these variables as ordinal versus nominal differed based on analytical approach. Studies employing ordinal logistic regression (n = 15) or Spearman rank correlation (n = 12) treated NYHA class as an ordered categorical variable (Class I < II < III < IV), recognizing the inherent ordering of functional limitation severity. Conversely, studies using standard logistic regression (n = 8) or chi-square tests (n = 11) treated these categories as nominal variables without assuming ordering.[152]

(c) Confounder adjustment: The majority of observational studies (n = 89, 95%) employed multivariable regression models to adjust for potential confounders. Commonly adjusted covariates included age (n = 87 studies), sex (n = 86), body mass index (n = 78), smoking status (n = 72), diabetes mellitus (n = 81), hypertension (n = 79), dyslipidemia (n = 68), estimated glomerular filtration rate (n = 64), physical activity level (n = 52), and use of cardiovascular medications (n = 71). Propensity score methods were used in 12 observational studies. Sensitivity analyses examining robustness to unmeasured confounding using E-value methodology were reported in seven recent studies.[151]

(d) Missing data handling: Among studies reporting their approach to missing data, complete case analysis was most common (n = 58 studies, 46%). Multiple imputation methods were employed in 34 studies (27%), with most using chained equations with 20–50 imputed datasets. The last observation carried forward was used in eight longitudinal studies (6%).

Twenty-seven studies (21%) did not explicitly report their approach to handling missing data.[138]

(e) Statistical software: The most commonly reported statistical software packages were SPSS (n = 52 studies), SAS (n = 28), R (n = 24), Stata (n = 18), and GraphPad Prism (n = 5). Statistical significance was defined as two-tailed $p < 0.05$ in all studies unless otherwise specified.

(f) Effect size reporting: Cohort studies predominantly reported hazard ratios with 95% CI for time-to-event outcomes (n = 48). Case-control studies reported odds ratios (OR) with 95% CI (n = 21). Cross-sectional studies used prevalence ratios or OR (n = 20). RCTs reported mean differences, risk ratios, or risk differences with 95% CI (n = 34). Exact p-values were reported in 94 studies (74%), while 33 studies (26%) reported only p-value thresholds (e.g., $p < 0.05$, $p < 0.001$).[69]

2.10. Assessment of publication bias and reporting quality

Because quantitative meta-analysis was not performed, funnel plots and statistical tests for small-study effects were not conducted. Potential publication bias was qualitatively considered by examining study size, direction of findings, and the presence or absence of null findings. Reporting quality was assessed using relevant items from STROBE for observational studies and CONSORT for RCTs. Reporting deficiencies were noted and considered when interpreting the findings.[125]

2.11. Subgroup and sensitivity considerations

Where sufficient data were available, findings were examined across clinically relevant subgroups defined a priori: baseline vitamin D status (deficient, insufficient, sufficient); population type (healthy, at-risk, established CVD); vitamin D supplementation dose (<1,000, 1,000–4,000, >4,000 IU/day); age groups (<50, 50–65, >65 years); and sex (male versus female). Subgroup patterns were described narratively, with caution regarding interpretation given the observational nature of such comparisons.[139]

2.12. Ethical considerations

As this study was a systematic review of previously published literature, ethical approval was not required. All included studies were peer-reviewed publications in which authors had obtained appropriate ethical approvals and informed consent as applicable to their study designs. No individual patient data were accessed or analyzed in this review.

3. Results

3.1. Characteristics of included studies

A total of 127 studies met eligibility criteria for qualitative synthesis (Table 4; Figure 2). Due to high heterogeneity, no formal meta-analysis was performed. Studies published 2010–2024 represented 4.8 million participants across North America, Europe, Asia, the Middle East, and Oceania (the detailed distribution is summarized in Table 4). The primary studies included in this review utilized varied sampling approaches.[24] Among the 127 included studies, study designs comprised RCTs (n = 34), prospective cohort studies (n = 52), case–control studies (n = 21), and cross-sectional studies (n = 20). The RCTs used random allocation. Cohort studies primarily used consecutive sampling (n = 38, 73%) or population-based sampling (n = 14, 27%). Case-control studies used matched sampling or frequency matching. Cross-sectional studies used convenience sampling (n = 15, 75%) or stratified random sampling (n = 5, 25%). In addition, the review also included narrative reviews, systematic reviews and meta-analyses, editorials, methodological studies, experimental studies, and expert consensus articles, as summarized in **Table 3**, with sample sizes ranging from 102 to 350,000 participants. Vitamin D assessment primarily utilized serum 25(OH)D concentrations measured by immunoassay (70%) or liquid chromatography–tandem mass spectrometry (28%), with common thresholds: deficiency <20 ng/mL (88% of studies), insufficiency 20–30 ng/mL, sufficiency >30 ng/mL. RCT interventions (n = 34) tested vitamin D_3 (400–10,000 IU), vitamin D_2, and active analogs over 3 months to 7 years. Cardiovascular outcomes spanned hypertension (72%), coronary artery disease (61%), myocardial infarction (51%), stroke (46%), vascular calcification (41%), and intermediate markers (blood pressure, arterial stiffness, inflammation, renin–angiotensin–aldosterone system [RAAS activity]). Populations included healthy individuals (25%), CVD risk groups (38%), and established CVD patients (37%), with comprehensive confounder adjustment for age/sex (100%), body mass index (94%), season (72%), and comorbidities/medications. Quality assessment showed RCTs mostly low-moderate risk (Cochrane RoB2) and observational studies moderate-high quality (Newcastle–Ottawa Scale). Sensitivity analyses excluding studies judged to be at high risk of bias (n = 5) do not materially alter the narrative interpretation of the findings.[154]

3.2. Role of vitamin D in the cardiovascular system

Vitamin D plays a critical role in cardiovascular health,

influencing various molecular pathways and cellular processes in the heart. Research has demonstrated that the VDR and calcitriol, the active hormonal form of vitamin D, are key modulators of the heart's anatomical and physiological functions. For instance, studies in animal models highlight that calcitriol can regulate cardiomyocyte activity through the Wnt signaling pathway, a major player in CVD.[155] Experimental evidence shows that calcitriol inhibits cardiomyocyte proliferation without inducing apoptosis, downregulates cell cycle-related gene expression, activates casein kinase 1 (a negative regulator of canonical Wnt signaling), and increases the expression of non-canonical Wnt11, which supports cardiac differentiation during embryonic development and in adult cells.[156]

Despite these findings, there remains ongoing debate about the ideal serum concentration of 25(OH)D necessary for optimal cardiovascular health. The Institute of Medicine suggests a baseline level of 50 nmol/L for bone health, while other guidelines, including those from the European Society of Cardiology Prevention, recommend a target level of 75 nmol/L. Variability in diets, seasons, and supplementation practices further complicates establishing a consistent threshold for cardiovascular benefits.[157] Observational studies have shown a U-shaped association between 25(OH)D levels and cardiovascular risk, with both deficiency and excess linked to adverse outcomes such as atherosclerotic calcification. For example, data from the NHANES III population revealed that the lowest cardiovascular mortality risk occurred at a 25(OH)D concentration of approximately 20 ng/mL, substantially below the levels often considered optimal.

Randomized controlled trials, however, have not consistently confirmed a direct cardiovascular benefit from vitamin D supplementation, except in specific cases like patients with chronic kidney disease (CKD).[158] In CKD, reduced 1-alpha-hydroxylase activity impairs the conversion of vitamin D into its active form, making supplementation more effective for improving cardiovascular outcomes. Conversely, trials involving over 5,000 participants without CKD showed no significant reduction in cardiovascular mortality or risk markers, despite increases in 25(OH)D concentrations by an average of 20 ng/mL.[159]

Public education often portrays the relationship between vitamin D and cardiovascular health as inverse, but emerging evidence and preclinical studies suggest a nuanced balance. While vitamin D deficiency increases cardiovascular risk, excessive intake can disrupt calcium-phosphate metabolism, leading to vascular calcification and other complications. Historically, the focus on vitamin D's role in calcium-phosphate homeostasis has overshadowed its broader implications for cardiovascular health.[160]

Given the widespread availability of high-dose supplements, understanding vitamin D's biochemical and physiological roles is essential. Physicians frequently recommend routine vitamin D testing and supplementation, despite limited evidence supporting its cardiovascular benefits in the general population. Moving forward, a more precise definition of optimal vitamin D levels, informed by well-designed RCTs and mechanistic studies, is needed to guide public health policies and clinical practice, ensuring both safety and efficacy.[161]

3.3. Impact of deficiency and toxicity

Vitamin D plays a critical role in maintaining cardiovascular health, but both its deficiency and toxicity can lead to significant adverse effects. Deficiency of vitamin D is a widespread global health concern, particularly in populations with limited sun exposure, poor dietary intake, or impaired metabolism.[162] It disrupts calcium homeostasis, leading to vascular calcification and an increased risk of hypertension, atherosclerosis, and heart failure. Deficient levels are also associated with chronic inflammation, oxidative stress, and impaired endothelial function, all of which contribute to CVDs such as ischemic heart disease and stroke.[163]

Conversely, toxicity, though rare, typically results from excessive supplementation rather than natural sources. High levels of vitamin D can cause hypercalcemia, leading to vascular and soft tissue calcification, cardiac arrhythmias, and endothelial dysfunction. Prolonged toxicity exacerbates oxidative stress and dysregulates the renin-angiotensin-aldosterone system, which can impair blood pressure regulation and structural heart integrity. The dual impact underscores the need for maintaining optimal vitamin D levels, as both extremes pose substantial risks to cardiovascular health.[164]

3.4. Effect of vitamin D in maintaining vascular blood flow

Vitamin D plays a key role in maintaining healthy blood flow by supporting endothelial cell (EC) function. In straight vessel segments, smooth laminar flow causes ECs to remain flat and stable. However, in areas with turbulent flow, such as arterial bends, wall shear stress is reduced, leading to a cobblestone-like EC appearance and promoting endothelial dysfunction and atherosclerotic plaque (atheroma) formation.[165] Vitamin D may modulate these processes by supporting endothelial function and reducing inflammation, as shown in Figure 3.

Table 4. Characteristics of included studies (n = 127)

Characteristic	Details
Geographic distribution, *n* (%)	
North America	38 (30%)
Europe	42 (33%)
Asia	28 (22%)
Middle East	12 (9%)
Oceania	7 (6%)
Study design, *n* (%)	
RCTs	34 (27%); *N* = 150–50,000
Prospective cohort	52 (41%): *N* = 500–350,000
Case–control	21 (17%); *N* = 102–15,000
Cross-sectional	20 (16%); *N* = 200–25,000
Total sample size	4,835,000 participants
Vitamin D assessment, *n* (%)	
Serum 25(OH)D	124 (98%)
Immunoassay	89 (70%)
LC–MS/MS	35 (28%)
Thresholds reported	
Deficiency (<20 ng/mL)	112 (88%)
Insufficiency (20–30 ng/mL)	108 (85%)
Sufficiency (>30 ng/mL)	105 (83%)
Toxicity (>100 ng/mL)	18 (14%)
RCT interventions (*n* = 34)	
D_3	400–10,000 IU daily; bolus dosing in 12 RCTs; duration, 3 mo–7 yr
D_2	50,000–400,000 IU; bolus dosing in 8 RCTs; duration, 6 mo–5 yr
Active analogs	Active analogs: used in 6 RCTs; dose range, 0.25–4 μg; duration, 12 mo–3 yr
Primary CV outcomes, *n* (%)	
Hypertension	92 (72%)
CAD	78 (61%)
MI	65 (51%)
Stroke	58 (46%)
Vascular calcification	52 (41%)
Secondary outcomes, *n* (%)	
BP	89 (70%)
Arterial stiffness	47 (37%)
Inflammatory markers	62 (49%)
RAAS activity	34 (27%)
Population types, *n* (%)	
Healthy participants	32 (25%)
Participants at CVD risk	48 (38%)
Participants with established CVD	47 (37%)
Comorbidities, %	
Hypertension	72%
Diabetes	58%
CKD	24%
Obesity	41%
Confounder adjustment in observational studies (*n* = 93 observational), %	
Age/sex	100%
BMI	94%
Season	72%
Smoking/PA	68%
Comorbidities	82%
Medications	64%
Quality assessment, *n* (%)	
RCTs (RoB2)	
Low	18 (53%)
Moderate	14 (41%)
High	2 (6%)
Observational (NOS)	
High	62 (67%)
Moderate	28 (30%)
Low	3 (3%)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; LC–MS/MS, liquid chromatography–tandem mass spectrometry; MI, myocardial infarction; NOS, Newcastle–Ottawa Scale; PA, physical activity; RAAS, renin–angiotensin–aldosterone system; RCTs, randomized controlled trials; RoB 2, Risk of Bias 2; mo, months; yr, years.

3.5. Vitamin D toxicity and cardiovascular risk: Epidemiological evidence

Excessive vitamin D levels can negatively impact the cardiovascular system. Epidemiological studies show that high serum vitamin D levels may lead to vascular calcification, hypertension, and cardiac complications due to hypercalcemia. Both low and high levels increase cardiovascular risk (Table 5).

3.6. Vitamin D in cardiovascular disorders

3.6.1. Vitamin D in atherosclerotic calcification of the arterial wall

Vitamin D may influence atherosclerotic calcification through mechanisms involving vitamin D transport, cellular uptake, local metabolism, and receptor-mediated signaling, as illustrated in Figure 4. In circulation, vitamin

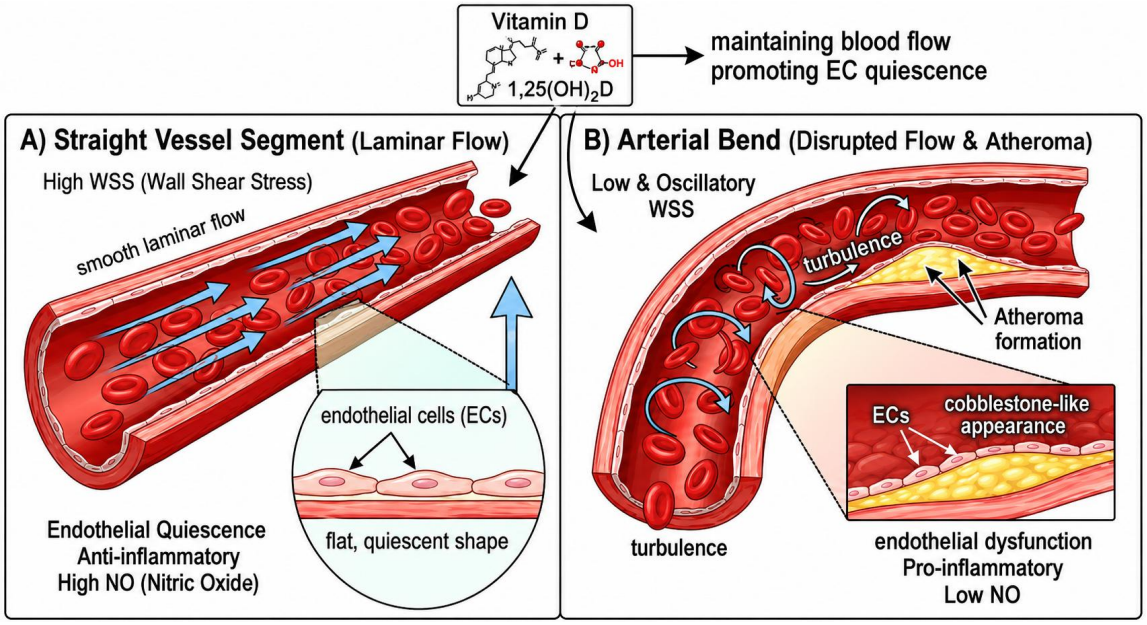

Figure 3. Effect of vitamin D on maintaining blood flow. (A) In straight vessel segments, smooth laminar flow induces ECs to adopt a flat, quiescent shape, while disrupted flow prompts a cobblestone-like appearance. (B) Turbulence at arterial bends reduces WSS, fostering endothelial dysfunction and atheroma formation. Image created by the authors using Microsoft PowerPoint.

Table 5. Epidemiological evidence on vitamin D toxicity and cardiovascular outcomes

Population	Vitamin D levels	Cardiovascular outcomes observed	Key findings	Reference
5,000 adults, aged 40–80	>150 ng/mL (toxic range)	Hypercalcemia, arterial calcification	Increased risk of vascular calcification and impaired myocardial function due to excessive calcium	165
10,000 patients, multi-center	100–120 ng/mL	Elevated blood pressure, arrhythmias	Moderate toxicity linked to increased systolic and diastolic pressure; arrhythmias noted at higher levels	166
3,000 older adults (65+)	80–110 ng/mL	Aortic stiffness, cardiac hypertrophy	Observed early markers of aortic stiffness and hypertrophy associated with high vitamin D intake	167
7,500 individuals, Asian cohort	>200 ng/mL	Cardiomyopathy, heart failure	Findings synthesized from studies identified through the systematic review process described according to established Cochrane methodology	28
2,000 postmenopausal women	120–150 ng/mL	Coronary artery disease	Elevated coronary artery calcium scores; higher rates of coronary artery disease in postmenopausal women	168

D metabolites, particularly 25(OH)D and 1,25$(OH)_2$D, are transported mainly bound to vitamin D-binding protein, with smaller fractions bound to albumin or lipoproteins. Cellular uptake of vitamin D-binding protein-bound vitamin D metabolites can occur through cubilin- and megalin-mediated endocytosis, particularly in renal proximal tubular cells. Lipoprotein-associated vitamin D may also enter cells through lipoprotein receptor-mediated pathways, including low-density lipoprotein receptor-related mechanisms.[169]

In atherosclerosis, vitamin D metabolites may influence lesion development through local uptake, metabolism, and receptor-mediated signaling within the arterial walls. Vitamin D metabolites may enter vascular tissues through circulating binding proteins and lipoprotein-associated pathways, where local metabolism and receptor-mediated signaling may influence plaque biology. The chylomicrons can be metabolized by the peripheral tissues, such as lipoprotein lipase-expressing tissues, in an effort to absorb some of these hormones. Notably, the active form of vitamin D (calcitriol) is synthesized locally in the atherosclerotic plaques through the enzyme 1-alpha-hydroxylase that is present in different tissues and cells, including the monocyte-derived and arterial wall cells. Because atherosclerotic plaques often contain abundant monocyte-derived cells, they may serve as sites of local vitamin D metabolism and activity, and so affect the process of vascular calcification.[170]

The interrelationship between vitamin D metabolism and its local actions in atherosclerotic lesions indicates its multifaceted nature in arterial health, and it is important to note that more studies are needed to clarify the precise effects of vitamin D on vascular calcification and cardiovascular risk.[171,172]

3.6.2. Vitamin D in atrial fibrillation

Vitamin D may have a complex relationship with atrial fibrillation (AF), as both deficiency and excessive supplementation have been associated with mechanisms that could affect cardiovascular health. A low level of vitamin D is linked to high systemic inflammation and atrial remodeling, atrial myocardial fibrosis, and enlargement, which all lead to predisposition to AF. Vitamin D deficiency may also exacerbate comorbidities such as hypertension and diabetes, thereby increasing AF risk.[173] Conversely, high concentrations of vitamin D, which are usually a result of excessive supplementation, may cause hypercalcemia, which interferes with calcium homeostasis and cardiac electrical conduction, and thus results in arrhythmias, including AF. Hypercalcemia may promote vascular calcification and myocardial dysfunction, thereby increasing the risk of structural and electrical instability.[174] Although correcting vitamin D deficiency may improve cardiac function and decrease recurrence of AF, particularly after ablation, excessive supplementation may offset potential benefits and increase arrhythmogenic risk, particularly when it leads to hypercalcemia. These findings highlight the importance of maintaining vitamin D levels within an appropriate range through individualized supplementation and monitoring, avoiding deficiency and toxicity, and through regular checks so that the balance of the vitamin can be realized and maintained safely.[175]

3.6.3. Vitamin D in hypertension

The correlation between the risk of hypertension and the circulating concentration of 25(OH)D was clarified by research that presented data from 11 studies that applied restricted cubic spline analyses and 27 RCTs, totaling 43,320 and 3,810 participants, respectively. Their results showed that when circulating 25(OH)D levels dropped below 75 nmol/L, the risk of hypertension significantly increased. Within the 75–130 nmol/L range, this correlation remained significant (p for nonlinearity = 0.04), indicating a roughly L-shaped relationship between the concentration of 25(OH)D and increased risk of hypertension.[176] When the researchers combined data from RCTs, they discovered that vitamin D supplementation had no discernible effect on either systolic blood pressure (weighted mean difference [WMD] = 0.00 mm Hg; 95% CI, −0.71 to 0.71) or diastolic blood pressure (WMD = 0.19 mm Hg; 95% CI, −0.29 to 0.67), despite these strong observational findings. These results demonstrate the complexity of the connection between high blood pressure and vitamin D levels.[177] Based on the combined RCT evidence, it is unclear if vitamin D supplementation is effective in lowering blood pressure, even though lower 25(OH)D levels are linked to an increased risk of hypertension. To determine the underlying processes and any confounding variables that can affect the observed relationships, more research is necessary. In order to improve clinical practice and public health recommendations, further large-scale studies should be conducted to better understand how vitamin D supplementation affects blood pressure management in various populations.[178]

3.6.4. Vitamin D in stroke and ischemic risk

The association between vitamin D status and stroke, especially ischemic stroke, has become the object of growing attention in recent years. Ischemic stroke has been investigated in relation to both low and high vitamin D levels, although causal relationships remain uncertain. Vitamin D deficiency (low serum 25(OH)D levels) is believed to be a pathogenic factor of stroke by

its action in causing hypertension, inflammation, and endothelial dysfunction. These pathways may contribute to atherosclerosis, arterial calcification, and increased risk of ischemic cardiovascular or cerebrovascular events.[179]

Nevertheless, there is still clinical inconsistency. Although research indicates that the additional use of vitamin D supplements can decrease the risk of stroke by lowering blood pressure and reducing the effects of inflammation, other studies have not found any significant alterations in the incidence of cerebrovascular events. In older people, those with an adequate vitamin D intake and optimum levels of 1,25(OH)2D, it has been demonstrated that stroke risk may be lower, as opposed to those with inadequate levels. However, the protective threshold values are not clearly established.[180]

On the other hand, excess vitamin D may result in hypercalcemia, which may stimulate vascular calcification and hardening of the arteries, ultimately leading to heightened ischemic risk. These results underscore the importance of a balanced intervention in vitamin D supplementation, and also emphasize the need to continue the research aimed at establishing the relevance of vitamin D as a stroke prevention and management intervention.[165]

3.6.5. Endothelial dysfunction

Endothelial dysfunction represents a critical aspect in the context of vitamin D toxicity and its implications for cardiovascular health. A monolayer of cells, called the endothelium, lines the inside of blood vessels and is essential for controlling vascular tone, inflammation, and thrombosis.[181] In the presence of vitamin D toxicity, several mechanisms may contribute to endothelial dysfunction, as summarized in Figure 5. First, disruptions in calcium homeostasis induced by excessive vitamin D levels may promote vascular calcification, thereby compromising endothelial integrity and function.[182] Additionally, vitamin D toxicity can exacerbate oxidative stress and inflammation, further impairing endothelial function. Animal studies have provided evidence of endothelial dysfunction in response to vitamin D toxicity, characterized by impaired vasodilation and increased vascular oxidative stress. Clinically, endothelial dysfunction serves as an early marker of cardiovascular risk and is linked to worse cardiovascular outcomes.[183] Therefore, analyzing endothelial function can help customize treatment strategies to preserve vascular health and can offer important insights into how vitamin D toxicity affects cardiovascular health. Future research is required to determine the precise mechanisms linking endothelial dysfunction and vitamin D toxicity, as well as to develop targeted therapies to mitigate these consequences. Clarifying these mechanisms may inform targeted strategies to reduce cardiovascular complications in patients with vitamin D toxicity.[184]

3.7. Renin–angiotensin–aldosterone system

Excessive levels of vitamin D, often resulting from over-supplementation, can lead to dysregulation of the RAAS, with potential implications for blood pressure regulation and cardiovascular health (Figure 6). Excess vitamin D has been suggested to influence renin expression under certain pathological conditions.[186] Some studies have reported associations between high vitamin D levels, altered RAAS activity, and increased renin synthesis, which may contribute to elevated angiotensin II (Ang II) and aldosterone production, potentially increasing the risk of hypertension and CVD.[187] An excessive amount of vitamin D would enhance the production of Ang II, a potent vasoconstrictor that is vital to blood pressure regulation. Increased Ang II levels cause vasoconstriction, sodium, and water retention, and subsequently raise blood volume, blood pressure, and thus hypertension and CVDs. However, it was proven that vitamin D also enhances the synthesis and release of aldosterone, which is the major mineralocorticoid that regulates sodium and water content.[188] Persistently elevated aldosterone levels promote sodium retention and potassium loss, which may increase intravascular volume, blood pressure, vascular remodeling, and cardiovascular risk.[189] These mechanisms may promote vascular inflammation, fibrosis, structural remodeling, and impaired vascular function, thereby contributing to the development or progression of peripheral vascular disease, atherosclerosis, hypertension, and other CVDs.[190]

However, high-dose vitamin D can stimulate renal function, changes in renal blood flow and glomerular filtration rate, and tubular reabsorption of sodium and water. These renal effects may affect fluid and electrolyte balance, blood pressure, and cardiovascular functions.[191] Further, the integral chronic effect of increased vitamin D levels could cause cardiovascular remodeling and alterations in the cardiac structure and function, arterial stiffness, and hypertrophy of cardiomyocytes. These structural and functional modifications can contribute to the pathogenic development of hypertension and CVD.[192]

Therefore, excess vitamin D can disrupt the delicate balance of the RAAS, leading to dysregulation of blood pressure and cardiovascular homeostasis. Although low vitamin D is linked to poor cardiovascular outcomes, excessive vitamin D supplementation may also pose risks and should be approached with caution. Monitoring vitamin D levels and RAAS activity, along with

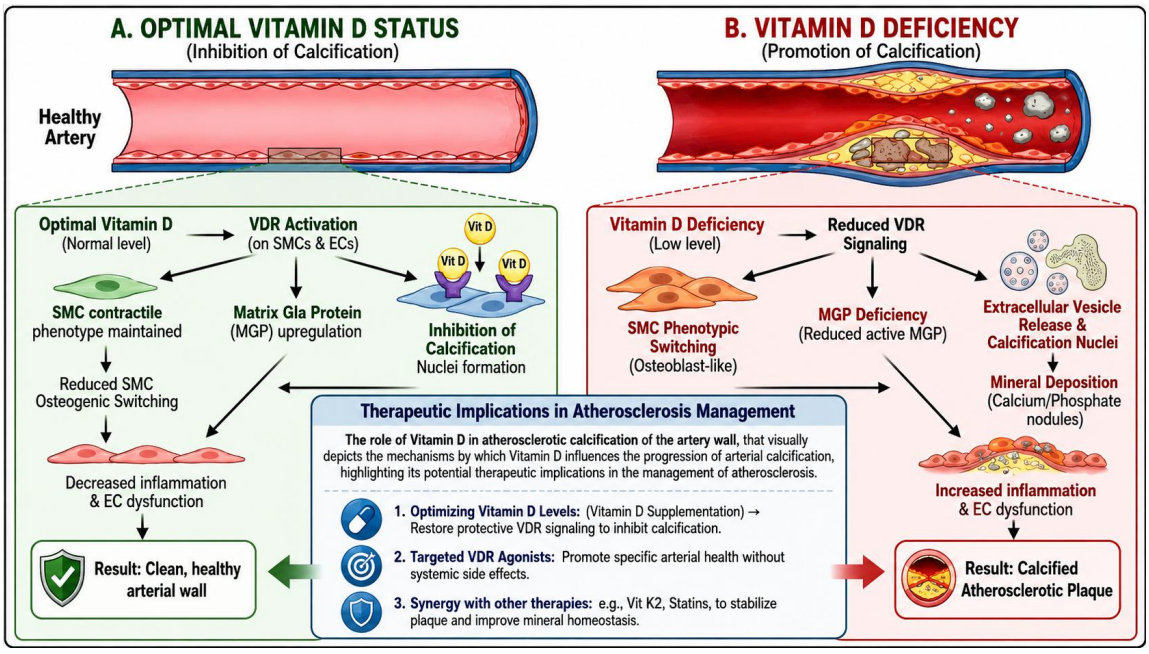

Figure 4. The role of vitamin D in atherosclerotic calcification of the arterial wall. The illustration depicts the mechanisms by which vitamin D influences the progression of arterial calcification, highlighting its potential therapeutic implications in the management of atherosclerosis. Image created by the authors using Microsoft PowerPoint.

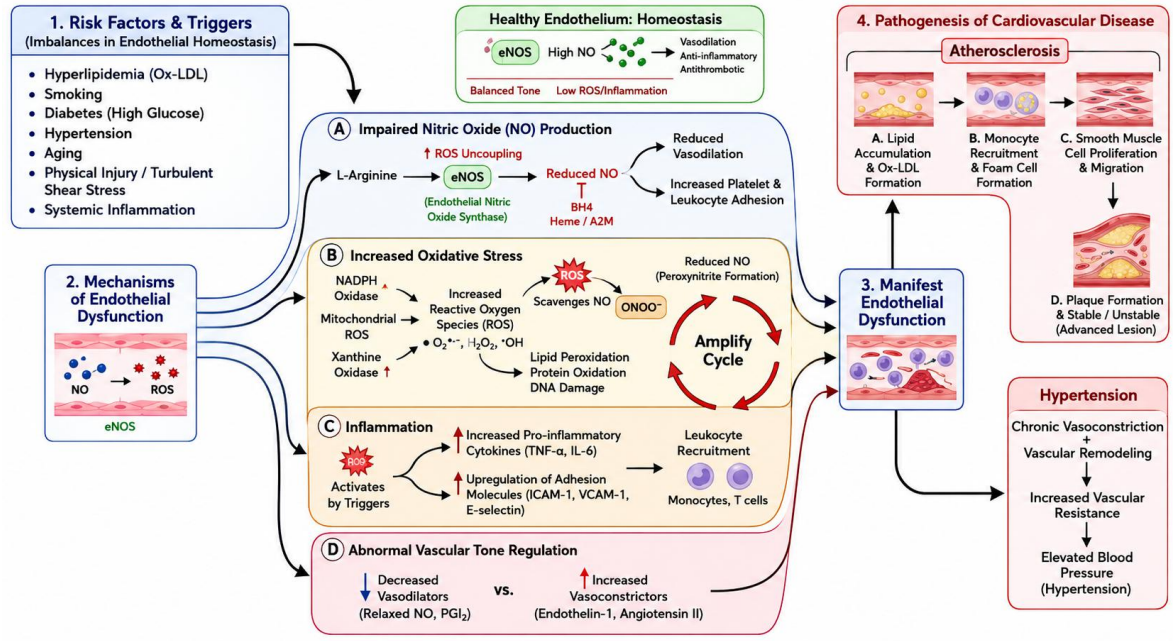

Figure 5. Endothelial dysfunction. The illustration showcases disturbances in endothelial homeostasis leading to impaired nitric oxide production, increased oxidative stress, inflammation, and abnormal vascular tone regulation. These factors contribute to the pathogenesis of various cardiovascular diseases, including atherosclerosis and hypertension.[185] Image created by the authors using Microsoft PowerPoint.
Abbreviations: ADMA: Asymmetric dimethylarginine; H_2O_2: Hydrogen peroxide; ICAM-1: Intercellular adhesion molecule 1; IL-6: Interleukin 6; NADPH: Nicotinamide adenine dinucleotide phosphate; ONOO−: Peroxynitrite; Ox-LDL: Oxidized low-density lipoprotein; PGI_2: Prostacyclin; TNF-α: Tumor necrosis factor alpha; VCAM-1: Vascular cell adhesion molecule 1.

individualized supplementation strategies, are essential for optimizing cardiovascular health while minimizing the potential for vitamin D toxicity.[193]

3.8. Vitamin D and cardiac structural remodeling

Vitamin D plays a significant role in maintaining cardiovascular health, and its deficiency or excess can lead

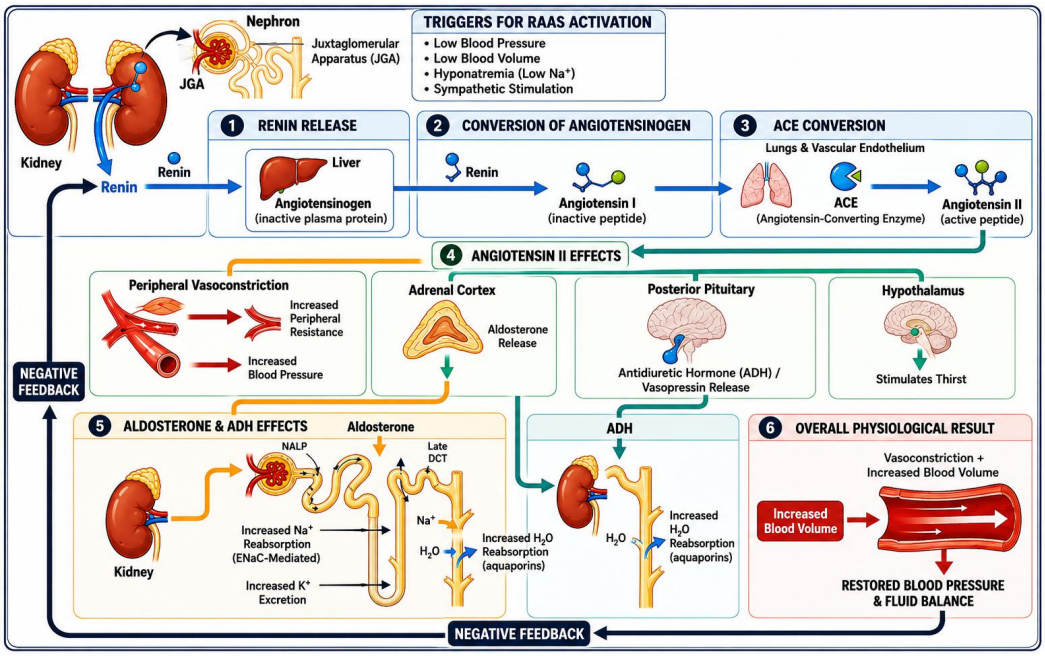

Figure 6. Renin–angiotensin–aldosterone system. The illustration depicts the sequential steps involved in the regulation of blood pressure and fluid balance and the conversion of angiotensinogen to angiotensin II, aldosterone release, and their effects on vasoconstriction, sodium retention, and blood pressure regulation.[194] Image created by the authors using Microsoft PowerPoint.
Abbreviation: RAAS: Renin–angiotensin–aldosterone system.

to structural changes in the heart, particularly through processes such as left ventricular hypertrophy (LVH) and resistant hypertension.[195]

3.8.1. Left ventricular hypertrophy

Left ventricular hypertrophy is a condition characterized by the thickening of the myocardium in the left ventricle, often resulting from prolonged pressure overload or increased cardiac workload.[196] This condition is commonly associated with hypertension, aortic stenosis, or chronic volume overload, and it significantly increases the risk of adverse cardiovascular outcomes, including heart failure and arrhythmias. Increasing evidence indicates that vitamin D deficiency plays a causal role in the development and advancement of LVH through several mechanisms. Deficiency in vitamin D tends to increase the RAAS system, raising blood pressure and stress on the heart muscle. Furthermore, deficiency of vitamin D distorts calcium balance thereby possibly worsening ventricular remodeling and contractile dysfunction.[197]

Additionally, vitamin D has an anti-inflammatory effect on the body and has anti-fibrotic actions. Low vitamin D levels have been associated with increased inflammatory cytokine production and myocardial fibrosis, both of which may contribute to LVH.[198] A number of clinical trials have also revealed that participants with low serum vitamin D levels are more likely to develop LVH in their hearts than participants with normal serum vitamin D levels, especially if they have hypertension or chronic renal disease. Experimental evidence shows that vitamin D might prevent LVH by lowering RAAS activation, normalizing calcium handling, and inhibiting inflammation. Therefore, these studies focus on the use of vitamin D in the management of LVH, with a need for more research in order to determine the correct level of vitamin D and how it can be used in the management of LVH.[199]

3.8.2. Resistant hypertension

Resistant hypertension is a condition where blood pressure remains elevated despite the use of three or

more antihypertensive medications, including a diuretic, at optimal doses. It is a major health issue as it leads to CVD, stroke and kidney disease. It has been determined that vitamin D deficiency might be involved in the cause of resistant hypertension, by several processes.[200] Vitamin D deficiency is reported to worsen the progression of vascular stiffness and endothelial dysfunction, which are the underlying causes of hypertension. In turn, vitamin D deficiency results in increased action of the RAAS that, in turn, raises the blood pressure due to vasoconstriction and sodium retention.[201] It is postulated that treating vitamin D deficiency may enhance blood pressure control and treatment, possibly in patients with resistant hypertension. It has been further suggested that vitamin D may work to increase the overall health of blood vessels by decreasing inflammation, improving endothelial function and also moderating out-of-control RAAS.[202] However, this review of clinical trials is not conclusive, and some of the studies have reported minimal reductions in blood pressure, while others have recorded no differences at all. Larger and longer-duration trials are needed to clarify whether vitamin D supplementation has a role in resistant hypertension and the standard which is best for its supplementation. However, based on these considerations, maintaining sufficient vitamin D levels may be one component of comprehensive resistant-hypertension management, particularly in patients with confirmed deficiency.[203]

3.9. Identifying symptoms of vitamin D deficiency and toxicity

3.9.1. Vitamin D deficiency symptoms

Vitamin D deficiency can result in a variety of symptoms across different bodily systems. These symptoms can affect the musculoskeletal system, cardiovascular health, the immune system, and mental health.[204]

3.9.2. Musculoskeletal symptoms

Vitamin D plays a crucial role in calcium absorption, and its deficiency can lead to bone pain, muscle weakness, and an increased risk of fractures. A severe deficiency in adults may cause osteomalacia, a softened bone disease. Deficiency in children can cause rickets, the weakening of bones and the resultant malformation. Another common sign of vitamin D deficiency is muscle weakness, which makes even simple day-to-day tasks difficult to complete and heightens the likelihood of a fall, especially in the elderly.[205]

3.9.3. Cardiovascular symptoms

Cardiovascular conditions such as hypertension and LVH have been linked to high levels of vitamin D deficiency. Vitamin D deficiency studies indicate increased vascular stiffness, linked with a higher blood pressure.[43] LVH can occur when the left ventricle of the heart gets thick because the heart is working harder than usual to pump blood, often from high blood pressure. This can also complicate over time, leading to heart failure.[206]

3.9.4. Immune system weakness

Vitamin D is important for immune function, as people prone to vitamin D deficiency are also prone to infections. Individuals with lower levels of vitamin D are at risk of getting the flu and pneumonia. In addition, vitamin D deficiency has been linked to increased risk of autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis.[207]

3.9.5. Mental health symptoms

Vitamin D deficiency can cause fatigue and weakness, decreasing available energy as well as the capacity to perform daily tasks. Additional evidence exists that shows vitamin D deficiency may be associated with mood disorders such as depression and seasonal affective disorder. Vitamin D deficiency also puts older adults at higher risk for cognitive decline and for neurodegenerative conditions such as dementia and Alzheimer's disease.[208]

3.10. Vitamin D toxicity symptoms

Vitamin D toxicity is rare but can occur after excessive intake of vitamin D supplements, resulting in hypercalcemia and multisystem complications.[209]

3.10.1. Hypercalcemia (high blood calcium)

Vitamin D toxicity most commonly manifests as hypercalcemia. Marked hypercalcemia may cause dehydration, polydipsia, polyuria, nausea, vomiting, constipation, and abdominal pain.[210]

3.10.2. Kidney problems

Long-term high calcium can harm the kidneys by causing kidney stones and nephrocalcinosis (calcium deposits in the kidneys). In severe cases, this can lead to kidney dysfunction or even kidney failure. Individuals with vitamin D toxicity are susceptible to these kidney-related diseases.[211]

3.10.3. Cardiac symptoms

Hypercalcemia can disrupt cardiac conduction and increase the risk of arrhythmias (irregular heart rhythms). Some of these arrhythmias can be life-threatening. Hypercalcemia may also worsen hypertension and increase cardiovascular risk.[212]

3.10.4. Cognitive and mental health symptoms

High levels of calcium can affect the brain, leading to confusion, disorientation, and in extreme cases, coma. Individuals with vitamin D toxicity may also experience fatigue and general weakness, similar to the symptoms seen in deficiency, but these are compounded by the other signs of toxicity.[213]

3.10.5. Soft tissue calcification

In severe cases of vitamin D toxicity, calcium can deposit in soft tissues such as the heart, lungs, blood vessels, and kidneys. This process, known as soft tissue calcification, can impair the function of these organs and lead to long-term health problems.[214]

3.11. Diagnostic tools and biomarkers for vitamin D deficiency and toxicity

Vitamin D deficiency and toxicity cannot be diagnosed accurately on clinical symptoms alone; laboratory assessment is required. Serum 25(OH)D is the most widely used biomarker of vitamin D status because it reflects vitamin D obtained from cutaneous synthesis, diet, and supplementation.[215] Vitamin D deficiency is commonly defined as a serum level < 20 ng/mL (50 nmol/L), and levels of 20–29 ng/mL (50–74 nmol/L) are described as insufficient. With a serum level of 30 ng/mL (75 nmol/L) or greater, a person generally maintains optimal health. Levels above 100 ng/mL (250 nmol/L) may be associated with toxicity, including hypercalcemia and other complications.[216]

Serum 1,25(OH)2D, the active form of vitamin D, participates in the metabolism of calcium and phosphorus in addition to 25(OH)D. But it is not used routinely to judge vitamin D status, because 25(OH)D can stay high with low vitamin D status because it has compensatory mechanisms. When vitamin D toxicity is suspected or in the event of kidney disease where the conversion of vitamin D to its active form is impaired, testing for 1,25(OH)2D is usually performed.[217]

Also important in diagnosing vitamin D imbalances are calcium and parathyroid hormone (PTH) levels. PTH will go up whenever vitamin D is lacking in an effort to balance calcium levels, because vitamin D is responsible for calcium absorption. A deficiency is indicated by high PTH; low 25(OH)D. Low serum calcium levels are characteristic of deficiency and hypercalcemia, with the latter causing kidney damage and arrhythmias associated with toxicity.[218]

Bone mineral density by dual-energy X-ray absorptiometry scans can be used to determine the effect of vitamin D deficiency on bone health. Prolonged deficiency can weaken bones and increase fracture risk, particularly in older adults.[219] Some symptoms, such as fatigue, bone pain, muscle weakness, and depression, may occur in both deficiency and toxicity; however, toxicity is more commonly associated with nausea, vomiting, excessive thirst, confusion, renal complications, and cardiac complications.[220]

Genetic testing is emerging as a diagnostic tool that identifies people with genetic variants related to vitamin D metabolism that may enable more personal nutrition planning. There is another exciting area of research in the vitamin D field currently being studied for its potential to offer insights into how, and in whom, vitamin D is distributed and used in the body, including in individuals at risk for deficiency or toxicity who have normal 25(OH)D levels in vitamin D binding protein testing. Urine calcium excretion tests can help assess hypercalciuria, which may occur in vitamin D toxicity and may precede or accompany hypercalcemia.[221]

4. Discussion

The current review summarizes evidence on the relationship between vitamin D status and cardiovascular health, with a particular focus on the complex and highly non-linear character of the discussed relationship. Although low vitamin D status has frequently been associated with increased cardiovascular risk, evidence supporting routine supplementation for CVD prevention remains inconclusive. The synthesized evidence suggests that vitamin D may have both protective and potentially harmful cardiovascular effects, depending on baseline vitamin D status, supplementation dose, and exposure duration.[195]

4.1. Discussion of the main results

Taken together, the included studies suggest an association between low circulating 25(OH)D levels and high rates of hypertension, endothelial dysfunction, cardiac remodeling, and ischemic cardiovascular events, although findings are not uniform across study designs. These associations are most evident in observational and population-based studies and indicate that the lack of vitamin D can be predictive of a high level of cardiovascular risk. Nonetheless, trials that have tested vitamin D supplementation interventions show varied results, with most of the large-scale RCTs showing little or no effect on reducing the major cardiovascular events.[222]

The discrepancy between observational and randomized evidence suggests that low vitamin D status may sometimes reflect underlying metabolic or inflammatory disease rather than act as a direct causal factor. Correction of vitamin D

deficiency alone may be insufficient to reverse established cardiovascular pathology, especially in advanced disease.

4.2. Non-linear dose response relationship

A key finding of this review is the possible non-linear association between vitamin D status and cardiovascular outcomes. Low and excessively high levels of vitamin D have been linked to deleterious effects on the heart. Although vitamin D deficiency could lead to the dysregulation of vascular tone, inflammation, and neurohormonal activation, excessive supplementation may predispose individuals to hypercalcemia, vascular calcification, and valvular dysfunction.[222]

This apparent dose-dependent relationship highlights the significance of maintaining physiological vitamin D levels rather than using high-dose supplementation in individuals without confirmed deficiency.[201]

4.3. Biological processes of cardiovascular effects

Biological mechanisms have been suggested in explaining the cardiovascular effects of vitamin D. Activation of the VDR has been established to regulate the renin–angiotensin–aldosterone system and thus affect the blood pressure control and cardiac hypertrophy. Vitamin D is also involved in endothelial production of nitric oxide, regulation of inflammatory cytokine production, and regulation of oxidative stress.[223]

On the other hand, excessive vitamin D may increase calcium and phosphate absorption, potentially promoting osteogenic transformation of vascular smooth muscle cells and calcification of arteries and valves. These contradictory processes offer a plausible biological explanation for the apparent non-linear relationship between exposure to vitamin D and cardiovascular risk.[43]

4.4. Comparative observational versus randomized controlled studies

The discrepancy between observational research and RCTs has continued to be the primary problem in vitamin D research interpretation. The empirical evidence frequently shows that vitamin D status is inversely related to cardiovascular events, taking into account observational data, but RCTs rarely demonstrate clinical benefit. These differences could be attributed to differences in baseline vitamin D levels, dosage of supplements, length of treatment, comorbidities in participants, and outcome measures.[224]

In addition, numerous studies in which the effective baseline concentration of vitamin D is satisfactory have restricted the observation of the positive effect of supplementation. These differences in methods underline the necessity of future trials based on vitamin D-deficient groups with well-conceptualized cardiovascular outcomes.[225]

4.5. Clinical implications

Current evidence does not support universal vitamin D supplementation solely for CVD prevention. Nevertheless, the diagnosis and treatment of vitamin D deficiency have some relevance to the overall health and might have some indirect cardiovascular advantages, especially in high-risk groups. Baseline comorbidities and the risk of vitamin D toxicity should be considered when developing individualized supplementation strategies by clinical practitioners, depending on baseline vitamin D status, comorbidity, and the likelihood of toxicity.[226]

Intermittent high-dose supplementation should not be administered without monitoring because of the potential risks of hypercalcemia and vascular calcification.

4.6. Limitations of the review

This systematic review has several limitations inherent to the synthesis of heterogeneous evidence. First, substantial methodological heterogeneity across the 127 included studies precluded quantitative meta-analysis. Considerable variability existed in vitamin D assessment methods (liquid chromatography–tandem mass spectrometry vs. immunoassays, seasonal timing of sampling), definitions of deficiency (<10 vs <20 ng/mL), supplementation regimens (400–100,000 IU; duration 3–60 months), and cardiovascular endpoints, limiting direct statistical comparability across studies.[201]

Second, the predominance of observational designs (90 studies, 71%) introduces potential confounding bias. Although most studies adjusted for major covariates such as age, sex, body mass index, and comorbidities, residual confounding by unmeasured factors—including dietary calcium intake, physical activity, socioeconomic status, sunlight exposure, and genetic polymorphisms affecting vitamin D metabolism—cannot be excluded despite multivariable adjustment.[192]

Third, publication and language bias remain possible despite comprehensive database searching. Non-English studies were included only when English abstracts provided sufficient methodological detail, which may have led to the exclusion of relevant regional evidence.

Fourth, population representativeness is limited by the geographic clustering of included studies. Studies conducted in Middle Eastern (9%) and South Asian (22%)

populations were overrepresented, reflecting the high prevalence of vitamin D deficiency in these regions. This may restrict generalizability to populations with different genetic backgrounds, dietary patterns, healthcare systems, and sunlight exposure.[159]

Fifth, the inclusion of cross-sectional studies (20 studies, 16%) limits causal inference, as temporal relationships between vitamin D status and cardiovascular outcomes cannot be established. Associations observed in these studies require confirmation through prospective cohorts and RCTs.[151]

Sixth, measurement variability in serum 25(OH)D assays across studies (coefficients of variation 8–15%) may have attenuated true associations. The lack of assay standardization against Liquid chromatography–tandem mass spectrometry reference methods in approximately 67% of studies introduces random measurement error and potential misclassification.[168]

Despite these limitations, the review demonstrates several methodological strengths, including rigorous PRISMA 2020 compliance, dual independent screening and data extraction with high inter-reviewer agreement ($\kappa = 0.89$), comprehensive quality assessment, and a large cumulative participant population across the included studies ($n = 4{,}835{,}000$). Collectively, the findings generate robust, testable hypotheses and highlight the need for adequately powered RCTs evaluating vitamin D supplementation across varying deficiency severities and specific CVD phenotypes.[227,228]

4.7. Future research directions

Future research should prioritize rigorously designed, multicenter RCTs with adequate sample sizes, particularly in populations with confirmed vitamin D deficiency. Such studies should use standardized dosing regimens and carefully evaluate dose–response relationships, supplementation duration, and baseline nutritional status. Long-term follow-up is necessary to evaluate the efficacy and safety of chronic vitamin D supplementation, especially in older adults and patients with chronic inflammatory or metabolic diseases[229,230]

Further studies are also recommended to determine optimal serum vitamin D levels by analyzing correlations between circulating levels of vitamin D in serum and clinically significant events such as immune function, bone health, cardiovascular risk, and metabolic control. Assays to measure serum vitamin D should also be harmonized in order to improve comparability across studies.[231]

Further analyses of VDR signaling pathways, ligand–receptor interactions, and downstream gene regulation are needed to clarify the molecular mechanisms underlying vitamin D effects. In-depth studies of genetic polymorphisms of VDR and vitamin D metabolizing enzymes, as well as epigenetic modifications and transcriptomic profiles, have the potential to explain inter-individual differences in responsiveness to supplementation. Also, the combination of phenotypic, environmental, and lifestyle factors, including diet, sunlight exposure, and comorbid conditions, will assist in identifying subgroups, which might benefit most from targeted or personalized vitamin D interventions.[52,228]

5. Conclusion

The systematic review synthesizes current evidence on the complex relationship between vitamin D status and cardiovascular health across the spectrum from deficiency to toxicity. The results suggest that vitamin D deficiency has frequently been associated with adverse cardiovascular outcomes, including hypertension, endothelial dysfunction, atherosclerotic alterations, and increased cardiovascular risks. Conversely, excessive vitamin D intake may contribute to vascular and valvular calcification, supporting a possible non-linear association between vitamin D and cardiovascular risk.

Observational evidence suggests that maintaining sufficient vitamin D levels may be associated with better cardiovascular profiles, especially in deficient populations. However, large RCTs have generally not shown consistent cardiovascular benefits of routine supplementation in vitamin D-replete individuals. These inconsistencies highlight the significance of baseline vitamin D status, supplementation dosage, and population characteristics in determining cardiovascular outcomes.

Current evidence does not support routine vitamin D supplementation solely for CVD prevention in vitamin D-replete individuals. A more appropriate strategy may be targeted correction of confirmed deficiency, monitoring of serum vitamin D levels, and avoidance of excessive supplementation. Further well-designed studies in deficient and high-risk populations are needed to define optimal vitamin D thresholds, standardized cardiovascular outcomes, and long-term safety.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Saikat Santra, Bhaskar Pal
Visualization: Rajdip Goswami, Mainak Chakraborty
Writing–original draft: Bhaskar Pal, Pinki Biswas, Debdutta Chakraborty, Debasmita Kundu
Writing–review & editing: Saikat Santra, Mainak Chakraborty, Rajdip Goswami
All authors have reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Pál É, Ungvári Z, Benyó Z, Várbíró S. Role of Vitamin D Deficiency in the Pathogenesis of Cardiovascular and Cerebrovascular Diseases. *Nutrients*. 2023;15(2):334.

   doi: 10.3390/nu15020334

2. Mattumpuram J, Maniya MT, Faruqui SK, *et al.* Cardiovascular and cerebrovascular outcomes with vitamin D supplementation: a systematic review and meta-analysis. *Curr Probl Cardiol*. 2024;49(1 Pt C):102119.

   doi: 10.1016/j.cpcardiol.2023.102119

3. Ruiz-García A, Pallarés-Carratalá V, Turégano-Yedro M, *et al.* Vitamin D Supplementation and Its Impact on Mortality and Cardiovascular Outcomes: Meta-Analysis of 80 RCTs. *Nutrients*. 2023;15(8):1810.

   doi: 10.3390/nu15081810

4. Tamborino F, *et al.* Pathophysiology and Main Molecular Mechanisms of Urinary Stone Formation and Recurrence. *Int J Mol Sci*. 2024;25(5):3075.

   doi: 10.3390/ijms25053075

5. Agarwal P, Agarwal Y, Hameed M. Recent Advances in Association Between Vitamin D Levels and Cardiovascular Disorders. *Curr Hypertens Rep*. 2023;25(8):185-209.

   doi: 10.1007/s11906-023-01246-4

6. Zavatta G, Clarke BL. Normocalcemic Primary Hyperparathyroidism: Need for a Standardized Clinical Approach. *Endocrinol Metab*. 2021;36(3):525-535.

   doi: 10.3803/EnM.2021.1061

7. Jun HS, Kang Y. Factors contributing to chronic obstructive pulmonary disease patients' functional performance: Structural equation modelling based on theory of unpleasant symptoms. *Nurs Open*. 2023;10(5):3132-3144.

   doi: 10.1002/nop2.1563

8. Dey SK, Kumar S, Rani D, *et al.* Implications of Vitamin D Deficiency in Systemic Inflammation and Cardiovascular Health. *Crit Rev Food Sci Nutr*. 2024;64(28):10438-10455.

   doi: 10.1080/10408398.2023.2224880

9. Wang Y, *et al.* Network analysis of symptoms, physiological, psychological and environmental risk factors based on unpleasant symptom theory in patients with chronic heart failure. *Int J Nurs Pract*. 2024;30(5):e13246.

   doi: 10.1111/ijn.13246

10. Voulgaridou G, Papadopoulou SK, Detopoulou P, *et al.* Vitamin D and Calcium in Osteoporosis, and the Role of Bone Turnover Markers: A Narrative Review of Recent Data from RCTs. *Diseases*. 2023;11(1):29.

    doi: 10.3390/diseases11010029

11. Su Y, Cappock M, Dobres S, Kucine AJ, Waltzer WC, Zhu D. Supplemental mineral ions for bone regeneration and osteoporosis treatment. *Eng Regen*. 2023;4(2):170-182.

    doi: 10.1016/j.engreg.2023.02.003

12. Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, März W, Pilz S. Vitamin D and Cardiovascular Disease: An Updated Narrative Review. *Int J Mol Sci*. 2021;22(6):2896.

    doi: 10.3390/ijms22062896

13. Gallo G, Volpe M, Savoia C. Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Front Med.* 2022;8:798958.

    doi: 10.3389/fmed.2021.798958

14. Schmid A, Walther B. Natural vitamin D content in animal products. *Adv Nutr*. 2013;4(4):453-462.

    doi: 10.3945/an.113.003780

15. Christakos S, Li S, De La Cruz J, Bhutani V. Vitamin D-Mediated Regulation of Intestinal Calcium Absorption. *Nutrients*. 2022;14(16):3351.

    doi: 10.3390/nu14163351

16. Mattila PH, Valaja J, Rossow L, Venäläinen E, Tupasela T. Effect of vitamin D2- and D3-enriched diets on egg vitamin D content, production, and bird condition during an entire production period. *Poult Sci*. 2004;83(3):433-440.

    doi: 10.1093/ps/83.3.433

17. Fuerniss HF, Gifford CL, Mortensen EG, *et al.* Nutrient Analysis of Raw United States Beef Offal Items. *Nutrients*. 2024;16(18):3104.

    doi: 10.3390/nu16183104

18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic*

Reviews of Interventions. Version 6.4. Cochrane. 2023.

doi: 10.1002/9781119536604

19. Giosuè A, Calabrese I, Lupoli R, Riccardi G, Vaccaro O, Vitale M. Relations between the Consumption of Fatty or Lean Fish and Risk of Cardiovascular Disease and All-Cause Mortality: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2022;13(5):1554-1565.

doi: 10.1093/advances/nmac006

20. Ahmad S, Anwar S, Pratap PD. The cod liver oil insights: from folklore to facts. *Int J Res Granthaalayah*. 2025;13(8):95-109.

doi: 10.29121/granthaalayah.v13.i8.2025.6334

21. Réhault-Godbert S, Guyot N, Nys Y. The golden egg: nutritional value, bioactivities, and emerging benefits for human health. *Nutrients*. 2019;11(3):684.

doi: 10.3390/nu11030684

22. Grosso G, Micek A, Godos J, *et al.* Total, red and processed meat consumption and human health: an umbrella review of observational studies. *Int J Food Sci Nutr*. 2022;73(6):726-737.

doi: 10.1080/09637486.2022.2050996

23. Pilz S, Trummer C, Theiler-Schwetz V, *et al.* Fortification of staple foods for household use with vitamin D: an overview of systematic reviews. *Nutrients*. 2023;15(17):3742.

doi: 10.3390/nu15173742

24. Althubaiti A. Sample size determination: A practical guide for health researchers. *J Gen Fam Med*. 2023;24(2):72-78.

doi: 10.1002/jgf2.600

25. Guo E, Gupta M, Deng J, *et al.* Automated paper screening for clinical reviews using large language models: data analysis study. *J Med Internet Res*. 2024;26:e48996.

doi: 10.2196/48996

26. Miao Y, Zhang L, Zhang D, *et al.* Effects of vitamin D and/or calcium intervention on sleep quality in individuals with prediabetes: a post hoc analysis of a randomized controlled trial. *Eur J Nutr*. 2024;63(4):1187-1201.

doi: 10.1007/s00394-024-03345-7

27. Bouillon R. Optimal vitamin D supplementation strategies. *Endocrine*. 2017;56(2):225-226.

doi: 10.1007/s12020-017-1245-1

28. Lefebvre C, Glanville J, Briscoe S, *et al.* Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, *et al.*, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.4. Cochrane. 2023.

doi: 10.1002/9781119536604.ch4

29. Zittermann A, Schleithoff SS, Koerfer R. Vitamin D and vascular calcification. *Curr Opin Lipidol*. 2007;18(1):41-46.

doi: 10.1097/MOL.0b013e328011c6fc

30. Ding X, Lai J, Zhang H, Guo Z. Vitamin D, vitamin D supplementation and atrial fibrillation risk in the general population: updated systematic review and meta-analysis of prospective studies. *Front Nutr*. 2023;10:1246359.

doi: 10.3389/fnut.2023.1246359

31. Chandler PD, Chen WY, Ajala ON, *et al.* Effect of vitamin D3 supplements on development of advanced cancer and cardiovascular disease. *JAMA Netw Open*. 2020;3(11):e2025850.

doi: 10.1001/jamanetworkopen.2020.25850

32. Bouillon R, Marcocci C, Carmeliet G, *et al.* Skeletal and extraskeletal actions of vitamin D: current evidence and open questions. *Endocr Rev*. 2018;40(4):1109-1151.

doi: 10.1210/er.2018-00126

33. Verdoia M, Solli M, Ubertini E, *et al.* Low vitamin D levels affect left ventricular wall thickness in severe aortic stenosis. *J Cardiovasc Med*. 2020;21(11):905-911.

doi: 10.2459/JCM.0000000000001084

34. Rainer KW, Earle W, Michos ED, *et al.* Effects of vitamin D supplementation on cardiac biomarkers: Results from the STURDY trial. *Am J Prev Cardiol*. 2024;20:100871.

doi: 10.1016/j.ajpc.2024.100871

35. Zhang R, Naughton DP. Vitamin D in health and disease: Current perspectives. *Nutr J*. 2010;9:65.

doi: 10.1186/1475-2891-9-65

36. Ahmadieh H, Arabi A. Association between vitamin D and cardiovascular health: Myth or Fact? A narrative review of the evidence. *Womens Health*. 2023;19:17455057231158222.

doi: 10.1177/17455057231158222

37. Jeong HY, Park KM, Lee MJ, Yang DH, Kim SH, Lee SY. Vitamin D and Hypertension. *Electrolyte Blood Press*. 2017;15(1):1-11.

doi: 10.5049/EBP.2017.15.1.1

38. Ameri P, Canepa M, Milaneschi Y, *et al.* Relationship between vitamin D status and left ventricular geometry in a healthy population: results from the Baltimore Longitudinal Study of Aging. *J Intern Med*. 2013;273(3):253-264.

doi: 10.1111/joim.12007

39. Lugg ST, Howells PA, Thickett DR. Optimal Vitamin D Supplementation Levels for Cardiovascular Disease Protection. *Dis Markers*. 2015;2015:864370.

doi: 10.1155/2015/864370

40. Barsan M, Brata AM, Ismaiel A, *et al.* The Pathogenesis of Cardiac Arrhythmias in Vitamin D Deficiency. *Biomedicines*. 2022;10(6):1239.

doi: 10.3390/biomedicines10061239

41. Dogdus M, Burhan S, Bozgun Z, *et al.* Cardiac autonomic

dysfunctions are recovered with vitamin D replacement in apparently healthy individuals with vitamin D deficiency. *Ann Noninvasive Electrocardiol*. 2019;24(6):e12677.

doi: 10.1111/anec.12677

42. Jude EB, Ling SF, Allcock R, Yeap BXY, Pappachan JM. Vitamin D Deficiency Is Associated With Higher Hospitalization Risk From COVID-19: A Retrospective Case-control Study. *J Clin Endocrinol Metab*. 2021;106(11):E4708-E4715.

doi: 10.1210/clinem/dgab439

43. Tsuprykov O, Buse C, Skoblo R, Hocher B. Comparison of free and total 25-hydroxyvitamin D in normal human pregnancy. *J Steroid Biochem Mol Biol*. 2019;190:29-36.

doi: 10.1016/j.jsbmb.2019.03.008

44. Bischoff-Ferrari HA, de Godoi Rezende Costa Molino C, Rival S, *et al.* DO-HEALTH: Vitamin D3 - Omega-3 - Home exercise - Healthy aging and longevity trial - Design of a multinational clinical trial on healthy aging among European seniors. *Contemp Clin Trials*. 2021;100:106124.

doi: 10.1016/j.cct.2020.106124

45. Amrein K, Scherkl M, Hoffmann M, *et al.* Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*. 2020;74(11):1498-1513.

doi: 10.1038/s41430-020-0558-y

46. Schoenmakers I. Vitamin D supplementation and mortality. *Lancet Diabetes Endocrinol.* 2022;10(2):88-90.

doi: 10.1016/S2213-8587(22)00002-X

47. Abouzid M, Kruszyna M, Burchardt P, *et al.* Vitamin D receptor gene polymorphism and vitamin D status in population of patients with cardiovascular disease—a preliminary study. *Nutrients*. 2021;13(9):3117.

doi: 10.3390/nu13093117

48. Young MF, Ou J, Duong C, *et al.* Assessment of Vitamin D status and association with inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. *Am J Clin Nutr*. 2023;117(1):175-183.

doi: 10.1016/j.ajcnut.2022.10.018

49. Qiu H, Wang M, Mi D, Zhao J, Tu W, Liu Q. Vitamin D status and the risk of recurrent stroke and mortality in ischemic stroke patients: Data from a 24-month follow-up study in China. *J Nutr Health Aging*. 2017;21(7):766-771.

doi: 10.1007/s12603-016-0821-z

50. Rasouli MA, *et al.* Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 134000 Individuals in 29 Randomized Clinical Trials and 157000 Individuals in 30 Prospective Cohort Studies: An Updated Systematic Review and Meta-analysis. *J Res Health Sci*. 2023;23(4):e00594.

doi: 10.34172/jrhs.2023.129

51. Mattioli AV, Coppi F, Severino P, *et al.* A Personalized Approach to Vitamin D Supplementation in Cardiovascular Health Beyond the Bone: An Expert Consensus by the Italian National Institute for Cardiovascular Research. *Nutrients*. 2025;17(1):115.

doi: 10.3390/nu17010115

52. Nepal R, Karki P, Uraw S, Lamsal M. Prevalence of Vitamin D Deficiency among Patients of Acute Coronary Syndrome in a Tertiary Care Center of Eastern Nepal. *JNMA J Nepal Med Assoc*. 2021;59(235):225-229.

doi: 10.31729/jnma.5166

53. Burgess S, Gill D. Genetic evidence for vitamin D and cardiovascular disease: choice of variants is critical. *Eur Heart J*. 2022;43(18):1740-1742.

doi: 10.1093/eurheartj/ehab870

54. Zhang J, Cai L, Gui Z, *et al.* Air pollution-associated blood pressure may be modified by diet among children in Guangzhou, China. *J Hypertens*. 2020;38(11):2215-2222.

doi: 10.1097/HJH.0000000000002521

55. Haider F, Ghafoor H, Hassan OF, Farooqui K, Bel Khair AOM, Shoaib F. Vitamin D and Cardiovascular Diseases: An Update. *Cureus*. 2023;15(11):e49734.

doi: 10.7759/cureus.49734

56. Bouillon R, LeBoff MS, Neale RE. Health Effects of Vitamin D Supplementation: Lessons Learned From Randomized Controlled Trials and Mendelian Randomization Studies. *J Bone Miner Res*. 2023;38(10):1391-1402.

doi: 10.1002/jbmr.4888

57. Drechsler C, Pilz S, Obermayer-Pietsch B, *et al.* Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. *Eur Heart J*. 2010;31(18):2253-2261.

doi: 10.1093/eurheartj/ehq246

58. Driggin E, Madhavan MV, Gupta A. The role of vitamin D in cardiovascular disease and COVID-19. *Rev Endocr Metab Disord*. 2022;23(2):293-301.

doi: 10.1007/s11154-021-09674-w

59. Saliba W, Barnett O, Rennert HS, Rennert G. The Risk of All-Cause Mortality Is Inversely Related to Serum 25(OH)D Levels. *J Clin Endocrinol Metab*. 2012;97(8):2792-2798.

doi: 10.1210/jc.2012-1747

60. Alagacone S, Verga E, Verdolini R, Saifullah SM. The association between vitamin D deficiency and the risk of resistant hypertension. *Clin Exp Hypertens*. 2020;42(2):177-180.

doi: 10.1080/10641963.2019.1601204

61. van den Heuvel EGHM, Lips P, Schoonmade LJ, Lanham-

New SA, van Schoor NM. Comparison of the Effect of Daily Vitamin D2 and Vitamin D3 Supplementation on Serum 25-Hydroxyvitamin D Concentration (Total 25(OH)D, 25(OH)D2, and 25(OH)D3) and Importance of Body Mass Index: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2024;15(1):100133.

doi: 10.1016/j.advnut.2023.09.016

62. Hiemstra TF, Lim K, Thadhani R, Manson JE. Vitamin D and Atherosclerotic Cardiovascular Disease. *J Clin Endocrinol Metab*. 2019;104(9):4033-4050.

doi: 10.1210/jc.2019-00194

63. Rist PM, Buring JE, Cook NR, Manson JE, Rexrode KM. Effect of vitamin D and/or omega-3 fatty acid supplementation on stroke outcomes: a randomized trial. *Eur J Neurol*. 2021;28(3):809-815.

doi: 10.1111/ene.14623

64. Abdollahzadeh R, Shushizadeh MH, Barazandehrokh M, *et al.* Association of Vitamin D receptor gene polymorphisms and clinical/severe outcomes of COVID-19 patients. *Infect Genet Evol*. 2021;96:105098.

doi: 10.1016/j.meegid.2021.105098

65. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. *Clin Endocrinol*. 2012;77(3):343-350.

doi: 10.1111/j.1365-2265.2012.04434.x

66. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ*. 2011;342:d2040.

doi: 10.1136/bmj.d2040

67. Zhang Y, Fang L, Zhang J, *et al.* Effect of vitamin D supplementation for major adverse cardiovascular events: a meta-analysis based on randomised controlled trials. *Eur J Prev Cardiol*. 2025;32(10):1123-1135.

doi: 10.1017/S0007114525103954

68. Marshall Brinkley D, Ali OM, Zalawadiya SK, Wang TJ. Vitamin D and Heart Failure. *Curr Heart Fail Rep*. 2017;14(5):410-420.

doi: 10.1007/s11897-017-0355-7

69. Rockwell M, Kraak V, Hulver M, Epling J. Clinical management of low vitamin D: A scoping review of physicians' practices. *Nutrients*. 2018;10(4):493.

doi: 10.3390/nu10040493

70. Nie S, Huang P, Niu H, *et al.* Vitamin D deficiency enhances platelet activation and thrombosis by regulating VDR/Akt pathway based on platelet proteomics. *Eur J Pharmacol*. 2025;999:177684.

doi: 10.1016/j.ejphar.2025.177684

71. Theiler-Schwetz V, Trummer C, Grübler MR, *et al.* Effects of Vitamin D Supplementation on 24-Hour Blood Pressure in Patients with Low 25-Hydroxyvitamin D Levels: A Randomized Controlled Trial. *Nutrients*. 2022;14(7):1360.

doi: 10.3390/nu14071360

72. Sokol SI, Srinivas V, Crandall JP, *et al.* The effects of vitamin D repletion on endothelial function and inflammation in patients with coronary artery disease. *Vasc Med*. 2012;17(6):394-404.

doi: 10.1177/1358863X12466709

73. Shikuma CM, Seto T, Liang CY, *et al.* Vitamin D Levels and Markers of Arterial Dysfunction in HIV. *AIDS Res Hum Retroviruses*. 2012;28(8):793-797.

doi: 10.1089/aid.2011.0086

74. Malihi Z, Lawes CMM, Wu Z, *et al.* Monthly high-dose vitamin D3 supplementation and self-reported adverse events in a 4-year randomized controlled trial. *Clin Nutr*. 2019;38(4):1581-1587.

doi: 10.1016/j.clnu.2018.07.034

75. Pilz S, Gaksch M, Kienreich K, *et al.* Effects of vitamin D on blood pressure and cardiovascular risk factors: a randomized controlled trial. *Hypertension*. 2015;65(6):1195-1201.

doi: 10.1161/HYPERTENSIONAHA.115.05319

76. Manson JE, Bassuk SS, Buring JE. Vitamin D, Calcium, and Cancer. *JAMA*. 2017;317(12):1217.

doi: 10.1001/jama.2017.2155

77. Latoch E, Kozłowski K, Konończuk K, *et al.* Vitamin D Deficiency and Carotid Media-Intima Thickness in Childhood Cancer Survivors. *Nutrients*. 2023;15(10):2333.

doi: 10.3390/nu15102333

78. Wimalawansa SJ. Vitamin D and cardiovascular diseases: causality. *J Steroid Biochem Mol Biol*. 2018;175:29-43.

doi: 10.1016/j.jsbmb.2016.12.016

79. Kasiri H, *et al.* A 3-Year-Old Child With Incidental High-Dose Vitamin D Intoxication: A Case Report and Literature Review. *Case Rep Endocrinol*. 2025;2025:6614996.

doi: 10.1155/crie/6614996

80. Scragg R, Camargo CA. Vitamin D Supplementation and Cardiovascular Disease Risk—Reply. *JAMA Cardiol*. 2017;2(11):1282.

doi: 10.1001/jamacardio.2017.2941

81. Manson JE, Cook NR, Lee IM, *et al.* Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med*. 2019;380(1):33-44.

doi: 10.1056/NEJMoa1809944

82. Zendehdel A, Shakarami A, Moghadam ES. Physiological Evidence and Therapeutic Outcomes of Vitamin D on Cardiovascular Diseases. *Curr Cardiol Rev*. 2024;20(1):e180124225801.

doi: 10.2174/011573403X263417231107110618

83. Kheiri B, Abdalla A, Osman M, *et al.* Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. *Clin Hypertens*. 2018;24:9.

doi: 10.1186/s40885-018-0094-4

84. Hribar M, Hristov H, Gregorič M, *et al.* Nutrihealth Study: Seasonal Variation in Vitamin D Status Among the Slovenian Adult and Elderly Population. *Nutrients*. 2020;12(6):1838.

doi: 10.3390/nu12061838

85. Chua GT, Chan YC, Cheng SW. Vitamin D status and peripheral arterial disease: evidence so far. *Vasc Health Risk Manag*. 2011;7:671-675.

doi: 10.2147/VHRM.S24876

86. Lim S, Shin H, Kim MJ, *et al.* Vitamin D Inadequacy Is Associated with Significant Coronary Artery Stenosis in a Community-Based Elderly Cohort: The Korean Longitudinal Study on Health and Aging. *J Clin Endocrinol Metab*. 2012;97(1):169-178.

doi: 10.1210/jc.2011-1580

87. Meredith AJ, McManus BM. Vitamin D in heart failure. *J Card Fail*. 2013;19(10):692-711.

doi: 10.1016/j.cardfail.2013.09.002

88. Raina AH, Allai MS, Shah ZA, Changal KH, Raina MA, Bhat FA. Association of Low Levels of Vitamin D with Chronic Stable Angina: A Prospective Case-Control Study. *N Am J Med Sci*. 2016;8(3):143-148.

doi: 10.4103/1947-2714.179130

89. Pilz S, Zittermann A, Trummer C, *et al.* Vitamin D testing and treatment: a narrative review of current evidence. *Endocr Connect*. 2019;8(2):R27-R43.

doi: 10.1530/EC-18-0432

90. Hung M, Birmingham WC, Ocampo M, Mohajeri A. The role of vitamin D in cardiovascular diseases. *Nutrients*. 2023;15(16):3547.

doi: 10.3390/nu15163547

91. Liu LCY, Voors AA, van Veldhuisen DJ, *et al.* Vitamin D status and outcomes in heart failure patients. *Eur J Heart Fail*. 2011;13(6):619-625.

doi: 10.1093/eurjhf/hfr032

92. Chitalia N, Ismail T, Tooth L, *et al.* Impact of vitamin D supplementation on arterial vasomotion, stiffness and endothelial biomarkers in chronic kidney disease patients. *PLoS ONE*. 2014;9(3):e91363.

doi: 10.1371/journal.pone.0091363

93. Vitezova A, Cartolano NS, Heeringa J, *et al.* Vitamin D and the risk of atrial fibrillation: the Rotterdam Study. *PLoS ONE* 2015;10(5):e0125161.

doi: 10.1371/journal.pone.0125161

94. Koh J, Shah SU, Chua PEY, Gui H, Pang J. Vitamin D and Stroke: Effects on Incidence, Severity, and Outcome and the Potential Benefits of Supplementation. *Front Neurol*. 2020;11:384.

doi: 10.3389/fneur.2020.00384

95. Vadlamudi S, Nobul Rao K, Uday Kumar N. A Study of Association of Serum Vitamin D Levels with Acute Ischemic Stroke. *Eur J Cardiovasc Med*. 2025;15(3):715-721.

doi: 10.5083/ejcm/25-03-123

96. Nolte K, Herrmann-Lingen C, Platschek L, *et al.* Vitamin D deficiency in patients with diastolic dysfunction or heart failure with preserved ejection fraction. *ESC Heart Fail*. 2019;6(2):262-270.

doi: 10.1002/ehf2.12413

97. Ajabshir S, Asif A, Nayer A. The effects of vitamin D on the renin-angiotensin system. *J Nephropathol*. 2014;3(2):41-43.

doi: 10.12860/jnp.2014.09

98. Tamez H, Zoccali C, Packham D, *et al.* Vitamin D reduces left atrial volume in patients with left ventricular hypertrophy and chronic kidney disease. *Am Heart J*. 2012;164(6):902-909.e2.

doi: 10.1016/j.ahj.2012.09.018

99. Jiang WL, Gu HB, Zhang YF, Xia QQ, Qi J, Chen JC. Vitamin D Supplementation in the Treatment of Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials. *Clin Cardiol*. 2016;39(1):56-61.

doi: 10.1002/clc.22473

100. Kunadian V, Ford GA, Bawamia B, Qiu W, Manson JE. Vitamin D deficiency and coronary artery disease: a review of the evidence. *Am Heart J*. 2014;167(3):283-291.

doi: 10.1016/j.ahj.2013.11.012

101. Zittermann A. Vitamin D status, supplementation and cardiovascular disease. *Anticancer Res*. 2018;38(2):1179-1186.

doi: 10.21873/anticanres.12338

102. Achinger SG, Ayus JC. The role of vitamin D in left ventricular hypertrophy and cardiac function. *Kidney Int Suppl*. 2005;67(95):S37-S42.

doi: 10.1111/j.1523-1755.2005.09506.x

103. Zhang Q, Zhang M, Wang H, *et al.* Vitamin D supplementation improves endothelial dysfunction in patients with non-dialysis chronic kidney disease. *Int Urol Nephrol*. 2018;50(5):923-927.

doi: 10.1007/s11255-018-1829-6

104. Savastio S, Pozzi E, Tagliaferri F, *et al.* Vitamin D and Cardiovascular Risk: Which Implications in Children? *Int J Mol Sci*. 2020;21(10):3536.

doi: 10.3390/ijms21103536

105. Wang TJ, Pencina MJ, Booth SL, *et al.* Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117(4):503-511.

doi: 10.1161/CIRCULATIONAHA.107.706127

106. Tokarz A, Kuśnierz-Cabała B, Kuźniewski M, Gacoń J, Mazur-Laskowska M, Stępień EL. Seasonal effect of vitamin D deficiency in patients with acute myocardial infarction. *Kardiol Pol*. 2016;74(8):786-792.

doi: 10.5603/KP.a2016.0002

107. Young KA, Snell-Bergeon JK, Naik RG, *et al.* Vitamin D Deficiency and Coronary Artery Calcification in Subjects With Type 1 Diabetes. *Diabetes Care*. 2011;34(2):454-458.

doi: 10.2337/dc10-0757

108. Motiwala SR, Wang TJ. Vitamin D and cardiovascular risk. *Curr Hypertens Rep*. 2012;14(3):209-218.

doi: 10.1007/s11906-012-0262-y

109. Kim YS, Hwang JH, Song MR. The Association Between Vitamin D Deficiency and Metabolic Syndrome in Korean Adolescents. *J Pediatr Nurs*. 2018;38:e7-e11.

doi: 10.1016/j.pedn.2017.11.005

110. Pirrotta F, Cavati G, Mingiano C, *et al.* Vitamin D Deficiency and Cardiovascular Mortality: Retrospective Analysis "Siena Osteoporosis" Cohort. *Nutrients*. 2023;15(15):3303.

doi: 10.3390/nu15153303

111. Zhang Y, Fang F, Tang J, *et al.* Association between vitamin D status and arterial stiffness: a systematic review and meta-analysis. *BMJ.* 2020:370:m2329

doi: 10.1136/bmj.m2329

112. Beveridge LA, Struthers AD, Khan F, *et al.* Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. *JAMA Intern Med*. 2015;175(5):745-754.

doi: 10.1001/jamainternmed.2015.0237

113. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83(4):754-759.

doi: 10.1093/ajcn/83.4.754

114. Yeung WC, Toussaint ND, Badve SV. Vitamin D therapy in chronic kidney disease: a critical appraisal of clinical trial evidence. *Clin Kidney J*. 2024;17(8):sfae227.

doi: 10.1093/ckj/sfae227

115. Forman JP, Scott JB, Ng K, *et al.* Effect of Vitamin D Supplementation on Blood Pressure in African-Americans. *Hypertension*. 2013;61(4):779-785.

doi: 10.1161/HYPERTENSIONAHA.111.00659

116. Busa V, Dardeir A, Marudhai S, *et al.* Role of Vitamin D Supplementation in Heart Failure Patients With Vitamin D Deficiency and Its Effects on Clinical Outcomes: A Literature Review. *Cureus*. 2020;12(10):e10840.

doi: 10.7759/cureus.10840

117. Muscogiuri G, Sorice GP, Ajjan R, *et al.* Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. *Nutr Metab Cardiovasc Dis*. 2012;22(2):81-87.

doi: 10.1016/j.numecd.2011.11.001

118. Zittermann A, Kuhn J, Dreier J, Knabbe C, Gummert JF, Börgermann J. Vitamin D status and the risk of major adverse cardiac and cerebrovascular events in cardiac surgery. *Eur Heart J*. 2013;34(18):1358-1364.

doi: 10.1093/eurheartj/ehs468

119. Norman PE, Powell JT. Vitamin D and cardiovascular disease. *Circ Res*. 2014;114(2):379-393.

doi: 10.1161/CIRCRESAHA.113.301241

120. Vimaleswaran KS, Cavadino A, Berry DJ, *et al.* Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. *Lancet Diabetes Endocrinol*. 2014;2(9):719-729.

doi: 10.1016/S2213-8587(14)70113-5

121. Dobnig H, Pilz S, Scharnagl H, *et al.* Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med*. 2008;168(12):1340-1349.

doi: 10.1001/archinte.168.12.1340

122. Judd SE, Tangpricha V. Vitamin D Deficiency and Risk for Cardiovascular Disease. *Am J Med Sci*. 2009;338(1):40-44.

doi: 10.1097/MAJ.0b013e3181aaee91

123. Verdoia M, Ceccon C, Nardin M, Suryapranata H, De Luca G. Vitamin D deficiency and periprocedural myocardial infarction in patients undergoing percutaneous coronary interventions. *Cardiovasc Revasc Med*. 2018;19(7 Pt A):744-750.

doi: 10.1016/j.carrev.2018.03.002

124. Karur S, Veerappa V, Nanjappa MC. Study of vitamin D deficiency prevalence in acute myocardial infarction. *Int J Cardiol Heart Vessel*. 2014;3:57.

doi: 10.1016/j.ijchv.2014.03.004

125. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007;167(16):1730-1737.

doi: 10.1001/archinte.167.16.1730

126. Abboud M. Vitamin D Supplementation and Blood Pressure in Children and Adolescents: A Systematic Review and Meta-Analysis. *Nutrients*. 2020;12(4):1163.

doi: 10.3390/nu12041163

127. Cozzolino M, Ronco C. The impact of paricalcitol on left ventricular hypertrophy. *Contrib Nephrol*. 2011;171:161-165.

doi: 10.1159/000327170

128. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008;168(11):1174-1180.

doi: 10.1001/archinte.168.11.1174

129. De Boer IH, Kestenbaum B, Shoben AB, Michos ED, Sarnak MJ, Siscovick DS. 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. *J Am Soc Nephrol*. 2009;20(8):1805-1812.

doi: 10.1681/ASN.2008111157

130. Hsu S, Zelnick LR, Bansal N, *et al.* Vitamin D metabolites and risk of cardiovascular disease: the CRIC study. *J Am Heart Assoc*. 2023;12(14):e028561.

doi: 10.1161/JAHA.122.028561

131. Saponaro F, Marcocci C, Zucchi R. Vitamin D status and cardiovascular outcome. *J Endocrinol Invest*. 2019;42(11):1285-1290.

doi: 10.1007/s40618-019-01057-y

132. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, *et al.* Vitamin D measurement standardization: The way out of the chaos. *J Steroid Biochem Mol Biol*. 2017;173:117-121.

doi: 10.1016/j.jsbmb.2016.12.002

133. Afzal S, Brøndum-Jacobsen P, Bojesen SE, Nordestgaard BG. Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. *BMJ*. 2014;349:g6330.

doi: 10.1136/bmj.g6330

134. Della Nera G, Sabatino L, Gaggini M, Gorini F, Vassalle C. Vitamin D Determinants, Status, and Antioxidant/Anti-inflammatory-Related Effects in Cardiovascular Risk and Disease: Not the Last Word in the Controversy. *Antioxidants*. 2023;12(4):948.

doi: 10.3390/antiox12040948

135. Mirza AMW, Almansouri NE, Muslim MF, *et al.* Effect of vitamin D supplementation on cardiovascular outcomes: an updated meta-analysis of RCTs. *Ann Med Surg*. 2024;86(11):6665-6672.

doi: 10.1097/MS9.0000000000002458

136. Myung SK, Kim HB, Lee YJ, Choi YJ, Oh SW. Calcium Supplements and Risk of Cardiovascular Disease: A Meta-Analysis of Clinical Trials. *Nutrients*. 2021;13(2):368.

doi: 10.3390/nu13020368

137. Chen S, Sun Y, Agrawal DK. Vitamin D Deficiency and Essential Hypertension. *J Am Soc Hypertens*. 2015;9(11):885-901.

doi: 10.1016/j.jash.2015.08.009

138. Pilz S, Verheyen N, Grübler MR, Tomaschitz A, März W. Vitamin D and cardiovascular disease prevention. *Nat Rev Cardiol*. 2016;13(7):404-417.

doi: 10.1038/nrcardio.2016.73

139. Khaw KT, Luben R, Wareham N. Serum 25-hydroxyvitamin D, mortality, and incident cardiovascular disease, respiratory disease, cancers, and fractures: a 13-y prospective population study. *Am J Clin Nutr*. 2014;100(5):1361-1370.

doi: 10.3945/ajcn.114.086413

140. Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol*. 2014;14:45.

doi: 10.1186/1471-2288-14-45

141. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Vitamin D and cardiovascular health. *Clin Nutr*. 2021;40(5):2946-2957.

doi: 10.1016/j.clnu.2020.12.025

142. Hlaing SM, Garcia LA, Contreras JR, Norris KC, Ferrini MG, Artaza JN. 1,25-Vitamin D3 Promotes Cardiac Differentiation through Modulation of the Wnt Signaling Pathway. *J Mol Endocrinol*. 2014;53(3):303-317.

doi: 10.1530/JME-14-0168

143. de Boer IH, Levin G, Robinson-Cohen C, *et al.* Serum 25-Hydroxyvitamin D Concentration and Risk for Major Clinical Disease Events in a Community-Based Population of Older Adults: A Cohort Study. *Ann Intern Med*. 2012;156(9):627-634.

doi: 10.7326/0003-4819-156-9-201205010-00004

144. Christodoulou M, Aspray TJ, Schoenmakers I. Vitamin D supplementation for patients with chronic kidney disease: a systematic review and meta-analyses of trials investigating the response to supplementation and an overview of guidelines. *Calcif Tissue Int*. 2021;109(2):157-178.

doi: 10.1007/s00223-021-00844-1

145. Kaur G, Singh J, Kumar J. Vitamin D and cardiovascular disease in chronic kidney disease. *Pediatr Nephrol*. 2019;34(12):2509-2522.

doi: 10.1007/s00467-018-4088-y

146. Ku YC, Liu ME, Ku CS, Liu TY, Lin SL. Relationship between vitamin D deficiency and cardiovascular disease. *World J Cardiol*. 2013;5(9):337-346.

doi: 10.4330/wjc.v5.i9.337

147. Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. *Metabolites*. 2021;11(4):255.

doi: 10.3390/metabo11040255

148. El Hoss K, Salla M, Khaled S, Krayem M, Hassan H, El Khatib S. Update on vitamin D deficiency and its impact on human health: major challenges and technical approaches. *J Agric Food Res*. 2023;12:100616.

doi: 10.1016/j.jafr.2023.100616

149. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D Deficiency. *J Am Coll Cardiol*. 2008;52(24):1949-1956.

doi: 10.1016/j.jacc.2008.08.050

150. Al Mheid I, Patel R, Murrow J, *et al.* Vitamin D Status Is Associated With Arterial Stiffness and Vascular Dysfunction in Healthy Humans. *J Am Coll Cardiol*. 2011;58(2):186-192.

doi: 10.1016/j.jacc.2011.02.051

151. Aune D, Mahamat-Saleh Y, Kobeissi E, *et al.* Blood pressure, hypertension and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol*. 2023;38(2):145-178.

doi: 10.1007/s10654-022-00914-0

152. Zagura M, Serg M, Kampus P, *et al.* Aortic stiffness and vitamin D are independent markers of aortic calcification in patients with peripheral arterial disease and in healthy subjects. *Eur J Vasc Endovasc Surg*. 2011;42(5):689-695.

doi: 10.1016/j.ejvs.2011.07.027

153. Kuller LH, Matthews KA, Edmundowicz D, Chang Y. Incident Coronary Artery Calcium Among Postmenopausal Women. *Atherosclerosis*. 2008;200(2):278-285.

doi: 10.1016/j.atherosclerosis.2007.12.057

154. Khanolkar S, Hirani S, Mishra A, *et al.* Exploring the Role of Vitamin D in Atherosclerosis and Its Impact on Cardiovascular Events: A Comprehensive Review. *Cureus*. 2023;15(7):e42470.

doi: 10.7759/cureus.42470

155. Graczyk S, Grzeczka A, Pasławska U, Kordowitzki P. The Possible Influence of Vitamin D Levels on the Development of Atrial Fibrillation—An Update. *Nutrients*. 2023;15(12):2725.

doi: 10.3390/nu15122725

156. Rafaqat S, Khurshid H, Rafaqat S. Electrolyte imbalance role in atrial fibrillation: Pharmacological management. *Int J Arrhythmia*. 2022;23(1):1-10.

doi: 10.1186/s42444-022-00065-z

157. Tebben PJ, Singh RJ, Kumar R. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment. *Endocr Rev*. 2016;37(5):521-547.

doi: 10.1210/er.2016-1070

158. Zhang D, Cheng C, Wang Y, *et al.* Effect of Vitamin D on blood pressure and hypertension in the general population: An update meta-analysis of cohort studies and randomized controlled trials. *Prev Chronic Dis*. 2020;17:E03.

doi: 10.5888/pcd17.190307

159. Gepner AD, Haller IV, Krueger DC, Korcarz CE, Binkley N, Stein JH. A Randomized Controlled Trial of the Effects of Vitamin D Supplementation on Arterial Stiffness and Aortic Blood Pressure in Native American Women. *Atherosclerosis*. 2015;240(2):526-532.

doi: 10.1016/j.atherosclerosis.2015.04.795

160. Marek K, Cichoń N, Saluk-Bijak J, Bijak M, Miller E. The Role of Vitamin D in Stroke Prevention and the Effects of Its Supplementation for Post-Stroke Rehabilitation: A Narrative Review. *Nutrients*. 2022;14(13):2761.

doi: 10.3390/nu14132761

161. Kim HA, Perrelli A, Ragni A, *et al.* Vitamin D Deficiency and the Risk of Cerebrovascular Disease. *Antioxidants*. 2020;9(4):327.

doi: 10.3390/antiox9040327

162. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: Results from the third national health and nutrition examination survey. *PLoS Med*. 2005;2(6):e160.

doi: 10.1371/journal.pmed.0020160

163. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol*. 2004;15(8):1983-1992.

doi: 10.1097/01.ASN.0000132474.50966.DA

164. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and Endothelial Function. *Nutrients*. 2020;12(2):575.

doi: 10.3390/nu12020575

165. Cui P, Hou H, Song B, Xia Z, Xu Y. Vitamin D and ischemic stroke — association, mechanisms, and therapeutics. *Ageing Res Rev*. 2024;96:102244.

doi: 10.1016/j.arr.2024.102244

166. Alnafisah RY, *et al.* Increasing Prevalence of Potential Vitamin D Toxicity and Its Risk Factors in Korea: A Large Population-Based Study. *Nutrients*. 2025;17(16):2614.

doi: 10.3390/nu17162614

167. Forrester SJ, Booz GW, Sigmund CD, *et al.* Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. *Physiol Rev*. 2018;98(3):1627-1738.

doi: 10.1152/physrev.00038.2017

168. Ray A, Ch. Maharana K, Meenakshi S, Singh S. Endothelial dysfunction and its relation in different disorders: Recent update. *Health Sci Rev*. 2023;7:100084.

doi: 10.1016/j.hsr.2023.100084

169. Bikle DD, Schwartz J. Vitamin D Binding Protein, Total and Free Vitamin D Levels in Different Physiological and Pathophysiological Conditions. *Front Endocrinol*. 2019;10:317.

doi: 10.3389/fendo.2019.00317

170. Caturano A, *et al.* Oxidative Stress and Cardiovascular Complications in Type 2 Diabetes: From Pathophysiology to Lifestyle Modifications. *Antioxidants*. 2023;12(3):655.

doi: 10.3390/antiox14010072

171. Ginsberg C, Hoofnagle AN, Katz R, *et al.* Vitamin D Metabolite Ratio and Coronary Artery Calcification in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2023;16(3):e015055.

doi: 10.1161/CIRCIMAGING.122.015055

172. Giamundo DM, Pastena P, Varzideh F, *et al.* Vitamin D and Cardiovascular Disease: The "Good", the "Bad", and the "Unknown". *Rev Cardiovasc Med*. 2025;26(10):40001.

doi: 10.31083/RCM40001

173. Han L, Xu XJ, Zhang JS, Liu HM. Association between vitamin D deficiency and levels of renin and angiotensin in essential hypertension. *Int J Clin Pract*. 2022;2022:8975396.

doi: 10.1155/2022/8975396

174. Kaur J, Khare S, Sizar O, Givler A. Vitamin D Deficiency. In: *Endocrinology and Diabetes: A Problem-Oriented Approach*. 2nd ed. Springer. 2025:245-256.

doi: 10.1007/978-3-030-90684-9_23

175. Scragg R. Clinical trials of vitamin D supplementation and cardiovascular disease: A synthesis of the evidence. *J Steroid Biochem Mol Biol*. 2025;250:106733.

doi: 10.1016/j.jsbmb.2025.106733

176. Sha S, Xie R, Gwenzi T, Wang Y, Brenner H, Schöttker B. Real-world evidence for an association of vitamin D supplementation with atherosclerotic cardiovascular disease in the UK Biobank. *Clin Nutr.* 2025;49:118-127.

doi: 10.1016/j.clnu.2025.04.017

177. Scragg R, Stewart AW, Waayer D, *et al.* Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the Vitamin D Assessment Study. *JAMA Cardiol*. 2017;2(6):608-616.

doi: 10.1001/jamacardio.2017.0175

178. Saleem A, Padakanti SS, Hajjaj M, *et al.* Effects of Vitamin D Supplementation on Cardiovascular Outcomes in Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis. *Cureus*. 2025;17(7):e87378.

doi: 10.7759/cureus.87378

179. Torres-Lopez R, *et al.* Efficacy of Vitamin D Supplementation on the Risk of Falls Among Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. *J Clin Med*. 2025;14(17):6117.

doi: 10.3390/jcm14176117

180. Zheng Y, Chen J, Xu L, *et al.* A systematic review and meta-analysis of the linkage between low vitamin D and the risk as well as the prognosis of stroke. *Brain Behav*. 2024;14(6):e3577.

doi: 10.1002/brb3.3577

181. Tobias DK, *et al.* Vitamin D supplementation vs. placebo and incident type 2 diabetes in an ancillary study of the randomized Vitamin D and Omega-3 Trial. *Nat Commun*. 2025;16(1):3332.

doi: 10.1038/s41467-025-58721-6

182. Pan S, Yang K, Shang Y, *et al.*. Effect of regulated vitamin D increase on vascular markers in patients with chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials.*Nut. Metab Cardiovasc Dis*. 2024;34(1):33-44.

doi: 10.1016/j.numecd.2023.09.015

183. Amer SA, *et al.* Calcium, magnesium, and vitamin D supplementations as complementary therapy for hypertensive patients: a systematic review and meta-analysis. *BMC Complement Med Ther*. 2025;25(1):89.

doi: 10.1186/s12906-025-04809-x

184. Lu Q, *et al.* The effects of vitamin D supplementation on serum lipid profiles in people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Front Nutr*. 2024;11:1419747.

doi: 10.3389/fnut.2024.1419747

185. Virtanen JK, *et al.* The effect of vitamin D3 supplementation on atrial fibrillation in generally healthy men and women: The Finnish Vitamin D Trial. *Am Heart J*. 2023;264:177-182.

doi: 10.1016/j.ahj.2023.05.024

186. Loh HH, Azizan EA, Sukor N. Connecting the dots: renin-angiotensin-aldosterone system, vitamin D, and hypertension. *J Hypertens*. 2025;43(7):1136-1145.

doi: 10.1097/HJH.0000000000004046

187. John H, Gondalia S, Sharma J, Shankar G.Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review. *Cureus*. 2025.

doi: 10.7759/cureus.81150

188. Ko CC, *et al.* Vitamin D deficiency and risk of incident atrial fibrillation/flutter: A multicenter longitudinal cohort study. *Medicine*. 2026;105(5):e41327.

doi: 10.1097/md.0000000000047326

189. Zhou Y, Jiang M, Sun JY, *et al.* The association between vitamin D levels and the 10-year risk of atherosclerotic cardiovascular disease: a population-based study. *J Cardiovasc Nurs.* 2023;38(5):E178-E186.

doi: 10.1097/JCN.0000000000000943

190. Khetan SP, Suvarna SS. The role of Vitamin D supplementation in cardiovascular health: A reappraisal. *Global Cardiol Sci Pract*. 2025;2025(1):10.

doi: 10.21542/gcsp.2025.10

191. Li Z, *et al.* Associations of vitamin D with coronary revascularization and heart rate variability in hypertensive patients. *Front Cardiovasc Med*. 2025;12:1590701.

doi: 10.3389/fcvm.2025.1590701

192. Balasubramanian A, *et al.* Association of Vitamin D Deficiency as an Independent Risk Factor for Myocardial Infarction and Its Therapeutic Implications: A Systematic Review. *Cureus*. 2025.

doi: 10.7759/cureus.77375

193. Ayer A, Dominguez A, Cruz Rodriguez JB. Effects of calcium and vitamin D supplementation on cardiovascular disease outcomes: A review of interventional studies. *Trends Cardiovasc Med.* 2026;36(1):58-64.

doi: 10.1016/j.tcm.2025.07.012

194. Reese JA, *et al.* Vitamin D Deficiency and Cardiovascular Disease Risk Factors Among American Indian Adolescents: The Strong Heart Family Study. *Prev Chronic Dis.* 2025;22:240354.

doi: 10.5888/pcd22.240354

195. Ebrahimi R, Masouri MM, Salehi Amniyeh Khozani AA, Mohammad Soltani S, Nejadghaderi SA. Effects of Vitamin D Supplementation on Blood Pressure in Patients With Type 1 Diabetes Mellitus: A Systematic Review of Clinical Trials. *Health Sci Rep.* 2025;8(3).

doi: 10.1002/hsr2.70524

196. Zhu K, Austin N, Devine A, Bruce D, Prince RL. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. *J Am Geriatr Soc*. 2010;58(11):2063-2068.

doi: 10.1111/j.1532-5415.2010.03142.x

197. Amrein K, Papinutti A, Mathew E, Vila G, Parekh D. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. *Endocr Connect*. 2018;7(12):R304-R315.

doi: 10.1530/EC-18-0184

198. Ashraf T, *et al.* Vitamin D supplementation among postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting: a systematic review and meta-analysis. *Ann Med Surg*. 2025.

doi: 10.1097/MS9.0000000000003426

199. Wu X, *et al.* Advances in cardiovascular supplementation: mechanisms, efficacy, and clinical perspectives. *Front Mol Biosci*. 2026;12.

doi: 10.3389/fmolb.2025.1699492

200. Kampka Z, *et al.* Vitamin D Supplementation in Heart Failure—Confusion Without a Cause? *Nutrients*. 2025;17(11):1839.

doi: 10.3390/nu17111839

201. Dumbre D, Upendra S, Zacharias BS, *et al.* Unraveling the Relationship Between Vitamin D and Noncommunicable Diseases: A Systemic Review and Meta-Analysis. *Public Health Nurs*. 2025;42(3):1302-1314.

doi: 10.1111/phn.13521

202. Jayedi A, Daneshvar M, Zargar MS, *et al.* Serum 25(OH) D Concentration, Vitamin D Supplementation, and Risk of Cardiovascular Disease and Mortality in Patients with Type 2 Diabetes or Prediabetes: a Systematic Review and Dose-Response Meta-Analysis. *Am J Clin Nutr*. 2023;118(3):697-707.

doi: 10.1016/j.ajcnut.2023.07.012

203. Cao M, *et al.* The effects of vitamin D on all-cause mortality in different diseases: an evidence-map and umbrella review of 116 randomized controlled trials. *Front Nutr*. 2023;10:1132528.

doi: 10.3389/fnut.2023.1132528

204. Yeung WCG, Toussaint ND, Badve SV. Vitamin D Therapy in Adults With CKD: A Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2023;82(5):543-558.

doi: 10.1053/j.ajkd.2023.04.003

205. Patel S, Thami T. Vitamin D and Musculoskeletal System. In: Kumar V, Patel S, eds. *Vitamin D: A Comprehensive Guide for Medical Professionals*. Springer. 2025:245-256.

doi: 10.1007/978-981-96-6491-7_9

206. Sofianopoulou E, *et al.* Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. *Lancet Diabetes Endocrinol.* 2024.

doi: 10.1016/S2213-8587(23)00287-5

207. Thompson B, *et al.* Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. *BMJ*. 2023;381:e075230.

doi: 10.1136/bmj-2023-075230

208. Afraie M, *et al.* The Effect of Vitamin D Supplementation on Glycemic Control and Cardiovascular Risk Factors in Type 2 Diabetes: An Updated Systematic Review and Meta-Analysis of Clinical Trials. *J Diabetes Res*. 2024;2024:9960656.

doi: 10.1155/2024/9960656

209. Iqhrammullah M, *et al.* Association of serum vitamin D and the risk of cardiovascular diseases among diabetic patients: A systematic review and meta-analysis. *Clinical Nutrition ESPEN. 2024;62:66-75.*

doi: 10.1016/j.clnesp.2024.04.018

210. Wood JC, *et al.* Vitamin D deficiency, cardiac iron and cardiac function in thalassaemia major. *Br J Haematol.* 2008;141(6):891-894.

doi: 10.1111/j.1365-2141.2008.07135.x

211. Sluyter JD, Camargo CA, Stewart AW, *et al.* Effect of monthly, high-dose, long-term vitamin D supplementation on central blood pressure parameters: A Randomized Controlled Trial Substudy. *JAHA*. 2017;6(10).

doi: 10.1161/jaha.117.006802

212. Madadi R, *et al.* Assessment of the Relationship Between Serum Vitamin D Level and Its Cardiovascular Outcomes: A Systematic Review and Meta-analysis Study. *J Saudi Heart Assoc*. 2025;37(2):14.

doi: 10.37616/2212-5043.1432

213. Candemir B, Yamak BA, Candemir M. The utility of Vitamin D levels in predicting the severity of coronary artery disease in obese patients. *Cardiovasc Surg Int*. 2025;12:15-20.

doi: 10.5606/e-cvsi.2025.1769

214. May HT, Le V, Anderson JL, *et al.* A randomized clinical trial evaluating vitamin D normalization on major adverse cardiovascular-related events among acute coronary syndrome patients: the TARGET-D trial. Abstract 4382525. Presented at: American Heart Association Scientific Sessions; November 7-10, 2025; New Orleans, LA. Available from: medicaldigest:scientific-contents/interview:randomized-clinical-trial-evaluating-vitamin-d-normalization-major-adverse-cardiovascular-related-events-among-acute-coronary-syndrome-patients-target-d-trial

215. Barbarawi M, Kheiri B, Zayed Y, *et al.* Vitamin D supplementation and cardiovascular disease risks in more than 83000 individuals in 21 randomized clinical trials. *JAMA Cardiol*. 2019;4(8):765-776.

doi: 10.1001/jamacardio.2019.1870

216. Elamin MB, Abu Elnour NO, Elamin KB, *et al.* Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2011;96(7):1931-1942.

doi: 10.1210/jc.2011-0398

217. Glueck C, Jetty V, Rothschild M, *et al.* Association Between Serum 25-Hydroxyvitamin D and lipids, lipoprotein cholesterols, and homocysteine. *North Am J Med Sci*. 2016;8(7):284. .

doi: 10.4103/1947-2714.187137

218. Latic N, Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. *Int J Mol Sci*. 2020;21(18):6483.

doi: 10.3390/ijms21186483

219. Dalan R, Liew H, Tan WK, *et al.* Vitamin D and the endothelium: basic, translational and clinical research updates. *IJC Metab Endocr*. 2014;4:4-17.

doi: 10.1016/j.ijcme.2014.06.003

220. Pludowski P, Holick MF, Grant WB, *et al.* Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol.* 2018;175:125-135.

doi: 10.1016/j.jsbmb.2017.01.021

221. Acharya P, Dalia T, Ranka S, *et al.* The effects of vitamin D supplementation and 25-hydroxyvitamin D levels on the risk of myocardial infarction and mortality. *J Endocr Soc*. 2021;5(10):bvab124.

doi: 10.1210/jendso/bvab124

222. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc*. 2013;88(7):720-755.

doi: 10.1016/j.mayocp.2013.05.011

223. Wang H, Xia N, Yang Y, Peng DQ. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. *Lipids Health Dis*. 2012;11:42.

doi: 10.1186/1476-511X-11-42

224. Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. *Prog Lipid Res*. 2015;54:1-11.

doi: 10.1016/j.plipres.2011.05.001

225. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. *J Hypertens*. 2009;27(10):1948-1954.

doi: 10.1097/HJH.0b013e32832f075b

226. Vaidya A, Forman JP, Williams JS. Vitamin D and the vascular sensitivity to angiotensin II in obese Caucasians with hypertension. *J Hum Hypertens*. 2011;25(11):672-678.

doi: 10.1038/jhh.2010.110

227. Pilz S, Tomaschitz A, Drechsler C, *et al.* Vitamin D deficiency and myocardial diseases. *Mol Nutr Food Res*. 2010;54(8):1103-1113.

doi: 10.1002/mnfr.200900474

228. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2012;95(1):91-100.

doi: 10.3945/ajcn.111.014779

229. Holick MF, Binkley NC, Bischoff-Ferrari HA, *et al.* Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.

doi: 10.1210/jc.2011-0385

230. Parker J, Hashmi O, Dutton D, *et al.* Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas*. 2010;65(3):225-236.

doi: 10.1016/j.maturitas.2009.12.013

231. Bahrami LS, *et al.* Vitamin D supplementation effects on the clinical outcomes of patients with coronary artery disease: a systematic review and meta-analysis. *Sci Rep*. 2020;10:69762.

doi: 10.1038/s41598-020-69762-w