

# Vitamin D and cardiovascular diseases: A narrative review

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## ABSTRACT

Cardiovascular diseases (CVD) and vitamin D deficiency are becoming highly prevalent among general populations. Despite plausible biological mechanisms for the role of vitamin D in cardio-protection, a cause-and-effect relationship has not yet been established. The interest in vitamin D as a potential therapeutic target to attenuate cardiovascular risk has been raised. The question about the benefit of vitamin D supplementation for cardiovascular outcomes cannot be answered certainly for the moment. The association between hypovitaminosis D and CVD has been proven by some studies while other studies deny any such link. The present narrative review gives a comprehensive overview of studies on the potential impact of hypovitaminosis D on CVD. The potential role of vitamin D supplementation in the management of CVD is also evaluated. Particular emphasis is paid to those studies that achieve a high level of scientific evidence.

**Keywords:** 1,25-dihydroxyvitamin D, 25-Hydroxyvitamin D, coronary artery diseases, hypovitaminosis D, vitamin D supplementation

## Introduction

The significance of vitamin D in promoting bone health has been acknowledged for nearly a century, primarily due to its efficacy in curing rickets in infants and toddlers.<sup>[1]</sup> However, in the early 1920s, it was recognized that the administration of vitamin D was linked to soft tissue calcification in some children, suggesting that the positive effects of vitamin D on bone health might have adverse implications for the cardiovascular system.<sup>[1]</sup> A well-established concept is the biphasic effect of vitamin D on tissue calcification. However, a paradigm shift occurred with the observation that ultraviolet B radiation, through vitamin D formation, may protect against cardiovascular diseases (CVD).<sup>[2]</sup>

Maintaining an optimal vitamin D serum level is considered crucial not only for calcium homeostasis but also for reducing cardiovascular risk and achieving optimal blood pressure control. Although the precise mechanisms have not been fully established, some studies have proven the association between hypovitaminosis D and CVD, while others deny any such link.

CVD, encompassing myocardial infarction and coronary artery disease, remains the leading cause of death worldwide despite significant progress in primary prevention and treatment strategies.<sup>[3]</sup> Despite improvements in the treatment of traditional cardiovascular risk factors, the residual non-traditional cardiovascular risk is estimated in about 50% of individuals who are fully treated.<sup>[4]</sup> Impaired nutritional status, especially for vitamin D, could be a contributory factor. Low 25-Hydroxyvitamin D [25(OH) D] levels are becoming highly prevalent among general populations, and interest in vitamin D as a potential therapeutic target to attenuate cardiovascular risk has been raised.<sup>[5]</sup> As with CVD, the prevalence of vitamin D deficiency varies considerably with sex, age, latitude, ethnicity, and culture.<sup>[6]</sup>

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Prospective cohort studies support the assumption that poor vitamin D status is independently associated with cardiovascular risk. However, evidence from randomized controlled trials (RCT) for a beneficial vitamin D effect on cardiovascular risk is still lacking. Nevertheless, there are gaps in knowledge regarding the understanding of the role of vitamin D in the prevention of CVD. The present narrative review provides a comprehensive overview of studies on the potential impact of hypovitaminosis D on CVD. Results of experimental studies, cohort studies, and RCTs are used to discuss the effects of vitamin D deficiency. The potential role of vitamin D supplementation in the management of CVD is also evaluated, with particular emphasis on studies that achieve a high level of scientific evidence. The objective of this review is to offer a valuable reference for researchers, clinicians, and policymakers engaged in cardiovascular health, aiming to enhance patient outcomes and alleviate the impact of diseases associated with atherosclerosis.

## Background

Vitamin D plays a crucial role in regulating calcium and phosphate metabolism and maintaining optimal blood levels of these minerals. When serum ionized calcium concentrations are low, parathyroid hormone (PTH) activates renal 1,25-dihydroxyvitamin D [1,25(OH) 2D] synthesis, while high plasma calcium levels suppress PTH and the renal 1 $\alpha$ -hydroxylation of 25(OH) D.<sup>[7]</sup> Beyond its well-established effects on extracellular calcium homeostasis and bone metabolism, vitamin D has gained attention for its pleiotropic effects on the musculoskeletal and cardiovascular systems. In skeletal muscle cells, vitamin D influences cell proliferation and differentiation, facilitates the transport of calcium and phosphate across skeletal muscle cell membranes, suppresses myostatin expression (a negative regulator of muscle mass), upregulates the expression of follistatin and insulin-like growth factor 2, induces myogenic transcription factors, regulates muscle cell differentiation by inducing cell cycle arrest, prevents muscular degeneration, and alleviates myalgia.<sup>[8]</sup>

In the cardiovascular system, vitamin D has been observed to downregulate proinflammatory cytokines, metalloproteinases, and natriuretic peptides, while simultaneously upregulating matrix gla protein, anti-inflammatory cytokines, and inhibitors of metalloproteinases.<sup>[9,10]</sup> Osteoporosis and cardiovascular pathology share commonalities, including osteoprotegerin and receptor activator of nuclear factor  $\kappa$ B ligand involved in osteoclast activation and vascular calcification in atherosclerosis. Additionally, bone morphogenetic protein, implicated in osteoblastic differentiation and atherosclerotic lesions, and age-related estrogen deficiency contribute to the similarities between cardiovascular and bone disorders.<sup>[11]</sup>

Recognizing these parallels between cardiovascular and bone disorders and understanding how medication effects align with them could prompt clinicians to consider the indirect consequences of drug regimens when deciding on therapeutic

approaches for individuals managing both osteoporosis and atherosclerotic diseases.

## Vitamin D metabolism

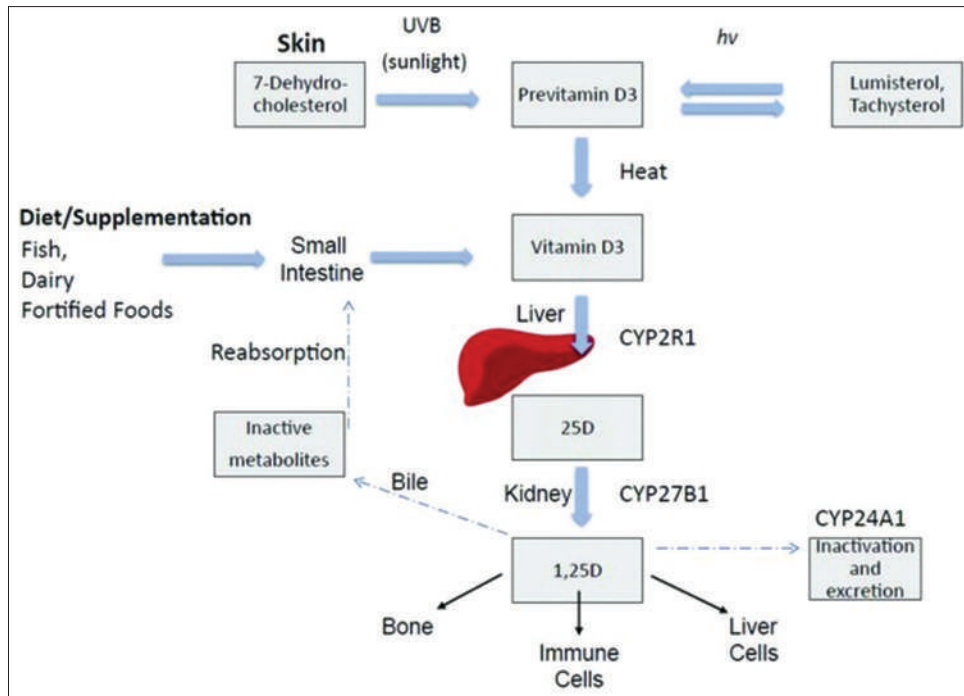
Vitamin D is a prohormone acquired through both internal and external sources. Sufficient vitamin D levels can be attained through dietary intake, the use of vitamin D supplements, and/or exposure of the skin to ultraviolet B radiation from the sun. Vitamin D exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is produced in the human epidermis through exposure to ultraviolet B irradiation, or it can be obtained from oily fish or supplements. Vitamin D2 is present in plants, resulting from the irradiation of ergosterol.<sup>[7]</sup> The metabolic process of vitamin D in the human body is illustrated in Figure 1. The biologically active form of vitamin D is 1,25(OH) 2D, but the most reliable indicator of vitamin D status in individuals without kidney disease is 25(OH) D. This form has a longer biological half-life and a higher concentration than 1,25(OH) 2D, reflecting the overall production of vitamin D from both internal and external sources.<sup>[12]</sup>

Vitamin D, through its activated form 1,25(OH) 2D, exerts biological effects by binding to the vitamin D receptor (VDR). VDRs are expressed in most human tissues and cells, and vitamin D influences genes that regulate various essential cellular functions, including cellular proliferation, differentiation, apoptosis, and angiogenesis.<sup>[14]</sup> In the cardiovascular system, VDRs have been identified in endothelial cells and cardiomyocytes. The presence of the enzymatic machinery necessary for producing the appropriate ligand for the receptor underscores the role of vitamin D in regulating cardiovascular health.<sup>[15]</sup>

## Classification of hypovitaminosis D

There is ongoing debate regarding the definition of vitamin D deficiency (or hypovitaminosis D), the optimal serum level of 25(OH) D, and the dietary requirements for vitamin D.<sup>[16]</sup> According to the Endocrine Society Clinical Practice Guideline, vitamin D deficiency is characterized by a 25(OH) D level below 50 nmol/L (20 ng/mL), with insufficiency defined as ranging from 52.5 to 72.5 nmol/L.<sup>[17]</sup> In contrast, the International Osteoporosis Foundation sets the threshold for deficiency at a 25(OH) D level below 25 nmol/L, insufficiency as below 50 nmol/L, and recommends a target level of 75 nmol/L.<sup>[18]</sup> The Institute of Medicine categorizes values below 30 nmol/L as deficient, 30–49.99 nmol/L as insufficient, 50–125 nmol/L as adequate, and above 125 nmol/L as potentially harmful.<sup>[19]</sup>

The lack of consensus, combined with inherent fluctuations related to season, diet, and supplements, complicates the assessment of the relationship between vitamin D status and CVD.<sup>[5]</sup> The variability in the assays used to measure serum 25(OH) D further exacerbates the lack of agreement between guidelines.<sup>[20]</sup> Additionally, concentrations of local vitamin D metabolites within the arterial wall may differ from circulating levels because vascular smooth muscle cells, endothelial cells,



**Figure 1:** Vitamin D synthesis and metabolism. Endogenous vitamin D synthesis occurs primarily through sunlight exposure, which produces pre-vitamin D3. It is hydroxylated by 1 of 4 cytochrome P450 enzymes (most importantly CYP2R1) in the liver producing 25-hydroxyvitamin D, the form usually considered as a circulating biomarker of vitamin D status. Subsequent conversion by  $1\alpha$ -hydroxylase (another cytochrome P450 enzyme; CYP27B1) into the physiologically active form,  $1,25$ -dihydroxyvitamin D or calcitriol, occurs primarily in the kidney.  $1,25(\text{OH})_2\text{D}$  acts in target sites in bone and immune cells, as well as liver cells. Abbreviations: CYP (cytochrome P450), UVB (ultraviolet B), hv (denotes photochemical reaction). Printed with permission<sup>[13]</sup>

macrophages, and dendritic cells all possess CYP27B1 activity, allowing them to produce  $1,25(\text{OH})_2\text{D}$  from  $25(\text{OH})\text{D}$ .<sup>[21,22]</sup>

### Vitamin D and inflammation

Compelling evidence supports the involvement of inflammation in the development of coronary artery diseases.<sup>[23]</sup> Vitamin D demonstrates cardiovascular protective effects through various mechanisms, including its anti-inflammatory properties, inhibition of proliferation in vascular smooth muscle cells, suppression of proatherogenic T lymphocytes, preservation of endothelial function, and defense against advanced glycation products.<sup>[24]</sup> Furthermore, vitamin D exhibits anti-atherogenic functions by impeding the formation of foam cells, reducing cholesterol uptake by macrophages, and facilitating the transport of high-density lipoprotein-cholesterol (HDL-C).<sup>[25]</sup> Additionally, vitamin D acts as an antioxidant, mitigating oxidative stress within endothelial cells.<sup>[26]</sup>

Deficiency in vitamin D compromises vascular endothelial functions, impacting vascular stiffness, oxidative stress, proinflammatory responses, platelet aggregation, nitric oxide synthesis, and increasing coronary artery calcium scores.<sup>[27]</sup> In individuals with vitamin D deficiency, elevated release of proinflammatory cytokines heightens oxidative stress and promotes the release of immature and activated platelets from the bone marrow, with an associated increase in mean platelet volume, a factor linked to arterial and venous diseases like

coronary artery disease (CAD), venous thromboembolism, and stroke.<sup>[21,28]</sup>

Vitamin D insufficiency may contribute to atherosclerosis and thrombus formation through diverse mechanisms, such as the inhibition of prostaglandin and cyclooxygenase pathways, upregulation of anti-inflammatory cytokines, reduction of cytokine-induced expression of adhesion molecules, decrease of matrix metalloproteinase-9, and downregulation of the renin-angiotensin-aldosterone system.<sup>[15]</sup> The link between lower  $25(\text{OH})\text{D}$  and endothelial dysfunction is partially mediated by nuclear factor  $\kappa\text{B}$ , a proinflammatory transcription factor found to be greater in deficient subjects compared to sufficient subjects ( $P < 0.05$ ). Inhibition of this factor by oral salsalate improved flow-mediated dilation more significantly in subjects with lower  $25(\text{OH})\text{D}$  levels.<sup>[29]</sup>

Vitamin D not only directly influences endothelial or vascular smooth muscle cells but also plays a role in immune or inflammatory modulation, contributing to an imbalance in vascular homeostasis, decreased arterial compliance, and the development or progression of atherosclerosis.<sup>[30]</sup> Some studies suggest an inverse association between vitamin D and early atherosclerosis, independent of traditional cardiovascular risk factors.<sup>[31,32]</sup> Additionally, certain RCTs indicate potential improvement in endothelial function with vitamin D supplementation, although not all studies support this finding.<sup>[33,34]</sup>

## Experimental evidence of vitamin D implication in CVD

Multiple experimental studies provide evidence for a biphasic impact of vitamin D on cardiovascular risk. In summary, both supra-physiological doses of the parent vitamin D substance and elevated levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> result in significant outcomes: (i) a notable increase in aortic calcium and phosphate content, (ii) acceleration of cell migration and facilitation of the transition of contractile vascular smooth muscle cells into an osteoblast-like phenotype, (iii) initiation of vascular calcification, destruction of elastic fibers, and arterial stiffness, and (iv) induction of left ventricular hypertrophy.<sup>[35,36]</sup> Consistent with the notion of a biphasic effect of vitamin D on CVD, mice lacking the VDR also exhibit several characteristics of premature aging, including ectopic calcification and a shortened lifespan.<sup>[37]</sup>

## Vitamin D deficiency and cardiovascular events

Several ecological studies propose a heightened CVD mortality in regions with lower ultraviolet B radiation exposure and during the winter season.<sup>[10]</sup> Studies with a lower baseline use of vitamin D showed a significantly elevated risk of mortality.<sup>[38]</sup> Observational studies suggest an inverse correlation between serum vitamin D levels and clinical cardiovascular events.<sup>[39]</sup> Notably, the Framingham Offspring Study and the Health Professionals Follow-up Study identified significant inverse associations between 25(OH) D levels and cardiovascular events. However, a nonlinear relationship was observed between 25(OH)D and CVD, with a plateau between 20 and 30 ng/mL (50 and 75 nmol/L) and a slight suggestion of increased risk at higher vitamin D levels.<sup>[39,40]</sup> In the Third National Health and Nutrition Examination Survey (NHANES-III), no significant association was found between 25(OH) D and CVD mortality rate, but those in the lowest quartile had a 26% increase in total mortality. Interestingly, both low (<20 ng/mL (<50 nmol/L)) and high (>50 ng/mL (>125 nmol/L)) levels of vitamin D were associated with higher total mortality.<sup>[39]</sup> While the relationship between plasma vitamin D levels and cardiovascular risk has been considered linear, there may be a biological range (20 to 30 ng/mL or 50 to 75 nmol/L) below which pro-atherosclerotic changes may occur. Additionally, very high levels may also be linked to increased cardiovascular risk.<sup>[41]</sup>

Numerous longitudinal studies support the connection between low vitamin D levels and elevated cardiovascular adverse events.<sup>[42,43]</sup> Vitamin D deficiency (defined as serum levels <30 ng/mL (<75 nmol/L)) was linked to various cardiovascular-related diseases, including hypertension and CAD, and emerged as a robust independent predictor of all-cause death.<sup>[43]</sup> Men with low vitamin D levels (serum level <15 ng/mL (<37.5 nmol/L)) had a higher incidence of acute myocardial infarction, even after adjusting for established cardiovascular risk factors in the Health Professionals Follow-up Study.<sup>[41]</sup> A population multi-center study found that almost all patients with acute myocardial infarction had vitamin D levels <30 ng/mL (<75 nmol/mL).<sup>[44]</sup> The National Health and

Nutrition Examination Survey (NHANES) reported that subjects with vitamin D levels <10 ng/mL (<25 nmol/L) exhibited significantly higher mean heart rate, systolic blood pressure, and rate-pressure product compared to those with vitamin D levels 25–35 ng/mL (62.5–87 nmol/L) or more.<sup>[45]</sup> Vitamin D status served as a prognostic indicator for major post-infarction adverse events, such as heart failure hospitalizations, recurrent acute myocardial infarction, death, or restenosis after percutaneous coronary intervention, signifying a higher risk for patients with lower vitamin D levels.<sup>[46]</sup> However, some longitudinal studies did not demonstrate a statistically significant association between low vitamin D levels and increased cardiovascular mortality and morbidity.<sup>[42,43,47]</sup>

While observational evidence indicates an elevated CVD risk with low vitamin D levels, factors such as obesity and behavioral aspects (e.g., reduced sunlight exposure due to difficult mobilization and outdoor physical activity in chronically ill patients) may contribute. Additionally, confounding factors like increased age, race, skin pigmentation, renin, PTH, calcium, and phosphorus levels cannot be definitively ruled out.

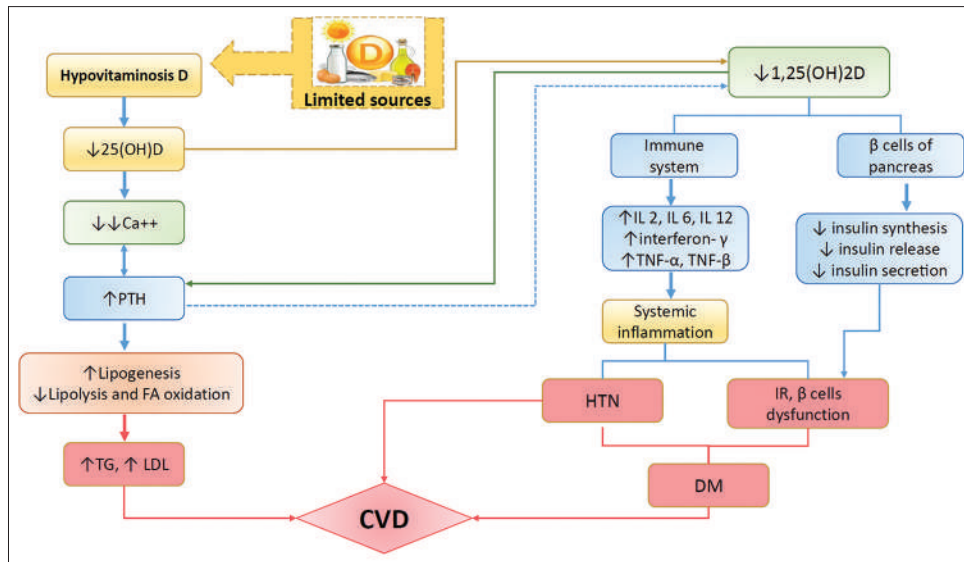
## Vitamin D and cardiovascular risk factors

Vitamin D deficiency may heighten cardiovascular risk through various mechanisms, including the development of electrolyte imbalances, dysfunction of pancreatic  $\beta$ -cells, and activation of the renin-angiotensin system.<sup>[43]</sup> Severe vitamin D deficiency disrupts adaptive immune responses, creating an inflammatory environment that fosters vascular dysfunction and insulin resistance.<sup>[29]</sup> Figure 2 summarizes the hypothesized mechanisms underlying the interrelationships among vitamin D deficiency and various CVD risk factors.

Obesity, among cardiovascular risk factors, is distinctly associated with low vitamin D levels. This association may stem from the sequestration of the lipophilic hormone in adipose tissue and/or a complex interplay between adipocytes and vitamin D.<sup>[48]</sup> Numerous cross-sectional studies indicate that elevated levels of 25(OH)D are linked to a favorable lipid profile.<sup>[49]</sup> In a comprehensive longitudinal assessment of vitamin D levels and blood lipids in a real-world setting, significant associations were found between changes in 25(OH)D and lipid levels, excluding HDL-C levels.<sup>[50]</sup> However, the results on vitamin D and blood lipids are inconsistent and may be confounded by the causal link between vitamin D and obesity. A bi-directional Mendelian Randomization study considered obesity as a causal risk factor for vitamin D deficiency, explaining about one-third of vitamin D deficiency.<sup>[51]</sup>

Observational studies and a meta-analysis from Denmark demonstrated a stepwise increase in stroke incidence with decreasing 25(OH)D level quartiles.<sup>[52]</sup> Vitamin D deficiency is a significant risk factor for insulin resistance, potentially leading to adverse clinical outcomes associated with type 2 diabetes mellitus and CVD, as evidenced by studies showing decreased insulin sensitivity in vitamin D-deficient subjects compared to





**Figure 2:** Hypothesized mechanisms underlying the interrelationships among vitamin D deficiency and cardiovascular disease risk factors such as insulin resistance, hypertension, and diabetes. Abbreviations: 1,25(OH) 2D: 1,25-dihydroxyvitamin D, 25(OH) D: 25-hydroxyvitamin D, CVD: cardiovascular diseases, DM: diabetes mellitus, HTN: hypertension, IL-2: interleukin-2, IL-6: interleukin-6, IL-12: interleukin-12, IR: insulin resistance, LDL: low-density lipoprotein, PTH: parathyroid hormone, TG: triglycerides, TNF- $\alpha$ : tumor necrosis factor- $\alpha$ , TNF- $\beta$ : tumor necrosis factor- $\beta$

vitamin D-sufficient subjects.<sup>[53]</sup> The hypothesis that insulin resistance and vitamin D deficiency are features of similar metabolic and cardiovascular disorders has been proposed.<sup>[54]</sup> A systematic review and meta-analysis, including only prospective studies, established an inverse association between circulating 25(OH) D and incident type 2 diabetes.<sup>[55]</sup> Lower serum 25(OH) D levels were associated with metabolic syndrome and its components, particularly HDL-C concentration.<sup>[56]</sup> Conversely, a cross-sectional analysis of NHANES-III data revealed that low vitamin D levels are linked to higher blood pressure.<sup>[57]</sup> The increased risk of CVD with vitamin D deficiency was observed in hypertensive participants but not in those without hypertension in the Framingham Offspring Study.<sup>[58]</sup> Despite observational evidence implicating vitamin D in cardiovascular risk factors, interventional studies have been inconsistent or inconclusive, as discussed in the following section. It is important to note that the disparity between findings in observational studies and inconclusive results from interventional clinical trials might be attributed to optimal vitamin D levels being the result, rather than the cause, of good health.

### Vitamin D supplementation and cardiovascular outcomes

The impact of short-term vitamin D supplementation following an acute myocardial infarction was observed to result in reduced levels of vascular cell adhesion molecules, C-reactive protein, and interleukin 6. This supports the idea that vitamin D possesses cardio-protective and anti-inflammatory effects on the vascular system.<sup>[59]</sup> Indeed, vitamin D signaling plays a crucial cardio-protective role post-myocardial infarction through anti-inflammatory, anti-fibrotic, and anti-apoptotic mechanisms.<sup>[60]</sup> Consequently, further research is needed to explore the potential of vitamin D repletion in preventing cardiac

remodeling after a myocardial infarction. Beneficial effects of vitamin D supplementation are often identified in patients with very low 25(OH)D levels, who appear to be at the highest risk for CVD.<sup>[43]</sup> However, it remains uncertain whether its impact is significant for healthy individuals or only meaningful in vitamin D-deficient chronically ill patients. Thus, the extent to which vitamin D supplementation provides significant benefits in the healthy population remains uncertain.

Some prospective studies examine the effect of vitamin D supplementation on cardiovascular events. An analysis from the Nurses' Health Study and the Health Professionals Follow-up Study demonstrated that higher daily vitamin D intake was associated with a decreased risk of CVD in men.<sup>[61]</sup> Several clinical trials, including the VitD-CHF trial, VINDICATE study, PRIMO trial, and OPERA trial, reported significant improvement in cardiac function among heart failure patients after receiving vitamin D supplementation.<sup>[62-65]</sup> The RECORD trial indicated that vitamin D supplementation might protect against cardiac failure in the elderly, though not against myocardial infarction or stroke, albeit using only 800 IU of vitamin D per day.<sup>[66]</sup> However, a daily combination of low-dose vitamin D (400 IU) and calcium (1,000 mg) over an average of 7 years showed that the intervention did not reduce the risk of CAD, stroke, or cancer, despite a small increase in serum levels of 25(OH) D.<sup>[67]</sup> The Copenhagen City Heart Study, following 10,170 patients for a mean of 29 years, demonstrated that lower levels of vitamin D were associated with cardiovascular morbidity and mortality.<sup>[68]</sup> The long-term follow-up, large sample size, and low frequency of vitamin D supplementation in this study may reinforce the association between vitamin D levels and cardiovascular outcomes. The Whitehall study data was combined in a meta-regression with 12 prospective studies (with 4,632 vascular deaths) and 18 prospective studies (with 11,734 all-cause deaths),

revealing that patients in the top quartile of 25(OH) D compared with the lowest quartile had 21% and 28% lower vascular and total mortality, respectively.<sup>[69]</sup> However, the lack of specificity on the associations of 25(OH)D with any particular causes of death raises doubts about the causal relevance of these associations.

Evidence from meta-analyses suggests that supplementation with vitamin D combined with calcium, but not vitamin D alone, improves all-cause mortality.<sup>[70]</sup> Moreover, a Cochrane Library Review concluded that vitamin D supplementation decreased all-cause mortality compared with placebo or no intervention but had no significant effect on cardiovascular mortality (risk ratio 0.98, 95% CI 0.90-1.07; n = 47,267). Unlike vitamin D3 supplementation, vitamin D2, alfa-calcidol, and calcitriol had no statistically significant beneficial effects on mortality.<sup>[71]</sup>

Contrary to the above trials, several RCT failed to prove a causal relationship between vitamin D repletion and the reduction of cardiovascular risk factors and CVD. This could be attributed to small sample sizes or inappropriate study designs, as most trials were initially designed for clinical endpoints other than cardiovascular events. In some cases, different dosages or different preparations of vitamin D were used, different durations of supplementation were applied, and serum 25(OH)D was not always measured at baseline and/or in the follow-up. The Andhra Pradesh children and parents study group did not find clear evidence for an association between serum vitamin D levels and CVD.<sup>[72]</sup> The analysis of the Women's Health Initiative implies that vitamin D supplementation has no effect on cardiovascular incidents, coronary calcification, or mortality rate.<sup>[73-75]</sup> Although this trial was not powered for cardiovascular endpoints, the inclusion of calcium supplementation may have counteracted the benefits of vitamin D, and the vitamin D dose may have been too small.<sup>[73]</sup> In the D-Health randomized controlled trial, vitamin D supplementation reduced the incidence of major cardiovascular events only in those taking statins or other cardiovascular drugs at baseline.<sup>[76]</sup> Despite different outcome definitions, both the vitamin D assessment study and the vitamin D and omega 3 trial (VITAL) found that vitamin D supplementation had no effect on CVD.<sup>[77,78]</sup> However, adverse cardiovascular effects were reported at daily vitamin D doses of 4,000 IU in the EVITA (effect of vitamin D on mortality in heart failure) study.<sup>[79]</sup>

A meta-analysis on the blood pressure-lowering effects of vitamin D supplementation found no effect of treatment across various patient subgroups, advising against using vitamin D for the treatment of hypertension.<sup>[80]</sup> Another meta-analysis of the influence of vitamin D supplementation on lipid profiles showed a beneficial effect in hypercholesterolemia patients with vitamin D insufficiency who are at high cardiovascular risk.<sup>[81]</sup> Furthermore, vitamin D supplementation was often combined with calcium intake, making it challenging to interpret the RCT results, especially since calcium intake may be associated with an increased cardiovascular risk.<sup>[82]</sup>

## Future outlook

While our comprehension of vitamin D deficiency and its implications is rapidly advancing, there remains a considerable amount to uncover. It can be hypothesized that any relevant effects of vitamin D on CVD outcomes may manifest primarily when initial circulating 25(OH)D levels fall within the deficiency range. Research needs to explore the dose-response relationship of potentially adverse vitamin D effects on the cardiovascular system. Currently, there is no clear consensus between observational and interventional studies, with significant heterogeneity in vitamin D doses, baseline concentrations, therapy durations and compounds, variations in absorption and metabolism among individuals, genetic differences in the VDR, personal use of vitamin D supplementation, biases from other comorbid diseases, study design-related issues, and differences in hypovitaminosis D definitions.<sup>[83]</sup>

Numerous confounding factors may interfere with the connection between low vitamin D status and CVD, such as age, body mass index, drug intake history, dietary habits, sunlight exposure, physical activity level, latency of the effect of vitamin D, different ethnic populations, autocrine and paracrine vitamin D systems, concomitant hyperphosphatemia and PTH levels, inappropriate follow-up times, or the lack of a control group with normal vitamin D levels.<sup>[44]</sup> Unresolved questions include the lack of standardization of the 25(OH)D assay, the subjectivity of assessing vitamin D status solely from dietary questionnaires, the reproducibility of findings from cell or animal models in humans, and determining the optimal dose for obtaining cardiovascular effects. Future investigations should also emphasize bioavailability rather than total 25(OH)D.

Even meta-analyses of clinical trials may lack conviction, particularly due to limited samples and low levels of significance. Bias stemming from participant selection, comparability of study groups, and the selection of outcomes of interest could contribute to disparate results. As lower doses of vitamin D2 supplementation and shorter intervention periods were associated with higher mortality,<sup>[38]</sup> the necessity of vitamin D supplementation solely in cases of deficiency for its cardio-protective effects remains unclear. The effectiveness of different types of vitamin D or vitamin D analogs is another unanswered question. Food-based strategies for enhancing vitamin D status in the population could potentially lower cardiovascular risk if a causal link between low vitamin status and cardiovascular pathology is demonstrated.<sup>[84]</sup> Furthermore, ensuring the safety and efficacy of vitamin D supplementation in reducing the risk of cardiovascular events, while considering diverse patient populations, dosages, and treatment durations, is highly recommended.

Despite plausible biological mechanisms for the role of vitamin D in cardio-protection, a cause-and-effect relationship has not yet been established. Well-designed and adequately powered prospective RCTs with vitamin D supplementation and CVD as primary outcomes are essential. Such trials could validate

the promising findings of observational studies, considering parameters like endothelial function, arterial stiffness, and patients undergoing percutaneous coronary interventions. Guidelines are needed to mandate genotyping for VDR variants in evaluating patients with CVD.<sup>[85]</sup>

## Conclusions

Despite advanced treatment strategies, CVD remains the foremost cause of death. Longitudinal studies provide evidence that vitamin D deficiency independently contributes to cardiovascular risk, correlating with an elevated likelihood of cardiovascular morbidity and mortality. However, establishing causation from these associations is challenging, as low vitamin D levels may merely act as a proxy for diminished exercise capacity and limited sunlight exposure. The direct influence of vitamin D on cardiovascular outcomes and whether supplementing vitamin D in CVD patients yields benefits are questions that require substantiation. Unidentified factors and interactions with other endocrine networks likely play a role in vitamin D biology, underscoring the necessity for additional clinical trials. These trials aim to clarify whether low vitamin D concentrations serve as markers for other processes, indicate a genetic predisposition to disease, or have a causal relationship with risk. Advancing our understanding of how vitamin D impacts cardiovascular events holds the potential to alleviate the burden of CVD and enhance the overall cardiovascular health of individuals.

## Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

## Authors' contributions

The author confirms sole responsibility for the following: study conception, data collection, analysis and interpretation of results, and manuscript preparation.

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## Conflicts of interest

There are no conflicts of interest.

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