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REVIEW

Relationship between vitamin D deficiency and cardiovascular disease

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Abstract

Epidemiological studies have found that low 25-hydroxyvitamin D levels may be associated with coronary risk factors and adverse cardiovascular outcomes. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. In this review, we analyze the association between vitamin D supplementation and the reduction in cardiovascular disease. The role of vitamin D deficiency in cardiovascular morbidity and mortality is still controversial, and larger scale, randomized placebo controlled trials are needed to investigate whether oral vitamin D supplementation can reduce cardiovascular risk. Given the low cost, safety, and demonstrated benefit of higher 25-hydroxyvitamin D levels, vitamin D supplementation should become a public health priority for combating common and costly chronic cardiovascular diseases.

Key words: Cardiovascular disease; Morbidity; Mortality; Review; Vitamin D

Core tip: We performed an extensive review to determine whether vitamin D supplementation reduces cardiovascular risk. Only double-blind, placebo- and randomized-controlled trials were included. The role of vitamin D deficiency in cardiovascular morbidity and mortality is still controversial, and larger scale, randomized placebo controlled trials are underway to address this issue. These results from these studies will likely not be available for another 3-5 years. At this stage, we propose recommendations for preventing of vitamin D deficiency and conclude that there is a benefit to vitamin D supplementation.

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INTRODUCTION

Vitamin D is likely one of the oldest hormones, having existed for at least 750 million years[1]. Studies have demonstrated that low levels of vitamin D represent a problem of global dimensions[2-13]. A recent Workshop Consensus for Vitamin D Nutritional Guidelines estimated that approximately 50% and 60% of the elderly in

North America and the rest of the world, respectively, do not have satisfactory vitamin D levels[14]. The situation is similar in younger subjects. Reasons for this widespread deficiency remain unclear but are likely related to factors such as urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, as well as decreases in the cutaneous production of vitamin D with age. Epidemiological pooled analysis of prospective observational studies of diverse populations demonstrates that hypovitaminosis D is associated with a modest risk of cardiovascular events[15-20]. The amount of vitamin D obtained from dietary sources is generally viewed as too low in many regions of the world to have an effect on the vitamin D status at the population level[14]. This review introduces the general concept of vitamin D, defines vitamin D deficiency, evaluates the relationship between vitamin D deficiency and cardiovascular disease, proposes a recommendation for preventing vitamin D deficiency and offers conclusions.

NATURE OF VITAMIN D

There are 2 major forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is found in plants and can be consumed in fortified foods or as a supplement. Vitamin D3 is obtained from either dietary sources or through the conversion of 7-dehydrocholesterol in the skin upon exposure to ultraviolet B (UVB) radiation[10,21]. Vitamin D3 from the skin is bound to the vitamin D-binding protein, whereas vitamin D2 and vitamin D3 from diet are bound to vitamin D-binding protein and lipoproteins. Both forms are hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D; D represents D2 or D3]. However, 25(OH)D is inactive and requires hydroxylation in the kidney to form 1,25-dihydroxyvitamin D[1,25(OH)2D, calcitriol]. Calcitriol [1,25(OH)2D] maintains calcium in the blood and has an array of effects on the body's organs. Calcitriol acts in an endocrine manner to regulate calcium metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton[10,19,22,23]. Although 1,25(OH)2D is considered to be the active form of vitamin D, its levels in the serum do not correlate with overall vitamin D status, whereas the 25(OH)D levels is a more clinically relevant marker[24]. Vitamin D activity is measured in μg of 25(OH)D (1 μg = 40 International Units, IU). The minimum desirable serum level of 25(OH)D has been suggested to be 20-30 ng/mL according to the consensus conference[14].

Dietary sources of vitamin D are limited to fatty fish (wild or farm salmon, mackerel, tuna fish, sardines, and cod liver oil) and products fortified with vitamin D, which include dairy products, cereals, margarine, flour, and orange juice[24,25].

DEFINITION OF VITAMIN D DEFICIENCY

Several measures have been used to define vitamin D deficiency, insufficiency, and adequacy. A 25(OH)D of < 20 ng/mL is associated with suppressible levels of parathyroid hormone when challenged with pharmacologic dosages of vitamin D[26]. Parathyroid hormone levels begin to reach their nadir when the 25(OH)D levels are > 30 ng/mL[27,28]. Intestinal calcium absorption in adults is maximized when 25(OH)D is > 30 ng/mL[29]. Thus, many experts define vitamin D deficiency, insufficiency, and sufficiency as levels of < 20, 21 to 29, and > 30 ng/mL, respectively. To achieve these levels, a minimum of 1000 IU of vitamin D2 or vitamin D3 is needed daily when sun exposure is either unavailable or inadequate for producing vitamin D3, such as during the winter or when a sunscreen is used[30,31].

In the United States, Europe, India, Asia, Middle East, New Zealand, and Australia, vitamin D deficiency is common in pregnant women, newborns, young and adolescent children, and the elderly[32-37]. Serum vitamin D levels are lower in European young adults than in North American young adults during winter[37]. Vitamin D deficiency is especially common in people of color or who avoid sunlight[38].

RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Numerous studies have found high rates of CV diseases among patients with lower levels of vitamin D. More recently, low levels of 25(OH)D have been linked to the presence of cardiovascular disease, hypertension, and the metabolic syndrome[39-42]. It is still unclear whether supplementation with vitamin D is beneficial to cardiovascular health. To this end, we have performed an extensive survey of published studies. Only double-blinded and randomized controlled trials (RCT) were included. The databases searched include MEDLINE, EMBASE, and PUBMED from January 1966 to May 2013. We selected search terms that capture generic and specific words relevant to the exposure and outcome on the basis of Medical Subject Heading terms and text words from a priori identified key articles. The terms selected for vitamin D were the following: "vitamin D intake, vitamin D supplement, calcidiol, calcitriol, cholecalciferol, and ergocalciferol". The terms selected for cardiovascular disease (CVD) were the following: "cardiovascular disease, ischemic heart disease, coronary artery disease, cardiovascular mortality, myocardial infarction, and stroke". We restricted the search to articles published in English and studies of humans that double-blinded and RCT. We applied the same search strategy to each database. Because of the limitations in assessing cause-effect relationships, we excluded ecological, cross-sectional, and retrospective case-control studies. By screening abstracts, we also excluded case reports, studies of vitamin D combination treatment (*e.g.*, combined vitamin D + calcium supplementation), and studies that did not assess the use of

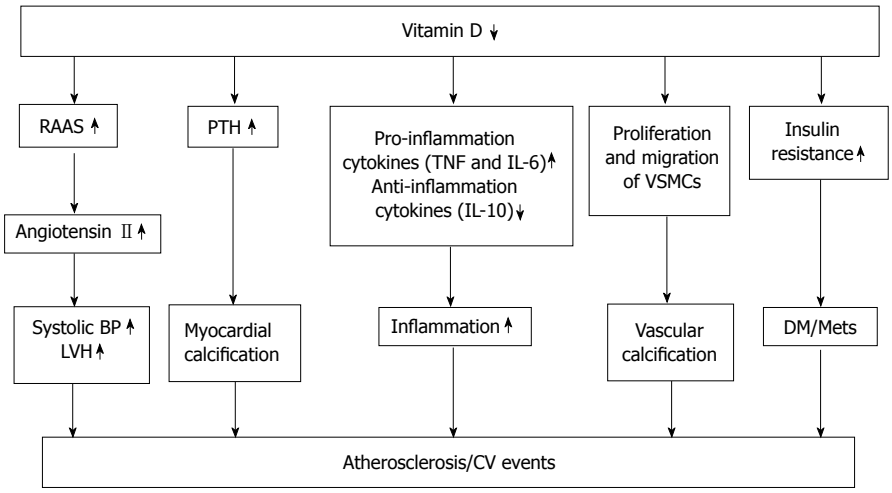

Figure 1 Potential mechanisms for cardiovascular effects of vitamin D deficiency. The data were modified from References 51, 52, and 54. RAAS: Renin-angiotensin-aldosterone system; PTH: Parathyroid hormone; BP: Blood pressure; LVH: Left ventricular hypertrophy; TNF: Tumor necrosis factor; IL-6: Interleukin-6; VSMCs: Vascular smooth muscle cells; DM: Diabetes mellitus; MetS: Metabolic syndrome; CV: Cardiovascular.

vitamin D supplementations. We retrieved articles that passed the abstract screening test for a full-text review, and we further excluded review articles, editorials, or letters to editors as well as studies lacking a comparison between participants who received vitamin D supplementation and non-recipients.

After the abstract screening and full-text review, we selected 19 eligible articles. Ten articles favored beneficial cardiovascular effects after supplementation with vitamin D (Table 1)[43-52]. A trial in the United States randomly assigned 283 African American subjects into a 4-arm, double-blind trial of placebo, 1000, 2000, or 4000 IU of oral cholecalciferol per day. At baseline and 3 mo, the systolic and diastolic pressure and 25(OH)D were measured. This study found that although cholecalciferol supplementation did not affect the diastolic pressure (P = 0.37), the difference in systolic pressure between baseline and 3 mo was +1.7 mmHg for those receiving placebo, -0.66 mmHg for 1000 U/d, -3.4 mmHg for 2000 U/d, and -4.0 mmHg for 4000 U/d of cholecalciferol (-1.4 mmHg for each additional 1000 U/d of cholecalciferol; P = 0.04). For each 1-ng/mL increase in the plasma 25(OH)D, there was a significant 0.2-mmHg reduction in the systolic pressure (P = 0.02)[43]. Larsen *et al*[45] investigated the effect of 3000 IU vitamin D per day for 20 wk in a randomized, placebo-controlled, double-blind study in 130 hypertensive patients residing in Denmark. Vitamin D supplementation reduced the systolic pressure significantly. In a post-hoc subgroup analysis of 92 subjects with baseline p-25(OH)D levels < 32 ng/mL, significant decreases in the 24-h systolic and diastolic BP were observed in response to cholecalciferol supplementation[45]. Similar reports[44,46-52] relevant to "vitamin D supplementation produces beneficial cardiovascular effects" are summarized in Table 1.

In contrast, the remaining nine articles did not find a cardioprotective effect of vitamin D supplementation (Table 2)[53-61]. In Ireland, 202 healthy adults (20-40 years old) and 192 healthy elders (≥ 64 years old) were recruited and received vitamin D supplementation at a dosage of 0, 200, 400, or 600 IU for 22 wk. Serum 25(OH)D, intact parathyroid hormone, systolic and diastolic blood pressure, fasting lipids, glucose and insulin, high-sensitivity CRP, matrix metalloproteinase-9, and its inhibitor (tissue inhibitor metalloproteinase-1) were measured at baseline and 22 wk later, which was the endpoint. This study revealed that there were no significant effects of supplementation on the CVD risk biomarkers in either age group[56]. Wood *et al*[60] conducted a parallel-group, double-blind, placebo- and randomized-controlled trial in 305 healthy postmenopausal women to test whether daily doses of vitamin D3 at 400 or 1000 IU/d for 1 year affected the conventional markers of cardiovascular disease risk. The serum lipid profile (total, high-density lipoprotein, and low-density lipoprotein cholesterol; triglycerides; and apolipoproteins A-1 and B100), insulin resistance (homeostatic model assessment), inflammatory biomarkers (high-sensitivity C-reactive protein, IL-6, and soluble intracellular adhesion molecule-1), and blood pressure were studied. They found that dietary vitamin D supplementation is unlikely to reduce CVD risk factors, such as serum lipid profile, insulin resistance, inflammatory biomarkers, and blood pressure[60]. Additional reports that did not find a cardioprotective effect of vitamin D supplementation are summarized in Table 2[53-55,57-59,61].

MECHANISMS FOR THE CARDIOVASCULAR EFFECTS OF VITAMIN D DEFICIENCY

The results of recent nationwide investigations showed an association between low 25(OH)D levels and important cardiovascular risk factors[40,62], and further supported the findings of preclinical and clinical investigations that demonstrated positive effects of vitamin D and its

Table 1 Double-blind, placebo- and randomized-controlled trials that favor supplement with vitamin D may have a beneficial cardiovascular effects

Ref.	Country	Participants	Intervention	Duration of follow-up	Results
Forman *et al*[43]	United States	283 African-American subjects	Oral vitamin D3 (cholecalciferol, 1000, 2000, or 4000 IU), or placebo per day for 3 mo	6 mo	Reduction in systolic pressure.
Harris *et al*[44]	United States	45 African-American adults	60000 IU monthly oral vitamin D(3) or placebo for 16 wk	16 wk	Effective at improving vascular endothelial function
Larsen *et al*[45]	Denmark	112 Hypertensive patients	75 μg (3000 IU) cholecalciferol per day or placebo for 20 wk	20 wk	Significant decreases in systolic blood pressure
Lind *et al*[46]	Sweden	65 subjects with impaired glucose tolerance	Alphacalcidol (0.75 microgram daily) or placebo over 12 wk	12 wk	Significant reduction of blood pressure
Lind *et al*[47]	Sweden	65 Hypertensive patients with primary hyperparathyroidism	Alphacalcidol, (1 microgram daily) or placebo over 6 mo	6 mo	Significant reduction of blood pressure
Longenecker *et al*[48]	United States	45 HIV-infected individuals with vitamin D deficiency	Vitamin D3 4000 IU daily or placebo for 12 wk	12 wk	Modestly improved cholesterol
Salehpour *et al*[49]	Iran.	77 healthy premenopausal overweight and obese women	Vitamin D (25 μg/d as cholecalciferol) or the placebo group for 12 wk	12 wk.	Significantly improvement of HDL-cholesterol, apoA-I concentrations and LDL-cholesterol: apoB-100 ratio.
Shedeed[50]	Egypt	80 infants with CHF	Vitamin D(3) oral drops or placebo oral drops for 12 wk	12 wk	Significant improvement of HF score, LV end-diastolic diameter, LV end-systolic diameter, LV ejection fraction%, and myocardial performance index.
Witham *et al*[51]	United Kingdom	58 stroke patients	100000 units of a single oral dose of vitamin D2 or placebo	16 wk	Short-term improvement in endothelial function (Flow mediated dilatation was significantly higher in the intervention group at 8 wk)
Zittermann *et al*[52]	Germany	200 healthy overweight subjects in a weight-reduction program	Vitamin D (83 microg/d) or placebo for 12 mo	12 mo	Significant improvement of cardiovascular disease risk markers

LV: Left-ventricular; CHF: Congestive heart failure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; IU: International units.

analogues on fibrinolysis, blood lipids, thrombogenicity, endothelial regeneration, and smooth muscle cell growth[63-69]. Together, these findings strongly suggest that 25(OH)D has beneficial effects, some involving the cardiovascular system, that are independent of calcium metabolism. Several mechanisms might be responsible for the protective effect of calcitriol on atherosclerotic lesions and vascular calcification (Figure 1). First, vascular smooth cells express vitamin D receptors. Calcitriol inhibits proliferation of these cells with an acute influx of calcium into the cells[69]. Second, a lack of calcitriol results in an increase in the serum parathyroid hormone (PTH) levels. Excess PTH levels may at least in part promote cardiovascular disease by increased the cardiac contractility and myocardial calcification[70]. Third, experimental studies have shown that calcitriol suppresses the release of the inflammatory cytokines such as tissue necrosis factor-α (TNF-α), IL-6, and IL-10. There is now increasing evidence that inflammatory processes play an important role in the development of a vascular insult[71-88]. Fourth, calcitriol is a negative endocrine regulator of the rennin-angiotensin-aldosterone system (RAAS) The RAAS plays a central role in the regulation of blood pressure, electrolytes, and volume hemostasis. Calcitriol treatment reduces blood pressure, plasma rennin activity and angiotensin Ⅱ levels[89]. Fifth, vascular smooth muscle cell proliferation and migration, as well as the osteogeneic processes may contribute to the vascular calcification, which may eventually cause the thrombogenesis[90]. Sixth, vitamin D plays a role in the insulin sensitivity, which has a role in diabetes and in metabolic syndrome[78,90].

Essential hypertension is related to several disturbances in the systemic and cellular calcium metabolism. Extracellular ionized or ultrafiltrable calcium levels are decreased while intracellular cytosolic calcium concentrations are increased. Dietary calcium intake is often lower and renal calcium loss is higher in hypertensive than in normotensive subjects. Epidemiologic studies have demonstrated an inverse association between serum 25(OH)D levels and diastolic blood pressure[91]. Moreover, Afro-Americans have a significantly higher prevalence of diastolic hypertension and have lower 25(OH)D levels compared with white Americans[88,92,93]. In clinical trials, the daily administration of 5 μg of vitamin D showed no effects on blood pressure in normotensive subjects. However, some studies have demonstrated a blood pressure lowering effect with 0.75 or 1.0 μg vitamin D/d in hypertensive patients[94]. Short-term supplementation with 20 μg of vitamin D/d significantly reduced diastolic blood pressure. A reduction in the diastolic and systolic blood pressure was observed in mildly hypertensive patients after 6 wk of UV-B exposure[88,94]. A normalization

Table 2 Double-blind, placebo- and randomized-controlled trials that do not favor supplementation with vitamin D

Ref.	Country	Participants	Intervention	Duration of follow-up	Results
Gepner *et al*[53]	United States	114 post-menopausal women	Vitamin D3 2500 IU or placebo, daily for 4 mo	4 mo	No significant effects of vitamin D supplementation to reduce cardiovascular disease risk
Jorde *et al*[54]	Norway	330 overweight or obese subjects	Vitamin D [cholecalciferol, vitamin D(3)] 40000 IU, vitamin D 20000 IU, or placebo per week for 1 yr	1 yr	No significant effect of vitamin D on glucose tolerance, blood pressure or serum lipids
Marckmann *et al*[55]	Denmark	52 chronic kidney disease patients with vitamin D deficiency	40000 IU of cholecalciferol orally per week for 8-wk	8 wk	No significant impact on functional markers and plasma concentrations of biomarkers related to cardiovascular disease
Muldowney *et al*[56]	Ireland	394 healthy participants	Cholecalciferol at doses of 0, 5, 10, or 15 μg/d (0-600 IU) for 22 wk	22 wk	No significant effects of supplementation on CVD risk biomarkers
Scragg *et al*[57]	United Kingdom	95 elderly adults	A single oral dose of 2.5 mg cholecalciferol or placebo	5 wk	No significant effect of vitamin D supplementation to change blood pressure or serum cholesterol
Stricker *et al*[58]	Switzerland	62 peripheral arterial disease patients with vitamin D deficiency	A single, oral supplementation of 100000 IU vitamin D3 or placebo	1 mo	Unlikely to influence endothelial function, arterial stiffness, coagulation and inflammation
Thadhani *et al*[59]	United States	227 patients with chronic kidney disease	Paricalcitol or placebo over 48 wk	48 wk	Unlikely to alter left ventricular mass index or improve certain measures of diastolic dysfunction
Wood *et al*[60]	United Kingdom	305 healthy postmenopausal women	A daily capsule of 400 or 1000 IU vitamin D(3) or placebo for 12 mo	12 mo	Unlikely to reduce CVD risk factors
Yiu *et al*[61]	Hong Kong	100 patients with type 2 DM	Oral vitamin D (5000 IU/d) or placebo per day for 12 wk	12 wk	No significant effect on vascular function or serum biomarkers of inflammation and oxidative stress

CVD: Cardiovascular disease; IU: International units; DM: Diabetes mellitus.

of the enhanced intracellular calcium levels seems to be an important measure for reducing blood pressure, which can explain the therapeutic effects of calcium-channel blockers in hypertensive patients[95,96]. Low adenylate cyclase activity can result in a decreased calcium re-uptake into the sarcoplasmic reticulum and can contribute to an accumulation of intracellular free calcium and to an increase in vascular reactivity and blood pressure[97]. Activity of the intracellular adenylate cyclase is calcitriol-dependent and improvement of the activity of this enzyme may thus reduce free cellular calcium concentrations.

Hyperlipidemia, diabetic mellitus, and an increase in blood coagulation factors, blood viscosity, and leukocyte counts are important risk factors for the development of arteriosclerosis. There is now increasing evidence that arteriosclerosis is a low-grade systemic inflammatory disease. An increase in serum C-reactive protein levels is an important indicator of inflammatory reactions and also of the risk of developing arteriosclerosis[98]. The synthesis of C-reactive protein is regulated by IL-6 and IL-10 as well as TNF-α[73,99]. Animal studies have demonstrated that IL-6 and IL-10 accelerate arteriosclerosis[100]. Calcitriol can suppress the secretion of TNF-α and IL-6 *in vitro* in a dose-dependent manner[101]. A recent study identified an inverse association between TNF-α and 25(OH)D levels in human subjects[102].

PREVENTION OF VITAMIN D INSUFFICIENCY

Preventive measures must take into account that there is a high risk of vitamin D insufficiency in the whole population during winter and that the elderly population, especially institutionalized subjects, are at an increased risk for vitamin D insufficiency or even deficiency. There are two prevention models available: increased exposure to ultraviolet light and increased oral vitamin D intake. Sunlight provides the most potent source of vitamin D, with approximately 3000 IU vitamin D3 for 5 to 10 min of mid-day, mid-year exposure of the arms and legs for a light-skinned Caucasian[10]. Adequate daily oral vitamin D intake could be an easy and effective measure for maintaining a physiological vitamin D status. In November 2010, the Institute of Medicine of the National Academies of United States provided an update to the recommended intakes of calcium and vitamin D. For vitamin D intake, the committee assumed that North Americans need on average 400 IU of vitamin D daily; people 71 years old and older may require as much as 800 IU per day[103]. However, nutrition experts have suggested that vitamin D intake of 800 to 2000 IU daily may be needed. These doses are quite difficult to obtain without routine supplementation, particularly in areas with extreme win-

ter climates and higher latitudes[104]. The United States Food and Drug Administration reported that a dose of 2000 IU daily is safe[21]. The Institute of Medicine of the National Academies has recently suggested a new tolerable upper intake level of only 4000 IU of vitamin D per day for the general adult population[103] because of the concern about potential toxicity at higher levels of 25(OH)D[103-106]. However, currently there is no recommended daily intake dose for vitamin D. For a practical approach, maintenance therapy can be continued by routine sunlight exposure or by administering vitamin D supplements, 800 to 2000 IU vitamin D3 daily or 50000 IU of either D2 or D3 every 2 wk[10,21,107].

RECOMMENDATIONS

It is still unproven whether supplementation with vitamin D reduces the cardiovascular risks. Autier *et al*[108] analyzed 18 independent randomized controlled trials of more than 57000 participants with mean follow-up of 5.7 years. Although there was considerable variability in the dose of vitamin D administered (from 300 to 2000 IU daily), the summary relative risk for all-cause mortality was reduced by 7% with vitamin D therapy[109]. Wang *et al*[106] performed a meta-analysis of 8 randomized trials, showing a slight, but statistically nonsignificant, 10% reduction in CV disease risk with vitamin D supplementation at moderate to high doses (approximately 1000 IU daily). Another meta-analysis evaluated the relationship between vitamin D levels and cardiovascular risk and reported that vitamin D was associated with nonsignificant effects on the patients' death, myocardial infarction and stroke rates[109]. However, this study did not focus on the effect of vitamin D supplementation in the reduction of cardiovascular risks. At the present stage, we still feel confident that the benefits of vitamin D will likely outweigh the risks. A large double-blind randomized placebo-controlled trial (Vitamin D and Omega-3 Trial, VITAL) sponsored by the National Institutes of Health and run by Harvard Medical School and the Brigham and Women's Hospital is underway[110]. This study should help to determine whether increasing low vitamin D levels will reduce the risk of CV events, depression, and death. O' Keefe *et al*[111] have claimed that several large scale trials have just started but the results of these trials will not be available for another 3-5 years or more; in the meantime, they recommend a daily intake of 1500 to 2000 IU of vitamin D3 for most American adults.

CONCLUSION

On the basis of this review, hypovitaminosis D has been observed worldwide, and many studies have demonstrated a strong association between vitamin D status and cardiovascular disease risk factors, including hypertension, diabetes, metabolic syndrome and inflammation. In the meantime, health professionals should be aware of the potential negative implications of vitamin D insufficiency and make recommendations for their patients to improve their vitamin D status. We suggest that to maintain health in younger and older adults and prevent hypertension, chronic heart diseases, and cardiovascular events, an increase in the current recommended intake of vitamin D is warranted. However, definitive randomized controlled trials are still needed to determine whether vitamin D therapy is beneficial to preventing cardiovascular disease. Given the low cost, safety, and demonstrated benefits of higher 25(OH)D concentration, vitamin D supplementation should become a public health priority to combat these common and costly chronic cardiovascular diseases.

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