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Vitamin D and Cardiovascular Disease: An Appraisal of the Evidence

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Abstract

Background—Supplementation with vitamin D (VitD) has received attention as a potential cardioprotective strategy. Biologically plausible mechanisms have been proposed to link VitD to coronary heart disease (CHD) prevention and observational studies suggest an inverse association between serum 25-hydroxyvitamin D (25OHD) concentrations and CHD. Few randomized clinical trials of VitD supplementation and CHD have been conducted, however, and no completed trial has been done with CHD as the primary pre-specified outcome.

Content—A search was conducted in PubMed to find prospective studies on the use of vitamin D supplementation and cardiovascular risk factors (RFs) and/or cardiovascular disease. The exact search query was ((vitamin D supplement*[Title/Abstract]) AND cardiovascular [Title/Abstract]) AND prospective [Title/Abstract]. This query yielded 42 results. Randomized Controlled Trial (article type) was employed as a filter in a subsequent query with the same search terms. We review the evidence that VitD supplementation modifies coronary RFs, such as blood pressure, lipids, and glucose tolerance, and/or affects the development of clinical CHD events. We address potential sources of confounding in observational epidemiologic studies of the relationship between serum 25OHD and CHD. We also address laboratory assay issues relevant to the reliable measurement of 25OHD.

Summary—Most VitD supplementation trials have not demonstrated improvement in cardiovascular disease, but have tested relatively low doses of VitD. Thus, the evidence remains inconclusive, highlighting the need for rigorous randomized trials of higher VitD doses, with cardiovascular events as prespecified outcomes. While awaiting ongoing trial results, the recommended dietary allowances from the Institute of Medicine remain the best guidepost for nutritional requirements.

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Background

Coronary heart disease (CHD) remains the leading cause of mortality in U.S. men and women[1,2]. Primary risk factors for CHD in both sexes include older age, smoking, diabetes mellitus, dyslipidemia, hypertension, physical inactivity, obesity, the metabolic syndrome, a family history of premature CHD (males <55 and females <65 years old), and a personal history of peripheral arterial disease[2–5]. However, few Americans achieve optimal control of these risk factors and furthermore, many CHD events are unexplained by these traditional factors[6]. Thus, novel approaches to reducing CHD risk remain of great interest.

Vitamin D has garnered recent attention for its potential cardio-protective properties and has become a topic of considerable interest in the clinical as well as the research communities. An increased incidence of CHD and hyperlipidemia in higher latitudes has been ecologically correlated with less sunlight[7]. Other studies report that those with a lower exposure to ultraviolet light had lower vitamin D concentrations and a higher risk of CHD, myocardial infarction, and hypertension[8–10]. Lower serum concentrations of vitamin D have also been associated with increased risk of sudden cardiac death[11], peripheral arterial disease[12], and greater carotid intima-medial thickness[13]. However, randomized trials of these relationships have been sparse and data related to these outcomes have been inconsistent. Postmenopausal women, as well as older men, may be at particularly high risk for vitamin D deficiency due to age-associated declines in skin photoisomerization of 7-dehydrocholesterol[14] and lower dietary intakes of oral vitamin D.

Vitamin D Production and Homeostasis

Vitamin D (calciferol) is a term that refers to a group of lipid soluble compounds with a four-ringed cholesterol backbone.In the skin, pro-vitamin D is photoisomerized to vitamin D_3 (cholecalciferol) by sunlight and ultraviolet light.The other major source of vitamin D is intestinal absorption.Vitamin D_3 is then transported to the liver where hydroxylation takes place to form 25-hydroxy-vitamin-D (25OHD), including both $25OHD_2$ and $25OHD_3$. 25OHD then travels to the kidney, where it is further hydroxylated to 1,25-dihydroxy-vitamin D ($1,25(OH)_2$-vitamin D or calcitriol)[15], the physiologically active form of vitamin D[16,17].The most representative measure of vitamin D status is the serum concentration of 25OHD[18,19]. Serum 25OHD is an excellent marker of vitamin D sufficiency, because it reflects the total stored quantity from both endogenous and exogenous sources[18]. As serum 25OHD concentrations decrease, parathyroid hormone (PTH) concentrations increase and positively influence the conversion of 25OHD to $1,25(OH)_2D$, which subsequently maintains normal intestinal absorption of calcium. Therefore, $1,25(OH)_2D$ is not representative of the total body storage of vitamin D as serum calcium and $1,25(OH)_2D$ concentrations will be normal or slightly increased during vitamin D deficiency as a result of secondary hyperparathyroidism[18,20].

Risk Factors for Vitamin D Deficiency

Risk factors for developing vitamin D deficiency, or lower serum concentrations of vitamin D, include age >65[21], dark skin pigmentation, obesity (resulting from storage in adipose tissue[22]), kidney and/or liver disease[23], disorders affecting fat absorption (e.g. celiac disease, Crohn's disease, ulcerative colitis, some types of bariatric surgery), and end organ insensitivity to calcitriol ($1,25[OH]_2D$). In addition, 25OHD deficiency is also known to be related to environmental variables resulting in decreased exposure to ultraviolet light, such as institutionalization, decreased outdoor physical activity, and frailty[24].

Potential Mechanisms for an Association between Vitamin D Deficiency and CHD

Vitamin D receptors (VDRs) have been identified in many tissues including vascular smooth muscle cells[25],cardiomyocytes, and coronary arteries[26,27]. Given the presence of VDRs in the vascular system, including the coronary arteries, there are several biologically plausible pathways through which vitamin D could lead to improved cardiovascular health. Activation of the VDR, for instance, has been shown to inhibit vascular smooth muscle cell proliferation, which is believed to be cardioprotective[28].In some studies, higher concentrations of 25-hydroxyvitamin D (25OHD) and/or vitamin D supplementation have also been associated with a systemic anti-inflammatory state via the effects on interleukins, C-reactive protein, and anti-inflammatory cytokines, a milieu which is again believed to foster cardioprotection[29–31]. Vitamin D may control blood pressure through its regulatory effects on the renin-angiotensin-aldosterone-system[32]. Limited research has suggested that vitamin D supplementation may decrease the incidence of impaired glucose tolerance and diabetes mellitus [33,34] along with improved lipid parameters[35]. Furthermore, the results of various studies have suggested a link between vitamin D and a lower likelihood of autoimmune conditions such as rheumatoid arthritis[36], diabetes (both type 1 and type 2)[37,38], and multiple sclerosis[39].

Observational Data

Much of the excitement concerning a correlation of vitamin D deficiency and CHD stems from observational data. As an example, Giovannucci, et al[9] followed 18,000 healthy male participants for 10 years. Individuals with vitamin D deficiency, defined as serum 25OHD concentrations ≤ 15 ng/mL, had a greater risk of a myocardial infarction than men with 25OHD concentrations ≥ 30 ng/mL,[9] with a relative risk of 2.42 (confidence interval [CI] 1.53 – 3.84, $P<0.001$). In the Framingham Offspring Study, a prospective analysis of 1,739 individuals with 25OHD concentrations < 15 ng/mL, the adjusted hazard ratio for a first incident cardiovascular event was 1.6 (95% CI 1.11 – 2.36, $P=0.01$). Those who had hypertension along with 25OHD deficiency had a hazard ratio of 2.1 (95% CI 1.3 –3.5, $P=0.003$) for a first cardiovascular event[18]. A meta-analysis of prospective but observational studies of 25OHD and cardiovascular events demonstrated a generally linear, inverse association up to 24 ng/mL (60 nmol/L), but no further reductions (threshold effect) at higher concentrations of 25OHD[40].

Limitations of the Observational Data

Despite considerable data demonstrating an association between vitamin D deficiency and poor cardiovascular outcomes, caution is advisable in interpreting the data from observational studies. Confounding by other lifestyle factors and a “healthy user” bias in nonrandomized studies may play a role in the current evidence suggesting an association. For example, age must be carefully controlled in analyses because older age[21] increases both the risk of vitamin D deficiency and the risk for myocardial infarction[41]. Decreased dietary intake and poor nutritional status can each lead to vitamin D nutritional deficiency. The lower intake could be a result of other disease(s) or could be linked to general malnutrition, either of which could increase the likelihood of CHD. Decreased ultraviolet light can be a result of less outdoor activity / exercise, and hence leading to an increased risk of CHD and low 25OHD. An additional confounding risk factor is obesity, which results in both an increased risk of CHD and low 25OHD concentrations, as 25OHD can be sequestered in adipose tissues[22].

Few observational studies are able to adjust fully for these confounding factors. Therefore, all of these risk factors, which are more likely to be associated with low 25OHD, may confound the relationship between 25OHD and CHD in nonrandomized studies. As pointed out earlier, vitamin D has been associated with a systemic anti-inflammatory milieu. While relevant pathways may include a beneficial interaction between vitamin D and C-reactive protein, interleukins, and/or cytokines[29–31], it has also been suggested that vitamin D deficiency may directly result from an inflammatory condition or state[42].

Randomized Controlled Trials

Few prospective randomized clinical trials evaluating the effects of vitamin D supplementation on CHD have been conducted, and currently none of the prospective trials have included CHD as the primary prespecified outcome[43–45]. Among the sparse randomized trials that have assessed CHD, or CHD risk factors, as a secondary or tertiary outcome, there has been no correlation identified for CHD and few for CHD risk factors (Table 1)[46–58]. In a study of 327 men and women over the age of 65, those receiving Vitamin D_3 actually had an increased risk of coronary death ($P < 0.001$)[58]. In a double-blind, placebo controlled, randomized clinical trial in the United Kingdom, conducted among 2,686 men and women 65–85 years of age, study participants received 100,000 IU of supplemental vitamin D_3 every 4 months (equivalent to ~833 IU daily) for 5 years[46]. There was no beneficial CHD effect attributable to vitamin D[46]. Additional results from the Women's Health Initiative (WHI) suggested that postmenopausal women receiving 400 IU/day of oral vitamin D_3 combined with calcium 1,000 mg/day had no reduction in their risk of CHD events or stroke[50]. In additional prospective trials, from sub-analyses of the WHI, calcium and Vitamin D_3 supplementation was not found to improve blood pressure[49] or coronary artery calcium scores[53]. Furthermore, there was no decrease in incident hypertension[59] or prevention of, or improvement in, the metabolic syndrome or diabetes[47]. In an 8 week prospective trial of 151 male and female vitamin D-deficient adults randomized to 50,000 IU of Vitamin D_3 vs. placebo, there was no improvement in lipid parameters[48]. Two small prospective trials looking at endothelial function revealed mixed results with one showing no effect[51] and the other showing short-term improvement in stroke patients with well controlled hypertension, however the effect was not sustained by the completion of the 16 week study[52].

Several small prospective studies have shown some improvement in CHD risk factors[55] and inflammation[30,56]. However, further data have shown no effect on glycemic control[54,57]. A recent prospective, randomized, double-blind, placebo-controlled clinical trial assessed the change in systolic and diastolic blood pressure in a healthy black population randomized to oral placebo, 1000, 2000, or 4000 IU/d of Vitamin D_3 for 3 months[60]. The results of this study revealed a 1.4 mm Hg decrease in systolic blood pressure for each additional 1,000 IU/d of Vitamin D_3 (P=0.04). While there was no statistically significant effect of oral Vitamin D_3 on diastolic blood pressure, for each 1 ng/mL increase in 25OHD there was a decrease of 0.2 mm Hg in systolic blood pressure (P=0.02). Despite the significant effect of oral Vitamin D_3 on systolic blood pressure, there appeared to be a threshold effect and those receiving 2000 IU/d and 4000 IU/d of Vitamin D_3 had similar results. Furthermore, those with 25OHD baseline concentrations ≥ 20 ng/mL had little benefit from supplementation compared to those with 25OHD baseline concentrations < 20 ng/mL (who had a 2.2 mm Hg decrease in systolic blood pressure; P=0.03). In addition, adjustment for baseline differences in blood pressure attenuated the study's findings. While this trial was designed to assess change in blood pressure, it is noteworthy that most other trials were designed to assess bone health, and cardiovascular outcomes were not pre-specified primary endpoints for most previous studies.

Meta-Analyses of Randomized Trials

Several meta-analyses have been done looking at both mortality and CHD risk related to vitamin D supplementation. A meta-analysis of 18 randomized clinical trials including 57,311 individuals was published in 2008[61]. In this analysis, a statistically significant 7% decrease in all-cause mortality in those receiving vitamin D supplementation was found[61]. However, a subsequent meta-analysis by Rejnmark, et al[62], which included 24 randomized trials of patients receiving vitamin D supplementation, with or without oral calcium, showed similar results but with the following important variation. While those patients supplemented with vitamin D and calcium had a similar 7% reduction in all-cause mortality as seen in the earlier study[61], those receiving vitamin D alone did not have a significant decrease in mortality. These results raise a number of questions, including the role calcium may have in any potential beneficial effect related to vitamin D supplementation. In consideration of a role of supplemental vitamin D, a recent systematic review and meta-analysis identified randomized trials published through August 2010 in patients randomized to Vitamin D supplementation vs. no treatment[63]. The outcome measures of interest included mortality, cardiovascular events, and CHD risk factors. A total of 51 studies were eligible. Of note, the analysis was not able to identify statistically significant differences in any of the outcomes, including myocardial infarction, stroke, all-cause mortality, or CHD risk factors such as lipid fractions, glucose, and systolic and diastolic blood pressure. Most of the trials, however, tested relatively low doses of vitamin D.

While the association between 25(OH)D deficiency and obesity is not new[22], the results of a recent large meta-analysis suggest that higher BMIs lead to lower plasma concentrations of 25(OH)D, implying a causative relationship. In contrast, lower concentrations of 25(OH)D did not appear to lead to high BMIs[64]. If these findings are confirmed, strategies to decrease obesity could also result in a lower prevalence of 25(OH)D deficiency.

Current Recommendations

The *Institute of Medicine* (IOM)[44] and the Agency for Healthcare Research and Quality (AHRQ)[43] reviewed the literature related to vitamin D and health related outcomes. Both came to the conclusion that, while there is sufficient evidence to support a role for calcium and vitamin D related to skeletal health, there was a lack of evidence supporting effects on non-bone-related health outcomes[44,45]. The IOM concluded that 600IU/day should be the recommended dietary allowance for ages 1–70 years, with 800IU/day recommended over age 70[18,61]. The IOM and AHRQ reports have generated some controversy and some investigators have stated that higher dietary allowances should be encouraged. The International Osteoporosis Foundation (IOF), for instance, recommends 800 – 1,000 IU/day as the average supplemental dose to achieve an appropriate plasma concentration of 25OHD[65]. The IOF adds that those at higher risk may need doses up to 2,000 IU/day to reach an appropriate concentration[65]. The *National Osteoporosis Foundation (NOF)* recommends 400–800 IU/day of oral vitamin D_3 for adults younger than 50 years of age and 800 – 1,000 IU/day for those older than 50[66]. In line with the IOF guidelines, they clarify that some people may need higher oral vitamin D_3 doses with 4,000 IU/day being noted as an upper limit of safety[66]. Similarly, the Endocrine Society's clinical guideline recommends at least 600 IU/day for adults 19 – 50 years of age and 600 – 800 IU/day for those older than 50. They also point out that for all adults, doses of 1,500 – 2,000 IU/day may be required to raise plasma concentrations of 25OHD above 30 ng/mL consistently[67]. Although controversy surrounds the 25OHD concentration to use as a cut point for vitamin D deficiency or insufficiency, the IOM suggests that a serum 25OHD concentration of at least 20 ng/mL will meet the vitamin D requirements for 97.5% or more of the U.S. and Canadian populations[68]. As discussed above, the recent study assessing oral Vitamin D_3 and blood

pressure[60] likewise supported a 25OHD concentration ≥ 20 ng/ml as being adequate. It was only those with 25OHD concentrations < 20 ng/ml at baseline who had a significant improvement in systolic blood pressure with Vitamin D_3 supplementation[60].

Laboratory Testing

The current assays available for 25OHD testing include antibody based methods and liquid chromatography (LC). The methodologies for plasma 25OHD analyses, however, have changed greatly over the years. The early testing methods utilized competitive protein binding assays, which were difficult to perform and lacked consistency. In the 1970's, early LC techniques were introduced, allowing for the first time the ability to separately detect $25OHD_2$ and $25OHD_3$. As the LC assays were being refined, in the 1980's, antibody based assays were introduced. More recently, the antibody assays have been modified to automated, multiwell plate-format, which has made them quite popular. A notable drawback is the inability to distinguish between $25OHD_2$ and $25OHD_3$. It is also noteworthy that much of the past research related to plasma concentrations of vitamin D are from antibody-based techniques. The variety of testing methods and questions about reliability of testing also adds to the complexity of interpreting previous research. Most recently, the LC method has made significant advances, with the incorporation of a tandem mass spectrometer (MS/MS), resulting in the Liquid Chromatography - Tandem Mass Spectrometry (LC MS/MS) technique. This has allowed for a very high specificity and sensitivity along with outstanding reproducibility[44].

Because a majority of previous data utilized the antibody-based assays, it is important to point out the concern related to inconsistencies between testing methods. Research looking at inter-laboratory comparisons has suggested a high and concerning degree of variability[44]. This has led to external quality assurance programs including the National Institute of Standards and Technology (NIST) reference standards[69,70], which utilize a "validated" LC MS/MS technique for calibration[44]. A Standard Reference Material (SRM) and a calibration solution are now available through the NIST to help assure accuracy and reliability of 25OHD measurments[44].

In a study by Lia et al, when comparing same subject samples, DiaSorin Liason testing compared to LC MS/MS (selected as the nominal gold standard) showed a 16% to 29% higher rate of vitamin D deficiency, respectively, just based on the laboratory test utilized. Also, the Diasorin Radioimmunoassay (RIA) has been shown to produce lower serum 25OHD values than the LC MS/MS[71]. The LC MS/MS, which is felt to be inherently more accurate[71] with high sensitivity, high specificity, and better reproducibility, tends to have values slightly higher than the RIA techniques[71]. Some have argued that LC MS/MS results may need to be adjusted downward based on a mathematical formula while others suggest the Diasorin RIA may need to be corrected upward[71]. Regardless, the value of using consistent and reliable laboratory testing, therefore, is of paramount importance and LC MS/MS is currently the preferred laboratory assay.

For quality assurance, it is critically important that test measurements are performed on standardized samples, with the inclusion of NIST samples and split replicate specimens for laboratory assessment. This allows labs to compute means, standard deviations, and coefficients of variations; samples should be protected from direct sunlight to ensure the accuracy and precision of assays[30,44,72]. The new NIST reference standards provide hope that 25OHD measurements can achieve improved accuracy and reliability, diminishing the variability between tests and laboratory centers seen in the past[44].

Future Research Directions

Although our understanding of vitamin D deficiency and its ramifications is rapidly expanding, there is still much to learn. Several large-scale randomized trials of moderate-to-high dose vitamin D supplementation in cardiovascular disease prevention are being conducted in the U.S. and throughout the world. As one example, the VITamin D and OmegA-3 TriaL (VITAL; Principal Investigator: J. Manson) is a randomized, double blind, placebo controlled clinical trial among more than 20,000 U.S. men and women above age 50, testing 2,000 IU/day of oral vitamin D_3 and omega 3 fatty acid supplements in a 2×2 factorial design, with cardiovascular disease and cancer as primary prespecified outcomes[73]. Results are expected in 2017. While we await the results of VITAL and other ongoing randomized trials of vitamin D, it is also important to point out that many of the trials will analyze the effects of vitamin D_3 supplementation in a general population of patients with, and without, 25OHD deficiency. There may be value, therefore, in stratifying by baseline concentrations or subsequently analyzing results in vitamin D deficient patients[74].

Although data have suggested that VDR concentration may be inversely correlated with the degree of coronary artery atherosclerosis (CAA)[26], the link or relationship to $25OHD_3$ plasma concentrations remains unclear. A recent study suggested that the highest $25OHD_3$ plasma concentration, along with the lowest VDR abundance, had the greatest degree of CAA[27], but these findings need corroboration. If confirmed, this may suggest a therapeutic window phenomenon, that high concentrations of $25OHD_3$, above an upper threshold, may be detrimental[18]. Data have also suggested a strong link between $25OHD_3$ deficiency and race/heritability[75–79]. A recent study[76] indicated that individual differences in 25OHD concentrations have both genetic and environmental associations, and the relative contribution to CHD outcomes remains unclear. In this particular study, the variations attributable to genetics were predominantly demonstrated in the winter when ultraviolet exposure was minimal, but not in the summer months, implying that environmental factors (mostly sun exposure) may compensate for vitamin D deficiency related to genetics[77].

As reviewed above, we are clearly in need of well-designed and adequately powered prospective randomized trials with vitamin D supplementation and CHD or CHD biomarkers as primary outcomes. It will be important to determine whether supplementation makes a clinically meaningful difference for CHD and whether the baseline 25OHD concentration modifies the response. This will help to elucidate whether low vitamin D concentrations represent a marker for other processes, are indicators of genetic predisposition to disease, or are causally related to risk. Assuming vitamin D supplementation truly is of value for preventing cardiovascular disease, what is the optimal dose, what role does calcium supplementation play in the equation, and is there a therapeutic window phenomenon, meaning that not only lower but also higher serum concentrations may result in detriment? In contrast, when looking at the completed randomized, prospective, placebo controlled trials (Table 1), a major weakness is that many trials have tested lower doses than currently postulated to be of benefit for extraskeletal outcomes. What role does the VDR play, would a VDR agonist be of benefit, or are there ways to prevent VDR loss and hence delay the onset of coronary atherosclerosis? As we await the results of ongoing research, we eagerly await answers to these questions.

Conclusions

While the IOM review suggested that higher plasma concentrations of vitamin D have not been shown to result in chronic disease reduction beyond the established bone health benefits, it recommended that more targeted research should continue to explore the role of vitamin D supplementation in preventing cardiovascular disease and other chronic illnesses.

Despite plausible biological mechanisms for a role of vitamin D in cardioprotection, a cause-and-effect relationship has not yet been established. While observational studies point to a potential association, data such as these are hampered by potential confounding and selection factors. If a correlation in an observational study exists, it does not prove causality. The available randomized trial data do not yet demonstrate a clear benefit. Therefore, and in line with the recommendations from the IOM and the AHRQ, additional research is needed to advance knowledge related to this subject. While awaiting results of ongoing randomized trials, including VITAL and several other trials world-wide, clinicians should be cautious to avoid overtreatment with high-dose vitamin D supplementation, as well as undertreatment, until we know the true risks and benefits.

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Table 1

Prospective randomized trials of Vitamin D supplementation and CHD events or CVD risk factors*

Design	Primary Outcome	Study outcome	Summary of study, sample size, patient age, & route/ dose of Rx	Length & Follow-up	Outcomes related to CHD or CHD risk factors	Preexisting conditions or disease?	Reference
DB, PC, RCT	Colorectal cancer prevention study	Change in SBP & DBP	283 blacks age 30 to 80 years (median age of 51) randomized for 3 months of oral placebo, 1000, 2000, or 4000 IU/d $vitD_3$ followed by 3 additional months off of treatment.	6 months	A −1.4 mm Hg change in SBP for each additional 1000 IU/d of $vitD_3$ (P=0.04). No significant effect on DBP. For each 1 ng/ml increase in 25OHD there was a −0.2 mm Hg in SBP (P=0.02)	Generally healthy patients. Patients with pre-existing disorders of the parathyroid or calcium metabolism, Type I DM, sarcoidosis, malignancy, or thyroid disease were excluded.	Forman JP, et al.[60]
DB, PC, RCT	Changes in brachial artery FMV, carotid-femoral PWV, and aortic augmentati on index	Same as primary outcomes	114 postmenopausal women with mean age (63.9+/−3) and with serum 25OHD concentrations >10 and <60 ng/mL, received $VitD_3$ (2,500 IU) or placebo, daily for 4 months	4 months	VitD supplementation did not improve endothelial function, arterial stiffness, or inflammation.	Generally healthy, community-dwelling, ambulatory women from Madison, Wisconsin. Patients with CVD were excluded.	Gepner et al..[51]
DB, PC, RCT	Change in small LDL particle number	Other lipid fractions	151 VitD insufficient male and female adults (25OHD ≤ 20ng/ml), received 50,000 IU $VitD_3$ weekly × 8 weeks	8 weeks	VitD repletion failed to improve the lipid profile.	Elevated risk for CVD (with at least 1 of numerous significant CVD risk factors).	Ponda et al. [48]
DB, PC, RCT	BP, FMV of the brachial artery, cholesterol, & other markers of vascular health	Same as primary outcomes	58 patients with mean age of 67 years received 100,000 units of oral $VitD_2$ or placebo at baseline	16 weeks follow-up	High dose oral VitD supplementation did not improve BP but produced short-term improvement in endothelial function in stroke patients with well-controlled baseline BP, which was not sustained by the end of the study.	History of stroke with baseline 25OHD concentrations <75 nmol/L	Witham MD, et al.[52]
DB, PC, RCT	Hip fractures	coronary artery calcium (CAC) score	WHI CaD trial (1) nested within WHI hormonal trial (2) (estrogen among women who underwent hysterectomy) 754 women aged 50 to 59 years received calcium carbonate (1,000 mg of elemental calcium daily) plus $VitD_3$ (400 IU daily)	7 years	CAC plaque burden measured at the end of the trial did not differ between treatment and placebo groups.	Generally healthy postmenopausal women.	Manson JE, et al. [53]
DB, PC, RCT	Fasting serum lipids, BP, &	Same as primary outcomes	438 obese or overweight patients, 21-70 years old, received $VitD_3$ (40, 000 IU	1 year	No significant effect of VitD on glucose	Overweight or obese subjects	Jorde R, et al.[56]

Design	Primary Outcome	Study outcome	Summary of study, sample size, patient age, & route/ dose of Rx	Length & Follow-up	Outcomes related to CHD or CHD risk factors	Preexisting conditions or disease?	Reference
	oral glucose tolerance test		per week, 20 000 IU per week, or placebo) and all received 500 mg calcium daily. 330 patients completed the study.		tolerance, BP or serum lipids.		
PC, RCT	glycemic control in subjects with type 2 DM	Same as primary outcomes	36 subjects received cholecalciferol (40,000 IU per week) versus placebo	6 months	VitD had no significant effect on glucose metabolism	Type 2 DM, treated with metformin and bed-time insulin	Jorde R, et al. [54]
DB, PC, RCT	weight loss & traditional & Nontraditio n al cardiovasc ular disease risk markers	Same as primary outcomes (parathyroid hormone, triglyceride levels, and inflammatory y markers).	200 subjects with mean baseline 25OHD concentrations of 30nmol/L received VitD 3320 IU/d or placebo while participating in a weight-reduction program.	12 months	VitD did not adversely affect weight loss and was able to significantly decrease PTH, TG, TNF (although LDL increased significantly) in overweight subjects with inadequate VitD status, while participating in a weight-reduction program.	Overweight	Zittermann A, et al.[55]
DB, PC, RCT	Hip fractures	Incident DM	WHI Ca/D trial, 36,282 postmenopausal women, 50-79 years old received 1,000 mg elemental calcium + 400 IU $VitD_3$ daily	7 years follow-up	No beneficial effects in reducing incidence of DM or the metabolic syndrome	Generally healthy postmenopausal women.	DeBoer et al.[47]
DB, PC, RCT	Hip fractures	Change in BP and the Developme nt of HTN	WHI Ca/D trial, 36,282 postmenopausal women received 1,000mg elemental calcium +400 IU $VitD_3$ daily	7 years follow-up	No significant beneficial effect in BP or prevention of incident HTN.	Generally healthy postmenopausal women.	Margolis, et al.[49]
DB, PC, RCT	Hip fractures	Risk of CHD	WHI Ca/D trial, 36,282 postmenopausal women ages 50–79 received 500mg calcium carbonate +200 IU $VitD_3$ Bid	7 years follow-up	No beneficial CHD effects attributable to Ca/D	Generally healthy postmenopausal women.	Hsia, et al.[50]
DB, PC, RCT	survival rate, biochemical variables, & cytokine profile	Same as primary outcomes	123 subjects received 2,000 IU/d of $VitD_3$ plus 500 mg Ca/D [D(+) group] or placebo plus 500 mg Ca/d [D(−) group] for 9 mo. 93 patients completed the study.	9 months intervene tion, 15 months follow-up	$VitD_3$ reduced the inflammatory milieu in CHF patients. While interleukin-10 increased, there was a significant improvement in PTH and TNF. However, there was no difference in survival.	Congestive heart failure	Schleithoff SS, et al.[56]

Design	Primary Outcome	Study outcome	Summary of study, sample size, patient age, & route/ dose of Rx	Length & Follow-up	Outcomes related to CHD or CHD risk factors	Preexisting conditions or disease?	Reference
DB, PC, RCT	Fracture incidence & total mortality by cause	Same as primary outcome. Additional data assessing CVD.	2,686 people (2,037 men and 649 women), 65-85 year old randomized to receive 100,000 IU of supplemental $VitD_3$ every 4 months for 5 years.	5 years, Britain	No beneficial CVD effects attributable to VitD.	Patients recruited from the general community. Excluded if there was a hx of renal stones, sarcoidosis, or malignancy.	Trivedi DP, et al.[46]
DB, PC, RCT	Fractures	Coronary mortality	327 patients (57 men & 270 women) over 65 (mean age 79.5) years received all possible combinations of calcium carbonate 3 g, VitD3 1000 IU, methandienone 2.5 mg and/ or placebos daily for 9 months.	9 months	Coronary mortality was higher among those taking all three active substances. A significant increase in coronary deaths was seen, most significant ($P < 0.001$) in those receiving $VitD_3$ & methandienone		Inkovaara J, et al.[58]

DB, double-blind; PC, placebo controlled; RCT, randomized clinical trial; N/A, not addressed; Hx, History; CVD, Cardiovascular disease; CHD, Coronary heart disease; HTN, hypertension; Vit, Vitamin; WHI, Women's Health Initiative; Ca/D, Calcium and Vitamin D; DM, diabetes mellitus; FMV, flow-mediated vasodilation; PWV, pulse wave velocity; BP, blood pressure (SBP, systolic BP and DBP, diastolic BP); PTH, parathyroid hormone; TG, tryglyceride; TNF, tumor necrosis factor; LDL, low density lipoprotein cholesterol; IU, international unit; d, day.

* Of note, because this is not an all-inclusive systematic review, this table may not list all RCTs reporting on vitamin D supplementation and CVDrisk factors as well as CVD events.