Annals of Internal Medicine | Review

Systematic Review: Vitamin D and Calcium Supplementation in Prevention of Cardiovascular Events

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Background: Vitamin D and calcium may affect the cardiovascular system independently and interactively.

Purpose: To assess whether vitamin D and calcium supplements reduce the risk for cardiovascular events in adults.

Data Sources: Studies published in English from 1966 to July 2009 in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials.

Study Selection: Two investigators independently selected 17 prospective studies and randomized trials that examined vitamin D supplementation, calcium supplementation, or both and subsequent cardiovascular events.

Data Extraction: Three investigators extracted and checked data about study designs, participants, exposures or interventions, outcomes, and data quality.

Data Synthesis: Five prospective studies of patients receiving dialysis and 1 study involving a general population showed consistent reductions in cardiovascular disease (CVD) mortality among adults who received vitamin D supplements. Four prospective studies of initially healthy persons found no differences in incidence of CVD between calcium supplement recipients and nonrecipients. Results of secondary analyses in 8 randomized trials showed a slight but statistically nonsignificant reduction in CVD risk (pooled relative risk, 0.90 [95% CI, 0.77 to 1.05]) with vitamin D supplementation at moderate to high doses (approximately 1000 IU/d) but not with calcium supplementation (pooled relative risk, 1.14 [CI, 0.92 to 1.41]), or a combination of vitamin D and calcium supplementation (pooled relative risk, 1.04 [CI, 0.92 to 1.18]) compared with placebo.

Limitations: Only articles published in English that reported cardiovascular event outcomes were included. The small number of studies, the lack of trials designed specifically to assess primary effects on cardiovascular outcomes, and important between-study heterogeneity preclude definitive conclusions.

Conclusion: Evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk, whereas calcium supplements seem to have minimal cardiovascular effects. Further research is needed to elucidate the role of these supplements in CVD prevention.

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Vitamin D and calcium insufficiency are highly prevalent among elderly persons in the United States and worldwide (1, 2). The Institute of Medicine currently recommends vitamin D intake of 200, 400, and 600 IU/d for adults aged 19 to 50 years, 51 to 70 years, and 71 years or older, respectively (3). However, evidence suggests that elderly adults may need 800 IU/d or more of vitamin D; persons with dark skin and limited sun exposure require an even higher amount (4). The currently recommended calcium intake for U.S. adults aged 50 years or older is 1200 mg/d, yet the reported average intakes are only 706 mg/d to 738 mg/d for men and 567 mg/d to 589 mg/d for women aged 50 years or older (2).

Beyond their pivotal role in bone health (5), vitamin D and calcium have received increasing attention for their potential effect on nonskeletal outcomes (5, 6), including cardiovascular disease (CVD). In vitro and in vivo experimental studies have shown that vitamin D and calcium, acting both independently and interactively, are involved in several physiologic processes that may modify CVD risk (7–9). In some (10–13), but not all (14–16), epidemiologic studies, inadequate vitamin D and calcium intake was associated with an adverse cardiovascular risk factor profile and increased risk for CVD events. Randomized trials have evaluated vitamin D supplementation, calcium supplementation, or their combination to prevent fracture and improve bone mineral density (17–19), but no completed trials to our knowledge have tested the effect of these supplements on CVD as the primary end point. With an increasing number of U.S. adults receiving vitamin D and calcium supplements for general health purpose (20), it is critical to better understand the risks and benefits related to these supplements. We conducted a systematic review of the literature to assess whether vitamin D supplements, calcium supplements, or a combination thereof may reduce the risk for cardiovascular events.

Methods

Data Sources and Literature Search

We developed and followed a standard protocol for this review. We searched the published literature on vita-

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Context

Does vitamin D and calcium supplementation reduce the risk for cardiovascular disease?

Contribution

This review reports that some prospective studies and randomized, controlled trials suggest reductions in cardiovascular disease risk among adults who receive vitamin D supplements, but studies show little to no differences in risk between calcium supplement recipients and nonrecipients or between recipients of combined supplementation (vitamin D plus calcium) and placebo.

Caution

None of the studies were trials designed specifically to assess effects of supplementation on cardiovascular outcomes.

Implication

Limited evidence suggests that vitamin D supplementation, but not calcium supplementation, may be associated with reduced cardiovascular disease risk.

—The Editors

min D supplements, calcium supplements, or their combination and CVD events by using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials from 1966 to week 4 of July 2009. We selected the search terms to 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. Terms selected for vitamin D included *vitamin D intake*, *vitamin D supplement*, *calcidiol*, *calcitriol*, *cholecalciferol*, and *ergocalciferol*. Terms selected for calcium included *calcium intake*, *calcium supplement*, *calcium carbonate*, and *calcium citrate*. Terms selected for CVD included *cardiovascular disease*, *ischemic heart disease*, *coronary artery disease*, *cardiovascular mortality*, *myocardial infarction*, and *stroke*. We restricted the search to articles published in English, studies of humans, and studies of adults aged 19 years or older. We applied the same search strategy to each database. We also manually searched reference lists of some retrieved articles for additional studies. Details of our literature search are available on request.

Study Selection

Two investigators independently reviewed all identified articles. Because of limitations in assessing cause–effect relationships, we excluded ecological, cross-sectional, and retrospective case–control studies. We also excluded case reports, studies of children and adolescents, and studies that did not assess use of vitamin D supplements, calcium supplements, or their combination on the basis of abstract review. We retrieved articles that passed abstract screening for a full-text review, and we further excluded review articles, editorials, or letters to editors; studies lacking a comparison between participants who received vitamin D supplements, calcium supplements, or a combination and nonrecipients; and studies that did not ascertain CVD events, including CVD death, nonfatal coronary heart disease (CHD) or myocardial infarction (MI), and nonfatal stroke. We noted the reasons for exclusion for each excluded study.

Data Extraction

One investigator extracted key information from selected studies (**Appendix Tables 1** to **3**, available at www.annals.org), and 2 investigators independently verified the extracted data for completeness and accuracy. The investigators resolved disagreements on data extraction by consensus. Data extracted for observational studies included country, study design, sample size, participant characteristics (including age, sex, and comorbid conditions), use of vitamin D or calcium supplements, CVD end points, follow-up period, and main study findings. Data extracted for randomized trials included country, sample size, participant characteristics, dosage and duration of intervention, follow-up period, primary end point(s), and main findings for CVD outcomes. For separate publications on different CVD end points from the same study population, we extracted the data from each publication individually.

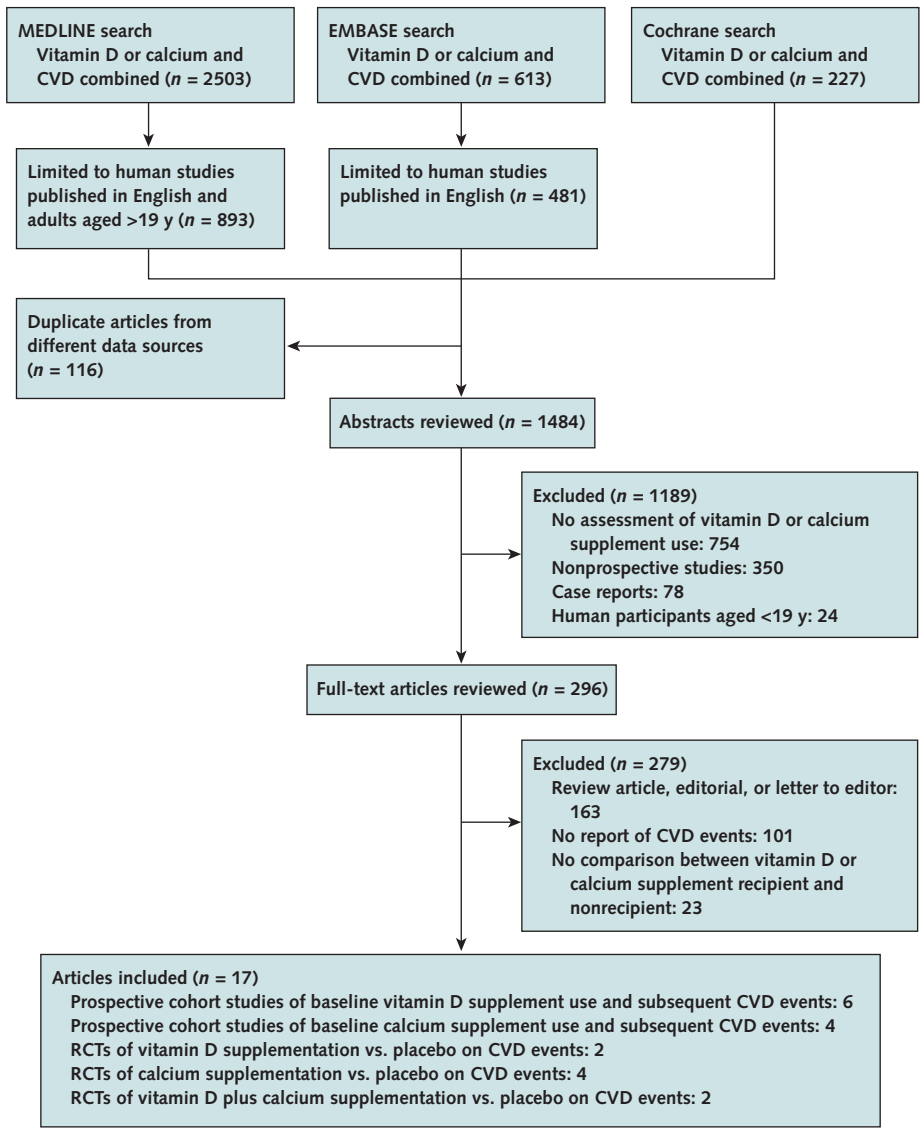
Study Quality Assessment

We applied a 3-category grading system to indicate the overall methodological quality of each selected article in assessing the effect of vitamin D supplements, calcium supplements, or both on CVD event risk. This generic grading system is applicable to all types of study design (21, 22). Each selected study was classified as good, fair, or poor. A study was graded as good if the commonly held criteria for a high-quality study (prospective design; no obvious bias based on participant selection, exposure assessment, or outcome ascertainment; completeness of follow-up; and appropriate analytic methods and reporting of results) were mostly adhered to. A study was graded as fair if not all the criteria for a high-quality study were met but bias was insufficient to invalidate the results. A study was graded as poor if substantial bias in study design, data collection, analysis, or reporting was found.

Statistical Analysis

We reported the data from all selected articles in **Appendix Tables 1** to **3** (available at www.annals.org). We also conducted meta-analyses combining the data from randomized trials. For 3 trials that did not report relative risks (RRs) for CVD events, we calculated the RRs and 95% CIs from the reported event rates in each treatment group. We applied the DerSimonian and Laird (23) random-effects model to calculate the pooled RRs and 95% CIs by using STATA statistical software (version 7.0, STATA, College Station, Texas). We assessed heterogeneity across studies by using the Cochrane Q statistic. We also assessed publication bias by using the Begg adjusted

Figure 1. **Literature search and selection.**



Search terms for vitamin D included *vitamin D intake*, *vitamin D supplement*, *calcidiol*, *calcitriol*, *cholecalciferol*, and *ergocalciferol*. Search terms for calcium included *calcium intake*, *calcium supplement*, *calcium carbonate*, and *calcium citrate*. Search terms for CVD included *cardiovascular disease*, *ischemic heart disease*, *coronary artery disease*, *cardiovascular mortality*, *myocardial infarction*, and *stroke*. The original search was further limited to articles published in English, human studies, and studies of adults aged ≥19 years. In each box, the sum of studies in all categories may exceed the total number of excluded or included studies because of overlapping classification. CVD = cardiovascular disease; RCT = randomized, controlled trial.

rank correlation test (24), although power was generally low because of the small number of studies.

Role of the Funding Source

This study was supported by a scientist development grant from the American Heart Association and a research grant from the National Heart, Lung, and Blood Institute. The funding sources had no role in the design, conduct, or analysis of the study; interpretation of the results; writing of the manuscript; or the decision to submit this manuscript for publication.

Results

We identified 1484 articles by using combined terms for vitamin D supplements, calcium supplements, and CVD events through our literature search (**Figure 1**). After abstract screening and full-text review, we selected 17 eligible articles. Nine were prospective studies that examined the association of baseline use of vitamin D supplements, calcium supplements, or both with subsequent CVD events, and 8 were randomized, controlled trials that reported CVD event rates or RRs in the vitamin D supple-

mentation, calcium supplementation, or combined treatment group compared with placebo. Of note, none of the randomized trials was designed specifically to evaluate the effect of vitamin D supplementation, calcium supplementation, or both on incident CVD as the primary end point.

Active Vitamin D Use and CVD Mortality in Prospective Studies of Patients With Kidney Disease

Patients with renal disease commonly have vitamin D deficiency and receive treatment with active vitamin D. We identified 5 studies among patients receiving dialysis that examined the association between active vitamin D use and CVD mortality (25–29) (**Appendix Table 1**, available at www.annals.org). A study of 143 Spanish patients receiving hemodialysis reported a lower percentage of calcitriol treatment (71.4% vs. 81%) among those who died of CVD than those who did not die of CVD (25). A Japanese study reported a 62% reduction in CVD mortality among 162 patients who received oral vitamin D compared with 80 patients who did not (26). In a large cohort of 51 037 U.S. patients receiving hemodialysis, those who received activated injectable vitamin D had lower CVD mortality (7.6 per 100 person-years) than those who did not receive the therapy (14.6 per 100 person-years) (27). A cohort study of 16 004 patients from 6 Latin American countries also found lower CVD mortality in patients who received oral active vitamin D (RR, 0.55) (29). Finally, in a case–control study nested in a large prospective cohort of U.S. patients receiving dialysis, the odds of 90-day CVD mortality was statistically significantly higher among patients who did not receive vitamin D than among those who did, regardless of the circulating 25-hydroxyvitamin D level (28).

Vitamin D Supplement Use and CVD Events in Prospective Studies of General Population

We identified only 1 prospective study that examined use of vitamin D supplements and risk for CVD events in the general population (10) (**Appendix Table 1**, available at www.annals.org). This study assessed nutrient intake by using validated questionnaires and identified CVD end points by using predetermined definitions. However, the study did not adequately evaluate participants' sun exposure and duration of supplement use. Among the 34 486 postmenopausal women in the United States without baseline CHD, the age-adjusted RR of CHD mortality for those who consumed 1 to 400 IU/d and greater than 400 IU/d of supplemental vitamin D was 0.81 (CI, 0.63 to 1.03) and 0.80 (CI, 0.57 to 1.13), respectively, compared with nonrecipients. Additional adjustment for other potential confounders modestly attenuated the corresponding RRs to 0.86 and 0.85, respectively.

Calcium Supplement Use and CVD Events in Prospective Studies of Initially Healthy Persons

Four prospective studies examined the association between baseline calcium supplement use and incident CVD events in initially healthy persons and obtained largely similar results (10, 14, 30, 31) (**Appendix Table 2**, available at www.annals.org). In the Health Professionals Follow-up Study, which compared men who received 400 mg/d or more of supplemental calcium with nonrecipients, the multivariate RRs of total stroke and ischemic stroke were 0.88 (CI, 0.60 to 1.27) and 0.83 (CI, 0.52 to 1.34), respectively (14). A subsequent analysis from the same cohort reported a multivariate RR of 0.87 (CI, 0.64 to 1.19) for total CHD, 1.02 (CI, 0.71 to 1.46) for nonfatal MI, and 0.61 (CI, 0.34 to 1.10) for CHD death in the highest quintile of calcium supplement use (median, 1000 mg/d) compared with the nonrecipients (30). In the Nurses' Health Study, the multivariate RR of total stroke comparing female nurses who received 400 mg/d or more of calcium supplements versus the nonrecipients was 0.88 (CI, 0.66 to 1.18) (31). The Iowa Women's Health Study also reported a multivariate RR of 0.88 (CI, 0.64 to 1.23) for CHD mortality among postmenopausal women who received greater than 500 mg/d of calcium supplements (10).

Vitamin D Supplementation and CVD Events in Randomized Trials

We identified 2 randomized trials that reported CVD event rates with supplementation of vitamin D versus placebo (**Appendix Table 3**, available www.annals.org) (32, 35). In a trial in the United Kingdom that randomly assigned 2037 men and 649 women to receive 100 000 IU of oral vitamin D supplements or placebo every 4 months, the risk for total CVD (RR, 0.90), CVD mortality (RR, 0.84), and nonfatal CHD (RR, 0.94) were all slightly but statistically nonsignificantly lower in the vitamin D group (32). A more recent trial in Australia investigated the effect of vitamin D supplements, 1000 IU/d, added to calcium supplements, 1000 IU/d; in 302 elderly women (35). Compared with women assigned to receive vitamin D placebo plus calcium supplementation, those assigned to both vitamin D and calcium supplementation had lower rates of ischemic heart disease (1.3% vs. 2.0%) but similar rates of stroke (2.0% for both).

Calcium Supplementation and CVD Events in Randomized Trials

Four randomized trials reported the occurrence of CVD events with calcium supplementation versus placebo (33, 36–38) (**Appendix Table 3**, www.annals.org). An early trial of 930 men and women in the United States found that similar proportions of participants who received 1200 mg/d of calcium supplements and those who received placebo had been hospitalized for cardiac disease (10% vs. 11%) or stroke (2% vs. 3%) during the 4-year intervention (36). A trial of 1460 women in Australia also found similar rates of CHD (RR, 1.12) in the groups of 1200-mg/d calcium supplements and placebo (37). A recent trial in New Zealand randomly assigned 1471 generally healthy postmenopausal women to receive calcium citrate, 1000 mg/d, or placebo. After 5 years of treatment, MI and composite CVD end points (MI, stroke, or sudden death) were

more commonly reported in the calcium supplement group than in the placebo group (33). When unreported events identified from a national database were added, however, the increased risk for MI (RR, 1.49) and composite CVD end points (RR, 1.21) in the calcium group were no longer statistically significant. Another trial of 323 men in New Zealand also found more self-reported composite vascular events in the calcium supplement group than in the placebo group, but the event rates were too low for meaningful statistical tests (38).

Combined Vitamin D Plus Calcium Supplementation and CVD Events in Randomized Trials

Two trials reported CVD events with combined vitamin D and calcium supplementation versus double placebo (34, 39) (**Appendix Table 3**, available at www.annals.org). In a multicenter trial conducted in France, 192 elderly women with vitamin D insufficiency (25-hydroxyvitamin D level ≤12 ng/mL) were randomly assigned to receive either a combination tablet containing 1000 mg of calcium carbonate and 800 IU of vitamin D_3 or a placebo tablet daily for 1 year (39). Only a few patients reported the occurrence of cardiovascular event, and the number was similar in the active supplement ($n = 6$) and placebo ($n = 5$) groups. In the United States, the Women's Health Initiative randomly assigned 36 282 postmenopausal women to daily supplementation with 1000 mg of calcium and 400 IU of vitamin D_3 or a placebo. Combined supplementation with vitamin D and calcium for 7 years did not affect CVD risk (RR for MI, CHD death, and stroke: 1.05, 1.01, and 0.95, respectively) (34).

Meta-analysis of Randomized Trials

When we combined the data from randomized trials, the pooled RRs of CVD were 0.90 (CI, 0.77 to 1.05) for vitamin D supplements versus placebo, 1.14 (CI, 0.92 to1.41) for calcium supplements versus placebo, and 1.04 (CI, 0.92 to 1.18) for combined vitamin D plus calcium supplements versus double placebo ($P > 0.05$ for all heterogeneity tests and $P > 0.05$ for all Begg tests) (24) (**Figure 2**).

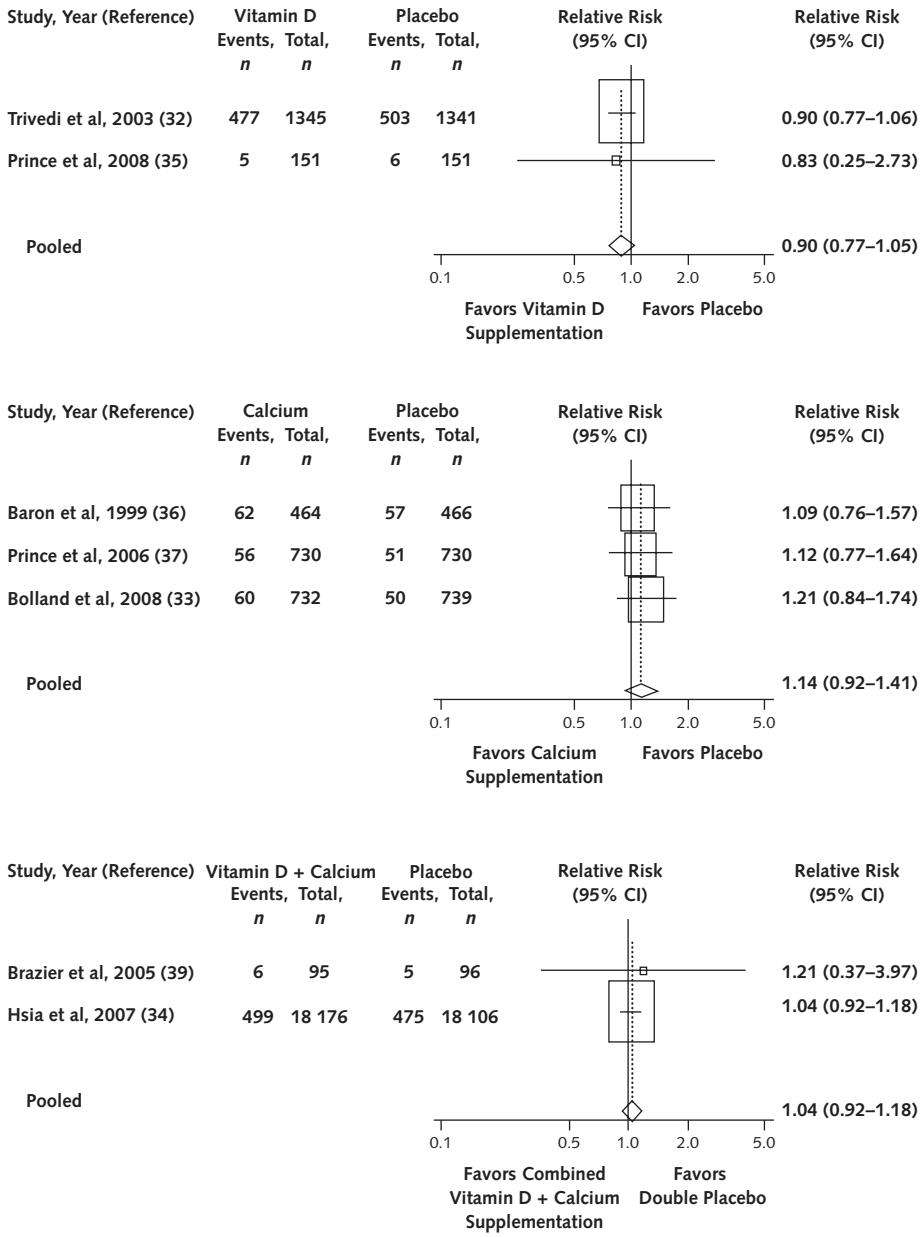
Discussion

When reviewing the evidence to assess the effect of vitamin D supplements, calcium supplements, or both on the risk for CVD events, we found only a small number published studies with considerable between-study heterogeneity in study designs, participant characteristics, and potential for bias. Prospective studies of dialysis patients and a single cohort study involving a general population showed consistent reductions in CVD mortality among those who received vitamin D supplements. Randomized trials reported a slight but statistically nonsignificant reduction in CVD risk with vitamin D supplementation at moderate-to-high doses. In contrast, both prospective studies and randomized trials showed no apparent effect of calcium supplementation, with or without vitamin D, on the risk for CVD.

Vitamin D and calcium are independently and interactively involved in many pathophysiologic processes related to the development of CVD. Vitamin D downregulates the renin–angiotensin system (40, 41), improves insulin secretion and sensitivity (42, 43), inhibits vascular smooth-muscle cell proliferation (44), protects normal endothelial cell function (45), and modulates inflammatory processes (46, 47). Epidemiologic studies have found an association between vitamin D insufficiency, reflected by low serum 25-hydroxyvitamin D levels, and higher rates of CVD morbidity (48, 49) and mortality (28, 50–53). High calcium intake promotes the influx of calcium into cells. Optimal intracellular calcium levels, also homeostatically controlled by active vitamin D and parathyroid hormone, inhibit fatty acid synthesis and activate lipolysis in adipocytes (54), improve insulin secretion from pancreatic β cells (55), enhance insulin sensitivity in peripheral organs (56–59), suppress platelet aggregation (60), attenuate vascular smooth-muscle tone (61), and augment vasorelaxation (62, 63). Findings on calcium intake and risk for CVD in epidemiologic studies have been inconsistent. Some but not all studies (12–16, 30, 64) have observed reductions in the risk for CHD (10) and stroke (31, 65) with high calcium intake.

A consistently strong inverse association between active vitamin D use and CVD mortality among patients receiving dialysis (25–29) suggests a potential cardioprotective effect of vitamin D. However, the generalizability and applicability of such findings to broader populations warrants more study. To our knowledge, only 1 population-based cohort study investigated CVD events among vitamin D supplement recipients versus nonrecipients and found a minimal reduction in CHD mortality with vitamin D supplements of 1 to 400 IU/d and greater than 400 IU/d (10). We identified a total of 4 randomized trials of vitamin D supplementation that reported CVD event rates. Two trials tested vitamin D supplements versus placebo and found a slight but statistically nonsignificant reduction in CVD risk with vitamin D supplementation at moderate to high doses (100 000 IU every 4 months [32] and 1000 IU/d [35], respectively). The other 2 trials tested combined supplementation of vitamin D and calcium versus double placebos, and both trials showed no differences in CVD event risk between treatment groups (34, 39). The Women's Health Initiative is the largest trial of vitamin D supplementation to date and has shown no effect of vitamin D plus calcium supplementation on CVD event risk (34). Notably, the vitamin D dosage of 400 IU/d used in the Women's Health Initiative increased median plasma 25-hydroxyvitamin D levels from 42.3 nmol/L to only 54.1 nmol/L (66). Extrapolating these data to achieve 25-hydroxyvitamin D levels above 75 nmol/L, the recommended level for several health outcomes (67), would require supplementation at least 1000 IU/d to determine

Figure 2. **Meta-analysis of the relative risk for cardiovascular events with vitamin D supplementation, calcium supplementation, or combination treatment versus placebo in randomized, controlled trials.**



whether improvements in vitamin D status may prevent CVD. These findings indicate that a protective effect of vitamin D supplementation on CVD is possible, but that a moderate to high dosage may be needed.

Null findings in 4 large-scale prospective studies of initially healthy participants (10, 14, 30, 31) suggest that calcium supplements are unlikely to confer a major effect on CVD risk. Secondary analyses in 4 randomized trials (33, 36–38) also have not demonstrated a clear effect of calcium supplementation on CVD risk. A recent study by Bolland and coworkers (33) raised concerns about a possible adverse effect of calcium supplements on the risk for MI (33). Although potentially important, this finding should be interpreted with caution. First, the trial was not specifically designed to test the effect of calcium supplementation on the risk for CVD. Second, the increased risk for MI in the calcium supplement group was not statistically significant when additional events were identified from a national database. Third, the study did not consider some potential confounders in the relation between calcium and CVD risk, including vitamin D status. Other trials of calcium supplementation using similar dosages,

with (34, 39) or without (36–38) vitamin D, found no important or statistically significant differences in CVD event rates between the calcium and placebo groups. Overall, the current available evidence does not support either beneficial or detrimental effects of calcium supplementation on the risk for CVD.

An increasing number of generally healthy adults in the United States take vitamin D and calcium supplements for bone health and other purported health benefits (20). Meanwhile, the incidence and mortality rates related to CVD remain high in the United States. Therefore, a better understanding of how vitamin D and calcium supplement use may affect the risk for CVD has major implications for both clinical medicine and public health. Although randomized, double-blind, placebo-controlled clinical trials are widely considered to provide the strongest evidence for causality, prospective observational studies remain an important complementary source of data in assessing the effects of long-term exposure on the development of chronic disease. We thus included both study types in our systematic review.

Our review has several limitations. First, we found few eligible studies and had limited power to draw a definitive conclusion on the effects of vitamin D supplements, calcium supplements, or both on CVD risk. Second, publication bias is a concern because our review was based solely on published studies that reported CVD outcomes. However, several reviewed studies reported null findings, suggesting that substantial selective reporting and publication of positive results was unlikely. In addition, the Beggs adjusted rank-correlation test (24) indicated no evidence of substantial publication bias for the meta-analysis results. Third, no studies included in our review could completely rule out the possibility of bias and residual confounding. Finally, we did not review vitamin D and calcium supplementation in relation to cardiovascular risk factors, biomarkers, or other intermediate markers. Although such associations are plausible, they may not translate into event occurrence.

In conclusion, very few studies have specifically investigated the effect of vitamin D supplements, calcium supplements, or a combination thereof on the risk for CVD in the general population. To date, evidence from prospective observational studies and randomized, controlled trials suggests that vitamin D supplementation at moderate to high doses may have beneficial effects on reducing the risk for CVD, whereas calcium supplementation seems to have no apparent effect on CVD risk. Future studies of vitamin D and calcium supplement use among initially healthy persons, particularly large-scale, randomized trials with adequate doses and with CVD ascertained as the primary end point, are urgently needed to elucidate the potential role of vitamin D and calcium supplementation in the prevention of CVD.

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Appendix Table 1. **Summary of Prospective Observational Studies That Examined the Association Between Vitamin D Supplement Use and Risk for CVD Events**

Study, Year (Reference)	Quality*	Country	Study Design	Participants	Supplement	CVD End Points	Follow-up	Factors Adjusted in Analysis	Main Findings
Kidney disease									
Marco et al, 2003 (25)	Poor	Spain	Cohort	143 patients receiving hemodialysis; mean age, 61.9 y	Calcitriol: 0.25–0.5 μg/d (n = 113); no use (n = 30)	Fatal CVD events: MI, cerebrovascular accident, ischemic peripheral vascular disease, sudden death (n = 35)	6 y	Unadjusted	71.4% of patients who died of CVD received calcitriol; 81% who did not die of CVD received calcitriol; P value statistically nonsignificant
Shoji et al, 2004 (26)	Fair	Japan	Cohort	242 patients receiving hemodialysis; mean age, 55.5–56.5 y	Oral alfacalcidol: use of 0.25–1.5 μg/d (n = 162); no use (n = 80)	Fatal CVD events: CHD, cerebrovascular disease, congestive heart failure, sudden death (n = 31)	61 ± 23 mo	Age, diabetes, systolic BP, non-HDL cholesterol level, presence of ischemic heart disease, carotid IMT, carotid artery calcification	Age- and diabetes-adjusted HR of CVD mortality rate in recipients vs. nonrecipients: 0.377 (CI, 0.246–0.578)
Teng et al, 2005 (27)	Poor	United States	Cohort	51 037 patients receiving hemodialysis; mean age, 61–63 y	Activated injectable vitamin D: any use (n = 37 173); no use (n = 13 864)	CVD-related mortality	2 y	Unadjusted	CVD mortality rate in recipients vs. nonrecipients: 7.6/100 person-years vs. 14.6/100 person-years; P <0.001
Wolf et al, 2007 (28)	Fair	United States	Nested case–control	1000 patients receiving hemodialysis (250 died within 90 d of initiating dialysis; mean age, 62 y; 750 survived >90 d after initiating dialysis; mean age, 71 y)	Activated vitamin D	CVD mortality	90 d	Age, sex, race, cause of renal failure, standardized mortality rates, BP, vascular access, serum albumin, creatinine, parathyroid hormone, calcium, phosphorus, hemoglobin, history of CHD, stroke, cancer, or congestive heart failure	Multivariate OR of CVD mortality in untreated vs. treated patients and 25(OH)D >30 ng/mL: 4.8 (CI, 1.5–15.0) if 25 (OH)D >30 ng/mL; 5.3 (CI, 1.8–15.4) if 25(OH)D 10–30 ng/mL; 8.3 (CI, 2.4–28.7) if 25(OH)D <10 ng/mL
Naves-Díaz et al, 2008 (29)	Fair	Latin America	Cohort	16 004 patients receiving hemodialysis; mean age, 53.9–55.6 y	Oral active vitamin D: any use (n = 7203); no use (n = 8801)	CVD mortality	Median, 16 mo	Age, sex, country, diabetes, time receiving dialysis, Kt/V, vascular access, baseline and time-varying weight, albumin, creatinine, hemoglobin, comorbid conditions	Multivariate HR of CVD mortality rate in recipient vs. nonrecipient: 0.55 (CI, 0.45–0.67)
General population									
Bostick et al, IWHS, 1999 (10)	Good	United States	Cohort	34 486 women aged 55–69 y; no history of heart disease	Oral vitamin D supplement: 0 IU/d, 1–400 IU/d, >400 IU/d	Ischemic heart disease deaths (n = 387)	8 y	Age; energy intake; BMI; waist–hip ratio; diabetes; smoking status; postmenopausal estrogen use; alcohol intake; education; marital status; physical activity; and vitamin E, calcium, saturated fat intake	Multivariate RR of CHD mortality in recipient vs. nonrecipient: 0.86 (CI, 0.62–1.21) for use of 1–400 IU/d; 0.85 (CI, 0.54–1.34) for use of >400 IU/d; P for trend = 0.48

25(OH)D = 25-hydroxyvitamin D; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; HR = hazard ratio; IMT = intima–media thickness; IWHS = Iowa Women's Health Study; Kt/V = dialyzer clearance multiplied by dialysis time over a patient's total body water volume; MI = myocardial infarction; OR = odds ratio; RR = relative risk.

* A generic 3-category grading system was applied to indicate the overall methodological quality of each selected article in assessing the effect of vitamin D supplementation, calcium supplementation, or a combination thereof on risk for CVD events.

Appendix Table 2. **Summary of Prospective Observational Studies That Examined the Association Between Calcium Supplement Use and Risk for Cardiovascular Events**

Study, Year (Reference)	Quality*	Country	Study Design	Participants	Supplement	CVD End Points	Follow-up, y	Factors Adjusted in Analysis	Main Findings
Ascherio et al, HPFS, 1998 (14)	Good	United States	Cohort	43 738 men aged 40–75 y; no history of CVD or diabetes	Supplemental calcium: 0 mg/d; ≥400 mg/d	Incident stroke (n = 328)	8	Age, energy intake, smoking status, alcohol consumption, history of hypertension, hypercholesterolemia, parental history of MI, profession, BMI, and physical activity	RR of stroke in participants who received ≥400 mg/d vs. nonrecipients: total stroke, 0.88 (95% CI, 0.60–1.27); ischemic stroke, 0.83 (CI, 0.52–1.34)
Bostick et al, IWHS, 1999 (10)	Good	United States	Cohort	34 486 women aged 55–69 y; no history of heart disease	Oral calcium supplement: 0 mg/d, 1–500 mg/d, >500 mg/d	Ischemic heart disease deaths (n = 387)	8	Age; energy intake; BMI; waist–hip ratio; diabetes; smoking status; postmenopausal estrogen use; alcohol intake; education; marital status; physical activity; and vitamin E, calcium, and saturated fat intake	RR of CHD mortality in recipients vs. nonrecipients: 0.76 (CI, 0.58–1.00) for use of 1–500 mg/d and 0.88 (CI, 0.64–1.23) for use of >500 mg/d; P value for trend = 0.46
Iso et al, NHS, 1999 (31)	Good	United States	Cohort	85 764 women aged 34–59 y; no diagnosis of CVD or cancer	Oral calcium supplement: 0 mg/d, <400 mg/d, ≥400 mg/d	Incident stroke (n = 690)	14	Age, smoking status, time interval, history of hypertension, diabetes, high cholesterol, BMI, alcohol intake, menopausal status, postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, vitamin E use, ω-3 fatty acid intake, and dietary calcium	RR of stroke in recipients of ≥400 mg/d vs. nonrecipients: 0.88 (CI, 0.66–1.18); P = 0.39
Al-Delaimy et al, HPFS, 2003 (30)	Good	United States	Cohort	39 800 men aged 40–75 y; no MI or other CVD	Quintiles of calcium supplement use: medians of 0, 57, 200, 325, 500, 1000 mg/d	Incident CHD (fatal CHD and nonfatal MI) (n = 1458)	12	Age, interval, energy intake, history of diabetes, hypercholesterolemia, family history of MI, smoking status, aspirin use, BMI, alcohol intake, physical activity, vitamin E intake, and other nutrient variables	RR for CVD in highest vs. lowest quintile: total CHD (0.87 [CI, 0.64–1.19]; P value for trend = 0.31); nonfatal MI (1.02 [CI, 0.71–1.46]; P value for trend = 0.84); CHD mortality (0.61 [CI, 0.34–1.10]; P value for trend = 0.05)

BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; HPFS = Health Professionals Follow-up Study; IWHS = Iowa Women's Health Study; MI = myocardial infarction; NHS = Nurses' Health Study; RR = relative risk.

* A generic 3-category grading system was applied to indicate the overall methodological quality of each selected article in assessing the effect of vitamin D, calcium supplementation, or the combination thereof on risk for CVD events.

Appendix Table 3. **Summary of Randomized, Controlled Trials That Reported Cardiovascular Event Rates in Groups Receiving Vitamin D or Calcium Supplementation Versus Placebo**

Study, Year (Reference)	Quality*	Country	Participants	Intervention	Duration, y	Primary End Points	Ascertainment of CVD Event	Main Findings on CVD End Points
Vitamin D supplement vs. placebo								
Trivedi et al, 2003 (32)	Fair	United Kingdom	2037 men and 649 women aged 65–85 y who live in the community	Oral vitamin D_3 (cholecalciferol), 100 000 IU every 4 mo (n = 1019 men and 326 women); placebo (n = 1018 men and 323 women)	5	Fracture, mortality	Self-report in questionnaires, death certification	Age-adjusted RR for CVD events in intervention vs. placebo group: CVD death (n = 101 vs. 117): 0.84 (CI, 0.65–1.10) for all; 0.83 (CI, 0.62–1.10) for men; 0.99 (CI, 0.43–2.30) for women. CHD death (n = 42 vs. 49): 0.84 (CI, 0.56–1.27) for all; 0.83 (CI, 0.54–1.28) for men; 0.99 (CI, 0.25–3.96) for women. Cerebrovascular death (n = 28 vs. 26): 1.04 (CI, 0.61–1.77) for all; 0.92 (CI, 0.52–1.61) for men; 3.98 (CI, 0.44–35.64) for women. Total CVD (n = 477 vs. 503): 0.90 (CI, 0.77–1.06) for all; 0.91 (CI, 0.76–1.09) for men; 0.89 (CI, 0.63–1.27) for women. Total CHD (n = 224 vs. 233): 0.94 (CI, 0.77–1.15) for all; 0.98 (CI, 0.78–1.22) for men; 0.79 (CI, 0.48–1.29) for women. Total cerebrovascular disease (n = 105 vs. 101): 1.02 (CI, 0.77–1.36) for all; 0.99 (CI, 0.72–1.36) for men; 1.19 (CI, 0.60–2.37) for women
Prince et al, 2008 (35)	Poor	Australia	302 women aged 70–90 y; serum 25 (OH)D ≤24 ng/mL	Ergocalciferol, 1000 IU/d (n = 151); placebo (n = 151); both groups received calcium citrate, 1000 mg/d	1	Fall	Self-reported adverse events in diary at 3-mo intervals	Rate of incident CVD events: ischemic heart disease (1.3% in vitamin D group; 2.0% in placebo group); stroke (2.0% in vitamin D group; 2.0% in placebo group)
Calcium supplement vs. placebo								
Baron et al, 1999 (36)	Fair	United States	672 men and 258 women; mean age, 61 y; recent history of colorectal adenoma	Calcium carbonate, 1200 mg/d (n = 464); placebo (n = 466)	4	Recurrence of colorectal adenoma	Hospitalized events	Hospitalized cardiac events (n = 50 [11%] in calcium group; n = 46 [10%] in placebo group); hospitalized stroke events (n = 12 [3%] in calcium group; n = 11 [2%] in placebo group)
Prince et al, 2006 (37)	Poor	Australia	1460 women aged >70 y	Calcium carbonate, 600 mg twice daily (n = 730); placebo (n = 730)	5	Clinical fracture; vertebral deformity	Self-reported adverse events in diary at 4-mo intervals	Diagnosis of CHD (n = 56 [7.7%] in calcium group; n = 51 [7.0%] in placebo group); HR = 1.12 (CI, 0.77–1.64)
Bolland et al, 2008 (33)	Fair	New Zealand	1471 postmenopausal women; mean age, 74 y	Calcium citrate, 1 g/d (n = 732); placebo (n = 739)	5	Fracture incidence; bone density	Medical review of self-reported adverse events; review of hospital records and death certificates; search of national database of hospital admissions for CVD	RR for verified CVD events in intervention vs. placebo group: MI, stroke, and sudden death, 1.21 (CI, 0.84–1.74); 1.49 (CI, 0.86–2.57) for MI; 1.37 (CI, 0.83–2.28) for stroke; 0.51 (CI, 0.13–2.01) for sudden death
Reid et al, 2008 (38)	Poor	New Zealand	323 men aged ≥40 y	Calcium, 1200 mg/d (n = 108); calcium, 600 mg/d (n = 108); placebo (n = 107)	2	Bone mineral density	Self-reported adverse events	Composite vascular events, including angina, MI, sudden death, coronary revascularization (n = 3 in 1200-mg/d calcium group; n = 2 in 600-mg/d calcium group; n = 0 in placebo group); P = 0.24
Vitamin D + calcium supplement vs. double placebo								
Brazier et al, 2005 (39)	Poor	France	192 women aged >65 y; serum 25 (OH)D ≤12 ng/mL	Calcium carbonate, 500 mg, + vitamin D, 400 IU twice daily (n = 95); placebo (n = 96)	1	Bone mineral density; biomarkers of bone formation and resorption	Self-reported and observed adverse events	Adverse cardiovascular events (n = 6 [6.3%] in treatment group; n = 5 [5.2%] in placebo group)
Hsia et al, 2007 (34)	Fair	United States	36 282 postmenopausal women aged 50–79 y	Calcium carbonate, 500 mg, + vitamin D_3, 200 IU twice daily (n = 18 176); placebo (n = 18 106)	7	Fracture incidence	Medical record review of all self-reported cases; central adjudication by trained physicians	RR for CVD events in intervention vs. placebo group: MI/CHD death/CABG/PCI, 1.08 (CI, 0.99–1.19); 1.04 (CI, 0.92–1.18) for MI/CHD death; 1.05 (CI, 0.91–1.20) for MI; 1.01 (CI, 0.79–1.29) for CHD death; 1.02 (CI, 0.91–1.15) for stroke/TIA; 0.95 (CI, 0.82–1.10) for stroke

25(OH)D =25-hydroxyvitamin D; CABG = coronary artery bypass graft; CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; RR = relative risk; TIA = transient ischemic attack.

* A generic 3-category grading system was applied to indicate the overall methodological quality of each selected article in assessing the effect of vitamin D, calcium supplementation, or a combination thereof on risk for CVD events.