JAMA Cardiology | Original Investigation

Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83 000 Individuals in 21 Randomized Clinical Trials
A Meta-analysis

Mahmoud Barbarawi, MD; Babikir Kheiri, MD, MRCP, PGDip; Yazan Zayed, MD; Owais Barbarawi, MD; Harsukh Dhillon, MD; Bakr Swaid, MD; Anitha Yelangi, MD; Saira Sundus, MD; Ghassan Bachuwa, MD, MS, MHSA; Mohammad Luay Alkotob, MD; JoAnn E. Manson, MD, DrPH

IMPORTANCE Observational studies have reported an association between low serum vitamin D levels and elevated risk of cardiovascular disease (CVD) events, but such studies cannot prove causation because of possible unmeasured confounding.

OBJECTIVE We conducted a meta-analysis of randomized clinical trials that tested the association of vitamin D supplementation with reduced CVD events and all-cause mortality.

DATA SOURCES Literature search through PubMed, the Cochrane Library, and Embase was completed by 2 reviewers from each database's inception to December 15, 2018.

STUDY SELECTION Inclusion criteria were randomized clinical trials that reported the effect of long-term (≥1 year) vitamin D supplementation on CVD events and all-cause mortality. Studies that did not include cardiovascular outcomes were excluded.

DATA EXTRACTION AND SYNTHESIS Data were abstracted independently by 2 authors. Random-effects models were used to report the risk ratios (RRs) and 95% CIs.

MAIN OUTCOMES AND MEASURES Major adverse cardiovascular events was the primary outcome, and rates of myocardial infarction, stroke or cerebrovascular accident, CVD mortality, and all-cause mortality were the secondary end points.

RESULTS Twenty-one randomized clinical trials were included (including 83 291 patients, of whom 41 669 received vitamin D and 41 622 received placebos). The mean (SD) age of trial participants was 65.8 (8.4) years; 61 943 (74.4%) were female. Only 4 trials had prespecified CVD as a primary end point. Vitamin D supplementation compared with placebo was not associated with reduced major adverse cardiovascular events (RR, 1.00 [95% CI, 0.95-1.06]; $P = .85$) nor the secondary end points of myocardial infarction (RR, 1.00 [95% CI, 0.93-1.08]; $P = .92$), stroke (RR, 1.06 [95% CI, 0.98-1.15]; $P = .16$), CVD mortality (RR, 0.98 [95% CI, 0.90-1.07]; $P = .68$), or all-cause mortality (RR, 0.97 [95% CI, 0.93-1.02]; $P = .23$). Results were generally consistent by sex, baseline 25-hydroxyvitamin D level, vitamin D dosage, formulation (daily vs bolus dosing), and presence or absence of concurrent calcium administration.

CONCLUSIONS AND RELEVANCE In this updated meta-analysis, vitamin D supplementation was not associated with reduced major adverse cardiovascular events, individual CVD end points (myocardial infarction, stroke, CVD mortality), or all-cause mortality. The findings suggest that vitamin D supplementation does not confer cardiovascular protection and is not indicated for this purpose.

JAMA Cardiol. doi:10.1001/jamacardio.2019.1870
Published online June 19, 2019.

Invited Commentary
Supplemental content

Author Affiliations: Department of Internal Medicine, Hurley Medical Center, Michigan State University, Flint (M. Barbarawi, Kheiri, Zayed, Dhillon, Swaid, Yelangi, Sundus, Bachuwa); Department of Internal Medicine, Mutah University, Al-Karak, Jordan (O. Barbarawi); Division of Cardiology, Hurley Medical Center, Michigan State University, Flint (Alkotob); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Manson).

Corresponding Author: Mahmoud Barbarawi, MD, Department of Internal Medicine, Hurley Medical Center, Michigan State University, Two Hurley Plaza, Ste 212, Flint, MI 48503 (mahmoud.albarbarawi@gmail.com; mbarbar1@hurleymc.com).

Observational studies have suggested an inverse association between serum 25-hydroxyvitamin D levels and risk of cardiovascular disease (CVD) events.[1-3] Specifically, low vitamin D levels have been linked to an increased risk of myocardial infarction (MI), stroke, CVD mortality, and heart failure in case-control and other prospective epidemiologic studies.[4,5] Additionally, vitamin D receptors are expressed in vascular tissues, including the myocardium and vascular smooth muscle,[6] directly influencing calcium influx, muscle relaxation, and diastolic function.[7] Vitamin D also has effects on the renin-angiotensin-aldosterone system and parathyroid hormone and may influence endothelial function and arterial thrombogenesis.[8-10]

Vitamin D level supplementation has increased in primary care settings in the United States.[11,12] Assessment of vitamin D supplementation for cardiovascular disease prevention has been a subject of growing interest in recent randomized clinical trials (RCTs).[13-16] Owing to insufficient data regarding cardiovascular benefits of screening and treatment of asymptomatic low vitamin D in adults, the US Preventive Services Task Force has not recommended vitamin D supplementation to prevent cardiovascular disease (via I statement, which indicates insufficient evidence).[11] Although previous randomized clinical trials assessing vitamin D supplementation and cardiovascular disease have been limited and inconclusive, several recent large-scale trials have added substantial data to the evidence base.[13-16] Therefore, we conducted a meta-analysis of all RCTs to date that evaluate the efficacy of vitamin D supplementation in the prevention of cardiovascular disease.

Key Points

Question Does vitamin D supplementation have any association with cardiovascular disease risk?

Findings In this meta-analysis of randomized clinical trials that included more than 83 000 participants, vitamin D supplementation was not associated with reduced risks of major adverse cardiovascular events, myocardial infarction, stroke, cardiovascular disease mortality, or all-cause mortality compared with placebo.

Meaning These results suggest that vitamin D supplementation may not confer cardiovascular protection and may not be indicated for this purpose.

Methods

Literature Search

For this meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed.[17] The meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO identifier: CRD42019120689). Published trials from Embase, MEDLINE/PubMed, and the Cochrane Library for relevant trials were identified independently by 2 reviewers (A.Y. and S.S.) from inception to December 2018. The search terms *vitamin D*, *cholecalciferol*, *ergocalciferol*, *cardiovascular*, *cardiac*, *myocardial*, and *heart* were used. Any inconsistency between reviewers was resolved by a third independent reviewer (O.B.). There were no language restrictions. The references of included trials and published meta-analysis were screened for other potential trials.

Eligibility Criteria

In this analysis, only RCTs that evaluated long-term supplementation (≥1-year intervention) with vitamin D, with or without concurrent calcium and with cardiovascular outcomes, were included in this meta-analysis. Any vitamin D or its analogue supplementation was qualified. Studies that did not include cardiovascular outcomes were excluded after reviewing supplementary materials.

Data Extraction

Two reviewers (H.D. and Y.Z.) extracted relevant data independently by using a predetermined data collection table. Any discrepancies between reviewers were resolved by an independent reviewer (B.K.).

Quality Assessment

The Cochrane Collaboration's tool was used to perform quality assessment and assess the risk of bias in the included RCTs for random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting, or other biases. Details are in eFigure 1 in the Supplement.

Outcomes of Interest

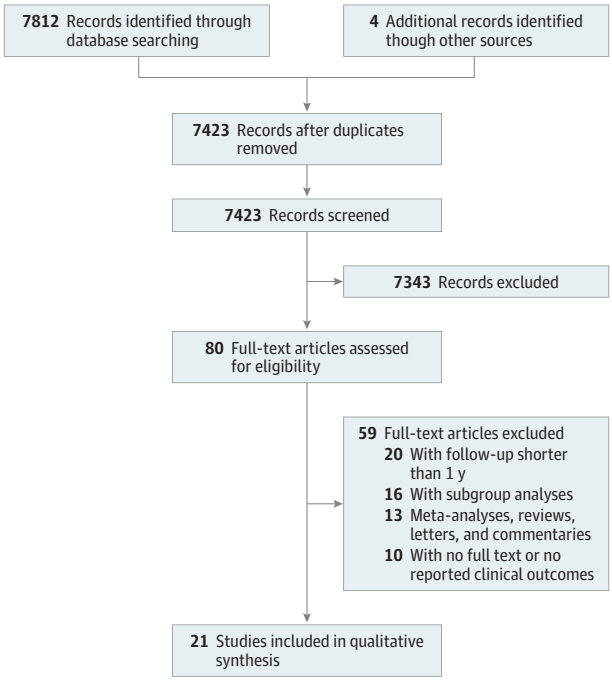
The primary end point was a composite of major adverse cardiovascular events (MACEs), as defined by each trial (eTable in the Supplement). Secondary end points were MI, stroke/cerebrovascular accident (CVA), CVD mortality, and all-cause mortality. The longest available follow-up time was used for each trial in the analysis.

Statistical Analysis

Results were presented as risk ratios (RRs) and 95% CIs on the basis of the Mantel-Haenszel random-effects model. Heterogeneity was evaluated by using the I^2 statistic. Publication bias of the primary end point was assessed by using the funnel plot. We conducted a sensitivity analysis of the primary end point by sequential removal of each trial. Sensitivity analyses of the primary MACE end point were conducted based on age, sex, inclusion of women who were postmenopausal only, use of pretreatment vitamin D level less than 25 ng/mL (to convert to nmol/L, multiply by 2.496), inclusion of patients with chronic kidney disease, exclusion of studies that used vitamin D analogues, and vitamin D dosage and formulation (daily vs bolus dosing). Meta-regression analyses based on study-level covariates (age, sex, follow-up duration, body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], and pretreatment with statin) were conducted to explain any heterogeneity.

To avoid potential spurious inferences from repetitive significance testing and underpowered meta-analysis, we performed trial sequential analysis. By applying trial sequential

Figure 1. The Study Selection Strategy



monitoring boundaries, similar to those of interim analysis in RCTs, we would be able to obtain reliable results.[18] We calculated the optimal information (sample) size to maintain a 2-sided type I error at .05 and a type II error at .20 (80% power), with a relative risk reduction of 25% and an incidence of 8.5% MACE in the placebo arm. Sensitivity analysis was performed using a MACE incidence of 7.86% from the included RCTs. We used Review Manager (RevMan) version 5.3 (Cochrane Community), Comprehensive Meta-analysis version 3 (Biostat), and Trial Sequential Analysis version 0.9.5.9 (Copenhagen Trial Unit) software to conduct all analyses. Data analysis was conducted from November 2018 to March 2019.

Results

After reviewing 7816 studies from the databases, 7796 studies were excluded. Twenty-one RCTs were included in the final analysis.[13-16,19-35] Eight trials included postmenopausal women,[22-25,27,29,33,34] 9 trials included older patients,[20-22,24,28,32-35] 2 trials included patients with chronic kidney disease,[14,26] 2 trials included patients with heart failure,[15,30] and 1 trial included patients with chronic obstructive pulmonary disease.[31] In total, 83 291 patients were included, 41 669 of whom received vitamin D supplementation and 41 622 of whom received placebo. The mean (SD) age was 65.8 (8.4) years, and 61 943 participants (74.4%) were female. Follow-up durations were variable between the included trials (range, 1-12 years). Fourteen trials used cholecalciferol,[13,15,16,19,21,23-25,27,30-33,35] 2 trials used ergocalciferol,[20,22] and 3 trials used vitamin D analogues (alfacalcidol, paricalcitol, and calcitriol).[14,26,34] The search strategy is illustrated in **Figure 1**. All of the included trials reported the incidence of mortality except the study by Prince et al.[20] On the other hand, 3 trials did not report the incidence of MI.[15,30,33] For the Women's Health Initiative trial, we included a follow-up and post hoc analysis that were done on the data.[36,37] The characteristics of the included trials with the patients' demographic features are presented in **Table 1** and **Table 2**.

Primary End Point

There was no significant difference of vitamin D supplementation between groups with regard to MACE incidence (6243 cases; RR, 1.0 [95% CI, 0.95-1.06]; P = .85; I^2 = 11%; **Figure 2** and **Figure 3**). A funnel plot examination for publication bias is provided in eFigure 2 in the Supplement. Sensitivity analyses through removal of each study sequentially and through stratifications by age, sex, inclusion of only postmenopausal women, pretreatment vitamin D levels of less than 25 ng/mL, inclusion of patients with chronic kidney disease, exclusion of studies that used vitamin D analogues, and vitamin D dosage and formulation (daily vs bolus dosing) showed nonsignificant results (eFigures 3-12 in the Supplement). Meta-regression analysis based on sex, BMI, follow-up duration, and age showed a significant association of reduced MACE incidence with advanced age (R^2 = 100%; b, −0.01; SE = .004; P = .04), but the P value was not adjusted for multiple comparisons (eFigure 13 in the Supplement).

In trial sequential analysis, the optimal information size was obtained (diversity adjusted), indicating firm evidence for the lack of an association of MACE reductions with vitamin D supplementation. Details are presented in eFigure 14 in the Supplement.

Secondary End Points

Vitamin D supplementation, compared with placebo, was not associated with a reduced risk of MI (2550 cases; RR, 1.00 [95% CI, 0.93-1.08]; P = .92; I^2 = 0%), stroke/CVA (2354 cases; RR, 1.06 [95% CI, 0.98-1.15]; P = .16; I^2 = 0%), cardiovascular mortality (2202 cases; RR, 0.98 [95% CI, 0.90-1.07]; P = .68; I^2 = 2%), or all-cause mortality (6502 cases; RR, 0.97 [95% CI, 0.93-1.02]; P = .23; I^2 = 0%). Figure 2 and Figure 3 present these data.

Discussion

In this comprehensive meta-analysis of randomized clinical trials (n = 83 291 participants) evaluating the cardiovascular effect of vitamin D, we found that vitamin D supplementation was not associated with reduced risk of incident MACE, MI, stroke/CVA, CVD mortality, or all-cause mortality. Observational studies have shown significant associations between low vitamin D level, CVD events, and all-cause mortality.[38] However, observational studies are susceptible to uncontrolled confounding by outdoor physical activity, nutritional status, and prevalent chronic disease, which may influence serum 25 hydroxyvitamin D levels.[39] Supplementation with vitamin D has not been associated with reduced rates of CVD in previous meta-analyses of RCTs.[40,41] In this updated meta-analysis, which extended the earlier findings and included several

Table 1. Characteristics of the Involved Trials

Source	Year	Patients, No.		Study Period	Vitamin D Type and Dosage	Study Follow-up, y	Country	Major Inclusion Criteria	Primary Outcome
		Vitamin D	Placebo						
Aloia et al[25]	1988	12	15	NA	Vitamin D^3, 400 IU/d	2	United States	Women who were postmenopausal and aged 50-80 y, with osteoporosis (diagnosed by the presence of ≥1 nontraumatic vertebral compression fracture)	Bone mineral measurements and fracture incidence
Ott et al[23]	1989	43	43	NA	Vitamin D^3, 1000 mg/d	2	United States	Women who were postmenopausal, aged 50-80 y, and ambulatory, with ≥2 compression fractures (>15% reduction in anterior height) and without history of serious trauma or current medications for osteoporosis (except calcium supplements in some cases)	Total body calcium, change in bone mineral density, and fracture rate
Komulainen et al[29]	1999	112	115	1989-1991	Vitamin D^3, 300 and 100 IU/d	5	Finland	Women in early postmenopause who were nonosteoporotic	Lumber and femoral neck bone mineral density
STOP IT/Gallagher et al[34]	2001	245	244	NA	Calcitriol, 0.25 µg twice daily	3	United States	Women aged 65-77 y with femoral neck density in normal range (SD, ≤2) for their age	Change in bone mineral density of the femoral neck and spine
Trivedi et al[35]	2003	1345	1341	1996-1997	Vitamin D^3, 100 000 IU/4 mo	5	United Kingdom	Participants aged 65-85 y	Fracture incidence and total mortality by cause
RECORD/Grant et al[32]	2005	2649	2643	1999-2002	Vitamin D^3, 800 IU daily	Median (IQR), 3.8 (3.1-4.3)	United Kingdom	Participants aged ≥70 y who had had a low trauma, osteoporotic fracture in the previous 10 y	The incidence of new low-energy fractures
Brazier et al[33]	2005	95	97	NA	Vitamin D^3, 400 IU twice daily	1	France	Ambulatory women aged >65 y	Vitamin D treatment–associated adverse events
WHI/Jackson et al[27]	2006	18 176	18 106	1995 and 2000	Vitamin D^3, 400 IU/d	12	United States	Women aged 50-79 y with no evidence of a medical condition associated with anticipated survival <3 y and no safety, adherence, or retention risks	Total number of fractures
Schleithoff et al[30]	2006	61	62	2002-2003	Vitamin D^3, 2000 IU/d	1.3	Germany	Participants with New York Heart Association functional class ≥II	Survival rates and biochemical variables, such as natriuretic peptides and cytokines
Berggren et al[28]	2007	102	97	2000-2002	Vitamin D^3, 800 IU/d	1	Sweden	Participants aged ≥70 y who had femoral neck fractures	Total number of falls
Zhu et al[22]	2008	39	81	1998	Vitamin D^3, 1000 IU/d	5	Australia	Women aged 70-80 y who were ambulatory	Change in hip bone mineral density, plasma 25-hydroxyvitamin D, biomarkers of bone turnover, parathyroid hormone, and intestinal calcium absorption
Prince et al[20]	2008	151	151	2003 - 2004	Vitamin D^3, 1000 IU/d	1	Australia	Women aged 70-90 y who were ambulatory	Number of falls
Vital D/Sanders et al[24]	2010	1131	1125	2003-2005	Vitamin D^3, 500 000 IU/y	Median (IQR), 2.96 (2.92-3.00)	Australia	Community-dwelling women aged ≥70 y at high risk of fracture (defined by criteria such as maternal hip fracture, past fracture, or self-reported fall)	Number of falls and fractures

(continued)

Table 1. Characteristics of the Involved Trials (continued)

Source	Year	Patients, No.		Study Period	Vitamin D Type and Dosage	Study Follow-up, y	Country	Major Inclusion Criteria	Primary Outcome
		Vitamin D	Placebo						
Lehouck et al[31]	2012	91	91	2008-2009	Vitamin D, 100 000 IU/mo	1	Belgium	Current or former smokers aged ≥50 y who had a chronic obstructive pulmonary disease per diagnosis Global Initiative for Chronic Obstructive Lung Disease definition (postbronchodilator ratio of first second of forced expiration to the forced vital capacity _0.7) and a first second of forced expiration <80% anticipated	Incidence of chronic obstructive pulmonary disease exacerbations
VITDISH/Witham et al[21]	2013	80	79	2009-2001	Vitamin D^3, 100 000 IU/3 mo	1	United Kingdom	Participants aged ≥70 y with isolated systolic hypertension (supine systolic blood pressure, >140 mm Hg; supine diastolic blood pressure, <90 mm Hg) and baseline 25-hydroxyvitamin D levels <30 ng/mL	Difference in in-office blood pressure, 24-h blood pressure, arterial stiffness, endothelial function, cholesterol level, insulin resistance, and B-type natriuretic peptide level
OPERA/Wang et al[26]	2014	30	30	2008-2010	Paricalcitol, 1 μg/d	1	Hong Kong	Participants with stages 3-5 chronic kidney disease and left ventricle hypertrophy	The change in left ventricle mass index measured by cardiac magnetic resonance imaging
Baron et al[19]	2015	1130	1129	2004-2008	Vitamin D^3, 1000 IU\day	3	United States	Participants aged 45-75 y who had ≥1 colorectal adenoma removed within 120 d before enrollment and no remaining polyps after a complete colonoscopy	Incidence of colonic adenoma
EVITA/Zitterman et al[15]	2017	199	201	2010-2013	Vitamin D^3, 4000 IU/d	3	Germany	Participants aged 18-79 y who were classified as having New York Heart Association functional class ≥II	All-cause mortality
VIDA/Scragg et al[16]	2017	2558	2550	2011-2015	Vitamin D^3, Initial 200 000 IU, then 100 000 IU/mo	Median (IQR), 3.3 (2.5-4.2)	New Zealand	Participants aged 50-84 y	Incident cardiovascular disease and death
J-DAVID/Shoji et al[14]	2018	488	476	2011-2015	Alfacalcidol, 0.5 μg/d	Median (IQR), Vitamin D: 4.0 (2.6-4.0)[a]; Placebo: 4.0 (3.5-4.0)	Japan	Participants aged 20-80 y who were receiving maintenance hemodialysis; had calcium ≤10.0 mg/dL, phosphate ≤6.0 mg/dL, and intact parathyroid hormone ≤180 pg/mL, and were not taking any vitamin D receptor activations at randomization	Composite measure of fatal and nonfatal cardiovascular events, including myocardial infarctions, hospitalizations for congestive heart failure, stroke, aortic dissection/rupture, amputation of lower limb owing to ischemia, and cardiac sudden death; coronary revascularization; and leg artery revascularization
VITAL/Manson et al[13]	2018	12 927	12 944	2011-2014	Vitamin D^3, 2000 IU/d	Median (IQR), 5.3 (3.8 to 6.1)[a]	United States	Participants had no history of cancer (except nonmelanoma skin cancer) or cardiovascular disease at trial entry	Incidence of invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes)

Abbreviations: EVITA, Effect of Vitamin D on All-Cause Mortality in Heart Failure patients; IQR, interquartile range; J-DAVID, Japan Dialysis Active Vitamin D; OPERA, Oral Paricalcitol in Retarding Cardiac Hypertrophy, Reducing Inflammation and Atherosclerosis in Stage 3-5 Chronic Kidney Disease; RECORD, Randomized Evaluation of Calcium or Vitamin D; STOP IT, Estrogen and Calcitriol in the Prevention of Age-Related Bone Loss; VIDA, Vitamin D Assessment, VITAL, Vitamin D and Omega-3 Trial; VITDISH, Vitamin D in Isolated Systolic Hypertension; WHI, Women's Health Initiative.

Table 2. Patients' Demographic and Clinical Characteristics

Source	Year	Patients, No.	Subgroup[a]	Age, Mean (SD), y	Male, No. (%)	Current Smoker, No. (%)	BMI, Mean (SD)	Total Cholesterol, Mean (SD), mg/dL	Baseline 25-Hydroxyvitamin D Level, Mean (SD), ng/mL	Statin User, No. (%)	Systolic Blood Pressure, mm Hg, Mean (SD)	Hypertension, No. (%)	Diabetes, No. (%)
Aloia et al[25]	1988	17	Vitamin D	64.1 (1.5)	0	NA	NA	NA	21.9 (7)	NA	NA	NA	NA
		17	Placebo	64.9 (1.7)	0	NA	NA	NA	26.6 (12)	NA	NA	NA	NA
Ott et al[23]	1989	43	Vitamin D	67.9 (1.0)	0	NA	NA	NA	26.7 (1.9)	NA	NA	NA	NA
		43	Placebo	67.1 (1.2)	0	NA	NA	NA	26.3 (2.4)	NA	NA	NA	NA
Komulainen et al[29]	1999	112	Vitamin D	53 (0.3)	0	NA	27.2 (0.3)	NA	NA	NA	NA	NA	4 (3.6)
		115	Placebo	53 (0.3)	0	NA	26.6 (0.4)	NA	NA	NA	NA	NA	3 (3)
STOP IT/ Gallagher et al[34]	2001	245	Vitamin D or vitamin D plus HRT	71 (3.5)	0	NA	27.3 (5)	NA	31.2 (11)	NA	NA	NA	NA
		244	Placebo or placebo plus HRT	71.4 (4)	0	NA	27.4 (6)	NA	32 (10)	NA	NA	NA	NA
Trivedi et al[35]	2003	1345	Vitamin D	74.8 (4.6)	1019 (75.8)	59 (4.4)	24.3 (3.4)	NA	NA	NA	NA	NA	NA
		1341	Placebo	74.7 (4.6)	1018 (75.9)	53 (4.0)	24.4 (3.0)	NA	NA	NA	NA	NA	NA
RECORD/Grant et al[32]	2005	2649	Vitamin D or vitamin D plus calcium	77 (6)	409 (15.4)	298 (11.2)	NA	NA	NA	NA	NA	NA	NA
		2643	Placebo and calcium	77 (6)	402 (15.2)	320 (12.1)	NA	NA	NA	NA	NA	NA	NA
Brazier et al[33]	2005	95	Vitamin D plus calcium	74.2 (6.4)	0	NA	27.0 (4.4)	NA	7.3	NA	138 (11)	NA	NA
		97	Placebo	75.0 (7.3)	0	NA	26.4 (4.3)	NA	7.0	NA	138 (14)	NA	NA
WHI/Jackson et al[27]	2006	18 176	Vitamin D plus calcium	62.4 (7.0)	0	1405 (7.7)	29.1 (5.9)	208.1	NA	1178 (6.5)	127 (17)	5447 (30.0)	1055 (5.8)
		18 106	Placebo	62.4 (6.9)	0	1356 (7.5)	29.0 (5.9)	208.1	NA	1149 (6.3)	128 (17)	5476 (30.2)	1036 (5.7)
Schleithoff et al[30]	2006	61	Vitamin D	57.6 (7.5)	52 (85.2)	9 (14.8)	26.3 (3.8)	NA	Median (IQR), 15.2 (12.0-22.1)	53 (86.9)	120 (6)	38 (62.3)	20 (32.8)
		62	Placebo	55.3 (9)	50 (80.6)	7 (11.3)	26 (3.1)	NA	Median (IQR), 15.2 (12.0-22.1)	42 (67.7)	125 (8)	32 (51.6)	23 (37.1)
Berggren et al[28]	2007	102	Vitamin D	82.3 (6.6)	28 (27.5)	NA	NA	NA	NA	NA	NA	NA	23 (22.5)
		97	Placebo	82.0 (5.9)	23 (23.7)	NA	NA	NA	NA	NA	NA	NA	17 (17.5)
Zhu et al[22]	2008	39	Vitamin D plus calcium	75.4 (2.7)	0	NA	27.6 (4)	NA	26.8 (10.4)	NA	NA	NA	NA
		81	Placebo or calcium	74.4 (2.4)	0	NA	28.2 (4.1)	NA	28 (10.4)	NA	NA	NA	NA
Prince et al[20]	2008	151	Vitamin D plus calcium	77.0 (4.2)	0	NA	29.6 (3.5)	NA	18.1 (5.0)	NA	NA	NA	NA
		151	Placebo plus calcium	77.4 (5.0)	0	NA	28.2 (3.2)	NA	17.7 (5.1)	NA	NA	NA	NA

(continued)

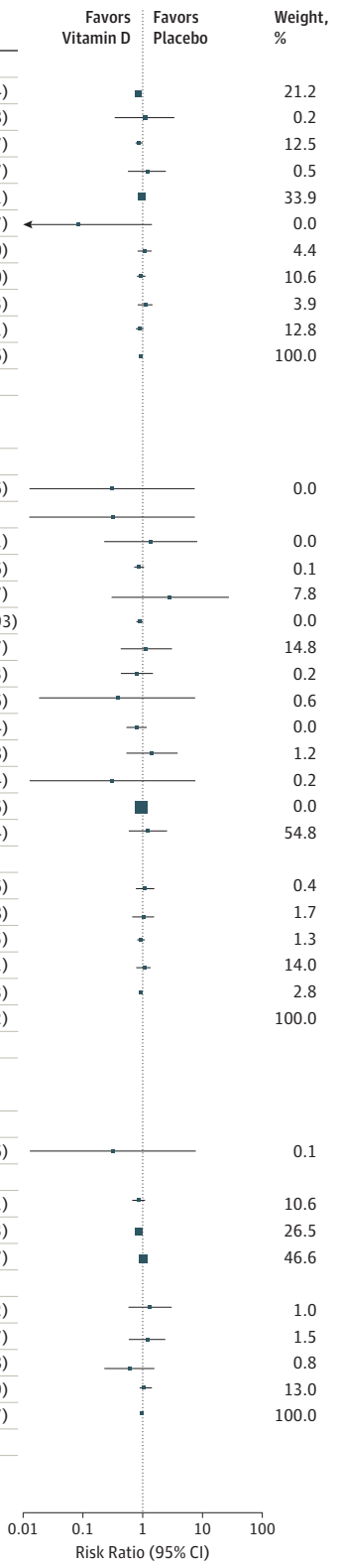
Table 2. Patients' Demographic and Clinical Characteristics (continued)

Source	Year	Patients, No.	Subgroup[a]	Age, Mean (SD), y	Male, No. (%)	Current Smoker, No. (%)	BMI, Mean (SD)	Total Cholesterol, Mean (SD), mg/dL	Baseline 25-Hydroxyvitamin D Level, Mean (SD), ng/mL	Statin User, No. (%)	Systolic Blood Pressure, mm Hg, Mean (SD)	Hypertension, No. (%)	Diabetes, No. (%)
Vital D/Sanders et al[24]	2010	1131	Vitamin D	76.4 (5.7)	0	NA	NA	NA	53 (7)	NA	NA	NA	NA
		1125	Placebo	76.5 (5)	0	NA	NA	NA	47 (5)	NA	NA	NA	NA
Lehouck et al[31]	2012	91	Vitamin D	68 (9)	72 (79.1)	13 (14.3)	25 (5)	NA	20 (12)	NA	NA	NA	NA
		91	Placebo	68 (8)	73 (80.2)	19 (20.9)	24 (5)	NA	20 (11)	NA	NA	NA	NA
VitDISH/Witham et al[21]	2013	80	Vitamin D	76.9 (4.8)	40 (50.0)	NA	28.5 (5.0)	189 (46)	18 (6)	41 (51.3)	136 (11)	80 (100.0)	11 (13.9)
		79	Placebo	76.7 (4.5)	42 (53.2)	NA	27.9 (4.5)	193 (42)	18 (6)	46 (58.2)	133 (11)	79 (100.0)	11 (13.9)
OPERA/Wang et al[26]	2014	30	Vitamin D	60.8 (10.2)	18 (60.0)	3 (10.0)	26.6 (4.4)	167 (39)	NA	18 (60.0)	131 (19)	30 (100.0)	8 (26.7)
		30	Placebo	62.2 (10.7)	14 (46.7)	3 (10.0)	26.2 (4.5)	185 (41)	NA	20 (66.7)	135 (15)	30 (100.0)	13 (43.3)
Baron et al[19]	2015	1130	Vitamin D plus calcium	58.1 (7)	712 (63.0)	119 (10.5)	28.9 (5.0)	NA	24.7 (8)	NA	NA	NA	NA
		1129	Placebo plus calcium	58.0 (7)	711 (63.0)	96 (8.5)	29.2 (5.1)	NA	24.4 (8)	NA	NA	NA	NA
EVITA/ Zitterman et al[15]	2017	199	Vitamin D	55 (10)	166 (83.4)	NA	27.8 (1.7)	NA	13 (3)	113 (56.8)	115 (19)	57 (28.6)	51 (26.7)
		201	Placebo	54 (8)	166 (82.6)	NA	27.9 (2.1)	NA	14 (3)	105 (52.2)	117 (18)	63 (31.3)	46 (22.9)
VIDA/Scragg et al[16]	2017	2558	Vitamin D	65.9 (8.3)	1512 (59.1)	164 (6.4)	27.9 (4.2)	185 (42)	25.5 (9.5)	NA	139 (19)	955 (37.3)	265 (10.4)
		2550	Placebo	65.9 (8.3)	1457 (57.1)	156 (6.1)	27.9 (5.7)	189 (42)	25.2 (9.4)	NA	139 (19)	930 (36.5)	239 (9.4)
J-DAVID/Shōji et al[14]	2018	488	Vitamin D	65 (10.4)	301 (61.7)	NA	21.1 (3)	153 (32)	NA	77 (15.8)	145 (22)	NA	NA
		476	Placebo	65 (9.67)	277 (58.2)	NA	21.1 (3)	150 (29)	NA	81 (17.0)	147 (19)	NA	NA
VITAL/Manson et al[13]	2018	12 927	Vitamin D	67.1 (7.0)	6380 (49.4)	921 (7.1)	28.1 (5.7)	NA	30.9 (10)	4822 (37.3)	NA	6352 (49.1)	1812 (14.0)
		12 944	Placebo	67.1 (7.1)	6406 (49.5)	915 (7.1)	28.1 (5.8)	NA	30.8 (10)	4702 (36.3)	NA	6439 (49.7)	1737 (13.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EVITA, Effect of Vitamin D on All-Cause Mortality in Heart Failure Patients; HRT, hormone therapy; IQR, interquartile range; J-DAVID, Japan Dialysis Active Vitamin D; NA, not available; OPERA, Oral Paricalcitol in Retarding Cardiac Hypertrophy, Reducing Inflammation and Atherosclerosis in Stage 3-5 Chronic Kidney Disease; RECORD, Randomized Evaluation of Calcium or Vitamin D; STOP IT, Estrogen and Calcitriol in the Prevention of Age-Related Bone Loss; VIDA, Vitamin D Assessment; VITAL, Vitamin D and Omega-3 Trial; VITDISH, Vitamin D in Isolated Systolic Hypertension; WHI, Women's Health Initiative.

Figure 2. Forest Plot Illustrating the Results of the Primary and Secondary End Points, Part 1

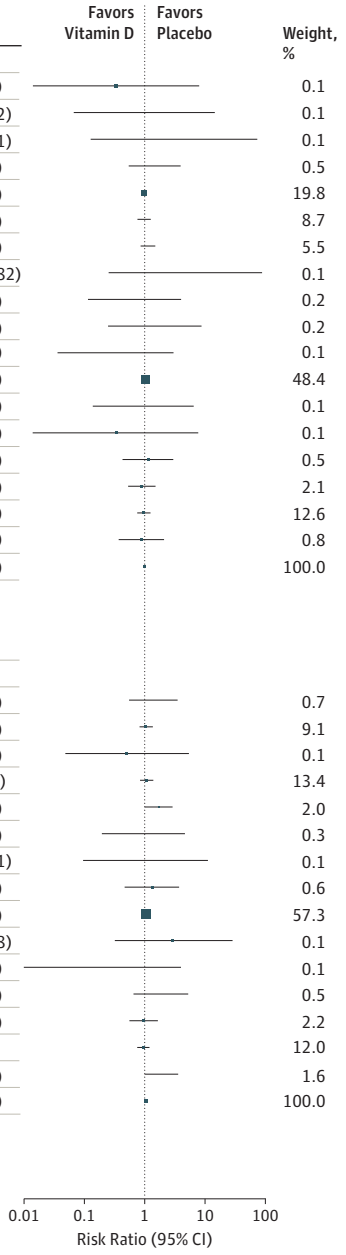
Study or subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Risk Ratio (95% CI)	Weight, %
MACE						
Trivedi et al,[35] 2003	477	1345	503	1341	0.95 (0.86-1.04)	21.2
Brazier et al,[33] 2005	6	95	5	97	1.23 (0.39-3.88)	0.2
Grant et al,[32] 2005	339	2649	363	2643	0.93 (0.81-1.07)	12.5
Sanders et al,[24] 2010	17	1131	13	1125	1.30 (0.63-2.67)	0.5
Jackson et al,[27] 2006	1405	18106	1363	18176	1.03 (0.96-1.11)	33.9
Wang et al, [26] 2014	0	30	5	30	0.09 (0.01-1.57)	0.0
Zitterman et al, [15] 2017	85	199	73	201	1.18 (0.92-1.50)	4.4
Scragg et al,[16] 2017	303	2558	293	2550	1.03 (0.89-1.20)	10.6
Shoji et al,[14] 2018	103	488	85	476	1.18 (0.91-1.53)	3.9
Manson et al,[13] 2018	396	12927	409	12944	0.97 (0.85-1.11)	12.8
Subtotal (95% CI)		39528		39583	1.00 (0.95-1.06)	100.0
Total events	3131		3112			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_9 = 10.07$, $P = .35$, $I^2 = 11\%$						
Test for overall effect: $z = 0.18$, $P = .85$						
All-cause mortality						
Ott et al,[23] 1989	0	43	1	43	0.33 (0.01-7.96)	0.0
Aloia et al,[25] 1988	0	17	0	17	Not estimable	
Komulainen et al,[29] 1999	0	112	1	115	0.34 (0.01-8.31)	0.0
Gallagher et al,[34] 2001	3	245	2	244	1.49 (0.25-8.86)	0.1
Trivedi et al,[35] 2003	224	1345	247	1341	0.90 (0.77-1.07)	7.8
Brazier et al,[33] 2005	3	95	1	97	3.09 (0.32-28.93)	0.0
Grant et al, [32] 2005	438	2649	460	2643	0.95 (0.84-1.07)	14.8
Schleithoff et al,[30] 2006	7	61	6	62	1.19 (0.42-3.33)	0.2
Berggren et al,[28] 2007	16	102	18	97	0.85 (0.46-1.56)	0.6
Zhu et al,[22] 2008	0	39	2	81	0.41 (0.02-8.34)	0.0
Sanders et al,[24] 2010	40	1131	47	1125	0.85 (0.56-1.28)	1.2
Lehouck et al,[31] 2012	8	91	0	91	1.50 (0.56-4.04)	0.2
Witham et al,[21] 2013	0	80	1	79	0.33 (0.01-7.96)	0.0
Jackson et al,[27] 2006	1775	18178	1823	18176	0.97 (0.92-1.04)	54.8
Wang et al,[26] 2014	0	30	0	30	Not estimable	
Baron et al,[19] 2015	15	1130	12	1129	1.25 (0.59-2.66)	0.4
Scragg et al,[16] 2017	85	5658	58	2550	1.12 (0.79-1.58)	1.7
Zitterman et al,[15] 2017	39	199	36	201	1.09 (0.73-1.65)	1.3
Manson et al,[13] 2018	485	12927	493	12944	0.99 (0.87-1.11)	14.0
Shoji et al,[14] 2018	89	488	80	476	1.09 (0.82-1.43)	2.8
Subtotal (95% CI)		41518		41541	0.97 (0.93-1.02)	100.0
Total events		3208		3294		
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_7 = 7.25$, $P = 0.98$, $I^2 = 0\%$						
Test for overall effect: $z = 1.19$ ($P = .23$)						
Cardiovascular death						
Ott et al,[23] 1889	0	43	1	43	0.33 (0.01-7.06)	0.1
Aloia et al,[25] 1988	0	17	0	17	Not estimable	
Trivedi et al,[35] 2003	101	1345	117	1341	0.86 (0.87-1.11)	10.6
Grant et al,[32] 2005	256	2648	291	2643	0.80 (0.75-1.03)	26.5
Jackson et al,[27] 2006	549	18178	525	18106	1.04 (0.93-1.17)	46.6
Wang et al,[26] 2014	0	30	0	30	Not estimable	
Zitterman et al,[15] 2017	12	199	9	201	1.35 (0.58-3.12)	1.0
Scragg et al,[16] 2017	18	2558	15	2550	1.20 (0.50-2.37)	1.5
Shoji et al,[14] 2018	7	488	11	476	0.82 (0.24-1.58)	0.8
Manson et al,[13] 2018	152	12927	138	12944	1.10 (0.88-1.39)	13.0
Subtotal (95% CI)		38432		38351	0.98 (0.00-1.07)	100.0
Total events	1095		1107			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_7 = 7.11$, $P = .42$, $I^2 = 2\%$						
Test for overall effect: $z = 0.41$ ($P = .68$)						



recent RCTs, we did not find any association between vitamin D supplementation and cardiovascular events. Interestingly, a stratified analysis according to age showed a significantly reduced MACE rate with advanced age, and this was

Figure 3. Forest Plot Illustrating the Results of the Primary and Secondary End Points, Part 2

Study or subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Risk Ratio (95% CI)	Weight, %
Myocardial infarction						
Ott et al,[23] 1989	0	43	1	43	0.33 (0.01-7.08)	0.1
Aloia et al,[25] 1988	1	17	1	17	1.00 (0.07-14.72)	0.1
Komulainen et al,[29] 1999	1	112	0	115	3.08 (0.13-74.81)	0.1
Gallagher et al,[34] 2001	9	245	6	244	1.49 (0.54-4.13)	0.5
Trivedi et al,[35] 2003	224	1345	233	1341	0.96 (0.81-1.13)	19.8
Grant et al,[32] 2005	114	2649	117	2643	0.97 (0.78-1.25)	8.7
Berggren et al,[28] 2007	47	102	40	97	1.12 (0.81-1.53)	5.5
Zhu et al,[22] 2008	1	39	0	81	8.15 (0.28-147.82)	0.1
Prince et al,[20] 2008	2	151	3	161	0.87 (0.11-3.83)	0.2
Sanders et al,[24] 2010	3	1131	2	1125	1.49 (0.25-8.91)	0.2
Lehouck et al,[31] 2012	1	81	3	91	0.33 (0.04-3.15)	0.1
Jackson et al,[27] 2006	659	18176	637	18106	1.03 (0.33-1.15)	48.4
Witham et al,[21] 2013	2	80	2	79	0.99 (0.14-8.84)	0.1
Wang et al,[26] 2014	0	30	1	30	0.33 (0.01-7.87)	0.1
Baron et al,[19] 2015	8	1130	7	1129	1.14 (0.42-3.14)	0.5
Scragg et al,[16] 2017	28	2558	31	2550	0.90 (0.64-1.50)	2.1
Manson et al,[13] 2018	169	12927	176	12944	0.96 (0.78-1.19)	12.6
Shoji et al,[14] 2018	10	488	11	478	0.89 (0.38-2.07)	0.8
Subtotal (95% CI)		41314		41262	1.00 (0.03-1.08)	100.0
Total events	1279		1271			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_{17} = 6.07$, $P = .99$, $I^2 = 0\%$						
Test for overall effect: $z = 0.10$ ($P = .92$)						
Cerebrovascular accident						
Gallagher et al,[34] 2001	10	245	7	244	1.42 (0.55-3.68)	0.7
Trivedi et al,[35] 2003	105	1345	101	1341	1.04 (0.60-1.35)	9.1
Brazier et al,[33] 2006	1	95	2	97	0.51 (0.05-5.54)	0.1
Grant et al,[32] 2005	160	2649	149	2643	1.07 (0.88-1.33)	13.4
Berggren et al,[28] 2007	27	102	15	97	1.71 (0.97-3.02)	2.0
Prince et al,[20] 2008	3	151	3	151	1.00 (0.21-4.88)	0.3
Zhu et al,[22] 2008	1	39	2	81	1.04 (0.10-11.11)	0.1
Sanders et al,[24] 2010	8	1131	6	1125	1.33 (0.48-3.81)	0.6
Jackson et al,[27] 2006	690	18176	659	18106	1.04 (0.94-1.18)	57.3
Witham et al,[21] 2013	3	80	1	79	2.96 (0.31-27.88)	0.1
Wang et al,[26] 2014	0	30	2	30	0.20 (0.01-4.00)	0.1
Baron et al,[19] 2015	9	1130	5	1129	1.80 (0.60-5.35)	0.5
Scragg et al,[16] 2017	26	2558	27	2550	0.96 (0.56-1.54)	2.2
Manson et al,[13] 2018	141	12927	149	12944	0.95 (0.75-1.18)	12.0
Shoji et al,[14] 2018	28	488	14	476	1.96 (1.04-3.86)	1.6
Subtotal (95% CI)		41146		41093	1.06 (0.98-1.15)	100.0
Total events		1212	1142			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_{14} = 11.35$, $P = .86$, $I^2 = 0\%$						
Test for overall effect: $z = 1.41$ ($P = .16$)						



suggested by the Manson et al[13] and Trivedi et al[35] studies, because vitamin D supplementation in elderly people showed a trend toward lower CVD events. On the other hand, a stratified analysis did not show significant differences by sex, concurrent calcium administration, pretreatment 25-hydroxyvitamin D level (<25 ng/mL vs higher), BMI, vitamin D dosage, formulation (daily vs bolus dosing), or other factors. The regression analysis findings for age should be interpreted cautiously owing to lack of adjustment for multiple comparisons.

In a previous meta-analysis of RCTs,[41] vitamin D supplementation showed no benefit in reducing MI, but a potential benefit for heart failure was observed. This meta-analysis confirms an absence of benefit for MI, as well as no reduction in stroke, CVD mortality, or a composite MACE end point. Despite the fact that we aimed in this analysis to study cardiovascular outcomes, most of the trials were not designed to assess CVD events as primary prespecified outcomes; rather, they were designed to assess effects of vitamin D on fracture or osteoporosis and tended to include primarily older patients and women who were postmenopausal.[20-22,24,28,32-35] Only 4 trials focused on cardiovascular events as a primary prespecified end point; however, these trials also did not show cardiovascular or mortality benefits.[13-16]

Although observational studies have suggested that low serum levels of 25-hydroxyvitamin D are associated with an

increased risk of CVD events, the effects of vitamin D supplementation did not appear to vary according to baseline 25-hydroxyvitamin D levels in either the Vitamin D and Omega-3 Trial (VITAL)[13]or Vitamin D Assessment (VIDA) trials.[16] Furthermore, in the sensitivity analysis for trials that had a mean 25-hydroxyvitamin D of 25 ng/mL or less, we did not find an association of vitamin D supplementation with significantly reduced CVD events or all-cause mortality in these participants. Moreover, although several studies focused on patients with chronic kidney disease[14,26] because they have low 25-hydroxyvitamin D levels and are at high risk of cardiovascular disease,[42] the sensitivity analysis of these trials did not show cardiovascular benefit of vitamin D supplementation in these patients.

Higher prevalence of lower 25-hydroxyvitamin D levels among racial/ethnic groups who are darker skinned than white people are, likely in association with lower vitamin D synthesis in the skin and differences in vitamin D metabolism, has been reported previously.[43] However, previous studies have shown no associations of such low levels with CVD events,[44] even with vitamin D supplementation.[13] Similarly, although low vitamin D levels have been associated with both the risk of CVA and the functional outcome after CVA in observational studies,[45] this meta-analysis did not demonstrate a protective effect of vitamin D supplementation with regard to stroke/CVA.[40,41] In summary, the included trials, although different in their inclusion criteria, showed consistent findings of no significant benefit of vitamin D supplementation in reducing CVD events and all-cause mortality.

Limitation

This study has limitations that warrant consideration. Most of the included trials had not prespecified CVD as the primary end point and were underpowered for CVD events. Also, the definition of MACE was variable in the included trials, and few trials included data on heart failure. In addition, the results of the subgroup analyses should be interpreted cautiously owing to low data counts, and additional large trials are needed for definitive conclusions. Finally, we lacked patient-level data and could not examine some of the subgroups of interest.

Conclusions

Vitamin D supplementation was not associated with reduced risks of MACE, MI, stroke, cardiovascular mortality, or all-cause mortality. Additional trials of higher-dose vitamin D supplementation, perhaps targeting members of older age groups and with attention to other CVD end points such as heart failure, are of interest.

ARTICLE INFORMATION

Accepted for Publication: April 10, 2019.

Published Online: June 19, 2019. doi:10.1001/jamacardio.2019.1870

Author Contributions: Dr Barbarawi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: M. Barbarawi, Kheiri, Zayed, Dhillon, Swaid, Bachuwa, Manson.
Acquisition, analysis, or interpretation of data: M. Barbarawi, Kheiri, Zayed, O. Barbarawi, Yelangi, Sundus, Alkotob, Manson.
Drafting of the manuscript: M. Barbarawi, Kheiri, Zayed, Dhillon, Sundus.
Critical revision of the manuscript for important intellectual content: M. Barbarawi, Kheiri, O. Barbarawi, Swaid, Yelangi, Sundus, Bachuwa, Alkotob, Manson.
Statistical analysis: M. Barbarawi, Kheiri, Zayed.
Administrative, technical, or material support: O. Barbarawi, Dhillon, Yelangi, Sundus, Manson.
Supervision: M. Barbarawi, Swaid, Bachuwa, Alkotob, Manson.

Conflict of Interest Disclosures: Dr Manson received funding from the US National Institutes of Health to conduct the Vitamin D and ω-3 Trial (VITAL). Vitamin D study pills were donated by Pharmavite LLC and Omega-3 supplements were donated by Pronova BioPharma and BASF. No other disclosures were reported.

REFERENCES

1. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008;168(11):1174-1180. doi:10.1001/archinte.168.11.1174

2. Pekkanen MP, Ukkola O, Hedberg P, et al. Serum 25-hydroxyvitamin D is associated with major cardiovascular risk factors and cardiac structure and function in patients with coronary artery disease. *Nutr Metab Cardiovasc Dis*. 2015;25(5):471-478. doi:10.1016/j.numecd.2015.02.005

3. Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. *Int J Cancer*. 2011;128(6):1414-1424. doi:10.1002/ijc.25439

4. Kheiri B, Abdalla A, Osman M, Ahmed S, Hassan M, Bachuwa G. Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. *Clin Hypertens*. 2018;24:9. doi:10.1186/s40885-018-0094-4

5. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol*. 2008;102(11):1540-1544. doi:10.1016/j.amjcard.2008.06.067

6. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr*. 2008;88(2):491S-499S. doi:10.1093/ajcn/88.2.491S

7. Simpson RU, Hershey SH, Nibbelink KA. Characterization of heart size and blood pressure in the vitamin D receptor knockout mouse. *J Steroid Biochem Mol Biol*. 2007;103(3-5):521-524. doi:10.1016/j.jsbmb.2006.12.098

8. Beveridge LA, Witham MD. Vitamin D and the cardiovascular system. *Osteoporos Int*. 2013;24(8):2167-2180. doi:10.1007/s00198-013-2281-1

9. Al Mheid I, Patel RS, Tangpricha V, Quyyumi AA. Vitamin D and cardiovascular disease: is the evidence solid? *Eur Heart J*. 2013;34(48):3691-3698. doi:10.1093/eurheartj/eht166

10. Al Mheid I, Quyyumi AA. Vitamin D and cardiovascular disease: controversy unresolved. *J Am Coll Cardiol*. 2017;70(1):89-100. doi:10.1016/j.jacc.2017.05.031

11. LeFevre ML; U.S. Preventive Services Task Force. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;162(2):133-140. doi:10.7326/M14-2450

12. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999-2012. *JAMA*. 2016;316(14):1464-1474. doi:10.1001/jama.2016.14403

13. Manson JE, Cook NR, Lee I-M, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380(1):33-44. doi:10.1056/NEJMoa1809944

14. Shoji T, Inaba M, Fukagawa M, et al; J-DAVID Investigators. Effect of oral alfacalcidol on clinical outcomes in patients without secondary hyperparathyroidism receiving maintenance hemodialysis: the J-DAVID randomized clinical trial. *JAMA*. 2018;320(22):2325-2334. doi:10.1001/jama.2018.17749

15. Zittermann A, Ernst JB, Prokop S, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. *Eur Heart J*. 2017;38(29):2279-2286. doi:10.1093/eurheartj/ehx235

16. Scragg R, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study : a randomized clinical trial. *JAMA Cardiol*. 2017;2(6):608-616. doi:10.1001/jamacardio.2017.0175

17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-e34. doi:10.1016/j.jclinepi.2009.06.006

18. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol*. 2009;38(1):276-286. doi:10.1093/ije/dyn179

19. Baron JA, Barry EL, Mott LA, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med*. 2015;373(16):1519-1530. doi:10.1056/NEJMoa1500409

20. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med*. 2008;168(1):103-108. doi:10.1001/archinternmed.2007.31

21. Witham MD, Price RJG, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA Intern Med*. 2013;173(18):1672-1679. doi:10.1001/jamainternmed.2013.9043

22. Zhu K, Devine A, Dick IM, Wilson SG, Prince RL. Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: a five-year randomized controlled trial. *J Clin Endocrinol Metab*. 2008;93(3):743-749. doi:10.1210/jc.2007-1466

23. Ott SM, Chesnut CH III. Calcitriol treatment is not effective in postmenopausal osteoporosis. *Ann Intern Med*. 1989;110(4):267-274. doi:10.7326/0003-4819-110-4-267

24. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815-1822. doi:10.1001/jama.2010.594

25. Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of postmenopausal osteoporosis. *Am J Med*. 1988;84(3 pt 1):401-408. doi:10.1016/0002-9343(88)90259-8

26. Wang AY-M, Fang F, Chan J, et al. Effect of paricalcitol on left ventricular mass and function in CKD—the OPERA trial. *J Am Soc Nephrol*. 2014;25(1):175-186. doi:10.1681/ASN.2013010103

27. Jackson RD, LaCroix AZ, Gass M, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *f Engl J Med*. 2006;354(7):669-683. doi:10.1056/NEJMoa055218

28. Berggren M, Stenvall M, Olofsson B, Gustafson Y. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-year follow-up. *Osteoporos Int*. 2008;19(6):801-809. doi:10.1007/s00198-007-0507-9

29. Komulainen M, Kröger H, Tuppurainen MT, et al. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab*. 1999;84(2):546-552. doi:10.1210/jcem.84.2.5496

30. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83(4):754-759. doi:10.1093/ajcn/83.4.754

31. Lehouck A, Mathieu C, Carremans C, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2012;156(2):105-114. doi:10.7326/0003-4819-156-2-201201170-00004

32. Grant AM, Avenell A, Campbell MK, et al; RECORD Trial Group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or Vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365(9471):1621-1628. doi:10.1016/S0140-6736(05)63013-9

33. Brazier M, Grados F, Kamel S, et al. Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2005;27(12):1885-1893. doi:10.1016/j.clinthera.2005.12.010

34. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab*. 2001;86(8):3618-3628. doi:10.1210/jcem.86.8.7703

35. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326(7387):469. doi:10.1136/bmj.326.7387.469

36. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. *J Womens Health (Larchmt)*. 2013;22(11):915-929. doi:10.1089/jwh.2013.4270

37. Hsia J, Heiss G, Ren H, et al; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115(7):846-854. doi:10.1161/CIRCULATIONAHA.106.673491

38. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med*. 2010;51(3-4):228-233. doi:10.1016/j.ypmed.2010.06.013

39. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press;2011. doi:10.17226/13050.

40. Elamin MB, Abu Elnour NO, Elamin KB, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2011;96(7):1931-1942. doi:10.1210/jc.2011-0398

41. Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M; RECORD Trial Group. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr*. 2014;100(3):746-755. doi:10.3945/ajcn.113.082602

42. Sarnak MJ, Levey AS, Schoolwerth AC, et al; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108(17):2154-2169. doi:10.1161/01.CIR.0000095676.90936.80

43. Harris SS. Vitamin D and African Americans. *J Nutr*. 2006;136(4):1126-1129. doi:10.1093/jn/136.4.1126

44. Zhang X, Tu W, Manson JE, et al. Racial/ethnic differences in 25-hydroxy Vitamin D and parathyroid hormone levels and cardiovascular disease risk among postmenopausal women. *J Am Heart Assoc*. 2019;8(4):e011021. doi:10.1161/JAHA.118.011021

45. Wang Y, Ji H, Tong Y, Zhang ZB. Prognostic value of serum 25-hydroxyvitamin D in patients with stroke. *Neurochem Res*. 2014;39(7):1332-1337. doi:10.1007/s11064-014-1316-0