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# Vitamin D and Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

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**Context:** Several studies found association between vitamin D levels and hypertension, coronary artery calcification, and heart disease.

**Objective:** The aim of this study was to summarize the evidence on the effect of vitamin D on cardiovascular outcomes.

**Design and Methods:** We searched electronic databases from inception through August 2010 for randomized trials. Reviewers working in duplicate and independently extracted study characteristics, quality, and the outcomes of interest. Random-effects meta-analysis was used to pool the relative risks (RR) and the weighted mean differences across trials.

**Results:** We found 51 eligible trials with moderate quality. Vitamin D was associated with nonsignificant effects on the patient-important outcomes of death [RR, 0.96; 95% confidence interval (CI), 0.93, 1.00; $P = 0.08$], myocardial infarction (RR, 1.02; 95% CI, 0.93, 1.13; $P = 0.64$), and stroke (RR, 1.05; 95% CI, 0.88, 1.25; $P = 0.59$). These analyses were associated with minimal heterogeneity. There were no significant changes in the surrogate outcomes of lipid fractions, glucose, or diastolic or systolic blood pressure. The latter analyses were associated with significant heterogeneity, and the pooled estimates were trivial in absolute terms.

**Conclusions:** Trial data available to date are unable to demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D. The quality of the available evidence is low to moderate at best. **(*J Clin Endocrinol Metab* 96: 0000–0000, 2011)**

Ecological evidence suggests an association between vitamin D status and cardiovascular disease (prevalent and incident heart disease, stroke, and risk factors for heart disease such as hypertension and coronary artery calcification) (1–6). Several mechanisms have been proposed including endothelial dysfunction, vascular compliance, inflammation, and effects relating to PTH, renin-angiotensin system, and others (1, 7–12). When this evidence is summarized by meta-analyses of observational studies, an inverse association between 25-hydroxyvitamin D and cardiovascular risk is suggested (13, 14).

Despite this observational and epidemiological evidence, it is unclear whether vitamin D in interventional studies would affect cardiovascular risk. The Endocrine Society assembled a task force of experts to develop clinical practice guidelines regarding the supplementation of

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Abbreviations: CI, Confidence interval; MI, myocardial infarction; RR, relative risk.

**TABLE 1.** Characteristics of the included trials

| First author, year (Ref.) | Age (yr) | % Women | Population description | Vitamin D status | Vitamin D used (as published) | Treatment duration (months) |
|---|---|---|---|---|---|---|
| Avenell, 2004 (31) | 77 | 82 | Elderly with history of osteoporotic fracture | NR/NC | Vitamin D3 800 IU | 12 |
| Baeksgaard,1998 (32) | 62 | 100 | Postmenopausal women | Not deficient | 14 $\mu$g (560 IU) of vitamin D3 (cholecalciferol) daily | 24 |
| Berggren, 2008 (33) | 87 | 74 | Elderly with femoral neck fractures | Not deficient | 800 IU/d vitamin D3 | 12 |
| Bischoff, 2003 (34) | 85 | 100 | Elderly women in long stay geriatric health care institutions | Deficient | 800 IU/d cholecalciferol | 3 |
| Bischoff-Ferrari, 2006 (35) | 71 | 55 | Healthy ambulatory elderly | Not deficient | 700 IU/d of cholecalciferol, orally | 36 |
| Bjoerkman, 2008 (36) | 85 | 82 | Elderly patients with chronically impaired mobility | Deficient | 400 IU/d (group II) and 1200 IU/d (group III) cholecalciferol, orally | 6 |
| Braam, 2004 (37) | 55 | 100 | Healthy Caucasian postmenopausal women | NR/NC | Vitamin D3, 8 $\mu$g | 36 |
| Brazier, 2005 (38) | 75 | 100 | Healthy ambulatory elderly women | Deficient | Single tablet containing vitamin D3 (cholecalciferol) 400 IU orally | 12 |
| Broe, 2007 (39) | 89 | 73 | Nursing home residents | Not deficient | Vitamin D2 at doses of 200, 400, 600, and 800 IU | 5 |
| Brohult, 1973 (21) | 52 | 68 | Patients with rheumatoid arthritis | NR/NC | Cholecalciferol 100,000 IU/d | 12 |
| Buckley, 1996 (40) | 54 | 76 | Patients with rheumatoid arthritis | Not deficient | Vitamin D3 500 IU/d | 24 |
| Bunout, 2006 (41) | 76 | 92 | Healthy elderly subjects | Deficient | Vitamin D3 (cholecalciferol) 400 IU/d | 9 |
| Burleigh, 2007 (42) | 83 | 59 | Elderly patients | Deficient | Once daily vitamin D 800 IU | 1 |
| Campbell, 2005 (22) | 84 | 68 | Elderly people with poor vision | NR/NC | Vitamin D tablets (two 1.25 mg calciferol tablets initially and then one monthly for 1 yr) | 12 |
| Chapuy, 2002 (43) | 85 | 100 | Elderly ambulatory patients | Not deficient | 800 IU/d oral vitamin D3 | 24 |
| Chapuy, 1992 (44) | 84 | 100 | Elderly ambulatory patients | Not deficient | 800 IU (29 $\mu$g) vitamin D3 In 2 pills (400 IU each) | 18 |
| Christiansen, 1980 (45) | 50 | 100 | Postmenopausal women | Not deficient | D3 2000 IU | 24 |
| Daly, 2009 (46) | 61 | 0 | Healthy older Caucasian men | Not deficient | 400 IU vitamin D3, twice daily via fortified milk | 24 |
| de Boer, 2008 (47) | 62 | 100 | Postmenopausal women | Not deficient | D3 200 IU PO twice daily | 84 |
| Flicker, 2005 (48) | 83 | 95 | Elderly in residential care | Not deficient | Ergocalciferol 10,000 IU PO weekly, changed to 1000 IU orally per day because of product discontinuation | 24 |
| Grant, 2005 (30) | 77 | 85 | Elderly with a low-trauma fracture | NR/NC | Oral vitamin D3 (800 IU/d) | 24 |
| Grove, 1981 (49) | 74 | 100 | Women with backache and compression fractures | Not deficient | Calciferol 50,000 IU orally twice weekly | 3 |
| Harwood, 2004 (50) | 82 | 100 | Elderly women after hip fracture | Deficient | Single injection of 300,000 U of vitamin D2, injected vitamin D2 plus 1 g/d oral calcium, 800 IU/d oral vitamin D3 plus 1 g/d calcium | 12 |
| Heikkinen, 1997 (51) | 53 | 100 | Postmenopausal women | NR/NC | Vitamin D3 300 IU/d | 36 |
| Inkovaara, 1983 (52) | 80 | 17 | Residents of elderly care homes | Deficient | Vitamin D3 (cholecalciferol) 1000 IU daily | 9 |
| Jackson, 2006 (25) and Hsia, 2007 (53) | 62 | 100 | Postmenopausal women | Not deficient | Vitamin D3 400 IU/d | 84 |
| Jorde, 2010 (54) | 48 | 64 | Overweight or obese adults | Not deficient | 40,000 IU cholecalciferol weekly | 12 |
| Khajehdehi, 2000 (55) | 31 | 49 | Hemodialysis patients | | Vitamin D3 50,000 IU | 3 |
| Komulainen,1999 (56) | 53 | 100 | Postmenopausal women | Not deficient | Vitamin D3 (cholecalciferol) 300 IU | 60 |
| Krieg, 1999 (57) | 62–98 | 100 | Postmenopausal women | Deficient | 440 IU vitamin D3 twice daily | 24 |
| Latham, 2003 (24) | 80 | 53 | Elderly patients with chronically impaired mobility | Not deficient | Calciferol 300,000 IU single oral dose | Single dose |
| Lips, 1996 (58) | 80 | 74 | Elderly patients | Not deficient | Vitamin D3 400 IU daily | 36 |
| Lyons 2007 (59) | 84 | 76 | Elderly nursing home residents | Not deficient | 1.25 mg ergocalciferol 3 times a year (100,000 IU four monthly) | 36 |
| Major, 2007 (60) | 43 | 100 | Premenopausal overweight or obese but otherwise healthy | NR/NC | Cholecalciferol 400 IU/d | 4 |
| Meier, 2004 (61) | 56 | 65 | Healthy subjects | Not deficient | Oral cholecalciferol (500 IU/d) | 6 |
| Meyer, 2002 (62) | 85 | 75 | Nursing home residents | Not deficient | D3 10 $\mu$g/d contained in cod liver oil | 24 |
| Nagpal, 2009 (63) | 44 | 0 | Centrally obese, nondiabetic, healthy men | NR/NC | 12,000 IU vitamin D3 every 2 wk | 1.4 |
| Pfeifer, 2001 (64) | 75 | 100 | Healthy elderly | Deficient | D3 400 IU twice daily (total 800/d) | 2 |
| Porthouse, 2005 (65) | 77 | 100 | Elderly women with risk factors for hip fracture | Not deficient | 800 IU cholecalciferol daily | 24 |
| Prince, 2008 (66) | 77 | 100 | Elderly women with a fall history and low serum vitamin D | Deficient | Ergocalciferol 1000 IU/d | 12 |
| Rajpathak, 2010 (67) | 62 | 100 | Postmenopausal women | NR/NC | 400 IU of vitamin D3/d | NR |
| Recker, 2006 (68) | 67 | 95 | Patients with osteoporosis | Deficient | Cholecalciferol 2800 IU weekly | 3.5 |
| Sanders, 2010 (69) | 76 | 100 | Community-dwelling women | Deficient | 500,000 IU cholecalciferol, one oral dose annually | 36–60 |
| Schleithoff, 2006 (11) | 56 | 17 | Chronic heart failure patients | Not deficient | Cholecalciferol 2000 IU/d | 9 |
| Scragg,1995 (70) | 70 | 55 | General population | Deficient | 100,000 IU cholecalciferol | Single dose |
| Sugden, 2008 (71) | 64 | 47 | Type 2 diabetes | Deficient | A single dose of 100,000 IU vitamin D2 (ergocalciferol) | Single dose |
| Trivedi, 2003 (72) | 76 | 24 | General population | Not deficient | One capsule containing 100,000 IU vitamin D3 every 4 months | 60 |
| Tuppurainen,1995 (73) | 53 | 100 | Perimenopausal women | NR/NC | Cholecalciferol 300 IU/d (no intake during June-August) | 12 |
| Wejse, 2009 (23) | 37 | 39 | Individuals with a diagnosis of tuberculosis | NR/NC | Cholecalciferol 100,000 IU at 0, 3, and 8 months | 8 |
| Zittermann, 2009 (74) | 48 | 67 | Between 18–70 and BMI >27 | NR/NC | Cholecalciferol 83.3 $\mu$g (3332 IU)/d | 12 |

NR, Not reported; NC, not clear; HRT, hormonal replacement therapy.

[a] This was based on a subset of 131 study participants (74 in intervention groups *vs.* 57 in the placebo group).

**TABLE 1.** Continued

| Other drugs coadministered with vitamin D | Comparison group | Follow-up duration (months) | Pre-vitamin D level (nmol/liter) | Post vitamin D level (nmol/liter) | Intervention raised vitamin D | Adherence |
|---|---|---|---|---|---|---|
| Placebo | Nothing | 12 | NR | NR | NR | 84.5% |
| 1000 mg calcium carbonate daily | Placebo | 24 | NR | NR | NR | NR |
| 1000 mg calcium | Nothing | 12 | NR | NR | NR | NR |
| 1200 mg/d calcium | 1200 mg/d calcium | 3 | 31 | 65 | Yes, by >71% | >90% |
| 500 mg/d oral calcium citrate malate | Placebo | 36 | 70–82 | 102–110 | Yes | 82% |
| Daily calcium carbonate of 500 mg | Placebo | 6 | 23 | Mean change >10 | Yes, by >100% | NR |
| 500 mg calcium, 10 mg zinc, 150 mg magnesium | Placebo | 36 | NR | NR | NR | NR |
| Calcium carbonate 500 mg | Placebo | 12 | 18 | 72 | Yes | 94% |
| None | Placebo | 5 | 49 | 60–75 | Yes | 97.6% |
| None | Placebo | 12 | NR | NR | NR | NR |
| Calcium carbonate 1000 mg/d | Placebo | 24 | NR | NR | NR | NR |
| 800 mg/d calcium | 800 mg/d calcium | 9 | 30 | 65 | Yes | NR |
| Calcium carbonate once daily 1,200 mg | Calcium 1,200 mg | 1 | 22 | Median change +25 | No | 88% |
| Exercise program for 1 yr | No exercise or vitamin D program | 12 | NR | NR | NR | NR |
| 1200 mg/d of oral elemental calcium | Placebo | 24 | 21 | NR | Yes | 95% |
| Tricalcium phosphate, 1.2 g/d | 2 pills containing lactose and a suspension of lactose, Kaolin, and starch each day | 18 | 40 | 105 | Yes, by 162% | 83% |
| None | Placebo, HRT, thiazide, fluoride, fluoride + D, 1$\alpha$ D3 | 24 | NR | NR | NR | 84% |
| Calcium 500 mg, twice daily via fortified milk | Regular diet | 24 | 78 | Change from baseline +5 | Yes | 85% |
| Oral 500 mg elemental Ca twice daily | Placebo | 72 | NR | NR | No | NC |
| 600 mg elemental calcium as $CaCO_3$ | 600 mg elemental calcium | 24 | 25–90 | NR | No | 86% |
| Calcium 1 g | Placebo | Up to 62 | NR | NR | NR | Unclear |
| Calcium 500 mg and sodium fluoride 20 mg twice daily | Placebo | 3 | NR | NR | NR | NR |
| Calcium 1 g/d | Nothing | 12 | 28–30 | 40–50 | Yes | NR |
| Calcium lactate 500 mg/d | Calcium lactate 500 mg/d | 36 | Normal | NR | NR | NR |
| Calcium carbonate 3g, methandienone 2.5 mg | Placebo | 12 | NR | NR | NR | NR |
| Calcium | Placebo | 84 | NR | NR | NR | 60% |
| Calcium 500 mg/d | Placebo | 12 | 58 | 140 | Yes | 95% |
| None | Placebo | 3 | NR | NR | NR | NR |
| Calcium 93 mg/d | Calcium lactate 500 mg/d | 60 | NR | NR | NR | 80% |
| 500 mg twice daily | Nothing | 24 | 30 | 66 | Yes, by 123% | NR |
| None | Placebo | 6 | 37 | NR | Yes, by 9% | 100% |
| None | Placebo | 48 | 27 | 62 | Yes | 85% |
| None | Placebo | NR | NR | NR | NR | 80% |
| Calcium 1200 mg/d | Placebo | 4 | NR | NR | NR | NR |
| Calcium 500 mg/d | Nothing | 24 | 75 | 87 | Yes | NR |
| Cod liver oil, which includes vitamin A and omega-3 fatty acids | Cod liver oil with D3 removed | 24 | 47 | 64 | Yes | 79% |
| None | Placebo | 6 wk | 37 | 72 | Yes | NR |
| Calcium 600 mg (elemental) twice daily | Calcium 600 mg (elemental) twice daily | 2 | 26 | 65 | Yes | 95% |
| Calcium 1000 mg/d and nurse visit | Leaflet on dietary calcium intake and prevention of falls only | 25 | NR | NR | NR | 63% |
| Calcium citrate 1000 mg/d | Placebo plus Ca citrate 1000 mg/d | 12 | 45 | 60 | Yes, by 28% | 86% |
| 1 g calcium carbonate | Placebo | Up to 108 | NR | NR | NR | NR |
| Alendronate 70 mg weekly | Alendronate 70 mg weekly | 3.5 | 56 | Change from baseline +3 | Yes | 93.9% |
| None | Placebo | 12 | 49[a] | 55–74[a] | Yes[a] | Unclear |
| 500 mg calcium/d | Placebo + 500 mg calcium/d | 4 | 36 | 67 | Yes | NR |
| None | Placebo | 1.25 | 36 | Change from baseline +18 | Yes | NR |
| None | Placebo | 2 | 40 | Change from baseline +23 | Yes | NR |
| None | Placebo | 60 | NR | 74.3 | Yes | 80% |
| None | Placebo, calcium lactate 500 mg/d | 12 | NR | NR | NR | NR |
| None | Placebo | 8 | 77 | 102 | Yes | 64% |
| None | Placebo | 12 | 30 | 86 | Yes | NR |

vitamin D. To assist in formulating these guidelines, we conducted a systematic review of the literature to quantitatively and qualitatively summarize the available evidence regarding the possible cardiovascular harms and benefits of vitamin D.

## Materials and Methods

The report of this protocol-driven systematic review adheres to the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of randomized clinical trials and reporting Meta-analyses of Observational Studies in Epidemiology (MOOSE) (15, 16) and was approved by the Vitamin D Task Force of The Endocrine Society. The quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods (17).

### Eligibility criteria

Eligible studies were randomized trials that enrolled adults who received vitamin D supplementation and a concurrent comparison group that did not receive this intervention. We excluded studies in which the intervention was calcitriol or one of its analogs. We were interested in studies measuring the impact of the intervention on patient-important outcomes such as death, stroke, myocardial infarction (MI), and peripheral vascular disease. Secondarily, we were interested in the effect of vitamin D on cardiovascular risk factors (blood pressure, glucose, and lipids). Studies were included regardless of their language, size, or duration of patient follow-up. Ineligible references were nonrandomized studies, review articles, commentaries, and letters that did not contain original data. We also excluded the studies that reported a correlation of vitamin D levels with outcomes, but in which participants did not receive an intervention to raise their vitamin D levels, making causal inferences very weak.

### Study identification

An expert reference librarian (P.J.E.) designed and conducted the electronic search strategy with input from study investigators with expertise in conducting systematic reviews. To identify eligible studies, we searched the electronic databases MEDLINE, EMBASE, Web of Science, SCOPUS, PEDRro (Physiotherapy Evidence Database); and regional medical databases (KoreanMed, Scielo, LILACs, Imbiomed, Index for Australian medical literature, Eastern Mediterranean Index, IndMed, ExtraMed) through August 2010. Search terms included vitamin D (as supplement, blood level, deficiency), vitamin D deficiency, individual metabolites of vitamin D, vitamin D2, vitamin D3 (explode cholecalciferols, ergocalciferols, adjusted for database-specific vocabulary), explode sunlight, hypoglycemia, hyperglycemia, blood glucose, exp diabetes mellitus; exp cardiovascular diseases, exp hypertension, ex cerebrovascular disorders/(including stroke), explode hyperlipidemia, exp lipids/bl; explode thromboembolism or explode thrombosis or cardiovascular risk (EMBASE), risk$ or mortality or incidence or prevalence or outcome, populations, specific study types such as crossover, observational studies. In addition, we reviewed the reference sections of eligible studies and available reviews and requested potentially eligible studies from content experts.

### Data collection

Teams of reviewers working independently and in duplicate used web-based standardized forms and screened all abstracts and titles and, upon retrieval of candidate studies, reviewed the full text publications and determined study eligibility. Disagreements were resolved by consensus. Reviewers extracted descriptive, methodological, and outcome data from all eligible studies.

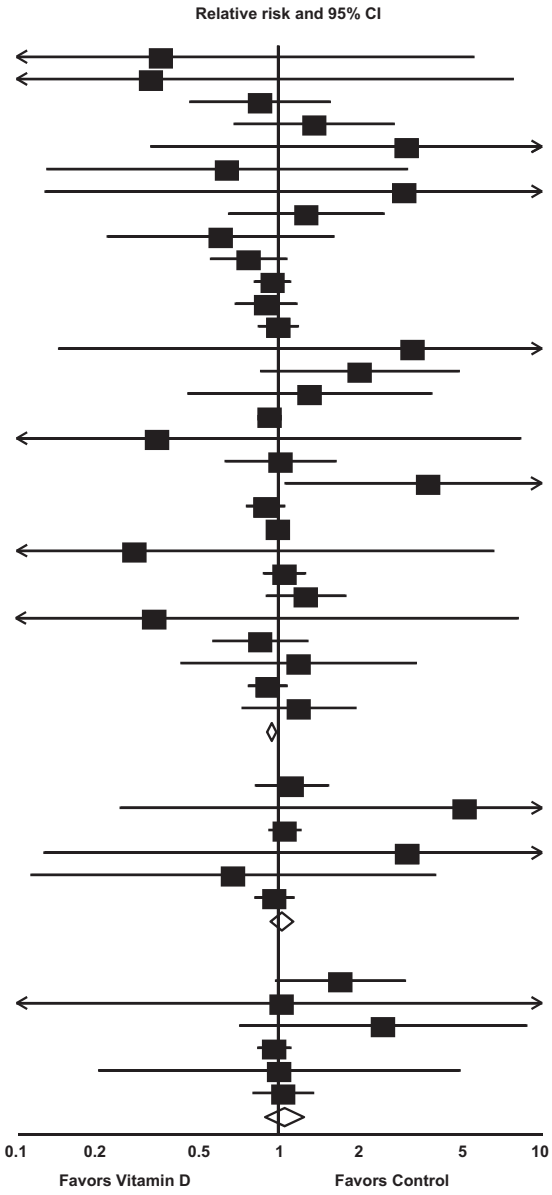
Data collected from studies included a description of the population (*e.g.* age, sex, dwelling, comorbidities, and vitamin D status), the intervention (the type of vitamin D raising intervention, dose, and route), study design and quality components, and data corresponding to the outcomes of interest (obtained at the end of treatment and before initiation of follow-up). We classified studies as including patients with vitamin D deficiency (probable, improbable, uncertain) based on: 1) author description; 2) reported serum 25-hydroxyvitamin D level (levels considered deficient were $<$20 ng/ml); or 3) enrollment of patients with at least two vitamin D deficiency risk factors including: elderly age, dark skin, living in a nursing home, living far from the equator, winter season, sunscreen use, wearing a veil, smoking, obesity, malabsorption disease, renal or liver disease, and use of medication such as anticonvulsants, glucocorticoids, antirejection and HIV medications (18). For dichotomous outcomes, a 2$\times$2 table was created from each study, and if not available, the most adjusted summary measure and confidence interval (CI) values were used. For continuous outcomes, we collected from each study arm the number of participants, mean and SD, or the mean difference. The methodological quality of the trials was evaluated by pairs of blinded reviewers focusing on allocation concealment, blinding, funding, and loss to follow-up.

### Statistical analysis

We performed random-effect meta-analysis (19) to pool relative risk (RR) and 95% CI across included studies. RR values under 1.00 are associated with decreased risk for a particular outcome as a result of a vitamin D-raising intervention. For continuous outcomes, we pooled the weighted mean difference across studies. The $I^2$ statistic, which estimates the percentage of total variation across studies that is due to heterogeneity rather than chance, was used to assess inconsistency (20). $I^2$ values of 25% or less, 50%, and at least 75% represent low, moderate, and high inconsistency, respectively. Treatment effect-subgroup interactions were assessed by the ANOVA method and meta-regression analysis. Statistical analysis was conducted using Comprehensive Meta-Analysis, version 2 (Biostat Inc., Englewood, NJ).

### Subgroup and sensitivity analyses

To explore the causes of inconsistency and subgroup-treatment interactions, we defined *a priori* subgroups based on patient characteristics (patients with or without vitamin D deficiency; patients with or without comorbid conditions including prior cardiovascular events; males *vs.* females); extent of use of preventive interventions (aspirin, statins, and antihypertensives); duration of intervention (short-term *vs.* long-term); ad-




| Study name | Relative risk | Lower limit | Upper limit | Events / Total Vitamin D | Events / Total Control |
|---|---|---|---|---|---|
| Avenell, 2004 | 0.35 | 0.02 | 5.50 | 1 / 99 | 1 / 35 |
| Baeksgaard,1998 | 0.32 | 0.01 | 7.79 | 0 / 65 | 1 / 63 |
| Berggren, 2008 | 0.85 | 0.46 | 1.56 | 16 / 102 | 18 / 97 |
| Björkman, 2008 | 1.36 | 0.68 | 2.73 | 27 / 150 | 9 / 68 |
| Brazier, 2005 | 3.06 | 0.32 | 28.93 | 3 / 95 | 1 / 97 |
| Broe, 2007 | 0.63 | 0.13 | 3.07 | 5 / 99 | 2 / 25 |
| Brohult, 1973 | 3.00 | 0.13 | 70.30 | 1 / 25 | 0 / 25 |
| Burleigh, 2007 | 1.27 | 0.64 | 2.50 | 16 / 101 | 13 / 104 |
| Campbell, 2005 | 0.60 | 0.22 | 1.61 | 6 / 196 | 10 / 195 |
| Chapuy, 2002 | 0.76 | 0.55 | 1.06 | 71 / 393 | 45 / 190 |
| Chapuy,1992 | 0.94 | 0.81 | 1.10 | 258 / 1634 | 274 / 1636 |
| Flicker, 2005 | 0.89 | 0.68 | 1.16 | 76 / 313 | 85 / 312 |
| Grant, 2005 | 0.99 | 0.83 | 1.18 | 217 / 1343 | 217 / 1332 |
| Grove, 1981 | 3.23 | 0.14 | 72.46 | 1 / 12 | 0 / 13 |
| Harwood, 2004 | 2.03 | 0.85 | 4.84 | 31 / 113 | 5 / 37 |
| Inkovaara, 1983 | 1.31 | 0.45 | 3.80 | 7 / 45 | 5 / 42 |
| Jackson, 2006 | 0.92 | 0.83 | 1.01 | 744 / 18176 | 807 / 18106 |
| Komulainen,1999 | 0.34 | 0.01 | 8.31 | 0 / 112 | 1 / 115 |
| Krieg, 1999 | 1.01 | 0.62 | 1.64 | 21 / 71 | 26 / 89 |
| Latham, 2003 | 3.70 | 1.06 | 12.92 | 11 / 121 | 3 / 122 |
| Lips, 1996 | 0.89 | 0.75 | 1.04 | 223 / 1291 | 251 / 1287 |
| Lyons 2007 | 0.99 | 0.93 | 1.05 | 947 / 1725 | 953 / 1715 |
| Meier, 2004 | 0.28 | 0.01 | 6.58 | 0 / 30 | 1 / 25 |
| Meyer, 2002 | 1.05 | 0.87 | 1.26 | 169 / 569 | 163 / 575 |
| Porthouse, 2005 | 1.26 | 0.90 | 1.79 | 57 / 1321 | 68 / 1993 |
| Prince, 2008 | 0.33 | 0.01 | 8.12 | 0 / 151 | 1 / 151 |
| Sanders, 2010 | 0.85 | 0.56 | 1.28 | 40 / 1131 | 47 / 1125 |
| Schleithoff, 2006 | 1.19 | 0.42 | 3.33 | 7 / 61 | 6 / 62 |
| Trivedi, 2003 | 0.90 | 0.77 | 1.07 | 224 / 1345 | 247 / 1341 |
| Wejse, 2009 | 1.19 | 0.72 | 1.95 | 30 / 187 | 24 / 178 |
| **Mortality-Pooled estimate** | **0.96** | **0.93** | **1.00** | **3209 / 31076** | **3284 / 31155** |
| Berggren, 2008 | 1.12 | 0.81 | 1.53 | 47 / 102 | 40 / 97 |
| Brazier, 2005 | 5.10 | 0.25 | 104.94 | 2 / 95 | 0 / 97 |
| Jackson, 2006 | 1.05 | 0.92 | 1.20 | 411 / 18167 | 390 / 18106 |
| Komulainen,1999 | 3.08 | 0.13 | 74.81 | 1 / 112 | 0 / 115 |
| Prince, 2008 | 0.67 | 0.11 | 3.93 | 2 / 151 | 3 / 151 |
| Trivedi, 2003 | 0.96 | 0.81 | 1.13 | 224 / 1345 | 233 / 1341 |
| **Myocardial Infraction-Pooled estimate** | **1.02** | **0.93** | **1.13** | **687 / 19972** | **666 / 19907** |
| Berggren, 2008 | 1.71 | 0.97 | 3.02 | 27 / 102 | 15 / 97 |
| Brazier, 2005 | 1.02 | 0.06 | 16.09 | 1 / 95 | 1 / 97 |
| Inkovaara, 1983 | 2.49 | 0.71 | 8.76 | 8 / 45 | 3 / 42 |
| Jackson, 2006 | 0.96 | 0.83 | 1.10 | 362 / 18167 | 377 / 18106 |
| Prince, 2008 | 1.00 | 0.21 | 4.88 | 3 / 151 | 3 / 151 |
| Trivedi, 2003 | 1.04 | 0.80 | 1.35 | 105 / 1345 | 101 / 1341 |
| **Stroke-Pooled estimate** | **1.05** | **0.88** | **1.25** | **506 / 19905** | **500 / 19834** |

**FIG. 1.** Forest plot representing the pooled result of mortality, MI, and stroke.

herence to the intervention; control interventions (placebo or no intervention *vs.* calcium supplementation); whether the intervention raised the level of 25-hydroxyvitamin D3 or not; study design (appropriate allocation concealment *vs.* not); follow-up duration (≥12 months *vs.* <12 months); number of patients lost to follow-up (≥10% *vs.* <10%); and source of study funding (for profit or not for profit).

We conducted sensitivity analyses to determine whether review conclusions were affected by the choice of statistical methods (random-effects model *vs.* fixed-effect model) or

**TABLE 2.** Meta-analysis of lipid fractions, glucose, and blood pressure

| | No. of studies included (no. of patients/controls) | Weighted mean difference (95% CI) | *P* value | Heterogeneity ($I^2$%) |
|---|---|---|---|---|
| Lipids (mmol/liter) | | | | |
| Cholesterol | 12 (1128/1139) | 0.00 (−0.06, 0.07) | 0.91 | 28 |
| Triglycerides | 11 (1042/1056) | −0.04 (−0.11, 0.03) | 0.25 | 56 |
| Low-density lipoproteins | 11 (1104/1106) | −0.09 (−0.24, 0.07) | 0.27 | 90 |
| High-density lipoproteins | 12 (1135/1150) | 0.06 (−0.11, 0.24) | 0.48 | 99 |
| Blood pressure (mm Hg) | | | | |
| Systolic | 14 (751/767) | −0.06 (−1.98, 1.87) | 0.95 | 61 |
| Diastolic | 14 (751/767) | −0.34 (−1.03, 0.35) | 0.33 | 0 |
| Blood glucose (mmol/liter) | 8 (1019/1062) | −0.10 (−0.31, 0.12) | 0.38 | 82 |

**TABLE 3.** Subgroup analyses

| Subgroup identification | No. of studies | No. of interventions (events/total) | No. control (events/total) | RR (95% CI) | $P_{Interaction}$ value |
|---|---|---|---|---|---|
| Mortality | | | | | |
| Adherence | | | | | |
| No/NR/NC (<80%) | 16 | 1,205/23,028 | 1,244/23,450 | 0.96 (0.89–1.04) | 0.97 |
| Yes (≥80%) | 14 | 2,004/8,048 | 2,040/7,705 | 0.97 (0.92–1.01) | |
| Allocation concealment | | | | | |
| No | 6 | 283/1,994 | 304/1,945 | 0.95 (0.82–1.10) | 0.79 |
| Yes | 24 | 2,926/29,082 | 2,980/29,210 | 0.97 (0.93–1.01) | |
| Comparison group | | | | | |
| Calcium | 20 | 1,553/24,387 | 1,584/24,567 | 0.95 (0.89–1.01) | 0.70 |
| Placebo | 10 | 1,656/6,689 | 1,700/6,588 | 0.97 (0.90–1.04) | |
| Funding sources | | | | | |
| Includes for-profit | 11 | 1,375/23,608 | 1,412/23,870 | 0.96 (0.88–1.05) | 0.83 |
| Not-for-profit | 18 | 1,827/7,423 | 1,867/7,243 | 0.97 (0.93–1.02) | |
| Gender | | | | | |
| Female | 26 | 2,931/28,494 | 2,979/28,585 | 0.97 (0.93–1.01) | 0.41 |
| Male | 4 | 278/2,582 | 305/2,570 | 0.91 (0.78–1.05) | |
| Intervention | | | | | |
| Only vitamin D | 10 | 165/6,689 | 1,700/6,588 | 0.97 (0.90–1.04) | 0.70 |
| Vitamin D and calcium | 20 | 1,553/24,387 | 1,584/24,567 | 0.95 (0.89–1.01) | |
| Intervention raised level of vitamin D (as published) | | | | | |
| No | 2 | 92/414 | 98/416 | 0.93 (0.73–1.20) | 0.85 |
| NR/NC | 12 | 1,997/23,221 | 2,081/23,731 | 0.97 (0.93–1.02) | |
| Yes | 16 | 1,120/7,441 | 1,105/7,008 | 0.95 (0.87–1.03) | |
| No. lost to follow-up | | | | | |
| High (≥10%) | 15 | 712/3,889 | 658/3,477 | 0.97 (0.89–1.07) | 0.76 |
| Low (<10%) | 14 | 2,490/27,142 | 2,621/27,636 | 0.96 (0.91–1.01) | |
| Population description | | | | | |
| Existing comorbidity | 14 | 421/3,982 | 375/4,412 | 1.08 (0.95–1.23) | 0.08 |
| Healthy individuals | 16 | 2,788/27,094 | 2,909/26,743 | 0.95 (0.91–1.00) | |
| Treatment duration | | | | | |
| Long (≥12months) | 22 | 2,165/28,620 | 2,274/28,868 | 0.96 (0.92–1.00) | 0.36 |
| Short (<12months) | 7 | 97/731 | 57/572 | 1.10 (0.83–1.44) | |
| Type of vitamin D used | | | | | |
| D2 | 4 | 1,028/2,288 | 1,041/2,203 | 0.98 (0.93–1.04) | 0.38 |
| D3 | 25 | 2,150/28,675 | 2,238/28,915 | 0.95 (0.90–1.00) | |
| Vitamin D baseline status | | | | | |
| Deficient | 9 | 175/2,044 | 131/1,891 | 1.11 (0.89–1.38) | 0.19 |
| Not deficient | 17 | 2,809/27,369 | 2,925/27,677 | 0.96 (0.92–1.00) | |
| Vitamin D dose used | | | | | |
| High (≥800 IU/d) | 20 | 2,011/10,287 | 2,013/10,573 | 0.98 (0.93–1.03) | 0.29 |
| Low (<800 IU/d) | 9 | 1,171/20,639 | 1,262/20,514 | 0.93 (0.86–1.00) | |
| MI | | | | | |
| Adherence | | | | | |
| No/NR/NC (<80%) | 2 | 458/18,269 | 430/18,203 | 1.06 (0.94–1.20) | 0.37 |
| Yes (≥80%) | 4 | 229/1,703 | 236/1,704 | 0.96 (0.82–1.14) | |
| Allocation concealment | | | | | |
| No | 1 | 2/95 | 0/97 | 5.10 (0.25–104.94) | 0.30 |
| Yes | 5 | 685/19,877 | 666/19,810 | 1.02 (0.92–1.13) | |
| Comparison group | | | | | |
| Calcium | 2 | 3/263 | 3/266 | 0.96 (0.20–4.51) | 0.93 |
| Placebo | 4 | 684/19,709 | 663/19,641 | 1.02 (0.93–1.13) | |
| Funding sources | | | | | |
| Includes for-profit | 2 | 413/18,262 | 390/18,203 | 1.09 (0.67–1.77) | 0.70 |
| Not-for-profit | 4 | 274/1,710 | 276/1,704 | 0.99 (0.86–1.15) | |
| Gender | | | | | |
| Female | 5 | 463/18,627 | 433/18,566 | 1.06 (0.94–1.20) | 0.33 |
| Male | 1 | 224/1,345 | 233/1,341 | 0.96 (0.81–1.13) | |
| Intervention | | | | | |
| Only vitamin D | 1 | 224/1,345 | 233/1,341 | 0.96 (0.81–1.13) | 0.33 |
| Vitamin D and calcium | 5 | 463/18,627 | 433/18,566 | 1.06 (0.94–1.20) | |

(*Continued*)

**TABLE 3.** Continued

| Subgroup identification | No. of studies | No. of interventions (events/total) | No. control (events/total) | RR (95% CI) | $P_{Interaction}$ value |
|---|---|---|---|---|---|
| Intervention raised level of vitamin D[a] | | | | | |
| No/NR | 3 | 459/18,381 | 430/18,318 | 1.06 (0.94–1.20) | 0.34 |
| Yes | 3 | 228/1,591 | 236/1,589 | 0.96 (0.81–1.13) | |
| No. lost to follow-up | | | | | |
| High (≥10%) | 2 | 49/197 | 40/194 | 1.14 (0.83–1.56) | 0.50 |
| Low (<10%) | 4 | 638/19,775 | 626/19,713 | 1.01 (0.91–1.12) | |
| Population description | | | | | |
| Existing comorbidity | 2 | 49/253 | 43/248 | 1.10 (0.80–1.50) | 0.64 |
| Healthy individuals | 4 | 638/19,719 | 623/19,659 | 1.02 (0.91–1.13) | |
| Type of vitamin D used | | | | | |
| D2 | 1 | 2/151 | 3/151 | 0.67 (0.11–3.93) | 0.64 |
| D3 | 5 | 685/19,821 | 663/19,756 | 1.03 (0.93–1.13) | |
| Vitamin D baseline status | | | | | |
| Deficient | 2 | 4/246 | 3/248 | 1.26 (0.20–7.98) | 0.83 |
| Not deficient | 4 | 683/19,726 | 663/19,659 | 1.02 (0.93–1.13) | |
| Vitamin D dose used | | | | | |
| High (≥800 IU/d) | 3 | 273/1,598 | 276/1,589 | 0.99 (0.85–1.15) | 0.52 |
| Low (<800 IU/d) | 3 | 414/18,374 | 390/18,318 | 1.06 (0.92–1.21) | |
| Stroke | | | | | |
| Adherence | | | | | |
| No/NR/NC (<80%) | 3 | 397/18,314 | 395/18,245 | 1.33 (0.77–2.29) | 0.41 |
| Yes (≥80%) | 3 | 109/1,591 | 105/1,589 | 1.04 (0.80–1.34) | |
| Allocation concealment | | | | | |
| No | 1 | 1/95 | 1/97 | 1.02 (0.06–16.09) | 0.97 |
| Yes | 5 | 505/19,810 | 499/19,737 | 1.08 (0.87–1.33) | |
| Comparison group | | | | | |
| Calcium | 1 | 3/151 | 3/151 | 1.00 (0.21–4.88) | 0.93 |
| Placebo | 5 | 503/19,754 | 497/19,683 | 1.08 (0.87–1.33) | |
| Funding sources | | | | | |
| Includes for-profit | 2 | 363/18,262 | 378/18,203 | 0.96 (0.83–1.10) | 0.25 |
| Not-for-profit | 3 | 135/1,598 | 119/1,589 | 1.18 (0.85–1.64) | |
| Gender | | | | | |
| Female | 4 | 393/18,515 | 396/18,451 | 1.09 (0.80–1.50) | 0.70 |
| Male | 2 | 113/1,390 | 104/1,383 | 1.28 (0.61–2.68) | |
| Intervention | | | | | |
| Only vitamin D | 1 | 105/1,345 | 101/1,341 | 1.04 (0.80–1.35) | 0.51 |
| Vitamin D and calcium | 5 | 401/18,560 | 399/18,493 | 1.21 (0.83–1.77) | |
| Intervention raised level of vitamin D[a] | | | | | |
| No/NR | 3 | 397/18,314 | 395/18,245 | 1.33 (0.77–2.29) | 0.41 |
| Yes | 3 | 109/1,591 | 105/1,589 | 1.04 (0.80–1.34) | |
| No. lost to follow-up | | | | | |
| High (≥10%) | 2 | 28/197 | 16/194 | 1.68 (0.96–2.92) | 0.06 |
| Low (<10%) | 3 | 470/19,663 | 481/19,598 | 0.97 (0.86–1.10) | |
| Population description | | | | | |
| Existing comorbidity | 2 | 30/253 | 18/248 | 1.61 (0.94–2.75) | 0.08 |
| Healthy individuals | 4 | 476/19,652 | 482/19,586 | 0.98 (0.87–1.11) | |
| Treatment duration | | | | | |
| Long (≥12 months) | 5 | 498/19,860 | 497/19,792 | 1.00 (0.89–1.13) | 0.16 |
| Short (<12 months) | 1 | 8/45 | 3/42 | 2.49 (0.71–8.76) | |
| Type of vitamin D used | | | | | |
| D2 | 1 | 3/151 | 3/151 | 1.00 (0.21–4.88) | 0.93 |
| D3 | 5 | 503/19,754 | 497/19,683 | 1.08 (0.87–1.33) | |
| Vitamin D baseline status | | | | | |
| Deficient | 3 | 12/291 | 7/290 | 1.65 (0.65–4.16) | 0.36 |
| Not deficient | 3 | 494/19,614 | 493/19,544 | 1.06 (0.85–1.31) | |
| Vitamin D dose used | | | | | |
| High (≥800 IU/d) | 4 | 143/1,643 | 122/1,631 | 1.27 (0.89–1.81) | 0.15 |
| Low (<800 IU/d) | 2 | 363/18,262 | 377/18,106 | 0.96 (0.83–1.10) | |

Only feasible analyses with sufficient data are shown. NR, Not reported; NC, not clear.

[a] According to published record.

when borderline eligible articles are included or excluded as well as the effect of excluding observational and cluster randomized studies.

## Results

The initial search of the literature yielded 5584 citations, of which 51 eligible studies were selected with a good inter-reviewer agreement ($\kappa = 0.80$) (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Contact of all authors was attempted to verify data collected from their publication as well as to request additional or missing information. If an author did not respond to our initial request, a second request was attempted. We successfully contacted around 75% of the primary or secondary authors. Table 1 summarizes the characteristics of the included studies. Most studies recruited elderly women and coadministered calcium with vitamin D, and none used sun exposure or interventions other than vitamin D supplementation. Most studies effectively concealed the random allocation and blinded caregivers and patients. The methodological quality of included studies is summarized in Supplemental Table 1.

### Meta-analyses

#### *Mortality*

Most of the included studies reported on mortality (n = 30). Pooling across studies showed a nonsignificant and potentially trivial reduction in mortality that was consistent across studies (RR, 0.96; 95% CI, 0.93, 1.00; $P = 0.08$; $I^2 = 0\%$) (Fig. 1).

### MI, stroke, and peripheral vascular disease

Six studies reported the outcome of MI, and six reported on stroke. Meta-analyses showed no significant effect of vitamin D on MI (RR, 1.02; 95% CI, 0.93, 1.13; $P = 0.64$; $I^2 = 0\%$) or stroke (RR, 1.05; 95% CI, 0.88, 1.25; $P = 0.59$; $I^2 = 15\%$) (Fig. 1). Five studies reported the outcome of peripheral vascular disease but with no events in either study arm.

### Serum lipids, blood pressure, and blood glucose

Table 2 shows pooled data for the effect of vitamin D on blood lipids, blood glucose, and blood pressure measurements. Vitamin D did not significantly affect any of the cardiovascular risk factors. However, the direction of vitamin D effect was consistent with reduction of all parameters measured except an increase in high-density lipoprotein cholesterol. Results were inconsistent across studies, and the pooled estimates were trivial in absolute terms.

### Subgroup and sensitivity analyses

The planned subgroup analyses did not show any significant subgroup-effect interactions (Table 3). This also includes the subgroup of studies reporting on vitamin D supplementation in vitamin D-deficient patients, in which we found no significant decrease in mortality, MI, or stroke ($P > 0.05$ for all outcomes).

The use of a fixed-effect model instead of a random-effects model did not change study conclusions about any outcome. Excluding a study reporting death of a patient irrelevant to the intervention (21) did not change the overall pooled mortality data (RR, 0.96; 95% CI, 0.93, 1.00; $P = 0.07$; $I^2 = 0\%$). Excluding a study in which the effects of vitamin D were possibly confounded by other interventions (22) did not change the overall mortality estimate (RR, 0.97; 95% CI, 0.93, 1.01; $P = 0.67$; $I^2 = 0\%$). Excluding a study, in which mortality was possibly confounded by the population's comorbidity (23) did not change the overall results (RR, 0.96; 95% CI, 0.93, 1.00; $P = 0.84$; $I^2 = 0\%$). We also excluded a study in which the intervention was a one-time high dose of vitamin D given im (24), which also did not affect the overall conclusion about mortality (RR, 0.96; 95% CI, 0.93, 1.00; $P = 0.66$; $I^2 = 0\%$). The same was true when we excluded a study that was heavily weighted in the analysis and used low vitamin D doses with poor adherence (25) (RR for mortality, 0.97; 95% CI, 0.93, 1.02; $P = 0.69$; $I^2 = 0\%$; RR for MI, 0.99; 95% CI, 0.86, 1.15; $P = 0.64$, $I^2 = 0\%$; RR for stroke, 1.16; 95% CI, 0.92, 1.46; $P = 0.41$; $I^2 = 0\%$). In general, analyses conducted in adherent patients (compliers) provided consistent trend of reduction in mortality, although results were nonsignificant.

We also conducted a sensitivity analysis in which we only included studies that increased vitamin D baseline levels as opposed to studies that administered low doses of vitamin D, which did not actually raise the blood level regardless of baseline. The pooled estimates were: mortality (16 studies)—RR, 0.95; 95% CI, 0.87, 1.03; $P = 0.22$; $I^2 = 6\%$; MI (three studies)—RR 0.96; 95% CI, 0.81, 1.13; $P = 0.51$; $I^2 = 0\%$; and stroke (three studies)—RR, 1.04; 95% CI, 0.80, 1.34; $P = 0.99$; $I^2 = 0\%$. When we only analyzed the studies that reported vitamin D repletion in vitamin D-deficient patients, we still did not see any statistically significant results (RR, 1.06; 95% CI, 0.81, 1.41; $P = 0.66$; $I^2 = 3\%$, in six studies for mortality; RR, 1.26; 95% CI, 0.20, 7.98; $P = 0.81$; $I^2 = 23\%$, in two studies for MI; and RR, 1.01; 95% CI, 0.25, 3.97; $P = 0.99$; $I^2 = 0\%$, in two studies for stroke). The latter CIs are clearly wide, suggesting underpowered analyses.

## Discussion

We conducted a systematic review and meta-analysis to summarize the best available research evidence regarding the effect of vitamin D on patient-important cardiovascular events and other cardiovascular risk factors. Previous systematic reviews of observational studies found significant associations between low vitamin D levels and the risk of cardiovascular disease (of variable definitions across the studies) and overall mortality (13, 14). Our analysis of randomized trials in which vitamin D was given as an intervention, as opposed to a blood level, did not demonstrate a significant effect on death, stroke, MI, lipid fractions (except a trivial increase in high-density lipoprotein), blood pressure, and blood glucose values. Our estimate for the mortality outcome, although nonsignificant, is in the same direction (*i.e.* reduction in risk) of that reported in another systematic review by Grandi *et al.* (13).

The limitations of this review stem from the fact that many of the included studies were not designed to evaluate cardiovascular outcomes; therefore, if the ascertainment of these endpoints was systematically different between the intervention and the control groups, which might have occurred in the 18% of the studies that were unblinded, results could be biased. Publication and reporting biases cannot be ruled out in any systematic review, although we attempted to contact study authors to reduce the effect of these biases. Lastly, the heterogeneity in some of the analyses makes the overall evidence to be of low to moderate quality. There remains the possibility that potential cardiovascular benefit of vitamin D remains undetected due to confounding baseline cardiac risk factors that randomization failed to correct or due to the coadministration of calcium that may have a detrimental cardiovascular effect (26). It is also important to note that randomized trials are likely to enroll participants without severe vitamin D deficiency who are less likely to benefit from vitamin D, which would drive the results toward the null. The strengths of this review relate to the comprehensive literature search and the bias protection measures undertaken during the conduct of the systematic review (*i.e.* selecting studies and evaluating outcomes and quality by blinded independent pairs of reviewers).

The effect of vitamin D on all-cause mortality remains unclear. Our analysis did not find an association, whereas a previous meta-analysis (27) found that vitamin D was associated with decreased all-cause mortality (RR, 0.93; 95% CI, 0.87–0.99). Our meta-analysis includes more trials (51 *vs.* 18). Nevertheless, it is obvious that the choice of which trials to include in the meta-analysis is affecting the inference; hence, inference regarding mortality is not robust to the inclusion of evidence. It is plausible that vitamin D affects certain disease-specific mortalities such as cancer mortality (28, 29), for example; and when data are aggregated, the noise-to-signal ratio hides such effect. It is also plausible that the current data, when restricted to studies with adequate protection of bias, sufficient follow-up, and documented increase in vitamin D level, become underpowered to detect benefits in cardiovascular outcomes. The answer to the mortality question will likely require a very large trial with long follow-up in which disease-specific mortality is measured and ascertained as a primary endpoint. Trials with factorial design similar to the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial (30) in which patients can be randomized to differing doses of vitamin D with and without calcium will be needed to determine the optimal dose and the nonskeletal effects of these interventions.

The practice implications of this systematic review indicate that recommending vitamin D to patients to reduce cardiovascular risk is not consistent with the current evidence. Individuals will require the age- and sex-appropriate daily intake of vitamin D and may require additional supplementation for other indications such as bone health, but not for cardiovascular risk reduction. The accompanying guideline document developed by the task force of the Endocrine Society will provide additional practical advice and detailed recommendations regarding vitamin D supplementation (75).

### Conclusion

Trial data available to date are unable to demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D. The quality of the available evidence is low to moderate at best.

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