Annals of Internal Medicine | Review

Systematic Review: Vitamin D and Cardiometabolic Outcomes

Anastassios G. Pittas, MD, MS; Mei Chung, MPH; Thomas Trikalinos, MD; Joanna Mitri, MD; Michael Brendel, BA; Kamal Patel, MPH; Alice H. Lichtenstein, DSc; Joseph Lau, MD; and Ethan M. Balk, MD, MPH

Background: Vitamin D may modify risk for cardiometabolic outcomes (type 2 diabetes, hypertension, or cardiovascular disease).

Purpose: To examine the association between vitamin D status, including the effect of vitamin D supplementation, and cardiometabolic outcomes in generally healthy adults.

Data Sources: English-language studies in MEDLINE (inception to 4 November 2009) and the Cochrane Central Register of Controlled Trials (fourth quarter of 2009).

Study Selection: 11 reviewers screened citations to identify longitudinal cohort studies that reported associations between vitamin D status and cardiometabolic outcomes, including randomized trials of vitamin D supplementation.

Data Extraction: 5 independent reviewers extracted data about study conduct, participant characteristics, outcomes, and quality. Differences were resolved by consensus.

Data Synthesis: 13 observational studies (14 cohorts) and 18 trials were eligible. Three of 6 analyses (from 4 different cohorts) reported a lower incident diabetes risk in the highest versus the lowest vitamin D status groups. Eight trials found no effect of vitamin D supplementation on glycemia or incident diabetes. In meta-analysis of 3 cohorts, lower 25-hydroxyvitamin D concentration was associated with incident hypertension (relative risk, 1.8 [95% CI, 1.3 to 2.4]). In meta-analyses of 10 trials, supplementation nonsignificantly reduced systolic blood pressure (weighted mean difference, −1.9 mm Hg [CI, −4.2 to 0.4 mm Hg]) and did not affect diastolic blood pressure (weighted mean difference, −0.1 mm Hg [CI, −0.7 to 0.5 mm Hg]). Lower 25-hydroxyvitamin D concentration was associated with incident cardiovascular disease in 5 of 7 analyses (6 cohorts). Four trials found no effect of supplementation on cardiovascular outcomes.

Limitations: Studies included primarily white participants. Observational studies were heterogeneous. Several trials reported post hoc analyses.

Conclusion: The association between vitamin D status and cardiometabolic outcomes is uncertain. Trials showed no clinically significant effect of vitamin D supplementation at the dosages given.

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For author affiliations, see end of text.

Increasing evidence suggests that vitamin D may have an important role in modifying risk for cardiometabolic outcomes, including type 2 diabetes, hypertension, and cardiovascular disease (1, 2). However, most studies that have shown an association between lower plasma or serum 25-hydroxyvitamin D, or 25(OH)D, concentration or vitamin D intake and increased risk for cardiometabolic outcomes are cross-sectional, which limits the strength of their conclusions. Ecological studies (3–5) have also reported higher rates of diabetes, hypertension, and coronary heart disease with increasing distance from the equator, which suggests a possible association with vitamin D insufficiency in regions with less sun exposure.

Recently, several longitudinal observational studies and trials of the relationship between vitamin D and cardiometabolic outcomes have been published. To determine the potential role of vitamin D in cardiometabolic outcomes, we performed a systematic review of longitudinal observational studies of vitamin D status and randomized, controlled trials of vitamin D supplementation on cardiometabolic outcomes.

Methods

This review is an expansion of an evidence report commissioned by the Agency for Healthcare Research and Quality (AHRQ) for an Institute of Medicine panel that is revisiting the dietary reference intakes for vitamin D and calcium (6). The AHRQ evidence report on vitamin D (and calcium) evaluated 17 clinical outcomes in the general healthy population, including incident hypertension and cardiovascular disease. We include an additional focused systematic review of cardiometabolic outcomes related to type 2 diabetes. We developed and followed a standard protocol for the overall review.

Data Sources and Study Selection

We conducted 2 independent searches of MEDLINE (inception to 4 November 2009) and the Cochrane Central Register of Controlled Trials (fourth quarter of 2009;

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Context

Does vitamin D modify risk for type 2 diabetes, hypertension, or cardiovascular disease?

Contribution

This review found cohort studies in healthy adults that reported that lower vitamin D status was associated with increased risk for hypertension and possibly cardiovascular disease. Data on associations with diabetes were unclear. Trials thus far show no consistent, statistically significant effect of vitamin D supplementation on blood pressure or glycemic or cardiovascular outcomes.

Implication

Lower vitamin D status seems to be associated with increased risk for hypertension and cardiovascular disease, but we do not yet know whether vitamin D supplementation will affect clinical outcomes.

—The Editors

last searched 4 November 2009). Each search included longitudinal observational studies of vitamin D status and randomized, controlled trials of vitamin D supplementation (cholecalciferol [D_3] or ergocalciferol [D_2], with or without calcium) in adults.

Our broad systematic review for the AHRQ evidence report identified longitudinal observational studies that assessed vitamin D status by measuring plasma or serum 25(OH)D concentration. This literature search, which was last conducted on 30 April 2009, included the cardiometabolic outcomes of incident hypertension, incident cardiovascular disease, and (in trials only) change in blood pressure. We included only generally healthy populations (<20% of study participants had major chronic diseases, such as diabetes, cancer, or cardiovascular disease, at baseline). We also included studies of calcium intake alone, which are not reported here.

Our focused literature search also included studies that assessed vitamin D status by self-reported vitamin D intake or predicted 25(OH)D concentration from self-reported data; studies with the diabetes-related outcomes of incident type 2 diabetes and (in trials only) change in glycemia (fasting plasma glucose, 2-hour glucose after oral glucose tolerance test, or hemoglobin A_{1c}); and all adult populations regardless of baseline disease (except those specifically excluded). We last conducted this literature search on 4 November 2009.

We combined terms for vitamin D, hypertension, and cardiovascular disease (both searches) and diabetes mellitus (focused search) and restricted our searches to English-language publications. We sought additional studies in personal reference lists and citation sections of recovered articles. We excluded cross-sectional or retrospective cohort studies, standard case–control studies, and short-term (<1 month) randomized trials. We included nested case–control studies in which data on vitamin D status were collected before outcome assessment. We excluded studies on type 1 diabetes, because of its different pathophysiology; studies in children, pregnant women, or participants with conditions that affect vitamin D metabolism (such as chronic kidney disease or hyperparathyroidism); and trials that used a vitamin D preparation other than D_3 or D_2 or nonoral vitamin D administration.

We screened the 2 literature searches independently. For the broad systematic review, 10 investigators performed single screening of search results for outcomes of interest. For the focused systematic review, 1 additional investigator screened all abstracts. We combined the results from the 2 independent searches if the studies met the specific criteria for the focused systematic review on cardiometabolic outcomes (type 2 diabetes, hypertension, and cardiovascular disease). We resolved the discrepancies by consensus in group conference.

Data Extraction and Quality Assessment

One reviewer extracted data independently from each study, and at least one other reviewer confirmed them. The extracted data included study design; participant characteristics; longest reported follow-up period; method of assessing vitamin D status or details of vitamin D supplementation; association between vitamin D status or supplementation and outcome; potential confounding variables adjusted for, with particular emphasis on age, race, weight, and variables related to sun exposure (such as season or location); method of ascertaining cardiometabolic outcome; and statistical analyses.

We assessed the methodological quality of each study on the basis of predefined criteria, in accordance with AHRQ's suggested methods for systematic reviews (7). The primary data extractor determined the study quality and at least one other reviewer confirmed it. Good-quality studies adhere most closely to the commonly held concepts of high quality, including clear descriptions of the population and setting; unbiased assessments of vitamin D status and outcomes; appropriate statistical analysis, including multivariate analysis adjusted for age, race, weight, and sun exposure; no obvious reporting omissions or errors; and fewer than 20% dropouts. Fair-quality studies have some deficiencies in these criteria, which are unlikely to cause major bias. Poor-quality studies have major deficiencies, such that we could not exclude major bias. We considered factors in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies (8), nutrition-specific items from a critical appraisal of micronutrient systematic reviews (9), and the CONSORT (Consolidated Standards of Reporting Trials) statement for reporting clinical trials (10).

Data Synthesis and Analysis

We performed random-effects model meta-analyses when similar data from 3 or more observational cohorts or trials were available (11). For observational studies, we syn-

thesized relative risks (RRs) or hazard or odds ratios that compared the extreme categories of vitamin D status (highest vs. lowest, as defined in each study), provided that the categories corresponded to similar levels of vitamin D intake or 25(OH)D concentration across studies. For randomized trials, we combined net differences for continuous outcomes and RR for dichotomous outcomes. We tested between-study heterogeneity with the Q statistic (significant when $P < 0.10$) and quantified its extent with I^2 (12).

Role of the Funding Source

The funding sources (National Institute of Diabetes and Digestive and Kidney Disease, Office of Dietary Supplements, U.S. Food and Drug Administration, AHRQ, and Public Health Agency of Canada) had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication, except that AHRQ participated in formulating the study questions for the evidence report (6).

Results

Search Results

Our independent searches identified 5739 and 2087 abstracts. We retrieved 106 articles for full-text review in the broad search and 127 articles in the focused search. We found 32 qualified studies from both searches combined. The **Appendix Figure**, available at www.annals.org, shows the reasons for exclusion.

Vitamin D and Type 2 Diabetes

Longitudinal Observational Cohort Studies

Three studies with 4 cohorts reported the association between vitamin D status and risk for type 2 diabetes (13–15) (**Appendix Table 1**, available at www.annals.org). The studies included 95 243 participants (98% white) who were followed from 9 to 20 years. Two fair-quality studies (13, 14) assessed vitamin D status by self-reported total vitamin D intake, and 1 good-quality study (15) measured serum 25(OH)D concentration. Ascertainment of type 2 diabetes was by validated self-report in 2 studies (13, 14) and by national registry–based data in the third (15). Two studies reported multivariate-adjusted results, whereas 1 study (13) adjusted only for age.

Among men, the association between higher vitamin D concentration and lower risk for incident type 2 diabetes was significant in the Mini-Finland Health Survey and nearly significant in the Finnish Mobile Clinic Health Examination Survey (15). No association was found in 3 of 4 analyzed groups of women (14, 15). Only the Women's Health Study cohort (13) showed an association between higher vitamin D intake and lower risk for incident type 2 diabetes. Variations in type of assessment and definitions of risk categories precluded meta-analyses.

Randomized Trials

Eight trials (16–23) reported the effect of vitamin D supplementation on glycemia (fasting plasma glucose or hemoglobin A_{1c}) or incident diabetes by self-report (19) (**Appendix Table 2**, available at www.annals.org). Three of the trials were designed for nonglycemic outcomes (16, 18, 19). Study duration varied from 2 months to 7 years, and dosages ranged from 400 to 5714 IU/d. Two studies gave vitamin D_3 in combination with calcium (18, 19). Only 2 trials were rated good quality (19, 20, 23). Among 5 trials of participants with normal glucose tolerance at baseline, vitamin D supplementation had no effect on fasting plasma glucose level (weighted mean difference [WMD] for vitamin D supplementation vs. placebo, −0.002 mmol/L [−0.04 mg/dL] [95% CI, −0.055 to 0.050 mmol/L {−0.99 to 0.90 mg/dL}]) (16, 18–21, 23) or incident diabetes (19). In a subgroup analysis of participants with impaired fasting glucose at baseline, combined vitamin D_3 (700 IU/d) and calcium carbonate (500 mg/d) supplementation attenuated the increase in fasting glycemia that normally occurs over time in this population (18). In 2 trials of participants with stable type 2 diabetes (17, 22), glycemic measures did not change after 8 or 24 weeks of vitamin D supplementation.

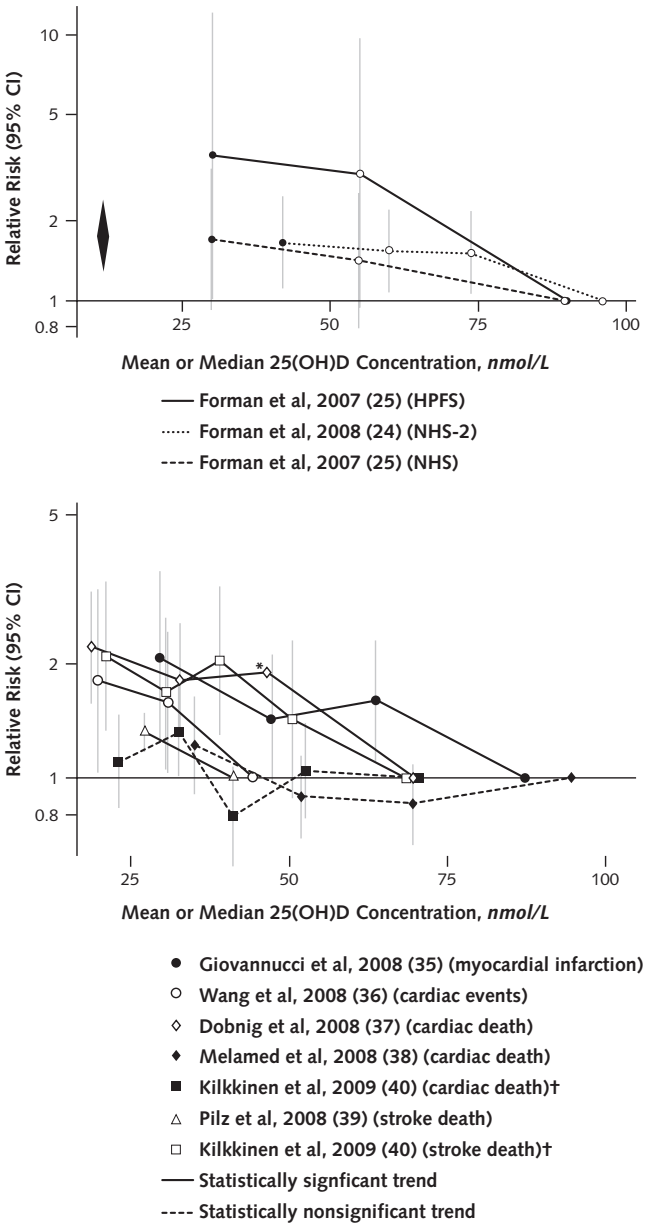
Vitamin D and Hypertension

Longitudinal Observational Cohort Studies

Three studies (24–26) reported data from 4 cohorts on the association between vitamin D status and risk for incident hypertension (**Appendix Table 1**, available at www.annals.org). The studies included 32 181 participants (98% white) with follow-up of 7 to 10 years. One study (26) assessed vitamin D status by self-reported vitamin D intake and the others (24, 25) measured 25(OH)D concentration. In all studies, hypertension was ascertained by validated self-report without actual measurement of blood pressure; we therefore graded them as fair quality. All studies reported multivariate-adjusted results.

Among 3 cohorts, 2 (1 of men [25] and 1 of women [24]) found a statistically significant association between lower 25(OH)D concentration and higher risk for incident hypertension after 7 or 8 years, whereas the third (25) reported an association in the same direction in women that was not statistically significant at 8 years. In 1 study (25), the association was reported to be stronger after 4 years of follow-up than after 8 years in both men (4-year RR, 6.13 [CI, 1.00 to 37.8] vs. 8-year RR, 3.53 [CI, 1.02 to 12.3]) and women (4-year RR, 2.67 [CI, 1.05 to 6.79] vs. 8-year RR, 1.70 [CI, 0.92 to 3.16]). Meta-analyses of these 3 cohorts (24, 25) found a statistically significant association between 25(OH)D concentration and incident hypertension after 7 to 8 years (RR, 1.76 [CI, 1.27 to 2.44]) when we compared results in the lowest concentration category (<37 to 51 nmol/L) with those in the highest (>75 to 81 nmol/L) (**Figure 1**, *top*), with no heterogeneity among studies ($I^2 = 0\%$).

Figure 1. **Association between vitamin D status and incident hypertension or cardiovascular disease in longitudinal observational cohorts.**



Relative risks (and 95% CIs) for each 25(OH)D concentration quartile compared with the highest concentration quartile. 25(OH)D = 25-hydroxyvitamin D; HPFS = Health Professionals Follow-up Study; NHS = Nurses' Health Study; NHS-2 = Nurses' Health Study 2.
Top. Association between vitamin D status and incident hypertension. The diamond represents the meta-analysis summary relative risk and 95% CI for the lowest quantiles (*black circles*) versus the highest quantiles (on the reference line); relative risk, 1.76 (CI, 1.27 to 2.44); $I^2 = 0\%$. **Bottom.** Association between vitamin D status and cardiovascular disease. Data from Marniemi and colleagues (34) were not included because the quantiles were not defined.
* Estimate from reported data; no CI data were available.
† To make studies graphically comparable, we converted data to provide estimates of relative risks if the lowest quintile was the reference group. The original study (40) used the highest quintile as the reference group.

One study evaluated the association between vitamin D intake and incident hypertension (26). A statistically significant trend across quintiles of dietary vitamin D intake was reported ($P = 0.02$); however, the direction of the adjusted RRs had no consistency across quintiles, and all were close to 1.0 (range, 0.95 to 1.04). The investigators found no association with supplemental vitamin D.

Randomized Trials

Ten trials (17, 20, 22, 27–33), 3 of good quality (20, 27, 32), 5 of fair quality (17, 22, 28–30), and 2 of poor quality (31, 33), reported the effect of vitamin D supplementation on blood pressure or incident hypertension (**Appendix Table 2**, available at www.annals.org). Vitamin D was given either alone (17, 20, 22, 27–32) or in combination with calcium (30–32) at dosages equivalent to 400 to 8571 IU/d. Eight studies used D_3 (27–32), and 1 used D_2 (17). Another trial compared ultraviolet B (UV-B) exposure (which increases cutaneous synthesis of vitamin D) with ultraviolet A (UV-A) exposure (which does not) (33). Follow-up varied from 5 to 52 weeks in most studies and was 7 years in the Women's Health Initiative trial (32). The total number of participants was 37 162, with the Women's Health Initiative trial contributing 36 282 participants. The study populations were heterogeneous and included healthy participants (32) and participants with established hypertension (33), heart failure (28), type 2 diabetes (17, 22), and overweight or obesity (20, 29).

Most trials found no statistically significant effects on either systolic or diastolic blood pressure. Two trials reported that vitamin D supplementation had relatively large net effects on systolic blood pressure of −7 mm Hg (30) and −14 mm Hg (17). The trial that compared UV-B with UV-A exposure (33) also reported a large net effect on systolic blood pressure (−6 mm Hg) that favored UV-B, but it was unclear whether the net effect was statistically significant. This study was the only one that found a large net difference in diastolic blood pressure with UV-B exposure.

In the largest and longest trial, the Women's Health Initiative (32), combined low-dose vitamin D_3 (400 IU/d) and calcium carbonate supplementation (1000 mg/d) had no effect on self-reported incident hypertension after 7 years of follow-up. In subgroup analyses from this trial, supplementation increased the risk for incident hypertension among black participants (RR, 1.2 [CI, 1.0 to 1.4) (32). A meta-analysis of all trials showed no significant effect of vitamin D supplementation on systolic blood pressure compared with placebo (WMD, −1.9 mm Hg [CI, −4.2 to 0.4 mm Hg]) (**Figure 2**, *top*), but with significant heterogeneity ($I^2 = 69\%$) and no significant effect on diastolic blood pressure (WMD, −0.1 mm Hg [CI, −0.7 to 0.5]; $I^2 = 23\%$) (**Figure 2**, *bottom*). The WMDs for systolic and diastolic blood pressures were similar when

we excluded the large, long-term Women's Health Initiative trial.

Change in systolic and diastolic blood pressure did not differ between trials that provided vitamin D alone and those that provided it in combination with calcium, and change in systolic blood pressure did not differ between trials that provided higher (≥1000 IU/d) and lower (<1000 IU/d) vitamin D dosages. Studies that used higher vitamin D dosages showed a significantly different effect on diastolic blood pressure (WMD, −1.5 mm Hg) than those that used lower dosages (0.1 mm Hg; $P = 0.039$).

Vitamin D and Cardiovascular Disease

Longitudinal Observational Cohort Studies

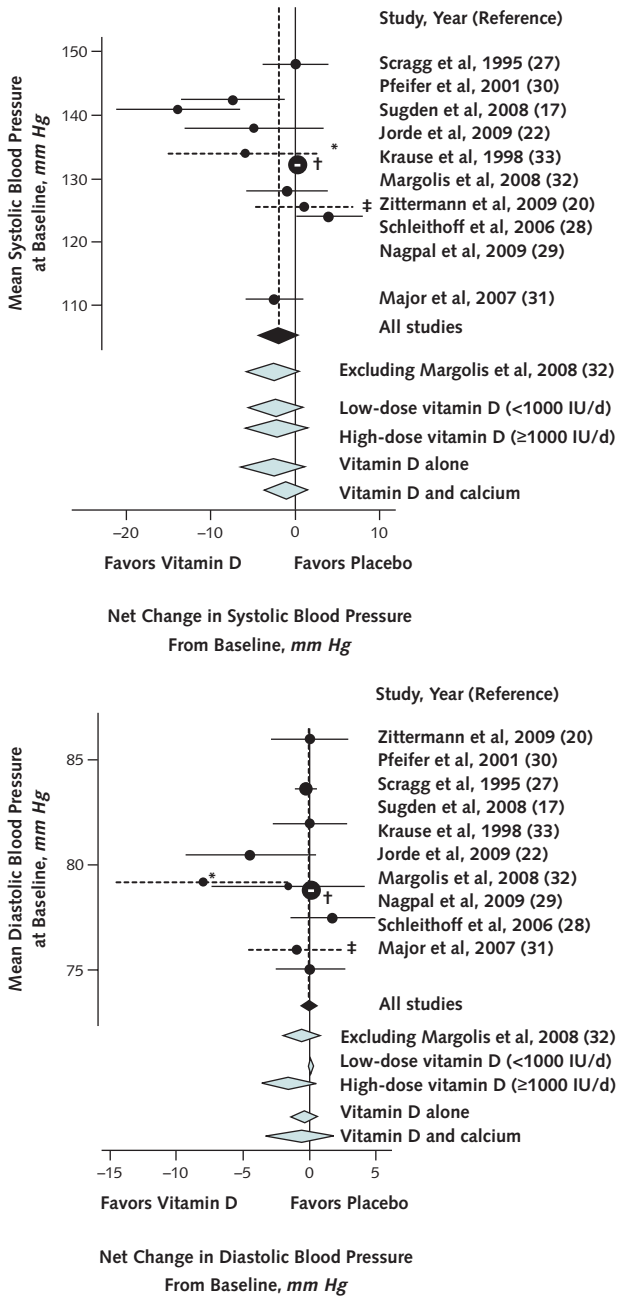
Seven studies (34–40), 5 of good quality (35–37, 39, 40) and 2 of poor quality (34, 38), analyzed vitamin D status and cardiovascular end points in 9 different analyses from 6 cohorts (**Appendix Table 1**, available at www.annals.org). The studies included 43 527 participants (89% white) who were followed from 5 to 27 years for incident cardiovascular disease. Cardiovascular end points included myocardial infarction (34, 35), cardiovascular-related death (37, 38, 40), a composite cardiovascular end point (36), and stroke (34, 39, 40). All studies measured 25(OH)D concentration, and all reported multivariate-adjusted results.

Overall, 5 of the 9 analyses (35–37, 39, 40) found that lower 25(OH)D concentration was associated with increased risk for incident cardiovascular disease (**Figure 1**, *bottom*, and **Appendix Table 1**, available at www.annals.org). The Framingham Offspring Study (36) found an association between lower 25(OH)D concentration and increased risk for overall cardiovascular events; however, this association seemed to be nonlinear (somewhat U-shaped) and subgroup analyses (not shown here) indicated that the association was statistically significant only among participants with hypertension at baseline. Among the studies that evaluated fatal cardiovascular events, 2 of 3 (37, 38, 40) found statistically significant associations that favored higher vitamin D concentration for all fatal cardiovascular events (cardiac or stroke), 2 (39, 40) found similar significant associations with fatal stroke, and 1 (40) found no significant association with fatal cardiac events. Of the 2 studies that evaluated myocardial infarction (34, 35), only the analysis in the men-only Health Professionals Follow-up Study (35) found a significant association between lower 25(OH)D concentration and increased risk. We did not perform a meta-analysis because of the heterogeneity of outcomes.

Randomized Trials

Four trials (23, 41–44), 3 of fair quality (41, 42, 44) and 1 of good quality (23, 43), reported the effect of vitamin D supplementation on incident cardiovascular disease (**Appendix Table 2**, available at www.annals.org). None reported a statistically significant effect of vitamin D sup-

Figure 2. **Meta-analyses of the effect of vitamin D supplementation on net change in blood pressure.**



Weighted mean difference and 95% CIs for change in blood pressure from vitamin D supplementation versus placebo. Studies are arranged according to baseline blood pressure. The circle sizes are proportional to the study size. The black diamond represents the primary meta-analyses, and the other diamonds represent sensitivity and subgroup analyses. Dashed lines indicate studies for which SEs were not reported. **Top.** Changes in systolic blood pressure. **Bottom.** Changes in diastolic blood pressure.

* We estimated the 95% CI from the reported full range of changes in blood pressure.

† The 95% CI is in the circle.

‡ We estimated the 95% CI from the reported interquartile ranges of changes in blood pressure.

plementation (with or without calcium) on various cardiovascular outcomes, including myocardial infarction, stroke, and other cardiac and cerebrovascular outcomes. Study participants were followed for 1, 5, or 7 years. The Women's Health Initiative investigators (23, 43) performed 12 analyses of different cardiovascular outcomes and reported a nearly significant harmful effect of combined vitamin D and calcium supplementation on a composite cardiac outcome that included nonfatal myocardial infarction, death from coronary heart disease, and need for revascularization (RR, 1.08 [CI, 0.99 to 1.19]). The interventions and outcomes were too heterogeneous for meta-analysis.

DISCUSSION

Cross-sectional studies have reported consistent associations between lower 25(OH)D concentration or vitamin D intake and prevalent cardiometabolic outcomes (1, 45). In the longitudinal observational studies reviewed here, lower 25(OH)D concentration or vitamin D intake was associated with increased risk for incident hypertension and possibly cardiovascular disease, but the strengths of these associations were attenuated compared with those from cross-sectional studies. The evidence from longitudinal studies of type 2 diabetes was sparse. In trials, vitamin D supplementation had no statistically significant effect on diastolic or systolic blood pressure or on glycemic or cardiovascular outcomes. However, evidence suggested that vitamin D supplementation reduced systolic blood pressure by a statistically nonsignificant 2 mm Hg. Further data are needed to adjudicate this observation.

Several plausible mechanisms explain how vitamin D may modify risk for cardiometabolic outcomes. Vitamin D may affect various mechanisms related to type 2 diabetes pathophysiology, including impaired pancreatic β-cell function and insulin resistance, either directly (by vitamin D receptor activation) or indirectly (by calcium homeostasis regulation) (1). Regarding cardiovascular outcomes, vitamin D regulates the renin–angiotensin system (46), suppresses proliferation of vascular cell smooth muscle (47), improves insulin resistance (18) and endothelial cell–dependent vasodilation (48, 49), inhibits anticoagulant activity (50) and myocardial cell hypertrophy (51–53), and may modulate macrophage activity (54) and cytokine generation (28, 55).

Several possible reasons may explain the lack of apparent concordance among the cross-sectional, longitudinal observational, and randomized studies. Several factors may confound the inverse association between vitamin D status and cardiometabolic outcomes. First, vitamin D status is an excellent marker of good health, including positive associations with young age, normal body weight, and a healthy lifestyle (56) and negative associations with smoking, parental history of myocardial infarction, and alcohol intake (2, 14, 35). Second, lower vitamin D status may reflect chronic nonspecific illness. Therefore, the inverse association seen in cross-sectional studies may be due to reverse causation. Third, additional components in foods rich in vitamin D (such as fish or fortified dairy products) may directly affect cardiometabolic disease or, alternatively, foods rich in vitamin D may replace other foods that increase risk for cardiometabolic disease (for example, fortified milk may replace sweetened drinks) (57). Finally, observational studies have used single measurements of serum or plasma 25(OH)D concentration as a proxy for vitamin D status, even though this may not reflect long-term vitamin D status.

The Women's Health Initiative, the largest trial on vitamin D and calcium supplementation to date, reported no statistically significant effects for all cardiometabolic outcomes examined. However, this trial used a relatively small dose of vitamin D (400 IU/d), had difficulties with adherence over 7 years, and allowed participants in both intervention groups to receive supplemental vitamin D. On the basis of dose and adherence, the effect of supplementation on 25(OH)D concentration has been estimated to be only 5 nmol/L in the Women's Health Initiative trial (58)—an increment unlikely to be associated with any change in risk for cardiometabolic outcomes, according to observational study data.

The Institute of Medicine is currently reviewing optimal 25(OH)D concentrations. For various skeletal and nonskeletal outcomes, Bischoff-Ferrari and colleagues (59) proposed that a 25(OH)D concentration less than 25 nmol/L defines vitamin D deficiency and a concentration greater 75 nmol/L is associated with improved bone- and non–bone-related outcomes. In the longitudinal observational studies, participants with a moderate 25(OH)D concentration (62 to 87 nmol/L) had a lower risk for cardiometabolic outcomes than those with relatively low levels (25 to 37 nmol/L). Evidence from several studies (24, 35–38) suggests an apparent threshold 25(OH)D concentration of 50 nmol/L beyond which risk for cardiovascular disease does not decrease further, which indicates that vitamin D deficiency may increase risk but higher 25(OH)D concentration may not lower risk proportionately. These data suggest that improving vitamin D status may have a clinically significant effect on cardiometabolic outcomes only among those with vitamin D deficiency.

Our review is limited by the quality of the published studies that we included. In the observational studies, the outcome was ascertained by self-report or from national registry data. A positive self-report is generally accurate in epidemiologic studies (60), and most of the included studies validated the outcome. However, early-stage cardiometabolic outcomes may have been undiagnosed and therefore not included in the analyses. We also found substantial heterogeneity among studies, especially in vitamin D thresholds used, doses analyzed, outcomes specified, and confounders adjusted for. Of note, not all studies adjusted for sun exposure. Finally, most study participants were white and approximately 40 to 70 years of age, which lim-

its the applicability of our findings to other racial groups and life stages.

In conclusion, a lower 25(OH)D concentration or vitamin D intake may be associated with higher risk for incident hypertension and cardiovascular disease, but the association with diabetes-related outcomes remains unclear. As a whole, the trials showed no statistically significant effect of vitamin D supplementation on cardiometabolic outcomes. The available data are inadequate to support the contention that cardiometabolic outcomes can be improved by increasing vitamin D intake or serum or plasma 25(OH)D concentrations. Adequate randomized trials, conducted in well-defined populations (such as persons with prediabetes or prehypertension or white vs. nonwhite persons), are needed to test the potential role of vitamin D in primary prevention or therapy. Vitamin D remains a promising, although unproven, new element in the prevention and management of cardiometabolic disease.

From Tufts Evidence-based Practice Center, Tufts Medical Center and Friedman School of Nutrition Science and Policy, and Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts.

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Requests for Single Reprints: Ethan M. Balk, MD, MPH, Tufts Evidence-based Practice Center, Tufts Medical Center, Box 63, 800 Washington Street, Boston, MA 02111; e-mail, ebalk@tuftsmedicalcenter.org.

Current author addresses and author contributions are available at www.annals.org.

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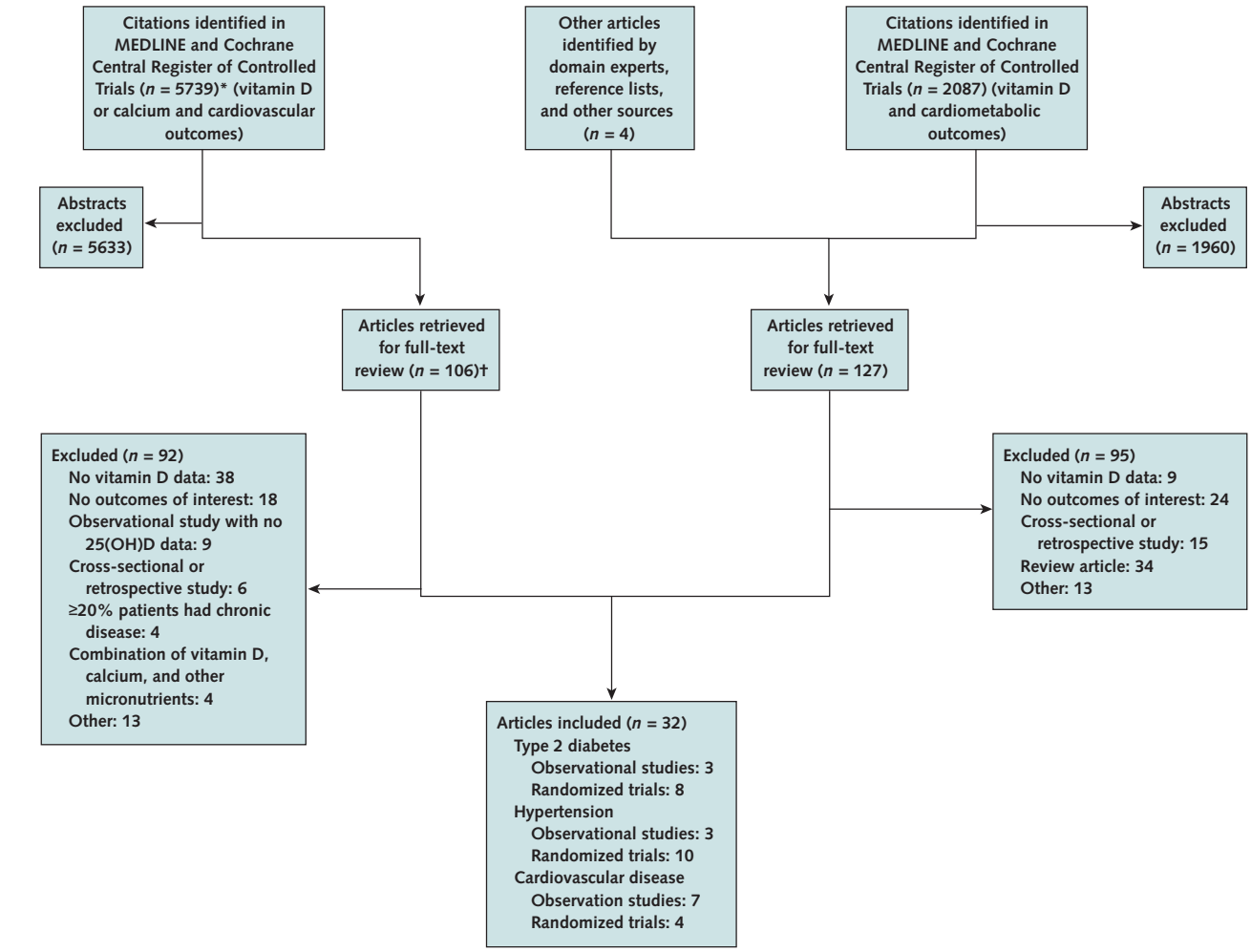
Current Author Addresses: Drs. Pittas and Mitri: Tufts Medical Center, 800 Washington Street, Box 268, Boston, MA 02111.
Drs. Trikalinos, Lau, and Balk; Ms. Chung; Mr. Brendel; and Mr. Patel: Tufts Medical Center, 800 Washington Street, Box 63, Boston, MA 02111.
Dr. Lichtenstein: Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111.

Author Contributions: Conception and design: A.G. Pittas, M. Chung, J. Mitri, A.H. Lichtenstein, J. Lau, E.M. Balk.
Analysis and interpretation of the data: A.G. Pittas, M. Chung, T. Trikalinos, J. Mitri, A.H. Lichtenstein, E.M. Balk.
Drafting of the article: A.G. Pittas, J. Mitri, E.M. Balk.
Critical revision of the article for important intellectual content: A.G. Pittas, M. Chung, T. Trikalinos, J. Mitri, A.H. Lichtenstein, J. Lau, E.M. Balk.
Final approval of the article: A.G. Pittas, M. Chung, T. Trikalinos, A.H. Lichtenstein, J. Lau, E.M. Balk.
Statistical expertise: M. Chung, T. Trikalinos, E.M. Balk.
Obtaining of funding: A.G. Pittas, J. Lau, E.M. Balk.
Administrative, technical, or logistic support: K. Patel, J. Lau.
Collection and assembly of data: A.G. Pittas, M. Chung, J. Mitri, M. Brendel, K. Patel, E.M. Balk.

Appendix Figure. **Literature search and selection.**



* We screened 16 733 citations for a wide array of clinical outcomes. The 5739 citations refer to those specifically from the cardiovascular outcomes search, but we also screened potentially relevant citations from searches for other outcomes for cardiovascular outcomes.
† We retrieved 584 full-text articles for review for a wide array of clinical outcomes. The 106 articles refer to those specifically marked as having a cardiovascular outcome, but we also screened potentially relevant citations from searches for other outcomes for cardiovascular outcomes.

Appendix Table 1. Longitudinal Observational Cohort Studies of Vitamin D Status and Cardiometabolic Disease

Study, Year (Reference)	Cohort	Men, %	Mean Baseline Age (Range), *y*	White, %	Participants (Incidence), *n/N**	Vitamin D Measure and Comparison†	Mean Follow-up (Date Range), *y*	Adjusted RR, OR, or HR (95% CI; *P* Value for Trend	Outcome and Ascertainment Method	Adjustments	Study Quality
Type 2 diabetes											
Liu et al, 2005 (13)	Women's Health Study (United States)	0	52 (45–75)	95	805/10 066 (8.0%)	Vitamin D intake (total); ≥511 vs. ≤159 IU/d	9 (ND)	0.73 (0.54–0.99)‡; *P* = 0.02	Type 2 diabetes; validated self-report	Age	Fair
Pittas et al, 2006 (14)	Nurses' Health Study (United States)	0	46 (30–55)	98	4843/83 779 (5.8%)	Vitamin D intake (total); >800 vs. ≤200 IU/d	20 (1980–2000)	0.87 (0.69–1.09); *P* = 0.67	Type 2 diabetes; validated self-report	Age, BMI, exercise, residence, and others§	Fair
Knekt et al, 2008 (15)	Finnish Mobile Clinic Health Examination Survey (Finland)	100	ND (40–74)	100	105/1628 (6.4%); nested case–control study with 206 control participants	25(OH)D concentration; 75 vs. 25 nmol/L (means)	9 (1973–1994)	0.49 (0.15–1.64); *P* = 0.06	Type 2 diabetes; medication-treated, registry-based	Age, BMI, exercise, season, residence, and others‖	Good
		0			125/1699 (7.4%); nested case–control study with 246 control participants	25(OH)D concentration; 61 vs. 22 nmol/L (means)		0.91 (0.37–2.23); *P* = 0.66			
	Mini-Finland Health Survey (Finland)	100	53 (40–69)	100	83/1948 (4.3%); nested case–control study with 245 control participants	25(OH)D concentration; 75 vs. 22 nmol/L (means)	9 (1978–1994)	0.17 (0.05–0.52); *P* < 0.001	Type 2 diabetes; medication-treated, registry-based	Age, BMI, exercise, season, residence, and others‖	Good
		0			99/2228 (4.4%); nested case–control study with 289 control participants	25(OH)D concentration; 61 vs. 20 nmol/L (means)		1.45 (0.58–3.62); *P* = 0.83			
Hypertension											
Forman et al, 2007 (25)	Health Professionals Follow-up Study (United States)	100	65 (40–75)	95	133/613 (22%)	25(OH)D concentration; <37 vs. ≥75 nmol/L	8 (1993–2001)	3.53 (1.02–12.3); ND	Hypertension; validated self-report without BP measurement	Age, BMI, exercise, race, and season	Fair
	Nurses' Health Study (United States)	0	57 (30–55)	95	274/1198 (23%)	25(OH)D concentration; <37 vs. ≥75 nmol/L	8 (1989–1997)	1.70 (0.92–3.16); ND	Hypertension; validated self-report without BP measurement	Age, BMI, exercise, season, race, and postmenopausal status	Fair
Forman et al, 2008 (24)	Nurses' Health Study 2 (United States)	0	43 (32–52)	~100	742/ND (ND); nested case–control study with 742 control participants	25(OH)D concentration; <51 vs. ≥81 nmol/L	7 (1997–2005)	1.66 (1.11–2.48); *P* = 0.01	Hypertension; validated self-report without BP measurement	Age, BMI, exercise, season, race, and others¶	Fair
Wang et al, 2008 (26)	Women's Health Study (United States)	0	54 (≥45)**	95	8526/28 886 (30%)	Vitamin D intake (dietary) 110 vs. 381 IU/d (medians)	10 (ND)	0.95 (0.8–1.02); *P* = 0.02	Hypertension; validated self-report without BP measurement	Age, BMI, exercise, race, and others††	Fair
						Vitamin D intake (supplement; 0 vs. 800 IU/d (median)	10 (ND)	1.09 (0.93–1.27); *P* = 0.27	Hypertension; validated self-report without BP measurement	Age, BMI, exercise, race, and others††	
CVD											
Marniemi et al, 2005 (34)	Finland	48	79 (65–99)	100	130/755 (17%)	25(OH)D concentration; ND (highest vs. lowest)	10 (1986–1996)	0.77 (0.47–1.27); ND	MI; national registry	Age, sex, and others‡‡	Poor
				100	70/755 (9.3%)	25(OH)D concentration; ND (highest vs. lowest)	10 (1986–1996)	1.00 (0.51–1.94); ND	Stroke; national registry	Age, sex, and others‡‡	
Giovannucci et al, 2008 (35)	Health Professionals' Follow-up Study (United States)	100	64 (40–75)	94	454/18 225 (2.5%); nested case–control study with 900 control participants	25(OH)D concentration; ≤37 vs. ≥75 nmol/L	10 (1993–2004)	2.09 (1.24–3.54); *P* = 0.02	MI; confirmed self-report (nonfatal MI) or National Death Index (fatal coronary heart disease)	Age, BMI, exercise, season, race, region, and others§§	Good

Appendix Table 1—**Continued**

Study, Year (Reference)	Cohort	Men, %	Mean Baseline Age (Range), *y*	White, %	Participants (Incidence), *n/N**	Vitamin D Measure and Comparison†	Mean Follow-up (Date Range), *y*	Adjusted RR, OR, or HR (95% CI); *P* Value for Trend	Outcome and Ascertainment Method	Adjustments	Study Quality
Wang et al, 2008 (36)	Framingham Offspring Study (United States)	45	59 (41–77)	100	120/1739 (6.9%)	25(OH)D concentration; <25 vs. ≥37 nmol/L	5 (1996–2003)	1.81 (1.03–3.18); $P = 0.01$	CVD composite‖ ‖; adjudicated review of medical records	Age, sex, BMI, and others¶¶	Good
Dobnig et al, 2008 (37)	LURIC study (Germany)	70	62 (ND)	100	463/3258 (14%)	25(OH)D concentration; 20 vs. 69 nmol/L (means)	8 (1997 to ~2005)	2.22 (1.57–3.13); $P < 0.001$	Fatal CVD; death certificates	Age, sex, BMI, exercise, and others***	Good
Melamed et al, 2008 (38)	NHANES III (United States)	46	45 (≥20)**	72	777/13 331 (5.8%)	25(OH)D concentration; >79 vs. <44 nmol/L	9 (1988–2000)	1.22 (0.90–1.65); ND	Fatal CVD; National Death Index	Age, sex, BMI, exercise, season, race, vitamin D supplementation, and others†††	Poor
Pilz et al, 2008 (39)	LURIC study (Germany)	68	69 (55–76)	100	42/3299 (1.3%)	25(OH)D concentration; 27 (stroke) vs. 42 nmol/L (survivors) (medians)	8 (1997 to ~2005)	0.67 (0.46–0.97); $P = 0.03$‡‡‡	Fatal stroke; death certificates	Age, sex, BMI, exercise, and others§§§	Good
Kilkkinen et al, 2009 (40)	Mini-Finland Health Survey (Finland)	45	49 (≥30)**	100	640/6219 (10%)	25(OH)D concentration; ~70 vs. ~22 nmol/L (medians)	27 (1978–2006)	0.91 (0.70–1.18); $P = 0.20$	Fatal cardiac event; national mortality registry	Age, sex, BMI, exercise, season, and others‖ ‖ ‖	Good
					293/6219 (4.7%)			0.48 (0.31–0.75); $P = 0.002$	Fatal stroke; national mortality registry	Age, sex, BMI, exercise, season, and others‖ ‖ ‖	
					933/6219 (15%)			0.76 (0.60–0.95); $P = 0.005$	Fatal cardiac event or stroke	Age, sex, BMI, exercise, season, and others‖ ‖ ‖	

25(OH)D = 25-hydroxyvitamin D; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; HR = hazard ratio; LURIC = Ludwigshafen Risk and Cardiovascular Health; MI = myocardial infarction; ND = no data; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; RR = relative risk.

* Case patients/control participants if nested case–control study.

† Highest and lowest risk category versus reference category.

‡ Estimated from reported data.

§ Family history of diabetes, hypertension, calcium intake, smoking, alcohol, coffee, and other dietary factors.

‖ Smoking, education, and medications.

¶ Family history of hypertension; menstrual cycle status; oral contraceptive use; and creatinine, parathyroid hormone, calcium, phosphate, and uric acid levels.

** Per eligibility criteria.

†† Postmenopausal status, diabetes, smoking, hypercholesterolemia, energy intake, alcohol, diet (other), multivitamin use, and randomly assigned treatment.

‡‡ Smoking and functional capacity.

§§ Family history of MI, diabetes, hypertension, smoking, diet (alcohol, vitamins, and ω-3 intake), fasting status, and cholesterol level.

‖ ‖ MI, coronary insufficiency, angina, stroke, transient ischemic attack, claudication, and congestive heart failure.

¶¶ Smoking; systolic BP; hypertension therapy; diabetes; and creatinine, cholesterol, and C-reactive protein levels.

*** Smoking; hypertension; diabetes; cholesterol, albumin, cystatin C, and *N*-terminal pro-brain natriuretic peptide levels; and use of bronchodilators, aspirin, statins, β-blockers, or angiotensin-converting enzyme inhibitors.

††† Smoking, hypertension, CVD, diabetes, cholesterol therapy, glomerular filtration rate, albumin level, albumin–creatinine ratio, C-reactive protein level, and socioeconomic status.

‡‡‡ Risk for fatal stroke per 25(OH)D *Z* value (binary logistic regression).

§§§ Smoking; hypertension; diabetes; glomerular filtration rate; and cholesterol, C-reactive protein, *N*-terminal pro-brain natriuretic peptide, calcium, and parathyroid hormone levels.

‖ ‖ ‖ Alcohol intake, smoking, and marital status.

Appendix Table 2. Randomized, Controlled Trials of Vitamin D Supplementation on Cardiometabolic Disease

Study, Year (Reference)	Country	Health Status of Participants	Men, %	Mean Baseline Age (Range), *y*	Baseline Mean 25(OH)D Concentration, *nmol/L*	Interventions	Study Duration	Outcome	Effect of Vitamin D Versus Placebo	Net Effect (95% CI); Reported *P* Value	Study Quality
Diabetes-related outcomes											
Nilas and Christiansen, 1984 (16)	Denmark	Postmenopausal, healthy	0	ND (45 to 54)	ND	D_3, 2000 IU/d (n = 25), vs. placebo (n = 103); all received calcium, 500 mg/d	2 y	FPG	Change, 0.12 vs. 0.13 mmol/L (2.16 vs. 2.34 mg/dL)	Net difference*, −0.005 (−0.2 to 0.2); P = 0.97†	Fair
Pittas et al, 2007 (18)	United States	Normal fasting glucose	38	71 (≥65)‡	75	D_3, 700 IU/d, plus calcium citrate, 500 mg/d (n = 108), vs. placebo (n = 114)	3 y	FPG	Change, 0.15 vs. 0.12 mmol/L (2.70 vs. 2.16 mg/dL)	Net difference*, 0.03 (−0.07 to 0.13)†; P = 0.55	Fair
		Impaired fasting glucose	52	71 (≥65)‡	75	D_3, 700 IU/d, plus calcium citrate, 500 mg/d (n = 45), vs. placebo (n = 47)	3 y	FPG	Change, 0.02 vs. 0.34 mmol/L (0.36 vs. 6.13 mg/dL)	Net difference*, −0.32 (−0.60 to −0.04)†; P = 0.042	
Hsia et al, 2007 (23)	United States	Postmenopausal	0	62 (50 to 79)	44§	D_3, 400 IU/d, plus calcium carbonate, 1000 mg/d (n = 1090), vs. placebo (n = 1086)‖	2 y	FPG	ND	Net difference*, −0.1 (−1.7 to 1.4); P = 0.90†	Good
de Boer et al, 2008 (19)	United States	Postmenopausal, nondiabetic	0	62 (50 to 79)	44§	D_3, 400 IU/d, plus calcium carbonate, 1000 mg/d (n = 16 999), vs. placebo (n = 16 952)	7 y	Diabetes¶	Incidence, 0.96% vs. 0.95% of cohort	HR, 1.01 (0.94 to 1.10); P = 0.95	Good
Sugden et al, 2008 (17)	United Kingdom	Stable type 2 diabetes	53	64 (ND)	37	D_2, 100 000 IU orally once (equivalent to 1785 IU/d) (n = 17), vs. placebo (n = 17)	8 wk	Hemoglobin A_{1c}	Change, 0.01% vs. −0.05%	Net difference*, 0.06 (−0.28 to 0.40)†; P = 0.74	Fair
von Hurst et al, 2009 (21)	New Zealand	Insulin resistance without diabetes and 25(OH)D concentration <50 nmol/L	0	42 (23 to 68)	~20§	D_3, 4000 IU/d (n = 42), vs. placebo (n = 39)	26 wk	FPG	Change, 0.1 vs. 0.1 mmol/L (1.80 vs. 1.80 mg/dL)§	Net difference*, 0.0 (ND); P = 0.82	Fair
Zittermann et al, 2009 (20)	Germany	Healthy, BMI >27 kg/m^2	33	48 (18 to 70)‡	30	D_3, 3332 IU/d (n = 100), vs. placebo (n = 100); all received weight reduction advice for 24 wk	1 y	Hemoglobin A_{1c}	Change, −0.25% vs. −0.25%	Net difference*, 0.00 (−0.07 to 0.07)†; P = 0.96	Good
								FPG	Change, 0.21 vs. −0.27 mmol/L (3.78 vs. 4.86 mg/dL)	Net difference*, 0.06 (−0.15 to 0.27)†; P = 0.39	
Jorde and Figenschau, 2009 (22)	Norway	Stable type 2 diabetes	50	56 (21 to 75)‡	59	D_3, 40 000 IU/wk (equivalent to 5714 IU/d) (n = 16), vs. placebo (n = 16)	26 wk	Hemoglobin A_{1c}	Change, −0.2% vs. −0.2%	Net difference*, 0.0 (−0.5 to 0.5)†; P = 0.90	Fair
								FPG	Change, −0.2 vs. 0.4 mmol/L (3.60 vs. 7.21 mg/dL)	Net difference*, −0.6 (−2.2 to 1.0)†; P = 0.43	
Blood pressure–related outcomes											
Scragg et al, 1995 (27)	United Kingdom	Healthy	46	70 (63 to 76)	32	D_3, 100 000 IU once (equivalent to 2857 IU/d) (n = 95), vs. placebo (n = 94)	5 wk	SBP	Change, −5 vs. −5 mm Hg	Net difference*, 0 (−4.2 to 4.2)†; P = 0.81	Good
								DBP	Change, −1 vs. −1 mm Hg	Net difference*, 0 (−2.6 to 2.6)†; P = 0.92	
Krause et al, 1998 (33)	ND	Hypertension	66	48 (26 to 66)	57	Whole-body ultraviolet B irradiation, 3 times/wk (n = 9), vs. whole-body ultraviolet A irradiation, 3 times/wk (n = 9)	6 wk	SBP	Change, −6 vs. 0 mm Hg	Net difference*, −6 (ND); ND	Poor
								DBP	Change, −6 vs. 2 mm Hg	Net difference*, −8 (ND); ND	

Appendix Table 2—Continued

Study, Year (Reference)	Country	Health Status of Participants	Men, %	Mean Baseline Age (Range), *y*	Baseline Mean 25(OH)D Concentration, *nmol/L*	Interventions	Study Duration	Outcome	Effect of Vitamin D Versus Placebo	Net Effect (95% CI); Reported *P* Value	Study Quality
Pfeifer et al, 2001 (30)	Germany	Healthy	0	74 (≥70)‡	25	D_3, 800 IU/d (n = 74), vs. placebo (n = 74); all received calcium carbonate, 1200 mg/d	8 wk	SBP	Change, −13.1 vs. −5.7 mm Hg	Net difference*, −7.4 (−12.9 to −1.9)†; P = 0.02	Fair
								DBP	Change, −7.2 vs. −6.9 mm Hg	Net difference*, −0.3 (−3.4 to 2.8)†; P = 0.10	
Schleithoff et al, 2006 (28)	Germany	Congestive heart failure	83	~55§ (ND)	~37§	D_3, 2000 IU/d (n = 17), vs. placebo (n = 17)	36 wk	SBP	Change, −3 vs. −4 mm Hg§	Net difference*, 1 (ND); P = 0.87	Fair
								DBP	Change, −3 vs. −2 mm Hg§	Change, −1 (ND); P = 0.38	
Major et al, 2007 (31)	Canada	Overweight	0	43 (ND)	ND	D_3, 400 IU/d, plus calcium carbonate, 1200 mg/d (n = 30), vs. placebo (n = 33); all participants followed an energy-restricted diet	15 wk	SBP	Change, −4.1 vs. −1.6 mm Hg	Net difference*, −2.5 (−6.1 to 1.1)†; P = 0.18	Poor
								DBP	Change, −3 vs. −3 mm Hg	Net difference*, 0 (–2.7 to 2.7)†; P = 1.0	
Sugden et al, 2008 (17)	United Kingdom	Stable type 2 diabetes	53	64 (ND)	37	D_2, 100 000 IU orally once (equivalent to 1785 IU/d) (n = 17), vs. placebo (n = 17)	8 wk	SBP	Change, −7.3 vs. 6.6 mm Hg	Net difference*, −13.9 (−21.2 to −6.6)†; P = 0.001	Fair
								DBP	Change, −2.2 vs. 2.3 mm Hg	Net difference*, −4.5 (−9.4 to 0.4)†; P = 0.08	
Margolis et al, 2008 (32)	United States	Postmenopausal without hypertension	0	ND (50 to 79)	ND	D_3, 400 IU/d, plus calcium carbonate, 1000 mg/d (n = 8597), vs. placebo (n = 8525)	7 y	Hypertension**	Incidence, 5.5% vs. 5.3% (annualized)	HR, 1.01 (0.96 to 1.06); P = 0.69	Good
		Postmenopausal	0	ND (50 to 79)	47.6§	D_3, 400 IU/d, plus calcium carbonate, 1000 mg/d (n = 18 176), vs. placebo (n = 18 106)	7 y	SBP	Change, about −1 mm Hg in both groups	Net difference*, 0.22 (−0.05 to 0.49); P = 0.11	
								DBP	Change, about −4 mm Hg in both groups	Net difference*, 0.11 (−0.04 to 0.27); P = 0.14	
Nagpal et al, 2009 (29)	India	Central obesity	100	44 (≥35)‡	37	D_3, 120 000 IU orally 3 times (equivalent to 8571 IU/d) (n = 35), vs. placebo (n = 36)	6 wk	SBP	Change, 0.6 vs. −3.4 mm Hg	Net difference*, 4.0 (−0.07 to 8.0); P = 0.058	Fair
								DBP	Change, 0.4 vs. −1.3 mm Hg	Net difference*, 1.7 (–1.5 to 4.9); P = 0.31	
Zittermann et al, 2009 (20)	Germany	Healthy, BMI >27 kg/m^2	33	48 (18 to 70)‡	30	D_3, 3332 IU/d (n = 100), vs. placebo (n = 100); all received weight reduction advice for 24 wk	1 y	SBP	Change, −4 vs. −3 mm Hg	Net difference*, −1 (−6 to 4)†; P = 0.66	Good
								DBP	Change, −3 vs. −3 mm Hg	Net difference*, 0 (−3 to 3)†; P = 0.95	
Jorde and Figenschau, 2009 (22)	Norway	Stable type 2 diabetes	50	56 (21 to 75)‡	59	D_3, 40 000 IU/wk (equivalent to 5714 IU/d) (n = 16), vs. placebo (n = 16)	26 wk	SBP	Change, −1.3 vs. −3.6 mm Hg	Net difference*, −4.9 (−13.2 to 3.4)†; P = 0.15	Fair
								DBP	Change, 1.6 vs. 3.2 mm Hg	Net difference*, −1.6 (−7.4 to 4.2)†; P = 0.25	
CVD											
Trivedi et al, 2003 (41)	United Kingdom	Healthy	76	75 (65 to 85)	ND	D_3, 100 000 IU every 4 mo (equivalent to 833 IU/d) (n = 1345), vs. placebo (n = 1341)	5 y	CVD††	Incidence, 35.5% vs. 37.5%	RR, 0.90 (0.77 to 1.06)‡‡; P = 0.22	Fair
Brazier et al, 2005 (42)	France	25(OH)D concentration <30 nmol/L	0	75 (≥65)‡	18	D_3, 800 IU/d, plus calcium carbonate, 1000 mg/d (n = 95), vs. placebo (n = 97)	1 y	Cardiovascular adverse event§§	Incidence, 6.3% vs. 5.2%	RR, 1.21 (0.38 to 3.84); P = 0.74†	Fair

Appendix Table 2—**Continued**

Study, Year (Reference)	Country	Health Status of Participants	Men, %	Mean Baseline Age (Range), *y*	Baseline Mean 25(OH)D Concentration, *nmol/L*	Interventions	Study Duration	Outcome	Effect of Vitamin D Versus Placebo	Net Effect (95% CI); Reported *P* Value	Study Quality
Hsia et al, 2007 (23) and LaCroix et al, 2009 (43)	United States	Postmenopausal	0	62 (50 to 79)	<79	D_3, 400 IU/d, plus calcium carbonate, 1000 mg/d (*n* = 18 176), vs. placebo (*n* = 18 106)	7 y	CHD composite‖ ‖ Stroke or TIA	Incidence, 0.39% vs. 0.37% (annualized) Incidence, 0.28% vs. 0.30% (annualized)	HR, 1.04 (0.92 to 1.18); *P* = 0.50 HR, 1.02 (0.91 to 1.15); *P* = 0.75	Good
Prince et al, 2008 (44)	Australia	Recent fall and 25(OH)D concentration <60 nmol/L	0	77 (70 to 90)	45	D_2, 1000 IU/d (*n* = 151), vs. placebo (*n* = 151); all received calcium citrate, 1000 mg/d	1 y	IHD Stroke	Incidence, 1.3% vs. 2% (annualized) Incidence, 2% vs. 2% (annualized)	RR, 0.67 (0.11 to 3.93); *P* = 0.65† RR, 1.00 (0.21 to 4.88); *P* = 1.0†	Fair

25(OH)D = serum or plasma 25-hydroxyvitamin D; BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; D_2 = ergocalciferol; D_3 = cholecalciferol; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HR = hazard ratio; IHD = ischemic heart disease; ND = no data; SBP = systolic blood pressure; RR = relative risk; TIA = transient ischemic attack.
* Vitamin D minus placebo.
† Estimated from reported data.
‡ Per eligibility criteria.
§ Median.
‖ FPG was measured and analyzed in a random 6% subsample of the entire cohort.
¶ Incident diabetes, self-reported by study participants.
** Incident hypertension, self-reported by study participants.
†† IHD or stroke, self-reported by study participants.
‡‡ Age-adjusted.
§§ Myocardial infarction, stroke, pulmonary edema, and atrial fibrillation (including death from CVD).
‖ ‖ Nonfatal myocardial infarction or fatal CHD; events centrally adjudicated.