REVIEW

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Calcium Intake and Cardiovascular Disease Risk

An Updated Systematic Review and Meta-analysis

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Background: Conflicting evidence exists regarding potential cardiovascular risks associated with high levels of calcium intake.

Purpose: To update and reanalyze 2 systematic reviews to examine the effects of calcium intake on cardiovascular disease (CVD) among generally healthy adults.

Data Sources: MEDLINE; Cochrane Central Register of Controlled Trials; Scopus, including EMBASE; and previous evidence reports from English-language publications from 1966 to July 2016.

Study Selection: Randomized trials and prospective cohort and nested case–control studies with data on dietary or supplemental intake of calcium, with or without vitamin D, and cardiovascular outcomes.

Data Extraction: Study characteristics and results extracted by 1 reviewer were confirmed by a second reviewer. Two raters independently assessed risk of bias.

Data Synthesis: Overall risk of bias was low for the 4 randomized trials (in 10 publications) and moderate for the 27 observational studies included. The trials did not find statistically significant differences in risk for CVD events or mortality between groups receiving supplements of calcium or calcium plus vitamin D and those receiving placebo. Cohort studies showed no consistent dose–response relationships between total, dietary, or supplemental calcium intake levels and cardiovascular mortality and highly inconsistent dose–response relationships between calcium intake and risks for total stroke or stroke mortality.

Limitations: CVD disease outcomes were secondary end points in all trials. Dose–response metaregression analysis of cohort studies was limited by potential confounding, ecological bias, and imprecise measures of calcium exposures. Data were scarce regarding very high calcium intake–that is, beyond recommended tolerable upper intake levels.

Conclusion: Calcium intake within tolerable upper intake levels (2000 to 2500 mg/d) is not associated with CVD risk in generally healthy adults.

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For author affiliations, see end of text.
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Calcium is a nutrient essential for maintaining bone health. A small proportion of total body calcium (less than 1%) also regulates vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion. Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations, enabling normal bone mineralization and preventing hypocalcemic tetany (1).

Although adequate calcium and vitamin D intake is critical for maintaining bone health, the role of calcium and vitamin D supplementation in older adults is unclear. Some systematic reviews showed that combined calcium and vitamin D supplementation reduced the risk for fractures in older adults (2, 3), whereas more recent systematic reviews reported inconsistent effects for fractures across randomized, controlled trials (4, 5). Experts have raised concerns about a potential effect of a high intake of calcium (with or without vitamin D) from foods and supplements on cardiovascular disease (CVD) outcomes (6–8). A meta-analysis of both study- and patient-level data from randomized trials showed that calcium with or without vitamin D supplementation increased the risk for myocardial infarction (pooled relative risk, 1.24 [95% CI, 1.07 to 1.45]) and stroke (pooled relative risk, 1.15 [CI, 1.00 to 1.32]) (9, 10). However, a more recent meta-analysis showed that calcium with or without vitamin D supplementation had no statistically significant effects on coronary heart disease events (pooled relative risk, 1.02 [CI, 0.96 to 1.09]) or mortality (pooled relative risk, 1.04 [CI, 0.88 to 1.21]) (11). Many researchers have questioned the strength of the body of evidence linking supplemental calcium intake with CVD risk, noting that cardiovascular outcomes have not been the primary end point of any trial investigating calcium or calcium and vitamin D supplementation to date (12, 13).

To inform a joint position statement from the National Osteoporosis Foundation (NOF) and American Society for Preventive Cardiology, NOF commissioned a focused update and reanalysis of 2 broader evidence reports examining the effects of calcium and vitamin D on a wide range of clinical and intermediate outcomes (5, 14). This update addresses the effects of calcium intake (from dietary or supplemental sources), alone or in combination with vitamin D, on CVD risk in generally healthy adults.

METHODS

This systematic review implemented the same methodology as the 2009 evidence report examining

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the effects of calcium and vitamin D (alone or in combination) on 17 health outcomes across all life stages that was produced to inform the Institute of Medicine committee charged with updating the dietary reference intake values for calcium and vitamin D (14). In 2014, the Agency for Healthcare Research and Quality commissioned an update of the 2009 evidence report focusing on studies of vitamin D alone or in combination with calcium (5). The effects of calcium intake (from foods or supplements) alone on CVD were not updated in the 2014 evidence report. Methodological details for the reviews were described in a protocol (15).

Data Sources and Searches

MEDLINE, the Cochrane Central Register of Controlled Trials, and Scopus (including EMBASE) were searched from 2009 to July 2016 for prospective cohort or nested case–control (or case–cohort) studies reporting an association between calcium intake (dietary or supplemental) and risk for incident CVD (cardiac, cerebrovascular, or peripheral vascular events and new hypertension), and for randomized, controlled trials on the effect of increasing calcium intake (by food or supplements) on the same outcomes. Analyses of combinations of calcium and micronutrients other than vitamin D that could not isolate the independent effects of calcium with or without vitamin D were not included. Studies or analyses that did not quantify the amount of calcium in the interventions or exposures also were excluded. The literature search strategy was adapted from the 2009 evidence report (14) but focused on calcium exposures and CVD outcomes. Unpublished data were not sought.

Study Selection

Two reviewers performed abstract and full-text screening to identify peer-reviewed, English-language studies of generally healthy adults in which no more than 20% of participants had known CVD. Studies involving participants with hypertension or elderly populations (>60 years of age) were included, whereas those restricted to pregnant women, persons with diabetes, or those receiving dialysis were excluded. Reference lists of relevant systematic reviews were cross-checked with lists of included studies to ensure that no relevant studies were missed. All cardiovascular event or mortality outcomes (defined by the original authors) were included.

Data Extraction and Risk-of-Bias (Quality) Assessment

All extracted data in the 2009 and 2014 evidence reports (5, 14) are accessible to the public on PubMed and PubMed Health. Relevant data in the 2 evidence reports were extracted from their evidence tables (**Appendix** C of the evidence reports) and are included in this update. Data from studies published after the 2 evidence reports were extracted by 1 reviewer and confirmed by at least 1 other using the same data extraction form. The risk of bias in randomized, controlled trials and that of observational studies was assessed separately, with the same assessment tools used in the 2009 and 2014 evidence reports (15). However, to be consistent with the current methodology recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, we did not assign an overall quality grade for each study in this update (16). Two reviewers did the risk-of-bias assessments independently; disagreements were discussed until consensus was reached.

Data Synthesis

We synthesized trials and cohort studies separately but based our conclusions on the total body of evidence. We did not perform a meta-analysis of trial data, because trials reported outcomes with heterogeneous definitions. For cohort studies, we charted dose–response curves by using adjusted results and did dose–response metaregressions if 4 or more studies reported analyses of similar exposure–outcome relationships. If more than 1 analysis model was reported in a study, we focused on the model that adjusted for the most potential confounders. Many cohort studies had several analyses reporting different calcium exposures or cardiovascular outcomes of interest. We planned our dose–response metaregressions carefully to ensure that study populations did not overlap in each analysis.

We performed linear and nonlinear dose–response metaregressions to examine the associations between calcium intake levels and the risk for CVD by using a 2-stage hierarchical regression model, implemented in the *dosresmeta R* package (17, 18). The method, first formalized by Greenland and Longnecker (19), uses estimates of the covariance matrix to account for the within-study correlations across dose levels and incorporates them into the estimation of the linear trend by using generalized least-squares regression. In addition, we applied a method developed by Hamling and colleagues (20) that allowed reconstruction of a table of cell counts ("effective counts") from reported adjusted risk estimates and CIs. We used this method to facilitate dose–response metaregressions and recalculate risk estimates comparing calcium dose categories greater than 1000 mg/d with those less than 1000 mg/d, the recommended dietary allowance for healthy adults (1). See the **Appendix** (available at www.annals.org) for details of these procedures.

Analyses were conducted by using SAS, version 9.3 (SAS Institute), and *R*, version 3.2.5 (R Foundation for Statistical Computing). All *P* values were 2-tailed, and a *P* value less than 0.05 was considered statistically significant.

Role of the Funding Source

This research was supported by an unrestricted educational grant from the NOF through Pfizer Consumer Healthcare. The authors were blind to the corporate funder until the final manuscript was submitted to the NOF. The funder reviewed the evidence synthesis for drafting the position statement but had no role in study selection, quality assessment, data analysis, or writing the manuscript.

RESULTS

Search Results

We included 4 randomized, controlled trials (in 10 publications [10, 21–29]), 1 nested case–control study (30), and 26 cohort studies (29, 31–55). One publication contained data from a randomized trial and a cohort study (29). Appendix Figure 1 (available at www.annals.org) shows the summary of literature searches and study selection flow for this update.

Randomized, Controlled Trials

Two trials (reported in 8 publications) examined the effects of calcium plus vitamin D supplementation (10, 21–26, 29), whereas 3 looked at the effects of calcium supplementation alone (21, 27, 28). Of these 5 trials, 1 (RECORD [Randomised Evaluation of Calcium or Vitamin D]) was a 2 × 2 factorial design of calcium and vitamin D that contributed to both comparisons (calcium vs. placebo, calcium plus vitamin D vs. placebo) (21). Cardiovascular disease outcomes were secondary end points in all trials (Appendix Table 1, available at www.annals.org). The overall risk of bias of the trials was low, although concerns were raised regarding poor adherence to the interventions in all trials (Appendix Table 2, available at www.annals.org). None of the trials reported levels of total calcium intake from dietary and supplemental sources.

Effects of Calcium Plus Vitamin D Supplementation

Overall, 2 trials (WHI [Women's Health Initiative] and RECORD) found no statistically significant differences in risk for CVD events or mortality (except for 2 subgroup analyses) between groups receiving calcium (1000 mg/d) plus vitamin D (400 or 800 IU/d) supplements and those receiving placebo. Individual trial results are shown in Appendix Table 3 (available at www.annals.org).

Several publications analyzed data from the WHI trial (10, 22–26, 29), which randomly assigned 36 282 postmenopausal U.S. women (aged 50 to 79 years) to receive either 1000 mg of calcium plus 400 IU of vitamin D_3 daily or placebo. Six reports examined CVD outcomes at the end of 7 years of supplementation (10, 23–26, 29), and 1 report (22) included CVD outcomes 5 and 12 years after intervention. Outcomes reported in these articles included myocardial infarction, coronary heart disease events or mortality, total heart disease, total CVD, CVD mortality, cerebrovascular death, coronary artery bypass grafting or percutaneous coronary intervention, confirmed angina, hospitalized heart failure, stroke (ischemic, hemorrhagic, or other), transient ischemic attack, and heart failure. Several publications reported post hoc subgroup analyses comparing effects in women using calcium supplements during the trial with those in women not using these supplements, across various age groups or between groups with low and high baseline CVD risk. Only 2 subgroup analyses revealed statistically significant differences between groups. One showed that use of personal calcium supplements altered the effect of calcium and vitamin D on CVD (10). In postmenopausal women receiving calcium supplements, the hazard ratios with calcium and vitamin D were 1.13 to 1.22 for CVD end points. In contrast, among those not taking supplements, the hazard ratios were 0.83 to 1.08. The other subgroup analysis found a lower risk for heart failure with calcium and vitamin D supplementation in postmenopausal women without preexisting heart failure precursors at baseline (hazard ratio, 0.63 [CI, 0.46 to 0.87]) but no statistically significant effect of supplementation in those with heart failure precursors and conditions (hazard ratio, 1.06 [CI, 0.90 to 1.24]) (Appendix Table 3) (23). The RECORD trial examined the effects of 3 years of daily supplementation with 1000 mg of calcium, 800 IU of vitamin D_3, or both on CVD deaths and cerebrovascular disease deaths among 5292 patients (85% female and older than 70 years) recruited from fracture clinics or orthopedic wards in England and Scotland (21). Calcium plus vitamin D supplementation had no statistically significant effect on all vascular disease deaths compared with placebo (risk ratio, 0.99 [CI, 0.82 to 1.20]).

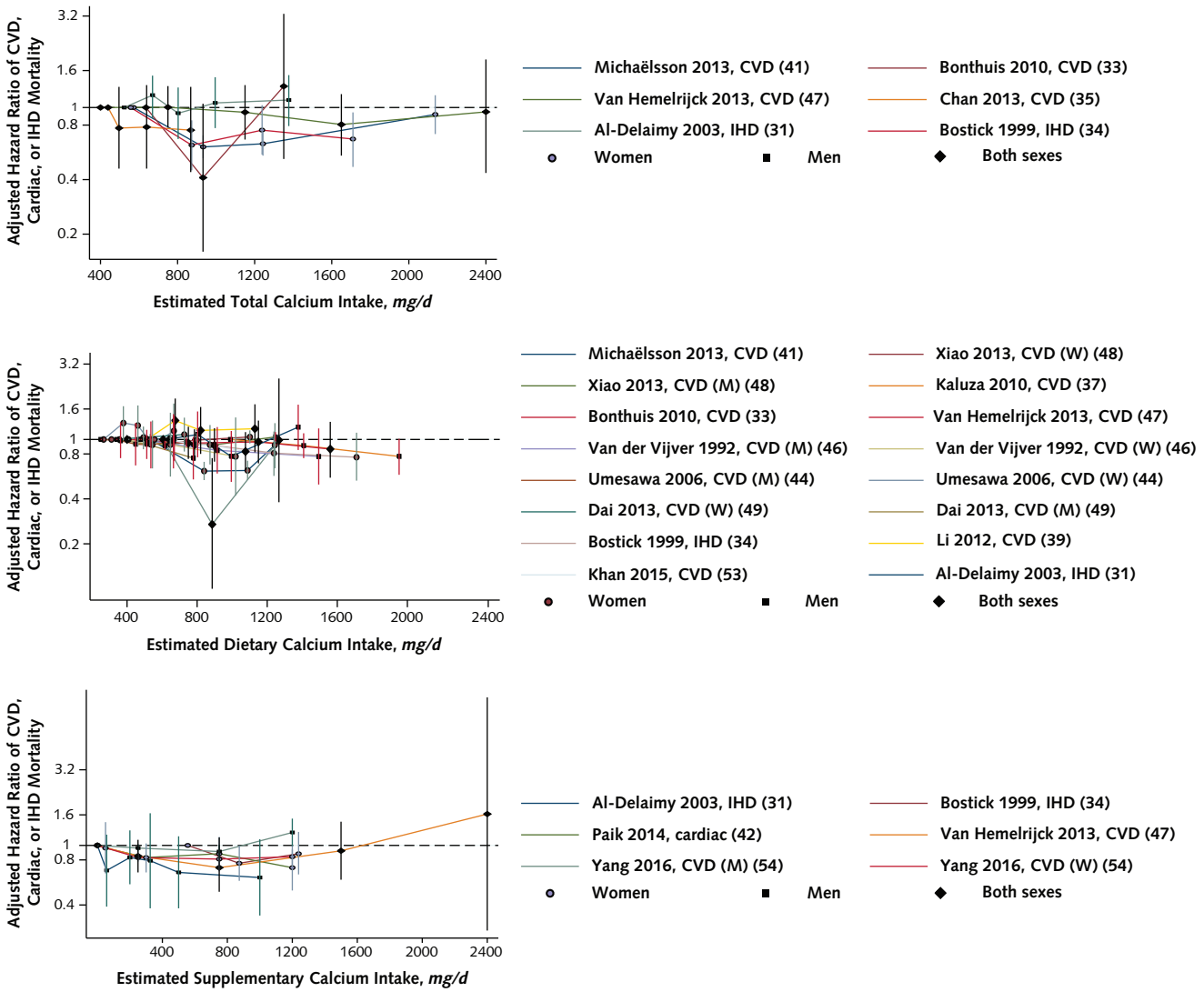
Effects of Calcium Supplementation

Three trials examined the effects of supplementation with calcium alone (doses ranging from 1000 to 1200 mg/d) on various CVD outcomes (21, 27, 28). CAIFOS (Calcium Intake Fracture Outcome Study) from Western Australia examined the effects of 1200 mg of calcium carbonate daily for 5 years on risks for atherosclerotic vascular disease among 1460 elderly women (older than 70 years) recruited from the general population (27). The Auckland calcium study randomly assigned 1471 postmenopausal women (older than 55 years) to receive 5 years of daily supplementation with 1000 mg of calcium citrate or placebo and examined the outcomes of myocardial infarction and stroke 5 years after intervention (28). The RECORD trial (described earlier) reported the effects of calcium supplementation alone on cardiovascular and cerebrovascular deaths (21). None of the studies found a statistically significant effect of calcium supplementation on CVD outcomes (hazard ratios, 0.82 to 1.43) (Appendix Table 3).

Prospective Cohort and Nested Case–Control Studies

Twenty-six cohort studies and 1 nested case–control study examined the relationships between calcium intake levels (from foods or supplements) and the risks for CVD outcomes among adults living in the United States (29, 31, 32, 34, 36, 42, 47, 48, 51, 52, 54), Europe (37–41, 43, 46, 55), Asia (30, 35, 44, 45, 49, 50), and Australia (33, 53). Of these investigations, 3 were conducted in the Nurses' Health Study (36, 42, 52) and 3 in the Health Professionals Follow-up Study (31, 32, 51) cohorts and 2 were done in the Swedish Mammography Cohort (41, 55). No overlaps occurred among other study populations. No study evaluated the interaction between calcium and vitamin D intake in relation to CVD outcomes. The baseline ages ranged from 17 to

Figure 1. Results of 15 cohort studies examining the relationships between total (6 studies [*top*]), dietary (12 studies [*middle*]), or supplemental (5 studies [*bottom*]) calcium intake and the risks for CVD, cardiac, or IHD mortality.



CVD = cardiovascular disease; IHD = ischemic heart disease; M = men; W = women.

99 years, and 2 cohorts exclusively enrolled individual persons older than 60 years (35, 40). Cohort sample sizes ranged from 755 to 388 229, and follow-up ranged from 8 to 30 years (**Appendix Table 4**, available at www.annals.org). Calcium intake was assessed by food-frequency questionnaires in all but 2 cohorts (40, 47). Most studies reported CVD mortality outcomes, assessed by death certificates, International Classification of Diseases codes, medical records, or self-report.

A wide variety of CVD outcomes was reported across the 27 studies, some of which analyzed different sources of calcium separately (**Supplement 1**, available at www.annals.org). The risk of bias of individual studies ranged from low to moderate (**Appendix Table 5**, available at www.annals.org). All studies reported at least 1 analysis of association between calcium intake levels and CVD mortality or stroke.

Relationships Between Calcium Intake Levels and Risks for CVD Mortality

Fifteen studies reported mortality risks (31, 33–35, 37, 39, 41, 42, 44, 46–49, 53, 54). Individual study results are presented in **Figure 1**, which shows analyses examining the associations between total (foods and supplements [*top*]), dietary (foods only [*middle*]), and supplemental (supplements only [*bottom*]) calcium intake levels and the risks for CVD, cardiac, or ischemic heart disease mortality. Total calcium intake levels ranged from 400 to 2400 mg/d, but few data points existed beyond 1600 mg/d. Overall, no consistent dose–response relationships were seen between calcium intake levels and risks for CVD, cardiac, or ischemic heart disease mortality. Overall risk of bias for these studies was moderate, primarily because they did

Table. Results of 2-Stage, Hierarchical Random-Effects Model Dose–Response Metaregressions of Prospective Cohort Studies

Models	Mean Calcium Intake, *mg/d*	Analyses, *n*	Studies, *n*	Follow-up, *y*	Dose Variable: per 100-mg/d Increase in Calcium Intake	Pooled Adjusted Hazard Ratio (95% CI)	*P* Value	I^2, %	*P* Value for Cochran *Q* Test
Dietary calcium intake and CVD/IHD mortality									
Linear model	250–2000	15	11	8–28	Dose	0.99 (0.97–1.00)	0.06	55	0.0055
Quadratic model	250–2000	15	11	8–28	Dose	0.91 (0.84–1.00)	0.14	70	<0.0001
	–	–	–	–	$Dose^2$	1.00 (0.99–1.01)	–	–	–
Total calcium intake and CVD/IHD mortality									
Linear model	400–2400	6	6	8–19	Dose	0.99 (0.97–1.01)	0.31	6.6	0.37
Quadratic model	400–2400	6	6	8–19	Dose	0.89 (0.80–0.98)	0.08	53	0.02
	–	–	–	–	$Dose^2$	1.00 (0.99–1.01)	–	–	–
Dietary or total calcium intake and stroke mortality									
Linear model	250–2200	8	5	8.9–19.0	Dose	1.00 (0.82–1.01)	0.68	23	0.27
Quadratic model	250–2200	8	5	8.9–19.0	Dose	0.97 (0.90–1.05)	0.71	35	0.09
	–	–	–	–	$Dose^2$	1.00 (0.99–1.01)	–	–	–
Dietary or total calcium intake and total stroke									
Linear model	200–2000	8	8	8.0–13.6	Dose	0.99 (0.97–1.01)	0.18	75	0.0003
Quadratic model	200–2000	8	8	8.0–13.6	Dose	0.93 (0.84–1.04)	0.49	52	0.01
	–	–	–	–	$Dose^2$	1.00 (0.99–1.01)	–	–	–

CVD = cardiovascular disease; IHD = ischemic heart disease.

not justify the final statistical models, designate primary outcomes, or report dietary assessment methods completely (Appendix Figure 2, *A* through *C*, available at www.annals.org). Dose–response metaregressions did not detect statistically significant linear or nonlinear relationships between levels of dietary (n = 11) or total (n = 6) calcium intake and the risk for CVD or ischemic heart disease mortality (Table).

Of the 15 studies, 12 reported data that allowed reanalysis using the effective counts to estimate the risk for CVD mortality, comparing calcium intake levels above with those below 1000 mg/d (reference group) (Figure 2). Three studies not included in the reanalysis were done in Asian countries (35, 44, 49); the highest intake levels in these cohorts were less than 1000 mg/d. Overall, the studies showed inconsistent results. Although most results did not reach statistical significance, 1 study (48) showed that dietary calcium intake levels greater than 1000 mg/d (reported mean calcium intake levels in quintile 5 was 1247 mg/d for men and 1101 mg/d for women) were associated with a higher risk for CVD mortality (adjusted hazard ratio, 1.06 [CI, 1.00 to 1.14] for women; adjusted hazard ratio, 1.10 [CI, 1.04 to 1.16] for men). This study also found that supplemental calcium intake (≥1000 mg/d) was associated with an elevated risk for CVD mortality compared with no supplemental intake (adjusted relative risk, 1.20 [CI, 1.05 to 1.36]) and that total calcium intake had a U-shaped association with total CVD mortality in men but not in women. The increased CVD mortality in men was observed at calcium intakes of 1500 mg/d and greater (48). Another study (54) showed that supplemental calcium intake of more than 1000 mg/d was associated with an increase in CVD mortality in men (adjusted relative risk, 1.24 [CI, 1.00 to 1.53]) but a decreased risk in women (adjusted relative risk, 0.92 [CI, 0.82 to 1.03]). In contrast, the Nurses' Health Study I found lower risks for CVD events or mortality among women who took more than 1000 mg of calcium supplements daily compared with those who did not take calcium supplements (adjusted relative risk, 0.82 [CI, 0.74 to 0.92]) (42).

Relationships Between Calcium Intake Levels and Risks for Stroke

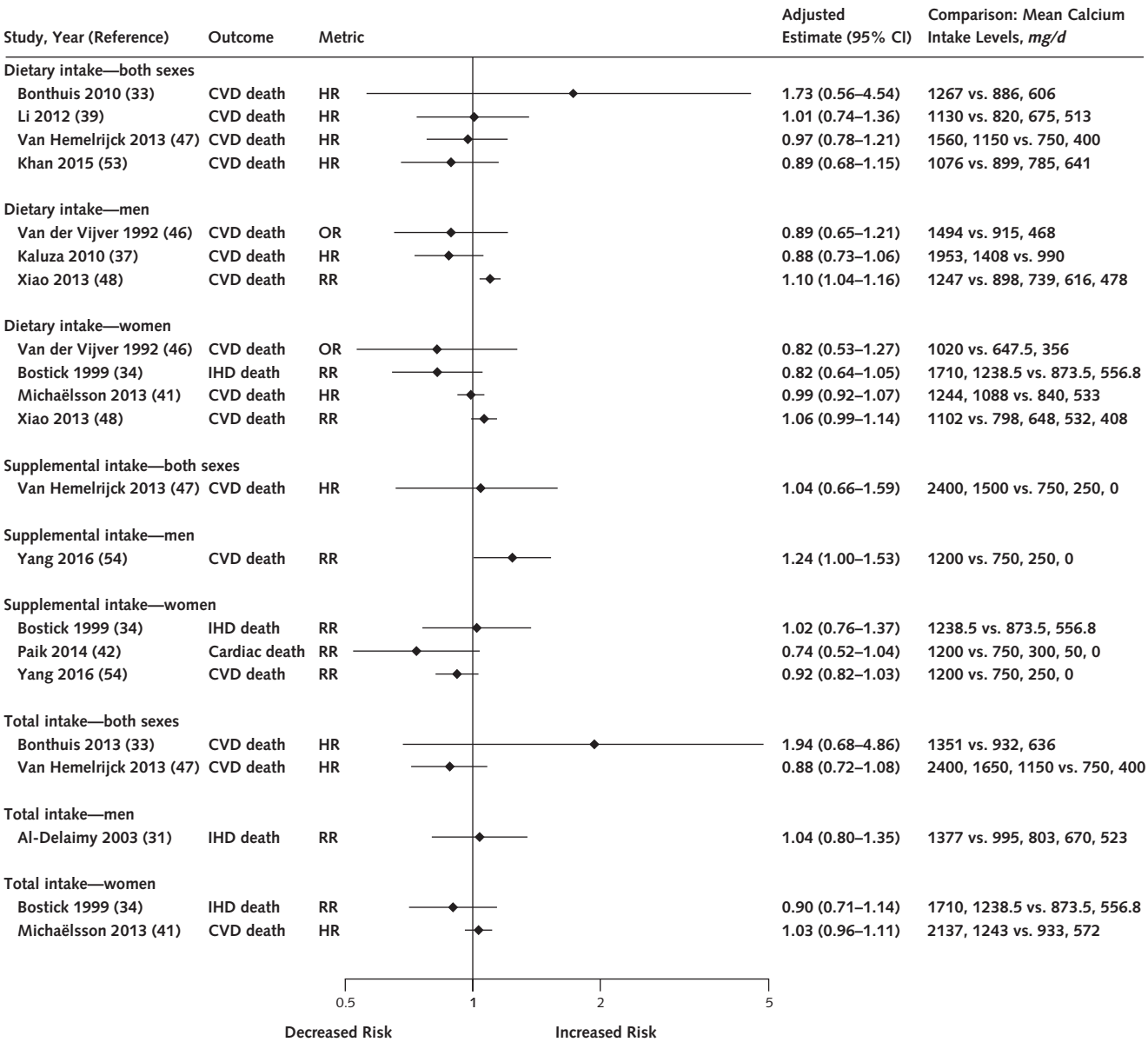
Twenty cohort studies assessed the association between calcium intake and stroke risk (29, 30, 32, 36, 39–41, 43–45, 47–55). Individual study results, shown in Figure 3, display analyses examining the associations between dietary or total calcium intake levels and the risks for total stroke (*top*) and stroke mortality (*bottom*). Total calcium intake levels ranged from 200 to 2400 mg/d, and very few data points extended beyond 1600 mg/d. The dose–response relationships between calcium intake levels and risks for total stroke or stroke mortality were highly inconsistent, with some studies showing opposite trends for total stroke risk. The inconsistencies could not be explained by the sex of the study populations. Risk of bias of these studies was moderate, primarily because they did not justify the final statistical models, designate which outcomes were

primary, or report dietary assessment methods completely (Appendix Figure 2, *D* and *E*). Dose–response metaregression analyses did not find statistically significant linear or nonlinear relationships between levels of dietary or total calcium intake and the risk for total stroke (n = 8) or stroke mortality (n = 5) (Table).

Nine studies contributed data to the reanalysis by using the effective counts to estimate the risks for stroke mortality (3 studies) or total stroke (6 studies), comparing calcium intake levels above with those below 1000 mg/d (reference group). Although the results were inconsistent (Figure 4), 2 studies showed that a dietary calcium intake level greater than 1000 mg/d was associated with an increase in total stroke risk in men (adjusted relative risk, 1.09 [CI, 0.99 to 1.21]) (38) and women (adjusted relative risk, 1.13 [CI, 1.02 to 1.26]) (55).

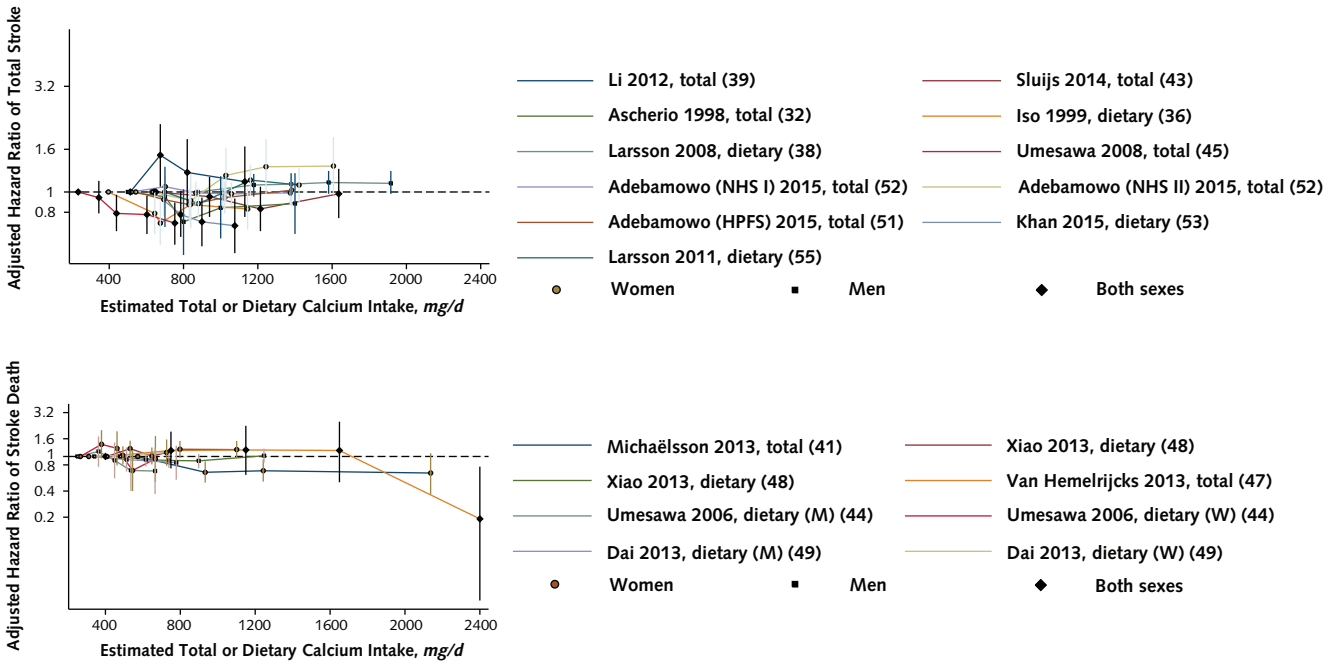
Data from 5 studies were not sufficient for plotting the dose–response relationships between calcium intake level and risk for stroke (29, 30, 40, 50, 54). Two of these studies reported only analyses of the association between supplemental calcium intake and the risk for stroke (29) or stroke mortality (54) compared with no calcium supplement intake. Neither study (the overall risk of bias was low) found statistically significant associations in men or women (adjusted relative risk, 0.80 to

Figure 2. Reanalysis of 12 cohort studies to examine the risks for CVD, cardiac, or IHD mortality, comparing calcium intake levels 1000 mg/d or greater with those less than 1000 mg/d.



CVD = cardiovascular disease; HR = hazard ratio; IHD = ischemic heart disease; OR = odds ratio; RR = relative risk.

Figure 3. Results of 15 cohort studies examining the relationships between dietary or total calcium intake and the risks for total stroke (10 studies [*top*]) and stroke mortality (5 studies [*bottom*]).



HPFS = Health Professionals Follow-up Study; M = men; NHS = Nurses' Health Study; W = women.

1.03). None of the other 3 cohort studies (2 in Asia [30, 50] and 1 in Finland [40]) showed statistically significant associations between dietary calcium intake levels and the risks for stroke events or mortality in men or women (30, 40, 50). However, these studies had small sample sizes (755 to 1772) and the overall risk of bias was moderate, primarily because of incomplete data reporting regarding calcium intake levels, dietary assessment methods, and inadequate justification of final statistical models.

DISCUSSION

On the basis of our assessments of internal validity, precision of risk estimates, and consistency of results from randomized trials and prospective cohort studies, we conclude that calcium intake (from either food or supplement sources) at levels within the recommended tolerable upper intake range (2000 to 2500 mg/d) are not associated with CVD risks in generally healthy adults. Although a few trials and cohort studies reported increased risks with higher calcium intake, risk estimates in most of those studies were small (±10% relative risk) and not considered clinically important, even if they were statistically significant.

The mechanisms by which high calcium intake might alter the risk for CVD or stroke among generally healthy adults are unclear. Very high calcium intake is difficult if not impossible to achieve by dietary sources alone. Therefore, the concerns regarding potential adverse cardiovascular risks are related to the use of calcium supplements, which has been associated with increased risk for kidney stones in postmenopausal women (56). Vascular calcification is 1 proposed mechanism for CVD events observed in trials of calcium supplements (9), but available data about calcification of vascular tissues associated with calcium supplementation are derived from persons with impaired renal function (57–59), not from the general population.

Our updated literature search identified several systematic reviews on the same topic, but none synthesized both trials and observational studies. Our findings are consistent with a recent meta-analysis of trials (11) and a meta-analysis of prospective cohort and nested case–control studies (60). However, they are inconsistent with those of several earlier meta-analyses of trials (9, 10) and cohort studies (61–63). Differences in the data synthesis methods may account for the apparent discordant results and conclusions. Earlier meta-analyses of trials did not appraise the risk of bias; some combined trials of calcium supplements used alone with those of calcium plus vitamin D supplements. All 3 earlier meta-analyses of cohort studies (61–63) reported a nonlinear dose–response relationship between calcium intake levels and stroke risks. The dose–response metaregression methods were unclear in 2 of the meta-analyses (62, 63), and results likely were incorrect because of limitations of the statistical package (*glst* command) for dose–response meta-analysis implemented in Stata (64). As Liu and colleagues (18) pointed out, *glst* does not provide solutions for pooling studies with different reference exposure doses, which is the case in all the dose–response meta-analyses of

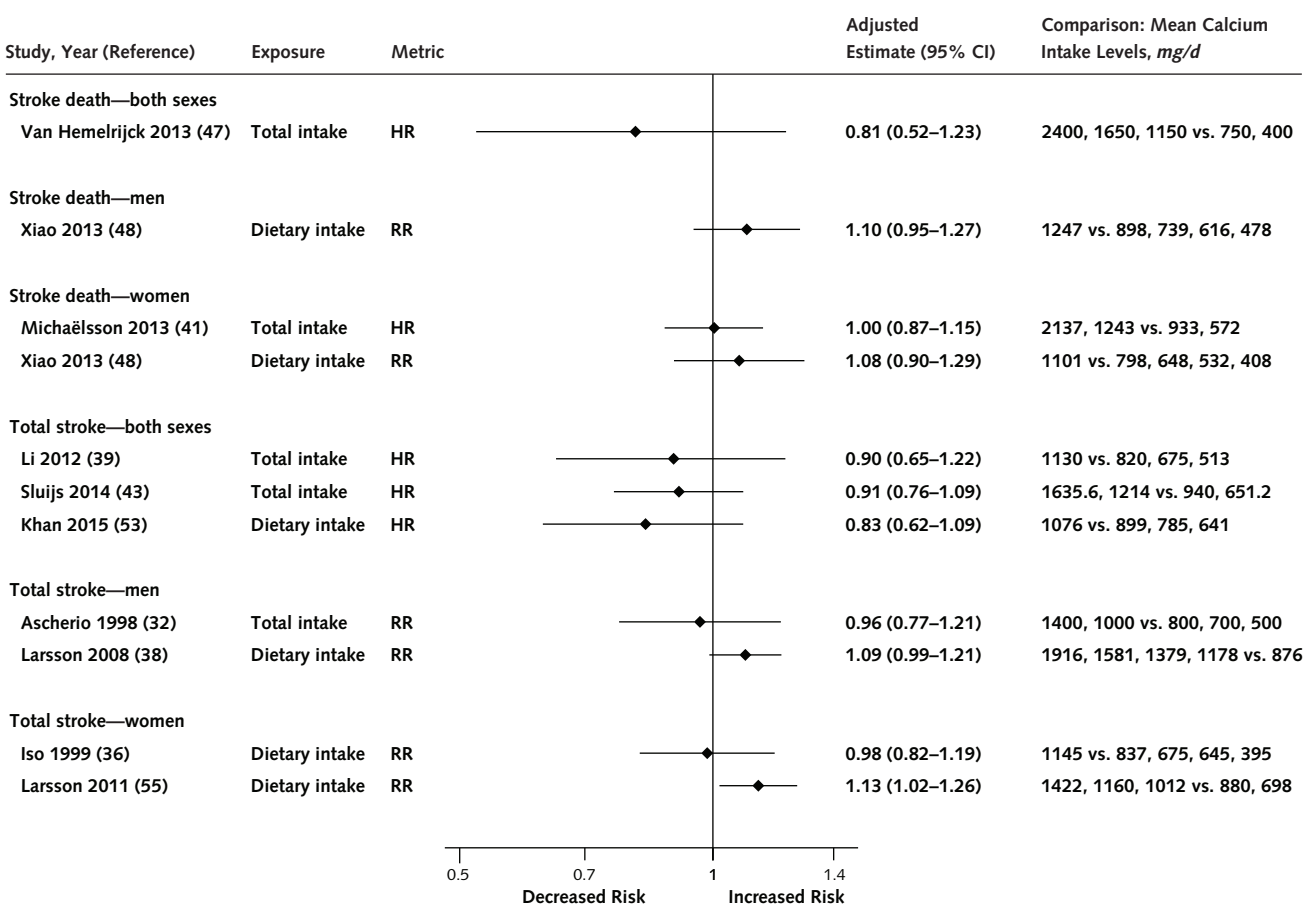
calcium intake and cardiovascular risk. Three meta-analyses of observational studies (60, 62, 63) also included "high-versus-low" or extreme-quantile meta-analyses, which produced uninterpretable pooled results, because the ranges of highest and lowest quantile categories of calcium intake varied substantially across studies. An empirical evaluation of meta-analytic approaches for nutrient and health outcome dose–response data discouraged those that use only data from extreme exposure categories, because the results typically are biased away from the null (65).

Our systematic review and meta-analyses had several limitations. We included only English-language publications; thus, language and publication bias cannot be ruled out. To date, data beyond the tolerable upper intake levels are lacking; thus, the CVD risks at very high calcium intake levels are uncertain. Our metaregressions of cohort studies had moderate risk of bias, potential residual confounding, ecological bias, and imprecise measurement of calcium exposures limited interpretations of data. Ascertainment of total calcium intake levels from foods and supplements was not well-estimated in trials because of adherence issues and was limited by the use of food-frequency questionnaires for assessing dietary exposures in observational studies. Lastly, because different cohort studies adjusted for different sets of confounders, using the risk estimates that adjusted for the most factors in the meta-analyses assumed that the different adjustments across studies would not affect the meta-analytic results—an assumption that we cannot verify without conducting simulation studies.

We believe a trial with sufficient statistical power to detect small differences in adverse cardiovascular outcomes is unlikely to be done. Our search on ClinicalTrials.gov (9 August 2016) identified no ongoing trials designed specifically to address this research question. We recommend future prospective population-based cohort studies that assess total, dietary, and supplemental calcium intake by using validated dietary assessment methodology; ascertain chronic disease outcomes by using standardized outcome measures; and use prospectively developed study protocols, power calculations, and analysis plans.

Systematic review and meta-analysis play an important role in evidence-based medicine. Apparently con-

Figure 4. Reanalysis of 10 cohort studies to examine the risks for total stroke or stroke mortality, comparing calcium intake levels 1000 mg/d or greater with those less than 1000 mg/d.



HR = hazard ratio; RR = relative risk.

flicting conclusions across several meta-analyses of the same topic may cause uncertainty in the health care community and confusion among the general public. To increase transparency, reduce research waste, minimize potential biases, and facilitate updating evidence-based information and its translation to practice or policy, we recommend that all data from systematic reviews and meta-analyses be made publicly available. Our systematic review, which synthesizes data from trials and cohort studies, has implications for a new evidence-based approach (66, 67) to establish dietary reference intake values that include chronic disease and long-term outcomes, for which direct evidence from randomized trials often is lacking. In the absence of direct evidence from trials, synthesis of large population-based cohort studies may improve the strength of evidence and provide complementary data for clinical or policy decision making.

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Reproducible Research Statement: *Study protocol:* Available from Agency for Healthcare Research and Quality (https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1529). *Statistical code:* See **Appendix** (available at www.annals.org). *Data set:* See Supplements (available at www.annals.org).

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References

1. **Institute of Medicine.** Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Pr; 2011.
2. **Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, et al.** Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess (Full Rep). 2007:1-235. [PMID: 18088161]
3. **Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA.** Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155:827-38. [PMID: 22184690] doi:10.7326/0003-4819-155-12-201112200-00005
4. **Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al.** Calcium intake and risk of fracture: systematic review. BMJ. 2015;351:h4580. [PMID: 26420387] doi:10.1136/bmj.h4580
5. **Newberry SJ, Chung M, Shekelle PG, Booth MS, Liu JL, Maher AR, et al.** Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update). Rockville: Agency for Healthcare Research and Quality; 2014.
6. **Paziana K, Pazianas M.** Calcium supplements controversy in osteoporosis: a physiological mechanism supporting cardiovascular adverse effects. Endocrine. 2015;48:776-8. [PMID: 25687221] doi:10.1007/s12020-015-0550-9
7. **Chrysant SG, Chrysant GS.** Controversy regarding the association of high calcium intake and increased risk for cardiovascular disease [Editorial]. J Clin Hypertens (Greenwich). 2014;16:545-50. [PMID: 24890035] doi:10.1111/jch.12347
8. **Silver DS.** Calcium and vitamin D controversies. Rheum Dis Clin North Am. 2011;37:351-63. [PMID: 22023896] doi:10.1016/j.rdc.2011.07.005
9. **Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al.** Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691. [PMID: 20671013] doi:10.1136/bmj.c3691
10. **Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR.** Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040. [PMID: 21505219] doi:10.1136/bmj.d2040
11. **Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, et al.** The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res. 2015;30:165-75. [PMID: 25042841] doi:10.1002/jbmr.2311
12. **Wang L, Manson JE, Sesso HD.** Calcium intake and risk of cardiovascular disease: a review of prospective studies and randomized clinical trials. Am J Cardiovasc Drugs. 2012;12:105-16. [PMID: 22283597] doi:10.2165/11595400-000000000-00000
13. **Heaney RP, Kopecky S, Maki KC, Hathcock J, Mackay D, Wallace TC.** A review of calcium supplements and cardiovascular disease risk. Adv Nutr. 2012;3:763-71. [PMID: 23153730] doi:10.3945/an.112.002899
14. **Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, et al.** Vitamin D and calcium: a systematic review of health outcomes. Evid Rep Technol Assess (Full Rep). 2009:1-420. [PMID: 20629479]
15. **Agency for Healthcare Research and Quality.** Evidence-based Practice Center Systematic Review Protocol. Project Title: Vitamin D and Calcium: A Systematic Review of Health Outcomes. 2013. Accessed at https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1529 on 6 September 2016.
16. **Higgins JPT, Green S, eds.** Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. March 2011. Accessed at http://handbook.cochrane.org on 6 September 2016.
17. **Crippa A, Orsini N.** Multivariate dose-response meta-analysis: the dosresmeta R package. J Stat Softw. 2016;72:1-15.
18. **Liu Q, Cook NR, Bergström A, Hsieh CC.** A two-stage hierarchical regression model for meta-analysis of epidemiologic nonlinear dose–response data. Comput Stat Data Anal. 2009;53:4157-67.
19. **Greenland S, Longnecker MP.** Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301-9. [PMID: 1626547]
20. **Hamling J, Lee P, Weitkunat R, Ambühl M.** Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med. 2008;27:954-70. [PMID: 17676579]
21. **Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, et al; RECORD Trial Group.** Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab. 2012;97:614-22. [PMID: 22112804] doi:10.1210/jc.2011-1309
22. **Cauley JA, Chlebowski RT, Wactawski-Wende J, Robbins JA, Rodabough RJ, Chen Z, et al.** Calcium plus vitamin D supplementa-

tion and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health (Larchmt). 2013;22: 915-29. [PMID: 24131320] doi:10.1089/jwh.2013.4270
23. **Donneyong MM, Hornung CA, Taylor KC, Baumgartner RN, Myers JA, Eaton CB, et al.** Risk of heart failure among postmenopausal women: a secondary analysis of the randomized trial of vitamin D plus calcium of the Women's Health Initiative. Circ Heart Fail. 2015; 8:49-56. [PMID: 25398967] doi:10.1161/CIRCHEARTFAILURE.114 .001738
24. **Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al; Women's Health Initiative Investigators.** Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115:846-54. [PMID: 17309935]
25. **LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, et al.** Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2009;64:559-67. [PMID: 19221190] doi:10.1093/gerona/ glp006
26. **Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al.** Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013;24:567-80. [PMID: 23208074] doi:10.1007/s00198-012-2224-2
27. **Lewis JR, Calver J, Zhu K, Flicker L, Prince RL.** Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res. 2011;26:35-41. [PMID: 20614474] doi:10.1002/jbmr.176
28. **Radford LT, Bolland MJ, Mason B, Horne A, Gamble GD, Grey A, et al.** The Auckland calcium study: 5-year post-trial follow-up. Osteoporos Int. 2014;25:297-304. [PMID: 24114400] doi:10.1007/s00198-013-2526-z
29. **Bolland MJ, Grey A, Gamble GD, Reid IR.** Concordance of results from randomized and observational analyses within the same study: a re-analysis of the Women's Health Initiative limited-access dataset. PLoS One. 2015;10:e0139975. [PMID: 26440516] doi:10.1371/journal .pone.0139975
30. **Ross RK, Yuan JM, Henderson BE, Park J, Gao YT, Yu MC.** Prospective evaluation of dietary and other predictors of fatal stroke in Shanghai, China. Circulation. 1997;96:50-5. [PMID: 9236416]
31. **Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB.** A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr. 2003;77: 814-8. [PMID: 12663277]
32. **Ascherio A, Rimm EB, Hernán MA, Giovannucci EL, Kawachi I, Stampfer MJ, et al.** Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation. 1998;98:1198-204. [PMID: 9743511]
33. **Bonthuis M, Hughes MC, Ibiebele TI, Green AC, van der Pols JC.** Dairy consumption and patterns of mortality of Australian adults. Eur J Clin Nutr. 2010;64:569-77. [PMID: 20372173] doi:10.1038/ejcn.2010 .45
34. **Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR.** Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol. 1999;149:151-61. [PMID: 9921960]
35. **Chan R, Leung J, Woo J.** A prospective cohort study examining the associations of dietary calcium intake with all-cause and cardiovascular mortality in older Chinese community-dwelling people. PLoS One. 2013;8:e80895. [PMID: 24224062] doi:10.1371/journal .pone.0080895
36. **Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, et al.** Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke. 1999;30:1772-9. [PMID: 10471422]
37. **Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, Wolk A.** Dietary calcium and magnesium intake and mortality: a prospective study of men. Am J Epidemiol. 2010;171:801-7. [PMID: 20172919] doi:10.1093/aje/kwp467
38. **Larsson SC, Virtanen MJ, Mars M, Männistö S, Pietinen P, Albanes D, et al.** Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. Arch Intern Med. 2008;168:459-65. [PMID: 18332289] doi:10.1001/archinte.168.5.459
39. **Li K, Kaaks R, Linseisen J, Rohrmann S.** Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart. 2012;98:920-5. [PMID: 22626900] doi:10.1136/heartjnl-2011-301345
40. **Marniemi J, Alanen E, Impivaara O, Seppänen R, Hakala P, Rajala T, et al.** Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. Nutr Metab Cardiovasc Dis. 2005;15:188-97. [PMID: 15955467]
41. **Michaëlsson K, Melhus H, Warensjö Lemming E, Wolk A, Byberg L.** Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346:f228. [PMID: 23403980] doi:10.1136/bmj.f228
42. **Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, et al.** Calcium supplement intake and risk of cardiovascular disease in women. Osteoporos Int. 2014;25:2047-56. [PMID: 24803331] doi: 10.1007/s00198-014-2732-3
43. **Sluijs I, Czernichow S, Beulens JW, Boer JM, van der Schouw YT, Verschuren WM, et al.** Intakes of potassium, magnesium, and calcium and risk of stroke. Stroke. 2014;45:1148-50. [PMID: 24519410] doi:10.1161/STROKEAHA.113.004032
44. **Umesawa M, Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, et al.** Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. Stroke. 2006;37:20-6. [PMID: 16339476]
45. **Umesawa M, Iso H, Ishihara J, Saito I, Kokubo Y, Inoue M, et al; JPHC Study Group.** Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. Stroke. 2008;39:2449-56. [PMID: 18635855] doi:10.1161/ STROKEAHA.107.512236
46. **Van der Vijver LP, van der Waal MA, Weterings KG, Dekker JM, Schouten EG, Kok FJ.** Calcium intake and 28-year cardiovascular and coronary heart disease mortality in Dutch civil servants. Int J Epidemiol. 1992;21:36-9. [PMID: 1544755]
47. **Van Hemelrijck M, Michaelsson K, Linseisen J, Rohrmann S.** Calcium intake and serum concentration in relation to risk of cardiovascular death in NHANES III. PLoS One. 2013;8:e61037. [PMID: 23593383] doi:10.1371/journal.pone.0061037
48. **Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y.** Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA Intern Med. 2013;173:639-46. [PMID: 23381719] doi: 10.1001/jamainternmed.2013.3283
49. **Dai Q, Shu XO, Deng X, Xiang YB, Li H, Yang G, et al.** Modifying effect of calcium/magnesium intake ratio and mortality: a population-based cohort study. BMJ Open. 2013;3. [PMID: 23430595] doi:10.1136/bmjopen-2012-002111
50. **Weng LC, Yeh WT, Bai CH, Chen HJ, Chuang SY, Chang HY, et al.** Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? Stroke. 2008;39:3152-8. [PMID: 18988909] doi:10.1161/STROKEAHA.108.524934
51. **Adebamowo SN, Spiegelman D, Flint AJ, Willett WC, Rexrode KM.** Intakes of magnesium, potassium, and calcium and the risk of stroke among men. Int J Stroke. 2015;10:1093-100. [PMID: 26044278] doi:10.1111/ijs.12516
52. **Adebamowo SN, Spiegelman D, Willett WC, Rexrode KM.** Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. Am J Clin Nutr. 2015;101:1269-77. [PMID: 25948665] doi:10.3945/ ajcn.114.100354
53. **Khan B, Nowson CA, Daly RM, English DR, Hodge AM, Giles GG, et al.** Higher dietary calcium intakes are associated with reduced risks of fractures, cardiovascular events, and mortality: a prospective cohort study of older men and women. J Bone Miner Res. 2015;30: 1758-66. [PMID: 25828852] doi:10.1002/jbmr.2515

54. **Yang B, Campbell PT, Gapstur SM, Jacobs EJ, Bostick RM, Fedirko V, et al.** Calcium intake and mortality from all causes, cancer, and cardiovascular disease: the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr. 2016;103:886-94. [PMID: 26864361] doi:10.3945/ajcn.115.117994
55. **Larsson SC, Virtamo J, Wolk A.** Potassium, calcium, and magnesium intakes and risk of stroke in women. Am J Epidemiol. 2011;174:35-43. [PMID: 21540318] doi:10.1093/aje/kwr051
56. **Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al; Women's Health Initiative Investigators.** Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669-83. [PMID: 16481635]
57. **Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, et al.** Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrol Dial Transplant. 2005;20:1653-61. [PMID: 15930018]
58. **Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al.** Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005;68:1815-24. [PMID: 16164659]
59. **Cozzolino M, Brancaccio D, Gallieni M, Slatopolsky E.** Pathogenesis of vascular calcification in chronic kidney disease. Kidney Int. 2005;68:429-36. [PMID: 16014020]
60. **Asemi Z, Saneei P, Sabihi SS, Feizi A, Esmaillzadeh A.** Total, dietary, and supplemental calcium intake and mortality from all-causes, cardiovascular disease, and cancer: a meta-analysis of observational studies. Nutr Metab Cardiovasc Dis. 2015;25:623-34. [PMID: 25912278] doi:10.1016/j.numecd.2015.03.008
61. **Larsson SC, Orsini N, Wolk A.** Dietary calcium intake and risk of stroke: a dose-response meta-analysis. Am J Clin Nutr. 2013;97:951-7. [PMID: 23553167] doi:10.3945/ajcn.112.052449
62. **Tian DY, Tian J, Shi CH, Song B, Wu J, Ji Y, et al.** Calcium intake and the risk of stroke: an up-dated meta-analysis of prospective studies. Asia Pac J Clin Nutr. 2015;24:245-52. [PMID: 26078241] doi:10.6133/apjcn.2015.24.2.22
63. **Wang X, Chen H, Ouyang Y, Liu J, Zhao G, Bao W, et al.** Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies. BMC Med. 2014;12:158. [PMID: 25252963] doi:10.1186/s12916-014-0158-6
64. **Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D.** Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2012;175:66-73. [PMID: 22135359] doi:10.1093/aje/kwr265
65. **Yu WW, Schmid CH, Lichtenstein AH, Lau J, Trikalinos TA.** Empirical evaluation of meta-analytic approaches for nutrient and health outcome dose-response data. Res Synth Methods. 2013;4:256-68. [PMID: 25379059]
66. **Chung M, Balk EM, Ip S, Lee J, Terasawa T, Raman G, et al.** Systematic review to support the development of nutrient reference intake values: challenges and solutions. Am J Clin Nutr. 2010;92:273-6. [PMID: 20504974] doi:10.3945/ajcn.2009.29092
67. **Taylor C.** Framework for DRI Development: Components "Known" and Components "To Be Explored." Washington, DC: National Academies Pr; 2008.

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Appendix: Technical Details

Dose–Response Metaregressions

Liu and colleagues (18) described how to use a 2-stage hierarchical metaregression model to estimate the summarized linear and nonlinear dose–response relationship. The model has been implemented in the *dosresmeta R* package (17). The aim of the first-stage analysis is to estimate for each study the (same) dose–response association between the adjusted log-relative risks and exposure levels, as described previously by Greenland and Longnecker (19). Their approach is based on constructing an approximate covariance estimate for the adjusted log-odds, -rate, or -risk ratios from a fitted table that conforms to the adjusted log-risk estimates and matches the crude 2 × 2 table margins. In the present analysis, an alternative approach was used. The method by Hamling and colleagues (20) was followed to get estimated cell counts, then the approach of Greenland and Longnecker was used to obtain covariance estimates and the weighted least-squares estimates. In the second-stage analysis, the study-specific estimates are combined by using the extension of the generalized least-squares method with restricted maximum likelihood estimation to fit the dose–response curves, as described by Berkey and colleagues (68).

To estimate study-specific linear trends, several approximations were made: The reported mean or the midpoint of calcium intake in each category was assigned to the corresponding relative risk. For the open categories, a mean of calcium intake was imputed that was 20% lower for the lowest category threshold or 20% higher for the highest category threshold. If the distributions of person-years or noncases were not provided but analyzed based on quantiles, they were divided equally across the quantiles. For studies that did not use the lowest category of calcium intake as the reference, the method by Hamling and colleagues (20) was used to estimate new relative risks and 95% CIs, setting the lowest category as the new reference. The Hamling group's method is described later in more detail.

Liu and colleagues (18) further described in detail how to construct the design matrix. As the dose-specific relative risks are estimated as contrasts to their reference exposure, the design matrices must be constructed similarly. In the *dosresmeta* function, this process is done internally by the default option center = TRUE. The argument is particularly important if the reference exposure levels vary across studies or for nonzero reference exposures. In addition, the dose–response model typically does not include the intercept, because the log-relative risk is 0 by definition for the referent value. Nonlinearity was investigated by adopting quadratic models. Statistical heterogeneity was tested using the Cochran Q statistic (considered significant if $P < 0.10$), and the extent of heterogeneity was quantified with the I^2 index.

The *R* codes used to perform linear and nonlinear dose–response metaregressions are described in **Appendix Table 6** (available at www.annals.org). The same models are used to analyze the dose–response relationships between calcium intake levels and risks for CVD mortality or for stroke events or mortality. Analytic datasets for the dose–response metaregressions in **Table 1** are in **Supplements 2 to 5** (available at www.annals.org). Two "dose" variables for the mean or the midpoint of calcium intake in each category are provided in the Supplements. The variable "dose2" is for sensitivity analysis.

Sensitivity analysis was performed to test the robustness of our dose–response metaregressions by changing the imputed mean of calcium intake for the open categories from 20% to 30% lower or higher for the lowest or highest category, respectively. The results shown in **Table 1** were not changed.

Reanalysis Using the Effective Counts

Hamling and colleagues (20) described a method to estimate cell counts—namely the effective counts—of the 2 × 2 table adjusted for confounding, then to estimate the asymptotic correlation between the adjusted log-risk estimates for each exposure level relative to the referent level, from which we can obtain the estimated covariance matrix for these study-specific estimates. The Hamling group's method has been implemented in SAS (available at www.pnlee.co.uk/Software.htm [accessed on 6 September 2016]). These calculations were done study by study, and the effective counts are recorded in **Supplement 1**.

Importantly, effective counts are assumed to be consistent with the risk estimate, 95% CI, and control

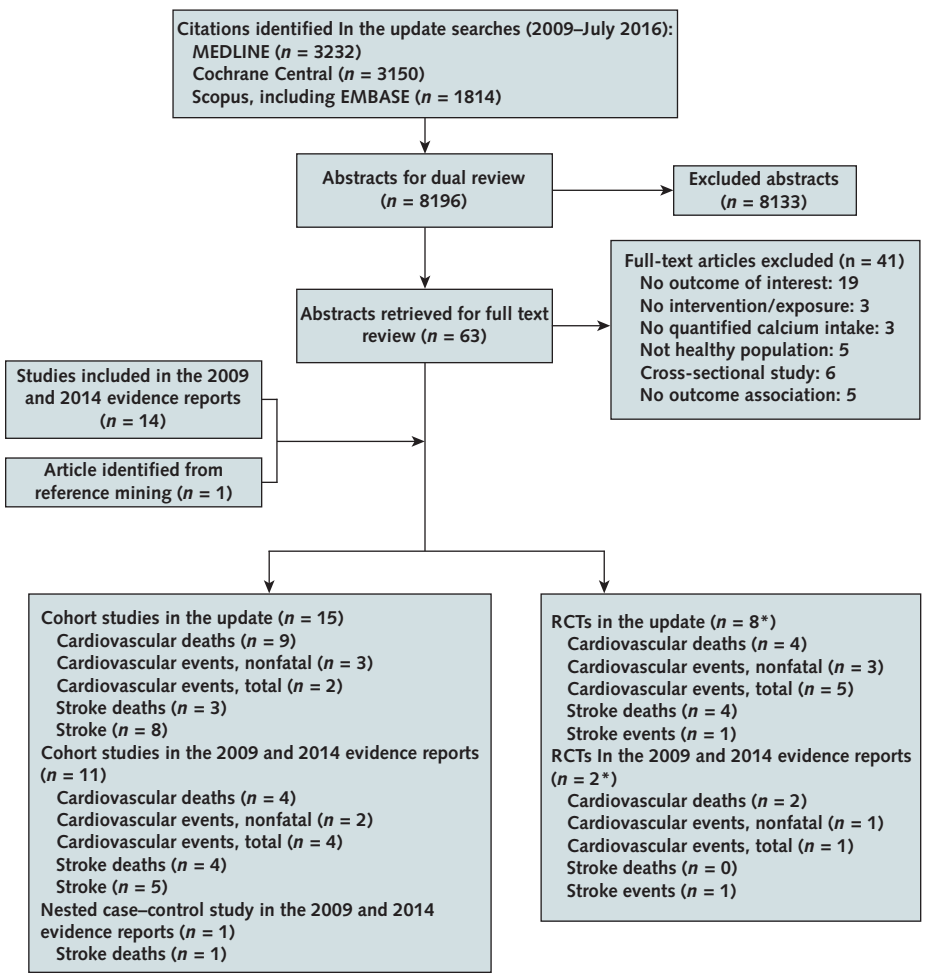
rates observed in the individual studies, but the data generated are neither synonymous with nor equivalent to the actual data. These estimates are simply devices used to estimate the underlying, unknown, variance–covariance matrix, which improves model fit and provides better estimates for the SEs and CIs. The numbers themselves have little or no substantive meaning.

For the reanalysis to obtain the risk estimate comparing calcium intake levels above with levels below the recommended daily allowance, we regrouped the exposure categories on the basis of the mean dose value (1000 mg/d or greater vs. less than 1000 mg/d) and calculated adjusted relative risk and its CI by using a 2 × 2 table of the effective counts of events and people at risk in each study. The contrast function also is available in the SAS codes.

Web-Only Reference

68. Berkey CS, Hoaglin DC, Antczak-Bouckoms A, Mosteller F, Colditz GA. Meta-analysis of multiple outcomes by regression with random effects. Stat Med. 1998;17:2537-50. [PMID: 9839346]

Appendix Figure 1. Summary of evidence searches and study selection flow.



Cardiovascular death includes death from ischemic heart disease, myocardial infarction, coronary heart disease, and any cardiovascular death. RCTs = randomized, controlled trials.
* Total of 4 unique RCTs in 10 publications.

Appendix Table 1. Characteristics of Randomized, Controlled Trials Examining the Effects of Calcium With or Without Vitamin D Supplementation on CVD Outcomes

Study, Year (Reference)	Location	Study Name	Baseline Health Status	Total Participants Analyzed, *n*	Female, %	Baseline Mean Age (SD or Range), *y*	Mean Body Mass Index, kg/m^2 (SD)	Intervention Groups	Interventions (Calcium or Vitamin D Daily Dose)	Duration of Intervention	Total Follow-up, *y*	Funding Source	Primary/ Secondary Outcome	Outcome Assessments
CaD														
Avenell et al, 2012 (21)	England and Scotland	RECORD trial*	With fracture	5292	85	77 (SD, 6)	ND	Vitamin D vs. calcium vs. CaD vs. placebo	Calcium group: 1000 mg elemental calcium CaD group: 800 IU vitamin D D3, 1000 mg elemental calcium	24-62 mo	3 y	Government; profit	Secondary: CVD deaths	ICD codes
Bolland et al, 2011 (10)	United States	WHI	Any	36 282	100	62 (range, 50–79)	29 (6)	CaD vs. placebo, by personal calcium use	1000 mg elemental calcium, 400 IU vitamin D D3	7 y	7 y	Government	Secondary: CVD events: nonfatal, total, total stroke	Medical history
Bolland et al, 2015 (29)	United States	WHI CaD trial	Any	15 646†	100	CaD: 62.8 (SD, 7.0) Placebo: 62.9 (SD, 7.0)	ND	CaD vs. placebo	1000 mg elemental calcium, 400 IU vitamin D D3	7.2 y	7.2 y	Government; nonprofit	Secondary: CVD event; stroke total, death	Medical records
Cauley et al, 2013 (22)	United States	WHI	Any	29 862	100	ND (range, 50–79)	ND	CaD vs. placebo	1000 mg elemental calcium, 400 IU vitamin D D3	7 y	11.1 y	Government	Secondary: CVD deaths, total events, total stroke	Medical records
Donneyong et al, 2015 (23)	United States	WHI	No HF	35 983	100	ND (range, 50–79)	ND	CaD vs. placebo	1000 mg elemental calcium, 400 IU vitamin D D3	7 y	7 y	Government	Secondary: CVD nonfatal events	Medical records
Hsia et al, 2007 (24)	United States	WHI	Any	36 282	100	62 (range, 50–79)	29 (6)	CaD vs. placebo	1000 mg elemental calcium, 400 IU vitamin D D3	7 y	7 y	Government	Secondary: CVD deaths, CVD nonfatal events, total stroke	Medical records
LaCroix et al, 2009 (25)	United States	WHI	Any	36 282	100	62 (range, 50–79)	29.0 (5.9)	CaD vs. placebo	1000 mg elemental calcium, 400 IU vitamin D D3	7 y	7 y	Government	Secondary: CVD deaths, stroke death	Medical records, autopsy reports, death certificates
Prentice et al, 2013 (26)	United States	WHI	No cancer	36 282	100	ND (range, 50–79)	ND	CaD vs. placebo	1000 mg elemental calcium, 400 IU vitamin D D3	7.2 y	7.2 y	Government	Secondary: CVD deaths, total events, total stroke	Medical records
Calcium alone														
Lewis et al, 2011 (27)	Australia	CAIFOS	Any	1460	0	ND (SD, >70)	ND	Calcium vs. placebo	1200 mg calcium carbonate	5 y	9.5 y	Government; nonprofit	Secondary‡: CVD deaths CVD event: nonfatal, total	ICD codes
Radford et al, 2014 (28)	New Zealand	Auckland calcium study	Any	1408	0	ND	ND	Calcium vs. placebo	1000 mg calcium citrate	5 y	9.1 y	Government; nonprofit	Secondary: CVD nonfatal events, stroke total	ICD codes

CaD = calcium plus vitamin D supplements; CAIFOS = Calcium Intake Fracture Outcome Study; CVD = cardiovascular disease; HF = heart failure; ICD = International Classification of Diseases; ND = no data; RECORD = Randomised Evaluation of Calcium or Vitamin D; WHI = Women's Health Initiative.

* Contributed to both comparisons (calcium vs. placebo and CaD vs. placebo). The vitamin D vs. placebo results are not included in this systematic review.

† The analyses used a subgroup of women not using personal calcium or vitamin D supplement in the WHI trial.

‡ The primary outcome was a composite outcome defined as an atherosclerotic event causing either death or hospitalization, including CVD deaths and events.

Appendix Table 2. Risk-of-Bias Assessment, Background Calcium Intake Levels, and Adherence in the Included Randomized, Controlled Trials

Study, Year (Reference)	Location	Study Name	Appropriate Randomization Technique	Allocation Concealment	Dropout Rate <20%	Blinded Outcome Assessment	Intention-to-Treat Analysis	Appropriate Statistical Analysis	Assessment for Confounding	Clear Reporting With No Discrepancies	Mean Background Calcium Intake (SD), *mg/d*	Adherence to the Interventions
Calcium plus vitamin D												
Avenell et al, 2012 (21)	England and Scotland	RECORD trial*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CaD: 818 (355) Vitamin D only: 813 (359) Calcium only: 814 (336) Placebo: 834 (861)	Adherence was measured by 4 monthly postal questionnaires asking participants how many days of the past 7 they took tablets. A random 10% sample returned unconsumed tablets for pill counting. Among those returning questionnaires (or after assuming nonresponders were nonadherent), the rates of pill takers were 67% (54%) at 12 mo and 63% (45%) at 24 mo.
Bolland et al, 2011 (10)	United States	WHI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Among participants with no personal calcium or vitamin D use– CaD: 801 (491) Placebo: 790 (470) Among participants with personal calcium or vitamin use– CaD: 828 (454) Placebo: 832 (455)	Not reported
Bolland et al, 2015 (29)	United States	WHI CaD trial	Yes	No data	Yes	No data	Yes	Yes	No	Yes	Personal, nonprotocol supplemental calcium intake– CaD: 0 (0) Placebo: 0 (0) Dietary calcium intake– CaD: 801(491) Placebo: 790 (470)	Not reported
Cauley et al, 2013 (22)	United States	WHI	Yes	Yes	Yes	Yes	No data	Yes	Yes	Yes	Not reported	Not reported
Donneyong et al, 2015 (23)	United States	WHI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HF subgroup: 811.07 (697.16) No HF subgroup: 875.04 (724.15)	23 601 of 35 983 women with >80% adherence to protocol
Hsia et al, 2007 (24)	United States	WHI	No data	No data	Yes	Yes	No data	Yes	Yes	Yes	CaD: 1148 (654) Placebo: 1154 (658)	60% of study participants took at least 80% of their study medication through year 6.
LaCroix et al, 2009 (25)	United States	WHI	Yes	No data	Yes	No data	Yes	Yes	Yes	Yes	CaD: 1148 (654) Placebo: 1154 (658)	97% of participants were followed to study completion. At trial closure, 76% of women enrolled were still taking study medications and 59% were taking at least 80% of study pills.
Prentice et al, 2013 (26)	United States	WHI	Yes	Yes	Yes	No data	Yes	Yes	Yes	Yes	Not reported	Not reported
Calcium alone												
Lewis et al, 2011 (27)	Australia	CAIFOS	Yes	Yes	Yes	No data	Yes	Yes	Yes	Yes	Calcium: 961 (356) Placebo: 970 (352)	The per-protocol group consisted of participants with ≥80% tablet adherence, resulting in an overall tablet adherence of 56.8% for the 5-y study.
Radford et al, 2014 (28)	New Zealand	The Auckland calcium study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Calcium: 865 (392) Placebo: 854 (382)	Calcium: adherence 55% Placebo: adherence 58%

CaD = calcium plus vitamin D supplements; CAIFOS = Calcium Intake Fracture Outcome Study; HF = heart failure; RECORD = Randomised Evaluation of Calcium or Vitamin D; WHI = Women's Health Initiative.

* Contributed to both comparisons (calcium vs. placebo and CaD vs. placebo). The vitamin D vs. placebo results are not included in this systematic review.

Appendix Table 3. Results From the 10 Randomized, Controlled Trial Publications Examining the Effects of Calcium With or Without Vitamin D Supplementation on CVD

Intervention Group, by Study, Year (Reference) [Location]; Study Name	Intervention Participants, *n*	Control Group	Control Participants, *n*	Subgroups	Outcomes	Follow-up Duration, *y*	Events, *n*		Metric	Estimate	95% Lower CI	95% Upper CI
							Intervention Group	Control Group				
Avenell et al, 2012 (21) [England and Scotland]; RECORD trial*												
Calcium (calcium; vitamin D + calcium)	2617	No calcium (vitamin D; placebo)	2675	Adjusted treatment-received analysis	All vascular disease deaths	3	371	355	HR	1.43	0.75	7.61
Calcium (calcium; vitamin D + calcium)	2617	No calcium (vitamin D; placebo)	2675	ITT analysis	All vascular disease deaths	3	371	355	HR	1.07	0.92	1.24
Calcium	1311	Placebo	1332	NA	All vascular disease deaths total	3	194	182	cRR	1.08	0.90	1.31
Calcium	1311	Placebo	1332	NA	Cardiovascular	3	91	85	cRR	1.09	0.82	1.45
Calcium	1311	Placebo	1332	NA	Cerebrovascular	3	54	51	cRR	1.08	0.74	1.57
Calcium	1311	Placebo	1332	NA	Other vascular disease deaths	3	49	46	cRR	1.08	0.73	1.61
CaD	1306	Placebo	1332	NA	All vascular disease deaths total	3	177	182	cRR	0.99	0.82	1.20
CaD	1306	Placebo	1332	NA	Cardiovascular	3	88	85	cRR	1.06	0.79	1.41
CaD	1306	Placebo	1332	NA	Cerebrovascular	3	56	51	cRR	1.12	0.77	1.62
CaD	1306	Placebo	1332	NA	Other vascular disease deaths	3	33	46	cRR	0.73	0.47	1.14
Bolland et al, 2011 (10) [United States]; WHI												
CaD	8429	Placebo	8289	No personal use of calcium supplements	Total MI	7	222†	182†	HR	1.20	0.99	1.47
CaD	9747	Placebo	9817	Any personal use of calcium	Total MI	7	193†	207†	HR	0.94	0.77	1.14
CaD	8429	Placebo	8289	No personal use of calcium supplements	Total MI or CHD death	7	268†	229†	HR	1.15	0.97	1.38
CaD	9747	Placebo	9817	Any personal use of calcium	Total MI or CHD death	7	238†	247†	HR	0.97	0.81	1.16
CaD	8429	Placebo	8289	No personal use of calcium supplements	Stroke	7	196†	163†	HR	1.17	0.95	1.44
CaD	9747	Placebo	9817	Any personal use of calcium	Stroke	7	156†	189†	HR	0.83	0.67	1.02
CaD	8429	Placebo	8289	No personal use of calcium supplements	Clinical MI or revascularization	7	442†	359†	HR	1.16	1.01	1.34
CaD	9747	Placebo	9817	Any personal use of calcium	Clinical MI or revascularization	7	394†	378†	HR	1.06	0.92	1.23
Bolland et al, 2015 (29) [United States]; WHI CaD trial												
CaD	7891	Placebo	7755	No personal calcium or vitamin D	MI	7 y	191	157	HR	1.2	0.97	1.48
CaD	7891	Placebo	7755	No personal calcium or vitamin D	Stroke	7 y	182	154	HR	1.15	0.93	1.43
CaD	18 176	Placebo	18 106	Entire cohort	MI	7 y	389	364	HR	1.06	0.92	1.23
CaD	18 176	Placebo	18 106	Entire cohort	Stroke	7 y	352	352	HR	0.99	0.85	1.15
Cauley et al, 2013 (22) [United States]; WHI												
CaD	15 025	Placebo	14 837	Intervention	CHD	7	518	488	HR	1.06	0.94	1.20
CaD	15 025	Placebo	14 837	Postintervention	CHD	4.9	374	372	HR	0.99	0.86	1.14
CaD	15 025	Placebo	14 837	Overall	CHD	11.9	877	845	HR	1.03	0.94	1.13
CaD	15 025	Placebo	14 837	Intervention	CHD death	7	139	139	HR	1.00	0.79	1.26
CaD	15 025	Placebo	14 837	Postintervention	CHD death	4.9	129	126	HR	1.00	0.78	1.28
CaD	15 025	Placebo	14 837	Overall	CHD death	11.9	268	265	HR	0.99	0.84	1.18
CaD	15 025	Placebo	14 837	Intervention	Clinical MI	7	393	366	HR	1.08	0.93	1.24
CaD	15 025	Placebo	14 837	Postintervention	Clinical MI	4.9	266	271	HR	0.97	0.08	1.15
CaD	15 025	Placebo	14 837	Overall	Clinical MI	11.9	659	637	HR	1.03	0.92	1.15
CaD	15 025	Placebo	14 837	Intervention	Stroke	7	371	372	HR	1.00	0.86	1.15
CaD	15 025	Placebo	14 837	Postintervention	Stroke	4.9	319	287	HR	1.10	0.94	1.29
CaD	15 025	Placebo	14 837	Overall	Stroke	11.9	690	659	HR	1.04	0.93	1.16

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Appendix Table 3–Continued

Intervention Group, by Study, Year (Reference) [Location]; Study Name	Intervention Participants, *n*	Control Group	Control Participants, *n*	Subgroups	Outcomes	Follow-up Duration, *y*	Events, *n*		Metric	Estimate	95% Lower CI	95% Upper CI
							Intervention Group	Control Group				
CaD	15 025	Placebo	14 837	Intervention	CVD death	7	240	255	HR	0.94	0.78	1.12
CaD	15 025	Placebo	14 837	Postintervention	CVD death	4.9	309	270	HR	1.14	0.97	1.34
CaD	15 025	Placebo	14 837	Overall	CVD death	11.9	549	525	HR	1.03	0.92	1.17
CaD	5729	Placebo	5602	Age 50–59 y	CHD	11.9	155	149	HR	1.01	0.81	1.27
CaD	6924	Placebo	6883	Age 60–69 y	CHD	11.9	409	413	HR	0.99	0.86	1.13
CaD	2372	Placebo	2352	Age 70–79 y	CHD	11.9	313	283	HR	1.10	0.94	1.30
CaD	5729	Placebo	5602	Age 50–59 y	Stroke	11.9	117	106	HR	1.08	0.83	1.31
CaD	6924	Placebo	6883	Age 60–69 y	Stroke	11.9	318	307	HR	1.03	0.88	1.21
CaD	2372	Placebo	2352	Age 70–79 y	Stroke	11.9	255	246	HR	1.02	0.86	1.22
CaD	5538	Placebo	5348	Vitamin D <200 mg/d	CHD	11.9	399	338	HR	0.96	0.82	1.11
CaD	2765	Placebo	2830	Vitamin D 200 to <400 mg/d	CHD	11.9	142	166	HR	0.86	0.69	1.08
CaD	3498	Placebo	3567	Vitamin D 400 to <600 mg/d	CHD	11.9	213	184	HR	1.19	0.98	1.46
CaD	2955	Placebo	2845	Vitamin D ≥600 mg/d	CHD	11.9	159	136	HR	1.13	0.90	1.43
CaD	5538	Placebo	5348	Vitamin D <200 mg/d	Stroke	11.9	242	227	HR	1.03	0.86	1.24
CaD	2765	Placebo	2830	Vitamin D 200 to <400 mg/d	Stroke	11.9	128	127	HR	1.08	0.84	1.38
CaD	3498	Placebo	3567	Vitamin D 400 to <600 mg/d	Stroke	11.9	174	153	HR	1.18	0.95	1.47
CaD	2955	Placebo	2845	Vitamin D ≥600 mg/d	Stroke	11.9	130	132	HR	0.97	0.76	1.24
CaD	8678	Placebo	8662	No personal use of calcium supplements	CHD	11.9	453	415	HR	1.08	0.95	1.23
CaD	6347	Placebo	6175	Personal use of calcium supplements	CHD	11.9	424	430	HR	0.99	0.86	1.13
CaD	8678	Placebo	8662	No personal use of calcium supplements	CHD death	11.9	130	136	HR	0.95	0.75	1.22
CaD	6347	Placebo	6175	Personal use of calcium supplements	CHD death	11.9	138	129	HR	1.03	0.81	1.32
CaD	8678	Placebo	8662	No personal use of calcium supplements	Clinical MI	11.9	347	309	HR	1.11	0.95	1.29
CaD	6347	Placebo	6175	Personal use of calcium supplements	Clinical MI	11.9	312	328	HR	0.96	0.82	1.12
CaD	8678	Placebo	8662	No personal use of calcium supplements	Stroke	11.9	340	305	HR	1.11	0.95	1.30
CaD	6347	Placebo	6175	Personal use of calcium supplements	Stroke	11.9	350	354	HR	0.99	0.85	1.15
CaD	8678	Placebo	8662	No personal use of calcium supplements	CVD death	11.9	262	257	HR	1.00	0.84	1.19
CaD	6347	Placebo	6175	Personal use of calcium supplements	CVD death	11.9	287	268	HR	1.06	0.90	1.25
Donneyong et al, 2015 (23) [United States]; WHI												
CaD	18 534	Placebo	17 449	Total–ITT	HF	7.1	363	381	HR	0.95	0.82	1.09
CaD	9307	Placebo	9227	Low-risk group–ITT	HF	7.1	302	285	HR	0.63	0.46	0.87
CaD	8716	Placebo	8733	High-risk group–ITT	HF	7.1	61	96	HR	1.06	0.90	1.24
CaD	11 608	Placebo	11 993	Total–PP	HF	7.1	188	190	HR	1.02	0.84	1.25
CaD	6186	Placebo	6320	Low-risk group–PP	HF	7.1	30	51	HR	0.60	0.38	0.94
CaD	5422	Placebo	5673	High-risk group–PP	HF	7.1	158	139	HR	1.19	0.95	1.49
Hsia et al, 2007 (24) [United States]; WHI												
CaD	18 176	Placebo	18 106	NA	MI	7	441	390	HR	1.05	0.91	1.20
CaD	18 176	Placebo	18 106	NA	CHD death	7	130	128	HR	1.01	0.79	1.29
CaD	18 176	Placebo	18 106	NA	MI or CHD death	7	499	475	HR	1.04	0.92	1.18
CaD	18 176	Placebo	18 106	NA	CABG or PCI	7	674	607	HR	1.09	0.98	1.22

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Appendix Table 3–Continued

Intervention Group, by Study, Year (Reference) [Location]; Study Name	Intervention Participants, *n*	Control Group	Control Participants, *n*	Subgroups	Outcomes	Follow-up Duration, *y*	Events, *n*		Metric	Estimate	95% Lower CI	95% Upper CI
							Intervention Group	Control Group				
CaD	18 176	Placebo	18 106	NA	MI/CHD death/CABG/PCI	7	920	841	HR	1.08	0.99	1.19
CaD	18 176	Placebo	18 106	NA	Angina	7	404	377	HR	1.08	0.94	1.24
CaD	18 176	Placebo	18 106	NA	Hospitalized heart failure	7	394	407	HR	0.95	0.83	1.10
CaD	18 176	Placebo	18 106	NA	Stroke	7	362	377	HR	0.95	0.82	1.10
CaD	18 176	Placebo	18 106	NA	Stroke–ischemic stroke	7	225	228	HR	0.98	0.82	1.18
CaD	18 176	Placebo	18 106	NA	Stroke–hemorrhagic stroke	7	58	68	HR	0.84	0.59	1.19
CaD	18 176	Placebo	18 106	NA	Stroke–other stroke	7	63	57	HR	1.11	0.77	1.59
CaD	18 176	Placebo	18 106	NA	Transient ischemic attack	7	213	182	HR	1.16	0.95	1.42
CaD	18 176	Placebo	18 106	NA	Stroke/transient ischemic attack	7	563	547	HR	1.02	0.91	1.15
LaCroix et al, 2009 (25) [United States]; WHI												
CaD	18 176	Placebo	18 106	Total	CVD death	7	226	244	HR	0.92	0.77	1.10
CaD	18 176	Placebo	18 106	Total	CHD death	7	130	128	HR	1.01	0.79	1.29
CaD	18 176	Placebo	18 106	Total	Cerebrovascular death	7	54	60	HR	0.89	0.62	1.29
CaD	15 003	Placebo	14 939	Younger than 70 y	CVD death	7.1	115	135	HR	0.85	0.66	1.08
CaD	15 003	Placebo	14 939	Younger than 70 y	CHD death	7.1	70	70	HR	0.99	0.71	1.38
CaD	15 003	Placebo	14 939	Younger than 70 y	Cerebrovascular death	7.1	21	33	HR	0.62	0.36	1.08
CaD	3173	Placebo	3167	70 y or older	CVD death	6.9	111	109	HR	1.01	0.78	1.32
CaD	3173	Placebo	3167	70 y or older	CHD death	6.9	60	58	HR	1.02	0.71	1.47
CaD	3173	Placebo	3167	70 y or older	Cerebrovascular death	6.9	33	27	HR	1.20	0.72	2.01
Prentice et al, 2013 (26) [United States]; WHI												
CaD	18 176	Placebo	18 106	All participants	MI	7.2	411	390	HR	1.03	0.09	1.19
CaD	18 176	Placebo	18 106	All participants	CHD	7.2	499	475	HR	1.03	0.09	1.17
CaD	18 176	Placebo	18 106	All participants	Total heart disease	7.2	1405	1363	HR	1.02	0.95	1.11
CaD	18 176	Placebo	18 106	All participants	Stroke	7.2	362	377	HR	0.10	0.92	1.10
CaD	18 176	Placebo	18 106	All participants	Total CVD	7.2	1832	1810	HR	1.00	0.94	1.07
CaD	7718	Placebo	7584	No personal supplements	MI	7.2	433	193	HR	1.11	0.90	1.37
CaD	7718	Placebo	7584	No personal supplements	CHD	7.2	545	229	HR	1.03	0.09	1.25
CaD	7718	Placebo	7584	No personal supplements	Total heart disease	7.2	1602	621	HR	1.02	0.91	1.14
CaD	7718	Placebo	7584	No personal supplements	Stroke	7.2	471	184	HR	1.12	0.90	1.39
CaD	7718	Placebo	7584	No personal supplements	Total CVD	7.2	2187	848	HR	1.03	0.93	1.13
Lewis et al, 2011 (27) [Australia]; CAIFOS												
Calcium	730	Placebo	730	Entire follow-up–ITT	Total vascular hospitalization and deaths	9.5	195	200	HR	0.92	0.74	1.15
Calcium	730	Placebo	730	Posttrial period–ITT	Total vascular hospitalization and deaths	5	104	103	HR	0.94	0.69	1.28
Calcium	420	Placebo	410	Entire follow-up–PP	Total vascular hospitalization and deaths	9.5	195	200	HR	0.95	0.70	1.30
Calcium	420	Placebo	410	Posttrial period–PP	Total vascular hospitalization and deaths	9.5	49	48	HR	1.05	0.68	1.63
Calcium	730	Placebo	730	Entire follow-up	Total vascular deaths	9.5	59	72	cRR	0.82	0.59	1.14
Calcium	730	Placebo	730	Posttrial period	Total vascular deaths	5	18	24	cRR	0.75	0.41	1.37
Calcium	730	Placebo	730	Entire follow-up	Deaths due to IHD	9.5	34	36	cRR	0.94	0.60	1.49
Calcium	730	Placebo	730	Posttrial period	Deaths due to IHD	5	13	9	cRR	1.44	0.62	3.36
Calcium	730	Placebo	730	Entire follow-up	Deaths due to arrhythmia	9.5	10	16	cRR	0.63	0.29	1.37

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Appendix Table 3–Continued

Intervention Group, by Study, Year (Reference) [Location]; Study Name	Intervention Participants, *n*	Control Group	Control Participants, *n*	Subgroups	Outcomes	Follow-up Duration, *y*	Events, *n*		Metric	Estimate	95% Lower CI	95% Upper CI
							Intervention Group	Control Group				
Calcium	730	Placebo	730	Posttrial period	Deaths due to arrhythmia	5	1	3	cRR	0.33	0.03	3.20
Calcium	730	Placebo	730	Entire follow-up	Deaths due to HF	9.5	14	27	OR	0.50	0.26	0.97
Calcium	730	Placebo	730	Posttrial period	Deaths due to HF	5	6	9	cRR	0.67	0.24	1.86
Calcium	730	Placebo	730	Entire follow-up	Deaths due to cerebrovascular disease	9.5	20	22	cRR	0.91	0.50	1.65
Calcium	730	Placebo	730	Posttrial period	Deaths due to cerebrovascular disease	5	6	8	cRR	0.75	0.26	2.15
Calcium	730	Placebo	730	Entire follow-up	Deaths due to peripheral arterial disease	9.5	1	4	cRR	0.25	0.03	2.23
Calcium	730	Placebo	730	Posttrial period	Deaths due to peripheral arterial disease	5	1	1	cRR	1.00	0.06	15.96
Calcium	730	Placebo	730	Entire follow-up	Total vascular hospitalization	9.5	160	169	cRR	0.95	0.78	1.15
Calcium	730	Placebo	730	Posttrial period	Total vascular hospitalization	5	91	91	cRR	1.00	0.76	1.31
Calcium	730	Placebo	730	Entire follow-up	Hospitalization due to IHD	9.5	85	85	OR	1.00	0.72	1.37
Calcium	730	Placebo	730	Posttrial period	Hospitalization due to IHD	5	50	54	OR	0.92	0.62	1.37
Calcium	730	Placebo	730	Entire follow-up	Hospitalization due to arrhythmia	9.5	39	40	cRR	0.98	0.63	1.50
Calcium	730	Placebo	730	Posttrial period	Hospitalization due to arrhythmia	5	21	16	cRR	1.31	0.69	2.49
Calcium	730	Placebo	730	Entire follow-up	Hospitalization due to HF	9.5	22	28	cRR	0.79	0.45	1.36
Calcium	730	Placebo	730	Posttrial period	Hospitalization due to HF	5	7	9	cRR	0.78	0.29	2.08
Calcium	730	Placebo	730	Entire follow-up	Hospitalization due to cerebrovascular disease	9.5	45	57	cRR	0.79	0.54	1.15
Calcium	730	Placebo	730	Posttrial period	Hospitalization due to cerebrovascular disease	5	30	25	cRR	1.20	0.71	2.02
Calcium	730	Placebo	730	Entire follow-up	Hospitalization due to peripheral arterial disease	9.5	19	18	cRR	1.06	0.56	1.99
Calcium	730	Placebo	730	Posttrial period	Hospitalization due to peripheral arterial disease	5	10	12	cRR	0.83	0.36	1.92
Radford et al, 2014 (28) [New Zealand]; The Auckland calcium study												
Calcium	732	Placebo	739	Entire follow-up	MI	9.1	70	68	HR	1.02	0.73	1.43
Calcium	698	Placebo	710	Posttrial period	MI	4.8	43	52	HR	0.82	0.55	1.23
Calcium	732	Placebo	739	Entire follow-up	Stroke	9.1	80	78	HR	1.01	0.74	1.39
Calcium	698	Placebo	710	Posttrial period	Stroke	4.8	50	59	HR	0.86	0.59	1.25

CABG = coronary artery bypass grafting; CaD = calcium plus vitamin D supplements; CAIFOS = Calcium Intake Fracture Outcome Study; CHD = coronary heart disease; cRR = calculated relative risk; CVD = cardiovascular disease; HF = heart failure; HR = hazard ratio; IHD = ischemic heart disease; ITT = intention-to-treat; MI = myocardial infarction; NA = not applicable; OR = odds ratio; PCI = percutaneous coronary intervention; PP = per protocol; RECORD = Randomised Evaluation of Calcium or Vitamin D; WHI = Women's Health Initiative.

* The vitamin D vs. placebo results are not included in this systematic review.

† Incident per 1000 patient-years.

Appendix Table 4. Characteristics of Prospective Cohort and Nested Case–Control Studies Examining the Associations Between Calcium Intake Levels and Risks for CVD

Study, Year (Reference)	Location	Study Name	Baseline Health Status	Total Participants Analyzed, *n*	Female, %	Baseline Mean Age (SD or Range), *y*	Mean Body Mass Index (SD), *kg/m²*
Adebamowo et al, 2015 (51)	United States	HPFS	No CVD or cancer	42 669	0	ND	ND
Adebamowo et al, 2015 (52)	United States	NHS I and NHS II	No CVD or cancer	18 0864	100	ND	ND
Al-Delaimy et al, 2003 (31)	United States	HPFS	No CVD	39 800	0	54 (9)	25.5 (3.2)
Ascherio et al, 1998 (32)	United States	HPFS	No CVD	43 738	0	50 (40–75)	ND
Bolland et al, 2015 (29)	United States	WHIOS*	No CVD	15 828	0	ND	ND
Bonthuis et al, 2010 (33)	Australia	Australian skin prevention cohort	Any	1529	ND	ND (25–78)	26.1 (4.1)
Bostick et al, 1999 (34)	United States	Iowa WHS	No IHD	34 486	100	61 (55–69)	ND
Chan et al, 2013 (35)	Hong Kong	Hong Kong osteoporosis risk cohort	No CVD or stroke	3139	ND	ND (≥65)	ND
Dai et al, 2013 (49)	China	SWHS, SMHS	Any	74 942; 61 500	ND	Men (40–74); women (40–70)	ND
Iso et al, 1999 (36)	United States	NHS I	No CVD	85 764	100	46 (32–57)	ND
Kaluza et al, 2010 (37)	Sweden	Cohort of Swedish Men	No CVD or DM	23 366	0	58 (45–79)	ND
Khan et al, 2015 (53)	Australia	The Melbourne Collaborative Cohort Study	No CVD or cancer	34 468	60	54.5	ND
Larsson et al, 2008 (38)	Finland	ATBC	No stroke	26 556	0	57 (50–69)	26.35
Larssonet al, 2011 (55)	Sweden	Swedish Mammography Cohort	Any	34 670	100	ND	ND
Li et al, 2012 (39)	Germany	Heidelberg cohort	No CVD or stroke	23 980	ND	ND (35–64)	ND
Marniemi et al, 2005 (40)	Finland	–	Any	755	52	79 (65–99)	ND
Michaëlsson et al, 2013 (41)	Sweden	Swedish Mammography Cohort	Any	61 433	100	ND	ND
Paik et al, 2014 (42)	United States	NHS I	No CVD or cancer	74 245	100	ND (30–55)	24.5 (4.4)
Ross et al, 1997 (30)†	China	–	Cases and controls	245 (case)/1225 (control)	0	ND (45–64)	ND
Sluijs et al, 2014 (43)	Netherlands	EPIC-NL	Any	36 094	75	49 (12; 21–70)	ND
Umesawa et al, 2006 (44)	Japan	Japan CC	No CVD	58 726	61	56 (40–79)	Men 22.7/women 22.9
Umesawa et al, 2008 (45)	Japan	Japan PHC	No CVD	41 526	52	49 (40–59)	23.5
Van der Vijver et al, 1992 (46)	Netherlands	Dutch civil servants	Any	2605	49	52 (40–65)	Men 24.6/women 26.3
Van Hemelrijck et al, 2013 (47)	United States	NHANES III	No heart disease	20 567	ND	ND (≥17)	ND
Weng et al, 2008 (50)	Taiwan	CVD-FACTS	No stroke, cancer	1772	56	57 (≥40)	24.5
Xiao et al, 2013 (48)	United States	NIH AARP Diet and Health	No CVD or cancer	388 229	43.57	ND (50–71)	26.7 (men 27/women 26.3)
Yang et al, 2016 (54)	Unites States	CPS II Nutrition Cohort	No CVD	132 823	55	62.6 (6.3)	ND

AARP = American Association of Retired Persons; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CaD = calcium plus vitamin D supplements; CPS = The Cancer Prevention Study; CVD = cardiovascular disease; CVD-FACTS = Cardiovascular Disease Risk Factor Two-township Study; DM = diabetes mellitus; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands; FFQ = food-frequency questionnaire; HPFS = Health Professionals Follow-up Study; ICD = International Classification of Diseases; IHD = ischemic heart disease; Japan CC = Japan Collaborative Cohort; Japan PHC = Japan Public Health Center study; ND = no data; NHANES I = First National Health and Nutrition Examination Survey; NHANES III = Third National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; NIH = National Institutes of Health; SMHS = Shanghai Men's Health Study; SWHS = Shanghai Women's Health Study; WHIOS = Women's Health Initiative Observational Study; WHS = Women's Health Study.

* Uses a smaller portion from the same WHI CaD population for analyses.

† A nested case–control study.

Appendix Table 4–Continued

Dietary Assessment Method	Follow-up Duration, *y*	Adjusted Confounders					Funding Source	Outcome Assessments
		Nutrients	Demographic	Anthropometry	Medical	Lifestyle		
FFQ	24	√	√	√	√	√	Government	Medical records
FFQ	NHS I: 30 NHS II: 22	√	√	√	√	√	Government	Medical records
FFQ	12	√	√	√	√	√	Government	Medical record and patient self-report
FFQ	8	√	√	√	√	√	Government	Patient self-report
FFQ	7.2	√	√	√	√	√	Government	Medical records
FFQ	14.4	√	√	√		√	Government	ICD codes
FFQ	8	√	√	√	√	√	Government	Death certificate and ICD codes
FFQ	9.1	√	√	√	√	√	Government, nonprofit	ICD codes
FFQ	13	√	√	√		√	Government	ICD codes
FFQ	14		√			√	Government	Self-reported, medical record, and death certificate
FFQ	10	√	√	√		√	Government	ICD codes
FFQ	13.3	√	√	√	√	√	Government and nonprofit	Self-report, medical records, and death certificate
FFQ	13.6	√	√	√	√	√	Government	ICD codes
FFQ	10.4	√	√	√	√	√	Government	ICD codes
FFQ	11	√	√	√	√	√	Government, nonprofit	Medical record and ICD codes
Interview, food recall	10	√	√			√	ND	ICD codes
FFQ	19	√	√	√		√	Government	ICD codes
FFQ	24	√	√	√	√	√	Government	Medical record
FFQ	12		√	√	√	√	Government	Death certificate
FFQ	12	√	√	√		√	Nonprofit	ICD codes
FFQ	8.9	√	√	√	√	√	Government	Death certificate
FFQ	13	√	√	√	√	√	Government	Medical record and ICD codes
FFQ	28		√	√		√	Government	Death certificate and ICD codes
24-h dietary recall	14.4	√	√	√	√	√	No funding	Death certificate and ICD codes
FFQ	10.6		√	√	√	√	Government	Self-report, medical records and death certificate
FFQ	12	√	√	√	√	√	Government	ICD codes
FFQ	4.5	√	√	√	√	√	Nonprofit	ICD codes

Appendix Table 5. Risk-of-Bias Assessment for 26 Cohort and 1 Nested Case–Control Studies

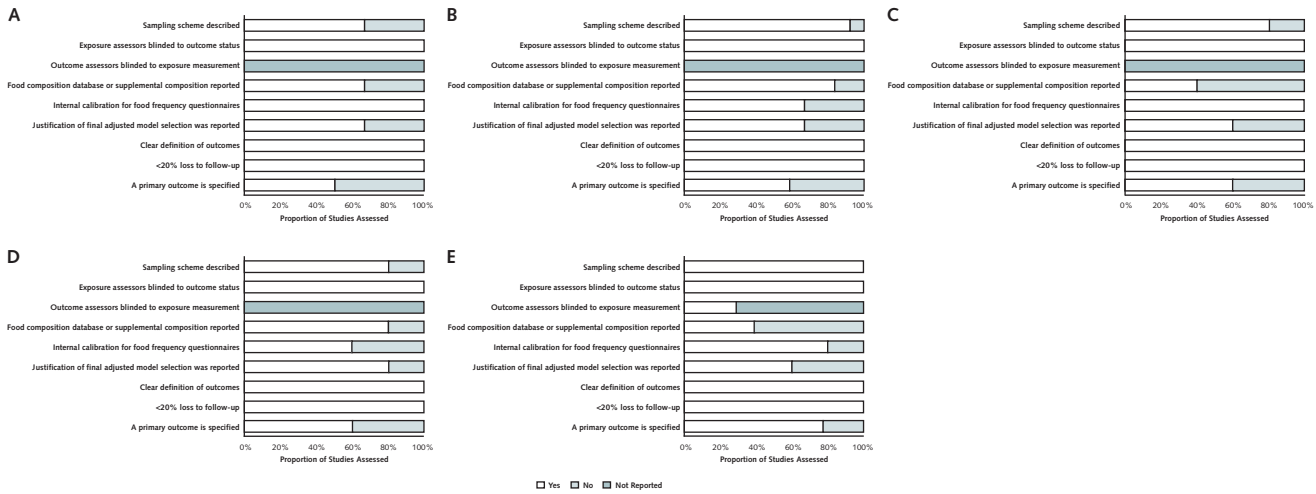
Study, Year (Reference)	Location	Study Name	Sampling Scheme Described	Exposure Assessors Blinded to Outcome Status	Outcome Assessors Blinded to Exposure Measurement	Dietary Assessment Method Reported	Food Composition Database or Supplemental Composition Reported	Internal Calibration of Method Performed (FFQ)	Justification of Final Adjusted Model Selection Was Reported	Clear Definition of Outcomes	<20% Loss to Follow-up	A Primary Outcome Is Specified
Adebamowo et al, 2015 (51)	United States	HPFS	Yes	Yes	Not reported	Yes	No	Yes	Yes	Yes	Yes	Yes
Adebamowo et al, 2015 (52)	United States	NHS I and NHS II	Yes	Yes	Not reported	Yes	No	Yes	Yes	Yes	Yes	Yes
Al-Delaimy et al, 2003 (31)	United States	HPFS	Yes	Yes	Not reported	Yes	Yes	Yes	No	Yes	Yes	Yes
Ascherio et al, 1998 (32)	United States	HPFS	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Bolland et al, 2015 (29)	United States	WHIOS*	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Bonthuis et al, 2010 (33)	Australia	Australian skin prevention cohort	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Bostick et al, 1999 (34)	United States	Iowa WHS	Yes	Yes	Not reported	Yes	No	Yes	No	Yes	Yes	Yes
Chan et al, 2013 (35)	Hong Kong	Hong Kong osteoporosis risk cohort	No	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Dai et al, 2013 (49)	China	SWHS, SMHS	Yes	Yes	Not reported	Yes	Yes	No	Yes	Yes	Yes	Yes
Iso et al, 1999 (36)	United States	NHS I	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Kaluza et al, 2010 (37)	Sweden	Cohort of Swedish Men	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Khan et al, 2015 (53)	Australia	The Melbourne Collaborative Cohort Study	Yes	Yes	Not reported	Yes	Yes	No	Yes	Yes	Yes	Yes
Larsson et al, 2008 (38)	Finland	ATBC	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Larsson et al, 2011 (55)	Sweden	Swedish Mammography Cohort	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Li et al, 2012 (39)	Germany	Heidelberg cohort	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Marniemi et al, 2005 (40)	Finland	–	Yes	Yes	Not reported	Yes	Yes	No	Yes	Yes	Yes	Yes
Michalesson et al, 2013 (41)	Sweden	Swedish Mammography cohort	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Paik et al, 2014 (42)	United States	NHS I	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Ross et al, 1997 (30)†	China	–	Yes	Yes	Not reported	Yes	Yes	No	No	Yes	Yes	Yes
Sluijs et al, 2014 (43)	Netherlands	EPIC-NL	Yes	Yes	Not reported	Yes	Yes	Yes	No	Yes	Yes	No
Umesawa et al, 2006 (44)	Japan	Japan CC	Yes	Yes	Not reported	Yes	Yes	No	No	Yes	Yes	Yes
Umesawa et al, 2008 (45)	Japan	Japan PHC	Yes	Yes	Not reported	Yes	No	Yes	No	Yes	Yes	Yes
Van der Vijver et al, 1992 (46)	Netherlands	Dutch civil servants	Yes	Yes	Not reported	Yes	Yes	No	No	Yes	Yes	Yes
Van Hemelrijck et al, 2013 (47)	United States	NHANES III	No	Yes	Not reported	Yes	No	Yes	Yes	Yes	Yes	No
Weng et al, 2008 (50)	Taiwan	CVD-FACTS	Yes	Yes	Not reported	Yes	No	No	Yes	Yes	Yes	No
Xiao et al, 2013 (48)	United States	NIH AARP Diet and Health	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	No
Yang et al, 2016 (54)	United States	CPS II Nutrition Cohort	Yes	Yes	Not reported	Yes	No	Yes	Yes	Yes	Yes	Yes

AARP = American Association of Retired Persons; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CaD = calcium plus vitamin D supplements; CPS = The Cancer Prevention Study; CVD-FACTS = Cardiovascular Disease Risk Factor Two-township Study; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands; FFQ = food-frequency questionnaire; HPFS = Health Professionals Follow-up Study; WHS = Women's Health Study; Japan CC = Japan Collaborative Cohort; Japan PHC = Japan Public Health Center study; NHANES III = Third National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; NIH = National Institutes of Health; SMHS = Shanghai Men's Health Study; SWHS = Shanghai Women's Health Study; WHIOS = Women's Health Initiative Observational Study; WHS = Women's Health Study.

* Uses a smaller portion from the same WHI CaD population for analyses.

† A nested case–control study.

Appendix Figure 2. Risk-of-bias assessment of prospective cohort or nested case–control studies examining the associations between calcium intake and risk for cardiovascular disease.



A. Six studies estimated the associations between total calcium intake levels and risks for cardiovascular or ischemic heart disease death. **B.** Twelve studies estimated the associations between dietary calcium intake levels and risks for cardiovascular or ischemic heart disease death. **C.** Five prospective cohort studies estimated the associations between supplemental calcium intake levels and risks for cardiovascular or ischemic heart disease death. **D.** Five studies estimated the associations between total or dietary calcium intake levels and risks for stroke death. **E.** Ten studies estimated the associations between total or dietary calcium intake levels and risks for total stroke.

Appendix Table 6. *R* Codes to Perform Linear and Nonlinear Dose–Response Metaregressions

Loading *doseresmeta* and Reading Data Set

```
require ("dosresmeta")
mydata <- read.table ("Total_Ca_CVDdeath.csv", header=TRUE,
    sep=",")
mydata
```

Dose-Response Metaregression Model

Linear

```
TotalCaCVD1 <- dosresmeta (formula = logrr ~ dose, id = Study,
  type = type, se = se, cases = cases, n = peryears, data = mydata,
  method = "mm")
summary (TotalCaCVD1)
```

Nonlinear

```
TotalCaCVD2 <- dosresmeta (formula = logrr ~ dose + I (dose^2), id
  = Study, type = type, se = se, cases = cases, n = peryears, data =
  mydata, method = "mm")
summary (TotalCaCVD2)
```