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Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review the evidence on the benefits and harms of supplementation with vitamin D, calcium, and vitamin D with calcium, for the primary prevention of fractures in unselected, community-dwelling adults without known osteoporosis or vitamin D deficiency.

Data Sources: PubMed, Embase, the Cochrane Library, and trial registries through March 21, 2017; bibliographies from retrieved articles; suggestions from experts; surveillance of the literature through December 31, 2017.

Study Selection: Two investigators independently selected English-language studies using a priori criteria. We selected randomized, controlled trials (RCTs) that evaluated supplemental vitamin D, calcium, or vitamin D with calcium at any dose and that reported incident fractures or harms (i.e., all-cause mortality, kidney stones, cardiovascular disease, and cancer). Prospective cohort and case-control study designs were also eligible for inclusion for harms. We excluded studies assessing treatment of vitamin D deficiency or osteoporosis and studies conducted in developing countries or with a majority of participants with prevalent or prior fractures or in institutionalized settings. Sensitivity analyses evaluated the contribution of studies with 20 to 50 percent of participants with prevalent or prior fracture and poor-quality trials.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality using predefined criteria.

Data Synthesis: We included a total of 11 RCTs (51,419 participants). Eight RCTs assessed the benefit of supplementation on incident fracture and nine assessed the harms. Doses of vitamin D and calcium ranged from 300 international units (IU) per day to 100,000 IU every 1 to 4 months for vitamin D, and from 600 to 1,600 mg per day for calcium.

Compared with placebo, supplementation with vitamin D for 3.5 to 5 years minimally decreased total fracture incidence, but findings were imprecise (1 RCT, 2,686 men and women; absolute risk difference [ARD], -2.26% (95% CI, -4.53% to 0.00%; relative risk [RR], 0.78 [95% CI, 0.61 to 0.99]) and it had no statistically significant effect on hip fracture (3 RCTs, 5,496 men and women; pooled ARD, -0.01% [95% CI, -0.80%, to 0.78%; I^2=0%]; pooled RR, 1.08 [95% CI, 0.79 to 1.48; I^2=0%]). Supplementation using vitamin D with calcium for 3 to 7 years had no statistically significant effect on total fracture incidence (1 RCT, 36,282 women; ARD, -0.35% [95% CI, -1.02% to 0.31%]; hazard ratio [HR], 0.96 [95% CI, 0.91 to 1.02]) or hip fracture incidence (2 RCTs, 36,727 men and women; ARD from the much larger trial, -0.14% [95% CI, -0.34% to 0.07%]; HR, 0.88 [95% CI, 0.72 to 1.08]). The evidence for calcium alone was limited to 2 RCTs (339 women) reporting on incident morphometric vertebral fractures; one trial also reported nonvertebral fractures (236 women; ARD, -1.01% [95% CI, -8.58% to 6.56%]; RR, 0.90 [95% CI, 0.41 to 1.96]).

Compared with placebo, supplementation with vitamin D alone or with calcium had no effect on all-cause mortality or incident cardiovascular disease; the ARDs for these harms ranged from -1.93% to 1.79%, with confidence intervals that spanned the null effect. The evidence for calcium alone also suggested no increased incidence, but was limited to one study for each harm.

Supplementation with calcium alone for 2 to 4 years did not increase the incidence of kidney stones (3 RCTs, 1,259 participants; pooled ARD, 0.00% [95% CI, -0.88% to 0.87%; I^2=0%]; pooled RR, 0.68 [95% CI, 0.14 to 3.36]). Vitamin D with calcium for 4 to 7 years increased the incidence of kidney stones (pooled ARD 0.33% [95% CI, 0.06% to 0.60%]; pooled RR, 1.18 [95% CI, 1.04 to 1.35]; I^2=0%; 3 RCTs; 39,213 participants). The evidence for the impact of supplementation with vitamin D or calcium alone on cancer incidence was inconsistent and imprecise; supplementation using vitamin D with calcium did not increase cancer incidence (pooled ARD -1.48% [95% CI, -3.32% to 0.35%]; I^2=70.9%; 3 RCTs, 39,213 participants).

Limitations: This body of evidence was limited by imprecise effect estimates largely because studies were not powered to assess fracture or other outcomes of interest. Other limitations include heterogeneity in outcome specification and ascertainment and the lack of fair- or good-quality trials that assess the impact of supplementation with calcium alone. The evidence is applicable to postmenopausal women; evidence for some fracture and harm outcomes is also applicable to men.

Conclusions: In unselected, community-dwelling populations without known osteoporosis or vitamin D deficiency, the evidence does not support a finding of fewer fractures with vitamin D supplementation alone or with calcium; the evidence for supplementation with calcium alone is limited. The evidence suggests that supplementation with vitamin D alone does not increase all-cause mortality or cardiovascular events, but the evidence is limited for other harms. The evidence suggests that supplementation with calcium alone does not increase the incidence of kidney stones, but the evidence is limited for other harms. The evidence suggests that vitamin D with calcium does not increase all-cause mortality, cardiovascular events, or cancer incidence, but it is associated with an increase in the incidence of kidney stones.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this review to update its 2013 recommendation on vitamin D with or without calcium supplementation to prevent fractures in adults.[1] The review in support of the 2013 recommendation focused on supplementation with vitamin D alone or in combination with calcium[2]; the USPSTF did not review the evidence or make a recommendation on supplementation with calcium alone.

This update was scoped to provide the USPSTF with answers to key questions (KQs) about the benefits and harms of supplemental vitamin D alone, calcium alone, or vitamin D combined with calcium to reduce fractures among community-dwelling adult populations typically found in primary care settings. In this context, supplementation refers to the use of vitamin D or calcium supplements without knowledge of a person's diet, nutritional status, or fracture risk. This review does not focus on the use of vitamin D analogues or preparations used to treat medical conditions (e.g., doxercalciferol) and does not include studies that used vitamin D or calcium supplements as adjunctive medical treatments, such as in treatment of osteoporosis. This review also does not address the use of vitamin D in institutionalized populations, populations known to be at high risk for falls or with vitamin D deficiency, or populations with a prior history of osteoporotic fractures.

Condition Definition

Osteoporotic fractures, also known as fragility, "low-energy," or "low-trauma" fractures occur most often in the spine, forearm, hip, and proximal humerus. They are defined as fractures sustained because of a fall from standing height or lower and that would not give rise to a fracture in most healthy individuals.[3] Osteoporotic fractures occur as a result of bone fragility resulting from bone loss or structural changes.[4] Supplementation refers to the untargeted use of supplements, without knowledge of an individual's diet, nutritional status, or fracture risk. Vitamin D, a fat-soluble prohormone obtained through synthesis in the skin and diet is one of several hormones that regulate calcium and phosphorus levels, which are critical to the mineralization of bone.[5] Calcium, a dietary micronutrient, forms the mineral hydroxyapatite, which deposits into the organic skeletal matrix to provide bone structure and strength.[5] Although not all osteoporotic fractures may be directly attributable to deficiencies in vitamin D or calcium, these nutrients are important modifiable contributors to optimal bone health.[6]

Etiology and Natural History

Osteoporotic fractures result when bone structure and composition are unable to be stiff yet flexible enough to absorb energy and resist deformation from loading forces.[7] Calcium is essential to bone structure and composition, and an array of hormones—parathyroid, calcitriol (the hormonally active form of vitamin D), and calcitonin—regulate its homeostasis and

contribute to bone metabolism.[5] Other hormones also influence bone metabolism, including testosterone, estrogen, growth hormone, thyroid hormone, and cortisol. Bone structure and composition, specifically bone mass, is influenced by genes, hormones, underlying medical conditions, physical activity, and diet, and evolves across life stages. These factors influence the ability to develop strong bones as a child or may cause excessive bone resorption or impair the replacement of lost bone in adulthood. As a result, osteoporotic fractures associated with low bone mass can result from different mechanisms; some may result from reduced bone formation, while others may result from increased bone resorption.[7] Genes are thought to be the chief determinant of "peak" bone mass; whether accretion, resorption, and remodeling can be influenced through dietary or supplemental calcium and vitamin D intake is not well understood.[5, 8] Because of vitamin D production in the skin and the fortification of food and beverages with vitamin D, clinical deficiency manifested as osteomalacia in adults is rare. Clinically overt calcium deficiency is also rare among unselected populations. However, when dietary calcium is insufficient, bone is resorbed to ensure that sufficient circulating levels of calcium are available to support neuromuscular junction functioning, nerve transmission, vasodilation, and hormone secretion.[5]

Risk Factors

Several studies have demonstrated an association between bone mineral density (BMD) and osteoporotic fracture; this risk of fracture increases 1.5- to 2.5-fold for every standard deviation decrease in BMD.[4, 9, 10] Despite this association, fractures can occur in persons with normal bone mass, and no bone mass threshold exists that reliably predicts fractures.[10]

In addition to low bone mass, advancing age and falls are the major risk factors for incident (i.e., first) osteoporotic fractures, although the precise contribution of each to fracture risk is difficult to determine as these factors are often confounded by comorbid conditions and increased incidence of falls among the elderly.[4] Fractures occur in 10 to 15 percent of falls,[4] and more than 90 percent of hip fractures are related to falls.[11] Other risks for low bone mass and fracture include female sex, smoking, use of glucocorticoids, and use of other medications that impair bone metabolism (e.g., aromatase inhibitors).[12, 13]

Considerable debate exists about the serum 25-hydroxy vitamin D (25[OH] D) levels associated with optimal bone health (**Appendix A Table 1**).[14-16] Experts agree that serum 25[OH] D levels are the best reflection of the vitamin D supply in the body, which constitutes vitamin D that is ingested and vitamin D that is synthesized in the skin.[5] Less clear is whether serum vitamin D levels are directly related to health outcomes. The 2009 and 2014 Agency for Healthcare Research and Quality (AHRQ) Evidence Reports prepared in support of the National Academy of Medicine (NAM, formerly Institute of Medicine) committee charged with updating the vitamin D and calcium Dietary Reference Intakes (DRI) found some evidence of an association between serum vitamin D levels and some bone health outcomes, including falls and bone mineral density (BMD), but the association with fractures in adults was inconsistent (**Appendix A** and **Appendix A Table 2**).[15, 17] Although results from observational studies suggest an association between vitamin D and bone mass; this relationship has not been supported in randomized controlled trials (RCT).[15, 17]

The level of 25[OH] D used to define vitamin D deficiency has varied over the previous two decades and large variations in laboratory measurement among different serum assays has presented further challenges to interpreting serum vitamin D data to understand the relationship between vitamin D status and health outcomes.[5, 18, 19] To determine threshold serum levels associated with sufficient vitamin D status, researchers have examined the level of 25[OH] D associated with maximal suppression of parathyroid hormone,[20-23] maximum calcium absorption,[24, 25] and reduced fracture risk.[26] The NAM suggests that serum 25[OH]D levels for optimal bone health in individuals have a distribution of values within a population, and no single threshold level can define deficiency.[5, 27] Using this perspective, NAM suggests that a distribution of serum levels with a mean of 40 nanomole per liter (nmol/L) and standard deviation (SD) of 5 nmol/L would mean that 70 percent of the population can meet their vitamin D needs for bone health at serum levels between 35 and 45 nmol/L.[5, 27]

Although most experts generally agree that 25[OH] D levels lower than 50 nmol/L may place some individuals at risk relative to bone health, many will have their needs met at this level.[5] Because of this, the specific level that should be promoted as a goal for optimal bone health across a population is not entirely clear, nor is the amount of supplementation that any one individual may require to meet a proposed goal. A goal of 50 nmol/L may label many as deficient, when in fact their needs are being met, and may result in harm to some people who would require supplementation above the tolerable upper intake level.[16, 28] Further, some organizations suggest that serum 25[OH] D levels should be greater than 75 nmol/L, particularly in older adults.[29-31] Some organizations also suggest that, because of variability in laboratory measurements, targeting a higher 25[OH] D level than the goal level (such as 100 nmol/L) better ensures that all persons meet goal levels. The NAM concluded that there may be a potential U-shaped relationship between 25[OH] D levels and some outcomes (e.g., mortality, cardiovascular disease, selected cancers, falls) at serum levels higher than 125 nmol/L.[5]

It is unclear whether serum vitamin D levels considered "optimal" for bone and mineral metabolism in whites are the same as those in nonwhite populations. Further, obesity is a confounder in the relationships among race, vitamin D serum levels, BMD, and fracture.[32, 33] For example, black postmenopausal women have lower mean serum vitamin D concentrations than white women.[34] However, after adjustment for body weight and other risk factors for fracture, black women have a lower fracture risk than white women at every level of BMD.[35]

Several types of risk factors exist for low vitamin D levels. These include physiological risks related to reduced skin synthesis (dark skin, residence at high latitudes, aging, seasonal reduction in sunlight), decreased bioavailability (malabsorption, sequestration in body fat of obese individuals), increased catabolism (anticonvulsants, antiretrovirals), and decreased conversion (liver or kidney disease).[36]

No accurate serum measure of whole-body calcium exists (calcium ion concentration is exquisitely regulated in extracellular fluid so that serum level does not increase in response to increases in intake); thus, identifying otherwise healthy individuals who are "calcium deficient" and at risk for bone resorption is not currently feasible. The lack of a measure to assess whole-body calcium stores and the complex interplay between vitamin D and calcium make it difficult to interpret data relative to calcium requirements, excess, and deficiency.[5] Chronic inadequate

calcium intake may be more common among the following populations: postmenopausal women, amenorrheic women, persons with lactose intolerance or cow's milk allergy.[37, 38]

Prevalence and Burden

Prevalence of Osteoporotic Fractures

Worldwide, age-standardized incidence rates of osteoporotic fractures have been decreasing. This decline is hypothesized to be attributed to increasing rates of obesity, increasing use of antiresorptive agents, and birth cohort effects.[39] In 2005, approximately 2 million osteoporotic fractures occurred in the United States.[40] The majority of fractures (71%) occur among women, and women accounted for more than three quarters of the total cost of incident fractures (>$16.9 billion). The total cost distribution by fracture type is skewed toward hip fractures, which account for 72 percent of total costs but represent only 14 percent of fractures.

Vertebral fractures are the most common fracture associated with low bone mass, accounting for an estimated 700,000 of the 1.5 million osteoporotic fractures annually in the United States.[41] Vertebral fractures may present with back pain; however, as many as two-thirds to three-quarters of vertebral fractures are not clinically diagnosed and are only identified because of vertebral body deformities on incidental radiographs (also called morphometric fractures).[41] Nearly 74 percent of nonvertebral fractures are in women age 65 years or older.[42] The incremental health care cost to Medicare per nonvertebral osteoporotic fracture was estimated to be $13,387 from 1999–2006, with inpatient and long-term care accounting for three quarters of the incremental cost.[43] Hip fractures, considered a subset of nonvertebral fractures, accounted for a large proportion of the mortality and morbidity related to fractures. Using Medicare claims data from 1986–2005, the annual rate of hip fractures in women was estimated at 957.3 per 100,000, and the rate in men was estimated at 414.4 per 100,000. The morbidity and mortality associated with hip fractures is high: 20 to 30 percent of patients die within 1 year of a hip fracture, with significantly higher mortality rates after fracture in men than women.[42] Nearly 40 percent of those who experience a fracture are unable to walk independently at 1 year, and 60 percent require assistance with at least one essential activity of daily living.[10]

Prevalence of Vitamin D and Calcium Insufficiency

The NAM selected bone health to serve as the basis for establishing DRIs for vitamin D and calcium.[5] These DRIs specify the estimated average requirements and the recommended dietary allowances, which represent the level of intake that will likely meet the bone health needs of 97.5 percent of the population. The DRIs also specify the tolerable upper intake level; these are levels above which the potential for harms increase. **Appendix A Table 3** depicts data from the 2011–2012 U.S. National Health and Nutrition Examination Survey (NHANES) regarding vitamin D and calcium intake from dietary and supplement sources along with current Recommended Dietary Allowance for meeting average requirements for adult men and nonpregnant lactating women.[5, 44] Based on 1 day of dietary intake data collected in a dietary intake interview, the 2009–2010 NHANES estimated that 42 percent of the U.S. population (age 2 years and older) does not take in the estimated average requirement for calcium.[45]

Because most vitamin D is produced by the skin—as opposed to being obtained through dietary sources—it is challenging to estimate the proportion of individuals who do not have an adequate level of vitamin D.[45, 46] Estimating intake from diet is challenging because of underreporting of calories and amounts of fortified foods.[47] For both reasons, estimates of intake from diet or supplements may not adequately reflect adequacy of vitamin D. Although serum 25[OH] D levels can be used to estimate vitamin D deficiency, prevalence estimates remain challenging because rates vary based on how deficiency is defined and the assay used to measure levels.[5, 18] The NAM developed a statistical procedure to derive prevalence estimates of nutritional inadequacy. According to this model, 19 percent of the U.S. adult population does not receive the estimated average requirement defined by NAM as a serum 25[OH] D less than 40 nmol/L.[48] This prevalence increases to 36 percent if a serum level of 50 nmol/L is used. Based on NHANES 2009–2010 data, 3.5 percent (95% CI, 2.2 to 4.7) of those age 20 to 64 years and 3.9 percent (95% CI, 2.3 to 5.4) of those age 65 or older had 25[OH] D levels less than 25 nmol/L.[49] Using this same data source and method, 34.2 percent (95% CI, 30 to 38.3) of adults age 20 to 64 years and 47.5 percent (95% CI, 42 to 53) of adults 65 and older have a 25 [OH] D level of 75 nmol/L or greater.

Prevention Approaches and Rationale

Although the role of vitamin D and calcium in bone metabolism is well-established, uncertainty exists about whether supplementing community-dwelling, unselected adult populations has benefits in terms of fracture prevention. If effective, supplementation, which does not rely on knowledge of a person's underlying fracture risk, bone mass, vitamin D status, or diet, could be a more efficient approach for fracture prevention than a preventive approach that requires laboratory testing, imaging, or dietary assessment to determine whether treatment with vitamin D or calcium, should be used. At the same time, it is important to understand the harms of supplementation with these agents, such as possible increased risk for cardiovascular events from the use of calcium supplements.[50, 51]

The NAM recommends a dietary intake between 400 international units (IU) and 800 IU per day of vitamin D for various age groups based on an assumption of minimal sun exposure.[5] The NAM suggests that health policy and public health applications of this recommendation may need to adjust the recommended intake based on the level of sunlight exposure within the target population of interest. The proportion of vitamin D obtained through diet is often from foods and beverages that have been fortified, because naturally occurring vitamin D in foods is rare, although recent research suggests animal products (e.g., meat, poultry, eggs) may contain the metabolized form of vitamin D, which is not typically measured when reporting the vitamin D content of food.[47] Vitamin D supplements are available for oral or injectable use and are formulated as either vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol). Both forms are generically referred to as calciferol and must undergo further metabolism into calcitriol, the biologically active form of vitamin D. The relationship between vitamin D supplementation and serum 25[OH] D levels appears to be nonlinear[5] (**Appendix A**).

The NAM established DRIs for calcium that vary by age and sex. Currently, the recommended calcium intake for all adults, male or female, ages 19 to 50 is 1,000 mg/day. The daily

recommended intake increases to 1,200 mg/day for women age 50 years or older and men age 70 years or older.[5] These requirements refer to intake from all sources, including food, beverages, and supplements. Dietary calcium is obtained through foods and beverages that naturally contain calcium or that have been fortified. Calcium supplements are typically formulated as salts; calcium carbonate and calcium citrate are the most common preparations, but other formulations are also available. Dosing is based on the amount of elemental calcium present.

Current Clinical Practice in the United States

Vitamin D and calcium—either alone or in addition to prescription medication and recommendations on physical activity—are often recommended for optimizing "bone health." Both are components of most multivitamin supplements. Vitamin D and calcium supplements are available over the counter at grocery stores, pharmacies, and other retail outlets. Based on the NHANES, the use of single vitamin D supplements (i.e., vitamin D alone and not as part of a multivitamin supplement) has increased from 5.1 percent of U.S. adults in 1999–2000 to 19 percent in 2011–2012.[52] The use of single calcium supplements has slightly decreased over the same time period (38% of U.S. adults in 1999 to 35% in 2011). **Appendix A Table 4** summarizes recommendations of professional organizations related to vitamin D and calcium intake.

Previous USPSTF Recommendation

In 2013, the USPSTF recommended against daily supplementation of 400 IU or less of vitamin D_3 and 1,000 milligram (mg) or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women (D recommendation) because of adequate evidence of no effect on primary prevention of fracture.[1] The USPSTF concluded that there was insufficient evidence to recommend vitamin D with or without calcium supplementation for the primary prevention of fractures in premenopausal women and in men. They also found the evidence insufficient to recommend vitamin D at doses greater than 400 IU with or without calcium (at doses greater than 1,000 mg) for noninstitutionalized, postmenopausal women. The USPSTF did not review evidence related to the benefits or harms of supplementation with calcium alone.

Other Related USPSTF Recommendations

The USPSTF has several recommendations related to fracture prevention or vitamin D. These include screening for vitamin D deficiency, screening for osteoporosis, vitamin supplementation to prevent cancer and cardiovascular disease, and falls prevention in older adults. The scope of these related reviews and the corresponding USPSTF recommendation are described in **Appendix A Table 5**. The review that informed the USPSTF recommendation on screening for vitamin D deficiency found a lack of direct evidence on screening for vitamin D deficiency on health outcomes and no effect on decreasing fractures among studies randomizing ambulatory or institutionalized, vitamin D-deficient individuals to treatment with vitamin D.[53] Other non-

fracture outcomes were also considered by the USPSTF and they concluded the evidence across all outcomes was insufficient to make a recommendation.[54] The review that informed the USPSTF recommendation on screening for osteoporosis found no direct evidence of screening on health outcomes, but found that treatment of individuals with osteoporosis is effective in reducing fractures.[55, 56] Thus, the USPSTF recommends screening for osteoporosis in women age 65 or older and in some younger women based on risk (B recommendation). An updated review for the USPSTF of screening for osteoporosis is currently in progress. The review in support of the USPSTF recommendation on vitamin supplementation to prevent cancer or cardiovascular disease found limited evidence about the use of vitamin D as a single or paired supplement, and the USPSTF concluded that the evidence was insufficient to make a recommendation.[57, 58] The 2012 review in support of the USPSTF recommendation on Falls Prevention in Older Adults included vitamin D supplementation as an eligible intervention.[59] However, the study populations eligible for that review included adults age 65 or older at increased risk for falls, which is a population not included in this review. An update to the Falls Prevention review and updated recommendation for Falls Prevention occurred concurrent to this review.[60, 61] The update review found evidence for the effectiveness of exercise interventions and multifactorial interventions to prevent falls but mixed findings, including possible harms, for vitamin D supplementation. As a result, the USPSTF now recommends against vitamin D supplementation to prevent falls in this population (D recommendation).[62]

Chapter 2. Methods

Key Questions and Analytic Framework

The Evidence-based Practice Center (EPC) investigators, USPSTF members, and AHRQ Medical Officers developed the scope and KQs for this review. The analytic framework illustrates the KQs that guided the review (**Figure 1**).

1. Does supplementation with vitamin D or calcium alone or vitamin D combined with calcium prevent fractures or reduce fracture-related morbidity and mortality? Do the benefits of supplementation vary by:
   a) dose or dosing interval?
   b) fracture type?
   c) subpopulation (including, but not limited to age, sex, or race/ethnicity)?
2. Are there harms of supplementation with vitamin D or calcium alone or vitamin D combined with calcium? Do the harms of supplementation vary by:
   a) dose or dosing interval?
   b) subpopulation (including, but not limited to age, sex, or race/ethnicity)?

In addition to our KQs, we also looked for evidence related to two contextual questions (CQs) relating to the association between vitamin D supplementation and changes in vitamin D serum levels, and the association between vitamin D serum levels and fracture outcomes. We do not show these questions in the analytic framework because they were not analyzed using the same systematic review process as the KQs. Findings related to the contextual questions are summarized in **Appendix A**.

Data Sources and Searches

This update builds on the prior 2011 evidence review for the USPSTF,[2] which itself was an update of a portion of a much larger AHRQ Evidence Report in support of NAM recommendations.[14, 15] The relationship among these evidence syntheses is depicted in **Appendix B1**.

We searched PubMed/MEDLINE, EMBASE, and the Cochrane Library for English-language articles. For the evaluation of vitamin D alone or vitamin D combined with calcium, we searched from January 1, 2011, through March 21, 2017, building on the literature published in the previous review for the USPSTF.[2] For calcium alone, we searched from inception through March 21, 2017. We used Medical Subject Headings as search terms (when available) and keywords to describe relevant interventions, outcomes, and study designs. Complete search terms and limits are detailed in **Appendix B2**. We also searched the clinicaltrials.gov registry and the World Health Organization International Clinical Trials Registry Platform. To supplement the electronic database search, we screened relevant systematic reviews and reference lists of included articles. We conducted literature surveillance through December 31, 2017, using article alerts and targeted searches of relevant journals to identify major studies published in the interim

that may affect conclusions.

Study Selection

We developed inclusion and exclusion criteria for selecting studies based on populations, interventions, comparators, outcomes, timing, settings, and study designs; these are described in detail in **Appendix B3**. We included studies of unselected, community-dwelling adults with no known disorders of bone metabolism. We excluded studies that selected patients for enrollment based on low serum vitamin D levels or known deficiency (as defined by the study); known high risk of fracture or falls; prior history of osteoporotic fractures or prevalent fractures at baseline; and known low BMD, osteoporosis, or other medical conditions or medication use affecting bone metabolism. We included studies with up to 20 percent of such participants in our main analysis; studies with between 20 and 50 percent of such participants were considered in sensitivity analyses.

Eligible vitamin D interventions included oral or intramuscular vitamin D_2 or vitamin D_3 (at any dosage or frequency. Vitamin D metabolites (e.g., calcitriol) or synthetic analogues (e.g., doxercalciferol) designed for treatment of deficiency associated with medical conditions were not eligible for selection. Eligible calcium interventions included oral calcium salt preparations (e.g., carbonate, citrate, malate, lactate) at any dose and frequency. Vitamin D with calcium interventions were eligible if the vitamin D and calcium components were individually eligible. We selected studies for which the comparator groups were no treatment, placebo, or lower or higher dose vitamin D or calcium regimens. Studies of vitamin D with calcium vs calcium alone were considered as vitamin D alone interventions. We excluded studies where the intervention and comparator arms would not allow for the evaluation of the independent contribution of vitamin D or calcium to the effect, for example, when these supplements were taken in a multivitamin or used as part of a multicomponent intervention that also included other pharmacologic agents or environmental/behavioral interventions. For KQ 1, we required the intervention duration to have been at least 1 month prior to measurement of outcomes; no such restriction was used to select studies for KQ 2.

For KQ 1, we selected studies that reported incident fractures and fracture-related morbidity and mortality. We selected studies reporting fractures regardless of whether fracture outcomes were considered the primary reported outcome. For KQ 2, we selected studies that reported on several prespecified harms including all-cause mortality, symptomatic acute or chronic vitamin D or calcium toxicity, incident kidney stones, incident cancer, incident cardiovascular disease (including stroke and venous thromboembolism), as well as other harms or adverse events possibly attributed to supplementation.

RCTs were eligible for KQ 1 and KQ 2; prospective cohort and case-control study designs that were specifically designed to evaluate the use of vitamin D or calcium supplementation and that took care to adequately measure and control for nonsupplement sources (e.g., dietary, sun exposure) were also eligible for KQ 2. Systematic reviews using study selection criteria similar to this review were also eligible for both KQs. We excluded studies and articles that were not published in English, were not original research, or were conducted in countries other than those

categorized as "very high" on the 2015 Human Development Index (as defined by the United Nations Human Development Programme).[63]

Two investigators independently reviewed titles and abstracts identified through the search. Those marked as potentially eligible by at least one reviewer were retrieved for full text review. Two reviewers independently reviewed full-text articles for eligibility using the study selection criteria. In addition, we reviewed studies included in the prior review for the USPSTF to confirm their eligibility, given scope changes for this update, mainly the exclusion of studies in institutionalized settings or studies where the majority of participants had a history of prior fracture.

Quality Assessment and Data Abstraction

For each included study, one investigator abstracted relevant study characteristics (i.e., population, intervention, comparator,) and data for eligible outcomes onto a structured form. A second investigator reviewed all data for completeness and accuracy, and the principal investigator reviewed all abstracted information for consistency across included studies.

Two reviewers independently assessed each study's quality. We used a risk of bias assessment adapted from the Cochrane Collaboration to individually assess each RCT on the following risk of bias domains: bias arising from selection or randomization; bias due to missing outcome data; bias due to departures from intended interventions; bias from measurement of outcomes; and bias from selective reporting of results.[64] Observational studies were additionally evaluated for their risk of bias due to confounding or inadequate measurement of the exposure. Each reviewer independently assessed bias on each domain as "low," "some concerns," or "high," and translated these assessments into an overall study quality rating using the predefined criteria developed by the USPSTF (**Appendix B4**), which uses study quality ratings of poor, fair, or good. Studies with at least one risk of bias domain rated as "high" were rated as poor quality. Studies with all domains assessed as "low" were rated as good quality. Studies with some concerns in some domains were generally rated as fair quality; however, studies with most domains rated as "some concerns" could also be rated as poor quality, if both reviewers concurred and provided justification. Studies reporting multiple outcomes may have been assigned different quality ratings for different outcomes. Disagreements in risk of bias domain assessments and study quality ratings were resolved with a third reviewer.

Data Synthesis and Analysis

We qualitatively synthesized findings for each KQ in tabular and narrative formats by intervention: vitamin D alone, calcium alone, or vitamin D with calcium. We included studies in our main analysis that met all study selection criteria and that were fair or good quality; this included studies from the prior review that informed the USPSTF's 2013 Recommendation that met the study selection criteria for this update. We also conducted sensitivity analyses using RCTs that were excluded for poor quality and for RCTs that were excluded because of mixed study populations (i.e., those with between 20 and 50 percent of the population having a history

of prior fracture.)

We assessed whether a quantitative synthesis was appropriate by evaluating the number of studies available and the clinical and methodological heterogeneity present among available studies based on established guidance,[65] which includes evaluating the similarities in study population, supplement type, dose, and frequency, and similarities in timing and specification of outcomes. When at least three independent and similar RCTs were available, we used random-effects models using the inverse-variance weighted method of DerSimonian and Laird to determine pooled effect estimates using Stata version 14 (College Station, TX).[66] We assessed statistical heterogeneity with the chi squared statistic and the I^2 statistic; an I^2 between 0 and 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, and 50 to 90 percent may represent substantial heterogeneity.[67] Because the inverse-variance method of DerSimonian and Laird may not perform well with small numbers of studies,[68] we also calculated pooled estimates using the restricted maximum likelihood estimator. Because fracture and harm events were rare in many studies, we used both absolute risk differences (ARD) and relative risk ratios (RR) for assessing effects. We assessed the strength of evidence for each outcome based on the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews, which specifies the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major outcome of interest.[69]

Expert Review and Public Comment

The draft analytic framework, research questions, and study selection criteria were made available for public comment between March 27, 2016 and April 27, 2016. They were subsequently revised for a Final Research Plan posted on the USPSTF Web site.[70] Four expert reviewers provided comments on the draft evidence report. Comments generally related to requests for additional clarification or detail. Most reviewers also offered comments related to the scope of the review; they expressed that the included population was too narrowly defined, resulting in limited applicability to primary care practice. The draft evidence report was made available for public comment between September 26, 2017, and October 26, 2017.

USPSTF Involvement

This review was funded by AHRQ. Staff of AHRQ and members of the USPSTF participated in developing the scope of work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 3,131 unique records and assessed 291 full-text articles for eligibility (**Figure 2**). We excluded 265 studies for various reasons detailed in **Appendix C**. Many studies could be excluded for multiple reasons; however, we report only one.

Eight RCTs (in 13 publications) were relevant to the benefits of supplementation on fracture prevention (KQ 1), and nine RCTs (in 22 publications) were relevant to the harms of supplementation (KQ 2). Ten RCTs that were excluded were used in sensitivity analyses for KQ 1 and 11 RCTs that were excluded were used in sensitivity analyses for KQ 2. Individual study characteristics and detailed findings of studies included in the main and sensitivity analyses are in **Appendix D**. Study quality assessments for all RCTs are in **Appendix E Tables 1−6**, and quality assessments for the observational studies identified as eligible for KQ 2 but excluded for poor quality are in **Appendix E Tables 7−14**. Pooled estimates generated by random effects models using the restricted maximum likelihood estimator were not substantively different from results using the method of DerSimonian and Laird, and are therefore not shown.

Results by KQ

KQ1. Direct Evidence for Supplementation With Vitamin D or Calcium Alone or Vitamin D Combined With Calcium for the Prevention of Fractures or Reduction in Fracture-Related Morbidity and Mortality

Summary of Results

Eight good- or fair-quality RCTs that randomized 47,672 participants examined the effect of supplementation with vitamin D alone, calcium alone, or vitamin D with calcium on fracture prevention. One RCT (Women's Health Initiative Calcium and Vitamin D [WHI CaD] trial[71]) enrolled 36,282 women; the other trials enrolled only women (3 RCTs,[72-74] 571 total participants) or both women and men (4 RCTs,[75-79] 10,819 total participants). Three studies stated that the effect on incident fracture was the study aim;[71, 76, 77] however, only one study (WHI CaD trial) used fractures as the primary end point to determine required sample size.[71] Aims in the other studies included evaluating changes in BMD or biochemical measures of bone metabolism. **Table 1** and **Figures 3−5** summarize study characteristics and findings from these RCTs. All but one[77] reported statistically nonsignificant differences in fracture incidence between supplementation and placebo groups over 3–7 years, with ARDs ranging from -6.99 percent to 7.26 percent, and RRs ranging from 0.36 to 1.34. Most estimates were imprecise. We did not identify any eligible studies evaluating the impact of supplementation on fracture-related morbidity or mortality, and too few studies were available to assess the impact of dose or dosing interval on fracture incidence.

Vitamin D Compared With Placebo: Study Characteristics

We identified one new good-quality RCT (Khaw, Scragg et al,[78, 79]) in addition to the three fair-quality RCTs that were included in the prior review (Trivedi et al,[77] Lips et al,[76] and Komulainen et al[72]). In the prior review, Komulainen et al[72] was considered a vitamin D with calcium intervention, as both the active treatment and placebo group received a modest dose of supplemental calcium. The authors of the prior review published an erratum after the USPSTF's 2013 recommendation that corrected the study's classification to the appropriate intervention and comparator (vitamin D compared with placebo) and revised the meta-analysis.[2, 80] We used the revised classification of this study in this update review.

Three RCTs included both men and women; Khaw, Scragg et al[78, 79] randomized 5,110 participants age 50 to 84 years (42% women) in New Zealand, Trivedi et al[77] randomized 2,686 participants age 65 to 85 years (24% women) in the United Kingdom, and Lips et al[76] randomized 2,578 participants age 70 years or older (74% women) in The Netherlands. Komulainen et al[72] randomized 232 postmenopausal women age 52 to 61 years in Finland.[72, 76] Studies evaluated oral vitamin D_3 compared with placebo over 3.3 to 5 years; two evaluated daily 300 or 400 IU doses,[72, 76] one evaluated 100,000 IU every 4 months,[77] and one evaluated an initial loading dose of 200,000 IU followed by monthly doses of 100,000 IU.[78, 79] The comparator group was a placebo control in all but one study.[72] The baseline serum vitamin D level among participants in the Khaw, Scragg et al study was 63 nmol/L. The median serum vitamin D level at baseline for both study groups in Lips et al was in the severe deficiency range (vitamin D group median 26 nmol/L, placebo group median 27 nmol/L), but this study did not use serum vitamin D as a study entry criterion. Baseline serum vitamin D was not reported by Trivedi et al or by Komulainen et al.

Incident fracture outcomes ascertained across studies included total fractures (traumatic or osteoporotic) at any site, hip fractures, clinical or morphometric vertebral fractures, nonvertebral fractures, and peripheral fractures (distal radius, humerus, ankle, foot, leg). Three studies confirmed fractures through practitioner verification, medical or hospital record review, radiographic review, or claims.[72, 78, 79, 81] Trivedi et al relied on death certificate causes and ascertainment through subject questionnaires, which the study authors considered valid and reliable given the proportion of study participants who were physicians.[77]

Two RCTs included in the prior review (Lyons et al [82] and Law et al[83]) were not eligible for this update because they were conducted among institutionalized participants. We identified four RCTs for use in sensitivity analysis.[84-87] One good-quality RCT by Sanders et al was included in the prior review that informed the 2013 USPSTF Recommendation, but we excluded it from our main analysis because 35 percent of the study population had a history of fracture and the trial enrolled subjects with a higher risk for fracture.[84] This trial was conducted among 2,258 community-dwelling Australian women age 70 years or older and compared an annual oral dose of 500,000 IU of vitamin D_3 (approximate daily equivalent of 1,370 IU) with placebo. We also used an RCT conducted by Peacock et al in a sensitivity analysis; it was excluded from the initial 2007 review and was not used in any subsequent updates.[86] This study compared 600 IU of vitamin D_3 with placebo over 4 years among 438 community-dwelling U.S. residents (72% women). This study was not eligible for our main analysis because although all subjects were

described as independently mobile, only 60 percent were characterized as free living and because we assessed it as poor quality based on a high risk of bias due to missing data and poor outcome measurement specification. Glendenning et al randomized women in Australia age 70 years and older to oral 150,000 IU vitamin D_3 at baseline, 3 months, and 6 months (approximate daily equivalent 1,667 IU) or placebo. Fracture outcomes were self-reported in an adverse event diary.[87] This study was rated poor quality because of measurement bias and the short period of followup (9 months). Last, we used an RCT conducted by Smith et al that was not included in the original 2007 AHRQ Evidence Report because findings were available only in abstract format at the time. This fair-quality RCT compared an annual 300,000 IU dose of vitamin D_2 (approximate daily equivalent 822 IU) with placebo for 1–3 years among 9,400 men and women over age 75 years in the United Kingdom. This study was not eligible for our main analysis because more than 20 percent of subjects had a history of nonvertebral fracture.

Vitamin D Compared With Placebo: Findings

The impact of vitamin D alone compared with placebo on incident fracture is summarized in **Table 1**; findings for studies also considered in sensitivity analyses are depicted in **Figure 3**.

Total Fractures

One RCT, Trivedi et al, reported a total fracture incidence of 8.8 percent in the vitamin D group and 11.1 percent in the placebo group over 5 years (unadjusted ARD, -2.26% [95% CI, -4.53% to 0.00%], age-adjusted RR, 0.78 [95% CI, 0.61 to 0.99]).[77] The unadjusted, calculated RR was 0.80 (95% CI, 0.63 to 1.00). In sensitivity analysis, Sanders et al reported a total fracture incidence of 13.7 percent in the vitamin D group and 11.1 percent in the placebo group over 3 years (ARD, 2.59% [95% CI, -0.12% to 5.31%]; HR, 1.26 [95% CI, 0.99 to 1.59]), a finding that was inconsistent with Trivedi et al[84] with respect to direction of effect; though both studies were imprecise and included the null effect. The other study used in sensitivity analysis, Glendenning et al,[87] reported an ARD of -0.17% (95% CI, -2.69% to 2.35%) and RR, 0.94 (95% CI, 0.40 to 2.24). Both Sanders et al and Glendenning et al used considerably higher doses than Trivedi et al.

Hip Fractures

The three RCTs that reported on incident hip fracture all reported numeric differences that were statistically not significant.[72, 76, 77] The incidence of hip fracture in the treatment groups was 4.5 percent, 1.6 percent, and 0.9 percent and in the respective placebo or control groups was 3.7 percent, 1.8 percent, and 1.7 percent. Compared with placebo or control, the pooled estimates of effect for incident hip fracture among the vitamin D groups over 3 to 5 years showed no difference (pooled ARD, -0.01% [95% CI, -0.80% to 0.78%; I^2=0%,]; pooled RR, 1.08, [95% CI, 0.79 to 1.48; I^2=0.0%]; 3 RCTs, N=5,496 participants, **Appendix F Figures 1** and **2**). A somewhat increased incidence was observed with the addition of two studies used in a sensitivity analysis (pooled RR, 1.24 [95% CI, 0.98 to 1.55]; I^2=0.0%, 5 RCTs, N=17,192 participants).[84, 85]

Nonvertebral Fractures

Khaw, Scragg et al[78, 79] reported a numeric but statistically nonsignificant increase in nonvertebral fracture incidence; the incidence was 6.1 percent in the vitamin D group and 5.3 percent in the placebo group over a median of 3.3 years (ARD 0.77%, [95% CI, -0.51% to 2.04%], adjusted HR, 1.19 [95% CI, 0.94 to 1.50]). Komulainen et al[72] reported a numeric but statistically nonsignificant decrease in nonvertebral fracture incidence; the incidence was 9.5 percent in the vitamin D group and 12.9 percent in the control group over 4.3 years (ARD, -3.45% [95% CI, -11.55% to 4.66%]; adjusted RR, 0.64 [95% CI, 0.29 to 1.42]). We used three additional studies[84-86] in a sensitivity analysis to generate a pooled estimate. The pooled ARD was 0.75 percent (95% CI, 0.02% to 1.48%; I^2=0%, 5 RCTs, 17,303 participants, **Appendix F Figure 3**) and the pooled RR was 1.13 (95% CI, 1.01 to 1.26; I^2=0%, **Appendix F Figure 4**).

Clinical Vertebral Fractures

One study, Trivedi et al,[77] reported a numeric but statistically nonsignificant decrease in incidence of clinical vertebral fractures; 1.3 percent in the vitamin D group and 2.1 percent in the placebo group over 5 years (ARD, -0.77% [95% CI, -1.73% to 0.23%]; age-adjusted RR, 0.63 [95% CI, 0.35 to 1.14]). In sensitivity analysis, Sanders et al reported a numeric but statistically nonsignificant increase in clinical vertebral fractures (ARD, 0.61% [95% CI, -0.75% to 1.96%]; RR, 1.24 [95% CI, 0.76 to 2.03]); this study was not eligible because 35 percent of its study population had a prior history of fracture.[84]

Peripheral Fractures

One study, Lips et al,[76] reported a numeric but statistically nonsignificant increase in incidence of peripheral fractures; 6.0 percent in the vitamin D group and 5.8 percent in the placebo group over 3.5 years (ARD, 0.21% [95% CI, -1.60% to 2.03%]; unadjusted HR, 1.03 [95% CI, 0.75 to 1.40]).

Calcium Compared With Placebo: Study Characteristics

Two fair-quality RCTs examined the effect of calcium alone on fracture prevention among women age 60 years or older.[73, 74] Both studies were conducted in the United States and were considered new to this update because the impact of calcium alone on fracture prevention was not included in the prior review. Recker et al randomized participants to 1,200 mg calcium carbonate or placebo over 4.3 years; for this review, we included data only from the subset of 103 participants without prevalent spine fractures at enrollment.[73] In this RCT, the baseline serum vitamin D level among randomized participants was 65.0 nmol/L in the placebo group and 62.5 nmol/L in the calcium group. Riggs et al randomized 236 participants to 1,600 mg calcium citrate or placebo over 4 years.[74] In this RCT, the baseline serum vitamin D level of participants was 74.1 nmol/L in the placebo group, and 75.9 nmol/L in the calcium group. Both studies reported the impact of calcium compared with placebo on morphometric vertebral fractures defined by radiologic criteria; Riggs et al also reported the impact on nonvertebral fractures.

Two fair-quality RCTs conducted among women in New Zealand and Australia were used in a

sensitivity analysis.[88-91] These two studies were not eligible for the main analysis because the proportion of participants with a prior fracture was between 20 and 49 percent. Reid et al randomized 1,417 participants to 1,000 mg of calcium citrate or placebo over 5 years.[88, 89] Approximately 29 percent of participants had a fracture resulting from minimal trauma after age 40. Prince et al randomized 1,460 participants to 1,200 mg calcium carbonate.[90, 91] In this study, the proportion of study participants with a history of fracture because of minimal trauma after age 50 years ranged from 25 to 32 percent.

Four poor-quality studies were also used in sensitivity analysis.[86, 92-94] These studies compared doses of elemental calcium ranging from 600 mg to 1,200 mg over 2 to 4 years versus placebo. One study conducted in New Zealand included only men[92]; the other three were conducted in New Zealand[93] and the United States[86, 94] among postmenopausal women. We assessed these studies as poor quality because of high risk of bias due to overall or differential attrition[86, 93, 94] or outcome measure specification and ascertainment.[86, 92, 95]

Calcium Compared With Placebo: Findings

The impact of calcium alone compared with placebo on incident fracture is summarized in **Table 1**; findings that also include studies considered in sensitivity analysis are depicted by outcome in **Figure 4**.

Total Fractures

No studies included in our main analysis reported on incident total fracture. We considered four studies in a sensitivity analysis.[88, 90, 92, 93] Using these studies, the pooled ARD was -2.39% (95% CI, -4.72% to -0.06%; I^2=0%; 4 RCTs; 3,483 participants; **Appendix F Figure 5**) and the pooled RR was 0.87 (95% CI, 0.74 to 1.02; I^2=0%; **Appendix F Figure 6)**.

Hip Fractures

No studies included in our main analysis reported on incident hip fracture. We considered two fair-quality studies in a sensitivity analysis that did not meet our population criteria for eligibility. One study, Reid et al,[88] reported a statistically significant increase in hip fracture incidence (ARD, 1.65% [95% CI, 0.40% to 2.89%]; RR, 3.43 [95% CI, 1.27 to 9.26]). The other study, Prince et al,[90] reported a numeric but statistically nonsignificant increase in incidence (ARD, 0.68% [95% CI, -0.42% to 1.78%]; RR, 1.83 [95% CI, 0.68 to 4.93]).

Nonvertebral Fractures

One study, Riggs et al,[74] reported a numeric but statistically nonsignificant decrease in incident nonvertebral fractures; 9.2 percent incidence in the calcium group and 10.3 percent in the placebo group over 4 years (ARD, -1.01% [95% CI, -8.58% to 6.56%]; RR, 0.90 [95% CI, 0.41 to 1.96]. In a sensitivity analysis, we pooled this study with two additional RCTs (Prince et al[90] and Peacock et al[86]) and found a numeric but statistically nonsignificant decrease (pooled ARD, -0.94% [95% CI, -3.72% to 1.84%]; I^2=0%; 3 RCTs, 1,883 participants, **Appendix F Figure 7**; pooled RR, 0.91 [95% CI, 0.71 to 1.16]; I^2=0%; **Appendix F Figure 8**).

Vertebral Fractures

No included studies in our main analysis reported on clinical vertebral fractures. We considered one study that did not meet population eligibility criteria in sensitivity analysis for this outcome.[90] In this study, Prince et al reported a numeric but statistically nonsignificant decrease in incidence (ARD, -0.14% [95% CI, -2.43% to 2.16%]; HR, 0.98 [95% CI, 0.63 to 1.54]).

Two included studies reported on incident morphometric vertebral fractures over 4 years; point estimates were inconsistent with respect to increasing or decreasing incidence.[73, 74] Recker et al reported an incidence of 28.6 percent in the calcium group and 21.3 percent in the placebo group (ARD, 7.26% [95% CI, -9.84% to 24.36%]; RR, 1.34 [95% CI, 0.68 to 2.64]).[73] Riggs et al reported an incidence of 6.7 percent in the calcium group and 7.7 percent in the placebo group (ARD, -0.97% [95% CI, -7.57% to 5.63%]; RR, 0.87 [95% CI, 0.35 to 2.19]).[74] In a sensitivity analysis, we pooled these studies with two additional RCTs (Prince et al[90] [did not meet population criteria] and Ruml et al[94] [poor quality]). The pooled ARD and RR estimates with these studies were consistent for no effect (**Appendix F Figures 9** and **10**).

Last, we considered two additional studies in sensitivity analysis that reported a combined vertebral fracture outcome that included both clinical and morphometric fractures (these fractures were not reported separately in these studies). Findings from these studies demonstrated somewhat larger effect sizes compared with the studies previously discussed; however, they were not statistically significant. The poor-quality study by Peacock et al had a RR of 0.58 (95% CI, 0.24 to 1.40), and the fair-quality Reid et al[88] study reported an HR of 0.72 (95% CI, 0.44 to 1.18).[86, 88]

Vitamin D With Calcium Compared With Placebo: Study Characteristics

Two fair-quality RCTs examined the effect of vitamin D with calcium on fracture prevention.[71, 75] Both were included in the prior review. No new studies were identified for inclusion, although we identified several subgroup analyses related to one of the included RCTs. The first RCT, Dawson-Hughes et al, reported findings from 445 healthy participants age 65 or older (55% women) randomized to daily 700 IU oral vitamin D_3 with 500 mg calcium citrate or placebo for 3 years.[75] The WHI CaD trial randomized 36,282 U.S. women ages 50 to 79 years to daily 400 IU oral vitamin D_3 with 1,000 mg calcium carbonate or placebo for 7 years.[71, 96] Participants enrolled in this trial were recruited from the participants in the WHI dietary modification trial and hormone therapy trials. Approximately 43.5 percent were using calcium and vitamin D supplements at baseline; personal use of supplements was allowed during the trial and approximately 84 percent of participants who reported use of supplements at baseline also reported use on their last questionnaire.[97]

Neither trial selected participants for enrollment based on serum vitamin D levels; however, both measured serum vitamin D at baseline. In the WHI CaD Trial, the mean serum vitamin D level was 49 nmol/L.[71, 96] The mean serum level among men in the Dawson-Hughes et al study was 83 nmol/L in both the treatment and placebo groups and for women was 61 nmol/L in the placebo group and 72 nmol/L in the treatment group.[75] The WHI CaD Trial reported the impact of vitamin D with calcium on incident hip and clinical vertebral fractures (excluding cervical

fractures) and on total fractures other than ribs, sternum, skull, face, fingers, toes, and cervical vertebra.[71] Dawson-Hughes et al reported the impact of vitamin D with calcium on incident nonvertebral fractures, which included face, clavicle, shoulder, humerus, forearm, hand, ribs, pelvis, hip, leg, and foot. Both studies verified fractures with medical records or operative or radiology reports.

The main WHI publication and three publications (new to this review) reported subgroup analyses from the WHI trial. The main WHI publication reported on subgroup analyses related to age, race/ethnicity, weight, smoking status, sunlight exposure, hormone therapy use, and use of calcium supplements at baseline.[71] Prentice et al published subgroup analyses related to the use of personal supplements at baseline,[98] Robbins et al reported subgroup analyses related to hormone therapy use,[99] and Bolland et al reported subgroup analyses related to personal use of calcium or vitamin D supplements.[97]

Seven RCTs included in the prior review were not included in this update. Porthouse et al,[100] Grant et al,[101] and Harwood et al[102] were excluded from this update because either all or a majority of the enrolled study population had a prior history of fracture. Pfeifer et al was excluded from this update because participants were selected based on a baseline serum vitamin D level less than 50 nmol/L, which is in the deficiency range.[103] Two studies by Chapuy et al[104, 105] and Flicker et al[106] were excluded because they were conducted among institutionalized populations. We used one poor-quality RCT by Salovaara et al that was included in the prior review in sensitivity analysis.[107] In addition to poor quality, this study was not eligible for our main analysis because approximately one third of enrolled participants had a prior history of fracture. This study, which was conducted in Finland, randomized 3,432 women ages 65 to 71 years to daily 800 IU oral vitamin D_3 with 1,000 mg elemental calcium or control (no placebo) over 3 years.

Vitamin D With Calcium Compared With Placebo: Findings

The impact of vitamin D combined with calcium on incident fracture is summarized in **Table 1**; findings that also include studies considered in a sensitivity analysis are depicted by outcome in **Figure 5**.

Total Fracture

The WHI CaD Trial reported a numeric but statistically nonsignificant decrease in total fracture incidence.[71] The incidence was 11.6 percent in the vitamin D with calcium group and 11.9 percent in the placebo group (ARD, -0.35% [95% CI, -1.02% to 0.31%]; HR, 0.96 [95% CI, 0.91 to 1.02]). Similar findings were reported by the one RCT (Salovaara et al[107]) used in sensitivity analysis; the total fracture incidence was 4.9 percent in the vitamin D with calcium group and 5.8 percent in the control group over 3 years (ARD, -0.92% [95% CI, -2.49% to 0.64%]; adjusted HR, 0.83 [95% CI, 0.61 to 1.12]).

Hip Fracture

Two included studies reported numeric but statistically nonsignificant decreases in hip fracture

incidence.[71, 75] Dawson-Hughes et al reported only one hip fracture (in the placebo group) over the duration of study followup.[75] In the WHI CaD Trial, the incidence of hip fracture was 1.0 percent in the vitamin D and calcium group and 1.1 percent in the placebo group at 7 years (ARD, -0.14% [95% CI, -0.34% to 0.07%]; HR, 0.88 [95% CI, 0.72 to 1.08]).[71] One RCT (Salovaara et al[107]) considered in sensitivity analysis reported a numeric but statistically nonsignificant increase over 3 years (ARD, 0.13% [95% CI, -0.17% to 0.43%]; RR, 2.03 [95% CI, 0.37 to 11.06]). The pooled estimates including this study was similar to the estimates from the WHI CaD Trial.

Nonvertebral Fracture

One study, Dawson-Hughes et al, reported a statistically significant decrease in the incidence of nonvertebral fractures.[75] The incidence was 5.9 percent in the the vitamin D with calcium group and 12.9 percent in the placebo group (ARD, -7.0% [95% CI, -12.7% to -1.3%]; RR, 0.50 [95% CI, 0.2 to 0.9]). When limited to only fractures considered to be osteoporotic (i.e., not resulting from major trauma), the RR was 0.40 (95% CI, 0.2 to 0.8). In sensitivity analysis, one RCT (Salovaara et al[107]) reported a numeric but statistically nonsignificant decrease in nonvertebral fractures over 3 years (ARD, -0.6% [95% CI, -2.1% to 0.9%]; adjusted HR, 0.87 [95% CI, 0.63 to 1.19]).

Vertebral Fracture

One study, the WHI CaD Trial, reported a numeric but statistically nonsignificant decrease in incident clinical vertebral fractures (exclusive of cervical vertebral fractures).[71] The incidence was 1.0 and 1.1 in the treatment and placebo groups, respectively (ARD, -0.09% [95% CI, -0.30% to 0.12%]; HR, 0.90 [95% CI, 0.74 to 1.10]). In sensitivity analysis, one RCT (Salovaara et al[107]) reported similar findings (ARD, -0.24% [95% CI, -0.81% to 0.33%]; adjusted HR, 0.67 [95% CI, 0.29 to 1.58]).

Subgroup Results

No studies reported subgroup findings by dose or dosing interval; some studies reported subgroup findings by age, sex, or other patient characteristics.

For Vitamin D alone, two studies reported subgroup results.[76, 77] Lips et al reported effect estimates for hip fracture incidence for the subset of study participants recruited from apartment homes for the elderly and for participants age 80 years or older. Results from both subgroup analyses were consistent with the overall analysis; no statistically significant differences in fracture incidence between treatment and placebo groups.[76] Trivedi et al reported effects on total, hip, and vertebral fracture incidence by sex.[74] Whereas the age-adjusted RR for total fracture incidence was 0.78 (95% CI, 0.61 to 0.99) the age-adjusted RR for women was 0.68 (95% CI, 0.46 to 1.01) and was 0.83 (95% CI, 0.61 to 1.13) for men. For hip fracture, the overall age-adjusted RR was 0.85 (95% CI, 0.47 to 1.53) and was 0.98 (95% CI, 0.41 to 2.36) for women and 0.76 (95% CI, 0.35 to 1.67) for men. For clinical vertebral fractures, the overall age-adjusted RR was 0.63 (95% CI, 0.35 to 1.14) with an age-adjusted RR of 0.65 (95% CI, 0.18 to 2.30) among women and 0.62 (95% CI, 0.32 to 1.22) among men.

For calcium alone, no studies reported findings by subpopulations.

For vitamin D with calcium, only the WHI Ca D trial reported findings by subpopulation. Fifteen subgroup analyses based on participant characteristics were reported in the main WHI study publication.[71] We summarize those relevant to age, prior history of falls, use of hormone therapy, and personal use of supplements at baseline. However, we note that randomization was only stratified by age and clinical center, not by the other participant characteristics for which subgroup analyses were reported.

A borderline statistically significant treatment effect by age was reported for hip fracture (p=0.05). Women age 50 to 59 had an increased risk of hip fracture (HR, 2.17 [95% CI, 1.13 to 4.18]); women age 60 to 69 and women age 70 to 79 had a risk similar to the overall main trial effect, which was not significant. Similarly, a treatment effect was reported based on number of falls in the 12 months prior baseline (p=0.05); an increasing risk of fracture among treatment group compared with placebo groups was seen with increasing number of falls in the 12 months prior to baseline. Participants with no history of falls who were assigned to vitamin D with calcium had a slightly reduced risk of fracture relative to participants assigned to placebo (HR, 0.74 ([95% CI, 0.56 to 0.98]); whereas participants with one, two, or three or more falls had an increasing likelihood of fracture with increasing number of falls if assigned to treatment relative to placebo participants, but the confidence intervals for the point estimates in these subgroups did not exclude a null effect. No interaction of treatment effect was observed for race or ethnic group, weight or body mass index, smoking status, or sunlight exposure.

WHI study authors also report several subgroup analyses related to hormone therapy use.[71, 99] In the main trial report, a borderline statistically significant interaction between treatment assignment in WHI Hormone Therapy trial and vitamin D with calcium treatment assignment was observed (p=0.07).[71] Participants assigned to active hormone therapy had a statistically significant reduced risk for hip fracture (HR, 0.58 [95% CI, 0.37 to 0.93]) while participants assigned to placebo hormone therapy had a numeric but statistically nonsignificant increase in hip fracture when assigned to vitamin D with calcium compared with placebo (HR, 1.15 [95% CI, 0.81 to 1.63]).[71] In a followup analysis, this interaction was evaluated across all 68,132 randomized participants in WHI clinical trials and this finding persisted (p for treatment interaction=0.01).[99] However, no interaction between hormone therapy use and vitamin D with calcium treatment allocation and incident total fractures (p=0.97) or clinical vertebral fractures (p=0.79) was identified. Further, the main trial report indicated that when the analysis included both active hormone therapy assignment and personal hormone use, the trend towards a treatment interaction for hip fracture was no longer present.[71]

Because the WHI CaD Trial allowed for personal use of supplements throughout the trial, considerable debate about whether the trial supplementation would have a different impact on naïve users of supplements has been postulated. The main WHI trial publication reported an HR for hip fracture of 0.70 (95% CI, 0.51 to 0.98) for nonusers of calcium supplements at baseline, an HR of 0.87 (95% CI, 0.61 to 1.24) among those taking less than 500 mg per day, and an HR of 1.22 (95% CI, 0.83 to 1.79) among those taking 500 mg or more per day (p for interaction=0.11).[71] In a separate analysis using the WHI CaD limited access data set, Bolland et al estimated effects for users and nonusers of vitamin D and calcium supplements at baseline.

This analysis found similar hip and total fracture incidences among these two subgroups; no statistically significant interactions were identified (p=0.72 for total fracture and p=0.65 for hip fracture).[97, 98] Similar findings were reported by the WHI study authors in an article published subsequent to the main trial findings.[98]

KQ2. Direct Evidence for the Harms of Supplementation With Vitamin D or Calcium Alone or Vitamin D Combined With Calcium

Summary of Results

Nine RCTs that randomized 51,375 participants reported on the effect of supplementation with vitamin D alone, calcium alone, or vitamin D with calcium on all-cause mortality, incident kidney stones, cardiovascular disease (CVD), or cancer. The evidence is dominated by the WHI CaD Trial,[71] which enrolled 36,282 women; the others enrolled only women (4 RCTs; 3,844 participants),[72, 74, 108, 109] only men (1 RCT),[92] or both women and men (3 RCTs).[76-79] Study characteristics and findings are summarized in **Tables 2−5**. Although studies reported on our KQ 2-specified outcomes, these outcomes were primary end points in only two studies. Studies reported statistically nonsignificant and imprecise effects over 3–7 years for all-cause mortality, incident cancer, and CVD.[108] No studies evaluated the impact of vitamin D alone on kidney stone incidence. Calcium alone did not increase the incidence of kidney stones over 2 to 4 years (pooled ARD, 0.0% [95% CI, -0.9% to 0.9%]; pooled RR, 0.68 [95% CI, 0.14 to 3.4]; I^2=0%, 3 RCTs, 1,292 participants), but vitamin D with calcium was associated with increased incidence over 4 to 7 years (pooled ARD, 0.3% [95% CI, 0.1% to 0.6%]; RR, 1.2 [95% CI, 1.04 to 1. 4]; I^2=0%, 3 RCTs, 39,659 participants).

All-Cause Mortality

Seven RCTs examined the effect of supplementation with vitamin D alone, calcium alone, or vitamin D with calcium on all-cause mortality.[71, 72, 76-79, 92, 109] Findings are summarized in **Table 2**.

Vitamin D Compared With Placebo: Study Characteristics

One new, good-quality RCT (Khaw, Scragg et al[78, 79] and three fair-quality RCTs (Trivedi et al,[110] Komulainen et al,[72] Lips et al[76]) all previously described reported on the effect of vitamin D alone on all-cause mortality. These studies examined doses of vitamin D that included 300 or 400 IU daily or 100,000 IU every month or 4 months over 3.3–5 years. They were conducted in New Zealand, United Kingdom, Finland, and The Netherlands, and three of the four studies included men. Three of the four studies were included in the prior review but all-cause mortality was not an outcome synthesized in the prior review. We identified two studies for use in sensitivity analyses. One study (Sanders et al[84]) was included in the prior review but was not eligible for the main analysis in this update because 35 percent of the study population had a history of fracture and the trial focused on enrolling subjects with a high risk for fracture. Another study (Hin et al[111]) was published since the last review but was not eligible for this update because 30 percent of the study population had a history of prior fracture.

Khaw, Scragg et al and Trivedi et al determined mortality outcomes using death certificates.[77, 111] Komulainen et al did not specifically describe how mortality was determined.[72] Lips et al determined mortality outcomes by asking participants' general practitioners or caretakers to immediately report deaths when they occurred and verifying all deaths with general practitioners.[76]

Vitamin D Compared With Placebo: Findings

All studies reported numeric but statistically nonsignificant decreases in all-cause mortality between vitamin D and placebo groups. The pooled ARD was -0.74% (95% CI, -1.80% to 0.32%; I^2=19.6%; 4 RCTs; 10,599 participants) and the pooled RR was 0.91 (95% CI, 0.82 to 1.01; I^2=0%). The results were similar when we included the two studies we identified for use in sensitivity analyses (**Appendix F Figures 11** and **12**).

Calcium Compared With Placebo: Study Characteristics

Reid et al, previously described, examined the effect of calcium alone on all-cause mortality.[92] This study randomized 323 healthy men age 40 years or older in New Zealand to 1,200 mg calcium citrate, 600 mg calcium citrate, or placebo over 2 years. The investigators did not provide detail about how mortality was ascertained.

We also included two fair-quality RCTs conducted in New Zealand and Australia in a sensitivity analysis.[88-91] These studies were not eligible for the main analysis because a third of the study populations had a history of prior fractures. Bolland and Reid et al[88, 89] compared 1,000 mg of oral calcium citrate with placebo over 5 years among 1,417 postmenopausal women age 55 or older and Prince and Lewis et al[90, 91] compared 1,200 mg of oral calcium carbonate with placebo over 4.5 years among 1,460 healthy, vitamin D-sufficient, women over age 70.

Calcium Compared With Placebo: Findings

Reid et al reported one death in each of the placebo, 600 mg calcium, and 1,200 mg calcium groups among the 290 participants with data at followup; effect estimates were not statistically significant and were imprecise.[92] The two RCTs included in a sensitivity analysis also reported statistically nonsignificant findings, though point estimates were on opposite sides of the null effect.[88-91] The pooled ARD including these studies was -0.15% (95% CI, -1.40% to 1.10%; I^2 = 0%; 3 RCTs, 3,240 participants) and the pooled RR was 0.95 (95% CI, 0.68 to 1.32; I^2 = 0%) (**Appendix F Figures 13** and **14**).

Vitamin D With Calcium Compared With Placebo: Study Characteristics

We identified one new trial reporting all-cause mortality for this update. Lappe et al[109] examined the effect of 2,000 IU of vitamin D_3 plus 1,500 mg of calcium carbonate daily compared with placebo for 4 years in 2,197 women (mean age 65 years).[109] The WHI CaD Trial, included in the prior review, also reported all-cause mortality.[96, 98, 112, 113] Ascertainment methods were not described in Lappe et al[109] while in the WHI CaD trial, mortality was ascertained by contacting participants' previously identified proxy informants, National Death Index searches, and obituary

notices.[112] In addition to effect estimates reported in the main WHI CaD Trial publication, a post hoc subgroup analysis by Bolland et al used the WHI limited access data set to report effect on all-cause mortality among participants who were using personal calcium or vitamin D supplements at baseline compared with those who were not.[97]

We also used the RCT conducted by Salovaara et al, described in a previous section, in a sensitivity analysis.[107] This study was not eligible for our main analysis because it was rated as poor quality and because approximately one-third of study participants had a prior history of fracture.

Vitamin D With Calcium Compared With Placebo: Findings

No significant differences in all-cause mortality were reported by either study. Lappe et al[109] reported 7 (0.6%) deaths in the vitamin D with calcium group and 9 (0.8%) deaths in the placebo group over 4 years (ARD -0.19% [95% CI, -0.90% to 0.52%]; RR, 0.77 [95% CI, 0.29 to 2.07]. The WHI CaD Trial reported 744 (4.1%) deaths in the vitamin D with calcium group and 807 (4.5%) deaths in the placebo group over 7 years (ARD, -0.36% [95% CI, -0.78% to 0.05%]; HR, 0.91 [95% CI, 0.83 to 1.01]).[98] In post hoc analyses using the WHI limited access dataset, Bolland et al reported no statistically significant interaction between use of personal supplements at baseline and treatment allocation (p for interaction=0.44).[97] The one trial used in a sensitivity analysis reported a numeric but statistically nonsignificant increase in all-cause mortality (RR, 1.17 [95% CI, 0.56 to 2.45]).[107]

Kidney Stones

Five RCTs examined the effect of supplementation with calcium alone or vitamin D combined with calcium on incident kidney stones.[71, 74, 92, 108, 109, 113, 114] No RCTs evaluating the effects of vitamin D alone on incident kidney stones were included in the prior review, and we identified no new eligible studies for this update. A summary of the findings is in **Table 3**.

Vitamin D Compared With Placebo: Study Characteristics

No RCTs evaluating the effects of vitamin D alone on incident kidney stones were identified. We identified three RCTs for use in a sensitivity analysis. Two were excluded from the main analysis because of poor quality related to high attrition and lack of specification about ascertainment of kidney stone outcomes.[86, 115] The third study was excluded because more than 20 percent of its study population had prevalent fractures or prior history of fractures at baseline.[110] The studies in the sensitivity analysis examined between 120 and 408 participants from the United States and Australia over 3–5 years, and evaluated daily doses of vitamin D ranging from 600 to 2,000 IU. In one study, kidney stones were ascertained through a self-report diary; in the other two studies, the methods of ascertaining stones were not described.

Vitamin D Compared With Placebo: Findings

In the sensitivity analysis, no kidney stones developed among any participants in any of the three studies.[86, 110, 115]

Calcium Compared With Placebo: Study Characteristics

Three fair-quality RCTs examined the effect of calcium alone on incident kidney stones.[74, 92, 108] Lappe et al[108] and Riggs et al[74] enrolled postmenopausal women (mean age 66 to 67 years) in the United States; Reid et al[92] enrolled healthy men from New Zealand who were age 40 years or older (mean age 56). In these studies, participants were randomized to oral calcium (600 to 1,600 mg daily) or placebo for 2–4 years. Reid et al ascertained kidney stones by self-report at each visit. The other studies did not describe how kidney stones were ascertained. The mean baseline serum 25-hydroxyvitamin D level among all women in the Lappe et al[108] trial was 71.8 nmol/L.

We considered five studies in a sensitivity analysis.[73, 86, 88, 90, 91, 93, 95] Three[73, 86, 93, 95] were excluded from the main analysis for poor quality because they did not specify how kidney stones were ascertained and had high attrition. Two were excluded from the main analysis because more than 20 percent of the study population had a history of fractures at baseline.[88-91] The studies in the sensitivity analysis examined the effects of daily 750–1,200 mg of calcium compared with placebo for 4–5 years. In these studies, kidney stone ascertainment was either by self-report or not described by study authors.

Calcium Compared With Placebo: Findings

In the three included studies,[74, 92, 108] which randomized 1,292 participants, six kidney stones occurred overall, three among those randomized to calcium and three in those assigned to placebo (**Table 3**). The pooled ARD for incident kidney stones was 0.00% (95% CI, -0.88% to 0.87%) and the pooled RR was 0.68 (95% CI, 0.14 to 3.36, I^2=0%, 3 RCTs, 1,259 participants) for calcium compared with placebo over 2–4 years of use. We added five additional studies in a sensitivity analysis.[73, 86, 88, 90, 91, 93, 95] Overall, a numeric but statistically nonsignificant decrease in incidence remained, though the magnitude of the relative decrease was attenuated because of mixed effects found among studies used in sensitivity analysis (**Appendix F Figures 15** and **16**).

Vitamin D Combined With Calcium Compared With Placebo: Study Characteristics

The 2007 RCT by Lappe et al[108] and the WHI CaD Trial,[71, 96, 113, 114] both rated as fair-quality for this outcome, were conducted in postmenopausal women in the United States and were included in the previous review. We identified one new fair-quality RCT, also conducted by Lappe et al for this update.[109] Lappe et al[108] examined the effect of 1,000 IU of vitamin D with 1,400–1,500 mg of oral calcium compared with placebo for 4 years in 734 women (mean age 67 years).[108] The WHI CaD Trial examined 36,282 postmenopausal women ages 50 to 79 years (mean age 62 years) who were randomized to 400 IU of oral vitamin D_3 with 1,000 mg of calcium daily or placebo for 7 years. Lappe et al[109] examined the effect of 2,000 IU of vitamin D_3 plus 1,500 mg of calcium carbonate daily compared with placebo for 4 years in 2,197 women (mean age 65 years).[109] In the WHI CaD Trial, kidney or bladder stones were self-reported at semiannual study visits or identified from a review of medical records for any subjects hospitalized for 48 hours or more. Lappe et al did not describe how kidney stones were ascertained in either the 2007 or 2017 trial.

We used one fair-quality study by Zhu & Prince et al in a sensitivity analysis; it was not eligible

for the main analysis because more than 20 percent of its study population had a history of fracture due to minimal trauma since age 50.[90, 110] This study, which was conducted in Australia, recruited relatively healthy and ambulatory women over the age of 70 years. The first 120 sequential participants of a larger trial were enrolled in this substudy and randomized to either 1,200 mg of calcium carbonate, 1,200 mg of calcium carbonate with 1,000 IU vitamin D_2, or daily placebo for 5 years.[110] The mean baseline serum 25-hydroxyvitamin D concentration was 68 nmol/L. Kidney stones were ascertained by a self-report adverse event diary.

Vitamin D Combined With Calcium Compared With Placebo: Findings

Lappe et al[108] reported one kidney stone in the vitamin D and calcium combined group (0.2%) and one in the placebo group (0.4%) for an ARD of -0.12% (95% CI, -0.93% to 0.69%) and RR of 0.65 (95% CI, 0.04 to 10.28) for participants randomized to vitamin D and calcium compared with placebo.[108] Lappe et al[109] reported 16 (1.5%) kidney stones in the vitamin D and calcium group and 10 (0.9%) in the placebo group for an ARD of 0.54% (95% CI, -0.36% to 1.44%) and RR of 1.59 (95% CI, 0.72 to 3.49).[109] In the WHI CaD Trial, a statistically significant increase in incidence was observed; 449 women (2.5%) in the vitamin D with calcium group developed kidney or bladder stones compared with 381 women (2.1%) in the placebo group (ARD, 0.37% [95% CI, 0.06 to 0.67]; RR, 1.17 [95% CI, 1.03 to 1.34]).[71, 96, 113, 114] The pooled ARD and RR showed a statistically significant increase in incidence (pooled ARD 0.33% [95% CI, 0.06% to 0.60%]; pooled RR, 1.18 [95% CI, 1.04 to 1.35]; I^2=0%, 3 RCTs, 39,213 participants) (**Appendix F Figures 17** and **18**). No kidney stones occurred in either the placebo or treatment group of the one study considered in sensitivity analysis.[110]

Cardiovascular Disease

Five RCTs examined the effect of supplementation with vitamin D alone,[72, 77-79] calcium alone,[92] or vitamin D with calcium[71, 98, 116-118] on CVD outcomes. Findings are summarized in **Table 4**.

Vitamin D Compared With Placebo: Study Characteristics

We identified one new, good-quality RCT that examined the effect of supplementation with vitamin D alone on CVD outcomes.[78, 79] In addition, we included two fair-quality RCTs from the prior review.[72, 77] Both RCTs have been previously described in detail under KQ 1. Briefly, Khaw, Scragg et al [78, 79] randomized 5,110 men and women ages 50 to 84 to an initial dose of 200,000 IU followed by 100,000 IU every month for a median of 3.3 years. Trivedi et al[77] randomized 2,037 men and 649 women ages 65 to 85 years in the United Kingdom to 100,000 IU of oral vitamin D_3 or placebo every 4 months over 5 years. Komulainen et al[72] randomized 232 postmenopausal women age 52 to 61 years in Finland to 300 IU of vitamin D_3 with 93 mg of calcium or to 93 mg of calcium alone and evaluated outcomes over a mean of 4.3 years.[72, 76] In all studies, treatment and control groups were balanced on the CVD risks that were measured at baseline. Khaw, Scragg et al ascertained outcomes through national data on cause of death and hospital discharges.[78, 79] Trivedi et al ascertained incidence of CVD using events reported on participant followup questionnaires or from causes listed on death certificates that were coded using an industry-standard classification system.[77] Komulainen et al did not specify how CVD events were ascertained, but they were reported as serious adverse events and, thus, were likely

captured as part of trial safety monitoring.[72, 119]

We identified three RCTs for use in sensitivity analysis.[84, 87, 120] The Sanders et al RCT (which we rated as fair quality for CVD outcomes) was included in the prior review for the USPSTF for fracture outcomes, but a synthesis of cardiovascular harm outcomes was not included.[84] As described under KQ 1, this study was conducted in Australia and randomized women (median age 76 years) to an annual 500,000 IU dose of vitamin D_3 or placebo for up to 5 years. It was not eligible for our main analysis because one third of its participants had a history of fracture since age 50. The other two studies considered in sensitivity analysis were excluded from the main analysis because of poor quality. These included the RCT by Cherniak et al,[120] which was conducted among 46 U.S. male veterans age 70 years or older who were randomized to oral vitamin D_3 2,000 IU daily or placebo for 6 months and the RCT by Glendenning et al,[87] which was a 9-month RCT of oral vitamin D_3 150,000 IU every 3 months versus placebo in 686 community-dwelling ambulatory women over age 70 years in Western Australia. Both studies were rated as poor quality because of measurement bias due to outcome specification and ascertainment and because they were conducted over relatively short periods of followup precluding a distinction between prevalent and incident cases.

Vitamin D Compared With Placebo: Findings

No statistically significant differences in incident cardiovascular or cerebrovascular outcomes were found for vitamin D compared with placebo; however, estimates were imprecise. Khaw, Scragg et al reported myocardial infarction over 3.3 years in 28 (1.1%) vitamin D group participants and in 31 (1.2%) placebo group participants (ARD, -0.12%, [95% CI, -0.71% to 0.47%]; HR, 0.90 [95% CI, 0.54 to 1.50]).[78] Similar, nonsignificant findings were found for stroke, venous thromboembolism (VTE), and heart failure outcomes reported by this study. Trivedi et al reported incident ischemic heart disease over 5 years in 224 participants (16.7%) assigned to vitamin D versus 233 participants (17.4%) assigned to placebo (ARD, -0.72% [95% CI, -3.56% to 2.12%]; age-adjusted RR, 0.94 [95% CI, 0.77 to 1.15]).[77] Among women, the age-adjusted RR was 0.79 (95% CI, 0.48 to 1.29) and among men was 0.98 (95% CI, 0.78 to 1.22). For incident cerebrovascular disease, 105 (7.8%) of participants in the vitamin D group versus 101 (7.5%) participants in the placebo group had events (ARD, 0.27% (95% CI, -1.74% to 2.29%); age-adjusted RR, 1.02 [95% CI, 0.77 to 1.36]). For this outcome, the age-adjusted RR for women was 1.19 (95% CI, 0.60 to 2.37) and was 0.99 (95% CI, 0.72 to 1.36) for men. CVD events in the other RCT (Komulainen et al[72]) were rare; in the vitamin D group, one woman had a myocardial infarction and one had a coronary bypass operation. No cardiovascular events were reported in the placebo group. We considered three additional trials in a sensitivity analysis (ARD range from -0.63% to 0.35%, RR range from 0.47 to 1.42), which reported nonsignificant findings for stroke and ischemic heart disease.

Calcium Compared With Placebo: Study Characteristics

One fair-quality RCT examined the association between supplementation with calcium alone and incident cardiovascular events. Reid et al randomized 323 predominantly white, healthy men age 40 years or older in New Zealand to daily oral placebo, 600 mg calcium citrate, or 1,200 mg calcium citrate.[92] Study groups were balanced on baseline CVD risk factors except for smoking;

the prevalence of smoking was higher in the placebo group (6%) than in the 600-mg per day (3%) and 1,200-mg per day (1%) calcium groups. Adverse events possibly influenced by calcium intake, including cardiovascular events, were prespecified in the trial protocol and asked about and recorded at each study visit.

We identified two RCTs[89, 91] for use in sensitivity analysis; both were excluded from the main analysis because the proportion of subjects with prevalent fracture at baseline was between 20 and 49 percent. Bolland and Reid et al[89] reported on a 5-year RCT in 1,471 postmenopausal women in New Zealand randomized to 1,000 mg calcium citrate daily or placebo. Data on incident myocardial infarction or stroke were collected during assessment of adverse events at every study visit. Lewis & Prince et al reported cardiovascular outcomes over 5 years from an RCT conducted among 1,460 women age 70 years or older recruited from the general population in Western Australia and randomized to 1,200 mg calcium carbonate daily or placebo.[90, 91] Atherosclerotic deaths and first-time hospitalizations were retrieved from the Western Australian Data Linkage System and events were defined using industry-standard diagnosis codes.

Calcium Compared With Placebo: Findings

Of participants who reported taking the assigned study medication at the end of the study, Reid et al reported no CVD events in the placebo group, one event in the 600 mg calcium group (ARD, 1.02% [95% CI, -1.75% to 3.80%]; RR, 3.03 [95% CI, 0.12 to 73.49]), and two events in the 1,200 mg calcium group (ARD, 2.15% [95% CI, -1.38% to 5.68%]; RR, 5.32 [95% CI, 0.26 to 109.35]).[92] The two studies considered in sensitivity analysis reported small numeric but statistically nonsignificant increases in incidence of myocardial infarction, stroke, or incident ischemic heart disease diagnosis (ARD range -0.81% to 1.43%; RR range 0.76 to 1.49).

Vitamin D and Calcium Compared With Placebo: Study Characteristics

Although the WHI CaD Trial was included in the prior review for the USPSTF, cardiovascular outcomes were not included in the synthesis. This fair-quality trial compared 400 IU of oral vitamin D_3 with 1,000 mg of calcium carbonate among 36,282 postmenopausal U.S. women.[71, 96, 98] Baseline CVD risk factors were balanced between groups. Of note, 51.9 percent of participants were users of hormone therapy at baseline, and 22.4 percent were allocated to the active hormone therapy group of the WHI Hormone Therapy Trial. Medical records related to self-reported myocardial infarction, stroke, and coronary revascularization were adjudicated centrally by physician adjudicators using standardized definitions.[71, 96, 98] Silent myocardial infarctions were diagnosed using serial electrocardiograms during the WHI CaD Trial; we only considered clinical myocardial infarction events in our synthesis.

In addition to the outcomes reported in the main study publication, we identified four additional analyses of CVD outcomes from the WHI CaD Trial.[98, 116-118] Two were analyses to evaluate the effect of supplementation among subgroups of women defined by use of personal calcium and vitamin D supplements at baseline. Bolland et al used the WHI CaD Trial limited access dataset to evaluate the risk of cardiovascular events, comparing women who did (54% of trial participants) and did not take personal supplements at the time of randomization.[116] In this analysis,[116] CVD risks were balanced between the vitamin D with calcium group and the placebo

group for the subgroup of participants that did not take personal calcium or vitamin D supplements and were similar to the baseline values reported by the main WHI CaD Trial.[71, 96] This analysis prespecified four cardiovascular end points and their combinations, which were slightly different from how CVD outcomes were specified in the main WHI trial.[116] The WHI study authors also published findings from a subgroup analysis related to personal use of supplements at baseline.[98]

The other two WHI CaD analyses reported on the effect of supplementation on incident VTE outcomes[117] and heart failure hospitalizations.[118] Blondon et al reported on incident VTE events; for women enrolled in the WHI CaD and Hormone Therapy Trials, events were confirmed and adjudicated while events for women enrolled in the WHI CaD and Dietary Modification Trial were self-reported.[117] In these analyses, relevant baseline characteristics, including history of VTE, history of CVD, history of cancer, current smoking, and WHI Hormone Therapy Trial participation, were balanced at baseline. Donneyong et al assessed incident heart failure by local and central (for a subset of subjects) physician adjudication of medical records for any hospitalization related to heart failure.[118] This analysis excluded 299 WHI CaD participants with a diagnosis of heart failure at enrollment. The investigators included a comparison of low-risk and high-risk subgroups defined by American College of Cardiology criteria for risk of heart failure (presence of hypertension, diabetes mellitus, coronary heart disease [CHD], or vascular disease). Compared with the low-risk subgroup, the high-risk subgroup was on average older, less white, and had a higher prevalence of family history of CVD.

We identified one study for use in sensitivity analysis. The Zhu et al substudy[110] enrolled the first 120 sequential participants of the main trial conducted by Prince and Lewis et al[90, 91] to one of three groups: calcium 1,200 mg; 1,000 IU vitamin D_2 with 1,200 mg calcium; or placebo. CVD events were ascertained with adverse event diaries.

Vitamin D and Calcium Compared With Placebo: Findings

Incident CVD and stroke. In the WHI CaD Trial, no statistically significant differences were reported in cardiovascular outcomes including for participants assigned to vitamin D with calcium compared with placebo.[98] For incident myocardial infarction (MI), 411 participants (2.3%) in the vitamin D and calcium group had an event and 390 participants (2.2%) in the placebo group had an event at 7 years (ARD, 0.11% [95% CI, -0.20% to 0.41%]; HR, 1.03; 95% CI, 0.90 to 1.19). Similar findings were reported for CHD and stroke (CHD ARD, 0.12% [95% CI, -0.21% to 0.45%]; HR, 1.03 [95% CI, 0.90 to 1.17]; stroke ARD, -0.09% [95% CI, -0.38% to 0.20%]; HR, 0.95 [95% CI, 0.82 to 1.10]).

In the one study considered in a sensitivity analysis, Zhu et al[110] reported no statistically significant difference in incident ischemic heart disease or stroke in the vitamin D with calcium group compared with placebo; however, events were rare and estimates were imprecise.

VTE. No statistically significant differences in any VTE events (idiopathic or secondary deep vein thrombosis (DVT) or pulmonary embolus [PE]) in women taking vitamin D with calcium compared with placebo over 7 years (ARD, -0.16% (95% CI, -0.44% to 0.12%); HR, 0.92 [95% CI, 0.79 to 1.07]) were observed in the WHI CaD Trial.[117] Similar findings were observed when

study authors considered DVT and PE events individually. A statistically significant lower risk of idiopathic VTE in women taking vitamin D with calcium compared with placebo was observed (HR, 0.62; 95% CI, 0.42 to 0.92) but this finding was sensitive to whether VTE events occurring in participants taking hormone therapy were considered as idiopathic or secondary events. The HR would have been 0.82 (95% CI, 0.64 to 1.06) had VTE events in women on hormone therapy been considered idiopathic and not secondary events.

Heart failure. No statistically significant difference in heart failure hospitalizations was observed between the vitamin D with calcium group (2.0%) compared with placebo group (2.1%) (ARD, -0.11% [95% CI, -0.40% to 0.18%); HR, 0.95 [95% CI, 0.82 to 1.09]).[118] In a subgroup analysis by baseline risk of heart failure, a statistically significant decrease in incident heart failure was seen for the low-risk subgroup (HR, 0.63 [95% CI, 0.46 to 0.87]) but not for the high-risk subgroup (HR, 1.06 [95% CI, 0.90 to 1.24)].

Cancer

Four RCTs examined the effect of supplementation with vitamin D alone,[72, 77, 119] calcium alone,[108] or vitamin D with calcium[71, 96-98, 113, 121, 122] on incident cancer. Findings are summarized in **Table 5**.

Vitamin D Compared With Placebo: Study Characteristics

Two fair-quality RCTs (Trivedi et al[77] and Komulainen et al[72]) examined the effect of vitamin D alone on cancer outcomes.[72, 77, 119] Both were included in the prior review for the USPSTF[2] for fracture outcomes, but only the trial by Trivedi et al[77] was included in the synthesis of cancer outcomes.

Study characteristics have been previously described; briefly Trivedi et al evaluated 100,000 IU of oral vitamin D_3 compared with placebo every 4 months over 5 years among 2,686 men and women ages 65 to 85 years in the United Kingdom; 24 percent of participants were women and 6 percent of participants reported a history of cancer, including skin cancer.[77] Komulainen et al randomized 232 women age 52 to 6 1 years in Finland to 300 IU of oral vitamin D_3 with 93 mg of elemental calcium daily or control (93 mg of elemental calcium daily only) and evaluated outcomes over a mean of 4.3 years.

Cancer outcomes included all incident cancers, all incident cancers excluding skin cancer, colon cancer, and respiratory cancer. Trivedi et al[77] ascertained incident cancer from self-reported questionnaires and cause of death on death certificates, while Komulainen et al described malignancies as serious adverse events.[119] Neither study described validation of cancer diagnoses by medical records or through clinical adjudicators.

We identified one good-quality RCT by Sanders et al[84] and one poor-quality RCT by Glendenning et al,[87] both conducted among women in Australia, for use in a sensitivity analysis. Sanders et al was excluded from our main analysis because 35 percent of the study participants had a history of fracture. This trial randomized 2,258 participants age 70 years and older to receive an annual dose of 500,000 IU of vitamin D_3 or placebo over 3–5 years. Cancer outcomes

were reported as adverse events.[84] Glendenning et al was rated poor quality because of measurement bias and the short period of followup (9 months) may have resulted in ascertainment of prevalent rather than incident cancer. Participants were age 70 years and were randomized to oral 150,000 IU vitamin D_3 at baseline, 3 months, and 6 months or placebo. Cancer diagnoses were self-reported in an adverse event diary.[87]

Vitamin D Compared With Placebo: Findings

Both included trials reported no statistically significant difference in the incidence of cancer between the placebo and vitamin D groups after 5 years. Trivedi et al reported incident cancer in 188 (14%) participants in the vitamin D group compared with 173 (13%) in the placebo group (ARD, 1.08% [95% CI, -1.50% to 3.66%; age-adjusted RR, 1.09 [95% CI, 0.86 to 1.36)]).[77] Trivedi et al also reported no statistically significant difference in the incidence of colon cancer overall and no differences in effect between men and women for any of the reported cancer outcomes (**Appendix D Table 3**).[77] Consistent with its younger study population, Komulainen et al reported a lower overall incidence of cancer: two cases (1.8%) in the vitamin D group and three cases (2.6%) in the placebo group (ARD, -0.82% [95% CI, -4.63% to 2.99%]; RR, 0.68 [95% CI, 0.12 to 4.02]).[119] Findings from the studies used in sensitivity analysis (Sanders et al[84] and Glendenning et al[87]) reported numeric but statistically nonsignificant decrease and increase in incidence, respectively.

Calcium Compared With Placebo: Study Characteristics

The RCT by Lappe et al described in a previous section examined the effect of calcium alone on cancer outcomes; it was rated as good quality for cancer outcomes.[108] In this RCT, 733 postmenopausal women age 55 years or older in rural Nebraska were randomized to daily supplementation (either 1,400 mg calcium citrate or 1,500 mg of calcium carbonate) or placebo for 4 years. Women were excluded if they had a history of cancer within the prior 10 years. Incident cancers were a secondary end point in the trial; participants self-reported any cancer diagnoses at each study visit, and all reported cancers were verified with medical records. Investigators reported results for total nonskin cancers, breast cancer, and colon cancer.

We used the fair-quality study by Zhu & Prince et al previously described in a sensitivity analysis; it was not eligible for the main analysis because more than 20 percent of its study population had a history of fracture.[90, 110] Outcomes for self-reported total incident cancer, including and excluding skin cancer, were reported.[110]

Calcium Compared With Placebo: Findings

In the study by Lappe et al, 17 (3.8%) women who took calcium reported a nonskin cancer diagnosis compared with 20 (6.9%) women who took placebo (ARD, -3.12% [95% CI, -6.56% to 0.31%]; RR, 0.55 [95% CI, 0.29 to 1.03]).[108]The overall number of breast cancer cases and colon cancer cases was small; effect estimates were not statistically significant and were imprecise (**Appendix D Table 3**).[108] The one RCT used in a sensitivity analysis reported a numeric but nonsignificant increase in incidence but estimates were very imprecise.[110]

Vitamin D With Calcium Compared With Placebo: Study Characteristics

One good-quality[108] trial and two fair-quality trials[71, 96-98, 109, 113, 121, 122] evaluated the effect of vitamin D plus calcium supplementation on cancer outcomes. Two trials[71, 108] were included in the previous review for the USPSTF[2]; one[109] is new to this update.

Lappe et al[108] evaluated 1,000 IU vitamin D_3 with 1,400 or 1,500 mg of calcium daily and Lappe et al[109] evaluated 2,000 IU vitamin D_3 with 1,500 mg of calcium daily; both compared supplements with placebo over 4 years.[108, 109] The WHI CaD Trial, previously described, evaluated daily oral 400 IU vitamin D_3 with 1,000 mg of calcium carbonate compared with placebo among 36,282 postmenopausal women age 50 to 79 years over 7 years.[71, 96, 98, 113, 121, 122] At baseline, 18 percent of women in the WHI CaD Trial had a family history of breast cancer and 16 percent had a family history of colorectal cancer. Eight percent of women were current smokers and 40 percent reported smoking in the past.[96] All studies reported total, breast, and colon cancer and confirmed self-reported cancers by medical records. In addition, the WHI CaD Trial reported incident melanoma skin cancer and additional subgroup analyses among women without a history of cancer[122] and among women with and without use of personal supplementation at baseline.[97] Bolland et al also reported WHI subgroup analyses related to the personal use of supplements at baseline.[97]

The Zhu & Prince et al substudy, previously described, was also identified for use in a sensitivity analysis of vitamin D with calcium compared with placebo.[90, 110]

Vitamin D With Calcium Compared With Placebo: Findings

Lappe et al[108] reported statistically significant decreases in incident total nonskin cancers. In this study, 13 women (2.9%) who took vitamin D with calcium, compared with 20 (6.9%) who took placebo, developed incident nonskin cancer for an ARD of -4.03% (95% CI, -7.35% to -0.70%) and RR of 0.42 (95% CI, 0.21 to 0.83) over 4 years.[108] The number of incident breast cancers and colon cancers was small and effect estimates were not significant and imprecise (**Appendix D Table 3**). These finding were not replicated in the Lappe et al[109] study, which reported no significant differences in total, breast or colon cancer.[109] In the WHI CaD Trial, 1,366 (7.5%) women had incident invasive cancer in the treatment group compared with 1,411 (7.8%) women in the placebo group (ARD, -0.28% [95% CI, -0.82% to 0.27%]; HR, 0.96 [95% CI, 0.89 to 1.04]).[98] With respect to cancer types, the WHI CaD Trial reported no statistically significant differences between the supplementation and placebo groups for incident colorectal, breast, non-melanoma skin cancer, or melanoma skin cancer (**Appendix D Table 3**).[121] Pooled estimates from these three trials (39,213 participants) found no significant association between vitamin D with calcium and total cancer incidence (pooled RR, 0.73 [95% CI, 0.49 to 1.10], I^2=75.8%; pooled ARD -1.48% [95% CI, -3.32% to 0.35%], I^2=70.9%), breast cancer (pooled RR, 0.82 [95% CI, 0.56 to 1.19], I^2=39.5%) or colon cancer (pooled RR, 1.07 [95% CI, 0.87 to 1.33], I^2=0%) (**Appendix F Figure 19** and **20**).

The one study we used in sensitivity analysis reported a numeric but statistically nonsignificant decrease in incident cancer between the group who received vitamin D with calcium and the group who received placebo, but events were rare and estimates were imprecise (ARD, -6.57%

[95% CI, -23.56% to 10.43%]; RR, 0.70 [95% CI, 0.28 to 1.79]).[110]

Subgroup Results

No studies of vitamin D alone or vitamin D with calcium reported subgroup findings by dose or dosing interval. As previously reported, one study of calcium alone (Reid et al [92]) reported findings by dose. (600 mg calcium citrate or 1,200 mg calcium citrate versus placebo). No difference in all-cause mortality, CVD, or kidney stone incidence was observed for either dose compared with placebo though all estimates were very imprecise.

One study of vitamin D alone (Trivedi et al[77] reported findings by sex. The overall RR for incident all-cause mortality was 0.90 (95% CI, 0.77 to 1.07) and was similar among women (RR 0.92 [95% CI, 0.54 to 1.55]) and men (RR 0.90 [95% CI, 0.76 to 1.07]). Similarly, this study reported no statistically significant effect on incident ischemic heart disease, cerebrovascular disease, or cancer among women or men, though all findings were imprecise (**Appendix D Table 3**).

Several subgroup analyses have been reported for vitamin D with calcium from the WHI CaD trial. In a 2011 publication using data from the WHI limited access dataset, Bolland et al[116] reported a statistically significant interaction between treatment allocation and use or nonuse of personal calcium or vitamin D supplements at the time of randomization for the outcomes of clinical myocardial infarction (p=0.04) and for stroke (p=0.02). For clinical myocardial infarction, the HR comparing vitamin D and calcium-allocated group with the placebo group was 0.92 (95% CI, 0.75 to 1.13) among women who were users of supplements at baseline. Among women who were nonusers of supplements at baseline, the HR was 1.22 (95% CI, 1.00 to 1.50). For stroke, the HR was 0.83 (95% CI, 0.67 to 1.02) among users of supplements at baseline and 1.17 (95% CI, 0.95 to 1.44) among nonusers. These authors reported no statistically significant interaction for the outcomes of coronary revascularization or death from CHD from this subgroup analysis. In a 2013 publication, WHI investigators also reported on subgroup analyses related to CVD event. Among women not taking supplements at baseline, the HR for myocardial infarction was 1.11 (95% CI, 0.90 to 1.37) for women allocated to treatment, compared with control.[98] Similar HRs were observed among baseline nonusers of supplements for CHD (HR, 1.03 [95% CI, 0.85 to 1.25]) and stroke (HR, 1.12 [95% CI, 0.90 to 1.39]). Differences in CVD outcome specification between the two subgroup analyses may explain the differences in findings.

With respect to cancer outcomes, Bolland et al reported statistically significant interactions between the CaD treatment allocation and use or nonuse of personal vitamin D or calcium supplementation at baseline for total incident cancer (p for interaction=0.003), invasive breast cancer (p for interaction=0.005), and invasive colorectal cancer (p for interaction=0.044).[97] Overall, 57 percent of women reported no use of personal supplementation at baseline, and among these women, significantly fewer cases of incident total cancer and incident breast cancer occurred among those who received vitamin D with calcium compared with those who received placebo. For the women who reported supplement use at baseline, findings were similar to those main analysis in that no statistically significant differences between treatment and placebo groups were found.[97] Findings were the same in a similar subgroup analysis subsequently

reported by the WHI study authors.[98]

Other Adverse Events

Other adverse events reported by included studies are detailed in **Appendix D Table 4**. The most common adverse event reported was constipation. It was more common in treatment groups than placebo studies in some, but not all studies that reported this event. A few studies reported on serious adverse events other than those already discussed in KQ 2; these events were rare and were noted by study authors to be unrelated to study medication.

Chapter 4. Discussion

Summary of Evidence

Table 6 provides a summary of findings and applicability organized by KQ and then by intervention (vitamin D alone, calcium alone, or vitamin D with calcium). In addition to a summary of effect estimates, this table also includes an assessment of consistency and precision of the effect estimate(s), body of evidence limitations, and study quality, which we used to assign a strength of evidence rating for each intervention and outcome.

Evidence for Effect of Supplementation on Fracture Prevention

Among the community-dwelling populations without prior history of fractures or known vitamin deficiency or osteoporosis included in this review, we rated the strength of evidence as low for no benefit of supplementation with vitamin D alone or vitamin D with calcium on fracture prevention over 3–7 years. This is consistent with the findings of the prior review and is not surprising given that only one new study was identified. Findings were imprecise and confidence intervals in all but one study included the null effect and the absolute differences in incidence reported may not be clinically meaningful. Few studies were powered for fractures as a primary end point, and even those that were (i.e., the WHI CaD Trial) were powered based on an effect size that was nearly twice as large as what was observed in the trial. Although the primary intent-to-treat analysis in the WHI CaD Trial was a null effect, some consider the bone density changes observed, the favorable per-protocol analyses of adherent participants, and some of the favorable subgroup analyses among nonusers of supplements at baseline and among older participants as evidence of a favorable effect on bone health.[71] We did not consider any subgroup analyses findings in our assessment of the strength of evidence because of the known methodologic limitations and challenges associated with interpreting subgroup findings.[123]

We found limited evidence to draw conclusions regarding the impact of calcium alone on fracture prevention and rated the strength of evidence as insufficient. We found only two eligible studies (N=339). Only one reported a clinical fracture outcome in addition to incident morphometric vertebral fractures; the other reported only morphometric vertebral fractures. Small sample sizes and relatively rare event rates in the studies led to imprecise effect estimates.

The body of evidence on vitamin D alone is applicable to men and postmenopausal women, while the body of evidence for vitamin D with calcium and for calcium alone was limited to postmenopausal women. Daily doses of vitamin D ranged from 300 to 700 IU; one study used a 100,000 IU oral dose every 4 months (equivalent to 833 IU per day). Daily oral doses of calcium ranged from 500 to 1,600 mg. However, not enough eligible studies were identified to ascertain the influence of dose, route, or frequency on incident fractures.

We found some evidence of reporting bias for this KQ. One study (N=1,180) comparing calcium alone, vitamin D with calcium, or placebo was designed with fractures as a primary outcome and was completed in 2005, although no fracture outcomes have been published to date. Other study

findings have been published.[108, 124] Per the study author, data from the study suggested no effect on fracture incidence; however, the study was not published because of concerns related to study contamination because of participant use of alendronate, which came to market during the study (personal communication with author). The identification of other unpublished studies with null findings would increase the certainty for drawing conclusions about the lack of effect of supplementation on fracture prevention.

Evidence for Effect of Supplementation on Harms

This review focused primarily on four harms; all-cause mortality, kidney stones, CVD, and cancer. We were unable to ascertain the impact of dose, duration, or frequency on these harms because not enough eligible studies were available. Though cohort and case-control studies of supplementation were eligible for KQ 2 outcomes in this review, we excluded those identified through our search for poor quality because of many of the methodologic limitations also noted by others.[125, 126] Further, we did not consider studies evaluating the association between serum vitamin D levels and all-cause mortality, kidney stones, CVD, or cancer incidence as this has been previously synthesized.[15] Thus, the evidence for harms that we summarized on behalf of the USPSTF comes from randomized controlled trials.

The evidence for the effect of supplementation with vitamin D alone or with calcium on all-cause mortality over 3–7 years suggests no clinically meaningful harm. The absolute risk differences ranged from -1.9 percent to 0.1 percent, but findings were imprecise; thus, we assigned a low strength of evidence to this finding. This body of evidence is applicable to men and postmenopausal women. We found the evidence for calcium alone to be limited for assessing impact on all-cause mortality. The single study available suggests no effect on mortality, but was very imprecise, and only included men. Thus, the strength of evidence for calcium alone on this outcome was rated as insufficient.

The evidence for the impact of supplementation on incident kidney stones was mixed. We identified no eligible studies of vitamin D alone that reported this outcome, resulting in an insufficient strength of evidence rating. The evidence for calcium alone suggests no increased incidence of kidney stones over 2–4 years, although findings are imprecise. Further, this body of evidence was limited by lack of information on how kidney stone outcomes were ascertained; thus, we assigned a low strength of evidence to this finding. The body of evidence on vitamin D with calcium comes from three RCTs. One of the trials (the WHI CaD Trial) was large and provided reasonably precise estimates of a small harm, and when pooled with two smaller studies with nonsignificant differences, this harm persisted. %%%Thus, we assigned a moderate strength of evidence for harm.

The evidence for the effect of supplementation with vitamin D alone or with calcium suggests no clinically meaningful harm with respect to CVD outcomes over 4–7 years. The body of evidence related to vitamin D alone included three RCTs that were consistent, but the estimates of effect were imprecise. The body of evidence for vitamin D with calcium was limited to a single study in women (WHI CaD Trial) with a sufficient sample size and event rate for precise estimates. Thus, we assigned a low strength of evidence for no harm for vitamin D alone or with calcium interventions. Findings from one of the two post hoc analyses of the WHI CaD Trial suggested

that trial participants assigned to supplementation with vitamin D and calcium who were not taking personal supplements at the time of randomization had a marginally increased risk of cardiovascular events relative to those who were taking personal supplements at the time of randomization.[116] However, the post hoc analysis by the WHI CaD study authors did not report similar findings,[98] possibly because of slight differences in the way in which outcomes were specified between the two analyses.

We found the evidence limited for assessing the effect of calcium alone on CVD outcomes. The single study suggested no effect over 2 years but was limited by imprecise estimates and minimal information about outcome specification and ascertainment; thus, we rated this body of evidence as insufficient. The role of dietary and supplemental calcium on intermediate CVD outcomes (i.e., vascular calcification) and clinical CVD outcomes has been the subject of recent debate, with several analyses and meta-analyses published related to this issue in the past several years.[125-130] Most of the meta-analyses and systematic reviews on this topic included broader study populations and settings (e.g., institutionalized elderly, participants with prior history of fracture) than specified in our review. These analyses have found mixed results, some suggesting a small increased risk for CVD[126, 128] and others suggesting no effect (either harm or benefit)[125, 129] or inconclusive findings.[127] Several of these reviews included observational study designs. Of particular concern in using observational evidence to assess this relationship is that osteoporosis (a common indication for calcium supplement) and CVD risk factors overlap (e.g., smoking, physical activity), leading to high potential for confounding when looking at the association between calcium use and CVD events.

Last, we found the evidence for the impact of vitamin D alone and calcium alone to be limited for drawing conclusions related to the impact of supplementation on cancer incidence; thus, we rated these bodies of evidence as insufficient. Two RCTs of vitamin D alone reported inconsistent and imprecise findings; only a single study reported the impact of calcium alone and its findings were imprecise. The evidence for vitamin D with calcium supplementation over 4–7 years suggests no increased cancer incidence, but results were somewhat inconsistent; thus, we assigned a low strength of evidence to this finding. These findings are only applicable to postmenopausal women.

Limitations of the Evidence

Most studies were not powered for the fracture or harm outcomes considered in this review; thus, small sample sizes and low event rates resulted in imprecise effect estimates. Some studies, notably the WHI CaD Trial, allowed for use of personal calcium and vitamin D supplements during the study; thus, these trials could be characterized as trials of provider-directed supplementation, and some have suggested this design feature as an explanation for the null intention-to-treat analysis findings reported by the WHI CaD Trial.[131]

Heterogeneity in outcome specification is another limitation of this body of evidence. The specific types of fractures that were considered as contributing to "total fracture" included both traumatic and osteoporotic in most studies, and the specific sites contributing to total fractures varied across studies. Author queries were required to determine whether some studies reporting vertebral fractures were reporting clinical or morphometric fractures. Studies evaluating harms

varied in specificity of definition or rigor of harm outcome ascertainment. Because harms were rarely the main study aim, little information was provided regarding how harms were defined, ascertained, or validated. Some studies relied on self-report, some on adverse event reporting during study monitoring; others relied on secondary data sources (registries, claims, death certificates) to identify cases. Although some evidence on men exists, the majority of this body of evidence is applicable to postmenopausal women, and few studies include populations that are racially representative of the U.S. population. Finally, only a few studies evaluated doses more than 800 IU per day. The evidence on calcium included doses ranging from 400 mg to 1,600 mg per day.

Because this review was narrower in scope than other published reviews of vitamin D (with or without calcium), the conclusions differ somewhat from the conclusions drawn from reviews with a broader or different scope. Bolland and Grey discuss the issue of discordant results from different meta-analyses on the same topic using vitamin D supplementation and fracture as an example.[132] In their analysis, differences in trial selection, outcome definitions used, and analytic approaches explain the majority of differences in findings. Across a body of evidence of 25 trials, they found strong statements concluding both benefit and no benefit. Thus, it is important to consider the scope of the populations and interventions included when drawing conclusions from the body of evidence in this review to avoid inappropriate comparisons to reviews with a different scope. We contrast our findings with two recent systematic reviews below.

The 2014 Cochrane review evaluated vitamin D and vitamin D analogues for preventing fractures and, similar to our review, found no benefit for vitamin D alone; however, they concluded that vitamin D with calcium may prevent fracture.[133] The study populations considered in the Cochrane review included participants with osteoporosis and institutionalized participants and secondary prevention populations. The fracture benefits overall appear to be largely attributable to benefits among the high-risk populations, with little to no benefit in lower-risk populations (1 fewer hip fracture per 1,000 community-dwelling adults per year [95% CI, 0 to 2]). Like our review, the Cochrane review concluded that vitamin D with calcium was associated with increased gastrointestinal and renal disease, but did not adversely affect the risk of death.

The 2016 systematic review and meta-analysis of calcium and vitamin D supplementation conducted on behalf of the National Osteoporosis Foundation (NOF) included eight trials.[134-136] Two were conducted in institutional settings, two were exclusively secondary prevention trials, and the study population of one trial had more than 50 percent of participants with a prior fracture; thus, all these studies were out of scope for our update review. Of the remaining three trials in the NOF analysis, we used one in our sensitivity analyses because it had between 20 and 50 percent of subjects with a history of prior fracture.[107] The other two trials, Dawson-Hughes et al[75] and the WHI CaD trial,[71] were included in our review; however, the NOF analysis used data from WHI CaD subgroups related to adherence to assigned pills and personal supplement use, not data from the intent-to-treat analysis. The NOF analysis reported an overall RR for total fracture incidence of 0.86 (95% CI, 0.75 to 0.98) and for hip fractures of 0.61 (95% CI, 0.46 to 0.82).

Limitations of the Review

This review has several limitations. The review was scoped to focus on community-dwelling populations not known to have vitamin D deficiency or existing metabolic bone disease (e.g., osteoporosis), a high risk for falls, or prior history of fracture, for applicability to unselected primary care populations. Although some patients at higher fracture risk may be included in this population, our review does not directly address the effect of supplementation on higher risk, selected populations, including those in institutional settings. This review was largely focused on supplementation for the primary prevention of fracture, yet studies included participants with and without a prior history of osteoporotic fracture. When studies did not report the proportion of subjects with a history of prior osteoporotic fracture, we contacted study authors to determine whether such data were available; in most cases data were not available. Thus, we included these studies in the review because baseline characteristics in these studies were similar to characteristics reported in the studies that were largely focused on primary prevention.

We limited our review to oral or injectable vitamin D and oral calcium preparations that are available as dietary supplements. We did not consider vitamin D analogues or formulations typically dispensed with a prescription for the treatment of disease. Our review was limited to fracture outcomes for KQ 1; thus, studies that only reported the impact on intermediate bone outcomes (such as bone turnover markers or bone mineral density) or falls would not have been included. However, the USPSTF has a separate evidence review related to interventions to prevent falls that included vitamin D as an eligible intervention. Our literature search for KQ 2 was focused on the harms we prespecified; however, other harms that were reported in eligible studies were captured.

Future Research Needs

RCTs that enroll unselected primary care populations with study aims powered to assess fracture outcomes and protocols designed to minimize contamination would address the major limitations of the current body of evidence. Because fractures are relatively uncommon in unselected populations, RCTs with sample sizes of similar magnitude as the WHI CaD Trial would likely be needed to conclude with high certainty that no effect of supplementation on fracture exists. Similarly, for harms, RCTs with larger sample sizes and valid and reliable outcome ascertainment methods are needed to conclude with high certainty that no important harms exist. We are aware of seven ongoing trials of vitamin D supplementation; study details are provided in **Appendix G**. These trials may offer additional evidence related to the impact of vitamin D on mortality and incident cancer; however; none are powered for fractures as a primary study end point.

We identified no ongoing trials of calcium supplementation. Because of the controversy related to calcium supplementation and CVD outcomes, a single good-quality RCT powered for primary cardiovascular end points conducted in healthy community-dwelling adults would be influential. Future research involving calcium supplementation should consider designs that exclude existing

users of supplements from enrollment or that prespecify analyses based on use of supplements at baseline.

Analyses that assess the burden of fractures among unselected populations and the relative importance of fracture prevention in these populations relative to other health needs may help to clarify the focus of future supplementation research in this population. Future research in this population could involve higher doses of vitamin D or vitamin D analogues.

Conclusion

In unselected, community-dwelling populations without known osteoporosis or vitamin D deficiency, the evidence does not support a finding of fewer fractures with vitamin D supplementation alone or with calcium; the evidence for supplementation with calcium alone is limited. The evidence suggests that supplementation with vitamin D alone does not increase all-cause mortality or cardiovascular events, but the evidence is limited for other harms. The evidence suggests that supplementation with calcium alone does not increase the incidence of kidney stones, but the evidence is limited for other harms. The evidence suggests that vitamin D with calcium does not increase all-cause mortality, cardiovascular events, or cancer incidence, but it is associated with an increase in the incidence of kidney stones.

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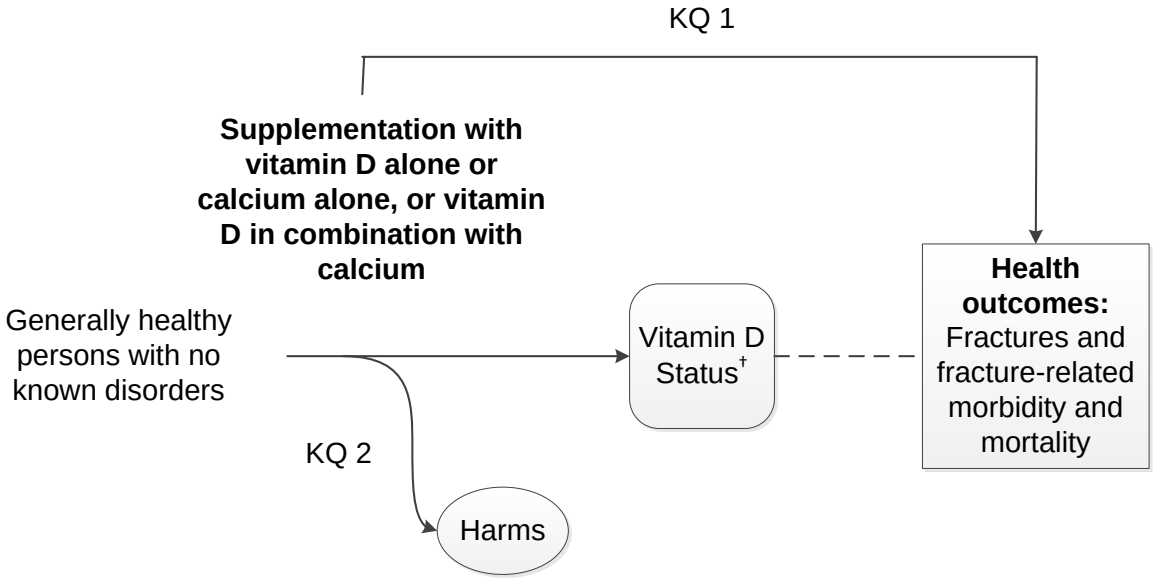
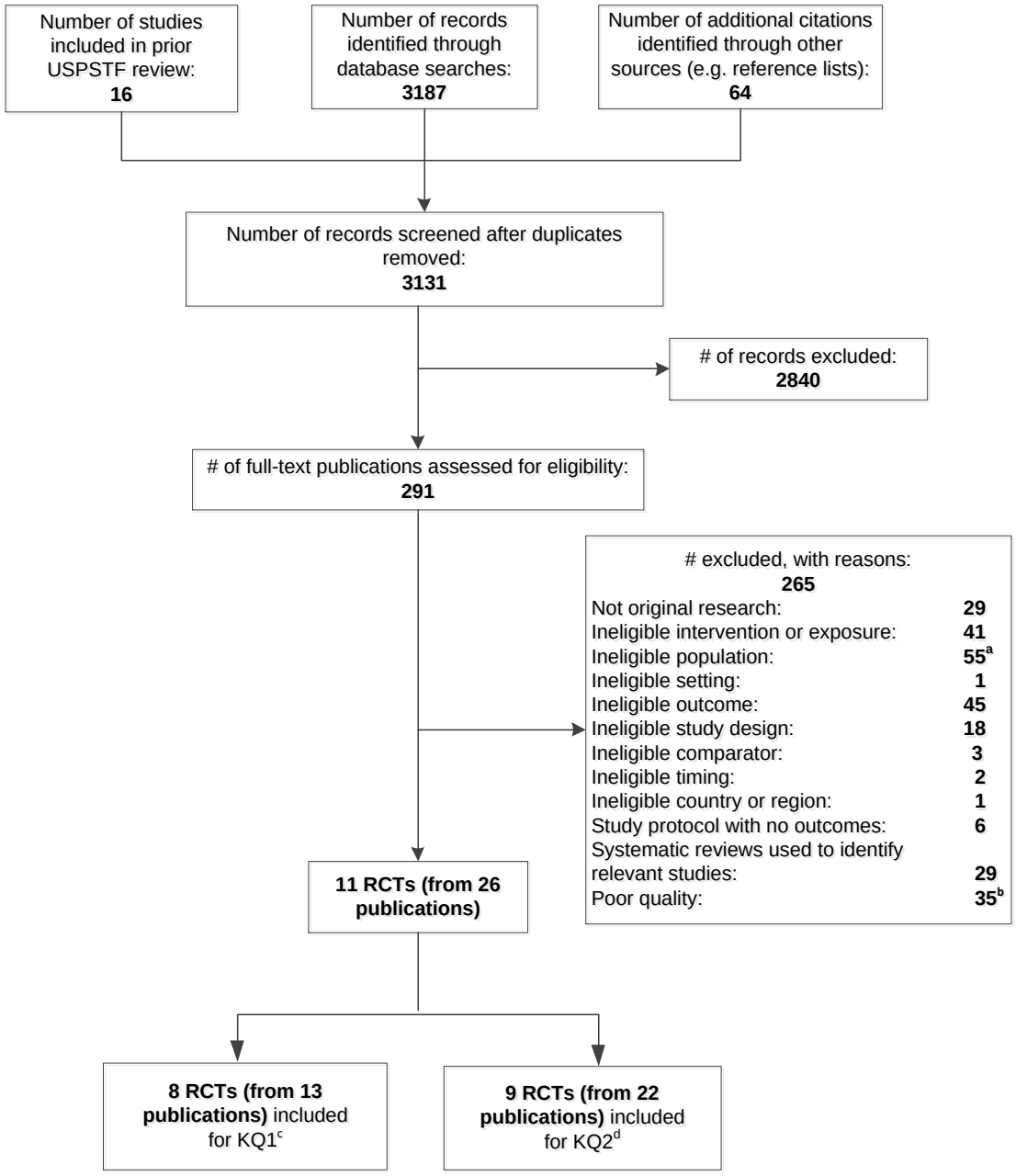
Figure 1. Analytic Framework



† Measures of whole body calcium status do not exist; thus the indirect evidence pathway for calcium cannot be evaluated.

Figure 2. Literature Search Flow Diagram



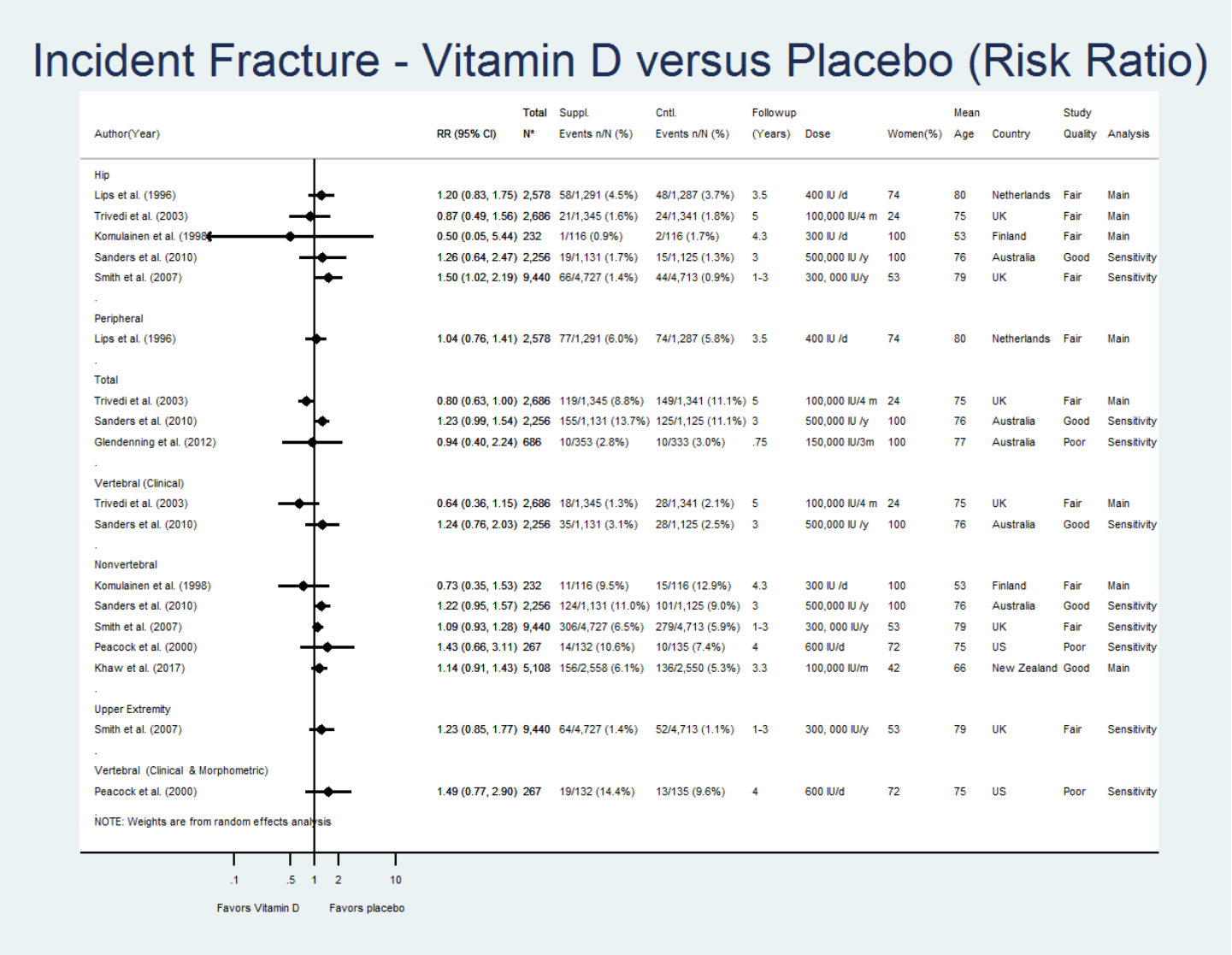
[a]Five RCTs (in 7 publications) that were excluded for ineligible study population were used in sensitivity analyses (the study populations in these studies included between 20 and 50% of participants with prior or prevalent fracture).

[b]Eight RCTs (in 9 publications) and 22 cohort or case-control studies (in 26 publications) were excluded for poor quality. Seven of the poor quality RCTs were used in sensitivity analyses.

[c]Ten RCTs (in 13 publications) were used in sensitivity analyses for KQ1; 4 were excluded from the main analyses because of ineligible population, 5 were excluded because of poor quality, and 1 was excluded for both ineligible population and poor quality.

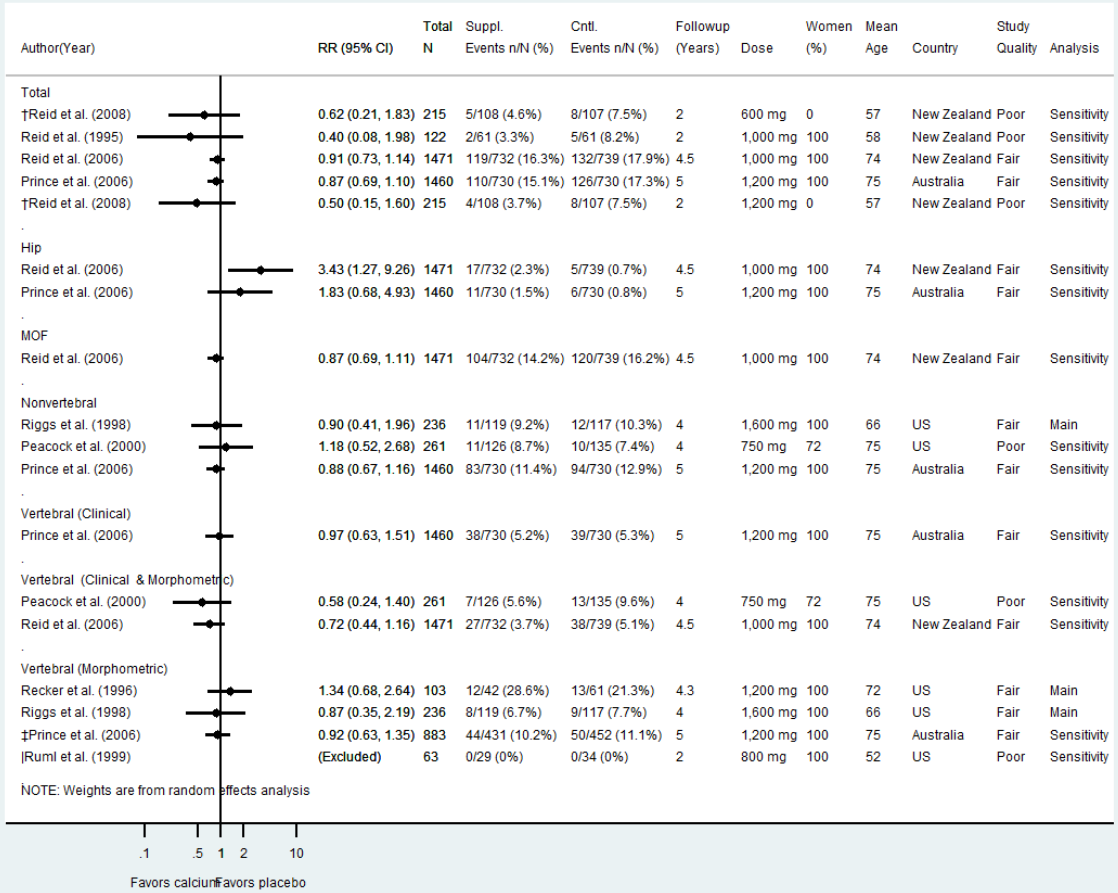
[d]Eleven RCTs (in 15 publications) were used in sensitivity analyses for KQ2; 4 were excluded from the main analyses because of ineligible population, 6 were excluded because of poor quality, and 1 was excluded for both ineligible population and poor quality.

Figure 3. Impact of Vitamin D Supplementation on the Prevention of Fractures



Note: fractures were not the primary study aim for most included studies; only Lips et al and Trivedi et al indicated fracture incidence as a primary study aim.
* Represents N analyzed, which may differ from the N randomized in some studies.
Abbreviations: CI=confidence interval; Cntl=control or placebo; d=days; IU=international units; m=months; n or N=number of participants; RR=relative risk ratio; UK=United Kingdom; US=United States

Incident Fracture - Calcium versus Placebo (Risk Ratio)

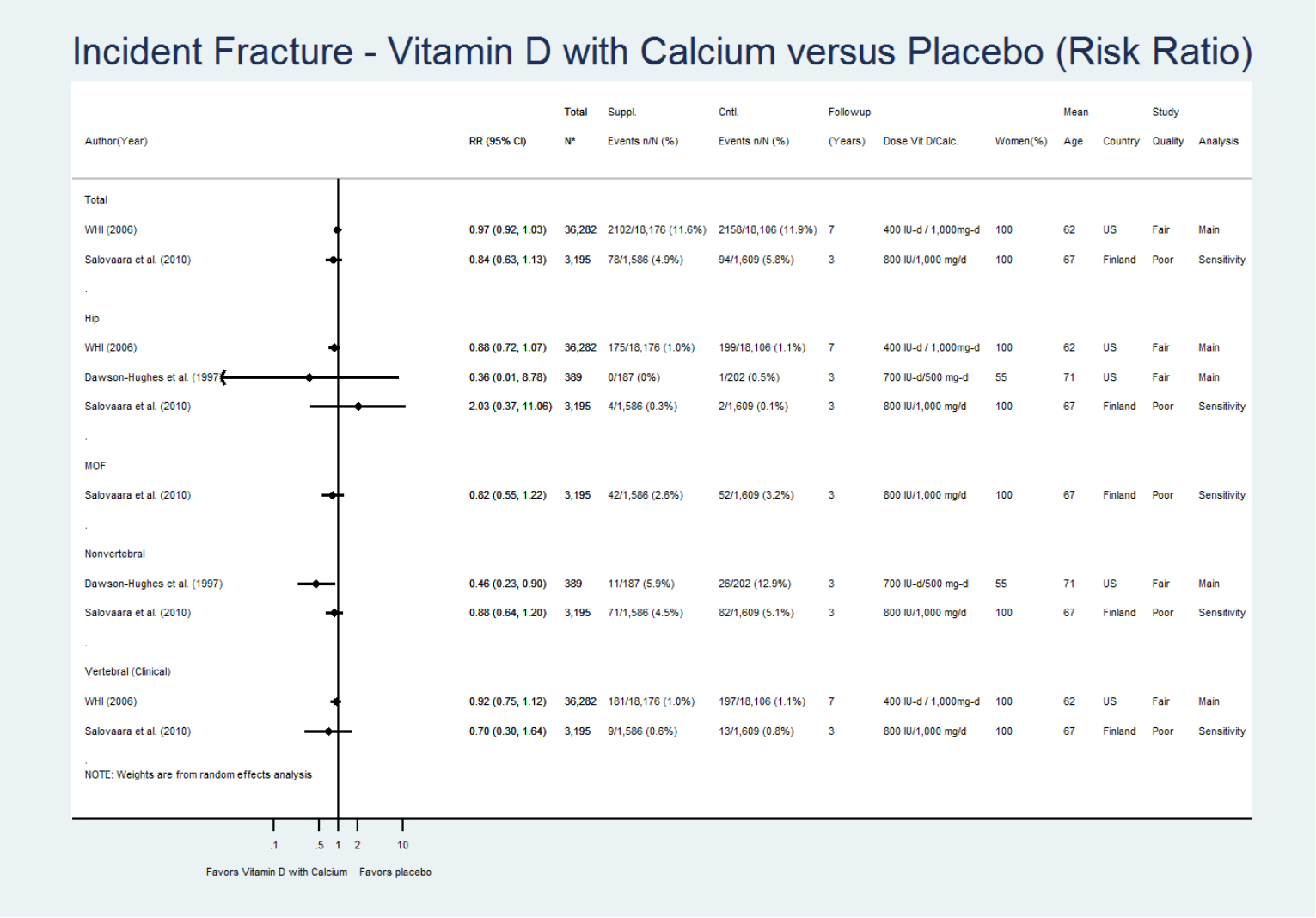


Author(Year)	RR (95% CI)	Total N	Suppl. Events n/N (%)	Cntl. Events n/N (%)	Followup (Years)	Dose	Women (%)	Mean Age	Country	Study Quality	Analysis
Total											
†Reid et al. (2008)	0.62 (0.21, 1.83)	215	5/108 (4.6%)	8/107 (7.5%)	2	600 mg	0	57	New Zealand	Poor	Sensitivity
Reid et al. (1995)	0.40 (0.08, 1.98)	122	2/61 (3.3%)	5/61 (8.2%)	2	1,000 mg	100	58	New Zealand	Poor	Sensitivity
Reid et al. (2006)	0.91 (0.73, 1.14)	1471	119/732 (16.3%)	132/739 (17.9%)	4.5	1,000 mg	100	74	New Zealand	Fair	Sensitivity
Prince et al. (2006)	0.87 (0.69, 1.10)	1460	110/730 (15.1%)	126/730 (17.3%)	5	1,200 mg	100	75	Australia	Fair	Sensitivity
†Reid et al. (2008)	0.50 (0.15, 1.60)	215	4/108 (3.7%)	8/107 (7.5%)	2	1,200 mg	0	57	New Zealand	Poor	Sensitivity
.											
Hip											
Reid et al. (2006)	3.43 (1.27, 9.26)	1471	17/732 (2.3%)	5/739 (0.7%)	4.5	1,000 mg	100	74	New Zealand	Fair	Sensitivity
Prince et al. (2006)	1.83 (0.68, 4.93)	1460	11/730 (1.5%)	6/730 (0.8%)	5	1,200 mg	100	75	Australia	Fair	Sensitivity
.											
MOF											
Reid et al. (2006)	0.87 (0.69, 1.11)	1471	104/732 (14.2%)	120/739 (16.2%)	4.5	1,000 mg	100	74	New Zealand	Fair	Sensitivity
.											
Nonvertebral											
Riggs et al. (1998)	0.90 (0.41, 1.96)	236	11/119 (9.2%)	12/117 (10.3%)	4	1,600 mg	100	66	US	Fair	Main
Peacock et al. (2000)	1.18 (0.52, 2.68)	261	11/126 (8.7%)	10/135 (7.4%)	4	750 mg	72	75	US	Poor	Sensitivity
Prince et al. (2006)	0.88 (0.67, 1.16)	1460	83/730 (11.4%)	94/730 (12.9%)	5	1,200 mg	100	75	Australia	Fair	Sensitivity
.											
Vertebral (Clinical)											
Prince et al. (2006)	0.97 (0.63, 1.51)	1460	38/730 (5.2%)	39/730 (5.3%)	5	1,200 mg	100	75	Australia	Fair	Sensitivity
.											
Vertebral (Clinical & Morphometric)											
Peacock et al. (2000)	0.58 (0.24, 1.40)	261	7/126 (5.6%)	13/135 (9.6%)	4	750 mg	72	75	US	Poor	Sensitivity
Reid et al. (2006)	0.72 (0.44, 1.16)	1471	27/732 (3.7%)	38/739 (5.1%)	4.5	1,000 mg	100	74	New Zealand	Fair	Sensitivity
.											
Vertebral (Morphometric)											
Recker et al. (1996)	1.34 (0.68, 2.64)	103	12/42 (28.6%)	13/61 (21.3%)	4.3	1,200 mg	100	72	US	Fair	Main
Riggs et al. (1998)	0.87 (0.35, 2.19)	236	8/119 (6.7%)	9/117 (7.7%)	4	1,600 mg	100	66	US	Fair	Main
‡Prince et al. (2006)	0.92 (0.63, 1.35)	883	44/431 (10.2%)	50/452 (11.1%)	5	1,200 mg	100	75	Australia	Fair	Sensitivity
ǀRuml et al. (1999)	(Excluded)	63	0/29 (0%)	0/34 (0%)	2	800 mg	100	52	US	Poor	Sensitivity

NOTE: Weights are from random effects analysis

Note: fractures were not the primary study aim for any included studies.
* Represents N analyzed, which may differ from the N randomized in some studies.
† This study had three study groups: placebo, 600 mg, and 1,200 mg; this figure reflects the comparison between each active comparator and placebo separately.
‡ The total N with available data for this outcome was different from the other outcomes analyzed in this study.
ǀ This study is excluded from the metaanalysis because of 0 events in both groups.
Abbreviations: CI=confidence interval; Cntl=placebo; d=day; mg=milligram; MOF=major osteoporotic fracture (defined as all fractures except those of head, hands, feet and ankles and those resulting from major trauma); n or N=number of participants; RR=relative risk ratio; US=United States; y=year.

Figure 5. Impact of Vitamin D With Calcium Supplementation on the Prevention of Fractures



Note: fractures were not the primary study aim for most included studies; only the WHC indicated fracture incidence as a primary study aim.
* Represents N analyzed, which may differ from the N randomized in some studies.
Abbreviations: Calc=calcium; CI=confidence interval; Cntl=placebo; d=day; IU=international units; mg=milligram; MOF=major osteoporotic fracture (defined as clinical vertebral, hip, forearm, and proximal humerus); n or N=number of participants; RR=relative risk ratio; US=United States; Vit D=vitamin D; WHI=Women's Health Initiative; y=year.

Table 1. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Fracture Type	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI) RR or HR (95% CI)	Study Quality
Vitamin D Compared With Placebo or Control									
Komulainen et al, 1998[72]	232*	Community-dwelling women ages 52 to 61 years between 6 and 24 months postmenopause	300 IU oral vitamin D_3 with 93 mg calcium† daily, 93 mg calcium† daily	Mean 4.3 (range 0 to 5.9)	Hip	2 (1.7)	1 (0.9)	ARD, -0.86% (-3.77% to 2.04%)‡ RR, 0.50 (0.05 to 5.44)‡	Fair
					Non-vertebral	15 (12.9)	11 (9.5)	ARD, -3.45% (-11.55% to 4.66%)‡ RR, adjusted for baseline femoral neck BMD and previous fractures, 0.64 (0.29 to 1.42)	
Lips et al, 1996[76]	2,578	Healthy adults 70 years or older (74% women) recruited from general practitioners or from apartment houses or homes for the elderly§	400 IU oral vitamin D_3 daily, placebo daily	Median 3.5	Hip	48 (3.7)	58 (4.5)	ARD, 0.76% (-0.77% to 2.30%)‡ Unadjusted HR, 1.18 (0.81 to 1.71)	Fair
					Peripheral‖	74 (5.8)	77 (6.0)	ARD, 0.21% (-1.60% to 2.03%)‡ Unadjusted HR, 1.03 (0.75 to 1.40)	
Trivedi et al, 2003[77]	2,686	Community dwelling adults 65 to 85 years (24% women)	100,000 IU oral vitamin D_3 every 4 months, placebo every 4 months	Planned 5	Total¶	149 (11.1)	119 (8.8)	ARD, -2.26% (-4.53% to 0.00%)‡ Age-adjusted RR, 0.78 (0.61 to 0.99)#	Fair
					Hip	24 (1.8)	21 (1.6)	ARD, -0.23% (-1.20% to 0.74%)‡ Age-adjusted RR, 0.85 (0.47 to 1.53)**	
					Vertebral (clinical)	28 (2.1)	18 (1.3)	ARD, -0.75% (-1.73% to 0.23%)‡ Age-adjusted RR, 0.63 (0.35 to 1.14)	
Khaw, Scragg et al, 2017[78, 79]	5,108	Community dwelling adults 50 to 84 years (42% women) recruited from general practices	200,000 IU vitamin D_3 initial dose followed by 100,000 IU monthly, initial placebo and every month	Median 3.3 (range 2.5 to 4.2)	Non-vertebral	136 (5.3)	156 (6.1)	ARD, 0.77% (-0.51% to 2.04%)‡ Adjusted HR, 1.19 (0.94 to 1.50)	Good

Table 1. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Fracture Type	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI) RR or HR (95% CI)	Study Quality
Calcium Compared With Placebo									
Recker et al, 1996[73]	103	Community-dwelling women age 60 years or older who were ambulatory and living independently; only data for the subgroup of subjects without prevalent vertebral fracture at baseline were included in this review	1,200 mg oral calcium[††] daily, placebo daily	Mean 4.3 (SD 1.1)	Vertebral (morpho-metric)	13 (21.3)	12 (28.6)	ARD, 7.26% (-9.84% to 24.36%)[‡] RR, 1.34 (0.68 to 2.64)[‡]	Fair
Riggs et al, 1998[74]	236	Community-dwelling women ages 61 to 70 years who were postmenopausal for at least 10 years	1,600 mg oral calcium[‡‡] daily, placebo daily	Planned 4	Vertebral (morpho-metric)	9 (7.7)	8 (6.7)	ARD, -0.97% (-7.57% to 5.63%)[‡] RR, 0.87 (0.35 to 2.19)[‡]	Fair
					Non-vertebral	12 (10.3)	11 (9.2)	ARD, -1.01% (-8.58% to 6.56%)[‡] RR, 0.90 (0.41 to 1.96)[‡]	
Vitamin D With Calcium Compared With Placebo									
Dawson-Hughes et al, 1997[75]	389[lll]	Community-dwelling adults age 65 years or older (55% women)	700 IU vitamin D_3 with 500 mg calcium[§§] daily, placebo daily	Planned 3	Hip	1 (0.5)	0 (0)	ARD, -0.50% (-1.88% to 0.89%)[‡] RR, 0.36 (0.01 to 8.78)[‡]	Fair
					Non-vertebral[¶¶]	26 (12.9)	11 (5.9)	ARD, -6.99% (-12.71% to -1.27%)[‡] RR, 0.46 (0.23 to 0.90)	
WHI Calcium and Vitamin D Trial, 2006[71]	36,282	Community-dwelling postmenopausal women ages 50 to 79 years participating in	400 IU oral vitamin D_3 with 1,000 mg calcium[††] daily, placebo daily	Mean 7.0 (SD 1.4)	Total[##]	2,158 (11.9)	2,102 (11.6)	ARD, -0.35% (-1.02% to 0.31%)[‡] HR, 0.96 (0.91 to 1.02)	Fair
					Hip	199 (1.1)	175 (1.0)	ARD, -0.14% (-0.34% to 0.07%)[‡] HR, 0.88 (0.72 to 1.08)	

Table 1. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Fracture Type	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI) RR or HR (95% CI)	Study Quality
		either the WHI Dietary Modification or Hormone Therapy trials			Vertebral (clinical)	197 (1.1)	181 (1.0)	ARD, -0.09% (-0.30% to 0.12%)‡ HR, 0.90 (0.74 to 1.10)	

Note: fractures were not the primary study aim for most included studies; studies identified with italics are the only studies that indicated fracture incidence as a primary study aim.
* This study randomized a total of 464 women; only the 232 women randomized to vitamin D or placebo were included in this review.
† Participants in both study groups received 93 mg of elemental calcium as lactate.
‡ Calculated based on raw data provided in published article.
§ Participants recruited from practitioners lived independently, participants recruited from apartments/homes for the elderly received some care (but less than they would receive in a nursing home per study report).
‖ Includes fractures of the humerus, distal radius, ankle, foot, leg, and fractures other than hip or spine. These fractures were based on self-report.
¶ Includes fractures at any site.
# The unadjusted, calculated RR was 0.80 (95% CI, 0.63 to 1.00). The RR was lower among women than in men and neither were statistically significant (adjusted RR, 0.68, [95% CI, 0.46 to 1.01, in women]; adjusted RR, 0.83, [95% CI, 0.61 to 1.13, in men]).
** The adjusted RR for women was 0.98 (95% CI, 0.41 to 2.36) and for men was 0.76 (95% CI, 0.35 to 1.67).
†† Elemental calcium as carbonate.
‡‡ Elemental calcium as citrate.
§§ Elemental calcium as citrate malate.
‖‖ Although 445 participants were randomized, analyses were based on 389 participants with followup data.
¶¶ When outcomes were limited to nonvertebral fractures classified as osteoporotic, the RR, was 0.40 (95% CI, 0.2 to 0.8).
Total fractures were defined as all fractures at any site other than ribs, sternum, skull, face, fingers, toes, and cervical vertebrae.

Abbreviations: ARD=absolute risk difference; BMD=bone mineral density; CI=confidence interval; HR=hazard ratio; No.=number; RCT= randomized, controlled trials; RR=relative risk; WHI=Women's Health Initiative.

Table 2. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation on All-Cause Mortality

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI); RR or HR (95% CI)	Study Quality
Vitamin D Compared With Placebo/Control								
Komulainen et al, 1998[72]	232*	Community-dwelling women ages 52 to 61 years between 6 and 24 months postmenopause	300 IU oral vitamin D_3 with 93 mg calcium† daily, 93 mg calcium† daily	Mean 4.3 (range 0 to 5.9)	1 (0.9)	0 (0)	ARD, -0.87% (-3.26% to 1.52%)‡ RR, 0.34 (0.01 to 8.31)‡	Fair
Lips et al, 1996[76]	2,578	Healthy adults age 70 years or older (74% women) recruited from general practitioners or from apartment houses or homes for the elderly§	400 IU oral vitamin D_3 daily, placebo daily	Median 3.5	306 (23.8)	282 (21.8)	ARD, -1.93% (-5.17% to 1.31%)‡ RR, 0.92 (0.80 to 1.06)‡	Fair
Trivedi et al, 2003[77]	2,686	Community-dwelling adults ages 65 to 85 years (24% women)	100,000 IU oral vitamin D_3 every 4 months, placebo every 4 months	Planned 5	247 (18.4)	224 (16.7)	ARD, -1.76% (-4.64% to 1.11%)‡ Age-adjusted RR, 0.88 (0.74 to 1.06)	Fair
Khaw, Scragg et al, 2017[78, 79]	5,108	Community-dwelling adults 50 to 84 years (42% women) recruited from general practices	200,000 IU vitamin D_3 initial dose followed by 100,000 IU monthly, initial placebo and every month	Median 3.3 (range 2.5 to 4.2)	65 (2.6)	58 (2.3)	ARD, -0.33% (-1.16% to 0.51%)‡ RR, 0.87 (0.61 to 1.24)	Good
Calcium Compared With Placebo								
Reid et al, 2008[92]	290‖	Healthy, predominantly white men age 40 years and older	600 mg oral calcium¶ daily, placebo daily	Planned 2	1 (1.0)	1 (1.0)	ARD, -0.02% (-2.65% to 2.61%)‡ RR, 0.98 (0.06 to 15.48)‡	Fair
			1,200 mg oral calcium¶ daily, placebo daily		1 (1.0)	1 (1.1)	ARD, 0.05% (-2.67% to 2.77%)‡ RR,1.05 (0.07 to 16.57)‡	

Table 2. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation on All-Cause Mortality

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI); RR or HR (95% CI)	Study Quality
Vitamin D With Calcium Compared With Placebo								
WHI Calcium and Vitamin D Trial, 2013[71, 98]	36,282	Community-dwelling postmenopausal women ages 50 to 79 years participating in either the WHI Dietary Modification or Hormone Therapy trials	400 IU oral vitamin D_3 with 1,000 mg calcium[#] daily, placebo daily	Mean 7.0 (SD 1.4)	807 (4.5)	744 (4.1)	ARD, -0.36% (-0.78% to 0.05%)[‡] HR, 0.91 (0.83 to 1.01)	Fair
Lappe et al, 2017[109]	2,197**	Community-dwelling postmenopausal women older than age 55 years	1,500 mg[#] oral calcium with 2,000 IU vitamin D_3 daily, placebo daily	Planned 4	9 (0.8%)	7 (0.6%)	ARD, -0.19% (-0.90% to 0.52%)[‡] RR, 0.77 (0.29 to 2.07)[‡]	Fair

[*] This study randomized a total of 464 women; only the 232 women randomized to vitamin D or placebo were included in this review.
[†] Participants in both study groups received 93 mg of elemental calcium as lactate.
[‡] Calculated based on raw data provided in published article.
[§] Participants recruited from practitioners lived independently; participants recruited from apartments/homes for the elderly received some care (but less than they would receive in a nursing home).
[‖] Although 323 participants were randomized, analyses are based on 290 participants with followup data available.
[¶] Elemental calcium dose as citrate.
[#] Elemental calcium as carbonate.
**Although 2,303 were randomized, analyses are based on 2,197 participants with followup data available.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; HR=hazard ratio; No.=number; RCT=randomized, controlled trial; RR=relative risk; WHI=Women's Health Initiative.

Table 3. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation on Incident Kidney Stones

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD, (95%CI); RR or HR (95% CI)	Study Quality
Vitamin D Compared With Placebo/Control								
None	--	--	--	--	--	--	--	--
Calcium Compared With Placebo								
Lappe et al, 2007[108]	733*	Community-dwelling postmenopausal women age 55 years or older	1,400 mg† or 1,500 mg‡ oral calcium daily, placebo daily	Planned 4	1 (0.4))	3 (0.7)	ARD, 0.33% (-0.69% to 1.35%)§ RR, 1.94 (0.20 to 18.57)§	Fair
Reid et al, 2008[92]	290‖	Community-dwelling healthy men age 40 years or older	600 mg† oral calcium daily, placebo daily	Planned 2	1 (1.0)	0 (0)	ARD, -1.01% (-3.77% to 1.75%)§ RR, 0.34 (0.01 to 8.17)§	Fair
			1,200 mg† oral calcium daily, placebo daily	--	--	0 (0)	ARD, -1.01% (-3.81% to 1.79%)§ RR, 0.35 (0.01 to 8.60)§	
Riggs et al, 1998[74]	236	Community-dwelling women ages 61 to 70 years who were postmenopausal for at least 10 years	1,600 mg† oral calcium daily, placebo daily	Planned 4	1(0.9)	0 (0)	ARD, -0.85% (-3.18% to 1.47%)§ RR, 0.33 (0.01 to 7.97)§	Fair
Vitamin D With Calcium Compared With Placebo								
Lappe et al, 2007[108]	734*	Community-dwelling postmenopausal women older than age 55 years	1,400 mg† or 1,500 mg‡ oral calcium daily and 1,000 IU vitamin D_3, placebo daily	Planned 4	1 (0.4)	1 (0.2)	ARD, -0.12% (-0.93% to 0.69%)§ RR, 0.65 (0.04 to 10.28)§	Fair
Lappe et al, 2017[109]	2,197¶	Community-dwelling postmenopausal women older than age 55 years	1,500 mg‡ oral calcium with 2,000 IU vitamin D_3 daily, placebo daily	Planned 4	10 (0.9%)	16 (1.5%)	ARD, 0.54% (-0.36% to 1.44%)§ RR, 1.59 (0.72 to 3.49)§	Fair
WHI Calcium and Vitamin D Trial, 2013[71]	36,282	Community-dwelling postmenopausal women ages 50 to 79 years participating in either the WHI Dietary Modification or Hormone Therapy trials	400 IU oral vitamin D_3 with 1,000 mg‡ calcium daily, placebo daily	Mean 7.0 (SD 1.4)	381 (2.1)	449 (2.5)	ARD, 0.37% (0.06% to 0.67%)§ RR, 1.17 (1.03 to 1.34)	Fair

* One woman was excluded from the study after entry because of hypoparathyroidism after thyroidectomy and daily use of 50,000 IU of vitamin D (reported in Lappe et al, 2006).[137] This study randomized 288 women to placebo, 445 women to calcium alone, and 446 women to vitamin D with calcium.[108]

† Elemental calcium dose as citrate.

‡ Elemental calcium as carbonate.

§ Calculated based on raw data provided in published article.

‖ Although 323 participants were randomized, analyses are based on 290 participants with followup data available.

¶ Although 2,303 participants were randomized, analyses are based on 2,197 participants with followup data available.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; HR=hazard ratio; No.=number; RCT=randomized, controlled trial; RR=relative risk; WHI=Women's Health Initiative.

Table 4. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation on Incident Cardiovascular Outcomes

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Outcome Event	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI); RR or HR (95% CI)	Study Quality
Vitamin D Compared With Placebo/Control									
Komulainen et al, 1998[72, 119]	232*	Community-dwelling women ages 52 to 61 years between 6 and 24 months postmenopause	300 IU oral vitamin D_3 daily with 93 mg calcium† daily, 93 mg calcium† daily	Mean 4.3 (range 0 to 5.9)	Myocardial infarction or CABG	0 (0)	2 (1.8)	ARD, 1.79% (-1.18% to 4.75%)‡ RR, 5.13 (0.25 to 105.73)‡	Fair
Trivedi et al, 2003[77]	2,686	Community-dwelling adults ages 65 to 85 years (24% women; 27.4% of placebo group and 29.3% of vitamin D group had CVD at baseline)	100,000 IU oral vitamin D_3 every 4 months, placebo every 4 months	Planned 5	Ischemic heart disease	233 (17.4)	224 (16.7)	ARD, -0.72% (-3.56% to 2.12%)‡ Age-adjusted RR, 0.94 (0.77 to 1.15)	Fair
					Cerebrovascular disease	101 (7.5)	105 (7.8)	ARD, 0.27% (-1.74% to 2.29%)‡ Age-adjusted RR, 1.02 (0.77 to 1.36)	
Khaw, Scragg et al, 2017[78, 79]	5,110	Community-dwelling adults 50 to 84 years (42% women) recruited from general practices	200,000 IU vitamin D_3 initial dose followed by 100,000 IU monthly, initial placebo and every month	Median 3.3 (range 2.5 to 4.2)	Myocardial infarction	31 (1.2)	28 (1.1)	ARD, -0.12% (-0.71% to 0.47%)‡ HR, 0.90 (0.54 to 1.50)	Good
					Stroke	27 (1.1)	26 (1.0)	ARD -0.04% (-0.60% to 0.51%)‡ HR, 0.95 (0.55 to 1.62)	
					VTE	15 (0.6)	11 (0.4)	ARD -0.16% (-0.55% to 0.23%)‡ HR, 0.74 (0.34 to 1.61)	
					Heart failure	57 (2.2)	69 (2.7)	ARD, 0.46% (-0. 39% to 1.31%)‡ HR, 1.19 (0.84 to 1.68)	
Calcium Compared With Placebo									
Reid et al, 2008[92]	290‖	Community-dwelling healthy men age 40 years or older	600 mg oral calcium§ daily, placebo daily	Planned 2	Myocardial Infarction	0 (0)	1 (1.0)	ARD, 1.02% (-1.75% to 3.80%)‡ RR, 3.03 (0.12 to 73.49)‡	Fair
			1,200 mg oral calcium§ daily, placebo daily			0 (0)	2 (2.2)	ARD, 2.15% (-1.38% to 5.68%)‡ RR, 5.32 (0.26 to 109.35)‡	

Table 4. Results of RCTs Evaluating the Impact of Vitamin D, Calcium, or Combined Supplementation on Incident Cardiovascular Outcomes

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Outcome Event	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD (95%CI); RR or HR (95% CI)	Study Quality
Vitamin D Combined With Calcium Compared With Placebo									
WHI Calcium and Vitamin D Trial, 2006[71, 98]	36,282	Community-dwelling postmenopausal women ages 50 to 79 participating in either the WHI Dietary Modification or Hormone Therapy Trials	400 IU oral vitamin D_3 with 1,000 mg calcium[¶] daily versus placebo	Mean 7.0 (SD 1.4)	Myocardial infarction[#]	390 (2.2)	411 (2.3)	ARD, 0.11% (-0.20% to 0.41%)[‡] HR, 1.03 (0.90 to 1.19)	Fair
					Coronary heart disease[#]	475 (2.6)	499 (2.8)	ARD, 0.12% (-0.21% to 0.45%)[‡] HR, 1.03 (0.90 to 1.17)	
					Stroke[#]	377 (2.1)	362 (2.0)	ARD, -0.09% (-0.38% to 0.20%)[‡] HR, 0.95 (0.82 to 1.10)	
					VTE (idiopathic or secondary)[**]	348 (1.9)	320 (1.8)	ARD, -0.16% (-0.44% to 0.12%)[‡] HR, 0.92 (0.79 to 1.07)	
					Deep vein thrombosis[**]	256 (1.4)	246 (1.4)	ARD, -0.06% (-0.30% to 0.18%)[‡] HR, 0.97 (0.82 to 1.16)	
					Pulmonary embolism[**]	149 (0.8)	135 (0.7)	ARD, -0.08% (-0.26% to 0.10%)[‡] HR, 0.92 (0.73 to 1.16)	
					Heart failure hospitalization[††]	381 (2.1)	363 (2.0)	ARD, -0.11% (-0.40% to 0.18%)[‡] HR, 0.95 (0.82 to 1.09)	

[*] This study randomized a total of 464 women; only the 232 women randomized to vitamin D or placebo were included in this review.
[†] Participants in both study groups received 93 mg of elemental calcium as lactate.
[‡] Calculated based on raw data provided in published article.
[§] Elemental calcium as citrate.
[‖] Although 323 participants were randomized, analyses are based on 290 participants with followup data available.
[¶] Elemental calcium as carbonate.
[#] The outcomes reported here are those reported by the WHI Calcium and Vitamin D Trial investigators as published in Prentice et al.[98] Post hoc subgroup analyses by the study investigators and by other investigators (who used the limited access data set) reported findings based on baseline use of personal calcium supplements at baseline. Among women not taking personal supplements at baseline, WHI Calcium and Vitamin D Trial investigators reported HR, 1.11 (95% CI, 0.90 to 1.37) for myocardial infarction; HR, 1.03 (95% CI, 0.85 to 1.25) for coronary heart disease; and HR, 1.12 (95% CI, 0.90 to 1.39) for stroke.[98] Bolland et al[116] reported HR, 1.22 (95% CI, 1.00 to 1.5) for clinical myocardial infarction, which excluded silent myocardial infarctions detected on serial ECG monitoring conducted as part of study monitoring; and HR, 1.17 (95% CI, 0.95 to 1.44) for stroke.
[**] As reported by Blondon et al[117]; this outcome includes deep vein thrombosis and pulmonary embolism events.
[††] As reported by Donneyang et al[118]; sample size used was 35,983 because of exclusion of participants with history of heart failure at the time of enrollment from the analysis. Subgroup analysis by baseline risk of heart failure as defined by American College of Cardiology criteria (presence of HTN, DM, coronary heart disease, or CVD): low-risk subgroup: HR, 0.63 (95% CI, 0.46 to 0.87), high-risk subgroup HR, 1.06 (95% CI, 0.90 to 1.24).

Abbreviations: ARD=absolute risk difference; CI=confidence interval; CABG=coronary artery bypass graft; CVD=cardiovascular disease; DM=diabetes mellitus; ECG=electrocardiogram; HR=hazard ratio; HTN=hypertension; RCT=randomized, controlled trials; RR=relative risk; VTE=venous thromboembolism; WHI=Women's Health Initiative.

Table 5. Results of RCTs Evaluating the Association Between Vitamin D, Calcium, or Combined Supplementation and Incident Cancer

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Outcome Event	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD, (95%CI), RR, or HR, (95% CI)	Study Quality
Vitamin D Compared With Placebo/Control									
Komulainen et al, 1998[72, 119]	232*	Community-dwelling women ages 52 to 61 years between 6 and 24 months postmenopause	300 IU oral vitamin D_3 with 93 mg calcium† daily, 93 mg calcium† daily	Mean 4.3 (range 0 to 5.9)	Incident cancer‡	3 (2.6)	2 (1.8)	ARD, -0.82% (-4.63% to 2.99%)§ RR, 0.68 (0.12 to 4.02)§	Fair
Trivedi et al, 2003[77]	2,686	Community-dwelling adults ages 65 to 85 years (24% women)	100,000 IU oral vitamin D_3 every 4 months, placebo every 4 months	Planned 5	Any incident cancer	173 (12.9)	188 (14.0)	ARD, 1.08% (-1.50% to 3.66%)§ Age-adjusted RR, 1.09 (0.86 to 1.36)	Fair
					Any incident cancer, excluding skin	130 (9.7)	144 (10.7)	ARD, 1.01% (-1.28% to 3.30%)§ Age-adjusted RR, 1.11 (0.86 to 1.42)	
					Incident colon cancer	27 (2.0)	28 (2.1)	ARD, 0.07% (-1.00% to 1.14%)§ Age-adjusted RR, 1.02 (0.60 to 1.74)	
					Incident respiratory cancer	15 (1.1)	17 (1.3)	ARD, 0.15% (-0.68% to 0.97%)§ Age-adjusted RR, 1.12 (0.56 to 2.25)	
Calcium Compared With Placebo									
Lappe et al, 2007[108]	733‖	Community-dwelling postmenopausal women age 55 years or older without prevalent cancer or a history of cancer within the prior 10 years	1,400 mg¶ or 1,500 mg# calcium daily, placebo daily	Planned 4	Total nonskin cancers**	20 (6.9)	17 (3.8)	ARD, -3.12% (-6.56% to 0.31%)§ RR, 0.55 (0.29 to 1.03)§	Good
					Breast cancer	8 (2.8)	6 (1.4)	ARD, -1.43% (-3.61% to 0.75%)§ RR, 0.49 (0.17 to 1.4)§	
					Colon cancer	2 (0.7)	0 (0)	ARD, -0.69% (-1.81% to 0.42%)§ RR, 0.13 (0.01 to 2.69)§	

Table 5. Results of RCTs Evaluating the Association Between Vitamin D, Calcium, or Combined Supplementation and Incident Cancer

Author (Year)	No. of Participants	Population	Intervention, Comparator	Followup (Years)	Outcome Event	No. (%) With Event: Control Group	No. (%) With Event: Intervention Group	Summary Effect ARD, (95%CI), RR, or HR, (95% CI)	Study Quality
Vitamin D With Calcium Compared With Placebo									
Lappe et al, 2007[108]	734[‖]	Community-dwelling postmenopausal women age 55 years or older without prevalent cancer or a history of cancer within the prior 10 years	1,000 IU vitamin D_3 with 1,400 mg[¶] or 1,500 mg[#] calcium daily, placebo daily	Planned 4	Incident cancer, excluding skin[**]	20 (6.9)	13 (2.9)	ARD, -4.03% (-7.35% to -0.70%)[§] RR, 0.42 (0.21 to 0.83)[§]	Good
					Incident breast cancer	8 (2.8)	5 (1.1)	ARD, -1.66% (-3.79% to 0.48%)[§] RR, 0.40 (0.13 to 1.22)[§]	
					Incident colon cancer	2 (0.7)	1 (0.2)	ARD, -0.47% (-1.52% to 0.58%)[§] RR, 0.32 (0.03 to 3.54)[§]	
WHI Calcium and Vitamin D Trial, 2006[††]	36,282[‡‡]	Postmenopausal women ages 50 to 79 years who were participating in the WHI Diet Modification and/or Postmenopausal Hormone Therapy Trials	400 IU vitamin D_3 with 1,000 mg[#] calcium daily, placebo daily	Mean 7.0 (SD 1.4)	Total excluding non-melanoma skin cancer	1,411 (7.8)	1,366 (7.5)	ARD, -0.28% (-0.82% to 0.27%)[§] HR, 0.96 (0.89 to 1.04)	Fair
					Colorectal cancer	154 (0.9)	168 (0.9)	ARD, 0.07% (-0.12% to 0.27%)[§] HR, 1.06 (0.85 to 1.32)[§§]	
					Breast cancer	546 (3.0)	528 (2.9)	ARD, -0.11% (-0.46% to 0.24%)[§] HR, 0.96 (0.85 to 1.08)	
					Non-melanoma skin cancer	1,655 (9.1)	1,683 (9.3)	ARD, 0.12% (-0.48% to 0.71%)[§] HR, 1.02 (0.95 to 1.07)	
					Melanoma skin cancer	94 (0.5)	82 (0.5)	ARD, -0.07% (-0.21% to 0.07%)[§] HR, 0.86 (0.64 to 1.16)	
Lappe et al, 2017[109]	2,197[‖]	Community-dwelling postmenopausal women older than age 55 years	1,500 mg[‡] oral calcium with 2,000 IU vitamin D_3 daily, placebo daily	Planned 4	Total excluding non-melanoma skin cancer	64 (5.8%)	45 (4.1%)	ARD, -1.76% (-3.58% to 0.05%)[§] RR, 0.70 (0.48 to 1.01) [§]	Fair
					Breast cancer	23 (2.1%)	16 (1.5%)	ARD, -0.65% (-1.75% to 0.46%)[§] RR, 0.69 (0.37 to 1.30)	
					Colorectal cancer	4 (0.4%)	4 (0.4%)	ARD, 0.00% (-0.51% to 0.50%)[§] RR, 0.99 (0.25 to 3.96) [§]	

[*] This study randomized a total of 464 women; only the 232 women randomized to vitamin D or placebo were included in this review.

[†] Participants in both study groups received 93 mg of elemental calcium as lactate.

[‡] Described as malignancies and reported as serious adverse events.[119]

[§] Calculated based on raw data provided in published article.

[‖] One woman was excluded from the study after entry because of hypoparathyroidism after thyroidectomy and daily use of 50,000 IU of vitamin D (reported in Lappe et al, 2006).[137] This study randomized 288 women to placebo, 445 women to calcium alone, and 446 women to vitamin D with calcium.[108]

Table 5. Results of RCTs Evaluating the Association Between Vitamin D, Calcium, or Combined Supplementation and Incident Cancer

[¶] Elemental calcium dose as citrate.
[#] Elemental calcium as carbonate.
** Investigators also performed an analysis of total nonskin cancers that developed after the first year of followup: the denominators were 266 (placebo), 416 (calcium alone), and 403 (vitamin D plus calcium) as opposed to the 288, 445, and 446 women who were randomized to those groups, respectively. Results were similar to those from the ITT analysis.
[††] Findings reported from the WHI Calcium and Vitamin D Trial in the following publications: Jackson et al, 2003,[96] Jackson et al, 2006[71] Wactawski-Wende et al, 2006,[113] Tang et al, 2011,[121] Brunner et al, 2011,[122] Bolland et al, 2011,[97] Prentice et al, 2012.[98]
[‡‡] This is the total number randomized in the WHI Calcium and Vitamin D Trial; however, cancer outcomes were not the primary trial endpoint and some analyses reporting incident cancer outcomes were based on a smaller sample size because participants with a recent history of cancer were excluded from the analyses of incident cancer outcomes.
[§§] The HR reported by Wactawski-Wende et al[113] was slightly different (1.08; 95% CI, 0.86 to 1.34) than that reported in Prentice et al[98]; however, counts of invasive colorectal cancer cases were reported the same in both.
[||] Although 2,303 participants were randomized, analyses are based on 2,197 participants with followup data.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; HR=hazard ratio; ITT=intent to treat; No.=number; RR=relative risk; WHI=Women's Health Initiative.

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
KQ 1—Benefits related to prevention of fractures								
Vitamin D alone	k=4 RCTs; N=10,606	Over 3.3 to 5 years: Total Fracture (1 RCT; N=2,686): ARD, -2.26% (95% CI, -4.53% to 0.00%) RR*, 0.78 (95% CI, 0.61 to 0.99) Hip (3 RCTs; N=5,416; I^2=0%): Pooled ARD, -0.01% (95% CI, -0.80% to 0.78%) Pooled RR, 1.08 (95% CI, 0.79 to 1.48) Nonvertebral (2 RCTs, N=5,340): Smaller study (n=232): ARD, -3.45% (95% CI, -11.55% to 4.66%) RR, 0.64 (95% CI, 0.29 to 1.42) Larger study (n=5,108): ARD, 0.77% (95% CI, -0.51% to 2.04%) Adjusted HR, 1.19 (95% CI, 0.94 to 1.50) Clinical vertebral (1 RCT, N=2,686): ARD, -0.75% (95% CI, -1.73% to 0.23%) RR, 0.63 (95% CI, 0.35 to 1.14) Two studies used in sensitivity analyses reported increases in incidence (one fracture type has a significant increase), one study reported nonsignificant decrease.	Consistent/ imprecise	Undetected	Studies not powered for fracture outcomes; variability in populations and outcome specification and ascertainment; not enough studies to evaluate the influence of dose, route, or frequency on incidence.	Three of the four studies included men, studies conducted outside U.S. but likely applicable to U.S. settings, doses include 300 IU and 400 IU per day, 100,000 IU every 4 months, and 100,000 IU every month (after an initial 200,000 IU loading dose)	Fair	Low for no benefit

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
Calcium alone	k=2 RCTs; N=339	Over 4 years: Nonvertebral (1 RCT, N=236): ARD, -1.01% (95% CI, -8.58% to 6.56%) RR, 0.90 (95% CI, 0.41 to 1.96) Morphometric vertebral (2 RCTs, N=339): ARDs, 7.26% (95% CI, -9.84% to 24.36%) and -0.97% (95% CI, -7.57% to 5.63%) RRs, 1.34 (95% CI, 0.68 to 2.64) and 0.87 (95 % CI, 0.35 to 2.19) Studies used in sensitivity analyses reported mostly nonsignificant increases and decreases in various fracture outcomes.	Inconsistent/ imprecise	Detected†	Studies not powered for fracture outcomes; limited fracture outcomes reported; not enough studies to evaluate the influence of dose, route, or frequency on incidence.	Post-menopausal women in U.S., doses included 1,200 mg and 1,600 mg per day	Fair	Insufficient
Vitamin D with calcium	k=2 RCTs; N=36,727	Over 3 to 7 years: Total fracture (1 RCT; N=36,282): ARD, -0.35% (95% CI, -1.02% to 0.31%) HR, 0.96 (95% CI, 0.91 to 1.02) Hip (2 RCTs, N=36,671): Larger trial (N=36,282)‡: ARD, -0.14% (95% CI, -0.34% to 0.07%) HR, 0.88 (95% CI, 0.72 to 1.08) Nonvertebral fractures (1 RCT, N=389): ARD, -6.99% (95% CI, -12.71% to -1.27%) RR, 0.46 (95% CI, 0.23 to 0.90) Clinical vertebral (1 RCT, N=36,282): ARD, -0.09% (95% CI, -0.30% to 0.12%) HR, 0.90 (95% CI, 0.74 to 1.10) Study used in sensitivity analyses reported nonsignificant increases and decreases in various fracture outcomes.	Inconsistent/ imprecise	Detected†	Not enough studies to evaluate the influence of dose, route, or frequency on incidence; participants allowed to take personal vitamin D and calcium supplements during the trial in the larger of the two trials.	Post-menopausal women in U.S.; the smaller of the two trials included men; vitamin D doses were 400 IU and 700 IU per day, calcium doses were 500 mg and 1,000 mg per day.	Fair	Low for no benefit§

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
KQ 2—Harms of supplementation								
All-cause mortality								
Vitamin D alone	k=4 RCTs; N=10,599	Over 3.3 to 5 years: Pooled ARD, -0.74% (95% CI, -1.80% to 0.32%; I^2=19.6%) Pooled RR, 0.91 (95% CI, 0.82 to 1.01; I^2=0%) Studies used in sensitivity analysis reported a similar nonsignificant decrease in incidence.	Consistent/ imprecise	Undetected	Studies not powered to assess all-cause mortality.	Older men and post-menopausal women in non-U.S. countries though likely applicable to U.S.; doses were 300 IU and 400 IU per day and 100,000 IU every month or 4 months.	Fair	Low for no harm
Calcium alone	k=1 RCT; N=290	Over 2 years: ARD[ll], 0.01% (95% CI, -2.29% to 2.32%) RR[ll], 1.01 (95% CI, 0.09 to 11.06) Studies used in sensitivity analysis reported nonsignificant increases and decreases in incidence.	Unknown consistency (single study)/very imprecise[ll]	Undetected	Study not powered to assess all-cause mortality; no reporting of how mortality ascertained.	Predominantly white men age 40 years and older in New Zealand though likely applicable to U.S., doses include 600 mg and 1,200 mg per day.	Fair	Insufficient
Vitamin D with calcium	k=2 RCTs; N=38,479	Over 4 years (smaller trial, n=2,197): ARD, -0.19% (95% CI, -0.90% to 0.52%) RR, 0.77 (95% CI, 0.29 to 2.07) Over 7 years (larger trial, n=36,282): ARD, -0.36% (95% CI, -0.78% to 0.05%) HR, 0.91 (95% CI, 0.83 to 1.01) Study used in sensitivity analysis reported a nonsignificant increased incidence.	Consistent/ imprecise	Undetected	Studies not powered to assess all-cause mortality; participants allowed to take personal vitamin D and calcium supplements in larger trial.	Post-menopausal women in U.S.; vitamin D dose 400 or 2,000 IU per day, calcium dose 1,000 to 1,500 mg per day.	Fair	Low for no harm

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
Incident kidney stones								
Vitamin D alone	No eligible studies in main analysis	NA	NA	NA	NA	NA	NA	Insufficient
Calcium alone	k=3 RCTs; N=1,259	Over 2 to 4 years: Pooled ARD, 0.00% (95% CI, -0.88% to 0.87%; I^2=0%) Pooled RR, 0.68 (95% CI, 0.14 to 3.36; I^2=0%) Nonsignificant increases and decreases in studies used in sensitivity analysis.	Consistent/ imprecise	Undetected	Studies not powered to assess incident kidney stones; limited information on outcome specification and ascertainment.	Post-menopausal women in U.S. and New Zealand, doses ranging from 600 mg to 1,600 mg per day.	Fair	Low for no harm
Vitamin D with calcium	k=3 RCTs; N=39,213	Pooled ARD, 0.33% (95% CI, 0.05% to 0.60%; I^2=0%) Pooled RR, 1.18 (95% CI, 1.04 to 1.35; I^2=0%) No events reported in either study group by study used in sensitivity analysis.	Consistent/ precise (primarily considering the largest of 2 trials)¶	Undetected	Studies not powered to assess incident kidney stones; participants allowed to take personal vitamin D and calcium supplements during in largest trial.	Post-menopausal women in U.S.; vitamin D dose 400 IU, 1,000 IU and 2,000 IU per day, calcium dose 1,000 mg and 1,400 to 1,500 mg per day.	Fair	Moderate for harm

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
Incident CVD								
Vitamin D alone	k=3 RCTs; N=8,021	Over 3.3 to 5 years in the two larger trials (n=2,686 and n=5,108)[#]: Myocardial infarction: ARD, -0.72% (95% CI, -3.56% to 2.12%) RR, 0.94 (95% CI, 0.77 to 1.15) and ARD, -0.12% (95% CI, -0.71% to 0.47%) HR, 0.90 (95% CI, 0.54 to 1.50) Cerebrovascular disease/Stroke: ARD, 0.27% (95% CI, -1.74% to 2.29%) RR, 1.02 (95% CI, 0.77 to 1.36) and ARD, -0.04% (95% CI, -0.60% to 0.51%) HR, 0.95, (95% CI, 0.55 to 1.62) Nonsignificant increases and decreases in incidence in studies used in sensitivity analysis.	Consistent/ imprecise	Undetected	Only one study powered for CVD events; varying control event rates suggest heterogeneity in populations, outcome specifications, and ascertainment methods.	Post-menopausal women and men in U.S., U.K., and New Zealand; doses include 300 IU per day and 100,000 IU every 1 to 4 months.	Fair	Low for no harm
Calcium alone	k=1 RCT; N=290	Over 2 years: Myocardial infarction: 600 mg dose: ARD, 1.02% (95% CI, -1.75% to 3.80%) RR, 3.03 (95% CI, 0.12 to 73.49) 1,200 mg dose: ARD, 2.15% (95% CI, -1.38% to 5.68%) RR, 5.32 (95% CI, 0.26 to 109.35) Mostly nonsignificant increases in incidence in studies used in sensitivity analysis.	Unknown consistency (single study)/Very imprecise[**]	Undetected	Study not powered for CVD events.	Predominantly white men age 40 and older in New Zealand though likely applicable to U.S., doses include 600 mg and 1,200 mg per day.	Fair	Insufficient

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
Vitamin D with calcium	k=1 RCT; N=36,282	Over 7 years: Myocardial infarction: ARD, 0.11% (95% CI, -0.20% to 0.41%) HR, 1.03 (95% CI, 0.90 to 1.19) Stroke: ARD, -0.09% (95% CI, -0.38% to 0.20%) HR, 0.95 (95% CI, 0.82 to 1.10) VTE: ARD, -0.16% (95% CI, -0.44% to 0.12%) HR, 0.92 (95% CI, 0.79 to 1.07) Heart failure hospitalization: ARD, -0.11% (95% CI, -0.40% to 0.18%) HR, 0.95 (95% CI, 0.82 to 1.09) Nonsignificant decrease in incidence in study used in sensitivity analysis, but estimates were very imprecise.	Unknown consistency (single study)/ precise	Undetected	Study not powered for CVD events; participants allowed to take personal vitamin D and calcium supplements during the trial in the larger of the two trials.	Post-menopausal women in U.S.; vitamin D dose 400 IU per day, calcium dose 1,000 mg per day.	Fair	Low for no harm
Incident cancer								
Vitamin D alone	k=2 RCTs; N=2,918	Over 5 years: Any incident cancer: ARDs, 1.08% (95% CI, -1.50% to 3.66%) and -0.82% (-4.63% to 2.99%) RRs, 1.09 (95% CI, 0.86 to 1.36) and 0.68 (95% CI, 0.12 to 4.02) Nonsignificant increases and decreases in incidence in studies used in sensitivity analyses.	Inconsistent/ Imprecise	Undetected	Studies not powered for cancer outcomes; no validation of self-reported cancers.	Older men and post-menopausal women; doses include 300 IU per day and 100,000 IU every 4 months	Fair	Insufficient

Table 6. Summary of Evidence for Fracture Prevention and Harms of Supplementation With Vitamin D, Calcium, or Combined Supplementation

Intervention	No. of Studies and Design (k); No. of Participants (N)	Summary of Findings	Consistency/ Precision	Reporting Bias	Body of Evidence Limitations	Applicability	Overall Quality	EPC Assessment of Strength of Evidence
Calcium alone	k=1 RCT; N=733	Over 4 years: Any incident nonskin cancer: ARD, -3.12% (-6.56% to 0.31%) RR, 0.55 (95% CI, 0.29 to 1.03) Nonsignificant increase in incidence in study used in sensitivity analysis, but estimates very imprecise.	Unknown consistency (single study)/ Imprecise	Undetected	Study not powered for cancer outcomes.	Post-menopausal women in the U.S. without a recent history of cancer, dose 1,400 to 1,500 mg per day	Good	Insufficient
Vitamin D with calcium	k=3 RCTs; N=39,213	Over 4 to 7 years: Total (nonskin cancer) Pooled ARD, -1.48% (95% CI, -3.32% to 0.35%; I^2=70.9%) Pooled RR, 0.73 (95% CI, 0.49 to 1.10; I^2=75.8%) Nonsignificant decrease in incidence in study used in sensitivity analysis, but estimates very imprecise.	Inconsistent/ Precise (primarily considering the largest of the trials)	Undetected	Largest study not powered for cancer outcomes; participants allowed to take personal vitamin D and calcium supplements during the trials.	Post-menopausal women in U.S.; vitamin D dose 400 IU/d, 1,000 IU/d, 2,000 IU/d, calcium dose 1,000 mg/d and 1,400 to 1,500 mg/d.	Fair	Low for no harm

* Adjusted estimate reported by the study; unadjusted estimate based on raw data in article was 0.80 (95% CI, 0.63 to 1.00).
† We identified one RCT that was registered with a primary study aim of evaluating the impact of calcium alone and vitamin D with calcium supplementation on fracture incidence. According to the study's corresponding author, alendronate became available during the study and about 20 percent of the study population was started on it; the trial found null findings with respect to fracture incidence and were not published. (Personal communication with Joan Lappe 12/22/2016).
ǂ Only one hip fracture (in control group) occurred in the smaller of the two trials.[75]
§ Though findings between trials were inconsistent, we primarily relied on the larger trial (WHI CaD Trial) to derive the strength of evidence assessment.
‖ Reflects effect estimates of the 600 mg or 1,200 mg calcium dose compared with placebo. This trial is considered very imprecise because the outcome was very rare; only one participant in each active study group died.
¶ The smaller trial (N=734) was considered very imprecise because the outcome was very rare; only one participant in each study group had kidney stones.[108]
# The smallest trial (N=232) reported one myocardial infarction and one CABG in treatment group; no events in control group.[72]
** This trial is considered very imprecise because the outcome was rare; no participants in the control group had any events, one participant in the 600 mg group had an event and two participants in the 1,200 mg group had an event.[92]

Abbreviations: ARD=absolute risk difference; CABG=coronary artery bypass graft; CI=confidence interval; CVD=cardiovascular disease; d=day; EPC=Evidence-Based Practice; HR=hazard ratio; IU=international units; KQ=Key Question; mg=milligram; N or No=Number; NA=Not Applicable; RCT=randomized, controlled trial; RR=relative risk ratio; U.S.=United States; VTE=venous thromboembolism.

Appendix A Table 1. Serum Vitamin D Level Reference Ranges

Serum Level (nmol/L)	Equivalent Range in ng/ml	NAM Description*	Qualitative Term Used to Describe This Range†
<30 nmol/L	<12 ng/ml	Persons with levels in this range are at risk of deficiency relative to bone health outcomes	Severe deficiency
Between 30–50 nmol/L	Between 12–20 ng/ml	Some, but not all, persons in this range are at risk of deficiency relative to bone health outcomes	Deficiency
Between 50–75 nmol/L	Between 20–30 ng/dl	Most, but not all, persons with levels in this range are sufficient relative to bone health outcomes	Some refer to this range as insufficiency; others contend this range is sufficiency.
>75 nmol/L	>30 ng/ml	Persons with levels in this range do not consistently have an increased benefit relative to bone health outcomes	Sufficiency
Above 125 nmol/L	Above 50 ng/ml	Levels in this range may be cause for concern	–

* As described in: *Dietary Reference Intakes for Calcium and Vitamin D*. IOM (Institute of Medicine). 2011 Washington, DC: The National Academies Press.[5]

† These are not terms attributed by NAM; rather, these are descriptors commonly found in the literature describing these ranges. Experts disagree about the terms that should be used to describe these ranges, whether these ranges adequately reflect the evidence, and whether these ranges reflect clinical thresholds for action related to supplementation.

Abbreviations: NAM=National Academy of Medicine (formerly Institute of Medicine); ng/ml=nanogram per milliliter; nmol/L=nanomole per liter.

Contextual Question 1. What are the effects of vitamin D supplementation alone or combined with calcium on change in vitamin D status?

Summary of Findings

For the question related to vitamin D supplementation and change in vitamin D status, the 2014 updated AHRQ evidence report[17] identified one systematic review of 76 studies and 13 relevant randomized, controlled trials (RCTs) that were new since the 2009 AHRQ evidence report.[15]

The report investigators presented bubble plots of the association between supplementation and status, overall and for subgroups, using data from 44 RCTs with 50 comparisons among adults and children. Among the adult populations studied, about three quarters of the included studies were among community-dwelling populations, and the mean baseline serum 25[OH] D levels among these studies was in the sufficiency range. There was an increase in serum concentrations of 25[OH] D with vitamin D supplementation in all studies. The authors did not report a summary measure of effect for dose response because of substantial heterogeneity that was attributed to the following: wide variation in the dosages of vitamin D; various adherence rates; differences in calcium intake; different vitamin D assays and measurement; differences in baseline serum 25[OH] D levels; or lack of adjustment for skin pigmentation or background sun exposure. We identified three additional RCTs, newly published since the 2014 AHRQ Evidence Report, which evaluated the association between vitamin D supplementation and serum concentrations of vitamin D.[137-139] All three trials reported an increase in serum vitamin D concentrations with vitamin D supplementation despite differences in patient population, dosages, frequency, and duration.

Detailed Findings From AHRQ Evidence Reports

The 2014 AHRQ Evidence Report relied on a new (since 2009) systematic review published in *The Journal of Clinical Endocrinology and Metabolism* of 12,203 participants from 76 randomized placebo controlled and open-label trials of vitamin D supplementation.[140] In these trials, daily vitamin D intake ranged from 200 IU to 10,000 IU (mean=800 IU); most vitamin D was administered orally. Of the 76 trials, 58 (76%) were among community-dwelling participants, 24 of which had a primary endpoint of serum 25[OH] D changes. Three fourths of participants were 50 to 79 years of age and all were Caucasian. The median (range) baseline serum 25[OH] D level was lower among institutionalized participants (26.2 [11.7–53.9] nmol/L) than among community-dwelling participants (48.2 [17.7–90.6] nmol/L). There was a general increase in the serum concentration of vitamin D with supplementation. A meta-regression showed an average increase of 1.95 nmol/L in serum concentration of vitamin D for each 40 IU of vitamin D supplemented; review authors found considerable variation in response for similar doses of vitamin D intake (i.e., three- to four-fold variations). Being institutionalized or of an older age did not affect the dose response relationship between supplementation and serum 25[OH] D levels. Cosupplementation with calcium resulted in nonsignificant smaller increases in serum levels of 25[OH] D than supplementation with vitamin D alone, and there were smaller increases in serum levels of 25[OH] D with ergocalciferol (D_2) than with cholecalciferol (D_3).

The 2014 AHRQ Evidence Report also relied on 13 new (since 2009) RCTs that evaluated vitamin D intake via supplements among adults age 19 years or older. These RCTs also demonstrated a general increase in serum concentration of 25[OH] D with supplementation. Results varied by age group, baseline vitamin D status, dose, duration, and assay method.

Detailed Findings From Studies Published After the 2014 AHRQ Evidence Report

We identified three additional RCTs, new since the 2014 AHRQ Evidence Report that evaluated the association between vitamin D supplementation and serum concentrations of vitamin D.[137-139] All trials reported an increase in serum vitamin D concentrations with vitamin D supplementation; study populations, dosage, frequency, and duration varied across the trials. In a small trial in Argentina among 33 healthy participants age 24 to 46 years, both vitamin D_2 and vitamin D_3 were effective in increasing serum levels of vitamin D after a loading dose of 100,000 IU. At baseline, the mean serum 25[OH] D levels were 56.4, 40.7, and 60.7 nmol/L in the placebo, vitamin D_2, and vitamin D_3 groups, respectively. After 7 days, the absolute increment increase over baseline 25[OH] D levels was 50.7 nmol/L for D_2 and 41.7 nmol/L for D_3 and no participants remained in the deficient category (i.e., <49.9 nmol/L). The percentage increase from baseline was higher among participants with lower baseline levels. Subsequent daily supplementation with 4,800 IU vitamin D_2 or D_3 plus 500 mg calcium resulted in a sustained elevation of serum levels over 21 days; by day 77, there was no difference between the D_2 and placebo groups, while the D_3 group had higher serum 25[OH] D levels than both ($p<0.04$).[137]

In another trial in the United States, 118 premenopausal women, ages 18 to 50 years, with bacterial vaginosis received nine doses of 50,000 IU D_3 or placebo over 24 weeks. At baseline, 71 percent of women randomized to the D_3 group were deficient in vitamin D (i.e., <49.9 nmol/L) and after 24 weeks, only 16 percent remained deficient. In the placebo group, the percentage of women who were vitamin D deficient decreased from 68 percent at baseline to 57 percent at 24 weeks.[139]

Finally, a small trial in Nebraska evaluated 1,000 IU, 5,000 IU, and 10,000 IU of daily vitamin D_3 over 21 weeks in winter among 62 obese (but generally healthy) participants, age 19 to 68 years.[138] The mean baseline 25[OH] D level among participants was 58.2 nmol/L (standard deviation (SD) 25.7 nmol/L). Serum 25[OH] D levels increased among participants in all groups, although there was substantial variability (mean increases of 31.0 nmol/L [SD 24.2 nmol/L], 69.4 nmol/L [SD 25.5 nmol/L], and 126.5 nmol/L [SD 40.9 nmol/L] in the 1,000 IU, 5,000 IU, and 10,000 IU groups, respectively). When authors compared results to a similar study among nonobese participants, they reported that the vitamin D dose response was 30 percent lower in obese than in nonobese participants.[138]

Contextual Question 2. What is the association between vitamin D status and fracture outcomes?

Summary of Findings

Findings from observational studies regarding the association between vitamin D status as

measured by serum 25 [OH] D levels and fracture risk are mixed. Some studies demonstrated a significant negative relationship (lower serum levels associated with increased risk), fewer studies demonstrated no association, and a few studies demonstrated an unclear or complex association (i.e., a "J" shaped risk curve). Effect estimates for many studies were imprecise, with confidence intervals that span the null effect. The 2007 AHRQ Evidence Report[14] included 15 studies; these were summarized in both the 2009 AHRQ evidence report[15] and in the 2011 review for the USPSTF[2] with a conclusion of "mixed effects" on fracture incidence. The 2014 update to the AHRQ Evidence Report[17] identified eight new observational studies, seven of which are relevant to this question. Findings from these new studies were also inconsistent with respect to effect on several fracture types (osteoporotic, nonvertebral, and hip) overall and among subgroups identified by race and ethnicity. These studies were conducted among heterogeneous populations that were followed for a varied number of years.[17] We identified eight additional observational studies published since the 2014 AHRQ Evidence Report that evaluated the association between serum concentrations of vitamin D and fracture risk over periods from 1 to 19.6 years. The findings from these studies were largely consistent with the conclusions of the prior Evidence Reports, with some studies demonstrating a higher risk of fracture in association with lower serum 25 [OH] D levels and fewer studies demonstrating no effect. This body of evidence is limited by differences in the ways in which vitamin D exposure categories are defined.

Detailed Findings From AHRQ Evidence Reports

Findings from 3 prospective cohort and 12 case-control studies, first reported in the 2007 AHRQ Evidence Report[14] and summarized in both the 2009 AHRQ Evidence Report Update[15] and 2011 update for the USPSTF,[2] were inconsistent. One of three cohort studies reported higher fracture rates with lower serum 25[OH] D levels, and nine of 12 case-control studies reported lower serum 25[OH] D levels among cases when compared with controls.[14]

The 2014 AHRQ Evidence Report relied on seven observational studies, new since 2009, to evaluate the association between vitamin D status and fracture risk: two studies evaluated the risk of total osteoporotic fractures, two studies evaluated the risk of nonvertebral fractures, and five studies evaluated the risk of hip fractures.[17] Studies were assessed for quality with a checklist designed for nutritional epidemiology studies using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and graded (A, B, or C) according to the grading system in the *AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.*

Total Fractures. Two "A-quality" cohort studies among healthy, community-dwelling postmenopausal women evaluated total fractures over mean followup periods of 5.2 and 8.6 years. The study conducted in Saudi Arabia reported an increased risk of total osteoporotic fractures (RR, 1.25 [95% CI, 0.91 to 1.70]) for women with serum 25[OH] D levels less than 17.9 nmol/L as compared with higher levels. Among white women in the observational phase of the Women's Health Initiative (WHI), women with serum 25[OH] D levels greater than 50 nmol/L were 18 percent (serum 25[OH] D: 50 to <75 nmol/L) and 64 percent (serum 25[OH] D: ≥75 nmol/L) less likely to have a fracture than women with levels less than 50 nmol/L. Results among subgroups of women identified by race were inconsistent.

Nonvertebral Fractures. Two "B-quality" studies of nonvertebral fractures, one a nested case-control study among 777 older men (mean age 74 years) and the other a prospective cohort among 2,494 men and women, found no significant associations between serum 25[OH] D levels and nonvertebral fracture risk over periods of 4.6 and 2 years, respectively.

Hip Fractures. Five prospective cohorts (3 "A-quality" and 2 "B-quality") with median follow up periods of 6.4 to 11 years reported inconsistent results regarding an association between serum 25[OH] D and hip fractures. The WHI observational study reported a 33 percent increased risk for every decrease of 25 nmol/L of serum 25[OH] D among postmenopausal women over 7.1 years. This finding is consistent with the Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) among 21,774 men and women (mean age 72 years); there was a 38 percent increase in risk for hip fracture among participants with serum 25[OH] D less than 42.2. nmol/L compared with participants with levels greater than or equal to 67.9 nmol/L. Nonsignificant increases in risk of hip fractures with lower serum 25[OH] D levels were reported in three other cohort studies; in the National Health and Nutrition Examination Survey (NHANES) III, serum levels of 25 [OH] D were a predictor of hip fracture risk within 10 years of followup, but not after 10 years.

Detailed Findings From Studies Published After the 2014 AHRQ Evidence Report

We identified eight additional observational studies, new since the 2014 AHRQ Evidence Report that evaluated the association between serum concentrations of vitamin D and fracture risk (**Appendix A Table 2**).[141-148] Four of these studies reported an increased fracture risk in association with lower serum 25 [OH] D levels[142, 143, 147, 148]; one study reported no association between serum levels and fracture risk[144]; one study reported a J-shaped association between serum levels and fracture risk[145]; and two studies reported mixed findings depending on fracture type and level of vitamin D insufficiency.[141, 146] Populations, fracture type, followup time, and definitions of vitamin D deficiency and sufficiency varied across these studies.

Total Fractures. Four prospective cohort studies[142, 144, 145, 147] evaluated serum 25[OH] D levels and the risk of incident fractures over followup periods of 1 to almost 20 years; mean baseline serum 25[OH] D levels ranged from 49.9 to 62.0 nmol/L in the studies, and findings were inconsistent. In the Atherosclerosis Risk in Communities (ARIC) study, baseline serum 25[OH] D levels were higher among white participants (mean 63.9 nmol/L) than among black participants (mean 45.4 nmol/L); 23 percent of white and 61 percent of black participants had serum levels less than 49.9 nmol/L. There was a 21 percent increase in risk (HR, 1.21 [95% CI, 1.05 to 1.39]) of incident hospitalized fractures after 19.6 years among participants with baseline serum levels less than 49.9 nmol/L compared with levels greater than or equal to 49.9 nmol/L. These findings held true among white, but not black participants when the analysis was stratified by race, and for nonusers of vitamin D supplements at baseline.[142] In prospective cohort studies among older residents of Germany over 1 year[147] and of Sweden over 10 years,[144] there were no differences in incident fracture by baseline serum 25[OH] D levels. In the Swedish Osteoporotic Prospective Risk Assessment (OPRA) cohort there was an increase in risk among women with continuously low (<50 nmol/L) serum 25[OH] D levels over 10 years compared with women with continuously high (>75 nmol/L) serum 25[OH] D levels (HR, 1.7 [95% CI, 1.1 to 2.6]).[144] Finally, there was a U-shaped association between serum 25[OH] D levels and incident fractures

(confirmed by radiographic reports) among community-dwelling men, age 70 years or older, in the Australian Concord Health Ageing in Men Project (CHAMP) over a mean 4.3 years.[145] Hazard ratios were significantly increased for men with baseline serum levels in the first and the fifth quintiles (3 to 36 nmol/L and 72 to 148 nmol/L, respectively) when compared to the fourth quintile (>59 to 72 nmol/L); this relationship was similar among men who were not supplementing with vitamin D at baseline.[145]

Nonvertebral Fractures. There was no association between serum 25[OH] D levels and nonvertebral fracture risk in the Osteoporotic Fractures in Men (MrOS) case-cohort study.[141] In a hospital-based case-control study in Germany, where controls were orthopedic patients presenting with back pain without fracture, there was a significant difference in serum 25[OH] D levels; 78 percent of cases with nonvertebral fractures and only 52 percent of controls were categorized as vitamin D deficient (<30 nmol/L) (p=0.032). Results remained the same after adjusting for gender, renal failure, and other potential confounders.[143]

Hip Fractures. Four prospective cohort studies[142, 144, 146, 148] and one case-cohort study[149] evaluated serum 25[OH] D levels and the risk of hip fractures over followup periods of 5 to almost 20 years; mean baseline serum 25[OH] D levels ranged from 46.8 to 62.2 nmol/L and findings were relatively consistent among participants with the lowest serum 25[OH] D levels across the studies. The Health 2000 Survey in Finland reported a 46 percent increase in the risk of hip fractures over a mean 8.4 years for each serum 25[OH] D reduction of 17.5 nmol/L among men age 50 years or older (HR, 1.46 [95% CI, 1.15 to 1.83]).[148] A significant increase in hip fracture risk was associated with depleted (<30 nmol/L) but not inadequate (30 to <50 nmol/L) or high ($\geq$75 nmol/L) levels of serum 25[OH] D in a random selection of Iceland's population over a mean 5.4 years in the Ages Gene/Environment Susceptibility (AGES) study. Authors suggested that 15 percent of fractures may have been attributable to depleted vitamin D levels.[146] In Sweden's OPRA study, there were no differences in baseline serum 25[OH] D levels among those with and without hip fractures after 10 years, but there was a significant increase in hip fracture risk among women with continuously low serum 25[OH] D levels (HR, 2.7 [95% CI, 1.4 to 5.3]).[144] Hip fracture risk was also elevated in the ARIC study among participants with depleted serum 25[OH] D levels (<49.9 nmol/L)[142] and in the MrOS case-cohort study, where participants with serum levels in the first quartile (7.8 to 52.17 nmol/L) were compared with all other participants.[141]

Appendix A Table 2. Results of Studies Published Since the 2014 AHRQ Evidence Report[17] Evaluating the Association Between Serum Vitamin D Levels and Fractures

Author (Year) Study	Study Design Country	Population (N) Mean Age (SD)	Baseline Serum 25[OH]D levels	Length of Follow-up	Serum 25[OH] D Comparisons	Outcome (N)	Result(s)
Bleicher, 2014[145] Concord Health and Ageing in Men Project (CHAMP)	Prospective cohort Australia	Community-dwelling men, age 70 years and older (1,705) 77 (5.5)	Mean 55.8 nmol/L	Mean 4.3 yrs	Quintiles: 1: 3–36 nmol/L 2: >36–48 nmol/L 3: >48–59 nmol/L 4: >59–72 nmol/L 5: >72–148 nmol/L	Incident fractures confirmed by radiographic reports, excluding pathological fractures and fractures of hands, feet, and head (123)	1: HR, 3.5 (95% CI, 1.7 to 7.0)* 2: HR, 1.9 (95% CI, 0.9 to 4.0)* 3: HR, 1.4 (95% CI, 0.6 to 3.0)* 4: Reference 5: HR, 2.7 (95% CI, 1.3 to 5.4)*
Buchebner, 2014[144] Osteoporotic Prospective Risk Assessment (OPRA) Cohort	Prospective cohort Sweden	Random subset of women, age 75 years, in the longitudinal population-based cohort (1,044)† 75 (0.1)	Mean 62.0 nmol/L Low (<50 nmol/L): 28% Intermediate (50–75 nmol/L): 49% High (>75 nmol/L): 23%	10 years	Category of serum 25[OH]D at baseline Low: <50 nmol/L Intermediate: 50–75 nmol/L High: >75 nmol/L	Hip fractures (126)	Fracture Incidence Low: 14.8% Intermediate: 12.4% High: 9.7% p=0.20
						Major osteoporotic fractures (334)	Low: 35.2% Intermediate: 31.8% High: 33.1% p=0.18
Kauppi, 2013[148] Health 2000 Survey Follow up	Prospective cohort Finland	Participants of the Health 2000 Survey, age 50 years and older at baseline, with calcaneal quantitative ultrasound data (3,305) 63 (9.8)	46.8 nmol/L	Mean 8.4 years	Reduction of 17.5 nmol/L [1 SD of 25[OH] D]	First hip fractures (89)	HR, 1.46 (95% CI, 1.15 to 1.83)‡ for participants with lower serum levels compared to higher levels

Appendix A Table 2. Results of Studies Published Since the 2014 AHRQ Evidence Report[17] Evaluating the Association Between Serum Vitamin D Levels and Fractures

Author (Year) Study	Study Design Country	Population (N) Mean Age (SD)	Baseline Serum 25[OH]D levels	Length of Follow-up	Serum 25[OH] D Comparisons	Outcome (N)	Result(s)
Maier, 2015[143]	Hospital-based case-control Germany	Cases were patients admitted to the hospital with a vertebral fracture (246); Controls were orthopedic patients presenting with back pain without a fracture* (392) Cases: 69 (8.5) Controls: 63 (11)	NA	NA	Cases versus controls	Serum 25[OH] D levels	Significant difference in serum 25[OH] D levels between cases and controls (p=0.036) <u>Holick Standards</u> Vitamin D Sufficiency= ≥70 nmol/L 89% of cases had abnormally low levels (mean, 38.6 nmol/L [SD, 18.2 nmol/L]) compared to 60% of controls (mean, 49.1 nmol/L [SD, 20.8 nmol/L]) (p=0.036) <u>National Osteoporosis Society Thresholds</u> Deficient: <30 nmol/L Inadequate: 30-50 nmol/L Adequate: >50 nmol/L 78% of cases were deficient (mean, 38.6 nmol/L [SD, 23.7 nmol/L]) compared to 52% of controls (mean, 49.2 nmol/L [SD, 26.2 nmol/L]) (p=0.032)
Rothenbacher, 2013 [147] Activity and Function in the Elderly in Ulm (ActiFE Ulm) Study	Prospective cohort Germany	Population-based cohort of noninstitution-alized residents of Ulm and adjacent regions in Southern Germany, age 65 years or older (1,385) 75.6 (6.5)	49.9 nmol/L Deficient (<50 nmol/L): 684 (49%) Insufficient (50 to <75 nmol/L): 574 (41%) Normal (≥75 nmol/L): 127 (9%)	1 year	Category of serum 25[OH] D levels at baseline Deficient: <50 nmol/L Insufficient: 50–<75 nmol/L Normal: ≥75 nmol/L	Incident fractures reported via a falls calendar (44)	Fracture rate per 1,000 person-years Deficient: 35 (95% CI, 23 to 53) Insufficient: 36 (95% CI, 22 to 56) Normal: 8 (95% CI, 0 to 45)

Appendix A Table 2. Results of Studies Published Since the 2014 AHRQ Evidence Report[17] Evaluating the Association Between Serum Vitamin D Levels and Fractures

Author (Year) Study	Study Design Country	Population (N) Mean Age (SD)	Baseline Serum 25[OH]D levels	Length of Follow-up	Serum 25[OH] D Comparisons	Outcome (N)	Result(s)
Steingrimsdottir, 2014[146] Ages Gene/ Environment Susceptibility (AGES) Study	Prospective Cohort Iceland	Random selection from national registry of men and women living in Reykjavik, age 66 to 96 years (5,461) 76 (NR)	Men: 57 nmol/L Women: 51 nmol/L Depleted (<30 nmol/L): 938 (17%) Insufficient (30– <50 nmol/L): 1,620 (30%) Sufficient (50–<75 nmol/L): 1,989 (36%) High (≥75 nmol/L): 914 (17%)	Mean 5.4 years	Category of serum 25[OH]D at baseline Depleted: <30 nmol/L Inadequate: 30–<50 nmol/L Sufficient: 50–<75 nmol/L High: ≥75 nmol/L	Incident hip fractures, confirmed from medical and radiological records (261)	Depleted: HR, 2.08 (95% CI, 1.51 to 2.87)[§] Inadequate: HR, 1.11 (95% CI, 0.80 to 1.53)[§] Sufficient: Reference High: HR, 0.94 (95% CI, 0.62 to 1.41)[§]
Swanson, 2015[141] Osteoporotic Fractures in Men Study (MrOS)	Case-cohort US	Ambulatory men, age 65 years and older, without bilateral hip replacements (1,000)[‖] 74.6 (6.2)	62.2 (±19.5) Nonvertebral fracture cases: 61.2 nmol/L (SD, 19.2 nmol/L) Hip fracture cases: 52.2 nmol/L (SD, 19.2 nmol/L)	Mean 5.1 years	1 SD increase in serum 25[OH] D	Incident nonvertebral fractures (432)	HRs ranged from 0.97 to 1.02 in base and multivariable analyses, all nonsignificant
				Mean 5.3 years	1 SD increase in serum 25[OH]D 1st quartile (7.8 to 52.17 nmol/L) vs all other quartiles combined	Incident hip fractures (81)	HR, 0.69 (95% CI, 0.52 to 0.91)[¶] HR, 2.05 (95% CI, 1.28 to 3.29)[¶]
Takiar, 2015[142] Atherosclerosis Risk in Communities (ARIC)	Prospective cohort US	Middle-aged adults (12,781) 57 (5.7)	All: 59.2 nmol/L White: 63.9 nmol/L Black: 45.4 nmol/L	Mean 19.6 years	<49.9 nmol/L vs ≥49.9 nmol/L at baseline	Incident hospitalized fractures (1,122)	HR, 1.21 (95% CI, 1.05 to 1.39)
					<49.9 nmol/L vs ≥49.9 nmol/L at baseline	Hip fractures (267)	HR, 1.35 (95% CI, 1.02 to 1.79)

* Adjusted for age, country of birth, BMI, physical activity, season of blood draw, previous low-trauma fracture after age 50 (10% of men), calcium supplement, and vitamin D supplement.

† The number of women evaluated at 5 years was 715 and at 10 years was 382.

ǂ Adjusted for gender, age, height, weight, BMI, serum 25[OH] D, quantitative ultrasound index, alcohol consumption, smoking status, and physical activity.

§ Adjusted for age at recruitment, sex, height, BMI, current smoking, season of blood sampling, alcohol intake, and current physical activity.

‖ Includes 679 participants from the random cohort, including 111 nonvertebral fractures, and 321 nonvertebral fracture cases.

¶ Adjusted for age, race, site, season, physical activity, height, and weight.

Abbreviations: BMI=body mass index; CI, confidence interval; HR=hazard ratio; N=number; NA=not applicable; NR=not reported; nmol/L=nanomole per liter; SD=standard deviation; U.S.=United States; 25[OH] D=vitamin D.

Appendix A Table 3. Estimates of Current Vitamin D and Calcium Intake Compared With Recommended Dietary Allowance for Adults Age >20 Years

Nutrient	% Reporting Supplement Use (SE)*†	Average Intake From Supplements* (SE)	Average Dietary Intake Among Users of Supplements* (SE)	Average Dietary Intake Among Nonusers of Supplements* (SE)	Recommended Dietary Allowance‡
Vitamin D					
Men	27 (1.7)	1,224 IU (4.4)	248 IU (22.8)	208 IU (8)	600 IU 800 IU (> age 70)
Women	35 (2.0)	1,588 IU (148)	160 IU (6)	156 IU (6)	600 IU 800 IU (> age 70)
Calcium					
Men	26 (1.7)	338 mg (15.7)	1,168 mg (40.0)	1,099 mg (19.6)	1,000 mg 1,200 mg (> age 70)
Women	33 (2.0)	605 mg (28.0)	1,021 mg (26.8)	1,010 mg (14.5)	1,000 mg 1,200 mg (> age 50)

* Based on NHANES 2011-2012 24-hour dietary recall and includes both single vitamin or mineral supplement and multivitamin or mineral supplement.[44]

† Other authors used NHANES data to estimate the prevalence of single supplement use based on past 30-day self-reported recall. They reported a prevalence of vitamin D use among adults of 19 percent (95% CI, 17 to 22), and a prevalence of calcium use of 35 percent (95% CI, 33 to 37) based on 2011-12 NHANES data.[52]

‡ Based on: *Dietary Reference Intakes for Calcium and Vitamin D*. IOM (Institute of Medicine). 2011 Washington, DC: The National Academies Press.[5]

Abbreviations: IU=international units; mg=milligram; NHANES=National Health and Nutrition Examination Survey; SE=standard error.

Appendix A Table 4. Summary of Recommendations for Vitamin D and Calcium Intake

Organization (Year)	Recommendation*
American Academy of Family Physicians (2013)[150]	Same as current USPSTF recommendation
American Congress of Obstetricians and Gynecologists (2012)[151]	Same as NAM recommendations
National Academy of Medicine (formerly Institute of Medicine)[5]	Vitamin D: 600 IU/d age 19–70; 800 IU/D age >70 Calcium: 1,000 mg/d age 19–50 for women and age 19–70 for men; 1,200 mg/d > age 50 for women and age >70 for men
National Osteoporosis Foundation (2014)[30]	Vitamin D: 800–1,000 IU/d age >50 Calcium: same as NAM recommendation
American Association of Clinical Endocrinologists (2016)[152]	Vitamin D: Assess for deficiency, maintain serum 25 [OH] D levels ≥30 ng/ml (75 nmol/L) Calcium: 1,200 mg/d (diet and/or supplement) for women age >50
Osteoporosis Canada (2010)[153]	Vitamin D: 400 -1,000 IU/d supplementation for adults at low risk for vitamin D deficiency, 800-1,000 IU/d for adults > 50 at moderate risk of deficiency Calcium: 1,200 mg/d (through diet and supplements) for adults age >50
American College of Rheumatology (2010)[154]	These recommendations apply to patients receiving glucocorticoid therapy Vitamin D: 800–1,000 IU/d or amount required to achieve therapeutic levels Calcium: 1,200–1,500 mg/d from diet and supplements
American Association of Orthopedic Surgeons (2012)[155]	Same as NAM recommendations
Endocrine Society (2011)[156]	Vitamin D: Same as NAM recommendation, higher doses may be required to treat deficiency Calcium: None

* Some of the recommendations are specific to general dietary intake for all persons, while some are specific to persons with osteoporosis or who have risks for secondary osteoporosis.

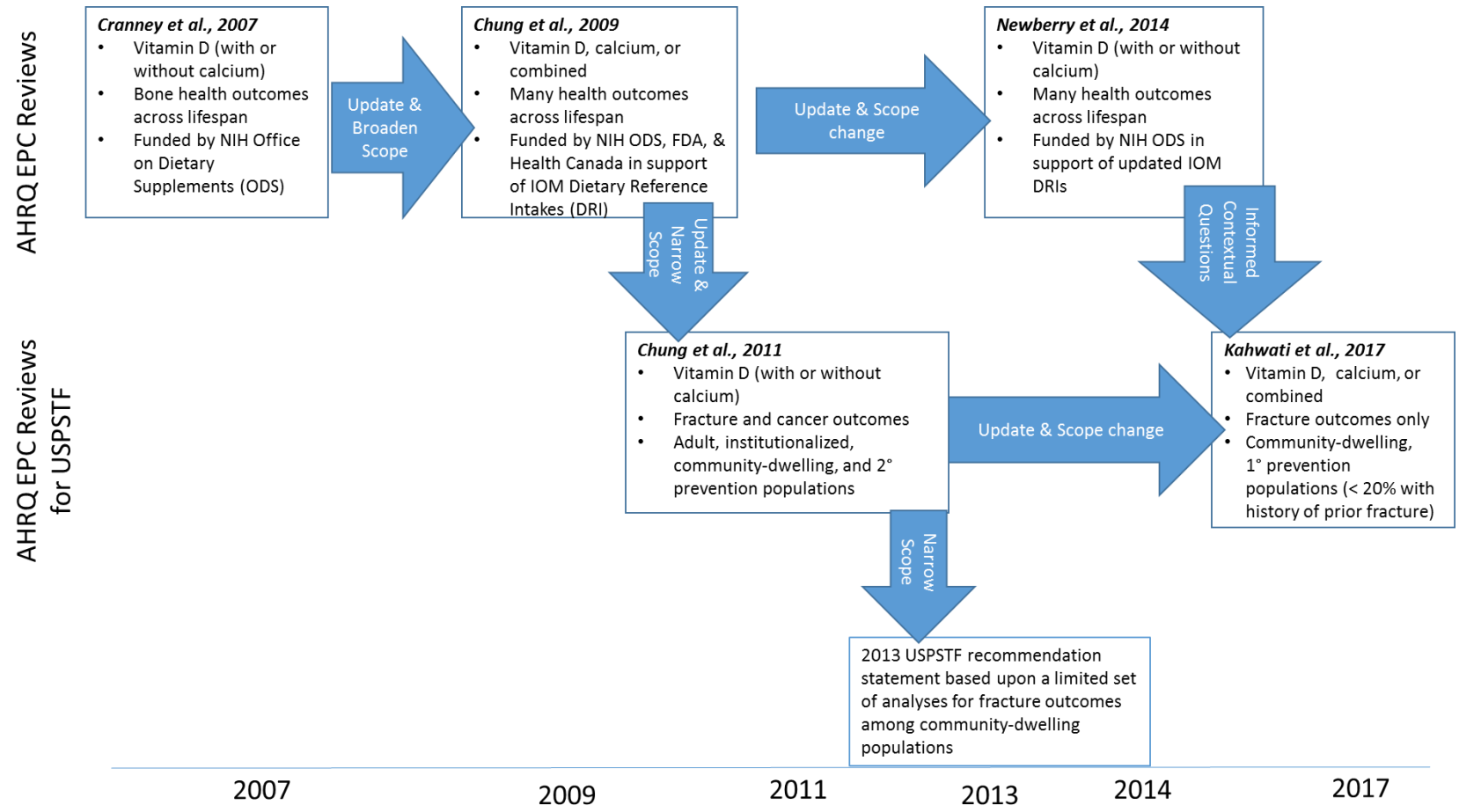
Abbreviations: d=day; IU=international units; mg=milligram; NAM=National Academy of Medicine (formerly Institute of Medicine); ng/ml=nanogram per milliliter; nmol/L=nanomole per liter; USPSTF=U.S. Preventive Services Task Force.

Appendix A Table 5. Related USPSTF Recommendations

Vitamin D and Calcium Supplementation (2013)[1]			
Population	Community-dwelling men or premenopausal women	Community-dwelling postmenopausal women	
Recommendation	I	I	D
Intervention	Vitamin D/Calcium	Vitamin D_3 >400 IU Calcium >1,000 mg	Vitamin D_3 ≤400 IU Calcium ≤1,000 mg
Balance of benefits and harms	Inadequate evidence to judge	Inadequate evidence to judge	No effect on incidence of fracture ≥ no net benefit
Vitamin D Screening (2015)[54]			
Population	Community-dwelling Adults		
Recommendation	I		
Intervention	Screening for vitamin D deficiency and treatment if deficient		
Balance of benefits and harms	Inadequate evidence to judge		
Falls Prevention Older Adults: Interventions (2018)[62]			
Population	Community-dwelling adults age ≥65 who are at increased risk for falls		
Recommendation	B	C	D
Intervention	Exercise interventions	Multifactorial interventions	Vitamin D supplementation
Balance of benefits and harms	Exercise interventions have a moderate benefit in preventing falls in older adults at increased risk for falls; harms are no greater than small.	Multifactorial interventions have a small benefit in preventing falls in older adults at increased risk for falls; harms are no greater than small.	Vitamin D supplementation has no benefit in preventing falls in older adults; harms of supplementation are small to moderate.
Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Counseling (2014)[58]			
Population	Healthy adults without special nutritional needs		
Recommendation	I	I	D
Intervention	Use of multivitamins to prevent cardiovascular disease or cancer	Single- or paired-nutrient supplements for prevention of cardiovascular disease or cancer	Use of β-carotene or vitamin E for prevention of cardiovascular disease or cancer
Balance of benefits and harms	Inadequate evidence to judge	Inadequate evidence to judge	Evidence of harms related to β-carotene and evidence of no effect related to vitamin E ->no net benefit
Screening for Osteoporosis (2011)[56]			
Population	Women age 65 or over	Women younger than 65 with fracture risk equivalent to 65-year-old woman	Men
Recommendation	B	B	I
Intervention	BMD assessment using DXA	BMD assessment using DXA	N/A
Balance of benefits and harms	Screening with DXA has at least moderate benefit.		Balance of harms and benefits cannot be determined.

Abbreviations: BMD=bone mineral density; DXA=dual-energy x-ray absorptiometry; IU=international units; mg=milligram; USPSTF=U.S. Preventive Services Task Force.

Appendix B1. Relationship of Current Update to Previous AHRQ Evidence Reviews



Cranney et al (2007)[14]
Chung et al (20009)[15]
Chung et al (2011)[2]-USPSTF Recommendation (2013)[1]
Newberry et al (2014)[17]

Appendix B2. Search Strategies

KQ 1 PubMed (January 1, 2011 through May 25, 2016)

	Terms	Results
#22	Search "Vitamin D"[Mesh] OR "Vitamin D"[tw]	67831
#23	Search "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Calcium"[tw]	535891
#25	Search (#22 OR #23)	576628
#26	Search ((Fracture, Bone (MeSH) OR fracture[tw]))	160977
#27	Search (#25 AND #26)	7631
#28	Search (#25 AND #26) Filters: Publication date from 2011/01/01	2424
#29	Search (#25 AND #26) Filters: Publication date from 2011/01/01; Humans	1559
#30	Search (#25 AND #26) Filters: Publication date from 2011/01/01; Humans; English	1404
##	Search (#25 AND #26) Filters: Systematic Reviews; Publication date from 2011/01/01; Humans Total	98
#31	Search (#25 AND #26) Filters: Systematic Reviews; Publication date from 2011/01/01; Humans; English	88
#32	Search ((((("Controlled Clinical Trial" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type]) OR "Meta-Analysis" [Publication Type]) OR "Comparative Study" [Publication Type])) OR (((((("Randomized Controlled Trial" [Publication Type]) OR "Single-Blind Method"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Random Allocation"[Mesh])	2200139
#33	Search (#29 AND #32)	266
#34	Search (#30 AND #32)	252
#39	Search ((("Cohort Studies"[Mesh]) OR "Epidemiologic Studies"[Mesh]) OR "Prospective Studies"[Mesh]) OR "Observational Study" [Publication Type]	1869921
#40	Search (#29 AND #39)	505
#41	Search (#30 AND #39)	484
#53	Search (#31 OR #34 OR #41)	681

Cochrane=23=new
Reviews=15=9 new
DARE=8=2 new
Cochrane Central Register of Controlled Trials=29=12 new

Embase=321=313 English=212 new
Total Database=232

Both Databases KQ 1=913

Calcium Alone PubMed (Database Inception Through 2010)

	Search Terms	Results
#22	Search "Vitamin D"[Mesh] OR "Vitamin D"[tw]	67831
#23	Search "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Calcium"[tw]	535891
#26	Search ((Fracture, Bone (MeSH) OR fracture[tw]))	160977
#32	Search ((((("Controlled Clinical Trial" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type]) OR "Meta-Analysis" [Publication Type]) OR "Comparative Study" [Publication Type])) OR (((((("Randomized Controlled Trial" [Publication Type]) OR "Single-Blind Method"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Random Allocation"[Mesh])	2200139
#33	Search (#23 AND #26)	6515
#34	Search (#33 NOT #22)	4220
#35	Search (#33 NOT #22) Filters: Humans	2608
#36	Search (#33 NOT #22) Filters: Publication date to 2010/12/31; Humans	1991
#37	Search (#33 NOT #22) Filters: Publication date to 2010/12/31; Humans; English	1717
#38	Search (#33 NOT #22) Filters: Systematic Reviews; Publication date to 2010/12/31; Humans; English	38
#39	Search (#33 NOT #22) Filters: Systematic Reviews; Publication date to 2010/12/31; Humans	45
#43	Search #32 AND #34 Filters: Publication date to 2010/12/31; Humans	430
#44	Search #32 AND #34 Filters: Publication date to 2010/12/31; Humans; English	400
#45	Search (#44 OR #38) Filters: Publication date to 2010/12/31; Humans; English	426

Cochrane=35
Reviews=5=3 new
DARE=6=2 new
Cochrane Central Register of Controlled Trials=56=30

Embase=114=91 English=64
Database Total=99

Both Databases KQ 1 Calcium Alone=525

KQ 2 PubMed (January 1, 2011 through May 25, 2016)

	Search Term	Results
#1	Search (((“Drug-Related Side Effects and Adverse Reactions”[Mesh])) OR ((“Dietary Supplements/adverse effects”[Mesh] OR “Dietary Supplements/toxicity”[Mesh]))) OR ((((((“Mortality”[Mesh]) OR “Neoplasms”[Mesh]) OR “Urinary Calculi”[Mesh]) OR “Nephrolithiasis”[Mesh]) OR “Cardiovascular Diseases”[Mesh]) OR “Cerebrovascular Disorders”[Mesh])	4936092
#2	Search (((“Cohort Studies”[Mesh] OR “Epidemiologic Studies”[Mesh] OR “Follow-up Studies”[Mesh] OR “prospective cohort” OR “prospective studies”[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))) OR “Observational Study” [Publication Type]	1889594
#3	Search (((((“Controlled Clinical Trial” [Publication Type]) OR “Clinical Trial, Phase IV” [Publication Type]) OR “Clinical Trial, Phase III” [Publication Type]) OR “Comparative Study” [Publication Type])) OR ((((“Randomized Controlled Trial” [Publication Type]) OR “Single-Blind Method”[Mesh]) OR “Double-Blind Method”[Mesh]) OR “Random Allocation”[Mesh])	2143507
#4	Search ((((“Vitamin D/adverse effects”[Mesh] OR “Vitamin D/drug therapy”[Mesh] OR “Vitamin D/poisoning”[Mesh] OR “Vitamin D/therapeutic use”[Mesh] OR “Vitamin D/therapy”[Mesh] OR “Vitamin D/toxicity”[Mesh]))) OR ((“Calcium/adverse effects”[Mesh] OR “Calcium/poisoning”[Mesh] OR “Calcium/therapeutic use”[Mesh] OR “Calcium/therapy”[Mesh] OR “Calcium/toxicity”[Mesh]))) OR ((“Calcium Compounds/adverse effects”[Mesh] OR “Calcium Compounds/poisoning”[Mesh] OR “Calcium Compounds/therapeutic use”[Mesh] OR “Calcium Compounds/therapy”[Mesh] OR “Calcium Compounds/toxicity”[Mesh]))	36152
#5	Search (#1 AND #4)	6231
#8	Search (#1 AND #4) Filters: Systematic Reviews; Publication date from 2011/01/01; Humans	124
#9	Search (#1 AND #4) Filters: Systematic Reviews; Publication date from 2011/01/01; Humans; English	115
#10	Search (#1 AND #4) Filters: Publication date from 2011/01/01; Humans; English	1325
#11	Search (#2 AND #10) Filters: Publication date from 2011/01/01; Humans; English	323
##	Total before English removed	334
#12	Search (#3 AND #10) Filters: Publication date from 2011/01/01; Humans; English	226
##	Total before English removed	230
#13	Search (#11 OR #12) Filters: Publication date from 2011/01/01; Humans; English	456
#23	Search (#9 OR #13)	552

Cochrane=39 New
Reviews=7=4 New
DARE=1=0 New
Cochrane Central Register of Controlled Trials=47=35 New

Embase=228=223 English=213 New

Database Total=252

Both Databases KQ 2=804

Appendix B2. Search Strategies

Calcium Alone PubMed (Database inception through 2010)

	Search Term	Results
#1	Search (((“Drug-Related Side Effects and Adverse Reactions”[Mesh])) OR ((“Dietary Supplements/adverse effects”[Mesh] OR “Dietary Supplements/toxicity”[Mesh]))) OR ((((((“Mortality”[Mesh]) OR “Neoplasms”[Mesh]) OR “Urinary Calculi”[Mesh]) OR “Nephrolithiasis”[Mesh]) OR “Cardiovascular Diseases”[Mesh]) OR “Cerebrovascular Disorders”[Mesh])	4936092
#2	Search (((“Cohort Studies”[Mesh] OR “Epidemiologic Studies”[Mesh] OR “Follow-up Studies”[Mesh] OR “prospective cohort” OR “prospective studies”[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))))) OR “Observational Study” [Publication Type]	1889594
#3	Search (((((“Controlled Clinical Trial” [Publication Type]) OR “Clinical Trial, Phase IV” [Publication Type]) OR “Clinical Trial, Phase III” [Publication Type]) OR “Comparative Study” [Publication Type])) OR ((((“Randomized Controlled Trial” [Publication Type]) OR “Single-Blind Method”[Mesh]) OR “Double-Blind Method”[Mesh]) OR “Random Allocation”[Mesh])	2143507
#4	Search (((((“Calcium/adverse effects”[Mesh] OR “Calcium/poisoning”[Mesh] OR “Calcium/therapeutic use”[Mesh] OR “Calcium/therapy”[Mesh] OR “Calcium/toxicity”[Mesh]))) OR ((“Calcium Compounds/adverse effects”[Mesh] OR “Calcium Compounds/poisoning”[Mesh] OR “Calcium Compounds/therapeutic use”[Mesh] OR “Calcium Compounds/therapy”[Mesh] OR “Calcium Compounds/toxicity”[Mesh]))))	21689
#5	Search (#1 AND #4)	3661
#7	Search “Vitamin D”[Mesh]	47935
#8	Search (#5 NOT #7)	2930
#11	Search (#5 NOT #7) Filters: Systematic Reviews; Publication date to 2010/12/31; Humans Total	64
#12	Search (#5 NOT #7) Filters: Systematic Reviews; Publication date to 2010/12/31; Humans; English	62
#13	Search (#5 NOT #7) Filters: Publication date to 2010/12/31; Humans;	1589
##	Search (#5 NOT #7) Filters: Publication date to 2010/12/31; Humans	1974
#14	Search (#2 AND #13) Filters: Publication date to 2010/12/31; Humans; English	312
##	Total before English removed	337
#15	Search (#3 AND #13) Filters: Publication date to 2010/12/31; Humans; English	308
##	Total before English removed	358
#16	Search (#14 OR #15) Filters: Publication date to 2010/12/31; Humans; English	518
#18	Search (#12 OR #16) Filters: Publication date to 2010/12/31; Humans; English	567

Cochrane=13
Reviews=10=3
DARE=1=1 New
Cochrane Central Register of Controlled Trials=10=9

Embase=91=80 New

Database Total=93

Both Databases KQ 2 Calcium Alone=660

Registry Searches (through November 16, 2016)

ClinicalTrials.gov
“Vitamin D” And Fracture=57
Calcium AND Fracture=26 unique not already picked up by Vitamin D search

WHO ICTRP
“Vitamin D” And Fracture=3 unique, not already picked up by clinicaltrials.gov
Calcium AND Fracture=1 unique, not already picked up by clinicaltrials.gov

NICE=0

Total=87 unique records

Update Search
KQ 1 PubMed (May 26, 2016 through March 21, 2017)

	Terms	Results
#2	Search "Vitamin D"[Mesh] OR "Vitamin D"[tw]	71201
#3	Search "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Calcium"[tw]	550586
#4	Search (#2 OR #3)	593840
#5	Search ((Fracture, Bone (MeSH) OR fracture[tw]))	168951
#6	Search (#4 AND #5)	7989
#7	Search (#4 AND #5) Filters: Humans	5820
#8	Search (#4 AND #5) Filters: Humans; English	5078
#9	Search (#4 AND #5) Filters: Publication date from 2016/03/01; Humans; English	85
#12	Search (#9 AND #11) Filters: Systematic Reviews	7
#13	Search (#9 AND #11)	7
#14	Search ((((("Controlled Clinical Trial" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type]) OR "Meta-Analysis" [Publication Type]) OR "Comparative Study" [Publication Type])) OR (((((("Randomized Controlled Trial" [Publication Type]) OR "Single-Blind Method"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Random Allocation"[Mesh])	2256005
#15	Search (#9 AND #14)	11
#16	Search ((("Cohort Studies"[Mesh]) OR "Epidemiologic Studies"[Mesh]) OR "Prospective Studies"[Mesh]) OR "Observational Study" [Publication Type]	1980834
#17	Search (#9 AND #16)	23
#18	Search (#13 OR #15 OR #17)	34

Cochrane=73
Reviews=5 + 2 New
DARE=0=New
Cochrane Central Register of Controlled Trials=68=61 new

Embase=English=88=64 new
Total Database=161

KQ 2 PubMed (May 26, 2016 through March 21, 2017)

	Search Term	Results
#2	Search ((((“Drug-Related Side Effects and Adverse Reactions”[Mesh])) OR ((“Dietary Supplements/adverse effects”[Mesh] OR “Dietary Supplements/toxicity”[Mesh]))) OR ((((((“Mortality”[Mesh]) OR “Neoplasms”[Mesh]) OR “Urinary Calculi”[Mesh]) OR “Nephrolithiasis”[Mesh]) OR “Cardiovascular Diseases”[Mesh]) OR “Cerebrovascular Disorders”[Mesh]))	5098289
#3	Search (((“Cohort Studies”[Mesh] OR “Epidemiologic Studies”[Mesh] OR “Follow-up Studies”[Mesh] OR “prospective cohort” OR “prospective studies”[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))))) OR “Observational Study” [Publication Type]	2002948
#4	Search (((((“Controlled Clinical Trial” [Publication Type]) OR “Clinical Trial, Phase IV” [Publication Type]) OR “Clinical Trial, Phase III” [Publication Type]) OR “Comparative Study” [Publication Type])) OR ((((“Randomized Controlled Trial” [Publication Type]) OR “Single-Blind Method”[Mesh]) OR “Double-Blind Method”[Mesh]) OR “Random Allocation”[Mesh])	2190914
#5	Search ((((“Vitamin D/adverse effects”[Mesh] OR “Vitamin D/drug therapy”[Mesh] OR “Vitamin D/poisoning”[Mesh] OR “Vitamin D/therapeutic use”[Mesh] OR “Vitamin D/therapy”[Mesh] OR “Vitamin D/toxicity”[Mesh]))) OR ((“Calcium/adverse effects”[Mesh] OR “Calcium/poisoning”[Mesh] OR “Calcium/therapeutic use”[Mesh] OR “Calcium/therapy”[Mesh] OR “Calcium/toxicity”[Mesh]))) OR ((“Calcium Compounds/adverse effects”[Mesh] OR “Calcium Compounds/poisoning”[Mesh] OR “Calcium Compounds/therapeutic use”[Mesh] OR “Calcium Compounds/therapy”[Mesh] OR “Calcium Compounds/toxicity”[Mesh]))	37372
#6	Search (#2 AND #5)	6428
#7	Search (#2 AND #5) Filters: Systematic Reviews	279
#8	Search (#2 AND #5) Filters: Systematic Reviews; Humans	279
#9	Search (#2 AND #5) Filters: Systematic Reviews; Humans; English	256
#10	Search (#2 AND #5) Filters: Systematic Reviews; Publication date from 2016/03/01; Humans; English	7
#11	Search (#2 AND #5) Filters: Publication date from 2016/03/01; Humans; English	71
#12	Search (#3 AND #11) Filters: Publication date from 2016/03/01; Humans; English	21

Appendix B2. Search Strategies

	Search Term	Results
#13	Search (#4 AND #11) Filters: Publication date from 2016/03/01; Humans; English	10
#14	Search (#12 OR #13) Filters: Publication date from 2016/03/01; Humans; English	27
#15	Search (#10 OR #14) Filters: Publication date from 2016/03/01; Humans; English	33

Cochrane=19
Reviews=3=2 New
DARE=0
Cochrane Central Register of Controlled Trials=16=New

Embase=English=31=27 New

Database Total=78

Registry Searches (through March 21, 2017)

ClinicalTrials.gov
(Vitamin D OR Calcium) AND Fracture=3

WHO ICTRP
(Vitamin D OR Calcium) AND Fracture=0

NICE=1

Total=198 unique records

Appendix B3. Eligibility Criteria for Study Selection

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
1. Does the article represent original research?	X1	Not original research	Published or unpublished original research.	Nonsystematic (narrative) review, letters or editorials, articles with no original data.
2. Does the study include an intervention of interest?	X2	Ineligible or no intervention	Supplementation with vitamin D2 or D3 alone or in combination with calcium or supplementation with calcium alone. Any dosage, route, or frequency.	Short-term supplementation use (<1 month); vitamin D preparations or metabolites designed for treatment not supplementation (e.g., calcitriol, alphacalcitriol, calcifediol); synthetic vitamin D analogs (i.e., doxercalciferol, paricalcitol, falecalcitriol, oxacalcitriol, alfacalcidol); multivitamin supplements that include vitamin D or calcium, unless the independent effects of vitamin D, calcium, or both can be evaluated; foods or beverages fortified with vitamin D, calcium, or both; and vitamin D obtained through natural or artificial ultraviolet light exposure.
3. Does the study report on the population of interest?	X3	Ineligible population	Community-dwelling adults with no known disorders related to bone metabolism. Mixed populations will be included if no more than 20% of the study population has any of the excluded conditions. Study populations with 20%–50% having a known condition will be considered in sensitivity analyses.	Children or adolescents age <18 years; pregnant or lactating women; studies for which patient eligibility is determined by testing to identify vitamin D deficiency or bone measurement testing, with selection based on low vitamin D or bone density level; studies with inclusion criteria designed to assemble populations with a specific condition or a group of closely related conditions, such as those with: • osteoporosis, or who take antiresorptive agents, or have a prior history of osteoporotic fractures, or have long-term use of systemic corticosteroids or other medications associated with osteoporosis (e.g., aromatase inhibitors, androgen deprivation therapy, antiretroviral therapy); • a history of falls or considered at high risk for falls; • medical conditions associated with vitamin D deficiency (e.g., hyperparathyroidism, rickets, calcium or phosphorus metabolism disorders, malabsorptive disorders, celiac disease, cystic fibrosis, short gut syndrome, cholestatic liver disease, hepatic failure, cirrhosis, chronic kidney disease, scleroderma, lupus, dermatomyositis); • bone disorders (e.g., osteogenesis imperfecta, osteopetrosis, osteitis deformans); • active cancer or history of cancer (excluding nonmelanoma skin cancer); • known coronary artery disease; and • nephrolithiasis or nephrocalcinosis.

Appendix B3. Eligibility Criteria for Study Selection

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
4. Is the study conducted in a clinical or community setting of interest?	X4	Ineligible setting	Community and primary care-relevant settings, including assisted and independent living facilities.	Skilled nursing facilities; postacute care and rehabilitation facilities
5. Does the study report on outcomes of interest?	X5	Ineligible or no outcomes	**KQ 1:** Total primary (i.e., incident) fractures at any site other than face, skull, finger, toe, and heel; total primary (i.e., incident) major osteoporotic fracture, defined as fracture of the hip; vertebral (clinical), proximal humerus, distal radius, and morphometric vertebral fractures; fracture-related morbidity (e.g., fracture nonunion) and mortality. **KQ 2:** All-cause mortality, symptomatic acute or chronic vitamin D or calcium toxicity, incident symptomatic nephrolithiasis, incident cancer (other than nonmelanoma skin cancer), incident cardiovascular disease (myocardial infarction, stroke, peripheral artery disease), and other harms reported as being definitely or probably related to study intervention.	**KQ 1:** Recurrent osteoporotic fracture (i.e., preventing a second fracture in patients known to have a previous osteoporotic fracture); change in BMD; other intermediate measures of bone or muscle strength or quality. **KQ 2:** Asymptomatic outcomes (soft-tissue calcification, nephrocalcinosis, artery calcification, hypercalcemia, hypercalciuria).
6. Does the study use a study design of interest?	X6	Ineligible study design	**KQ 1:** RCTs; systematic reviews that use study selection criteria similar to this review. **KQ 2:** RCTs; systematic reviews that use study selection criteria similar to this review; prospective cohort or case-control studies, if they: • were designed specifically to evaluate the use of vitamin D or calcium supplementation and • adequately measured and controlled for nonsupplemental sources of vitamin D or calcium.	Study designs not listed as specifically included (e.g., case reports, case series, studies without a comparison group).

Appendix B3. Eligibility Criteria for Study Selection

Include or Exclude Question	Exclusion Code	Reason for Exclusion	Inclusion Criteria	Exclusion Criteria
7. Does the study use a comparator of interest?	X7	Ineligible or no comparator	Placebo, no treatment, or lower- or higher-dose vitamin D or calcium regimens.	Intervention and comparison arms that do not allow for evaluation of the independent contribution of vitamin D or calcium, either alone or combined (e.g., studies assessing a multicomponent intervention that includes vitamin D as one of several components compared with no intervention would not be eligible unless the comparison arm included all of the other intervention components except vitamin D).
8. Does the study provide the intervention over a time period of interest?	X8	Ineligible timing	**KQ 1:** Intervention duration of ≥1 month **KQ 2:** Any duration	**KQ 1:** Intervention duration of <1 month **KQ 2:** No exclusions
9. Does the study include countries with an HDI similar to the United States?	X9	Ineligible country	Studies conducted in countries categorized as "very high" on the HDI (as defined by the United Nations Development Programme).	Studies conducted in countries not categorized as "very high" on the HDI (as defined by the United Nations Development Programme).
10. Is article published in English?	X10	Not published in English	Studies must be published in English.	Studies not published in English.
11. Is article a study protocol?	X11	Study protocol	Study protocols are not eligible for inclusion.	Study protocols that do not contain any results data.

Abbreviations: BMD=bone mineral density; HDI=Human Development Index; KQ=key question; RCT=randomized controlled trial.

RCTs and Cohort Studies

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Source: U.S. Preventive Services Task Force Procedure Manual. Appendix VI. Criteria for Assessing Internal Validity of Individual Studies. Available at: https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix C. Excluded Studies

List of Exclusion Codes:
X1: Not original research
X2: Ineligible or no intervention
X3: Ineligible population
X4: Ineligible setting
X5: Ineligible or no outcomes
X6: Ineligible study design
X7: Ineligible or no comparator
X8: Ineligible timing
X9: Ineligible country
X10: Not published in English
X11: Study protocol
X12: Systematic reviews used to identify primary research articles
X13: Poor quality

1. Link between calcium supplements and heart attack risk unclear. *Harv Womens Health Watch*. 2010 Oct;18(2):6-7. Exclusion Code: X1.
2. Do vitamin D supplements affect mortality? *Drug Ther Bull*. 2011;49(9):100. Exclusion Code: X1.
3. Calcium and vitamin D supplements linked to raised CVD risk. *Menopause International*. 2011;17(2):38-9. Exclusion Code: X1.
4. Calcium supplements could increase heart attack risks. *Harv Womens Health Watch*. 2012 Aug;19(12):8. PMID: 23033553. Exclusion Code: X1.
5. Calcium supplementation: Cardiovascular risk? *Prescrire Int*. 2013;22(139):152-3. Exclusion Code: X1.
6. Abbas S, Linseisen J, Rohrmann S, et al. Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Nutr Cancer*. 2013;65(2):178-87. doi: 10.1080/01635581.2013.752018. PMID: 23441605. Exclusion Code: X2.
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Appendix C. Excluded Studies

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Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Aloia et al, 2005[114] Total N=208 NA for Benefits; Poor for Harms	United States	Ambulatory postmenopausal African American women not receiving hormone therapy. Exclusion criteria included previous treatment with bone active agents and any medication or illness that affects skeletal metabolism.	Reported by study group only	Reported by study group only	208 (100)	Mean (SD) 25[OH]D level: Reported by study group only No. with prevalent or history of prior osteoporotic fractures: NR No. with use of supplemental calcium and/or vitamins: NR (47%) No. with hip BMD: Normal: (NR) 65.0% Osteopenic: (NR) 33.6% Osteoporotic: NR (1.4%) No. in nursing home or other institutionalized setting: NR	The primary study aim was to assess impact of vitamin D supplementation on bone loss specifically in African American women. Study reports outcomes relevant to the KQ 2 sensitivity analyses.
Placebo, plus some participants in this group received an unknown dose of calcium (n=104)	--	--	61.2 (6.3)	104 (100)	104 (100)	Mean (SD) 25[OH]D level: 42.9 nmol/L (16.6)* Mean (SD) hip BMD: 0.946 g/cm^2 (0.116)	--
Vitamin D_3 1,200 IU orally daily during the first 24 months, increasing to 2,000 IU daily thereafter, plus some participants in this group received an unspecified dose of calcium (n=104)	--	--	59.9 (6.2)	104 (100)	104 (100)	Mean (SD) 25[OH]D level: 48.2 nmol/L (20.9)* Mean (SD) hip BMD 0.932 g/cm^2 (0.146)	--

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Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Cherniack et al, 2011[119] Total N=46 NA for Benefits; Poor for Harms	United States	Community-dwelling veterans age 70 years and older recruited from a geriatric clinic. Deficient vitamin D serum levels were not listed as an inclusion criteria. Exclusion criteria included current use of vitamin D or corticosteroids, hypo- or hypercalcemia, hypercalciuria, hyperparathyroidism, serum creatinine chronically greater than 2.0 mg/dL, cholestatic liver disease, or were unable to take medication daily.	Reported for study group only	1 (2.2)	3 (6.5)	Mean (SD) 25[OH]D level: Reported by study groups only No. with prevalent or history of prior osteoporotic fractures: NR No. in nursing home or other institutionalized setting: NR (0%)	The primary study aim was to assess the impact of vitamin D supplementation on correcting hypovitaminosis. Study reports outcomes relevant to the KQ 2 sensitivity analysis.
Placebo, most but not all also received an unspecified dose of a calcium supplement (No. of participants NR)	--	--	79.5 (3.5)	NR	NR	Mean (SD) 25[OH]D level: 69.1 nmol/L (20.7)*	--
Vitamin D_3 2,000 IU orally daily, most but not all also received an unspecified dose of a calcium supplement (No. of participants NR)	--	--	79.7 (5.3)	NR	NR	Mean (SD) 25[OH]D level: 71.6 nmol/L (22.0)*	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Dawson-Hughes et al, 1997[74] Total N=445 randomized, 389 analyzed Fair for Benefits; NA for Harms	United States	Healthy, ambulatory men and women age 65 years or older who were living at home recruited through direct mailings and community presentations. Exclusion criteria included current cancer, hyperparathyroidism, kidney stones within prior 5 years, renal disease, bilateral hip surgery, therapy with antiresorptive or anabolic bone agents in past 6 months, BMD<2 SD below age/sex mean, dietary calcium exceeding 1,500 mg, abnormal kidney or liver laboratory measurements.	Reported by study groups only	213 (55)†	15 (3)‡	Mean (SD) 25[OH]D level: Reported by study groups only§ No. with prevalent or history of prior osteoporotic fractures: NR Femoral neck mean (SD) BMD: Reported by study groups only† No in nursing home or other institutionalized setting: NR (0%)	The primary study aim was to examine the effects of combined calcium and vitamin D supplementation on bone loss, bone metabolism, and nonvertebral fracture incidence. Study reports on outcomes relevant to the KQ 1 main analysis.
Placebo (n=202)	--	--	Women 72 (5) Men 71 (5)	112 (55)	NR	Mean (SD) 25[OH]D level: Women: 61.2 nmol/L (25.7) Men: 83.9 nmol/L (31.7) Femoral neck mean (SD) BMD: Women: 0.81 g/cm^2 (0.11) Men: 0.95 g/cm^2 (0.12)	--
Vitamin D_3 700 IU orally plus elemental calcium 500 mg (as malate salt) daily (n=187)	--	--	Women 71 (4) Men 70 (4)	101 (54)	NR	Mean (SD) 25[OH]D level: Women: 71.6 nmol/L (33.2) Men: 82.4 nmol/L (40.7) Femoral neck mean (SD) BMD: Women: 0.80 g/cm^2 (0.11) Men: 0.99 g/cm^2 (0.14)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Glendenning et al, 2012[86] Total N=686 Poor for Benefits; Poor for Harms	Australia	Community-dwelling women age 70 or older recruited from 4 general practice clinics and from the electoral rolls. Exclusion criteria included consumption of vitamin D supplementation either in isolation or as part of a combination treatment, cognitive impairment, and individuals who, in the investigators' opinion, would not be suitable for the study.	76.7 (4.1)	686 (100)	NR	Mean (SD) 25[OH]D level: 65.8 nmol/L (22.7)‖ No. with prevalent or history of prior osteoporotic fractures: NR No. with falls within prior 12 months: Reported by study groups only No. in nursing home or other institutionalized setting: NR (0%)	Primary study aim was to examine the effects of vitamin D supplementation on falls, muscle strength, and mobility. Study reports outcome relevant to the KQ 2 sensitivity analysis.
Placebo¶ (n=333)	--	--	76.5 (4.0)	333 (100)	NR (4.0)	Mean (SD) 25[OH]D level: 66.5 nmol/L (27.1)‖ No. with zero falls within prior 12 months: NR (75.5%)	--
Vitamin D_3 150,000 IU orally at baseline, 3 months, and 6 months¶ (n=353)	--	--	76.9 (4.0)	353 (100)	NR (3.2)	Mean (SD) 25[OH]D level: 65.0 nmol/L (17.8)‖ No. with zero falls within prior 12 months: NR (66.6%)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Hin et al, 2017[110] Total N=305 Varies by outcome	UK	Community-dwelling, ambulatory adults not currently taking vitamin D_3 in doses higher than 400 IU per day.	72(NR)	150(49%)	NR	Mean (SD) 25[OH]D level: Reported by group No. with prevalent or history of prior osteoporotic fractures: Reported by group	The primary study aim was to compare effects of vitamin D supplementation on biochemical markers of vitamin D status. Study reports on outcomes relevant to the KQ 2 sensitivity analyses.
Placebo (n=101)	--	--	72 (6)	49 (49)	--	Mean (SD) 25[OH]D level:47 nmol/L (1.5) No. with prevalent or history of prior osteoporotic fractures: 30 (30)	--
Vitamin D_3 4,000 IU orally daily (n=102)	--	--	71 (6)	50 (49)	--	Mean (SD) 25[OH]D level:49 nmol/L (1.5) No. with prevalent or history of prior osteoporotic fractures: 31 (30)	--
Vitamin D_3 2,000 IU orally daily (n=102)	--	--	72 (6)	51 (50)	--	Mean (SD) 25[OH]D level:55 nmol/L (2.2) No. with prevalent or history of prior osteoporotic fractures:30 (29)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Khaw, Scragg et al, 2017[77, 78] VIDA Total N=5,110 randomized, 5,108 analyzed Good	New Zealand	Community-dwelling adults aged 50 to 84 years recruited mostly (94%) from family medicine practices. Exclusion criteria included current use of vitamin D supplements, hypercalcemia, nephrolithiasis, sarcoidosis, or corrected serum calcium >10 mg/dL	65.9 (8.3)	2,141 (41.9)	857 (16.8)	Mean (SD) 25[OH]D level: reported by study group No. with prevalent or history of prior osteoporotic fractures: NR[#]	The primary study aid was to examine the effects of vitamin D supplementation on CVD incidence. Fractures and fall were designated as secondary outcomes. Study reports outcomes relevant to KQ 1 and KQ 2 main analyses.
Placebo (n=2,552)	--	--	--	1,093 (42.9)	424 (16.6)	Mean (SD) 25[OH]D level: 62.90 nmol/L (23.5)	--
Vitamin D_3 orally 200,000 IU initial dose followed by 100,000 IU every month (n=2,558)	--	--	--	1,046 (40.9)	431 (16.8)	Mean (SD) 25[OH]D level: 63.7 nmol/L (23.7)	--
Komulainen et al, 1998,[71] Komulainen et al, 1999[118] Osteoporosis Risk Factor and Prevention Study[**] Total N=232 Fair for Benefits; Fair for Harms	Finland	Women ages 52 to 61 years from Kuopio Province who were enrolled in the OSTPRE study and who were between 6 and 24 months postmenopause. Exclusion criteria included contraindications to HT, history of breast or endometrial cancer, thromboembolic disease, and medication-resistant hypertension.	Reported by study groups only	232 (100)	NR	Mean (SD) 25[OH]D level: NR No. with prevalent or history of prior osteoporotic fractures: 35 (15.0%) Means (SD) femoral neck BMD: Reported by study groups only Nursing home or other institutionalized setting: NR	The primary study aim was to examine the effects of menopausal hormone therapy + low-dose vitamin D supplementation on BMD (HT only and HT + Vitamin D groups not eligible for this review). Study reports on outcomes relevant to the KQ 1 and KQ 2 main analyses.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Elemental calcium 93 mg (as lactate salt) daily (no vitamin D placebo) (n=116)	--	--	52.6 (95% CI, 52.2 to 53.0)	116 (100)	--	No. with prevalent or history of prior osteoporotic fractures: 15 (12.9%) Mean (SD) femoral neck BMD: 0.95 g/cm^2 (95% CI, 0.93 to 0.97)	--
Vitamin D_3 300 IU[††] plus elemental calcium 93 mg daily (as lactate salt) (n=116)	--	--	52.8 (95% CI, 52.4 to 53.2)	116 (100)	--	No. with prevalent or history of prior osteoporotic fractures: 20 (17.2%) Mean (SD) femoral neck BMD: 0.932 g/cm^2 (95% CI, 0.91 to 0.95)	--
Lappe et al, 2007[107, 136] Total N=1,180[‡‡] randomized, 1,179 analyzed NA for Benefits; Good or Fair for Harms (varies by outcome)	United States	Community-dwelling, postmenopausal women age 55 years or older in rural areas of Nebraska recruited through random digit dialing. Exclusion criteria included prevalent cancer or history of cancer within the prior 10 years, or mental and physical status that could limit participation.	66.7 (7.3)	1,180 (100)	0 (0)	Mean (SD) 25[OH]D level: 71.8 nmol/L (20.3)[§§] No. with prevalent or history of prior osteoporotic fractures: NR No in nursing home or other institutionalized setting: NR Taking supplements containing vitamin D at baseline: 59.3% (includes multivitamin, paired supplements (with calcium), and single supplements).	Primary study aim was to evaluate impact of calcium alone, or calcium with vitamin D on fracture incidence (however, these outcomes were not published per author query December 2016). Secondary aim was to evaluate changes in serum vitamin D, parathyroid activity, bone density, falls, and cancer. Study reports on outcomes relevant to the KQ 2 main analysis.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Placebo (n=288)	--	--	NR	NR	0 (0)	Mean (SD) 25[OH]D level: 72.1 nmol/L (20.7)[§§]	--
Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D placebo (n=445)	--	--	NR	NR	0 (0)	Mean (SD) 25[OH]D level: 71.6 nmol/L (20.5)[§§]	--
Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D_3 1,000 IU orally daily (n=446)	--	--	NR	NR	0 (0)	Mean (SD) 25[OH]D level: 71.8 nmol/L (20.0)[§§]	--
Lappe et al, 2017[108] Total N=2,303 randomized, 2,197 analyzed NA for Benefits; Fair for Harms	United States	Community-dwelling, postmenopausal women age 55 years and older from rural areas of Nebraska.	65 (NR)	2,303 (100)	NR (0.5)	Mean (SD) 25[OH]D level: 81.9 nmol/L No. with prevalent or history of prior osteoporotic fractures: NR No. in nursing home or other institutionalized settings: 0	The primary study aim was to examine the effects of vitamin D with calcium supplementation on the risk of cancer. Study reports on outcomes relevant to KQ 2 main analyses.
Placebo (n=1,147)	--	--	65 (7.1)	1,147 (100)	NR (0.4)	Mean (SD) 25[OH]D level: 81.6 nmol/L	--
Vitamin D_3 2,000 IU orally daily with 1,500 mg calcium daily (as carbonate salt) (n=1,156)	--	--	65 (6.9)	1,156 (100)	NR (0.6)	Mean (SD) 25[OH]D level: 82.4 nmol/L	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Lips et al, 1996[75] Total N=2,578 Fair for Benefits; Fair for Harms	The Nether-lands	Adults age 70 years or older without a history of hip fractures recruited from general practitioners or from apartment houses or homes for the elderly.[lll] Participants recruited from practitioners lived independently. Other study participants were individuals living in an apartment or a home for the elderly where they received care (but less care than they would receive in a nursing home). Exclusion criteria included total hip arthroplasty, prior hip fracture, hypercalcemia, sarcoidosis, kidney stones within past 5 years. Patients who had diseases or who used medications that influence bone metabolism were not excluded.	Reported by study groups only	Reported by study groups only	NR	Median 25[OH]D level: 26 nmol/L (IQR, 19-37)[¶¶] Participants with prior hip fracture excluded. No. in nursing home or other institutionalized setting: NR (59%)[lll]	Primary study aim was to reduce incidence of hip and other osteoporotic fractures. Study reports on outcomes relevant to the KQ 1 main analysis and the KQ 2 sensitivity analysis.
Placebo (n=1,287)	--	--	80.0 (6.0)	958 (74.4)	--	Median 25[OH]D level: 27 nmol/L (IQR, 19-36)[¶¶] Nursing home or other institutionalized setting: NR (60%)[lll]	--
Vitamin D_3 400 IU orally daily (n=1,291)	--	--	80.0 (5.9)	958 (74.2)	--	Median 25[OH]D level: 26 nmol/L (IQR, 19-37)[¶¶] No. in nursing home or other institutionalized setting: NR (59%)[lll]	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Peacock et al, 2000[85] Total N=438 randomized (N=393 with baseline values, 282 analyzed) Poor for Benefits; Poor for Harms	United States	Community-dwelling adults age 60 or older from Franklin, Indiana, and surrounding community; 60% were free-living and all were independently mobile. Exclusion criteria include terminal illness; Paget's disease of bone; recurrent urinary stone disease treatment with sodium fluoride, bisphosphonate, steroids, or dilantin; history of renal disease; or exclusion by their primary physician.	Reported by study groups only[##]	316 (72) [##]	0 (0)	Mean (SD) 25[OH]D level: Reported by study groups only[##] No. with prevalent or history of prior osteoporotic fractures: NR No. in nursing home or other institutionalized setting: NR (40%)	The primary study aim was to examine the effects of calcium and vitamin D supplementation on hip bone mass and structure. Study reports outcome relevant to the KQ 1 and KQ 2 sensitivity analyses.
Placebo (n=135 with baseline values, n=98 analyzed)	--	--	75.4 (7.6)	NR	0	Mean (SD) 25[OH]D level: 65.0 nmol/L (30)	--
Vitamin D_3 600 IU oral daily in 3 divided doses (n=132 with baseline values, n=95 analyzed)	--	--	75.5 (7.2)	NR	0	Mean (SD) vitamin D level: 65.0 nmol/L (25)	--
Calcium 750 mg (as citrate malate salt) daily in 3 divided doses (n=126 with baseline values, n=89 analyzed)	--	--	76.0 (7.7)	NR	0	Mean (SD) vitamin D level: 67.5 (23) nmol/L	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Prince et al, 2006,[89] and Lewis et al, 2011[90] Calcium Intake Fracture Outcome Study Total N=1,460 Fair for Benefits; Fair for Harms	Australia	Relatively healthy, vitamin D-sufficient, ambulatory women, age >70 years, recruited from electoral rolls. Exclusion criteria includes taking medication for low bone mass, <5-year life expectancy, participation in another clinical trial, and unwillingness to be assigned to placebo. % in nursing home or other institutionalized setting NR.	75.1 (2.7)	1,460 (100)	NR	Mean (SD) 25[OH]D level***: Winter: 67 nmol/L (35) Summer: 87 nmol/L (30) No. with prevalent or history of prior osteoporotic fractures: Reported by study groups only No. in nursing home or other institutionalized setting: NR No. ever smoked: Reported by study groups only No. with diabetes: Reported by study groups only No. with atherosclerotic vascular disease: Reported by study groups only	Primary study aim was to examine whether calcium supplementation decreases clinical fracture risk. Study reports on outcomes relevant to the KQ 1 and KQ 2 sensitivity analyses.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Placebo (n=730)	--	--	75.1 (2.7)	730 (100)	--	Mean (SD) 25[OH]D level: NR No. with prevalent or history of prior osteoporotic fractures[†††]: Compliant[‡‡‡] NR (25.2%) Noncompliant[‡‡‡] NR (31.6%) No. ever smoked: 259 (35.5%) No. with diabetes: 47 (6.4%) No. with atherosclerotic vascular disease: 104 (14.2%)	--
Elemental calcium 1,200 mg (as carbonate salt) daily in 2 divided doses (n=730)	--	--	75.2 (2.7)	730 (100)	--	Mean (SD) 25[OH]D level: NR No. with prevalent or history of prior osteoporotic fractures[†††]: Compliant[‡‡‡] NR (26.2%) Noncompliant[‡‡‡] NR (27.7%) No. with smoking: 280 (38.4%) No. with diabetes: 48 (6.6%) No. with atherosclerotic vascular disease: 108 (14.8%)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Recker et al, 1996[72] Total N=103 (subgroup of overall participants) Fair for Benefits; Poor for Harms	United States	Healthy white women of European ancestry age 60 or older who were ambulatory and living independently and whose usual calcium intakes were estimated to be <1g/day. Participants were recruited from 55 government-sponsored meal sites. Exclusion criteria included known diagnoses or treatments affecting the skeleton. 48% of participants had prevalent vertebral fracture at baseline; however, analyses were conducted separately for the subgroup of participants (n=103) without prevalent vertebral fracture.	NR	NR (100)	NR (100)	Mean (SD) 25[OH]D level[§§§]: Reported by study groups only Prevalent or history of prior osteoporotic fractures: NA Nursing home or other institutionalized setting: 0%	The primary study aim was to test spine antifracture and bone sparing efficacy of calcium supplement. Study reports on outcome relevant to the KQ 1 main analysis and the KQ 2 sensitivity analysis.
Placebo (n=61)	--	--	72.1 (7.5)	61 (100)	NR (100)	Mean (SD) 25[OH]D level: 65.0 nmol/ml (22.5)[§§§]	--
Calcium 1,200 mg (as carbonate salt) daily in 2 divided doses (n=42)	--	--	72.8 (6.1)	42 (100)	NR (100)	Mean (SD) 25[OH]D level: 62.5 nmol/ml (15)[§§§]	--
Reid et al, 2006,[87] Bolland et al, 2008[88] Total N=1,471 Fair for Benefits; Fair for Harms	New Zealand	Community-dwelling, healthy, postmenopausal women aged 55 years or older. Exclusion criteria include currently receiving therapy for osteoporosis or taking calcium supplements, have major ongoing disease, serum creatinine more than 2.3 mg/d, serum 25[OH]D less than 25 nmol/L, and lumbar spine density below the age-appropriate normal range.	NR	1471 (100)	NR	Mean (SD) 25[OH]D level*: Reported by study groups only No. with fracture resulting from minimal trauma after age 40: Reported by study groups only No. with nursing home or other institutionalized setting: NR (0%)	Primary study aim was to assess the effect of calcium supplementation on long-term bone loss and fracture incidence. Study reports on outcome relevant to the KQ 1 and KQ 2 sensitivity analyses.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Placebo (n=739)	--	--	74.3 (4.3)	739 (100)	NR	Mean (SD) 25[OH]D level: 52 nmol/L (19.5) No. with fracture resulting from minimal trauma after age 40: NR (29.1)	--
Calcium 1,000 mg (as citrate salt) daily in 2 divided doses (n=732)	--	--	74.2 (4.2)	732 (100)	NR	Mean (SD) 25[OH]D level: 51.4 nmol/L (19.0) No. with fracture resulting from minimal trauma after age 40: NR (28.1)	--
Reid et al, 1995,[92] Reid et al, 1993[94] Total N=135 randomized; N=122 completed initial trial; N=78 completed trial extension Poor for Benefits; Poor for Harms	New Zealand	Healthy women at least 3 years postmenopause. Exclusion criteria include history of disorders of calcium metabolism, symptomatic vertebral fractures; renal, thyroid, or hepatic dysfunction; current systemic disease; HT use within the previous 3 years; supraphysiologic doses of glucocorticoid used for more than 6 months at any time; current use of glucocorticoid, anticonvulsant medication, or thiazide diuretic agent.	NR	135 (100)	0 (0)	Mean (SD) 25[OH]D level: Reported by study groups only No. with prevalent or history of prior osteoporotic fractures: NR No. in nursing home or other institutionalized setting: NR	The primary study aim was to examine the long-term effects of calcium supplementation on bone density. Study reports on outcome relevant to the KQ 1 and KQ 2 sensitivity analyses.
Placebo (n=61 in initial trial; n=40 in trial extension)	--	--	58 (5)[¶¶¶¶]	NR	0 (0)	Mean (SD) 25[OH]D level[¶¶¶]: 94.8 nmol/L (5.0)	--
Calcium 1,000 mg (as lactate-gluconate and carbonate salts) daily in 2 doses (n=61 in initial trial, 38 in trial extension)	--	--	58 (5)[¶¶¶¶]	NR	0 (0)	Mean (SD) 25[OH]D level[¶¶¶]: 92.4 nmol/L (5.0)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Reid et al, 2008[91] Total N=323 Poor for Benefits; Fair for Harms	New Zealand	Healthy men age 40 years or older in good health, recruited through newspaper advertisement. Exclusion criteria include any major active disease, estimated 5-year cardiovascular risk greater than 15% use of medications altering BMD (e.g., anabolic or glucocorticosteroids, bisphosphonates), BMD Z score less than 2, or serum 25[OH]D levels <25 nmol/L.	Reported by study groups only	0 (0)	NR###	Mean (SD) 25[OH]D level*: Reported by study groups only No. with prevalent or history of prior osteoporotic fractures: NR Mean (SD) total hip BMD T score: Reported by study groups only No. in nursing home or other institutionalized setting: NR (0%)	The primary study aim was to test the effects of calcium supplementation on bone loss. Study reports on outcomes relevant to the KQ 1 sensitivity analysis and the KQ 2 main analysis.
Placebo (n=107)	--	--	57 (10)	0 (0)	--	Mean (SD) 25[OH]D level: 94.8 nmol/L (32.4) Mean (SD) total hip BMD T score: -0.1 (1.0)	--
Calcium 600 mg (as citrate salt) daily (n=108)	--	--	55 (10)	0 (0)	--	Mean (SD) 25[OH]D level: 94.8 nmol/L (34.9) Mean (SD) total hip BMD T score: -0.2 (1.0)	--
Calcium 1,200 mg (as citrate salt) daily (n=108)	--	--	57 (10)	0 (0)	--	Mean (SD) 25[OH]D level: 87.4 nmol/L (30.0) Mean (SD) total hip BMD T score: 0.0 (1.1)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Riggs et al, 1998[73] Total N=236 Fair for Benefits; Fair for Harms	United States	Ambulatory women ages 61 to 70 years who were postmenopausal for at least 10 years in a single U.S. state, invited after identification through medical record review from health system that provides care to the majority of women residents in the county. Exclusion criteria were history of prior osteoporotic fracture, Z scores on DXA of ≤2.0, history of kidney stones, impaired renal function, hypercalcemia or hypercalciuria, or diseases known to impact bone or calcium metabolism.	66.3 (NR)	236 (100)	0 (0)	Mean (SD) 25[OH]D level[****]: Reported for study groups only No. with prevalent or history of prior osteoporotic fractures: 0 (0%) No. in nursing home or other institutionalized setting: NR (0%)	Primary aim was to assess impact of calcium supplementation on bone loss, serum PTH, and markers of bone turnover. Study reports outcomes relevant to the KQ 1 and KQ 2 main analyses.
Placebo (n=117)	--	--	66.3 (2.6)	NR (100)	0 (0)	Mean (SD) 25[OH]D level: 74.1 nmol/L (25.7)	--
Calcium 1,600 mg daily in 4 divided doses (as citrate salt) (n=119)	--	--	66.2 (2.5)	NR (100)	0 (0)	Mean (SD) 25[OH]D level: 75.9 nmol/L (26.2)	--
Ruml et al, 1999[93] Total N=63 Poor for Benefits; NA for Harms	United States	Postmenopausal women no more than 10 years after natural or surgical menopause and not taking estrogen; recruited through posted notices and newspaper advertisements. Exclusion criteria included smoking 1/2 pack or more of cigarettes, history of kidney stones, renal, hepatic or intestinal diseases, prior osteoporotic fractures or vertebral fractures on screening spine radiographs, taking medications known to affect calcium metabolism, or lumbar bone density >1 SD, above average of age-matched control value.	52 (NR)[‡‡‡‡]	63 (100)	6 (10.7)[††††]	Mean (SD) 1, 25$[OH]_2$D level[††††]: Reported for study groups only No. with prevalent or history of prior osteoporotic fractures: 0 (0%) Mean (SD) femoral neck BMD[††††]: Reported for study groups only No. in nursing home or other institutionalized setting: NR	The primary study aim was to assess the impact of calcium on bone density and physiologic mechanisms of calcium action. Study reports outcomes relevant to the KQ 1 sensitivity analysis.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Placebo (n=34)	--	--	51.7 (3.8)	NR (100)	6 (19.4)	Mean (SD) 1, 25[OH]$_2$D level: 36 pg/mL (9) Mean (SD) femoral neck BMD: 0.68 g/cm^2 (0.09)	--
Calcium 800 mg daily in 2 divided doses (as citrate salt) (n=29)	--	--	52.1 (4.1)	NR (100)	0 (0)	Mean (SD) 1, 25[OH]$_2$D level: 34 pg/mL (12) Mean (SD) femoral neck BMD: 0.73 g/cm^2 (0.12)	--
Salovaara et al, 2010[106] Total N=3,432 Poor for Benefits; Poor for Harms	Finland	Women ages 65 to 71 years recruited from participants enrolled in the OSTPRE observational cohort study, a population-based sample of all women living in the region. Exclusion criteria included previous participation in an OSTPRE study of BMD or trial.	Reported for study group only	3,432 (100)	NR	Mean (SD) 25[OH]D level[‡‡‡‡]: Reported by study groups only No. with prevalent or history of prior osteoporotic fracture: Reported by study groups only No. with secondary osteoporosis[§§§§]: Reported by study groups only Mean (SD) femoral neck BMD[‡‡‡‡]: Reported by study groups only No. in nursing home or other institutionalized setting: NR	The primary study aim was to assess the impact of vitamin D with calcium on fracture prevention. Study reported outcomes relevant to the sensitivity analyses for KQ 1 and KQ 2.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Control (no placebo) (n=1,714)	--	--	67.3 (1.8)	1,714 (100)	--	Mean (SD) 25[OH]D level: 49.1 nmol/L (17.7) No. with prevalent or history of prior osteoporotic fracture: NR (33.4%) No. with secondary osteoporosis: NR (20.0%) Mean (SD) femoral neck BMD: 0.866 g/cm^2 (0.120)	--
Vitamin D_3 800 IU daily plus calcium 1,000 mg (as carbonate salt) daily in 2 divided doses (n=1,718)	--	--	67.4 (1.9)	1,718 (100)	--	Mean (SD) 25[OH]D level: 50.0 nmol/L (18.7) No. with prevalent or history of prior osteoporotic fracture: NR (37.3%) No. with secondary osteoporosis: NR (21.5%) Mean (SD) femoral neck BMD: 0.866 g/cm^2 (0.132)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Sanders et al, 2010[83] Total N=2,258 randomized (N=2,256 analyzed) Good for Benefits; Varies for Harms (Good for mortality, Fair for incident CVD and cancer)	Australia	Community-dwelling women age 70 years or older with increased risk of hip fracture (e.g., prior fracture, maternal history of fracture, self-reported history of falls) who were recruited through electoral rolls. Exclusion criteria included permanent residence in a high-level care facility, decreased kidney function, current use of vitamin D, calcitriol, or antifracture therapy.	Reported for study groups only	2,258 (100)	NR	Median 25[OH]D level[lllll]: Reported for study groups only No. with prevalent or history of prior osteoporotic fractures[¶¶¶¶]:727 (34.6%) No. in nursing home or other institutionalized setting: NR (0%) No. with self or physician-reported high risk of falling: Reported for study groups only	The primary study aim was reduction in fractures, secondary aims include reduction in falls. Study reported outcomes relevant to the sensitivity analyses for KQ 1 and KQ 2 sensitivity analysis.
Placebo (n=1,127)	--	--	76 (IQR, 73.0 to 79.7)	NR	--	Median 25[OH]D level: 45 nmol/L (IQR, 45 to 57) No. with prevalent or history of prior osteoporotic fractures: 343 (32.7%) No. with self or physician-reported high risk of falling: 429 (38.1%)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Vitamin D_3 500,000 IU orally annually (n=1,131)	--	--	76 (IQR, 73.1 to 80.2)	NR	--	Median 25[OH]D level: 53 nmol/L (IQR, 40 to 65) No. with prevalent or history of prior osteoporotic fractures: 384 (36.5%) No. with self or physician-reported high risk of falling: 449 (39.7%)	--
Smith et al, 2007[84] Total N=9,440 Fair for Benefits; NA for Harms	United Kingdom	Men and women age 75 years or older recruited from general practice registers in a primary care research network. Exclusion criteria included current cancer, history of treated osteoporosis, bilateral total hip replacement, renal failure, kidney stones, hypercalcemia or sarcoidosis. People taking ≥400 IU or more of vitamin D supplementation daily were also excluded.	Reported by study groups only	Reported by study groups only	NR	Mean (SD) 25[OH]D level: 141 nmol/L (59.2)[####] No. with prevalent or history of prior osteoporotic fracture: Reported by study groups only No. in nursing home or other institutionalized setting: NR (8.3%)	The primary study aim was to assess the impact of vitamin D on nonvertebral fractures. Study reports outcomes relevant to the KQ 1 sensitivity analysis.
Placebo (n=4,713)	--	--	Median 79.1 (IQR 76.9 to 82.6)	2,518 (53.4)	--	Mean (SD) 25[OH]D level: NR No. with any nonvertebral fracture: NR (38.5%) No. with hip or femur fracture: NR (2.9%) No with fracture of wrist (including radius, ulna, or Colles): NR (14.0%)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Vitamin D_2 300,000 IU IM annually (n=4,727)	--	--	Median 79.1 (IQR 76.9 to 82.7)	2,568 (54.3)	--	Mean (SD) 25[OH]D level: NR No. with any nonvertebral fracture: NR (37.2%) No. with hip or femur fracture: NR (2.7%) No. with fracture of wrist (including radius, ulna, or Colles): NR (13.0%)	--
Trivedi et al, 2003[76] Total N=2,686 Fair for Benefits; Fair for Harms	United Kingdom	Community-dwelling men and women ages 65 to 85 years. 83.0% (2,907 out of 3,504) recruited from the British Doctor's Study (thus were physicians); 17.0% (597 out of 3,504) recruited from the register of a general practice (thus, were nonphysicians). Exclusion criteria included history of kidney stones, sarcoidosis, cancer, or already taking vitamin D supplements.	Reported for study groups only	Reported for study groups only	NR	Mean (SD) 25[OH]D level: NR No. with prevalent or history of prior osteoporotic fractures: NR No. in nursing home or other institutionalized setting: NR No. with current use of steroids: Reported by study groups only No. with use of HT (women only): Reported by study groups only No. with history of CVD*****: Reported by study groups only No. with history of cancer: Reported by study groups only	The primary study aim was to assess impact of vitamin D on fracture and mortality; the study was described as a pilot to assess the feasibility of a larger community trial (which was not subsequently conducted). Study reports outcomes relevant to the KQ 1 and KQ 2 main analyses.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Placebo (n=1,341)	--	--	74.7 (4.6)	323 (24.0)	--	No. with current use of steroids: 70 (5.2%) No. with use of HT (women only): 21 (6.5%) No. with history of CVD: 367 (27.4%) No. with history of cancer: 79 (5.9%)	--
Vitamin D_3 100,000 IU orally every 4 months (n=1,345)	--	--	74.8 (4.6)	326 (24.2)	--	No. with current use of steroids: 60 (4.5%) No. with use of HT (women only): 21 (6.4%) No. with history of CVD: 394 (29.3%) No. with history of cancer: 82 (6.1%)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
WHI Calcium and Vitamin D Trial[††††] Total N=36,282[‡‡‡‡‡] Fair for Benefits and Harms	United States	Postmenopausal women ages 50 to 79 years participating in either the WHI Dietary Modification or Hormone Therapy trials from 40 clinical sites. Exclusion criteria included hypercalcemia, renal calculi, corticosteroid use, and calcitriol use.	Reported by study groups only	36,282 (100)	Reported by study groups only	Mean (SD) 25[OH]D level[§§§§‡]: Reported by study groups only No. with prevalent or history of prior osteoporotic fracture: Reported by study groups only No. with osteoporosis[‖‖‖‖‖‖]: NR (3.9%) No. with osteopenia[‖‖‖‖‖‖]: NR (38.2%) No. with use of personal supplements at baseline [97]: Vitamin D and calcium: 15,796 (43.5%) Calcium only: 3,419 (9.4%) Vitamin D only: 1,060 (2.9%) Mean (SD) hip BMD T score[¶¶¶¶]: Reported by study groups only No. in nursing home or other institutionalized setting: NR (0%)	The primary study aim was to assess impact of vitamin D with calcium supplementation on risk of hip fractures. Study reports outcomes relevant to the KQ 1 and KQ 2 main analysis.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Placebo (n=18,106)	--	--	62.4 (6.9)	18,106 (100)	3,000 (16.6)	Mean (SD) 25[OH]D level: 49.1 nmol/L (22.5) No. with prevalent or history of prior osteoporotic fracture: Fracture at any age: 6,228 (34.4%) Fracture after age 55: 1,968 (10.9%) No. with baseline calcium supplementation ≥500 mg/d: 5,313 (29.3%) Mean (SD) hip BMD T score: -0.77 (1.05) No. with T score: ≤-2.5: 48 (4%) -1.0 to -2.5: 459 (38.2%) >-1.0: 694 (57.8%)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Vitamin D_3 400 IU orally plus 1,000 mg elemental calcium (as carbonate salt) in 2 divided doses (n=18,176)	--	--	62.4 (7.0)	18,176 (100)	3,129 (17.2)	Mean (SD) 25[OH]D level: 49.3 nmol/L (22.7) No. with prevalent or history of prior osteoporotic fractures: Fracture at any age: 6,311 (34.7%) Fracture after age 55: 1,948 (10.7%) No. with baseline calcium supplementation ≥500 mg/d: 5,192 (28.6%) Mean (SD) baseline hip BMD T score: -0.65 (1.03) No. with T score: ≤-2.5: 37 (3%) -1.0 to -2.5: 436 (35.4%) ≥-1.0: 757 (61.5%)	--
Zhu et al, 2008[109] Total N=120 NA for Benefits; Fair for Harms	Australia	The study population comprises the first 120 sequential participants in the main Calcium Intake Fracture Outcome Study trial (Prince et al, 2006[89] and Lewis et al, 2011[90]). Briefly, healthy ambulatory women age 70 or older, recruited from electoral rolls. Exclusion criteria include taking medication for low bone mass, <5-year life expectancy, participation in another clinical trial, and unwillingness to be assigned to placebo.	74.8 (2.6)	120 (100)	NR	Mean (SD) 25[OH]D level: 68.0 nmol/L (28.7)##### No. with prevalent or history of prior osteoporotic fractures: NR No. in nursing home or other institutionalized setting: NR (0%)	The primary study aim was to evaluate the effects of vitamin D and calcium combined supplementation on hip BMD. Study reports on outcomes relevant to the KQ 2 sensitivity analysis.
Placebo (n=41)	--	--	74.8 (2.8)	41 (100)	--	Mean (SD) 25[OH]D level: 67.3 nmol/L (34.2)	--

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

Author, Year Trial Name, No. of Participants, Quality	Country	Population	Mean (SD) Age, Years	Women No. (%)	Nonwhite No. (%)	Relevant Conditions or Risks at Baseline	Study Aims and Relevant KQs
Calcium 1,200 mg (as carbonate salt) daily (n=40)	--	--	74.1 (2.0)	40 (100)	--	Mean (SD) 25[OH]D level: 66.6 nmol/L (25.9)	--
Calcium 1,200 mg (as carbonate salt) plus vitamin D_2 1,000 IU orally daily (n=39)	--	--	75.4 (2.7)	39 (100)	--	Mean (SD) 25[OH]D level: 70.2 nmol/L (25.6)	--

* Assay used was radioimmunoassay (DiaSorin, Stillwater, MN).
† Based on the 389 participants included in the ITT analyses.
ǂ Based on the 445 participants enrolled in the study.
§ Based on the 313 participants who completed the study interventions. Assay used was the method of Preece et al (1974).
ǁ Based on subsample of 40 participants, 20 from each study arm. Assay used was the automated Liaison method (DiaSorin, Stillwater, MN).
¶ Cointerventions: Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outside) and consuming 1,300 mg calcium per day using diet and/or supplements.
# Although the published study reported that 46% of participants reported a history of fracture, we queried the author as to whether this represented lifetime history of fracture or osteoporotic fractures sustained in adulthood. The prevalence of osteoporosis in the study population was 1–2%, and the author's response provided the specific items used to assess history of fracture, which clearly assessed lifetime history. Thus, in our judgement, this study remains eligible for the main analysis because the proportion of participants with prior fragility fractures is likely well below the threshold of 20% that we used to determine eligibility, given the low prevalence of osteoporosis in the study population.
** OSTPRE is a population-based study in Kuopio Province, Finland, that began in 1989 with mail recruitment of all women ages 47 to 56 years in the province, with 92.8% response to initial questionnaire. The study groups included in this evidence table are a subset of participants from OSTPRE who were recruited for the clinical trial in 1994. This trial also included two additional study groups that evaluated HT versus placebo (defined as the calcium-only group) and HT plus vitamin D3 versus placebo. These study groups were not eligible for this review.
†† No intake during June to August. Dose reduced to 100 IU during the fifth treatment year because of observed adverse lipid change during vitamin D treatment.
ǂǂ One subject was excluded after randomization.
§§ Assay used was radioimmunoassay, IDS kit (Fountain Hills, AZ).
ǁǁ The authors described that participants receive care (but less care than they would have received in a nursing home) in their apartment or home for the elderly. This study was included in the prior 2011 review for the USPSTF and was considered a community-dwelling population. We retained this study for this update because 93% of participants recruited from apartment homes for the elderly were able to walk independently, and other baseline measures reported suggested a higher level of physical function than other studies among institutionalized and nursing home populations.
¶¶ Based on nonrandom sample of participants in a substudy selected from among the participants recruited from apartment houses/homes for elderly. Assay used was competitive protein binding assay after purification by gradient high-pressure liquid chromatography.
Based on 393 participants who had a BMD measurement and at least one visit after baseline. Assay for serum vitamin D levels was binding protein from rat serum.
*** Based on a random subset of 81 participants. Assay used was extraction followed by competitive binding assay that measures 25-hydroxycholecalciferol and ergocalciferol equally.
††† Prevalent fractures were recorded if they occurred at age 50 years or older, were due to minimal trauma (e.g., failing from a height of less than 1 meter), and were not of the face, skull, fingers, or toes.
ǂǂǂ Noncompliance was defined as average yearly medication compliance of less than 80% based on pill counts.
§§§ Based on subsample of 38 members of the cohort at the beginning of the observation. Assay used was the competitive binding assay kit (Nichols Institute Diagnostics, San Juan Capistrano, CA). The study reported levels in units of nmol/ml, as opposed to nmol/L or ng/ml.

Appendix D Table 1. Characteristics of RCTs Included in the Main Analysis and in Sensitivity Analysis for Vitamin D and Calcium Supplementation Benefits and Harms (KQs 1 and 2)

[III] Based on the 122 participants among the 135 randomized in the original cohort who completed the initial 2-year trial.
[¶¶¶] Assay used was not reported.
[###] Study population is described as predominately white.
[****] Serum 25-hyroxyvitamin D level measured by the methods of Eisman et al[158] and Kumar et al [159].
[††††] Based on 56 participants who completed at least 1 year of trial. Serum 1,25 [OH]2 D was reported (not serum 25[OH]D); assay used was microassay described in Popoff et al[160] and Watanabe et al.[161]
[‡‡‡] Based on a subset of 574 participants (n=295 placebo, n=279 vitamin D with calcium). Assay used for serum 25[OH] D was radioimmunoassay from DiaSorin (Stillwater, MN).
[§§§§] Based on 3,195 participants included in the intention to treat analysis (n= 1609 placebo, n= 1586 vitamin D plus calcium). Early menopause (< age 45) was the reason for secondary osteoporosis in about three-quarters of participants.
[‖‖‖‖] Based on a subset of 131 participants (n=57 placebo, n=74 vitamin D). Assay used was from DiaSorin (Stillwater, MN).
[¶¶¶¶] Defined by study as broken bone since age 50.
[####] Based on a subsample of 43 participants. Assay used was RIA by Nicholls Diagnostics (San Juan Capistrano, CA).
[*****] Including ischemic heart disease, stroke, and other heart diseases.
[†††††] Study characteristics and results from this trial were reported across 13 different publications including: Jackson et al, 2003[95]; Jackson et al, 2006[70]; Wactawski-Wende et al, 2006[112]; LaCroix et al, 2009[111]; Bolland et al, 2011a[115]; Bolland et al, 2011b[96]; Brunner et al, 2011[121]; Tang et al, 2011[120]; Wallace et al, 2011[113]; Prentice et al, 2013[97]; Robbins et al, 2014[98]; Blondon et al, 2015[116]; Donneyong et al, 2015[117]; Hsia et al, 2007.[162]
[‡‡‡‡] The main trial included 36,282 randomized participants. The number of participants included in analyses related to secondary analyses varied because some participants with prevalent conditions at baseline may have been excluded.
[§§§§§] Based on a subsample of 2,464 participants in placebo group and 2,404 participants in treatment group that received serum vitamin D testing at baseline. Assay used was DiaSorin Liaison's chemiluminescent immunoassay system.[116]
[‖‖‖‖‖] Based on subsample of 2,529 participants that underwent bone density testing
[¶¶¶¶¶] Based on subsample of 1,201 participants in placebo group and 1,230 participants in the treatment group for whom bone density was measured. .
[#####] Assay used was competitive protein binding assay unspecified as to manufacturer.

Abbreviations: 25[OH] D=vitamin D; BMD=bone mineral density; CI=confidence interval; CVD=cardiovascular disease; DXA=dual-energy X-ray absorptiometry; HT=hormone therapy; IQR=interquartile range: ITT=intent to treat; IU=international units; KQ=key question; mg=milligram; N=number; NA=not applicable; nmol/L=nanomole per liter; NR=not reported; OSTPRE=Osteoporosis Risk Factor & Prevention Study; PTH=parathyroid hormone; SD=standard deviation; WHI=Women's Health Initiative.

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Main Analysis						
Dawson-Hughes et al, 1997[74] Fair Total N=445 randomized (N analyzed=389)	3 years	NR	ARD*, -0.50% (-1.88% to 0.89%) RR*, 0.36 (0.01 to 8.78)	37(9.5*) ARD*,-6.99% (95% CI, -12.71% to -1.27%) RR, 0.46 (95% CI, 0.23 to 0.90, p=0.02) Fractures resulting from minimal or no trauma: 28 (7.2*); RR, 0.40 (95% CI, 0.2 to 0.8) Subgroups: Women 32 (15.0) Men 5 (2.8)	NR	NR
Placebo n=202	--	NR	1 (0.5*)	26 (12.9) Subgroups: Women 22* (19.6) Men NR (NR)	NR	NR
Vitamin D_3 700 IU orally plus elemental calcium 500 mg (as malate salt) daily n=187	--	NR	0 (0*)	11 (5.9) Subgroups: Women 10* (9.9) Men NR (NR)	NR	NR
Khaw, Scragg et al, 2017[77, 78] VIDA Good Total N=5,110	3.3 years	NR	NR	ARD*, 0.77% (-0.51% to 2.04%) Adjusted HR, 1.19 (0.94 to 1.50)	NR	NR
Placebo N analyzed=2,550	--	NR	NR	136 (5.3)	NR	NR
Vitamin D_3 orally 200,000 IU initial dose followed by 100,000 IU every month n=2,558 analyzed	--	NR	NR	156 (6.1)	NR	NR

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Komulainen et al, 1998[71] Komulainen et al, 1999[118] OSTPRE[†] Fair Total N=232	5 years	NR	ARD[*], -0.86% (95% CI, -3.77% to 2.04%) RR* 0.50 (95% CI, 0.05 to 5.44)	ARD[*], -3.45% (95% CI, -11.55% to 4.66%) Unadjusted RR, 0.72[‡] (95% CI, 0.22 to 1.56) Adjusted[§] RR, 0.64 (95% CI, 0.29 to 1.42)	NR	--
Elemental calcium 93 mg (as lactate salt) daily (no vitamin D placebo) n=116	--	NR	2 (1.7*)	15 (12.9*)	NR	NR
Vitamin D_3 300 IU plus elemental calcium 93 mg (as lactate salt) daily[‖] n=116	--	NR	1 (0.9*)	11 (9.5*)	NR	NR
Lips et al, 1996[75] Fair Total N=2,578	Median 3.5 years	NR	ARD[*], 0.76% (95% CI, -0.77% to 2.30%) Unadjusted HR, 1.18 (95% CI, 0.81 to 1.71)[¶] RR[*], 1.20 (95% CI, 0.83 to 1.75)	NR	NR	Total peripheral fractures:[#] ARD[*], 0.21% (95% CI, 1.60% to 2.03%) Unadjusted HR, 1.03 (95% CI, 0.75 to 1.40) RR[*], 1.04 (95% CI, 0.76 to 1.41)
Placebo n=1,287	--	NR	48 (3.7)	NR	NR	Total peripheral fractures[#]: 74 (5.8) Subtypes: Colles fracture: 22 (1.7) Humerus fracture: 12 (0.9) Ankle/Foot/Leg fracture: 17 (1.3) Other fracture: 23 (1.8)

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Vitamin D_3 400 IU orally daily n=1,291	--	NR	58 (4.5)	NR	NR	Total peripheral fractures[#]: 77 (6.0) Subtypes: Colles fracture: 20 (1.5) Humerus fracture: 10 (0.8) Ankle/Foot/Leg fracture: 20 (1.5) Other fracture: 27 (0.2)
Recker et al, 1996[72] Fair Total N=103	4.3 years (1.1)	NR	NR	NR	Morphometric: ARD[*], 7.26% (95% CI, -9.84% to 24.36%) RR[*], 1.34 (95% CI, 0.68 to 2.64)	NR
Placebo n=61	--	NR	NR	NR	Morphometric: 13 (21.3[*])	NR
Calcium 1,200 mg (as carbonate salt) daily in 2 divided doses n=42	--	NR	NR	NR	Morphometric: 12 (28.6[*])	NR
Riggs et al, 1998[73] Fair Total N=236	4 years	NR	NR	ARD[*], -1.01% (95% CI, -8.58% to 6.56%) RR[*], 0.90 (95% CI, 0.41 to 1.96)	Morphometric: ARD[*], -0.97% (95% CI, -7.57% to 5.63%) RR[*], 0.87 (95% CI, 0.35 to 2.19)	NR
Placebo n=117	--	NR	NR	12 (10.3)	Morphometric fractures: 9 (7.7)	NR
Calcium 1,600 mg (as citrate salt) daily in 4 divided doses n=119	--	NR	NR	11 (9.2)	Morphometric fractures: 8 (6.7)	NR

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Trivedi et al, 2003[76] Fair Total N=2,686 (649 women; 2,037 men)	5	ARD*, -2.26% (95% CI, 4.53% to 0.00%) Age-adjusted RR, 0.78 (95% CI, 0.61 to 0.99) RR*, 0.80 (95% CI, 0.63 to 1.00) Subgroups: Women: age-adjusted RR, 0.68 (95% CI, 0.46 to 1.01) Men: age-adjusted RR, 0.83 (95% CI, 0.61 to 1.13)	ARD*, -0.23% (95% CI, -1.20% to 0.74%) Age-adjusted RR, 0.85 (95% CI, 0.47 to 1.53) RR*, 0.87 (95% CI, 0.49 to 1.56) Subgroups: Women: age-adjusted RR, 0.98 (95% CI, 0.41 to 2.36) Men: age-adjusted RR, 0.76 (95% CI, 0.35 to 1.67)	NR	Clinical fractures: ARD*, -0.75% (95% CI, -1.73% to 0.23%) Age-adjusted RR, 0.63 (95% CI, 0.35 to 1.14) RR*, 0.64 (95% CI, 0.36 to 1.15) Subgroups: Women: age-adjusted RR, 0.65 (95% CI, 0.18 to 2.30) Men: age-adjusted RR, 0.62 (95% CI, 0.32 to 1.22)	Hip, wrist or forearm, or vertebrae fractures: Age-adjusted RR, 0.67 (95% CI, 0.48 to 0.93) Subgroups: Women: Age-adjusted RR, 0.61 (95% CI, 0.37 to 1.02) Men: Age-adjusted RR, 0.83 (95% CI, 0.61 to 1.13)
Placebo n=1,341 (323 women; 1,018 men)	--	149 (11.1*) Subgroups: Women: 58 (18.0*) Men: 91 (8.9*)	24 (1.8*) Subgroups: Women: 10 (3.1*) Men: 14 (1.4*)	NR	Clinical fractures: 28 (2.1*) Subgroups: Women: 6 (1.9*) Men: 22 (2.2*)	Hip, wrist or forearm, or vertebrae fractures: 87 (6.5*) Subgroups: Women: 37 (11.5*) Men: 50 (4.9*)
Vitamin D_3 100,000 IU orally every 4 months n=1,345 (326 women; 1,019 men)	--	119 (8.8*) Subgroups: Women: 42 (12.9*) Men: 77 (7.6*)	21 (1.6*) Subgroups: Women:10 (3.1*) Men:11 (1.1*)	NR	Clinical fractures: 18 (1.3*) Subgroups: Women: 4 (1.2*) Men: 14 (1.4*)	Hip, wrist or forearm, or vertebrae fractures: 60 (4.5*) Subgroups: Women: 24 (7.4*) Men: 36 (3.5*)

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

WHI Calcium and Vitamin D Trial[**] Fair Total N=36,282	7 years (SD, 1.4)	ARD[*], -0.35% (95% CI, -1.02% to 0.31%) HR, 0.96 (95% CI, 0.91 to 1.02) [††] RR[*], 0.97 (95% CI, 0.92 to 1.03) Subgroups: *Personal use of calcium or vitamin D supplements at baseline*[97] Nonusers: HR, 0.97 (95% CI, 0.88 to 1.07) Users: HR, NR	ARD[*], -0.14% (95% CI, -0.34% to 0.07%) HR, 0.88 (95% CI, 0.72 to 1.08)[‡‡] RR[*], 0.88 (95% CI, 0.72 to 1.07) Subgroups: *Age 50 to 59* HR, 2.17 (95% CI, 1.13 to 4.18) *Age 60 to 60* HR, 0.74 (95% CI, 0.52 to 1.06) *Age 70 to 79* HR, 0.82 (95% CI 0.62 to 1.08) p for interaction=0.05 *Race/ethnic group* p for interaction=0.87 *Prior fracture* p for interaction 0.71 *Weight (<58 vs. ≥58 kg)* p for interaction 0.44 *BMI (<25, 25-29, ≥30)* p for interaction=0.36 *Sunlight exposure* p for interaction 0.73 *No. of falls in prior 12 months* 0: HR, 0.74 (95% CI 0.56 to 0.98) 1: HR, 0.96 (95% CI 0.62 to 1.49) 2: HR, 1.16 (95% CI, 0.63 to 2.16)	NR	Clinical fractures: ARD[*], -0.09% (95% CI, -0.30% to 0.12%) HR, 0.90 (95% CI, 0.74 to 1.10)[§§] RR[*], 0.92 (0.75 to 1.12)	Lower arm or wrist fracture: ARD[*], 0.03% (95% CI, -0.32% to 0.39%) HR, 1.01 (95% CI,.90 to 1.14) RR[*], 1.01 (95% CI, 0.90 to 1.13)

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
			≥3: HR, 2.51 (95% CI, 0.97 to 6.48) p for interaction=0.05 *Hormone therapy treatment assignment (WHI Trial)* Placebo HR, 1.15 (95% CI, 0.81 to 1.63) Active HR, 0.58 (95% CI 0.37 to 0.93) p for interaction=0.07 *Personal use of calcium supplements at baseline*[70] None: HR, 0.70 (95% CI, 0.51 to 0.98) <500 mg: HR, 0.87 (95% CI, 0.61 to 1.24) ≥500 mg: HR, 1.22 (95% CI, 0.83 to 1.79) p for interaction=0.11 *Personal use of calcium or vitamin D supplements at baseline*[97] Nonusers: HR, 0.86 (95% CI, 0.62 to 1.20) Users: HR, NR			
Placebo n=18,106	--	2,158 (11.9)	199 (1.1)	NR	Clinical fractures: 197 (1.1)	Lower arm or wrist fracture: 557 (3.1)
Vitamin D 400 IU orally with 1,000 mg elemental calcium (as carbonate salt) in 2 divided doses daily n=18,176	--	2,102 (11.6)	175 (1.0)	NR	Clinical fractures: 181 (1.0)	Lower arm or wrist fracture: 565 (3.1)

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Sensitivity Analysis						
Glendenning et al, 2012[86] Poor Total N=686	6 months/ 9 months	ARD*, -0.17% (95% CI, -2.69% to 2.35%) RR*, 0.94 (95% CI, 0.40 to 2.24) p=1.00[lll]	NR	NR	NR	NR
Placebo[¶¶] n=333	--	10* (3.0)[lll]	NR	NR	NR	NR
Vitamin D_3 150,000 IU orally at baseline, 3 months, and 6 months[¶¶] n=353	--	10* (2.8)[lll]	NR	NR	NR	NR
Peacock et al, 2000[85] Poor Total N=438 randomized	4 years	NR	NR	Comparing vitamin D with placebo: ARD*, 3.20% (95% CI, -3.66% to 10.06%)[##] RR*, 1.43 (95% CI, 0.66 to 3.11)[##] Comparing calcium with placebo: ARD*, 1.32% (95% CI, -5.30% to 7.94%)[##] RR*, 1.18 (95% CI, 0.52 to 2.68)[##]	Both clinical and morphometric fractures: Comparing vitamin D with placebo: ARD*, 4.76% (95% CI, -3.02% to 12.55%)[##] RR*, 1.49 (95% CI, 0.77 to 2.90)[##] Comparing calcium with placebo: ARD*, -4.07% (95% CI, -10.46% to 2.31%)[##] RR*, 0.58 (95% CI, 0.24 to 1.40)[##]	NR

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Placebo n=135 (98 women, 37 men)	--	NR	NR	10 (7.4) Subgroups: Women: 9 (9.2*) Men: 1 (2.7*)	Both clinical and morphometric fractures: 13 (9.6) Subgroups: Women: 10 (10.2*) Men: 3 (8.1*)	NR
Vitamin D_3 600 IU daily in 3 divided doses n=132 (95 women, 37 men)	--	NR	NR	14 (10.6) Subgroups: Women: 10 (10.5*) Men: 4 (10.8*)	Both clinical and morphometric fractures: 19 (14.4) Subgroups: Women: 15 (15.8*) Men: 4 (10.8*)	NR
Calcium 750 mg (as citrate malate salt) daily in 3 divided doses n=126 (89 women, 37 men)	--	NR	NR	11 (8.7) Subgroups: Women: 9 (10.1*) Men: 2 (5.4*)	Both clinical and morphometric fractures: 7(5.6) Subgroups: Women: 5 (5.6*) Men: 2 (5.4*)	NR
Prince et al, 2006,[89] and Lewis et al, 2011[90] Calcium Intake Fracture Outcome Study Fair Total N=1,460 (N analyzed for morphometric fracture outcome=883)	5 years	Atraumatic fractures: ARD*, -2.19% (95% CI, -5.97% to 1.58%) HR, 0.87 (95% CI, 0.67 to 1.12) RR*, 0.87 (95% CI, 0.69 to 1.10)	Atraumatic fractures: ARD*, 0.68% (95% CI, -0.42% to 1.78%); HR, 1.84 (95% CI, 0.68 to 4.96); RR*, 1.83 (95% CI, 0.68 to 4.93)	Atraumatic fractures: ARD*, -1.51% (95% CI, -4.85% to 1.84%); HR, 0.88 (95% CI, 0.65 to 1.18); RR*, 0.88 (95% CI, 0.67 to 1.16)	Morphometric: ARD*, -0.86% (95% CI, -4.92% to 3.21%) RR*, 0.92 (95% CI, 0.63 to 1.35) Atraumatic clinical: ARD*, -0.14% (95% CI, -2.43% to 2.16%) HR, 0.98 (95% CI, 0.63 to 1.54); RR*,0.97 (95% CI, 0.63 to 1.51)	NR

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Placebo n=730	--	126 (17.3)	6 (0.8)	94 (12.9)	Morphometric: 50 (11.1) Atraumatic clinical: 39 (5.3)	NR
Elemental calcium 1,200 mg (as carbonate salt) daily in 2 divided doses n=730	--	110 (15.1)	11 (1.5)	83 (11.4)	Morphometric: 44 (10.2) Atraumatic clinical: 38 (5.2)	NR
Reid et al, 2006,[87] Bolland et al, 2008[88] Fair Total N=1,471	Reported by study groups only	ARD*, -1.61% (95% CI, -5.45% to 2.24%) HR, 0.91 (95% CI, 0.71 to 1.17) RR*, 0.91 (95% CI, 0.73 to 1.14)	ARD*, 1.65% (95% CI, 0.40% to 2.89%) HR, 3.55 (95% CI, 1.31 to 9.63) RR*, 3.43 (95% CI, 1.27 to 9.26)	NR	Both clinical and morphometric fractures: ARD*, -1.45% (95% CI, -3.55% to 0.64%) HR, 0.72 (95% CI, 0.44 to 1.18) RR*, 0.72 (95% CI, 0.44 to 1.16)	Major osteoporotic fractures:*** ARD*, -2.03% (95% CI, -5.70% to 1.64%) HR, 0.87 (95% CI, 0.67 to 1.14) RR*, 0.87 (95% CI, 0.69 to 1.11) Distal forearm fracture: HR, 0.64 (95% CI, 0.40 to 1.03)
Placebo n=739	4.5 years	132 (17.9*)	5 (0.7*)	NR	Both clinical and morphometric fractures: 38 (5.1*)	Major osteoporotic fractures:*** 120 (16.2*)
Calcium 1,000 mg (as citrate sault) daily in 2 divided doses n=732	4.4 years	119 (16.3*)	17 (2.3*)	NR	Both clinical and morphometric fractures: 27 (3.7*)	Major osteoporotic fractures:*** 104 (14.2*)
Reid et al, 1995,[92] Reid et al, 1993[94] Poor Total N=122 randomized in initial trial (78 used in analysis)†††	2 years	ARD*, -4.92% (95% CI, -13.13% to 3.29%) RR*, 0.40 (95% CI, 0.08 to 1.98)	NR	NR	NR	NR

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Placebo n=61	--	5 (8.2*)	NR	NR	NR	NR
Calcium 1,000 mg (as lactate-gluconate and carbonate salts) daily in 2 doses n=61	--	2 (3.3*)	NR	NR	NR	NR
Reid et al, 2008[91] Poor Total N=323	2 years	All fractures, regardless of mechanism of injury‡‡‡: ARD*, -2.85% (95% CI, -9.21% to 3.52%) RR*, 0.62 (95% CI, 0.21 to 1.83) for 600 mg compared with placebo ARD*, -3.77% (95% CI, -9.90% to 2.35%) RR*, 0.50 (95% CI, 0.15 to 1.60) for 1,200 mg compared with placebo	NR	NR	NR	NR
Placebo n=107	--	8 (7.5*)	NR	NR	NR	NR
Elemental calcium 600 mg (as citrate salt) daily n=108	--	5 (4.6*)	NR	NR	NR	NR
Elemental calcium 1,200 mg (as citrate salt) daily n=108	--	4 (3.7*)	NR	NR	NR	NR
Ruml et al, 1999[93] Poor Total N=45	2	NR	NR	ARD and RR not calculable because of zero events in both groups	NR	NR

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Placebo n=28	--	NR	NR	0 (0)	NR	NR
Calcium 800 mg daily in 2 divided doses (as citrate salt) n=17	--	NR	NR	0 (0)	NR	NR
Salovaara et al, 2010[106] Poor Total N=3,195	Mean (SD) 3.0 (0.22)	ARD*, -0.92% (95% CI, -2.49% to 0.64%) Unadjusted HR, 0.85 (95% CI, 0.63 to 1.15) Adjusted§§§ HR, 0.83 (95% CI, 0.61 to 1.12) RR*, 0.84 (95% CI, 0.63 to 1.13) Subgroups‖‖‖‖	ARD*, 0.13% (95% CI, -0.17% to 0.43%) RR*, 2.03 (95% CI, 0.37 to 11.06)	ARD*, -0.62% (95% CI, -2.10% to 0.86%) Unadjusted HR, 0.89 (95% CI, 0.65 to 1.22) Adjusted§§§ HR, 0.87 (95% CI, 0.63 to 1.19) RR*, 0.88 (95% CI, 0.64 to 1.20) Subgroups‖‖‖‖	Clinical: ARD*, -0.24% (95% CI, -0.81% to 0.33%) Unadjusted HR, 0.71 (95% CI, 0.3 to 1.66) Adjusted§§§ HR, 0.67 (95% CI, 0.29 to 1.58) RR*, 0.70 (95% CI, 0.30 to 1.64) Subgroups‖‖‖‖	Major osteoporotic fractures: ARD*, -0.58% (95% CI, -1.75% to 0.59%) Unadjusted HR, 0.83 (95% CI, 0.55 to 1.25) Adjusted§§§ HR, 0.81 (95% CI, 0.54 to 1.22) RR*, 0.82 (95% CI, 0.55 to 1.22) Subgroups‖‖‖‖
Control (no placebo) n=1,609	--	94 (5.8)	2 (0.1)	82 (5.1)	Clinical fractures: 13 (0.8)	Major osteoporotic fractures: 52 (3.2)
Vitamin D_3 800 IU daily plus calcium 1,000 mg (as carbonate salt) daily in 2 divided doses n=1,586	--	78 (4.9)	4 (0.2)	71 (4.5)	Clinical fractures: 9 (0.6)	Major osteoporotic fractures: 42 (2.6)
Sanders et al, 2010[83] Good Total N=2,258 randomized (N=2,256 analyzed)	Median 3 years	ARD*, 2.59% (95% CI, -0.12% to 5.31%) HR, 1.26 (95% CI, 0.99 to 1.59) RR*, 1.23 (95% CI, 0.99 to 1.54)	ARD*, 0.35% (-0.66% to 1.35%) RR*, 1.26 (95% CI, 0.64 to 2.47)	ARD*, 1.99% (95% CI, -0.49% to 4.46%) RR*, 1.22 (95% CI, 0.95 to 1.57)	Clinical: ARD*, 0.61% (95% CI, -0.75% to 1.96%) RR*, 1.24 (95% CI, 0.76 to 2.03)	Other fracture types reported by study groups

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Placebo n=1,125	--	125 (11.1)	15 (1.3)	101 (9.0)	Clinical: 28 (2.5)	Colles: 23 (2.0) Other forearm: 7 (0.6) Humerus: 14 (1.2) Ribs: 7 (0.6) Clavicle/Scapula: 1 (0.1) Pelvis: 4 (0.4) Upper leg/Patella: 6 (0.5) Lower leg: 5 (0.4) Ankle: 12 (1.1) Foot/Toes: 12 (1.1) Hand/Fingers: 3 (0.3) Skull/Face: 4 (0.4)
Vitamin D_3 500,000 IU orally annually n=1,131	--	155 (13.7)	19 (1.7)	124 (11.0)	Clinical: 35 (3.1)	Colles: 26 (2.3) Other forearm: 14 (1.2) Humerus: 15 (1.3) Ribs: 6 (0.5) Clavicle/Scapula: 4 (0.4) Pelvis: 8 (0.7) Upper leg/Patella: 8 (0.7) Lower leg: 6 (0.5) Ankle: 8 (0.7) Foot/Toes: 17 (1.5) Hand/Fingers: 6 (0.5) Skull/Face: 8 (0.7)
Smith et al, 2007[84] Fair Total N=9,440	1 to 3	NR	Specified as "hip or femur" ARD*, 0.46% (-0.03% to 0.90%) HR, 1.49 (95% CI, 1.02 to 2.18) RR*, 1.50 (95% CI, 1.02 to 2.19) Subgroups: Women: HR, 1.80 (95% CI, 1.12 to 2.90) Men: HR, 1.02 (95% CI, 0.53 to 1.97)	ARD*, 0.55% (95% CI, -0.42% to 1.53%) HR, 1.09 (95% CI, 0.93 to 1.28) RR*, 1.09 (95% CI, 0.93 to 1.28) Subgroups: Women: HR, 1.21 (95% CI, 1.00 to 1.47) Men: HR, 0.81 (95% CI, 0.59 to 1.11)	NR	Wrist or radius, ulna, or Colles fracture: ARD*, 0.25% (95% CI, -0.19% to 0.69%) HR, 1.22 (95% CI, 0.85 to 1.76) RR*, 1.23 (95% CI, 0.85 to 1.77) Subgroups: Women: HR, 1.34 (95% CI, 0.91 to 1.98) Men: HR, 0.50 (95% CI, 0.15 to 1.66)

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures Risk or No. (%)	Hip Fractures Risk or No. (%)	Nonvertebral Fractures Risk or No. (%)	Vertebral Fractures Risk or No. (%)	Other Fractures Risk or No. (%)
Placebo n=4,713	--	NR	44 (0.9) Subgroups: Women: 26 (1.0) Men: 18 (0.8)	279 (5.9) Subgroups: Women: 194 (7.7) Men: 85 (3.9)	NR	Wrist or radius, ulna, or Colles fracture: 52 (1.1) Subgroups: Women: 44 (1.7) Men: 8 (0.4)
Vitamin D_2 300,000 IU IM annually n=4,727	--	NR	66 (1.4) Subgroups: Women: 48 (1.9) Men: 18 (0.8)	306 (6.5) Subgroups: Women: 238 (9.3) Men: 68 (3.1)	NR	Wrist or radius, ulna, or Colles fracture: 64 (1.4) Subgroups: Women: 60 (2.3) Men: 4 (0.2)

* Calculated based on data provided in the article.

† OSTPRE is a population-based study in Kuopio Province, Finland, that began in 1989 with mail recruitment of all women ages 47 to 56 years in the province, with 92.8% response to initial questionnaire. The study groups included in this evidence table are a subset of participants from OSTPRE who were recruited for the clinical trial in 1994. This trial also included two additional study groups that evaluated HT versus placebo (defined as the calcium-only group) and HT plus vitamin D_3 versus placebo. These study groups were not eligible for this review.

ǂ Includes symptomatic fractures of distal radius/wrist, ankle, foot, toe, ribs, humerus, hip, skull, and patella.

§ Adjusted for baseline femoral neck BMD and previous fractures.

ǁ No intake during June-August. Dose of vitamin D reduced to 100 IU during the fifth treatment year because of observed adverse lipid change during vitamin D treatment.

¶ Adjustments for covariates, exclusion of participants who regularly used supplements, and restriction to subgroups including residents of apartment homes for the elderly, active treatment compliance, and age 80 years or older did not substantively change this estimate.

Including Colles, humerus, ankle, foot, leg, and other (unspecified) fractures.

** Results based on data provided across four publications, Jackson et al, 2006[70]; Prentice et al, 2013[97]; Bolland et al, 2011b[96]; and Robbins et al, 2014.[98]

†† Subgroup analyses: HR 0.98 (95 % CI 0.89 to 1.07) among nonusers of personal supplements at baseline, HR 0.96 (95% CI 0.89 to 1.04) among users of supplements at baseline, p for interaction between treatment allocation and user of personal supplements at baseline=0.72.[96] Sub group analyses among participants randomized to hormone therapy groups of the WHI Hormone Therapy RCT; HR not reported by these subgroups but p for interaction between hormone therapy use and nonuse and treatment allocation was=0.97.[98]

ǂǂ Subgroup analyses: HR 0.85 (95% CI, 0.61 to 1.17) among nonusers of personal supplements at baseline, HR 0.93 (95% CI, 0.71 to 1.21) among users of personal supplements at baseline. P for interaction between treatment allocation (vitamin D and calcium versus placebo) and personal supplement use at baseline=0.65.[96] Subgroup analyses among participants randomized to hormone therapy groups of the WHI Hormone Therapy RCT: HR 0.59 (95% CI 0.38 to 0.93) among participants randomized to active hormone therapy; HR 1.20 (95% CI, 0.85 to 1.69) among participants randomized to placebo hormone therapy. P for interaction between treatment allocation (vitamin D and calcium versus placebo) and hormone therapy use=0.01.[98]

§§ Excludes cervical vertebral fractures. Subgroup analyses among participants randomized to hormone therapy groups of the WHI Hormone Therapy RCT; HR not reported by these subgroups but p=0.79[98] for interaction between hormone therapy use and nonuse and treatment allocation (vitamin D and calcium versus placebo).

ǁǁ Fractures were reported in a diary and coded using the International Classification of Primary Care (ICPC2 Plus) system database of disease coding; no additional description or details were reported. Fractures were considered as adverse events, not efficacy endpoints.

¶¶ Cointerventions: Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outside) and consuming 1,300 mg calcium per day using diet and/or supplements.

There were no significant sex main-effects or sex-by-treatment interactions in any of the variables; thus, men and women were combined in the analysis.

*** Major osteoporotic fractures are defined as all fractures except those of the head, hands, feet, and ankles, and that result from major trauma.

Appendix D Table 2. Benefits of Supplementation for Fracture Prevention From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 1)

[†††] Based on 78 of the original 122 participants who completed the first 2 years of the trial.
[‡‡‡] Fractures were specified as adverse events in the protocol and were not specified as to site. All fractures except for toe fractures were noted to have occurred after substantial trauma.
[§§§] Adjusted for age, BMI, smoking, use of alcohol, prior fracture, parental hip fracture, steroid use, diagnosed rheumatoid arthritis, and secondary osteoporosis.
[‖‖‖] No statistically significant difference between any of the subgroups analyzed. This includes age, calcium intake <700 mg/d, compliance levels, and exclusion of subjects with secondary osteoporosis.

Abbreviations: ARD=absolute risk difference; BMI=body mass index; CI=confidence interval; HR=hazard ratio; IU=international units; mg=milligram; N=Number; NR=not reported; RR=relative risk; WHI=Women's Health Initiative.

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Main Analysis					
Khaw, Scragg et al, 2017[77, 78] VIDA Good Total N=5,110	3.3	ARD, -0.33% (-1.16% to 0.51%)*; RR, 0.87 (0.61 to 1.24)	MI: ARD, -0.12% (-0.71% to 0.47%)* HR, 0.90 (0.54 to 1.50) Stroke: ARD -0.04 % (-0.60% to 0.51%)* HR, 0.95 (0.55 to 1.62) VTE: ARD -0.16% (-0.55% to 0.23%)* HR, 0.74 (0.34 to 1.61) Heart failure: ARD, 0.46% (-0.39% to 1.31%)* HR, 1.19 (0.84 to 1.68)	--	--
Placebo n analyzed=2,550	--	65 (2.5%)	MI: 31 (1.2%) Stroke, hemorrhage, infarct: 27 (1.1%) VTE: 15 (0.6%) Heart failure: 57 (2.2%)	--	--
Vitamin D_3 orally 200,000 IU initial dose followed by 100,000 IU every month n analyzed=2,558	--	58 (2.3%)	MI: 28(1.1%) Stroke, hemorrhage, infarct: 26 (1.0%) VTE: 11 (0.4%) Heart failure: 69 (2.7%)	--	--
Komulainen et al, 1998,[71] Komulainen et al, 1999[118] OSTPRE† Fair Total N=232	5	ARD*, -0.87% (-3.26% to 1.52%) RR*, 0.34 (0.01 to 8.31)	Myocardial infarction or coronary bypass operation: ARD*, 1.79% (-1.18% to 4.75%) RR*, 5.13 (0.25 to 105.73)	Malignancies, including breast, ventricle, melanoma, endometrial, and cervical: ARD*, -0.82% (95% CI, -4.63% to 2.99%); RR*, 0.68 (95% CI, 0.12 to 4.02)	NR
Elemental calcium 93 mg (as lactate salt) daily (no vitamin D placebo) n analyzed=115	--	1 (0.9*)	0 (0*)	3 (2.6*)	--
Vitamin D_3 300 IU plus elemental calcium 93 mg daily (salt not specified)‡ n analyzed=112	--	0 (0*)	2 (1.8*)	2 (1.8*)	--

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Lappe et al, 2007[107] Good for cancer outcomes; Fair for kidney stone outcome Total N=1,180 randomized, 1,179 analyzed	4	NR	NR	Total cancers[§] (excluding skin): ARD*, -3.12% (95% CI, -6.56% to 0.31%) RR*, 0.55 (95% CI, 0.29 to 1.03) for calcium compared to placebo ARD*, -4.03% (95% CI, -7.35% to -0.70%) RR*, 0.42 (95% CI, 0.21 to 0.83) for vitamin D with calcium compared with placebo Breast cancer: ARD*, -1.43% (-3.61% to 0.75%) RR*, 0.49 (0.17 to 1.38) comparing calcium to placebo ARD*, -1.66% (-3.79% to 0.48%) RR*, 0.40 (0.13 to 1.22) comparing vitamin D with calcium to placebo Colorectal cancer: ARD*, -0.69% (-1.81% to 0.42%) RR*, 0.13 (0.01 to 2.69) comparing calcium to placebo ARD*, -0.47% (-1.52% to 0.58%) RR*, 0.32 (0.03 to 3.54) comparing vitamin D with calcium to placebo	ARD*, 0.33% (95% CI, -0.69% to 1.35%) RR*, 1.94 (95% CI, 0.20 to 18.57) for calcium compared with placebo; ARD*, -0.12% (95% CI, -0.93% to 0.69%) RR*, 0.65 (95% CI, 0.04 to 10.28) for vitamin D with calcium compared with placebo
Placebo n=288	--	--	--	Total cancers (excluding skin): 20 (6.9) Breast: 8 (2.8) Colorectal: 2 (0.7)	1 (0.4)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D placebo n=445	--	--	--	Total cancers (excluding skin): 17 (3.8) Breast: 6 (1.4) Colorectal: 0(0)	3 (0.7)
Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D_3 1,000 IU orally daily n=446	--	--	--	Total cancers (excluding skin): 13 (2.9) Breast: 5 (1.1) Colorectal: 1 (0.2)	1 (0.2)
Lappe et al, 2017[108] Fair Total N=2,303 randomized, 2,197 analyzed	4	ARD*, -0.19% (-0.90% to 0.52%); RR*, 0.77 (0.29 to 2.07)	NR	Total excluding nonmelanoma skin cancer: ARD*, -1.76% (-3.58% to 0.05%) RR*, 0.70 (95% CI, 0.48 to 1.01) Breast cancer: ARD*, -0.65% (-1.75% to 0.46%) RR*, 0.69 (95% CI, 0.37 to 1.30) Colorectal cancer: ARD*, 0.00% (-0.51% to 0.50%) RR*, 0.99 (95% CI, 0.25 to 3.96)	ARD*, 0.54% (-0.36% to 1.44%) RR*, 1.59 (0.72 to 3.49)
Placebo (n analyzed=1,095)	--	9 (0.8%)	--	Total: 64 (5.8%) Breast: 23 (2.1%) Colorectal: 4 (0.4%)	10 (0.9%)
Vitamin D_3 2,000 IU orally daily with 1,500 mg calcium daily (as carbonate salt) (n analyzed=1,102)	--	7 (0.6%)	--	Total: 45 (4.1%) Breast: 16 (1.5%) Colorectal 4 (0.4%)	16 (1.5%)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Lips et al, 1996[75] Fair N=2,578	Median 3.5	ARD*, -1.93% (95% CI, -5.17% to 1.31%) RR*, 0.92 (95% CI, 0.80 to 1.06)	NR	NR	NR
Placebo n=1,287	--	306 (23.8)	--	--	--
Vitamin D_3 400 IU orally daily n=1,291	--	282 (21.8)	--	--	--
Reid et al, 2008[91] Fair Total N randomized=323, n analyzed=290‖	2	ARD*, -0.02% (-2.65% to 2.61%) RR*, 0.98 (95% CI, 0.06 to 15.48) for 600 mg compared with placebo ARD*, 0.05% (-2.67% to 2.77%) RR*, 1.05 (95% CI, 0.07 to 16.57) for 1,200 mg compared with placebo	Myocardial Infarction as a protocol-specified adverse event: ARD*, 1.02% (-1.75% to 3.80%) RR*, 3.03 (95% CI, 0.12 to 73.49) for 600 mg compared with placebo ARD*, 2.15% (-1.38% to 5.68%) RR*, 5.32 (95% CI, 0.26 to 109.35) for 1,200 mg compared with placebo	NR	Renal calculus as a protocol-specified adverse event ARD*, -1.01% (-3.77% to 1.75%) RR*, 0.34 (95% CI, 0.01 to 8.17) for 600 mg compared with placebo ARD*, -1.01% (-3.81% to 1.79%) RR*, 0.35 (95% CI, 0.01 to 8.60) for 1,200 mg compared with placebo
Placebo n=99 (104 for mortality)	--	1 (0.96)	0 (0)	--	1 (1.0)
Elemental calcium 600 mg (as citrate salt) daily n=98 (106 for mortality)	--	1 (0.94)	1 (1.0)	--	0 (0)
Elemental calcium 1,200 mg (as citrate salt) daily n=93 (99 for mortality)	--	1 (1.0)	2 (2.2)	--	0 (0)
Riggs et al, 1998[73] Fair Total N=236	4	NR	NR	NR	ARD*, -0.85% (95% CI, -3.18% to 1.47%) RR*, 0.33 (95% CI, 0.01 to 7.97)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Placebo n=117	--	--	--	--	1 (0.9)
Calcium 1,600 mg daily in 4 divided doses (as citrate salt) n=119	--	--	--	--	0 (0)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Trivedi et al, 2003[76] Fair Total N=2,686	5	ARD*, -1.76% (95% CI, -4.64% to 1.11%) Age-adjusted RR, 0.88 (95% CI, 0.74 to 1.06); RR*, 0.90 (95% CI, 0.77 to 1.07) Subgroups: Women: ARD*, -0.69% (95% CI, -4.87% to 3.49%) RR*, 0.92 (95% CI, 0.54 to 1.55) Men: ARD*, -2.08% (95% CI, -5.59% to 1.43%); RR*, 0.90 (95% CI, 0.76 to 1.07)	Total CVD: ARD*, -2.04% (95% CI, -5.68% to 1.60%) Age-adjusted RR, 0.90 (95% CI, 0.77 to 1.06) RR*, 0.95 (95% CI, 0.86 to 1.04) Ischemic heart disease: ARD*, -0.72% (95% CI, -3.56% to 2.12%) Age-adjusted RR, 0.94 (95% CI, 0.77 to 1.15) RR*, 0.96 (95% CI, 0.81 to 1.13) Cerebrovascular disease: ARD*, 0.27% (95% CI, -1.74% to 2.29%) Age-adjusted RR, 1.02 (95% CI, 0.77 to 1.36) RR*, 1.04 (95% CI, 0.80 to 1.35) Subgroups: Women: Ischemic heart disease: ARD*, -2.26% (95% CI, -7.12% to 2.60%); RR*, 0.82 (95% CI, 0.53 to 1.26) Cerebrovascular disease: ARD*, 0.87% (95% CI, -2.60% to 4.35%); RR*, 1.18 (95% CI, 0.62 to 2.25) Men: Ischemic heart disease: ARD*, -0.21% (95% CI, -3.61% to 3.18%); RR*, 0.99 (95% CI, 0.83 to 1.18) Cerebrovascular disease: ARD*, 0.09% (95 % CI, -2.32% to 2.50%); RR*, 1.01 (95% CI, 0.76 to 1.35)	Any cancer: ARD*, 1.08% (-1.50% to 3.66%) Age-adjusted RR, 1.09 (95% CI, 0.86 to 1.36)¶ RR*, 1.08 (95% CI, 0.89 to 1.31) Any cancer (excluding skin): ARD*, 1.01% (95% CI, -1.28% to 3.30%) Age-adjusted RR, 1.11 (95% CI, 0.86 to 1.42)# RR*,1.10 (0.88 to 1.38) Colon cancer: ARD*, 0.07% (-1.00% to 1.14%) Age-adjusted RR, 1.02 (95% CI, 0.60 to 1.74)** RR*, 1.03 (95% CI, 0.61 to 1.74) Respiratory: ARD*, 0.15% (95% CI, -0.68% to 0.97%) Age-adjusted RR, 1.12 (95% CI, 0.56 to 2.25)†† RR*, 1.13 (95% CI, 0.57 to 2.25) Subgroups: Any cancer Women: ARD*, -0.38% (95% CI, -4.52% to 3.76%) RR*, 0.95 (95% CI, 0.56 to 1.61) Men: ARD*, 1.56% (95% CI, -1.56% to 4.67%) RR,* 1.11 (95% CI, 0.90 to 1.36)	NR

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Placebo n=1,341	--	247 (18.4) Women 27 (8.4) Men 220 (21.6)	Total CVD: 503 (37.5) Ischemic heart disease: 233 (17.4) Women: 40 (12.4) Men: 193 (19.0) Cerebrovascular disease: 101 (7.5) Women: 16 (5.0) Men: 85 (8.4)	Any cancer: 173 (12.9) Women: 26 (8.1) Men: 147 (14.4) Any cancer (excluding skin): 130 (9.7) Colon cancer: 27 (2.0) Respiratory cancer: 15 (1.1)	--
Vitamin D_3 100,000 IU orally every 4 months n=1,345	--	224 (16.7) Women 25 (7.7) Men 199 (19.5)	CVD: 477 (35.5) Ischemic heart disease: 224 (16.7) Women: 33 (10.1) Men: 191 (18.7) Cerebrovascular disease: 105 (7.8) Women: 19 (5.8) Men: 86 (8.4)	Any cancer: 188 (14.0) Women: 25 (7.7) Men: 163 (16.0) Any cancer (excluding skin): 144 (10.7) Colon cancer: 28 (2.1) Respiratory cancer: 17 (1.3)	--

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

WHI Calcium and Vitamin D Trial[‡‡] Fair Total N=36,282	7	ARD[*], -0.36 % (-0.78% to 0.05%) HR, 0.91 (95% CI, 0.83 to 1.01) RR[*], 0.92 (95% CI, 0.83 to 1.01) No significant differences based on age (<70 years vs. ≥70 years, use of personal supplements at baseline, or race/ethnicity)[§§]	Total CVD: ARD[*], 0.08% (95% CI, -0.54% to 0.70%) HR, 1.00 (95% CI, 0.94 to 1.07) RR[*], 1.01 (95% CI, 0.95 to 1.07) No differences based on use of personal supplements at baseline.[‖‖] Myocardial infarction: ARD[*], 0.11% (95 % CI, -0.20% to 0.41%) HR, 1.03 (95% CI, 0.90 to 1.19) RR[*], 1.05 (95% CI, 0.92 to 1.20) Some differences based on personal supplement use at baseline[¶¶] Coronary heart disease (defined as MI or CHD death): ARD[*], 0.12% (95% CI, -0.21% to 0.45%) HR, 1.03 (95% CI, 0.90 to 1.17) RR[*],1.05 (95% CI, 0.92 to 1.18) No differences based on personal supplement use at baseline and no differences by age[##] Stroke: ARD[*], -0.09% (95% CI, -0.38% to 0.20%) HR, 0.95 (95% CI, 0.82 to 1.10) RR[*], 0.96 (95% CI, 0.83 to 1.10) Some differences based on personal supplement use at baseline[***] Heart failure hospitalization: ARD[*], -0.11% (95% CI, -0.40% to 0.18%) HR, 0.95 (95% CI, 0.82 to 1.09)[†††] RR[*], 0.95 (95% CI, 0.82 to 1.09) VTE (includes deep vein thrombosis and pulmonary embolus that were considered idiopathic or secondary events): ARD[*], -0.16% (95% CI, -0.44% to	Total invasive cancer: ARD[*], -0.28% (95% CI, -0.82% to 0.27%) HR[§§§] 0.96 (95% CI, 0.89 to 1.04) RR[*], 0.96 (95% CI, 0.90 to 1.04) No differences among age groups, race/ethnicity, or when limited to participants with no prior history of invasive cancer. Some differences based on personal supplement use at baseline[‖‖‖] Breast cancer: ARD[*], -0.11% (95% CI, -0.46% to 0.24%) HR, 0.96 (95% CI, 0.85 to 1.08) RR[*], 0.96 (95% CI, 0.86 to 1.08) Some differences based on personal supplement use at baseline[¶¶¶] Colorectal cancer: ARD[*], 0.07% (95% CI, -0.12% to 0.27%) HR, 1.06 (95% CI, 0.85 to 1.32) [###] RR[*], 1.09 (95% CI, 0.87 to 1.35) Some differences based on personal supplement use at baseline[****] Nonmelanoma skin cancer: ARD[*], 0.12% (95% CI, -0.48% to 0.71%) HR, 1.02 (95% CI, 0.95 to 1.07) RR[*], 1.01 (95% CI, 0.95 to 1.08)	ARD[*], 0.37% (95% CI, 0.06% to 0.67%) RR, 1.17 (95% CI, 1.03 to 1.34) No differences by age or race/ ethnicity.[‡‡‡]

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
			0.12%) HR, 0.92 (95% CI, 0.79 to 1.07) RR*,0.92 (95% CI, 0.79 to 1.06) Deep vein thrombosis: ARD*, -0.06% (95% CI, -0.30% to 0.18%) HR, 0.97 (95% CI, 0.82 to 1.16) RR*, 0.96 (95% CI, 0.80 to 1.14) Pulmonary embolism: ARD*, -0.08% (95% CI, -0.26% to 0.10%) HR, 0.92 (95% CI, 0.73 to 1.16) RR*, 0.90 (95% CI, 0.72 to 1.14) Idiopathic VTE: HR, 0.62 (95% CI, 0.42 to 0.92)‡‡‡ Secondary VTE: HR, 0.98 (95% CI, 0.83 to 1.16)	Melanoma skin cancer: ARD*, -0.07% (95% CI, -0.21% to 0.07%) HR, 0.86 (95% CI, 0.64 to 1.16) RR*, 0.87 (95% CI, 0.65 to 1.17) Some differences based on history of nonmelanoma skin cancer.††††	
Placebo n=18,106	--	807 (4.5)	Total CVD: 1,810 (10.0) Myocardial infarction: 390 (2.2) Coronary heart disease (defined as MI or CHD death): 475 (2.6) Stroke: 377 (2.1) Heart failure among participants without a history of heart failure at baseline: 381 (2.1) VTE: 348 (1.9) Deep vein thrombosis: 256 (1.4) Pulmonary embolism: 149 (0.8)	Total invasive cancer: 1,411 (7.8) Breast cancer: 546 (3.0) Colorectal cancer:154 (0.9) Melanoma skin cancer: 94 (0.5) Nonmelanoma skin cancer: 1,655 (9.1)	381 (2.1)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Calcium 1,000 mg daily in 2 divided doses as carbonate salt plus vitamin D_3 400 IU orally daily in 2 divided doses n=18,176	--	744 (4.1)	Total CVD: 1,832 (10.1) Myocardial infarction: 411 (2.3) Coronary heart disease (defined as MI or CHD death): 499 (2.8) Stroke: 362 (2.0) Heart failure among participants without a history of heart failure at baseline: 363 (2.0) VTE: 320 (1.8) Deep vein thrombosis: 246 (1.4) Pulmonary embolism: 135 (0.7)	Total invasive cancer: 1,366 (7.5) Breast cancer: 528 (2.9) Colorectal cancer: 168 (0.9) Melanoma skin cancer: 82 (0.5) Nonmelanoma skin cancer: 1,683 (9.3)	449 (2.5)
Sensitivity Analysis					
Aloia et al, 2005[114] Poor Total N=208	3	NR	NR	NR	ARD and RR not calculable because of zero events in both groups
Placebo, plus some participants in this group received an unknown dose of calcium n=104	--	--	--	--	0 (0)
Vitamin D_3 1,200 IU orally daily during the first 24 months, increasing to 2,000 IU daily thereafter, plus some participants in this group received an unspecified dose of calcium n=104	--	--	--	--	0 (0)
Cherniack et al, 2011[119] Poor Total N=34	6 months	NR	Myocardial infarction: ARD*, 0.00% (95% CI, -15.82% to 15.82%) RR*, 1.00 (95% CI, 0.07 to 14.72)	NR	NR

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Placebo, plus most also received an unspecified dose of a calcium supplement n=17	--	--	1 (5.8)	--	--
Vitamin D_3 2,000 IU orally daily, plus most also received an unspecified dose of a calcium supplement n=17	--	--	1 (5.8)	--	--
Glendenning et al, 2012[86] Poor Total N=686	9 months	NR	Stroke: ARD*, 0.25% (95% CI, -1.02% to 1.52%) RR*, 1.42 (95% CI, 0.24 to 8.42) Ischemic heart disease: ARD*, -0.63% (95% CI, -2.04% to 0.77%) RR*,0.47 (95% CI, 0.09 to 2.56)	RR*, 1.19 (95% CI, 0.62 to 2.31)	NR
Placebo§§§§ n=333	--	--	Stroke: 2* (0.6) Ischemic heart disease: 4 (1.2)	15* (4.5)	--
Vitamin D_3 150,000 IU orally at baseline, 3 months, and 6 months§§§§ n=353	--	--	Stroke: 3* (0.8) Ischemic heart disease: 2* (0.6)	19* (5.4)	--
Hin et al, 2017[110]	1	4,000 IU or 2,000 IU vs. placebo ARD*, -2.97% (95% CI, -6.75% to 0.81%) RR*, 0.14 (95% CI, 0.01 to 2.70)	Not eligible, poor quality	Not eligible, poor quality	NR
Placebo	--	3 (3.0)	--	--	--
Vitamin D3 4,000 IU daily	--	0 (0)	--	--	--
Vitamin D3 2,000 IU daily	--	0 (0)	--	--	--

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Peacock et al, 2000[85] Poor Total N=377	4	NR	NR	NR	ARD*, 0.81% (95% CI, -1.38% to 2.990%) RR*, 3.12 (95% CI, 0.13 to 75.87) comparing calcium to placebo. ARD and RR not calculable for the vitamin D vs placebo comparison due to zero events in both groups.
Placebo n=129	4	--	--	--	0 (0)
Vitamin D_3 600 IU daily in 3 divided doses n=124	--	--	--	--	NA
Calcium 750 mg (as citrate malate salt) daily in 3 divided doses n=124	--	--	--	--	1 (0.8)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Prince et al, 2006,[89] and Lewis et al, 2011[90] Calcium Intake Fracture Outcome Study Fair Total N=1,460	5	ARD*, -1.23% (95% CI, -3.38% to 0.91%) RR*, 0.76 (95% CI, 0.48 to 1.22)	Incident ischemic heart disease diagnosis: ARD*, 0.68% (95% CI, -1.99% to 3.36%) HR, 1.12 (95% CI, 0.77 to 1.64) RR*, 1.10 (95% CI, 0.76 to 1.58) Atherosclerotic vascular disease hospitalization or death: ARD*, 0.20% (95% CI, -3.17% to 3.56%) Adjusted HR, 0.94 (95% CI, 0.69 to 1.28) RR*, 1.01 (95% CI, 0.79 to 1.31) Atherosclerotic vascular hospitalization: ARD*, 0.00% (95% CI, -3.39% to 3.39%) RR*, 1.00 (95% CI, 0.76 to 1.31) Atherosclerotic vascular death: ARD*, -0.81% (95% CI, -2.60% to 0.98%) RR*, 0.76 (95% CI, 0.42 to 1.39)	NR	ARD*, 0.00% (95% CI, -0.54% to 0.54%) RR*, 1.00 (95% CI, 0.14 to 7.08)
Placebo n=730	--	38 (5.2)	Incident ischemic heart disease diagnosis: 51 (7.0) Atherosclerotic vascular disease hospitalization or death: 103 (14.1) Atherosclerotic vascular death: 24 (3.3) Atherosclerotic vascular hospitalization: 91 (12.5)	--	2 (0.3)
Elemental calcium 1,200 mg (as carbonate salt) daily in 2 divided doses n=730	--	29 (4.0)	Incident ischemic heart disease diagnosis: 56 (7.7) Atherosclerotic vascular disease hospitalization or death: 104 (14.2) Atherosclerotic vascular death: 18 (2.5) Atherosclerotic vascular hospitalization: 91 (12.5)	--	2 (0.3)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Recker et al, 1996[72] Poor Total N=103	4.3	NR	NR	NR	NR
Placebo n=61	--	--	--	--	0 (0)
Calcium 1,200 mg (as carbonate salt) daily in 2 divided doses n=42	--	--	--	--	0 (0)
Reid et al, 2006[87]; Bolland et al, 2008[88] Fair Total N=1471	4.5	ARD*, 0.72% (95% CI, -1.35% to 2.79%) RR*, 1.18 (95% CI, 0.73 to 1.92)	Myocardial infarction: ARD*, 1.39% (95% CI, -0.49% to 3.28%) RR*, 1.49 (95% CI, 0.86 to 2.57) Stroke: ARD*, 1.26% (95% CI, -0.74% to 3.27%) RR*, 1.37 (95% CI, 0.83 to 2.28) Myocardial infarction/Stroke composite outcome: ARD*, 1.43% (95% CI, -1.26% to 4.12%) RR*, 1.21 (95% CI, 0.84 to 1.74)	NR	ARD*, -0.27% (95% CI, -0.92% to 0.38%) RR*, 0.50 (95% CI, 0.09 to 2.75)
Placebo n=739	--	29 (3.9)	Myocardial infarction: 21 (2.8) NR for subgroup Stroke: 25 (3.4) NR for subgroup Myocardial infarction/Stroke composite outcome: 50 (6.8)	--	4 (0.5)
Calcium 1,000 mg (as citrate salt) daily in 2 divided doses n=732	--	34 (4.6)	Myocardial infarction: 31 (4.2) NR for subgroup Stroke: 34 (4.6) NR for subgroup Myocardial infarction/Stroke composite outcome: 60 (8.2)	--	2 (0.3)

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Reid et al, 1995,[92] Reid et al, 1993[94] Poor Total N=122	2	NR	NR	NR	ARD*, 1.64% (95% CI, -2.79% to 6.06%) RR*, 3.00 (95% CI, 0.12 to 72.23)
Placebo Initial trial: n=61	--	--	--	--	0[lllllll]
Calcium 1,000 mg (as lactate-gluconate and carbonate salts) daily in 2 doses n=61	--	--	--	--	1[lllllll]
Salovaara et al, 2010[106] Poor Total n=3,195	3	ARD*, 0.14% (95% CI, -0.51% to 0.78%) RR, 1.17 (95% CI, 0.56 to 2.45)	NR	NR	NR
Control (no placebo) n=1,609	--	13 (0.8)	--	--	--
Vitamin D_3 800 IU daily plus calcium 1,000 mg (as carbonate salt) daily in 2 divided doses n=1,586	--	15 (0.9)	--	--	--
Sanders et al, 2010[83] Good for all-cause mortality; Fair for incident CVD and incident cancer Total N=2,258 randomized (N=2,256 analyzed)	Median 3	ARD*, -0.64% (95% CI, -2.23% to 0.95%) RR*, 0.85 (95% CI, 0.56 to 1.28)	ARD*, 0.35% (95% CI, -0.60% to 1.29%) RR*, 1.30 (95% CI, 0.63 to 2.67)	ARD*, -0.27% (95% CI, -0.98% to 0.44%) RR*, 0.70 (95% CI, 0.27 to 1.82)	NR
Placebo n=1,125	--	47 (4.2)	13 (1.2)	10 (0.9)	--
Vitamin D_3 500,000 IU orally annually n=1131	--	40 (3.5)	17 (1.5)	7 (0.6)	--

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

Author, Year, Quality, and Sample Size Analyzed	Duration (years)	All-Cause Mortality Risk or No. (%)	Incident CVD or Stroke Risk or No. (%)	Incident Cancer Risk or No. (%)	Incident Kidney Stones Risk or No. (%)
Zhu et al, 2008[109] Fair Total N=120	5	NR	Stroke¶¶¶¶: ARD*, -2.38% (95% CI, -10.56% to 5.80%); RR*, 0.51 (95% CI, 0.05 to 5.43) for calcium vs. placebo ARD*, -4.88% (95% CI, -12.82% to 3.06%); RR*, 0.21 (95% CI, 0.01 to 4.24) for vitamin D with calcium vs. placebo Ischemic heart disease¶¶¶¶: ARD*, 2.62% (95% CI, -7.87% to 13.11%); RR*, 1.54 (95% CI, 0.27 to 8.72) for calcium vs. placebo ARD*, -4.88% (95% CI, -12.82% to 3.06%); RR*, 0.21 (95% CI, 0.01 to 4.24) for vitamin D with calcium vs. placebo	Cancer Including skin¶¶¶¶: ARD*, 5.55% (95% CI, -13.21% to 24.31%); RR*, 1.25 (95% CI, 0.58 to 2.69) for calcium vs. placebo ARD*, -6.57% (95% CI, -23.56% to 10.43%); RR*, 0.70 (95% CI, 0.28 to 1.79) for vitamin D with calcium vs. placebo Cancer excluding skin¶¶¶¶: ARD*, 5.43% (95% CI, -11.90% to 22.75%); RR*, 1.32 (95% CI, 0.54 to 3.20) for calcium vs. placebo ARD*, -9.38% (95% CI, -23.61% to 4.85%); RR*, 0.45 (95% CI, 0.13 to 1.62) for vitamin D with calcium vs. placebo	No events in any study group
Placebo n=41	--	--	Stroke: 2 (5.0) Ischemic heart disease: 2 (5.0)	Cancer including skin: 9 (22.0) Cancer excluding skin: 7 (17.1)	0 (0)
Calcium 1,200 mg (as carbonate salt) daily n=40	--	--	Stroke: 1 (2.5) Ischemic heart disease: 3 (7.5)	Cancer including skin: 11 (27.5) Cancer excluding skin: 9 (22.5)	0 (0)
Calcium 1,200 mg (as carbonate salt) plus vitamin D_2 1,000 IU orally daily n=39	--	--	Stroke: 0 (0) Ischemic heart disease: 0 (0)	Cancer including skin: 6 (15.4) Cancer excluding skin: 3 (7.7)	0 (0)

* Calculated based on data provided in the article.

† OSTPRE is a population-based study in Kuopio Province, Finland, that began in 1989 with mail recruitment of all women ages 47 to 56 years in the province, with 92.8% response to the initial questionnaire. The study groups included in this evidence table are a subset of participants from OSTPRE who were recruited for the clinical trial in 1994 (so were ages 52 to 61 at time of recruitment into the trial). This trial also included two additional study groups that evaluated HT versus placebo (defined as the calcium-only group) and HT plus vitamin D_3 versus placebo. These study groups were not eligible for this review. Five women were not included in the analysis because they were withdrawn after randomization due to osteoporosis (1 in placebo group and 4 in intervention group).

‡ No intake during June-August. Dose reduced to 100 IU during the fifth treatment year because of observed adverse lipid change during vitamin D treatment.

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

§ Study reported two cancer outcomes: Year 1 through Year 4, and Year 2 through Year 4 based on the hypothesis that Year 1 cancer outcomes are likely undetected prevalent cancers at baseline. ARD -3.2% (95% CI, -6.7% to 0.4%) and RR 0.53 (95% CI, 0.27 to 1.04) for calcium compared to placebo when cancers that occurred during the first year of followup were excluded. ARD, -4.8% (95% CI, -8.1% to -1.5%) and RR, 0.29 (95% CI, 0.13 to 0.67) for vitamin D with calcium compared to placebo when cancers that occurred during the first year of followup were excluded.

‖ Analysis based on 290 participants who reported taking tablets at the end of the study (99 participants analyzed in placebo group, 98 in 600 mg calcium group, and 93 in 1,200 mg calcium group).

¶ Age-adjusted estimate for men was 1.11 (95% CI, 0.87 to 1.42), estimate for women 0.95 (95% CI, 0.54 to 1.68).

Age-adjusted estimate for men was 1.17 (95% CI, 0.89 to 1.54), estimate for women 0.77 (95% CI, 0.39 to 1.55).

** Age-adjusted estimate for men was 1.18 (95% CI, 0.65 to 2.12), estimate for women was 0.49 (95% CI, 0.12 to 1.98).

†† Age-adjusted estimate for men was 1.29 (95% CI, 0.62 to 2.68), estimate for women was NR because no cases occurred among the treatment group.

‡ Results based on data provided across 12 WHI CaD trial publications Jackson et al, 2006[70]; Wactawski-Wende et al, 2006[112]; LaCroix et al, 2009[111]; Bolland et al, 2011[115]; Bolland et al, 2011[96]; Brunner et al, 2011[121]; Tang et al, 2011[120]; Wallace et al, 2011[113]; Prentice et al, 2013[97]; Blondon et al, 2015[116]; Hsia et al, 2007[162], and Donneyong et al, 2015.[117]

§§ Subgroup analyses based on age, personal use of supplements at baseline, and race/ethnicity. HR for age less than 70 years was 0.89 (95% CI, 0.80 to 0.99) and for age greater than or equal to 70 years was 0.95 (95% CI, 0.80 to 1.12); P for interaction between age and treatment allocation=0.10.[111] HR for participants with no personal supplement use at baseline (N=7,755 placebo, N=7,891 for CaD) reported in two different publications: HR 0.95 (95% CI, 0.81 to 1.11)[97] and HR 0.94 (95% CI, 0.81 to 1.10, P for interaction=0.44).[96] HR for participants with personal supplement use at baseline (N=10,351 placebo, N=10,285 CaD) was 0.88 (95% CI, 0.77 to 1.01).[96] Among racial/ethnically defined subgroups p for interaction with treatment allocation=0.30; white HR 0.89 (95% CI, 0.80 to 0.99), black HR 0.91 (95% CI 0.67 to 1.23), Hispanic HR 2.28 (95% CI, 1.07 to 4.87), American Indian HR 0.84 (95% CI, 0.16 to 4.48), Asian/Pacific Islander 1.60 (95% CI, 0.75 to 3.43); other/unknown 0.90 (95% CI, 0.45 to 1.80).[111]

‖‖ Subgroup analyses based on participants who did not use personal supplements at baseline: HR 1.03 (95% CI, 0.93 to 1.13).[97] Subgroup analyses reported by WHI CaD authors for myocardial infarction events, HR for nonusers was 1.11 (95% CI, 0.90 to 1.37).[97]

¶¶ Subgroup analysis of clinical myocardial infarction events (excluding silent MI) using the WHI limited access dataset of 16,718 women (N=8,289 placebo, N=8,429 CaD) who did not use personal supplements at baseline and 19,564 women (N=9,817 placebo, N=9,747 CaD) who used personal supplements at baseline; reported HR for nonusers was 1.11 (95% CI, 0.90 to 1.37) and HR for users was 1.22 (95% CI, 1.00 to 1.5); P for interaction=0.04.[115]

Based on a subgroup of 15,302 women (n=7,584 placebo, n=7,718 CaD) who did not use personal supplements at baseline. Participants with no personal supplement use at baseline: HR 1.03 (95% CI, 0.85 to 1.25).[97] and no use of personal vitamin D supplements at baseline (p for interaction =0.45).[162] HR by age groups (50 to 59, 60 to 69, and 70 to 79) showed no significant differences and p for interaction=0.53.[162]

*** Based on a subgroup analysis using the WHI limited access dataset of 16,718 women (n=8,289 placebo, n=8,429 CaD) who did not use personal supplements at baseline and 19,564 women (n=9,817 placebo, n=9,747 CaD) who used personal supplements at baseline.[115] Participants with personal supplement use at baseline: HR, 0.83 (95% CI, 0.67 to 1.02), participants with no personal supplement use HR, 1.17 (95% CI, 0.95 to 1.44), P for interaction=0.02. A similar finding reported by WHI study authors in a different publication; HR for nonusers of any personal supplements at baseline 1.12 (95% CI, 0.90 to 1.39).[97] and for nonuse of personal vitamin D supplements at baseline (p for interaction 0.12).

††† Based on 35,983 women who did not have a prior diagnosis of heart failure at baseline.[117] Subgroups based on risk status defined using American College of Cardiology criteria and based on the presence of hypertension, diabetes mellitus, coronary heart disease, or cardiovascular disease: high risk HR 1.06 (95% CI, 0.90 to 1.24), low risk HR 0.63 (95% CI, 0.46 to 0.87)

‡‡ Events for women on oral hormone therapy were considered secondary. If those events are considered idiopathic, the HR would have been 0.82 (95% CI, 0.64 to 1.06) (Blondon et al, 2015[116]).

§§§ This is the HR reported in Jackson et al, 2003[95] and Prentice et al, 2013[97], a slightly different HR (0.98 (95% CI, 0.91 to 1.05) was reported in Wactawski-Wende et al, 2006.[112]

‖‖‖ Subgroups by age categories: 50–59 years HR 1.02 (95% CI, 0.63 to 1.66), 60–69 years HR 1.01 (95% CI, 0.74 to 1.38), 70–79 years HR 1.24 (95% CI, 0.83 to 1.84). Subgroups by race/ethnicity: white: HR 1.12 (95% CI, 0.88 to 1.42), black: HR 0.85 (95% CI, 0.40 to 1.79), Hispanic: HR 0.84 (95% CI, 0.22 to 3.24), Indian/Alaska Native; NR, Asian or Pacific Islander: NR, Unknown: NR. HR 0.98 (95% CI, 0.90 to 1.05) based on a subgroup of 34,670 women (n=17327 placebo, n=17, 343 CaD) who did not have a prior history of invasive cancer at baseline.[121] As reported in Bolland et al (2011).[96] Based on a subgroup of 15,646 women (n=7,755 placebo, n=7891 for CaD) who did not use personal supplements at baseline and 20,636 (n=10,351 placebo; n=10,285 CaD) women who used personal supplements at baseline, participants with personal supplement use at baseline HR 1.06 (95% CI, 0.97 to 1.17) and participants with no personal supplement use at baseline HR 0.86 (95% CI, 0.78 to 0.96); p for interaction=0.003).[96] As reported in Wactawski-Wende et al (2006)[112], participants with no personal supplement use at baseline HR 0.88 (95% CI, 0.78 to 0.98).

Appendix D Table 3. Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis (KQ 2)

¶¶¶ Based on a subgroup of 15,646 women (n=7,755 placebo, n=7,891 for CaD) who did not use personal supplements at baseline and 20,636 women (n=10,351 placebo, n=10,285 CaD) who used personal supplements at baseline.[96, 112] As reported in Bolland et al (2011)[96], participants with no personal supplement use at baseline HR 0.80 (95% CI, 0.66 to 0.96), participants with personal supplement use at baseline HR 1.12 (95% CI, 0.96 to 1.31), p for interaction=0.005. As reported in Wactawski-Wende et al (2006)[112], participants with no personal supplement use at baseline HR 0.80 (95% CI, 0.66 to 0.96).
As reported in Jackson et al, 2003[95] and Prentice et al, 2013.[97] Wactawski-Wende et al report a slightly different estimate, HR 1.08 (95% CI, 0.86 to 1.34).[112]
**** Based on a subgroup of 15,646 women (n=7,755 placebo, n=7,891 for CaD) who did not use personal supplements at baseline and 20,636 women (n=10,351 placebo, n=10,285 CaD) who used personal supplements at baseline.[96, 112] As reported in Bolland et al[96] participants with no personal supplement use at baseline HR 0.83 (95% CI, 0.60 to 1.15), participants with personal supplement use at baseline HR 1.26 (95% CI, 0.94 to 1.69), p for interaction=0.044. As reported in Wactawski-Wende et al (2006)[112], participants with no personal supplement use at baseline HR 0.80 (95% CI, 0.66 to 0.96).
†††† Participants with no history of nonmelanoma skin cancer HR 1.02 (95% CI, 0.95 to 1.07), participants with history of nonmelanoma skin cancer HR 0.43 (95% CI, 0.21 to 0.90).[120]
‡‡‡‡ As reported by Wactawski-Wende et al, 2006[112] and Wallace et al, 2011.[113] Subgroups by age (P for interaction=0.194): 50–59 years HR 1.06 (95% CI, 0.84 to 1.33), 60–69 years HR 1.34 (95% CI, 1.10 to 1.63), 70–79 years HR 0.99 (95% CI, 0.72 to 1.38). Subgroups by race (P for interaction 0.806): white HR 1.21 (95% CI, 1.04 to 1.41), black HR 1.10 (95% CI, 0.71 to 1.71), Hispanic HR 0.90 (95% CI, 0.50 to 1.62), American Indian HR 0.84 (95% CI, 0.20 to 3.61), Asian/Pacific Islander HR 1.24 (95% CI, 0.49 to 3.17).
§§§§ Cointerventions: Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outside) and consuming 1,300 mg calcium per day using diet and/or supplements
IIII Kidney stones were reported as a reason for dropout and not necessarily a specific harm.
¶¶¶¶ Based on supplemental data supplied by the author.

Abbreviations: ADE=adverse drug events; ARD=absolute risk difference; CI=confidence interval; CVD=cardiovascular disease; ITT=intent to treat; MI=myocardial infarction; NR=not reported; RR=relative risk; SAE=serious adverse event; VTE=venous thromboembolism; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial; WHO GCP=World Health Organization Good Clinical Practice.

Appendix D Table 4. Other Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis

Author, Year Trial Name, No. of Participants	Other Harms Reported*
Aloia et al, 2005[114] Total N=208	AE total: 222 SAE (none were thought to be related to the study): Vitamin D with calcium group: 8 Calcium group: 7
Cherniack et al, 2011[119] Total N=46	No significant differences in adverse events between treatment and control groups, and all were considered unrelated to supplementation. AE resulting in withdrawal: Vitamin D group: 3 (ankle swelling, bradycardia due to sick sinus syndrome, MI) Placebo group: 4 (breast tenderness, cellulitis, atrial fibrillation, MI) AE not resulting in withdrawal: Vitamin D group: 1(diarrhea) Placebo group: 1 (neck pain and chills)
Dawson-Hughes et al, 1997[74] Total N=445	Discontinuations due to side effects: 9 Vitamin D with calcium group: 6 (3 constipation, 1 epigastric distress, 1 sweating, 1 hyper calciuria) Placebo group: 3 (2 epigastric distress, 1 flank pain)
Glendenning et al, 2012[86] Total N=686	Incident type 2 DM: Vitamin D group: 0.3% Placebo group: 0.5%
Hin et al, 2007[110] Total N=305	Serious AEs: Vitamin D 4,000 IU/d: 2.8% Vitamin D 2,000 IU/d: 2.9% Placebo: 2.5% None were considered treatment-related.
Komulainen et al, 1998,[71] Komulainen et al, 1999[118] Osteoporosis Risk Factor and Prevention Study[#] Total N=232	Serious AEs: Vitamin D group: 1 (endometrial hyperplasia) Placebo group: 1 (endometrial hyperplasia)
Lappe et al, 2007[107] Total N=1,180[††]	No SAEs were reported. "No patterns of adverse events were seen among the 3 groups."
Lips et al, 1996[75] Total N=2,578	NR
Peacock et al, 2000[85] Total N=438 randomized (N=393 with baseline values, N= 282 analyzed)	Gastrointestinal distress (mainly constipation) resulting in withdrawal: 12 Vitamin D group: NR Calcium group: 10 Placebo: NR

Appendix D Table 4. Other Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis

Author, Year Trial Name, No. of Participants	Other Harms Reported*
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109] Calcium Intake Fracture Outcome Study Total N=1,460	Total number of AE recorded: 92,000 Constipation was the only AE higher in the treatment group compared with placebo group. Calcium group: 13.4% Placebo group: 9.1% No difference in the number of participants who withdrew due to constipation.
Recker et al, 1996[72] Total N=103 (subgroup of overall participants)	Constipation (did not require study withdrawal) Calcium group: 7 Placebo group: 1
Reid et al, 2006,[87] Bolland et al, 2008[88] Total N=1,471	Constipation: Calcium group: 132 (18%) Placebo: 82 (11%) p=0.0002 Discontinuation of study treatment: Calcium group: 336 Placebo group: 296 p=0.02 Health reasons more often cited as reason for discontinuation in calcium group (n=133) compared with placebo (n=105), p=0.04, and was mostly attributed to constipation.
Reid et al, 1995,[92] Reid et al, 1993[94] Total N=135 randomized; N=122 completed initial trial	Withdrawals due to illness: 6 Of those, 4 were determined to be unrelated to study treatment: nasopharyngeal carcinoma, thyrotoxicosis, rheumatoid arthritis, chronic lymphatic leukemia Of the remaining 2 withdrawals: Calcium group: 1 (kidney stone) Placebo group: 1 dyspepsia
Reid et al, 2008[91] Total N=323	AE: Calcium 600 mg group: 69% Calcium 1,200 mg group: 70% Placebo group: 75% p=0.16 No significant differences in protocol-specified AEs including transient ischemic attack or constipation.
Riggs et al, 1998[73] Total N=236	Discontinuations due to side effects: 16 Calcium group: 10 Placebo group: 6 Excessive gastrointestinal symptoms (abdominal cramping, constipation, bloating, diarrhea) Calcium group: 9 Placebo group: 2 Arthralgia and depression: Calcium group: 0 Placebo group: 1

Appendix D Table 4. Other Harms of Supplementation From RCTs in the Main Analysis and in the Sensitivity Analysis

Author, Year Trial Name, No. of Participants	Other Harms Reported*
Ruml et al, 1999[93] Total N=63	NR
Salovaara et al, 2010[106] Total N=3,432	Discontinuation due to adverse effects:113 Gastrointestinal symptoms: 64 Nausea: 12 Skin reactions: 9
Sanders et al, 2010[83] Total N=2,258 randomized (N=2,256 analyzed)	Number of participants reporting at least one AE: Vitamin D group: 19.7% Placebo group: 17.8% SAE (defined as events requiring hospitalization or death): Vitamin D group: 244 Placebo group: 207 p=0.06 None of the SAEs were considered related to study medication.
Smith et al, 2007[84] Total N=9,440	NR
Trivedi et al, 2003[76] Total N=2,686	NR
WHI Calcium and Vitamin D Trial Total N=36,282	No significant differences in gastrointestinal symptoms: Moderate to severe constipation: Vitamin D with calcium group: 10.3% Placebo group: 8.9% Bloating or gas: Vitamin D with calcium group: 20.4% Placebo group: 19.5%

* Includes outcomes other than all-cause mortality, kidney stones, incident cardiovascular disease and incident cancer, which are reported in Appendix D Table 3.

Abbreviations: AE=adverse events; NR=not reported; SAE=serious adverse events; WHI CaD=Women's Health Initiative.

Appendix E Table 1. Quality Ratings for RCTS, Overall Rating: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	Bias arising from randomization or selection?	Comments
Aloia et al, 2005[114]	Poor	High risk of bias because of high attrition with rare outcome and no harm outcome specification/ ascertainment information; further, some concern for contamination due to varying calcium cointervention received by both study groups.	Yes	No information	Yes	Low	None
Cherniack et al, 2011[119]	Poor	High risk of bias for harms outcomes due no information on specification/ ascertainment of harms and inadequate duration of follow up. Also, high risk of bias due to varying calcium cointervention that some participants in each study group received.	Yes	Yes	Yes	Low	None
Dawson-Hughes et al, 1997[74]	Fair	Some concerns over selection of participants because of lack of information about randomization and allocation concealment and fidelity to intended intervention as only modest adherence at final follow up.	No information	No information	Yes	Uncertain because no information	No information about randomization or allocation concealment.
Glendenning et al, 2012[86]	Poor	High risk of bias for measurement of both fractures (self-reported) and harms and inadequate duration of follow up.	Yes	Yes	Probably yes	Low	Higher proportion of participants with a prior history of falls in the treatment group; this was accounted for in the analysis.
Hin et al, 2017[110]	Fair for all-cause mortality, Poor for others	Some concerns about randomization and harm specification and ascertainment.	Yes	Yes	Probably no	Some concerns	4,000 IU group had higher prevalence of existing heart disease than other two groups.

Appendix E Table 1. Quality Ratings for RCTS, Overall Rating: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	Bias arising from randomization or selection?	Comments
Khaw , Scragg et al, 2017[77, 78]	Good	Low risk of bias across all domains.	Yes	Yes	Yes	Low	None
Komulainen et al, 1998,[71] Komulainen et al, 1999[118]	Fair	Some concerns for bias due to lack of masking and minimal information on harms outcomes specification/ ascertainment (unclear whether based on self-report or clinically validated).	Yes	Yes	Yes	Low	None
Lappe et al, 2007[107]	Good for cancer; fair for kidney stones	Low risk of bias across all domains for the cancer outcomes, some concerns in measurement domain for kidney stone outcome.	Yes	No information	Probably yes	Low	Allocation concealment NR.
Lappe et al, 2017[108]	Fair	Some concerns related to departures from intended intervention and modest adherence.	Yes	Yes	Yes	Low	
Larsen et al, 2004[163]	Poor	High risk of bias introduced by the nonmasked intervention and low participation rates in the intervention. The results presented in the paper do not represent effect estimates of the individual four study groups and it is not possible to extract effect estimates for our interventions of interest apart from the environmental interventions that were also implemented. Also, fractures (except for hip) were self-reported. Some concerns related to selection bias because of the cluster randomization and failure to demonstrate equivalence of groups at baseline.	No information	No information	Probably yes	Some concerns	Few details regarding the cluster randomization and whether important geographic differences in the community may have led to important baseline differences; unable to assess baseline differences in groups between the two intervention arms of interest to this review.

Appendix E Table 1. Quality Ratings for RCTS, Overall Rating: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	Bias arising from randomization or selection?	Comments
Lips et al, 1996[75]	Fair	Some concerns due to contamination and modest adherence for both benefits and harms outcomes. Peripheral fractures were self-reported and not clinically validated.	Yes	Yes	Yes	Low	None
Peacock et al, 2000[85]	Poor	High risk of bias due to very high attrition, also some concerns because of lack of information about randomization/allocation concealment, fidelity to intervention, and specification/ascertainment of outcomes.	No information	No information	Yes	Some concerns	No description of randomization or allocation concealment.
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109]	Fair†	Some concerns because adherence to study medication was low.	Yes	Yes	Yes	Low	None
Recker et al, 1996[72]	Fair for Benefits Poor for Harms	Some concerns due to borderline high attrition, modest fidelity to intervention, and lack of information about randomization/assignment. For harms, no information about outcome specification/ascertainment.	No information	No information	Probably yes	Some concerns	No description of randomization or allocation concealment.
Reid et al, 1993,[94] Reid et al, 1995[92]	Poor	High risk of bias due to attrition and measurement of fractures as unclear whether self-reported or clinically validated. Also, some concerns for bias due to poorly specified harm measures in and uncertainty in selection bias domain because of missing information.	No information	No information	Yes	Uncertain as NR	None

Appendix E Table 1. Quality Ratings for RCTS, Overall Rating: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	Bias arising from randomization or selection?	Comments
Reid et al, 2006,[87] Bolland et al, 2008[88]	Fair	Some concerns for bias due to modest adherence.	Yes	Yes	Yes	Low	None
Reid et al, 2008[91]	Poor for Benefits Fair for Harms	High risk of bias in measurement of fractures as outcome not prespecified and was collected as an 'adverse event'; most were the result of substantial trauma and unclear whether clinically validated. Some concerns in measurement domain for harms due to no information on outcome specification/ ascertainment.	Yes	Yes	Yes	Low	None
Riggs et al, 1998[73]	Fair	Some concerns because of borderline high attrition and no information about how missing data for those with incomplete data were handled. Also, some concerns due to modest adherence.	No information	No information	Yes	Low	No information about randomization or allocation concealment.
Ruml et al, 1999[93]	Poor	High risk of bias from high overall attrition and differential attrition and lack of ITT analysis. Some concerns over lack of information about randomization and allocation concealment and intervention adherence.	No information	No information	Probably yes	Uncertain because no information	No information about randomization or allocation concealment.

Appendix E Table 1. Quality Ratings for RCTS, Overall Rating: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	Bias arising from randomization or selection?	Comments
Salovaara et al, 2010[106]	Poor	High risk of bias across multiple domains, including selection bias (lack of allocation concealment with open label trial and evidence of group imbalances at baseline), departure from intended interventions as personal use of supplements allowed by control group and increased over study duration.	Yes	No information	Probably no	High	Potential for bias given lack of allocation concealment in this open-label trial; some imbalances at baseline, but these were adjusted for in the analysis. 15 people in control group died after randomization but before start of trial. None died in intervention group before start. This suggests groups were not balanced at baseline.
Sanders et al, 2010[83]	Good for Benefits Good for all-cause mortality; fair for incident CVD and cancer	No risk of bias concerns in any domain for benefits outcomes. Some risk of bias concerns for some harms outcomes because of limited information on outcome specification/ascertainment.	Yes	Yes	Yes	Low	None
Smith et al, 2007[84]	Fair	Some concerns over attrition, and fidelity of intervention as this intervention could span from 1 to 3 annual doses over 3 years.	Yes	Yes	Yes	Low	None
Trivedi et al, 2003[76]	Fair	Some concerns because of study attrition, no information about randomization/ allocation concealment, departure from intended intervention due to use of supplements outside the study, and self-reported outcomes though most participants were physicians.	No information	No information	Yes	Uncertain because no information	No information about randomization or allocation concealment.

Appendix E Table 1. Quality Ratings for RCTS, Overall Rating: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	Bias arising from randomization or selection?	Comments
Women's Health Initiative Calcium and Vitamin D Trial Jackson et al, 2003,[95] Jackson et al, 2006,[70] Wactawski-Wende et al, 2006,[112] LaCroix et al, 2009,[111] Bolland et al, 2011,[115] Bolland et al, 2011,[96] Brunner et al, 2011,[121] Tang et al, 2011,[120] Wallace et al, 2011,[113] Prentice et al, 2013,[97] Robbins et al, 2014,[98] Blondon et al, 2015,[116] Donneyong et al, 2015[117]	Fair	Some concerns for bias as adherence to study intervention was modest, and personal use of supplements was allowed throughout the trial. Also, some concerns for bias in harms outcomes due to limited information on outcome specification/ ascertainment.	Yes	No information	Yes	Low	No information about allocation concealment.

* This is the overall study quality rating, which reflects the risk of bias across multiple domains, including selection bias, bias from missing data, bias from departures from intended intervention, measurement bias, and reporting bias. Each part of Tables 1 through 8 include a domain specific risk of bias assessment.
† All outcomes reported after 9.5 years of followup were not considered eligible as these outcomes represent 5 years of a randomized trial followed by 4.5 years of observation during which participants were not required to stay with assigned treatment, and no information is available about calcium use or nonuse during these additional 4.5 years.

Abbreviations: CVD=cardiovascular diseases; ITT=intent-to-treat; NR=not reported.

Appendix E Table 2. Quality Ratings for RCTs: Part 2

Author, Year, Trial Name	What were the overall attrition, attrition by group, and variation in attrition by outcome?	Did the study have low attrition?	Are the proportion of participants and reasons for data similar across interventions?	For benefits outcomes, was intent to treat analysis used?	Were appropriate statistical methods used to account for missing data?	Bias arising from missing outcome data?	Comments
Aloia et al, 2005[114]	Overall: (30+30)/208=28.8% Placebo: 30/104=28.8% Vit D: 30/104=28.8%	No	Yes	NA	Probably yes	High	High attrition with a rare outcome, no evidence of differential attrition.
Cherniack et al, 2011[119]	Overall: 12/46=26% for efficacy results only, safety results have 0% attrition	Yes for safety endpoints, No for efficacy endpoints	No information	NA	No information	Low	Although the study had somewhat high attrition for efficacy endpoints, safety results presented are for the entire study population consented and randomized, thus are likely low risk of bias.
Dawson-Hughes et al, 1997[74]	Overall: 56/445=12.6% Placebo: NR Vit D & Calcium: NR	Probably yes	No information	Yes	Probably yes	Low	Attrition by groups was NR.
Glendenning et al, 2012[86]	Overall: 48/686=7.0% Placebo: 22/333=6.2% Vit D: 26/353=7.8%	Yes	Yes	Yes	Yes	Low	None
Hin et al, 2017[110]	Overall: 15/305=4.9% Placebo: 6/101= 5.9% 4,000 IU/d: 5/102=4.9% 2,000 IU/d: 4/102=3.9%	Yes	Yes	NA	Probably yes	Low	
Khaw, Scragg et al, 2017[77, 78]	Placebo: 2/2552=0.1% Vit D: 0/2558=0%	Yes	Yes	Yes	Yes	Low	None

Appendix E Table 2. Quality Ratings for RCTs: Part 2

Author, Year, Trial Name	What were the overall attrition, attrition by group, and variation in attrition by outcome?	Did the study have low attrition?	Are the proportion of participants and reasons for data similar across interventions?	For benefits outcomes, was intent to treat analysis used?	Were appropriate statistical methods used to account for missing data?	Bias arising from missing outcome data?	Comments
Komulainen et al, 1998,[71] Komulainen et al, 1999[118]	Overall: 6/232=2.6% Calcium: 3/116=2.6% Vit D & Calcium: 3/116=2.6%	Yes	Yes	Yes	Probably yes	Low	None
Lappe et al, 2007[107]	Overall: 156/1,180=13.2% Attrition by group NR	Yes	No information	Yes	Yes	Low	None
Lappe et al, 2017[108]	Overall: 106/2,303=4.6% Placebo: 52/1,147=4.5% Vit D/Calcium 54/1,156=4.7%	Yes	Yes	Yes	No information	Low	None
Larsen et al, 2004[163]	NR by study group, but overall 17.4% died. 6 participants left the city during follow up	Yes	No information	Yes	Yes	Low	Use of hospital registration database for outcome, thus risk of missing outcome data is probably low.
Lips et al, 1996[75]	Placebo: 7/1287=0.5% Vit D: 7/1291=0.5%	Yes	Yes	Yes	Yes	Low	Loss to follow up was low overall and within each group. However, authors reported that only 63% of participants completed 3 years of the study: 18% died and 18% stopped treatment.
Peacock et al, 2000[85]	Overall: 236/437=54%; Placebo: 61/129=47% Vit D: 69/124=55.6%; Calcium: 71/124=57.3%.	No	Yes	Probably yes	Probably yes	High	46% overall attrition, and signal of some differential attrition between placebo and treatment groups, although not statistically significant.

Appendix E Table 2. Quality Ratings for RCTs: Part 2

Author, Year, Trial Name	What were the overall attrition, attrition by group, and variation in attrition by outcome?	Did the study have low attrition?	Are the proportion of participants and reasons for data similar across interventions?	For benefits outcomes, was intent to treat analysis used?	Were appropriate statistical methods used to account for missing data?	Bias arising from missing outcome data?	Comments
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109]	Overall: 232/1460=15.9% Placebo: 119/730=16.3% Calcium: 113/730=15.5% Specific to Zhu et al, 2008[109]: Overall: 13/120=10.8% Placebo: 5/41=12.2% Calcium: 2/40=5% Calcium & Vit D: 6/40=15%	Yes	Yes	Yes	Probably yes	Low	None
Recker et al, 1996[72]	Overall attrition: 54/251=22% Differential attrition: NR	Probably no	No information	Yes	Yes	Some concerns	Borderline high overall attrition; intent to treat analysis used, but a sizable proportion of participants screened as eligible declined to participate, introducing some risk for selection bias.
Reid et al, 1993,[94] Reid et al, 1995[92]	Original trial: 13/135=9.6% Extension trial: 8/86=9.3% Overall attrition: 57/135=42% Cannot judge attrition by group because the N originally randomized and the N agreeing to extension trial is not provided by group	Probably yes	No information	Yes	No information	High	Attrition for original trial and attrition limited to extension phase are both low. However, a proportion of participants did not reconsent to the extension trial, so if that loss is considered, overall attrition is high.

Appendix E Table 2. Quality Ratings for RCTs: Part 2

Author, Year, Trial Name	What were the overall attrition, attrition by group, and variation in attrition by outcome?	Did the study have low attrition?	Are the proportion of participants and reasons for data similar across interventions?	For benefits outcomes, was intent to treat analysis used?	Were appropriate statistical methods used to account for missing data?	Bias arising from missing outcome data?	Comments
Reid et al, 2006,[87] Bolland et al, 2008[88]	Overall: 216/1471=14.7% Placebo: 104/739=14.1% Calcium: 112/732=15.3%	Yes	No information	Yes	Probably yes	Low	ITT analyses run with and without imputation (maximum likelihood) of missing values, and with and without adjustment for compliance.
Reid et al, 2008[91]	Overall: 14/323=4.3% Placebo: 3/107=2.8% 600 mg Calcium: 2/108=1.9% 1,200 mg Calcium: 9/108=8.3%	Yes	Probably yes	Yes	Yes	Low	Compared with the other groups, in the 1,200-mg calcium group, a slightly higher number of participants did not complete follow up.
Riggs et al, 1998[73]	Overall: 59/236=25.0% Placebo: 28/117=23.9% Calcium: 30/119=25.2%	No	No information	Yes	No information	Some concerns	High attrition overall and no information about how missing data were handled regarding fractures for participants with incomplete follow up.
Ruml et al, 1999[93]	Overall: 18/63=28.6% Placebo: 6/34=17.6% Calcium: 12/29=41.4%	No	Probably yes	No information	No information	High	Moderate attrition and evidence of differential attrition. Also unclear whether ITT analysis was used.
Salovaara et al, 2010[106]	Overall: 237/3,432=6.9% Control: 105/1,714=6.5% Vit D & Calcium: 132/1,718=7.7%	Yes	Yes	Yes	Yes	Low	None
Sanders et al, 2010[83]	Placebo: 110/1,125=9.8% Vit D: 116/1,131=10.3%	Yes	Yes	Yes	Yes	Low	None

Appendix E Table 2. Quality Ratings for RCTs: Part 2

Author, Year, Trial Name	What were the overall attrition, attrition by group, and variation in attrition by outcome?	Did the study have low attrition?	Are the proportion of participants and reasons for data similar across interventions?	For benefits outcomes, was intent to treat analysis used?	Were appropriate statistical methods used to account for missing data?	Bias arising from missing outcome data?	Comments
Smith et al, 2007[84]	Unable to calculate; participants were recruited over 3 years. Therefore, not all contributed to the analysis at all time points. Appears that 71% of those recruited in first year contributed to the analysis at 36 months	No information	Yes	Yes	Probably yes	Some concerns	Unable to determine attrition given rolling recruitment over the 3-year study period, and unclear whether the figures describing the number of participants that did not return questionnaires are unique participants or include the same participants.
Trivedi et al, 2003[76]	Overall: 631/2,686=23.5% Placebo: 324/1,341=24.2% Vit D: 307/1,345=22.8% Taking into account those who died, only 6% did not complete for another reason	Probably yes	Probably yes	Yes	No information	Some concerns	Study attrition nearly a quarter of the randomized population, mostly due to deaths that were adjudicated centrally, no evidence of differential attrition. Authors reported no significant differences between participants who completed 5 years and those who discontinued questionnaire follow up.

Appendix E Table 2. Quality Ratings for RCTs: Part 2

Author, Year, Trial Name	What were the overall attrition, attrition by group, and variation in attrition by outcome?	Did the study have low attrition?	Are the proportion of participants and reasons for data similar across interventions?	For benefits outcomes, was intent to treat analysis used?	Were appropriate statistical methods used to account for missing data?	Bias arising from missing outcome data?	Comments
Women's Health Initiative Calcium and Vitamin D Trial Jackson et al, 2003,[95] Jackson et al, 2006,[70] Wactawski-Wende et al, 2006,[112] LaCroix et al, 2009,[111] Bolland et al, 2011,[115] Bolland et al, 2011,[96] Brunner et al, 2011,[121] Tang et al, 2011,[120] Wallace et al, 2011,[113] Prentice et al, 2013,[97] Robbins et al, 2014,[98] Blondon et al, 2015,[116] Donneyong et al, 2015[117]	Overall: 2,531/36,282=7.0% Placebo: 1,291/18,106=7.1% Vit D & Calcium: 1,240/18,176=6.8%	Yes	Yes	Yes	Yes	Low	None

Abbreviations: ITT=intent to treat; N=number; NA=not applicable; NR=not reported.

Appendix E Table 3. Quality Ratings for RCTs: Part 3

Author, Year, Trial Name	Were the participants unaware of their intervention status?	Were the trial personnel and clinicians unaware of the intervention status of participants?	Were outcome assessors unaware of the intervention status of participants?	Was intervention fidelity adequate (specifically adherence)?	Were cross-overs or contamination minimal such that it would not raise concern for bias?	Bias arising from departures from intended interventions?	Comments
Aloia et al, 2005[114]	Yes	Yes	Probably yes	Probably yes	Probably no	Some concerns	Mean adherence by pill count was 87.5% (SD 8%); participants in both study groups were given unknown, individually tailored dose of calcium supplements to achieve total daily intake of 1,200–1,500 mg.
Cherniack et al, 2011[119]	Yes	Yes	Yes	Probably no	No	High	19 participants in the treatment group and 22 in the control group with inadequate calcium intake (>1,200 mg/d) were given supplements to ensure adequate calcium intake.
Dawson-Hughes et al, 1997[74]	Yes	Yes	Yes	Yes	Yes	Some concerns	Participants instructed to avoid personal use of supplements. Adherence based on pill counts was ≥90% among participants who completed the study. 71.4% of those randomized were still taking study drug at follow up.
Glendenning et al, 2012[86]	Yes	Yes	Yes	Yes	Yes	Low	Medication was administered during clinic visits, so adherence was 100%.
Hin et al 2017[110]	Yes	Yes	No	Yes	Yes	Low	Vit D use <400 IU was allowed, but intervention doses were quite high (4,000 and 2,000 IU); thus, very little potential of contamination in placebo group by low levels of vitamin D use outside of study protocol.
Khaw, Scragg et al, 2017[77, 78]	Yes	Yes	Yes	Yes	No information	Low	Unclear whether continued use of personal supplements was allowed during study, but a relatively low proportion were using supplements at baseline so this is unlikely to result in serious bias.
Komulainen et al, 1998,[71] Komulainen et al, 1999[118]	Probably no	Probably no	No information	Yes	Yes	Some concerns	Study was described as "open" following randomization, suggesting that masking was not used. Approximately 10% of participants in both groups did not adhere to study medication.
Lappe et al, 2007[107]	Yes	Yes	No information	Yes	No information	Low	Mean adherence (defined as ≥80% of doses) was 85.7% for vitamin D (and its placebo) and 74.4% for calcium (and its placebo).
Lappe et al, 2017[108]	Yes	Yes	Yes	Probably yes	Probably no	Some concerns	Only moderate levels of adherence, and personal supplement use was allowed during the study.

Appendix E Table 3. Quality Ratings for RCTs: Part 3

Author, Year, Trial Name	Were the participants unaware of their intervention status?	Were the trial personnel and clinicians unaware of the intervention status of participants?	Were outcome assessors unaware of the intervention status of participants?	Was intervention fidelity adequate (specifically adherence)?	Were cross-overs or contamination minimal such that it would not raise concern for bias?	Bias arising from departures from intended interventions?	Comments
Larsen et al, 2004[163]	Probably no	No information	No information	Probably no	No information	High	55.7% of those offered the vitamin D/calcium-only intervention agreed to participate. Different rates of uptake of the intervention in each study group (47.8% in the 2,532 residents who were offered the pure Environment and Health Program, 55.7% in the 2,426 residents offered the pure Calcium and Vitamin D Program, and 45.0% in the 2,531 residents offered both programs), creating the potential for unmeasured confounding. When combined with likely differences in baseline, it is possible that baseline characteristics predicted uptake and outcomes.
Lips et al, 1996[75]	Yes	Yes	No information	Probably yes	Probably yes	Some concerns	18% of placebo group and of treatment group had stopped taking study drug by year 3. Similar proportions of participants in each group took vitamin or multivitamin supplements at two or more follow up visits.
Peacock et al, 2000[85]	Yes	Yes	No information	No information	No information	Some concerns	None
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109]	Yes	Yes	No information	No	No information	Some concerns	Adherence was 56.8% (defined as at least 80% adherent to study drug). No significant difference in adherence between placebo (56.1%) and calcium (57.5%). Zhu et al, 2008[109]: adherence rates similar across groups, ranging from 80% to 89%
Recker et al, 1996[72]	Yes	Yes	Yes	No	Yes	Some concerns	Median adherence was 64%, but no evidence of differential attrition.
Reid et al, 1993,[94] Reid et al, 1995[92]	Yes	Yes	No information	Probably yes	No information	Low	Adherence: Original trial: Placebo: 83% Calcium: 84%
Reid et al, 2006,[87] Bolland et al, 2008[88]	Yes	Yes	Probably yes	Probably yes	Probably no	Some concerns	Adherence by those remaining at end of trial was 85% overall. However, across entire study period, adherence was 55% in calcium group and 58% in placebo group.

Appendix E Table 3. Quality Ratings for RCTs: Part 3

Author, Year, Trial Name	Were the participants unaware of their intervention status?	Were the trial personnel and clinicians unaware of the intervention status of participants?	Were outcome assessors unaware of the intervention status of participants?	Was intervention fidelity adequate (specifically adherence)?	Were cross-overs or contamination minimal such that it would not raise concern for bias?	Bias arising from departures from intended interventions?	Comments
Reid et al, 2008[91]	Yes	Yes	No information	Yes	Yes	Low	Adherence by participants remaining at the end of follow up: Placebo: 93% Group 2: 91% Group 3: 86%
Riggs et al, 1998[73]	Yes	Yes	No information	Yes	No information	Some concerns	Mean dose based on tablet count was 1,234 mg/day, approximately 75% adherence.
Ruml et al, 1999[93]	Yes	Probably Yes	No information	No information	No information	Some concerns	No information about adherence to study drug.
Salovaara et al, 2010[106]	No	No	No information	Yes	Probably no	High	Open-label study, participants and investigators were not masked. Participants in control group were allowed to continue personal use of supplements, intake of vitamin D in control group increased from 3.8% to 16.1% over follow up. Mean adherence in intervention group was 78%.
Sanders et al, 2010[83]	Yes	Yes	No information	Yes	Probably yes	Low	Adherence with taking annual dose confirmed for all participants, other than those for whom dose withheld or dose declined. At study end: Placebo: 6% were taking more than 400 IU of vitamin D Vit D: 3% were taking more than 400 IU of vitamin D
Smith et al, 2007[84]	Yes	Yes	Probably yes	No	Yes	Some concerns	Study designed to provide an annual dose of vitamin D, but recruitment was over 3 years, so participants received between 1 and 3 annual doses depending on when they were recruited. Dose was administered by nursing staff.
Trivedi et al, 2003[76]	Yes	Yes	Probably Yes	Probably yes	No information	Some concerns	76% of participants took at least 80% of study drugs. No information about personal use of supplements at baseline or throughout study. Participants were told to continue any usual drug treatment and any new drugs that were advised. If they were advised to start vitamin D of >200 IU daily, they discontinued the trial intervention but continued to be followed.

Appendix E Table 3. Quality Ratings for RCTs: Part 3

Author, Year, Trial Name	Were the participants unaware of their intervention status?	Were the trial personnel and clinicians unaware of the intervention status of participants?	Were outcome assessors unaware of the intervention status of participants?	Was intervention fidelity adequate (specifically adherence)?	Were cross-overs or contamination minimal such that it would not raise concern for bias?	Bias arising from departures from intended interventions?	Comments
Women's Health Initiative Calcium and Vitamin D Trial Jackson et al, 2003,[95] Jackson et al, 2006,[70] Wactawski-Wende et al, 2006,[112] LaCroix et al, 2009,[111] Bolland et al, 2011,[115] Bolland et al, 2011,[96] Brunner et al, 2011,[121] Tang et al, 2011,[120] Wallace et al, 2011,[113] Prentice et al, 2013,[97] Robbins et al, 2014,[98] Blondon et al, 2015,[116] Donneyong et al, 2015[117]	Yes	Yes	Yes	Probably yes	Probably no	Some concerns	At the end of the trial, 76% were taking study drug, and 59% took 80% or more of it. Participants did not have to discontinue use of personal vitamin D or calcium supplements and concurrent use of calcium (up to 1,000 mg/day) and vitamin D (up to 600 IU per day) was allowed throughout the intervention.

Abbreviations: IU=international units, mg=milligram, SD=standard deviation.

Appendix E Table 4. Quality Ratings for RCTs: Part 4

Author, Year, Trial Name	Were benefit outcomes (e.g., fractures) adequately described, prespecified, valid, and reliable?	Were similar techniques used among groups to ascertain benefit outcomes?	Was the duration of follow up adequate to assess benefit outcomes?	Bias arising from measurement of benefit outcomes?	Comments
Aloia et al, 2005[114]	NA	NA	NA	NA	NA
Cherniack et al, 2011[119]	NA	NA	NA	NA	NA
Dawson-Hughes et al, 1997[74]	Yes	Yes	Yes	Low	Measures include total nonvertebral fractures and a subset of fractures deemed to be osteoporotic. Fractures confirmed by x-ray or hospital records.
Glendenning et al, 2012[86]	No	Yes	Probably no	High	Fractures were self-reported, were not specific to site or cause (traumatic vs. osteoporotic), no radiographic/clinical validation, and time period of follow up (9 months) may be too short to see benefit.
Hin et al, 2017[110]	NA	NA	NA	NA	NA
Khaw, Scragg et al, 2017[77, 78]	Yes	Yes	Yes	Low	None
Komulainen et al, 1998,[71] Komulainen et al, 1999[118]	Yes	Yes	Yes	Low	Self-reported fractures were validated by medical record.
Lappe et al, 2007[107]	NA	NA	NA	NA	NA
Lappe et al, 2017[108]	NA	NA	NA	NA	NA
Larsen et al, 2004[163]	Yes	Yes	Yes	Low	None
Lips et al, 1996[75]	Probably yes	Yes	Yes	Varies by outcome	Low for hip fracture, high for other fractures since based on self-report and not clinically validated.
Peacock et al, 2000[85]	Yes	Yes	Yes	Low	None
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109]	Yes	Yes	Yes	Low	None
Recker et al, 1996[72]	Probably no	Yes	Yes	Some concerns	Self-reported fractures were confirmed with radiographs in the extension trial, but no information about how fractures were defined or whether confirmed in the original trial.

Appendix E Table 4. Quality Ratings for RCTs: Part 4

Author, Year, Trial Name	Were benefit outcomes (e.g., fractures) adequately described, prespecified, valid, and reliable?	Were similar techniques used among groups to ascertain benefit outcomes?	Was the duration of followup adequate to assess benefit outcomes?	Bias arising from measurement of benefit outcomes?	Comments
Reid et al, 1993,[94] Reid et al, 1995[92]	No	Yes	Yes	High	Fractures other than vertebral, not defined and not specified as to whether self-reported or confirmed radiographically.
Reid et al, 2006,[87] Bolland et al, 2008[88]	Yes	Yes	Yes	Low	None
Reid et al, 2008[91]	No	Yes	Yes	High	Fracture outcomes not specified as to site, authors report that "except for toe fractures, all fractures occurred after substantial trauma." Adverse events were elicited from patients based on symptoms; fractures were not specifically elicited from participants during study visits, unclear whether radiographically or clinically confirmed.
Riggs et al, 1998[73]	Yes	Yes	Yes	Low	None
Ruml et al, 1999[93]	Probably yes	Yes	Yes	Low	Vertebral morphometric fractures as ascertained by spine radiographs.
Salovaara et al, 2010[106]	Yes	Yes	Yes	Low	Self-reported fractures were validated by medical records or radiologic reports.
Sanders et al, 2010[83]	Yes	Yes	Yes	Low	Fractures were radiologically validated.
Smith et al, 2007[84]	Yes	Yes	Yes	Low	None
Trivedi et al, 2003[76]	Probably yes	Yes	Yes	Low	Fractures were self-reported, although authors suggested that physicians (who comprised the majority of participants) were a reliable source of self-reported fracture data. The authors found no differences between physician participants and nonphysician participants in terms of outcome reporting.

Appendix E Table 4. Quality Ratings for RCTs: Part 4

Author, Year, Trial Name	Were benefit outcomes (e.g., fractures) adequately described, prespecified, valid, and reliable?	Were similar techniques used among groups to ascertain benefit outcomes?	Was the duration of followup adequate to assess benefit outcomes?	Bias arising from measurement of benefit outcomes?	Comments
WHI CaD Jackson et al, 2003,[95] Jackson et al, 2006,[70] Wactawski-Wende et al, 2006,[112] LaCroix et al, 2009,[111] Bolland et al, 2011,[115] Bolland et al, 2011,[96] Brunner et al, 2011,[121] Tang et al, 2011,[120] Wallace et al, 2011,[113] Prentice et al, 2013,[97] Robbins et al, 2014,[98] Blondon et al, 2015,[116] Donneyong et al, 2015[117]	Yes	Yes	Yes	Low	Total fractures were all clinical fractures other than those of ribs, sternum, skull, or face. Fractures were verified radiographically or through operative reports by centrally trained and blinded physician adjudicators at each site; hip fractures were verified by centralized adjudicators.

Abbreviations: NA=not applicable; vs.=versus; WHI CaD=Women's Health Initiative Calcium and Vitamin D Study.

Appendix E Table 5. Quality Ratings for RCTs: Part 5

Author, Year, Trial Name	Were harms outcomes adequately described, valid, and reliable?	Were similar techniques used among groups to ascertain harms outcomes?	Was the duration of follow up adequate to assess harms outcomes?	Bias arising from measurement of harms outcomes?	Comments
Aloia et al, 2005[114]	No information	No information	Yes	Uncertain because no information	Study does not describe how incidents of kidney stones are specified or ascertained.
Cherniack et al, 2011[119]	No information	No information	Probably no	High	Study does not describe how incidents of myocardial infarction are ascertained, no baseline characteristics about study population's risk for CVD or CVD risk factors, and the follow up time period (6 months) may not be long enough to observe this harm.
Dawson-Hughes et al, 1997[74]	NA	NA	NA	NA	NA
Glendenning et al, 2012[86]	Probably no	Yes	Probably no	High	Adverse events were self-reported in a diary with no clinical validation. Short time period to assess incident cancer and CVD (9 months). Observed harms were likely because of high baseline risk of disease (i.e., undiagnosed asymptomatic cancer or coronary arterial blockages) that became symptomatic during follow up.
Hin et al, 2017[110]	Probably yes	Yes	Probably no	Some concerns	12 months may not be adequate to evaluate harms with longer induction periods (CVD and cancer). Only all-cause mortality and the serious adverse event outcome were adequately specified for inclusion in this review.
Khaw, Scragg et al, 2017[77, 78]	Probably yes	Yes	Yes	Low	None
Komulainen et al, 1998,[71] Komulainen et al, 1999[118]	Probably no	Yes	Yes	Some concerns	No information about whether harms measured were clinically verified or based on self-report.
Lappe et al, 2007[107]	Varies by outcome	Yes	Yes	Varies by outcome	No information about how kidney stones outcome was specified or ascertained, thus some concerns for this outcome.
Lappe et al, 2017[108]	Yes	Yes	Yes	Low	None
Larsen et al, 2004[163]	NA	NA	NA	NA	NA
Lips et al, 1996[75]	Probably yes	Yes	Yes	Low	None

Appendix E Table 5. Quality Ratings for RCTs: Part 5

Author, Year, Trial Name	Were harms outcomes adequately described, valid, and reliable?	Were similar techniques used among groups to ascertain harms outcomes?	Was the duration of follow up adequate to assess harms outcomes?	Bias arising from measurement of harms outcomes?	Comments
Peacock et al, 2000[85]	No	Yes	Yes	Some concerns	No information on how kidney stones were specified or ascertained and data not explicitly provided by groups.
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109]	Probably no	Yes	Yes	Some concerns	Incident cancer, vascular disease, and kidney stone outcomes are self-reported by participants during follow up visits with a health care provider. No description of outcome ascertainment and whether clinically validated.
Recker et al, 1996[72]	No	No information	Yes	Uncertain because no information	Unclear how instances of kidney stones are specified or ascertained.
Reid et al, 1993,[94] Reid et al, 1995[92]	Probably no	Yes	Yes	Some concerns	Harms not specified, but rather reported as adverse events and/or reasons for dropout.
Reid et al, 2006,[87] Bolland et al, 2008[88]	Probably yes	Yes	Yes	Low	Systematic adjudication of most self- and family-reported harms, including cardiovascular events and all-cause mortality.
Reid et al, 2008[91]	Probably no	Yes	Yes	Some concerns	Harms outcomes not well specified, and method of ascertainment relied on patients to self-report symptoms or events vs. a systematic assessment of various harms.
Riggs et al, 1998[73]	No information	Yes	Yes	Low	None
Ruml et al, 1999[93]	NA	NA	NA	NA	NA
Salovaara et al, 2010[106]	Yes	Yes	Yes	Low	None
Sanders et al, 2010[83]	Varies by outcome	Yes	Yes	Varies by outcome	Low for all-cause mortality, some concerns for incident CVD and cancer, since not defined and not clear whether based on self-report or clinically validated with medical record review.
Smith et al, 2007[84]	NA	NA	NA	NA	NA
Trivedi et al, 2003[76]	Probably yes	Yes	Yes	Some concerns	Other than all-cause mortality and incident of selected conditions resulting in death, all harms were ascertained via self-reported questionnaire.

Appendix E Table 5. Quality Ratings for RCTs: Part 5

Author, Year, Trial Name	Were harms outcomes adequately described, valid, and reliable?	Were similar techniques used among groups to ascertain harms outcomes?	Was the duration of followup adequate to assess harms outcomes?	Bias arising from measurement of harms outcomes?	Comments
Women's Health Initiative Calcium and Vitamin D Trial Jackson et al, 2003,[95] Jackson et al, 2006,[70] Wactawski-Wende et al, 2006,[112] LaCroix et al, 2009,[111] Bolland et al, 2011,[115] Bolland et al, 2011,[96] Brunner et al, 2011,[121] Tang et al, 2011,[120] Wallace et al, 2011,[113] Prentice et al, 2013,[97] Robbins et al, 2014,[98] Blondon et al, 2015,[116] Donneyong et al, 2015[117]	Yes	Yes	Yes	Low*	Kidney stone incidence was based on self-report,[113] not validated by clinical records. Skin cancer was self-reported[120]; validity of self-report of skin cancer is high.[164, 165] Cancers based on central physician adjudicators masked to randomization status.[121] Approximately half of VTE outcomes were adjudicated; validity of self-reported VTE outcomes was assessed and was found to be valid.[116] Central adjudication of medical records for heart failure outcomes.[117]

* Some concerns for kidney stone outcomes reported in Wallace et al, 2011,[113] VTE outcomes reported in Blondon et al, 2015,[116] and heart failure outcomes reported in Donneyong et al, 2015.[117]

Abbreviations: CVD=cardiovascular disease; NA=not applicable; vs.=versus; VTE=venous thromboembolism.

Appendix E Table 6. Quality Ratings for RCTs: Part 6

Author, Year, Trial Name	Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments
Aloia et al, 2005[114]	Yes	Low	None
Cherniack et al, 2011[119]	Yes	Low	None
Dawson-Hughes et al, 1997[74]	Yes	Low	None
Glendenning et al, 2012[86]	Yes	Low	None
Hin et al, 2017[110]	Yes	Low	None
Khaw, Scragg et al, 2017[77, 78]	Yes	Low	None
Komulainen et al, 1998,[71] Komulainen et al, 1999[118]	Yes	Low	None
Lappe et al, 2007[107]	No	See comment	This study's primary aim was fracture incidence per its trial registry but these outcomes have not been published to date. Per personal communication with the study author, no effect on fracture incidence was observed and study contamination due to uptake by of alendronate (which came to market during the study) was suggested as a reason.
Lappe et al, 2017[108]	Yes	Low	None
Larsen et al, 2004[163]	Yes	Low	None
Lips et al, 1996[75]	Yes	Low	None
Peacock et al, 2000[85]	Yes	Low	None
Prince et al, 2006,[89] and Lewis et al, 2011[90] and Zhu et al, 2008[109]	Yes	Low	None
Recker et al, 1996[72]	Yes	Low	None
Reid et al, 1993,[94] Reid et al, 1995[92]	Yes	Low	None
Reid et al, 2006,[87] Bolland et al, 2008[88]	Yes	Low	None
Reid et al, 2008[91]	Yes	Low	None
Riggs et al, 1998[73]	Yes	Low	None
Ruml et al, 1999[93]	Yes	Low	None
Salovaara et al, 2010[106]	Yes	Low	None
Sanders et al, 2010[83]	Yes	Low	None
Smith et al, 2007[84]	Yes	Low	None
Trivedi et al, 2003[76]	Probably no	Some concerns	Multiple fracture outcomes reported, which are multiple variations of the same types of fractures.

Appendix E Table 6. Quality Ratings for RCTs: Part 6

Author, Year, Trial Name	Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments
Women's Health Initiative Calcium and Vitamin D Trial Jackson et al, 2003,[95] Jackson et al, 2006,[70] Wactawski-Wende et al, 2006,[112] LaCroix et al, 2009,[111] Bolland et al, 2011,[115] Bolland et al, 2011,[96] Brunner et al, 2011,[121] Tang et al, 2011,[120] Wallace et al, 2011,[113] Prentice et al, 2013,[97] Robbins et al, 2014,[98] Blondon et al, 2015,[116] Donneyong et al, 2015[117]	Yes/Probably yes	Low	Subgroups analyzed in Robbins et al (2014) appear to have been preplanned.[98] Rationale and biologic bases for the post hoc subgroup analyses seem sound.[96, 115]

Abbreviations: KQ=key question; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial.

Appendix E Table 7. Quality Ratings for Observational Studies: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating
Ahn et al, 2007[166]	Poor	High risk of bias due to selection bias, confounding, missing data, measurement of exposure, and departure from intended intervention.
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	Poor	High risk of bias in multiple domains, including measurement of exposure and departure from intended intervention. Some concerns related to confounding.
Cadeau et al, 2015[170]	Poor	High risk of bias in multiple domains, including confounding and exposure ascertainment and selection bias due to large proportion of missing data.
Cauley et al, 2013[171]	Poor	This study is the observational extension phase to the Women's Health Initiative Calcium and Vitamin D randomized, controlled trial. High risk of bias in multiple domains, including selection bias, confounding, and departure from intended intervention. Some concerns for outcome measurement bias, missing data, and exposure measurement.
Chan et al, 2013[172]	Poor	High risk of bias in multiple domains, including confounding and exposure ascertainment.
Cheng et al, 2014[173]	Poor	High risk of bias across multiple domains, including confounding, high amount of missing data on exposure and confounding variables, measurement of exposure.
Curhan et al, 1997[174]	Poor	High risk of bias across multiple domains, including confounding, measurement of exposure, and missing data; also, some concerns for selection bias.
Flood et al, 2005[175]	Poor	High risk of bias due to unclear definition of exposure groups and without adequate measurement post baseline to be confident subjects supplement use did not vary over time, significant baseline and time-varying confounding also present.
Langsetmo et al, 2013[176]	Poor	High risk of bias due to confounding, particularly for an outcome such as all-cause mortality. Further, measurement of exposure was based on self-report questionnaire at baseline and one other point in time over the 10-year period of follow up, high likelihood of departure from intended interventions and no measures of adherence/compliance done throughout the period of follow up.
Li et al, 2012[177]	Poor	Confounding, selection bias due to missing exposure data, and poorly defined exposure result in high risk of bias across multiple domains.
Lin et al, 2005[178]	Poor	High risk of bias in multiple domains, including measurement of exposure and departure from intended intervention. Some concerns related to residual confounding.
McCullough et al, 2003[179]	Poor	High risk of bias in multiple domains, including measurement of exposure and departure from intended intervention. Some concerns related to residual confounding and no information about missing data.
Michaelsson et al, 2013[180]	Poor	High risk of bias due to residual confounding, particularly for outcomes such as all-cause mortality. High risk of bias due to measure of exposure, which included multivitamin use in addition to single-tablet calcium, and high risk of bias due to departures from intended intervention, since adherence is not measured and likelihood of switches is high given changes in health and aging over time and availability of supplements.
Paik et al, 2014[181]	Poor	High risk of bias in multiple domains, including confounding and measurement of exposure, and contamination of study groups over course of observation; also, some concerns for selection bias,
Sorenson et al, 2012[182]	Poor	Some concerns in nearly all bias domains, including confounding, exposure ascertainment/definition. Residual confounding likely because dietary calcium intake was not included as covariate in multivariate analyses of association between nephrolithiasis and either calcium supplement dosing or history of use.
Sun et al, 1997[183]	Poor	High risk of bias in multiple domains, including confounding and measurement of exposure, and contamination of study groups over period of observation; also, some concerns about selection bias.
Sun et al, 2011[184]	Poor	High risk of bias across most domains, including confounding, measurement of outcome, measurement of exposure, and departure from intended intervention; also, some concerns about adequate length of follow up.

Appendix E Table 7. Quality Ratings for Observational Studies: Part 1

Author, Year, Trial Name	Overall Quality Rating*	Overall Rationale for Quality Rating
Terry et al, 2002[185]	Poor	High risk or some concerns across most bias domains. Confounding, assessment of calcium supplement intake, and the approach to handling missing data all contribute to a high risk of bias.
Waterhouse et al, 2015[186]	Poor	High risk of bias due to information bias stemming from differences in how vitamin D supplement intake was measured across the pooled 4 studies relevant to this review. Risk of misclassification of vitamin D supplement intake groups because of variations in the operationalized definitions of supplement use. Multiple other concerns based on lack of information, like similarity of baseline characteristics between supplement intake groups and how recall bias affects outcome ascertainment between cases vs. controls.
Wilson et al, 2015[187] and Kearney et al,1996[188]	Poor	High risk of bias due to confounding and definition/measurement of exposure, and in potential for departures from intended intervention, no measures of adherence and follow-up was only every 4 years.
Van Hemelrijck et al, 2013[189]	Poor	High risk of bias in multiple domains, including measurement of exposure and departure from intended intervention. Some concerns related to residual confounding and missing data.
Xiao et al, 2013[190]	Poor	High risk of bias due to residual confounding, particularly for outcomes such as cardiovascular mortality. High risk of bias due to measure of exposure, which included multivitamin use in addition to single tablet calcium, and high risk of bias due to departures from intended intervention, since adherence not measured and likelihood of switches is high given changes in health and aging over time, and availability of supplements.
Yang et al, 2016 [191]	Poor	High risk of bias due to confounding, measurement of exposure, missing data, and departure from intended intervention. Some concerns related to selection bias.

* This is the overall study quality rating, which reflects the risk of bias across multiple domains, including selection bias, bias from confounding, bias from missing data, bias from departures from intended intervention, and measurement bias. Each part of Tables 8 through 14 include one domain specific risk of bias assessment.

Appendix E Table 8. Quality Ratings for Observational Studies: Part 2

Author, Year, Trial Name	For Cohort Studies Only: Was selection of participants into the study unrelated to intervention or unrelated to outcome?	For Cohort Studies Only: Were post-intervention variables that influenced selection likely to be associated with the intervention or likely to be influenced by the outcome or a cause of the outcome?	For Cohort Studies Only: Do start of follow up and start of intervention coincide for most subjects?	For Cohort Studies Only: Were adjustment techniques used that are likely to correct for the presence of selection biases?	For Case-Control Studies Only: Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	Bias Arising From Selection	Comments
Ahn et al, 2007[166]	Probably no	Related to outcome	No	Probably no	NA	High	Not an inception cohort. All participants were in the screening arm of a prostate screening trial, received screening, and may have behaviors and/or diagnostics, and/or treatment interventions related to participation in the trial.
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Cadeau et al, 2015[170]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Cauley et al, 2013[171]	No	Yes	Yes	Probably no	NA	High	Not an inception cohort, observational extension phase following completion of the WHI CaD Trial. Participants were told of their treatment assignment at the end of the trial and reconsented to participate in the extension phase. Reconsenting participants were different than those who did not reconsent.
Chan et al, 2013[172]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Cheng et al, 2014[173]	NA	NA	NA	NA	Yes	Low	None

Appendix E Table 8. Quality Ratings for Observational Studies: Part 2

Author, Year, Trial Name	For Cohort Studies Only: Was selection of participants into the study unrelated to intervention or unrelated to outcome?	For Cohort Studies Only: Were post-intervention variables that influenced selection likely to be associated with the intervention or likely to be influenced by the outcome or a cause of the outcome?	For Cohort Studies Only: Do start of follow up and start of intervention coincide for most subjects?	For Cohort Studies Only: Were adjustment techniques used that are likely to correct for the presence of selection biases?	For Case-Control Studies Only: Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	Bias Arising From Selection	Comments
Curhan et al, 1997[174]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Flood et al, 2005[175]	Probably yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Langsetmo et al, 2013[176]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Li et al, 2012[177]	No	NA	No	Probably no	NA	High	Selection related to outcome, and not an inception cohort.
Lin et al, 2005[178]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
McCullough et al, 2003[179]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Michaelsson et al, 2013[180]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Paik et al, 2014[181]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Sorenson et al, 2012[182]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort.
Sun et al, 2011[183]	Yes	NA	No	Probably no	NA	Some concerns	Not an inception cohort
Sun et al, 2011[184]	NA	NA	NA	NA	Probably yes	Low	Population-based cancer registries used to select cases, controls were subjects randomly sampled from the provincial population.
Terry et al, 2002[185]	NA	NA	NA	NA	Probably yes	Low	Case patients sampled from Swedish regional cancer registries, while control patients sampled from Swedish population register including all of the country's residents.
Van Hemelrijck et al, 2013[189]	Yes	NA	No	NA	NA	Some concerns	Not an inception cohort.

Appendix E Table 8. Quality Ratings for Observational Studies: Part 2

Author, Year, Trial Name	For Cohort Studies Only: Was selection of participants into the study unrelated to intervention or unrelated to outcome?	For Cohort Studies Only: Were post-intervention variables that influenced selection likely to be associated with the intervention or likely to be influenced by the outcome or a cause of the outcome?	For Cohort Studies Only: Do start of follow up and start of intervention coincide for most subjects?	For Cohort Studies Only: Were adjustment techniques used that are likely to correct for the presence of selection biases?	For Case-Control Studies Only: Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	Bias Arising From Selection	Comments
Waterhouse et al, 2015[186]	NA	NA	NA	NA	Probably no	Some Concerns	No information about similarities/differences in sourcing by supplement use groups, but expected bias can be evaluated by looking at sources of overall case vs. control participant selection. Sources of case vs. control selection varied by individual study, meaning resulting bias varies by study.
Wilson et al, 2015[187] and Kearney et al,1996[188]	Yes	NA	No	NA	NA	Some concerns	Not an inception cohort.
Xiao et al, 2013[190]	Yes	NA	No	NA	NA	Some concerns	Not an inception cohort.
Yang et al, 2016[191]	Probably yes	NA	Yes	No	NA	Some Concerns	Not an inception cohort.

Abbreviations: NA=not applicable; vs=versus; WHI CaD Trial=Women's Health Initiative Calcium and Vitamin D Trial.

Appendix E Table 9. Quality Ratings for Observational Studies: Part 3

Author, Year, Trial Name	Is confounding of the effect of intervention unlikely in this study?	Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	Did the authors avoid adjusting for post-intervention variables?	Were participants analyzed according to their initial intervention group throughout followup?	Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias Arising From Confounding	Comments
Ahn et al, 2007[166]	Probably no	Probably yes	Probably no	NA	No information	No information	High	Relies on self-reported measures of confounding.
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	Probably no	Probably yes	Probably no	Probably no	No information	No information	High	Relies on self-reported measures, and potential for time-varying confounding.
Cadeau et al, 2015[170]	No	Probably yes	Probably no	Probably yes	Probably no	No information	High	Relies on self-reported measures, and possibility of time-varying confounding as change in use of supplements may be related to engagement in other health promotion behaviors or the start of menopause, which are both factors related to breast cancer.
Cauley et al, 2013[171]	No	Probably no	Probably no	Probably no	Yes	No	High	Adjustments for relatively few confounding variables; age, hormone trial participation, and baseline vitamin D and calcium intake and supplement use.
Chan et al, 2013[172]	No	No	No information	Yes	Yes	No	High	No measures or adjustment for CVD risks factors (HTN, DM, cholesterol); further confounders such as diet and physical activity assessed only at baseline, yet these are likely to change over time, as is the use of supplements. Thus, time-varying confounding is also a factor.

Appendix E Table 9. Quality Ratings for Observational Studies: Part 3

Author, Year, Trial Name	Is confounding of the effect of intervention unlikely in this study?	Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	Did the authors avoid adjusting for post-intervention variables?	Were participants analyzed according to their initial intervention group throughout follow up?	Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias Arising From Confounding	Comments
Cheng et al, 2014[173]	No	No	NA	No information	Probably yes	No	High	Odds ratios for supplemental vitamin D use appears to be unadjusted for any confounding variables, particularly smoking and asbestos exposure. Further, this study reports the r elationship betw een vitamin D and lung cancer over a period that included a trial component for vitamin A and an observational study component, because the trial w as ended early due to increase in lung cancer risk in treatment arm; this could have led to discontinuations and sw itches during the observational phase as a result.
Curhan et al, 1997[174]	Probably no	Probably yes	No	No information	No information	Probably no	High	Self-report measures, time-varying confounding likely.
Flood et al, 2005[175]	No	Probably yes	Probably no	Probably yes	Probably yes	Probably no	High	Sources of vitamin D (dietary) based on self-reported recall, no adjustment for sun exposure as source of vitamin D; colorectal cancer screening based on self-report and how specified w as not reported. No adjustment for family history of colorectal cancer or other medical conditions related to this type of cancer that might also influence likelihood to take preventive supplements such as calcium.

Appendix E Table 9. Quality Ratings for Observational Studies: Part 3

Author, Year, Trial Name	Is confounding of the effect of intervention unlikely in this study?	Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	Did the authors avoid adjusting for post-intervention variables?	Were participants analyzed according to their initial intervention group throughout followup?	Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias Arising From Confounding	Comments
Langsetmo et al, 2013[176]	No	No	NA	No	Yes	No	High	Adjusted estimates for low trauma fracture; baseline characteristics assessed only between groups based on total intake (including diet and supplements), not balanced by group on a variety of characteristics that were measured; numerous potential influences on all-cause mortality that were not measured at baseline.
Li et al, 2012[177]	Probably no	Probably yes	No	Probably yes	Probably yes	No information	High	Important confounders such as DM, HTN, and hyperlipidemia, were based on self-report, as was smoking status, and use of CVD-risk-lowering drugs.
Lin et al, 2005[178]	Probably no	Probably yes	Probably no	Probably no	No information	No information	High	Relies on self-reported measures, potential for time-varying confounding.
McCullough et al, 2003[179]	Probably no	Yes	Probably no	No information	No information	No information	High	Relies on self-reported measures.

Appendix E Table 9. Quality Ratings for Observational Studies: Part 3

Author, Year, Trial Name	Is confounding of the effect of intervention unlikely in this study?	Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	Did the authors avoid adjusting for post-intervention variables?	Were participants analyzed according to their initial intervention group throughout followup?	Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias Arising From Confounding	Comments
Michaelsson et al, 2013[180]	No	Probably yes	Probably yes	No information	Probably yes	Probably no	High	Authors relied on diagnostic codes for comorbidities, which is probably more suitable than self-report. However, these may not capture the severity of disease, thus residual confounding remains a concern. Time-updated information was used to adjust models, which offered different results than models with only baseline information, suggesting that time-varying confounding is a factor.
Paik et al, 2014[181]	No	Yes	Probably no	Probably no	No	Probably yes	High	Self-report measures, residual confounding, and time-varying confounding.
Sorenson et al, 2012[182]	No	Probably yes	Probably no	Probably yes	Yes	No information	Some concerns	Validated FFQ used to evaluate dietary confounders, others were self-reported, medication use evaluated by asking women to bring medications to clinic during visit and provide in-person medication history. Dietary calcium intake was not included in multivariate analyses for calcium supplementation as independent risk factor for nephrolithiasis.

Appendix E Table 9. Quality Ratings for Observational Studies: Part 3

Author, Year, Trial Name	Is confounding of the effect of intervention unlikely in this study?	Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	Did the authors avoid adjusting for post-intervention variables?	Were participants analyzed according to their initial intervention group throughout follow up?	Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias Arising From Confounding	Comments
Sun et al, 2011[183]	No	Yes	Probably no	Probably yes	No	Probably yes	High	Self-report measures, residual confounding, participants analyzed according to the supplement intake level they endorsed at the start of each intermediate follow-up period (i.e., between one follow-up survey and the next one).
Sun et al, 2011[184]	No	Probably yes	No	No	Probably yes	Probably no	High	Estimates adjusted for mediating variables on the direct effect of the intervention (multivitamin supplement use, physical activity). Discontinuations and switches likely to be related to factors prognostic for outcome (use of vitamins/ supplements during cancer treatment). Confounders measured based on self-report, inherent recall bias with case-control designs.
Terry et al, 2002[185]	No	Probably yes	No	Yes	Yes	Probably yes	High	Retrospective measurement of important confounding variables, particularly among cases.
Van Hemelrijck et al, 2013[189]	Probably no	Probably yes	Probably no	Probably no	No information	No information	High	Self-reported measures.
Waterhouse et al, 2015[186]	No	Probably no	No information	Probably yes	Yes	Probably no	High	Residual confounding, not clear that all important confounders were considered.

Appendix E Table 9. Quality Ratings for Observational Studies: Part 3

Author, Year, Trial Name	Is confounding of the effect of intervention unlikely in this study?	Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	Did the authors avoid adjusting for post-intervention variables?	Were participants analyzed according to their initial intervention group throughout follow up?	Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias Arising From Confounding	Comments
Wilson et al, 2015[187] and Kearney et al,1996[188]	No	No	NA	No	No information	Probably no	High	Did not adjust for factors such as presence of BPH, use of alpha reductase inhibitors, both of which may be related to prostate cancer risk or increased opportunities for cancer detection through regular urologic care. Other confounders measured by self-report and updated with each new questionnaire; thus, unclear how this was accounted for in the analysis.
Xiao et al, 2013[190]	No	Probably yes	Probably no	Probably yes	Yes	No	High	All confounders measured based on self-report, potential for residual confounding high for outcome of cardiovascular mortality given that few cardiovascular risks or related CHD conditions were measured at baseline. Also, likely time-varying confounding due to switches.
Yang et al, 2016[191]	No	Probably no	No	No information	Probably yes	Probably no	High	Differences in numerous covariates at baseline, severity and treatment of CVD comorbidities not assessed, all rely on self-reported measures.

Abbreviations: BPH=benign prostatic hyperplasia; CHD=coronary heart disease; CVD=cardiovascular disease; DM=diabetes mellitus; FFQ=food frequency questionnaire; HTN=hypertension.

Appendix E Table 10. Quality Ratings for Observational Studies: Part 4

Author, Year, Trial Name	Is intervention status well defined?	Was information on intervention status recorded at the time of intervention?	Was classification of intervention status unaffected by knowledge of the outcome or risk of the outcome?	Bias Arising From Measurement of the Intervention	Comments
Ahn et al, 2007[166]	No	Yes	Yes	High	Calcium use assessed based on self-report at baseline, and classified as current use or past use (within previous 2 or 5 years). Only mean dose of calcium (135 to 320 mg) provided, no additional information about duration of use and no information about ongoing use during period of study observation. Similarly, vitamin D use was dichotomized as users of <600 IU versus users of >600 IU.
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	No	Yes	Yes	High	Use of supplements based on single self-reported questionnaire at baseline. Categories of exposure determined by distribution of data.
Cadeau et al, 2015[170]	No	Probably yes	Probably yes	High	Supplement use assessed at baseline and via follow up questionnaires; categorized as "current use," "never use," "past use." Specific dose, frequency, and duration are not reported.
Cauley et al, 2013[171]	Yes	Yes	No information	Some concerns	Participants were informed of treatment assignment at the end of the trial period; participants were analyzed in their original treatment assignment groups at the end of the observational extension phase.
Chan et al, 2013[172]	No	Yes	Yes	High	Calcium use recorded as "yes" or "no" at baseline, no information about dose, frequency, or duration of use.
Cheng et al, 2014[173]	No	Yes	Yes	High	Information on the use of personal supplemental vitamins were collected during clinical visits. Information on doses and frequency were retrospectively calculated/extracted based on the brand names captured during baseline. Author noted potential measurement error since ascertainment of vitamin D dosage based on bottle labels was incomplete; and only the baseline assessment was used. Further, the analysis of supplement use was only provided as "any use" vs. "no use" and it is not clear what the range of doses, frequency, and duration was for the group of "any use."
Curhan et al, 1997[174]	No	No information	Probably yes	High	Exposure based on self-report use at baseline and every few years.

Appendix E Table 10. Quality Ratings for Observational Studies: Part 4

Author, Year, Trial Name	Is intervention status well defined?	Was information on intervention status recorded at the time of intervention?	Was classification of intervention status unaffected by knowledge of the outcome or risk of the outcome?	Bias Arising From Measurement of the Intervention	Comments
Flood et al, 2005[175]	No	No	Probably yes	High	Calcium supplement categories based on self-reported recall assessing usual intake over the prior year at baseline; no information about calcium supplementation use in years prior to the baseline recall, and in years subsequent to the baseline year recall.
Langsetmo et al, 2013[176]	Probably no	Yes	Probably yes	High	Calcium and vitamin D supplement use defined as yes/no, and then low, moderate, or high within the "yes" category; use based on baseline questionnaire for the first 5 years, and then updated from questionnaires for the second 5-year period.
Li et al, 2012[177]	Probably no	Probably yes	Probably yes	High	Self-reported use of supplements was coded using the Anatomical Therapeutic Chemical classification system, but data on dosage, frequency, and duration of use were not collected. Subjects classified as users if they reported daily use for at least 1 week, or nondaily use for at least 5 doses, all within the previous 4 weeks. Supplementation use documented at baseline and used for Model A analysis, follow up supplementation use was assessed but frequency was not specified, cumulative use of calcium from baseline through follow up assessed with Model D analysis.
Lin et al, 2005[178]	No	Yes	Yes	High	Calcium supplement use defined as <500 or >500 mg, use for vitamin D defined as 0 or between 0 and 400 IU. All based on single self-report at baseline.
McCullough et al, 2003[179]	No	Yes	Yes	High	Calcium supplement use ascertained only at baseline and during one single follow up by self-report.
Michaelsson et al, 2013[180]	No	Yes	Yes	High	Authors defined supplement use as use of single supplements (calcium tablets) but also estimated an additional dose from use of multivitamin supplements, of which 74% of subjects were users. Thus, the exposure in this analysis is not a single supplement calcium. Supplement use was not ascertained on the first questionnaire, and only 6% of subjects reported using supplements in the subsequent questionnaire.
Paik et al, 2014[181]	Probably no	No information	Probably yes	High	Average daily dosing information captured at baseline and during follow-up, limitations in ascertainment noted.
Sorenson et al, 2012[182]	Probably no	Probably yes	Probably yes	High	Calcium use specified as before study, since study, before and since study, and never. Dose, frequency, and duration not specified.
Sun et al, 2011[183]	Probably no	No information	Probably yes	High	Average daily dosing information captured at baseline and during follow-up, but had limitations.

Appendix E Table 10. Quality Ratings for Observational Studies: Part 4

Author, Year, Trial Name	Is intervention status well defined?	Was information on intervention status recorded at the time of intervention?	Was classification of intervention status unaffected by knowledge of the outcome or risk of the outcome?	Bias Arising From Measurement of the Intervention	Comments
Sun et al, 2011[184]	Probably no	No	No information	High	Exposure status documented retrospectively, based on self-report and analyzed as "yes/no" to use of supplements.
Terry et al, 2002[185]	No	No	Probably no	High	Assessment of calcium supplement intake likely more accurate among cases than controls. Also, definition of "occasional" supplement intake frequency not provided, so that category could have encompassed a broad variety of different intake levels from several times a week (but not daily) to only once or twice a week.
Van Hemelrijck et al, 2013[189]	No	Yes	Yes	High	Supplement use based on self-report at a single baseline measurement.
Waterhouse et al, 2015[186]	Probably no	No	Probably no	High	Inconsistent methods used to solicit information about vitamin D supplement intake from participants across studies, which means varying risk of bias from information bias. Risk of misclassified vitamin D supplement intake because of variation in operationalized definitions of supplement use.
Wilson et al, 2015[187] and Kearney et al,1996[188]	No	Yes	Yes	High	Calcium supplement use is defined as "yes" or "no" at baseline measurement; specific doses, frequency of use, and duration of use are not provided.
Xiao et al, 2013[190]	No	Yes	Yes	High	Supplement use defined based on use of single supplements plus supplements from multivitamin. Analysis is conducted comparing "users" to "nonusers," with no specification as to dose, frequency, or duration.
Yang et al, 2016[191]	No	Probably yes	Probably yes	High	Exposure based on self-report use at baseline and 2 additional time points separated by ~7 years.

Abbreviations: IU=international unit; mg=milligram.

Appendix E Table 11. Quality Ratings for Observational Studies: Part 5

Author, Year, Trial Name	Were outcome data available for all, or nearly all participants?	Were few or no participants excluded because of missing data on intervention status?	Were few or no participants excluded due to missing data on other variables needed for the analysis?	Were the proportion of participants and reasons for missing data similar across intervention groups?	Were appropriate statistical methods used to account for missing data or assess robustness to presence of missing data?	Bias Arising From Missing Outcome Data	Comments
Ahn et al, 2007[166]	Probably no	Probably no	Probably yes	No information	Probably no	High	More than 20% of the original cohort was excluded because of missing exposure data, or missing covariate data. No sensitivity analyses to assess robustness to missing data were performed.
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	Probably yes	Probably yes	Probably yes	No information	No information	Some concerns	None
Cadeau et al, 2015[170]	No	No	No information	No information	No	High	6,237 women who were premenopausal at the time of time 1995 survey were excluded, and 23,000 did not complete the dietary questionnaire in 1993 or 1995. The original cohort was 98,000; only 54,000 were used for this analysis.
Cauley et al, 2013[171]	Probably no	Yes	Probably yes	Yes	Yes	Some concerns	82.6% of original treatment group, and 81.9% of original placebo group reconsented to observational extension phase.
Chan et al, 2013[172]	Probably yes	Yes	No information	No information	No information	Some concerns	Of 4,000 in original cohort, 3,139 were included in analysis. Some were excluded for existing CVD, but specific numbers not provided.

Appendix E Table 11. Quality Ratings for Observational Studies: Part 5

Author, Year, Trial Name	Were outcome data available for all, or nearly all participants?	Were few or no participants excluded because of missing data on intervention status?	Were few or no participants excluded due to missing data on other variables needed for the analysis?	Were the proportion of participants and reasons for missing data similar across intervention groups?	Were appropriate statistical methods used to account for missing data or assess robustness to presence of missing data?	Bias Arising From Missing Outcome Data	Comments
Cheng et al, 2014[173]	Probably no	No	No	Probably yes	Probably no	High	The original case and control cohort size was 1,016. The final sizes were 749 vs. 679 after excluding those that had a history of disease in the intestines, liver, and kidney that prevent oral vitamin D absorption, and those who did not complete a food frequency questionnaire during follow up, among other reasons.
Curhan et al, 1997[174]	No	No	Probably yes	No information	No	High	Supplement use data missing for 29.7% of participants reporting symptomatic kidney stones because 1980 survey did not capture that information. Also unclear how many participants were excluded because of missing dietary information from each intermediate period making up the study's duration.
Flood et al, 2005[175]	Yes	Probably yes	Probably yes	No information	No information	Low	None
Langsetmo et al, 2013[176]	Yes	Yes	No information	No information	Probably yes	Low	Missing exposure status for a small proportion of participants; these subjects were excluded from the analysis.

Appendix E Table 11. Quality Ratings for Observational Studies: Part 5

Author, Year, Trial Name	Were outcome data available for all, or nearly all participants?	Were few or no participants excluded because of missing data on intervention status?	Were few or no participants excluded due to missing data on other variables needed for the analysis?	Were the proportion of participants and reasons for missing data similar across intervention groups?	Were appropriate statistical methods used to account for missing data or assess robustness to presence of missing data?	Bias Arising From Missing Outcome Data	Comments
Li et al, 2012[177]	Yes	No	Yes	No information	No information	High	Authors note that, because 44.5% of all vitamin/mineral users in the EPIC study did not report the names of their supplements, the number of calcium supplement users captured in this analysis only accounted for 3.6% of all cohort participants. There is a possibility that the unreported calcium supplementation would affect the accuracy of results on cardiovascular risks.
Lin et al, 2005[178]	Probably yes	Probably yes	Probably yes	No information	No information	Some concerns	None
McCullough et al, 2003[179]	Probably yes	Probably yes	Probably yes	No information	No information	Some concerns	Missing data for 19.4% of original cohort; outcomes for 245 subjects could not be confirmed.
Michaelsson et al, 2013[180]	No information	No information	Probably no	No information	Probably yes	Some concerns	Physical activity and smoking not assessed at baseline.
Paik et al, 2014[181]	No information	No information	No information	No information	No	Uncertain because no information	Unclear how many participants excluded due to missing data about intervention status or for any outcome.
Sorenson et al, 2012[182]	Probably yes	No information	No information	No information	No information	Uncertain because no information	None

Appendix E Table 11. Quality Ratings for Observational Studies: Part 5

Author, Year, Trial Name	Were outcome data available for all, or nearly all participants?	Were few or no participants excluded because of missing data on intervention status?	Were few or no participants excluded due to missing data on other variables needed for the analysis?	Were the proportion of participants and reasons for missing data similar across intervention groups?	Were appropriate statistical methods used to account for missing data or assess robustness to presence of missing data?	Bias Arising From Missing Outcome Data	Comments
Sun et al, 2011[183]	Probably yes	Yes	Probably yes	No information	No	Some Concerns	About 9.2% and 10.7% of eligible participants from two cohorts, respectively, excluded from analysis because of either missing baseline dietary/supplemental Vit D intake information or because of a baseline CVD/cancer diagnosis. Unclear what proportion of these participants were excluded because of missing baseline information.
Sun et al, 2011[184]	No	No	No	No information	No information	High	Only 65% of eligible cases and 53.5% of eligible controls provided responses to surveys.
Terry et al, 2002[185]	Probably no	Probably no	Yes	No	No	High	No statistical methods used to account for missing dietary information for controls who failed to return their mailed questionnaires and were excluded from this analysis (14.3% of the group). In contrast, 100% of case patients returned their questionnaires. Additionally, other patients excluded by investigators for reasons besides missing questionnaires (nonparticipation in both groups, and atypical hyperplasia among some cases), but no mention of how their baseline characteristics compared with those of the study sample.
Van Hemelrijck et al, 2013[189]	No information	No information	No information	No information	No information	Uncertain because no information	No information on how many participants had complete data.

Appendix E Table 11. Quality Ratings for Observational Studies: Part 5

Author, Year, Trial Name	Were outcome data available for all, or nearly all participants?	Were few or no participants excluded because of missing data on intervention status?	Were few or no participants excluded due to missing data on other variables needed for the analysis?	Were the proportion of participants and reasons for missing data similar across intervention groups?	Were appropriate statistical methods used to account for missing data or assess robustness to presence of missing data?	Bias Arising From Missing Outcome Data	Comments
Waterhouse et al, 2015[186]	No	No information	Probably yes	No information	No	Uncertain because no information	Only 4 of 9 pooled case-control studies reported vitamin D supplement intake data. Also, participants were excluded due to missing confounder data, but specific numbers are not provided.
Wilson et al, 2015[187] and Kearney et al,1996[188]	Probably yes	No information	No information	No information	Probably yes	Uncertain because no information	No information on the proportion of subjects with missing calcium supplement use data or missing data on confounding variables.
Xiao et al, 2013[190]	Probably yes	No information	No information	No information	No information	Uncertain because no information	Missing data not discussed by authors, and not evaluated based on supplement status.
Yang et al, 2016[191]	No	No	No	No information	Probably no	High	Some exclusions were appropriate, but over 25% of the original cohort was not included in the analysis.

Appendix E Table 12. Quality Ratings for Observational Studies: Part 6

Trial Name	Were there no or minimal deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Were important co-interventions balanced across intervention groups?	Did the study measure adherence with defined intervention?	Bias Arising From Departures From Intended Interventions	Comments
Ahn et al, 2007[166]	No information	No information	No information	No	Uncertain because no information	No attempts made to measure ongoing/continuing use of calcium or vitamin D throughout the study observation period.
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	No information	No information	No information	No	Uncertain because no information	No attempts made to measure ongoing/continuing use of calcium or vitamin D throughout the study observation period.
Cadeau et al, 2015[170]	Probably no	Probably yes	No information	No	High	No attempts made to measure ongoing/continuing use of calcium or vitamin D throughout the study observation period.
Cauley et al, 2013[171]	No information	No information	No information	No	High	Participants were unmasked at the end of the trial phase; no information about supplement use by the treatment and placebo groups throughout the observational extension phase.
Chan et al, 2013[172]	Probably no	No information	No information	No	High	No information about supplement use other than the single baseline interview assessment.
Cheng et al, 2014[173]	No information	No information	No information	No	Uncertain because no information	None
Curhan et al, 1997[174]	No information	No information	No information	No	Uncertain because no information	Unclear how dietary calcium intake and other nutrient intake levels changed over course of study.
Flood et al, 2005[175]	No information	No information	No information	Probably no	High	No data about subjects' use of calcium beyond the single measurement at baseline; thus, cannot tell if subjects stopped, started, or changed doses of calcium throughout the period of observation.
Langsetmo et al, 2013[176]	Probably no	No information	Probably no	No	High	Use was based on two questionnaires at baseline and at 5 years. No attempt to measure or characterize changes in use over the duration of the cohort.

Appendix E Table 12. Quality Ratings for Observational Studies: Part 6

Trial Name	Were there no or minimal deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Were important co-interventions balanced across intervention groups?	Did the study measure adherence with defined intervention?	Bias Arising From Departures From Intended Interventions	Comments
Li et al, 2012[177]	No information	No information	NA	No	Uncertain because no information	None
Lin et al, 2005[178]	No information	No information	No information	No	Uncertain because no information	No attempts made to measure ongoing/continuing use of calcium or vitamin D throughout the study observation period.
McCullough et al, 2003[179]	No information	No information	No information	No	Uncertain because no information	Only one follow up to ascertain ongoing exposure and no information provided as to how this was used.
Michaelsson et al, 2013[180]	No	No information	No information	Probably no	High	Baseline characteristics by supplement use were not provided. Use of supplements was measured by self-report on questionnaire and not clear how switches were handled in analysis.
Paik et al, 2014[181]	No	Yes	No information	No	High	Contamination of no-supplement-use group over time (proportion of users increased from 30.5% of participants at baseline in 1984 to 80% in 2004) likely introduced differential bias.
Sorenson et al, 2012[182]	Probably yes	NA	No information	No	Some concerns	Classification of patients into groups based on self-report, but confidence in their report of supplement use increased because of periodic in-person clinic visits involving complete medication histories. Still, the stability of self-reported supplement use between clinic visits was uncertain (e.g., frequency of use might have varied across time).
Sun et al, 2011[183]	Probably no	Probably yes	No information	No	High	Vit D supplement intake increased substantially over time in the NHS cohort, as calcium supplement intake increased by 49.5% from baseline through the Paik et al. (2014[181]) companion study.

Appendix E Table 12. Quality Ratings for Observational Studies: Part 6

Trial Name	Were there no or minimal deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Were important co-interventions balanced across intervention groups?	Did the study measure adherence with defined intervention?	Bias Arising From Departures From Intended Interventions	Comments
Sun et al, 2011[184]	No information	NA	No information	No information	Uncertain because no information	No information about supplement use other than the single questionnaire assessment about supplement use during the prior 1–2 years. Dose, duration and frequency not assessed.
Terry et al, 2002[185]	Probably yes	NA	No information	No	Some concerns	Unclear to what extent hormone therapy or oral contraceptive use were balanced across the different calcium supplement intake groups, although case vs. control group differences were apparent for both.
Van Hemelrijck et al, 2013[189]	No information	No information	No information	No	Uncertain because no information	No measures of ongoing supplement use.
Waterhouse et al, 2015[186]	Probably no	Probably yes	No information	No	Some concerns	Cases more likely to recall use vs. nonuse of supplements, but unclear in what direction their improved recall might have biased the findings. No information about the distribution of cointerventions between different supplement intake dose groups.
Wilson et al, 2015[187] and Kearney et al,1996[188]	No information	No information	No information	No	Uncertain because no information	No information about calcium supplement use provided beyond what was recorded at baseline. Subjects were analyzed according to their baseline use.
Xiao et al, 2013[190]	Probably no	No information	No information	Probably no	High	Baseline characteristics by supplement use were not provided. Use of supplements was measured by self-report on questionnaire; not clear how switches were handled in analysis.
Yang et al, 2016[191]	Probably no	No information	No information	No	Uncertain because no information	None

Abbreviations: CVD=cardiovascular disease; vs.=versus.

Appendix E Table 13. Quality Ratings for Observational Studies: Part 7

Author, Year, Trial Name	Was measurement of harms outcomes unlikely to have been influenced by knowledge of the intervention received?	Were methods of harm outcome assessment comparable across groups?	Was the duration of followup adequate to assess harm outcomes?	Bias Arising From Measurement of Harms Outcomes	Comments
Ahn et al, 2007[166]	Yes	Yes	Yes	Low	None
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	Yes	Yes	Yes	Low	None
Cadeau et al, 2015[170]	Probably yes	Yes	Yes	Low	None
Cauley et al, 2013[171]	Probably no	Yes	Yes	Some concerns	Participants were unmasked at end of trial phase; outcomes initially collected by self-report, then confirmed with medical records. Potential for recall bias for self-reported outcomes given that participants were unmasked from their treatment assignment during the observational extension phase.
Chan et al, 2013[172]	Yes	Yes	Yes	Low	None
Cheng et al, 2014[173]	Yes	Yes	Yes	Low	None
Curhan et al, 1997[174]	Probably yes	Yes	Yes	Low	Self-reported measures of kidney stones; however, random validity check of about 10% of participants' kidney stone reports found nearly 100% concordance with medical records.
Flood et al, 2005[175]	No information	Yes	Probably yes	Low	None
Langsetmo et al, 2013[176]	Yes	Yes	Yes	Low	None
Li et al, 2012[177]	No information	Probably yes	Yes	Low	None
Lin et al, 2005[178]	Yes	Yes	Yes	Low	None
McCullough et al, 2003[179]	Yes	Yes	Yes	Low	None
Michaelsson et al, 2013[180]	Yes	Yes	Yes	Low	None
Paik et al, 2014[181]	Yes	Yes	Yes	Low	Only outcome data verified as "confirmed" or "probable" by study investigators were used.

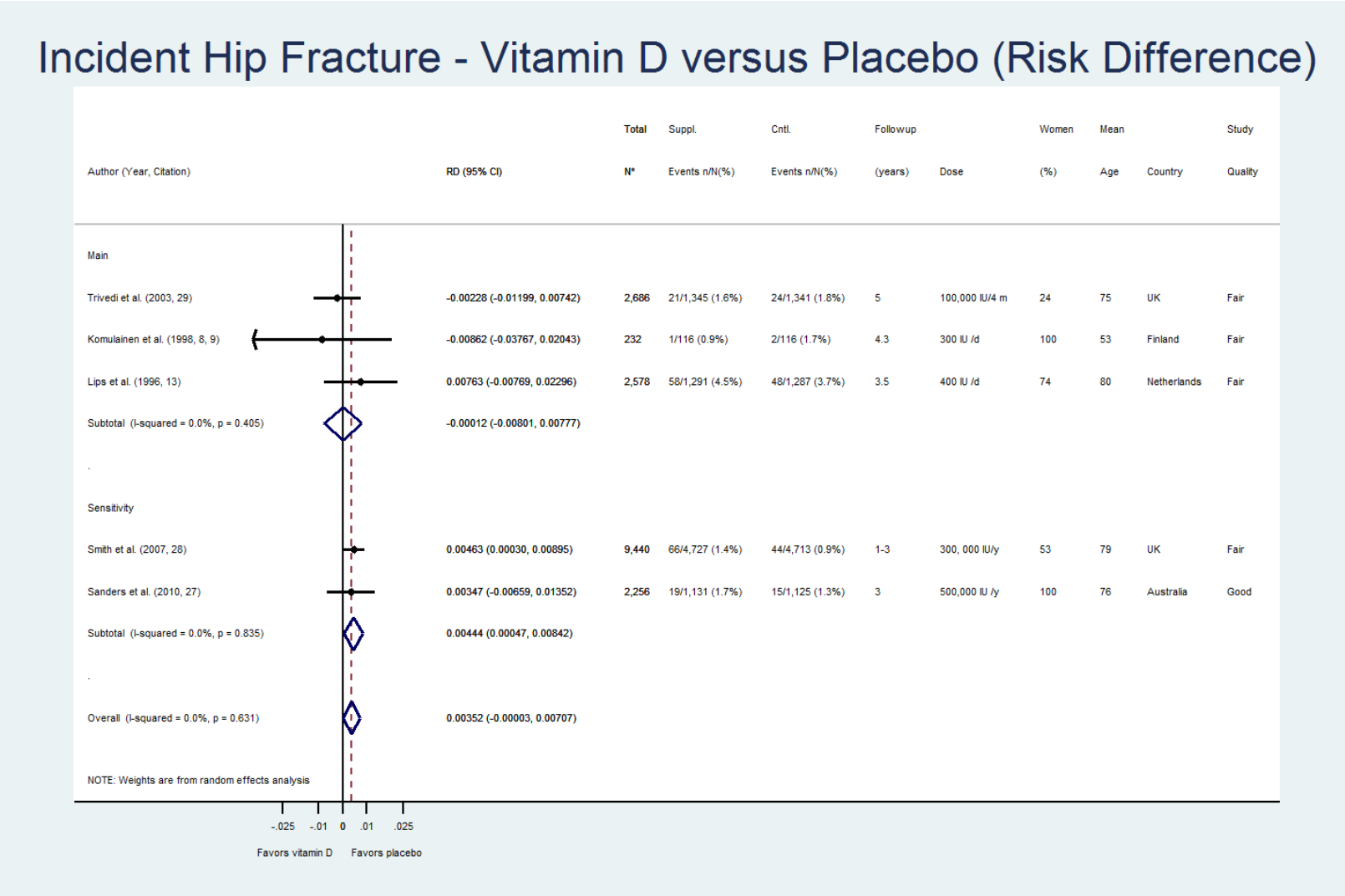
Appendix E Table 13. Quality Ratings for Observational Studies: Part 7

Author, Year, Trial Name	Was measurement of harms outcomes unlikely to have been influenced by knowledge of the intervention received?	Were methods of harm outcome assessment comparable across groups?	Was the duration of follow up adequate to assess harm outcomes?	Bias Arising From Measurement of Harms Outcomes	Comments
Sorenson et al, 2012[182]	Probably yes	Yes	Yes	Some concerns	Self-reported outcome measures.
Sun et al, 2011[183]	Yes	Yes	Yes	Low	Only outcome data verified as "confirmed" or "probable" by study investigators were used.
Sun et al, 2011[184]	NA	NA	Probably no	Some concerns	Length of follow up time may not be adequate.
Terry et al, 2002[185]	NA	Yes	Probably no	Some concerns	Length of follow up time may not be adequate.
Van Hemelrijck et al, 2013[189]	Yes	Yes	Yes	Low	None
Waterhouse et al, 2015[186]	NA	Yes	Probably no	Some concerns	Length of follow up time may not be adequate.
Wilson et al, 2015[187] and Kearney et al,1996[188]	Yes	Yes	Yes	Low	None
Xiao et al, 2013[190]	Yes	Yes	Yes	Low	None
Yang et al, 2016[191]	N/A	N/A	N/A	N/A	N/A

Appendix E Table 14. Quality Ratings for Observational Studies: Part 8

Author, Year, Trial Name	Is the reported effect estimate unlikely to be selected, on the basis of the results from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias Arising From Selection of Reported Results	Comments
Ahn et al, 2007[166]	Yes	Low	None
Bostick et al, 1993[167] and Sellers et al, 1998[168] and Mursu, 2011[169]	Yes	Low	None
Cadeau et al, 2015[170]	Yes	Low	None
Cauley et al, 2013[171]	Yes	Low	None
Chan et al, 2013[172]	Yes	Low	None
Cheng et al, 2014[173]	Yes	Low	None
Curhan et al, 1997[174]	Yes	Low	None
Flood et al, 2005[175]	Yes	Low	None
Langsetmo et al, 2013[176]	Yes	Low	None
Li et al, 2012[177]	No	High	This rating applies to models B and C analyses only.
Lin et al, 2005[178]	Yes	Low	None
Michaelsson et al, 2013[180]	Yes	Low	None
McCullough et al, 2003[179]	Yes	Low	None
Paik et al, 2014[181]	Yes	Low	None
Sorenson et al, 2012[182]	Probably no	Some concerns	Investigators did not report the results of the multivariate analysis for current calcium supplementation dose and nephrolithiasis, as they did for calcium supplement history. Likely a decision based on the lack of a statistically significant association.
Sun et al, 2011[183]	Yes	Low	None
Sun et al, 2011[184]	Yes	Low	None
Terry et al, 2002[185]	Yes	Low	None
Van Hemelrijck et al, 2013[189]	Yes	Low	None
Waterhouse et al, 2015[186]	Yes	Low	None
Wilson et al, 2015[187] and Kearney et al,1996[188]	Yes	Low	None
Xiao et al, 2013[190]	Yes	Low	None
Yang et al, 2016[191]	Yes	Low	None

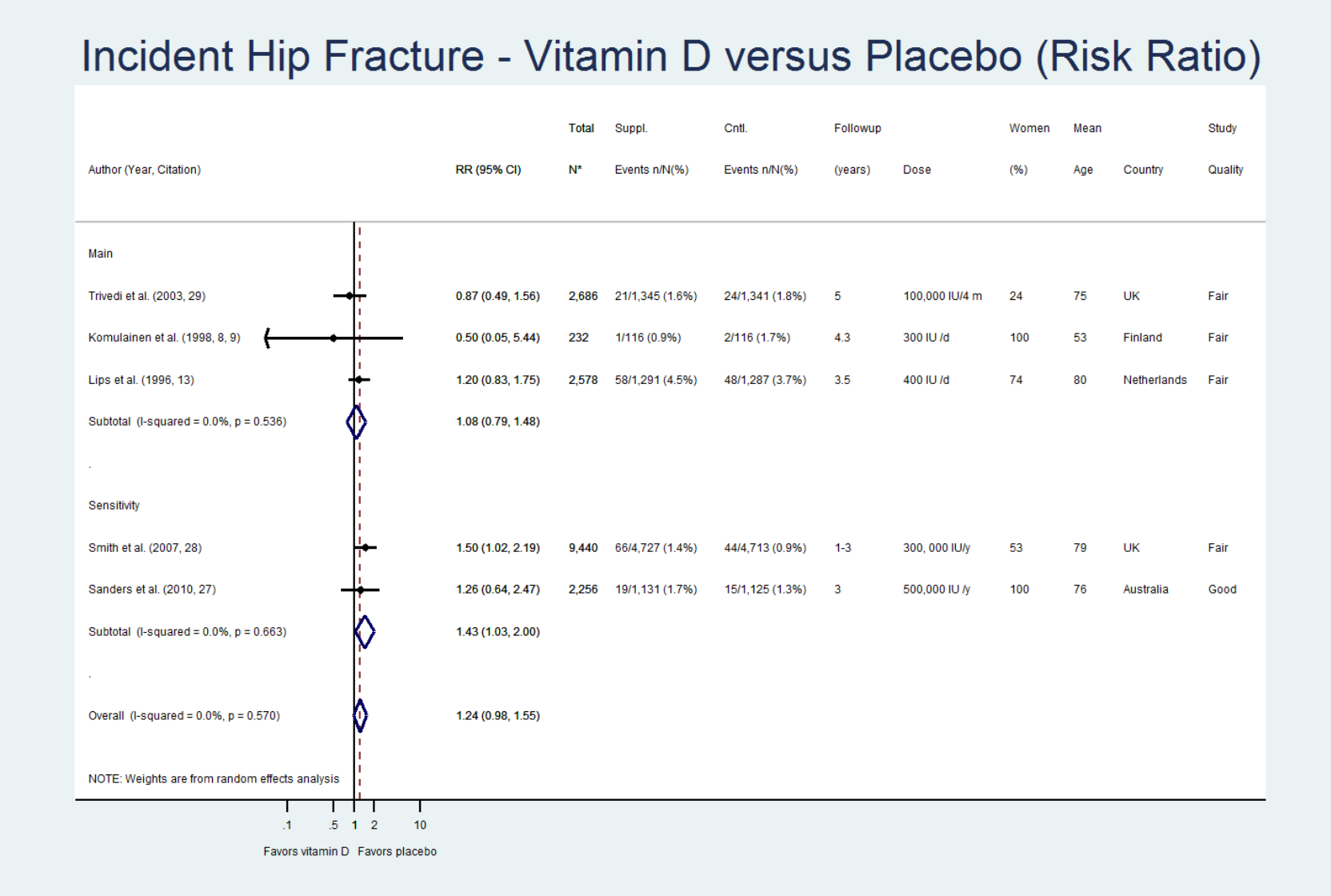
Appendix F Figure 1. Impact of Vitamin D Alone vs. Placebo on Incident Hip Fracture, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: CI=confidence interval; Cntl=control or placebo; d=day; IU=international units; m=month; n or N=number of participants; RD=risk difference; Suppl. = supplementation; UK=United Kingdom; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

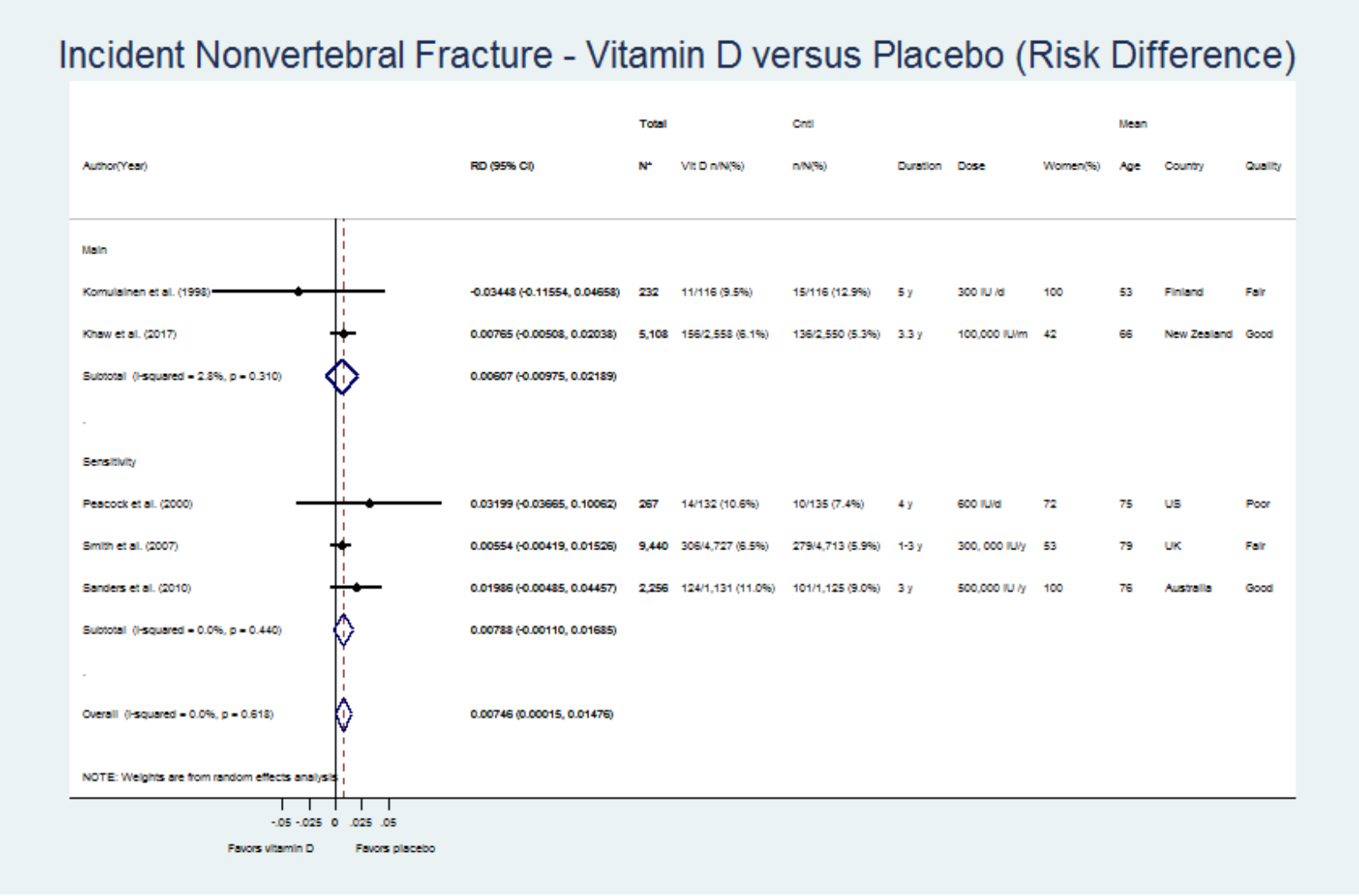
Appendix F Figure 2. Impact of Vitamin D Alone vs. Placebo on Incident Hip Fracture, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: CI=confidence interval; Cntl=control or placebo; IU=international units; m=month; n or N=number of participants; RR=relative risk ratio; Suppl. = supplementation; UK=United Kingdom; y=year.

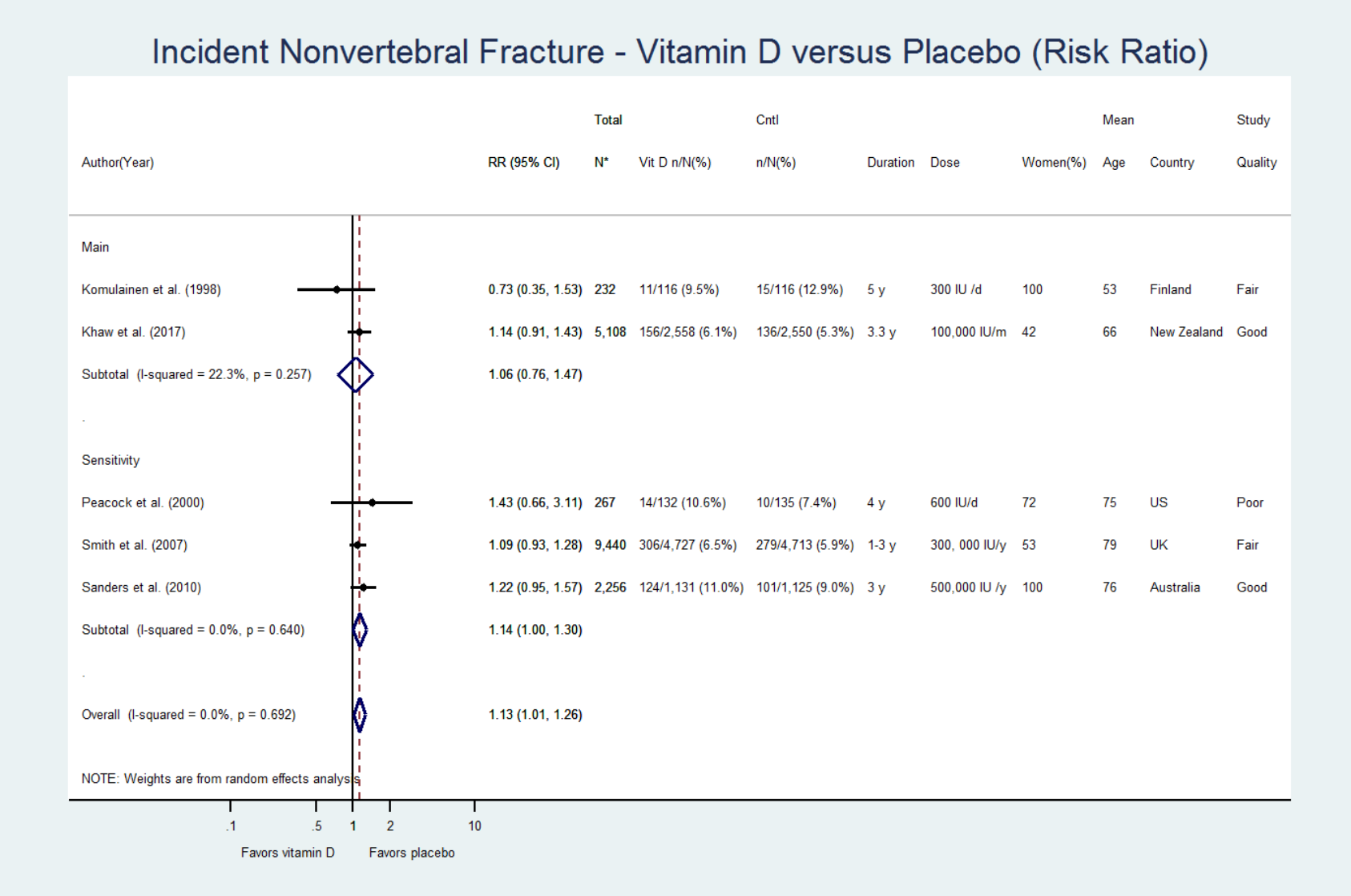
Appendix F Figure 3. Impact of Vitamin D Alone vs. Placebo on Incident Nonvertebral Fracture, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: CI=confidence interval; Cntl=control or placebo; d=day; IU=international units; n or N=number of participants; RD=risk difference; UK=United Kingdom; US=United States; Vit D=vitamin D; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

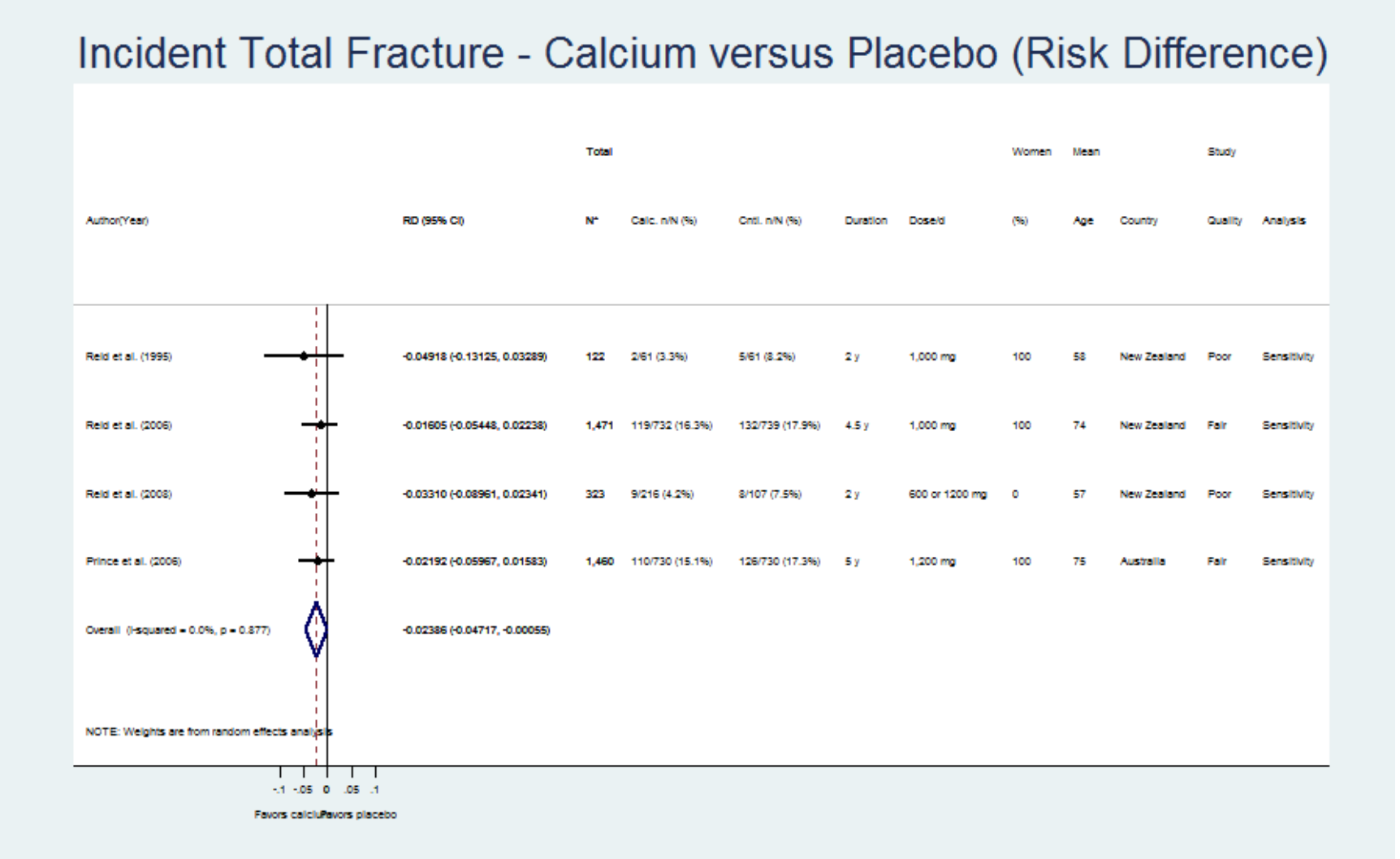
Appendix F Figure 4. Impact of Vitamin D Alone vs. Placebo on Incident Nonvertebral Fracture, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: CI=confidence interval; Cntl=control or placebo; n or N=number of participants; RR=relative risk ratio; UK=United Kingdom; US=United States; Vit D=vitamin D; y=year.

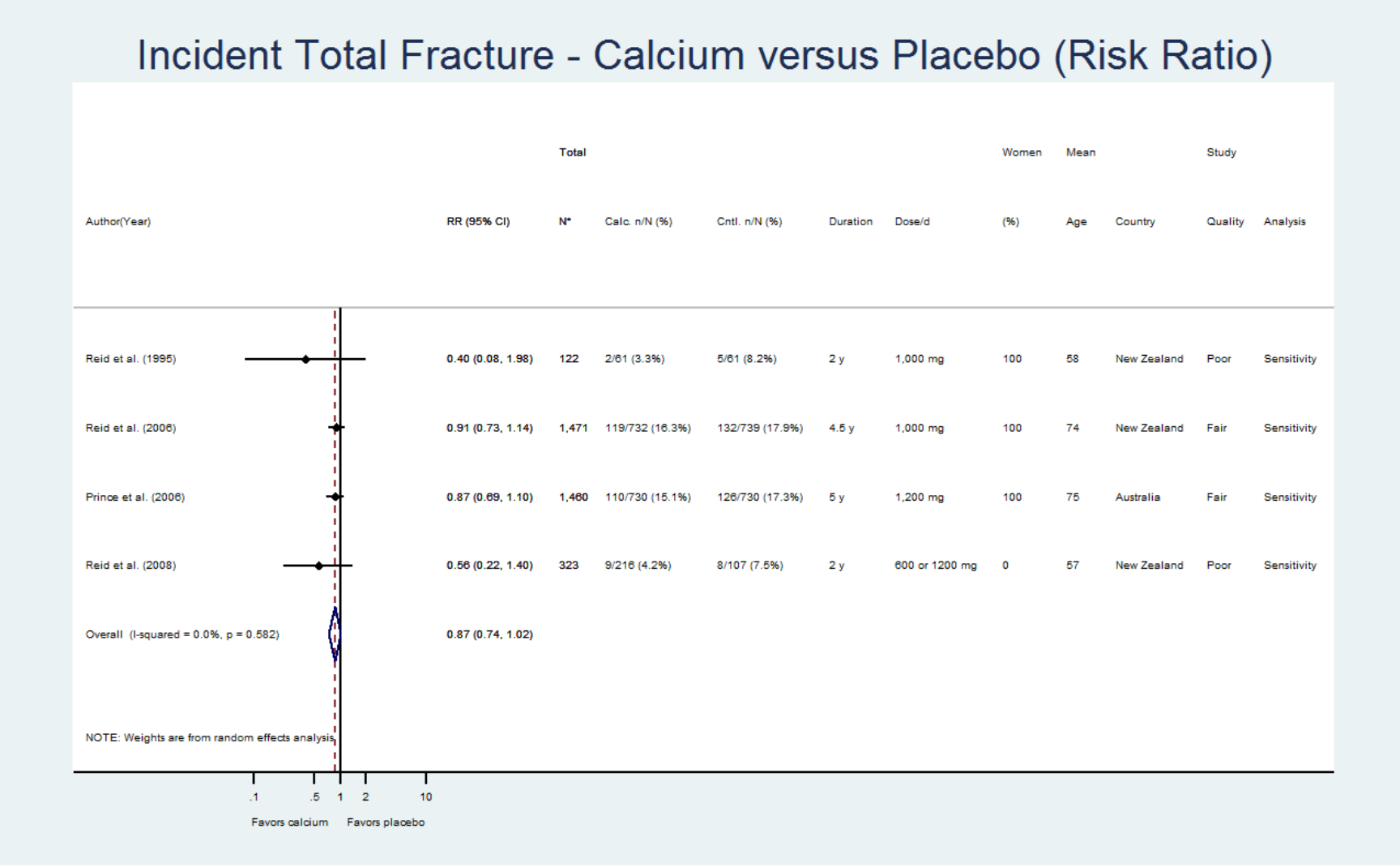
Appendix F Figure 5. Impact of Calcium Alone vs. Placebo on Incident Total Fracture, as Measured by Absolute Risk Difference, Sensitivity Analysis



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: Calc.=calcium; CI=confidence interval; Cntl=placebo; d=day; mg=milligram; n or N=number of participants; RD= risk difference; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

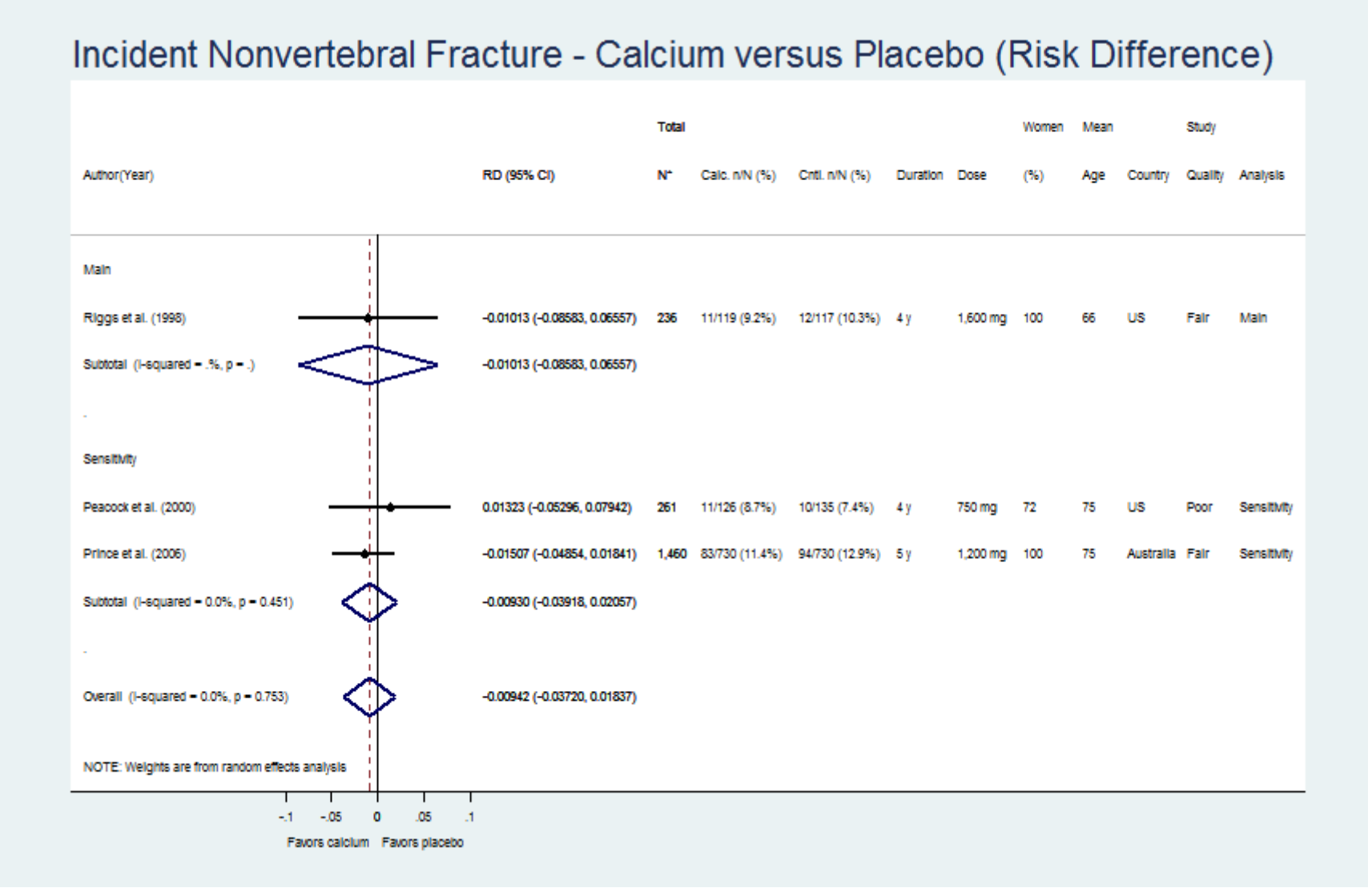
Appendix F Figure 6. Impact of Calcium Alone vs. Placebo on Incident Total Fracture, as Measured by Relative Risk Ratio, Sensitivity Analysis



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: Calc.=calcium; CI=confidence interval; Cntl=placebo; d=day; mg=milligram; n or N=number of participants; RR=relative risk ratio; y=year.

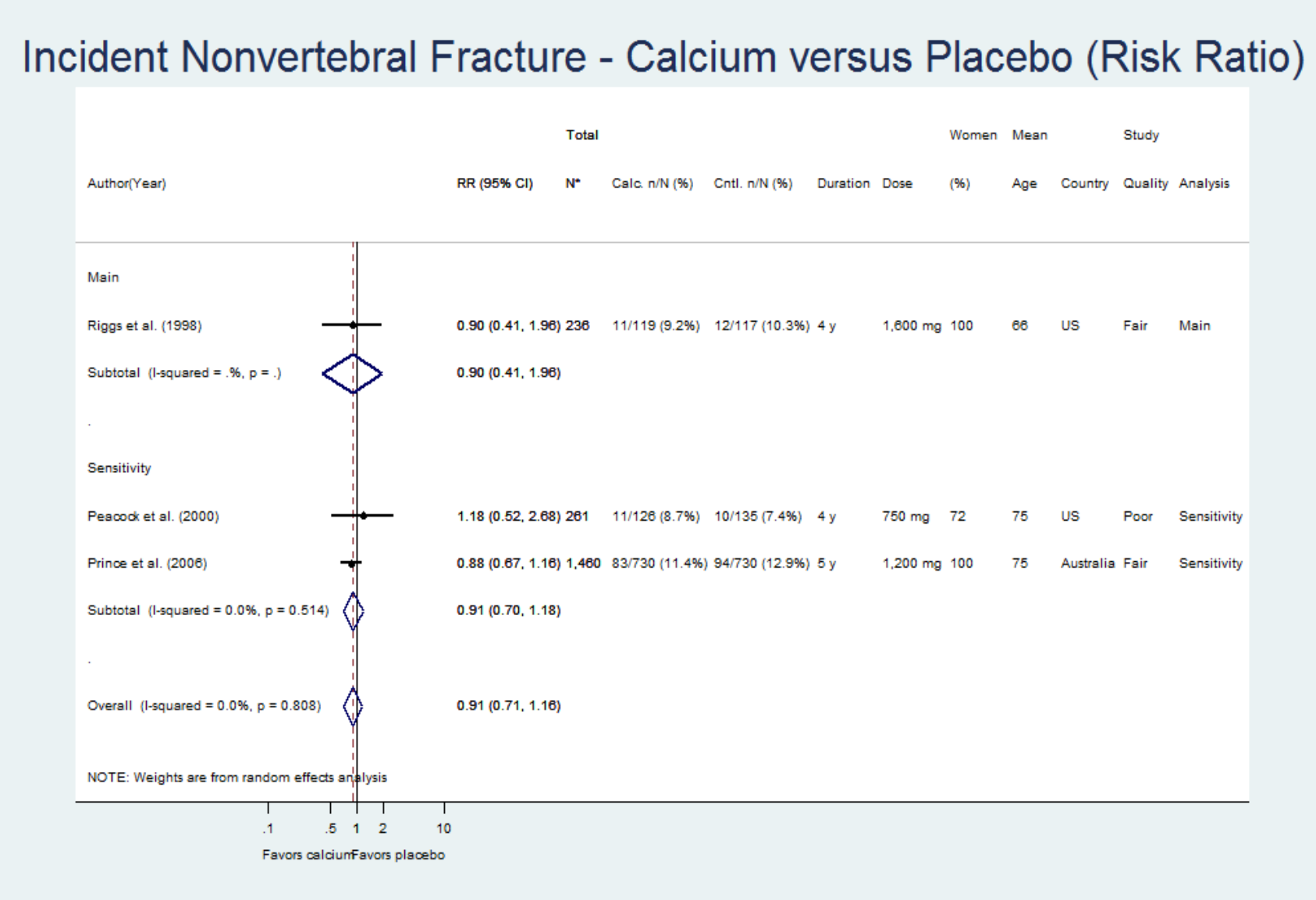
Appendix F Figure 7. Impact of Calcium Alone on Incident Nonvertebral Fracture, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: Calc.=calcium; CI=confidence interval; Cntl=placebo; d=day; mg=milligram; n or N=number of participants; RD= risk difference; US=United States; y=year. Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

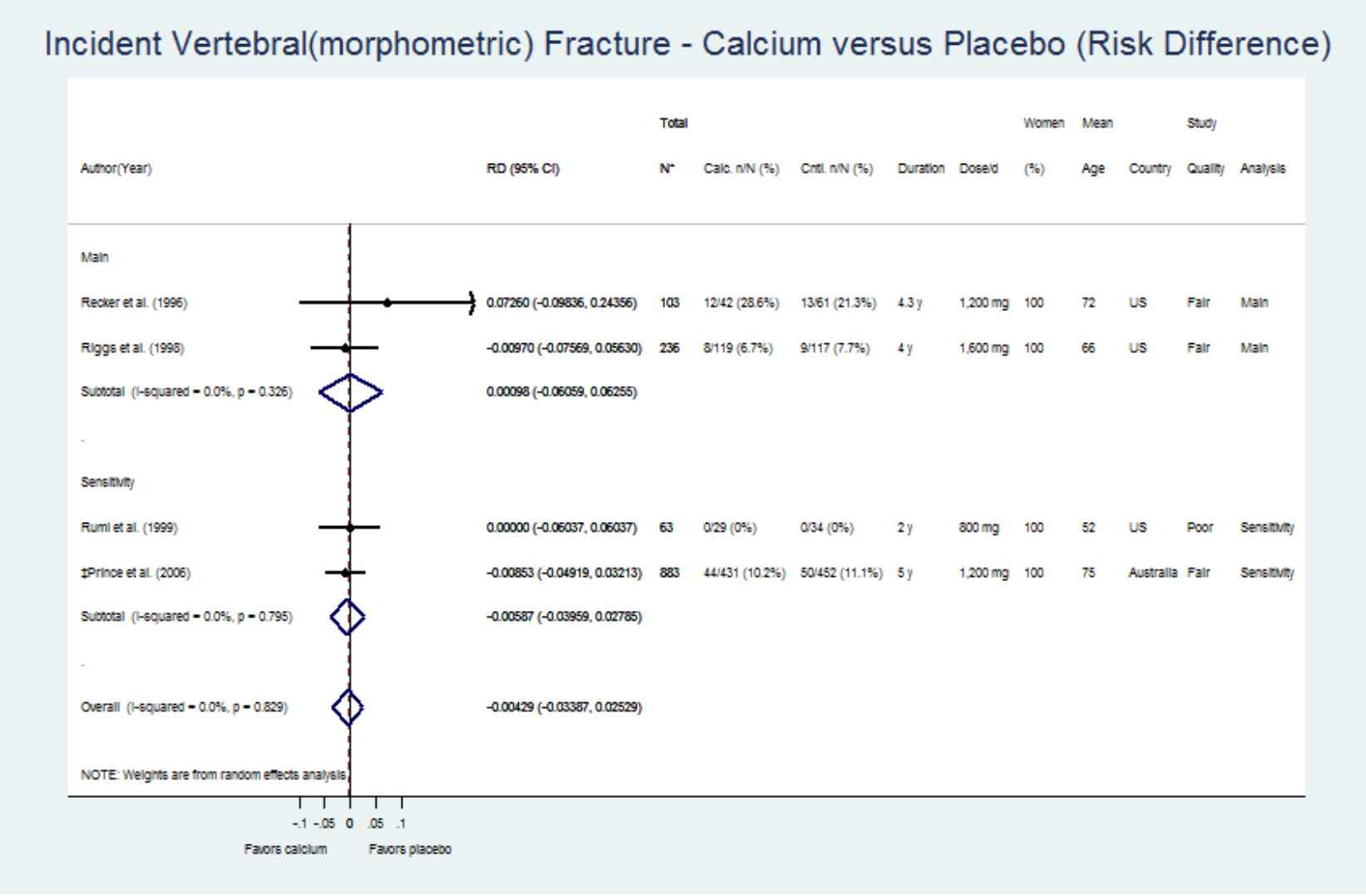
Appendix F Figure 8. Impact of Calcium Alone on Incident Nonvertebral Fracture, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: Calc.=calcium; CI=confidence interval; Cntl=placebo; d=day; mg=milligram; n or N=number of participants; RR=relative risk ratio; US=United States; y=year.

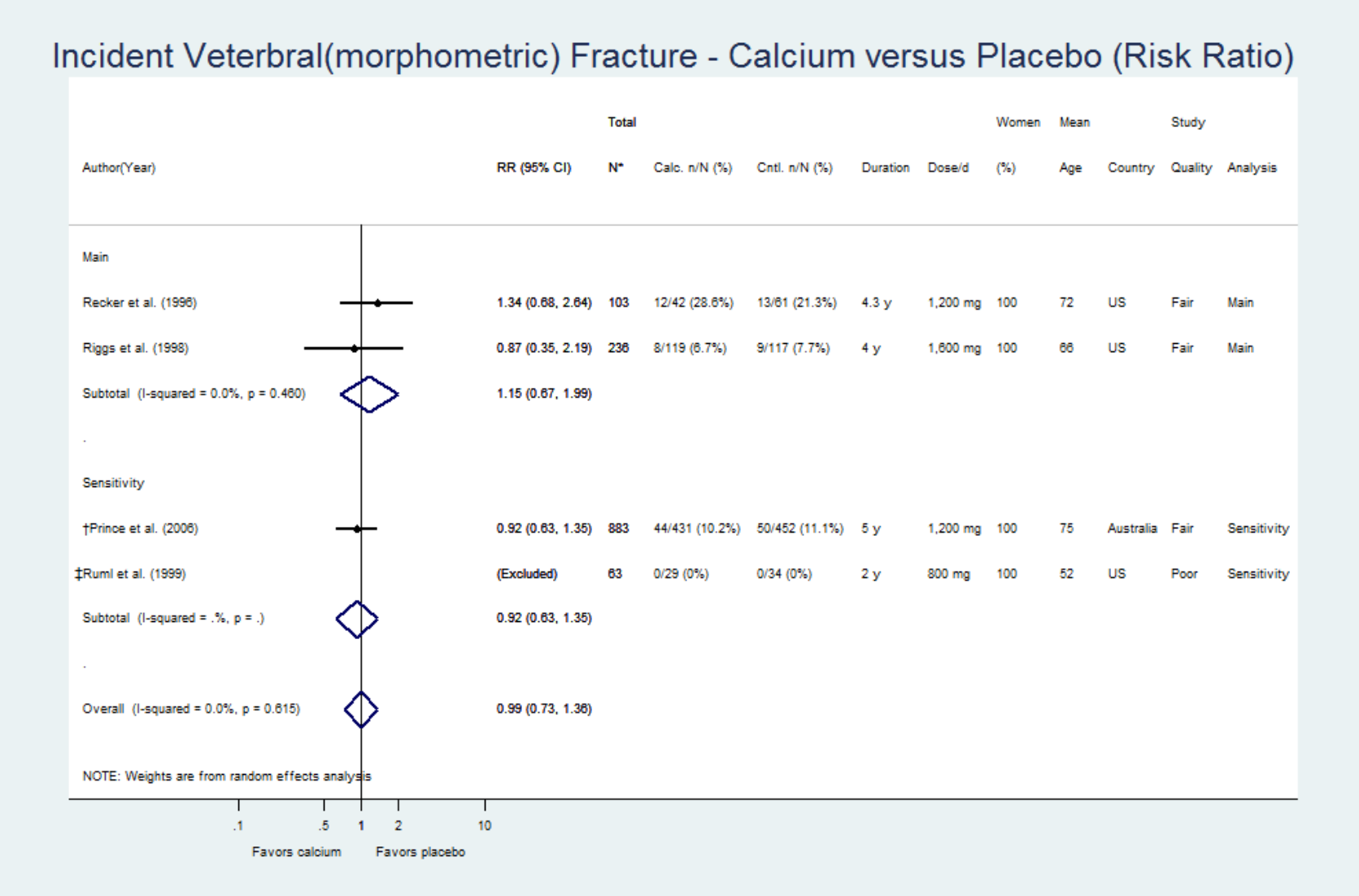
Appendix F Figure 9. Impact of Calcium Alone on Prevention of Morphometric Vertebral Fractures, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.
‡ The total N with available data for this outcome was different from the other outcomes analyzed in this study.

Abbreviations: Calc.=calcium; CI=confidence interval; Cntl=placebo; d=day; mg=milligram; n or N=number of participants; RD= risk difference; US=United States; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

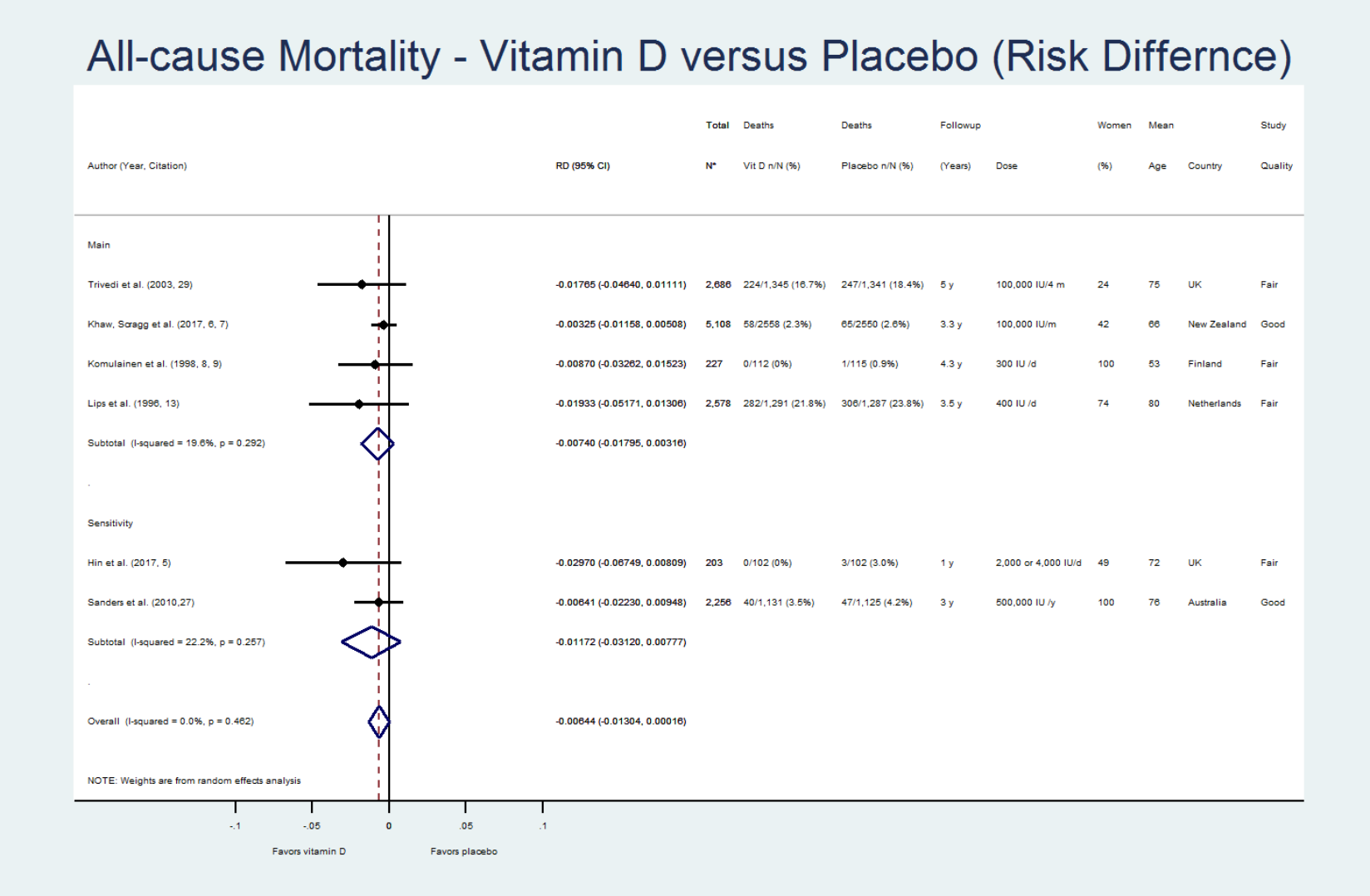
Appendix F Figure 10. Impact of Calcium Alone on Prevention of Morphometric Vertebral Fractures, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.
† The total N with available data for this outcome was different from the other outcomes analyzed in this study.
‡ This study is excluded from the meta-analysis because of 0 events in both groups.

Abbreviations: Calc=calcium; CI=confidence interval; Cntl=placebo; d=day; mg=milligram; n or N=number of participants; RR=relative risk ratio; US=United States; y=year.

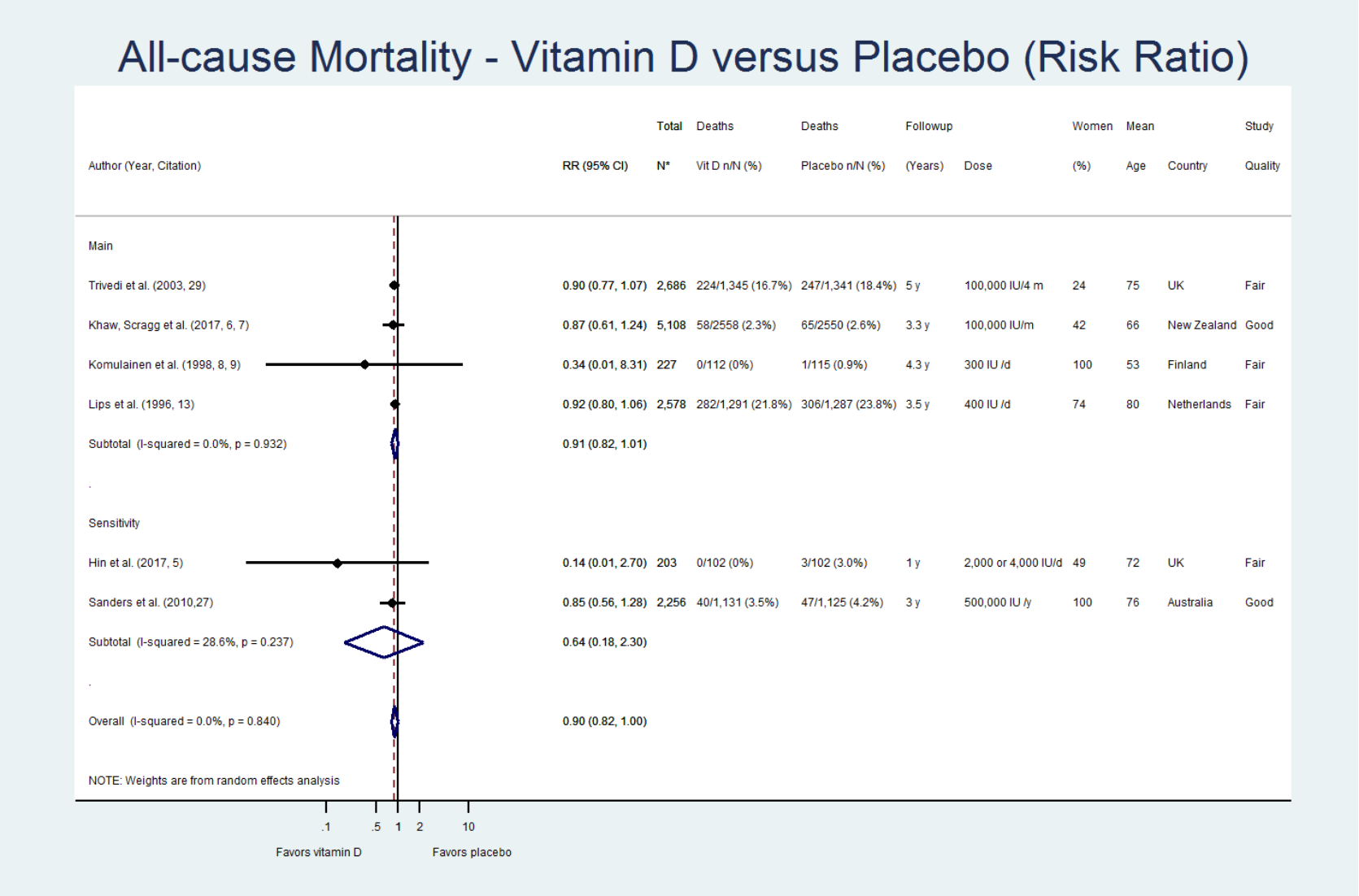
Appendix F Figure 11. Impact of Vitamin D Alone on All-Cause Mortality, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: CI=confidence interval; d=day; IU=international units; m=month; n or N=number of participants; RD= risk difference; UK=United Kingdom; Vit D=vitamin D; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

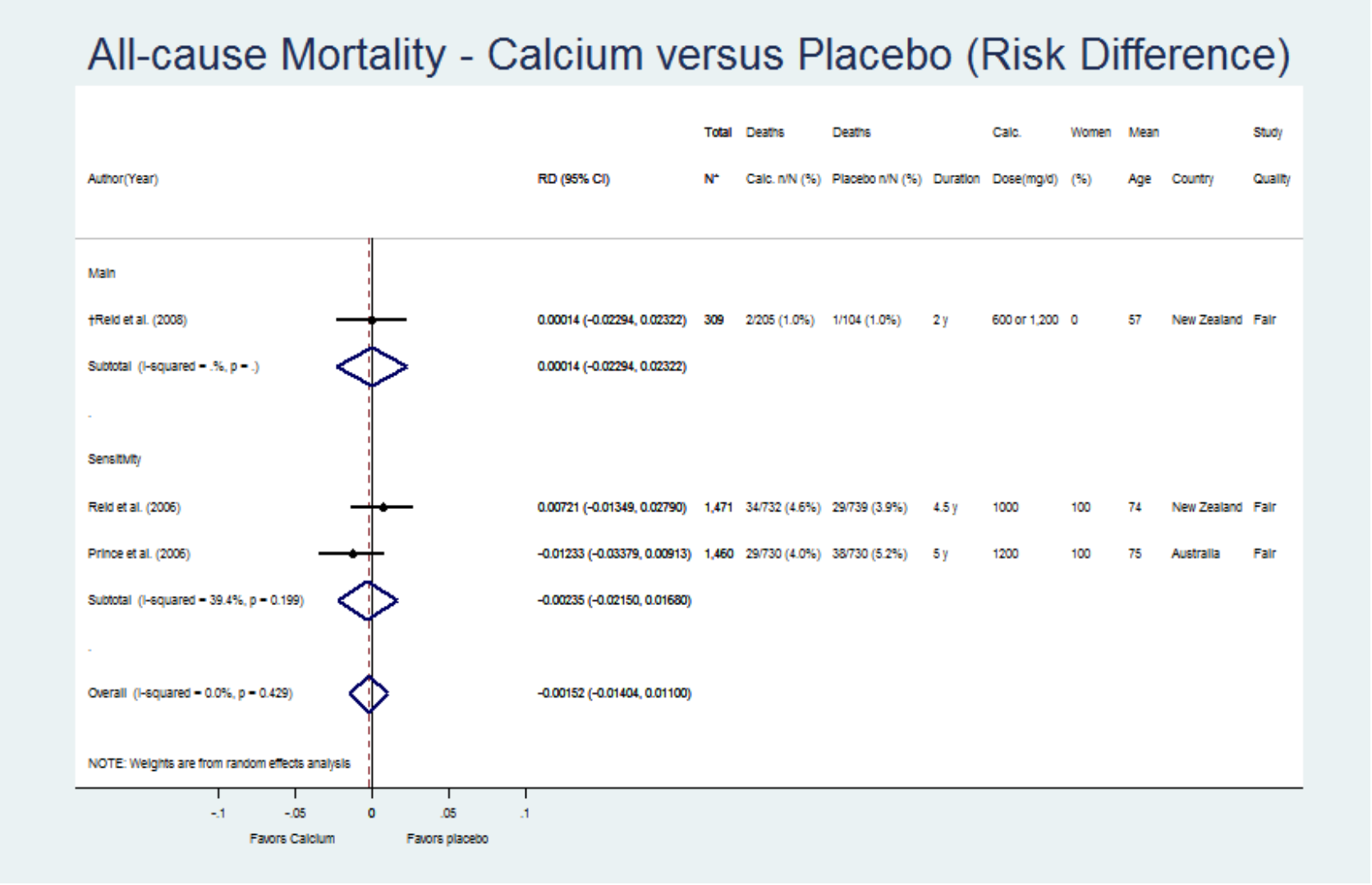
Appendix F Figure 12. Impact of Vitamin D Alone on All-Cause Mortality, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.

Abbreviations: CI=confidence interval; d=day; IU=international units; m=month; n or N=number of participants; RR=relative risk ratio; UK=United Kingdom; Vit D=vitamin D; y=year.

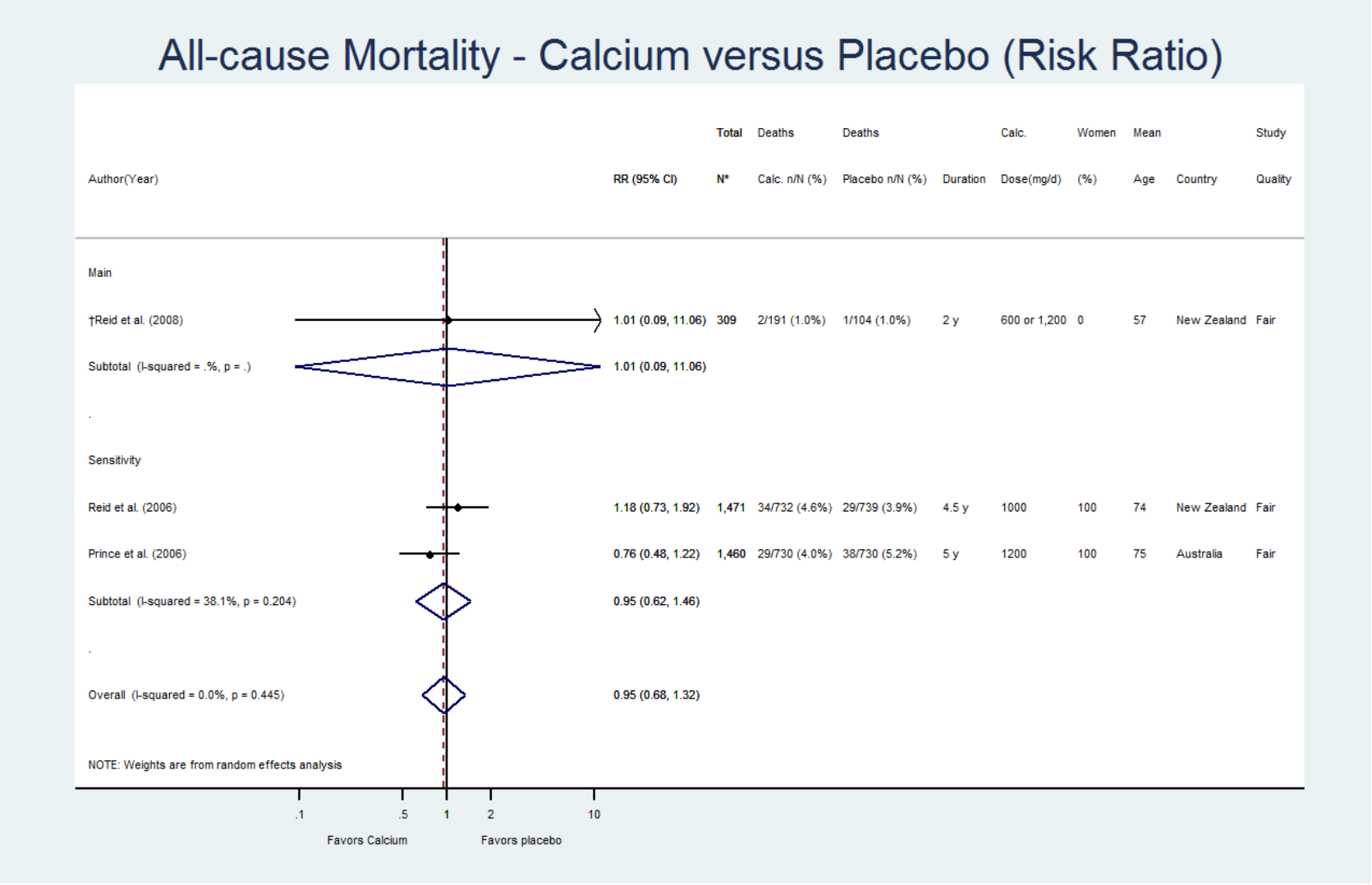
Appendix F Figure 13. Impact of Calcium Alone on All-Cause Mortality, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.
† The active comparator for this analysis is the combined 600 mg and 1,200 mg calcium study groups.

Abbreviations: Calc=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RD= risk difference; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

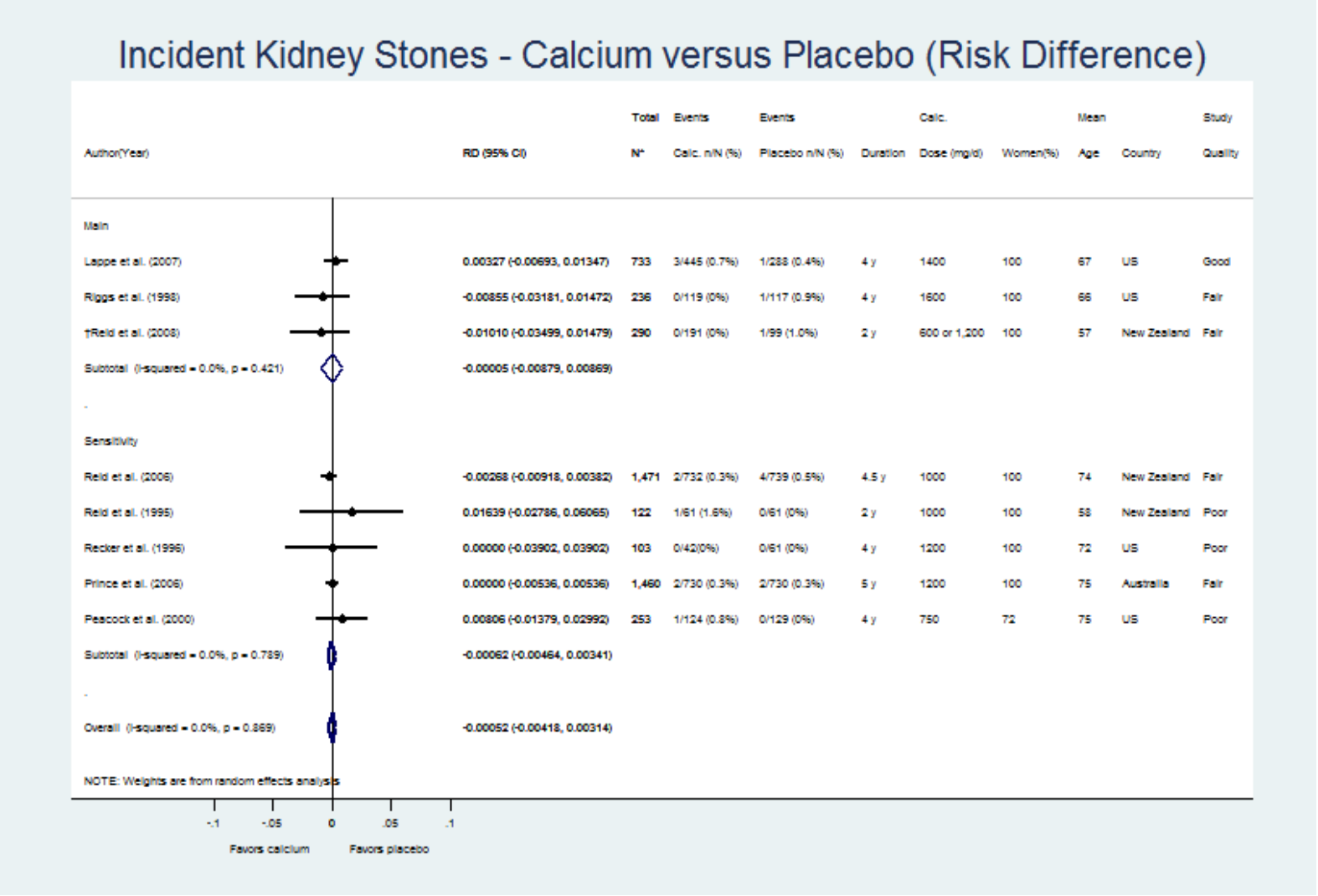
Appendix F Figure 14. Impact of Calcium Alone on All-Cause Mortality, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.
† The active comparator for this analysis is the combined 600 mg and 1,200 mg calcium study groups.

Abbreviations: Calc=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RR=relative risk ratio; y=year.

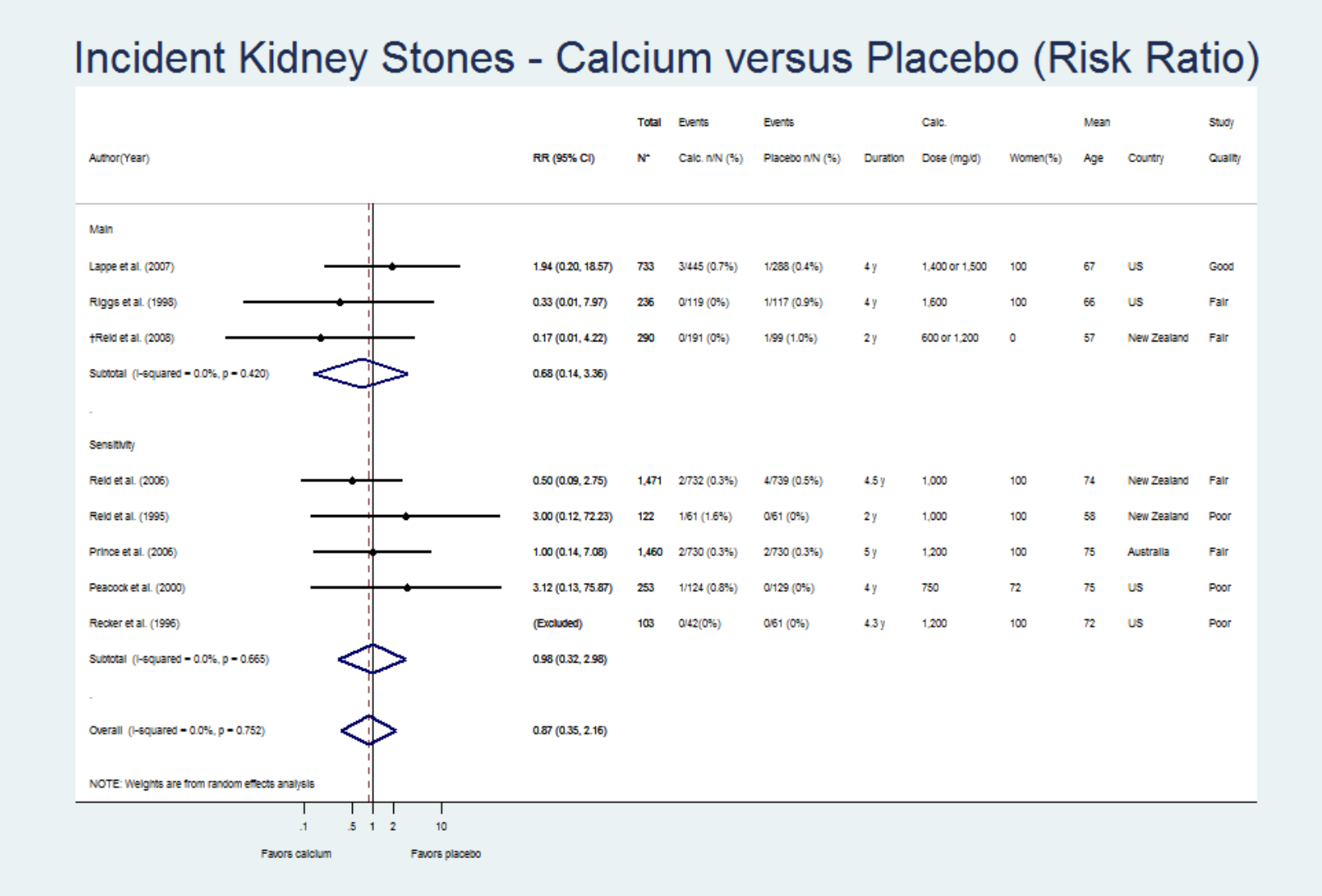
Appendix F Figure 15. Impact of Calcium Alone on Incident Kidney Stones, as Measured by Absolute Risk Difference



* Represents N analyzed, which may differ from the N randomized in some studies.
† The active comparator for this analysis is the combined 600 mg and 1,200 mg calcium study groups.

Abbreviations: Calc=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RD= risk difference; US=United States; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

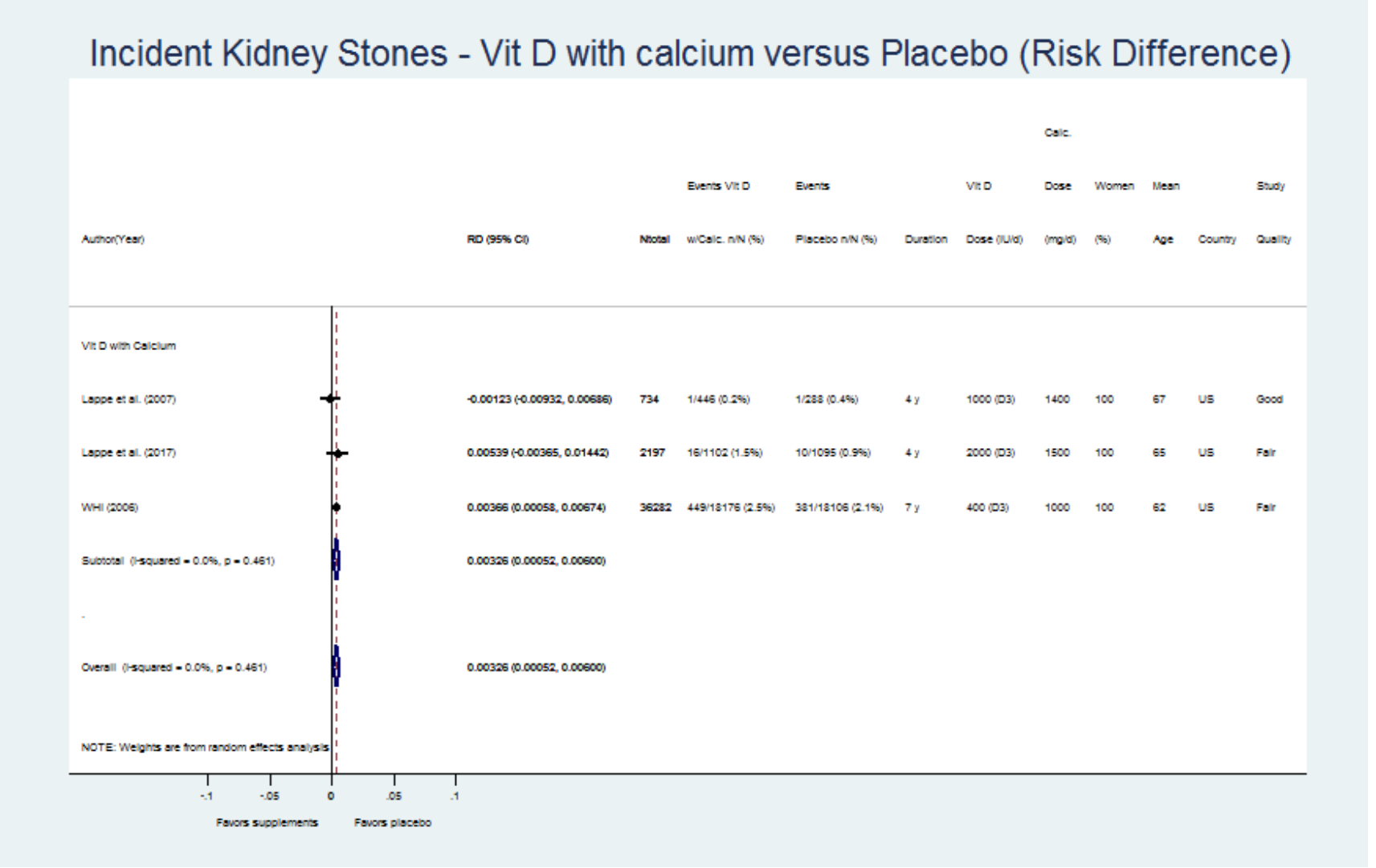
Appendix F Figure 16. Impact of Calcium Alone on Incident Kidney Stones, as Measured by Relative Risk Ratio



* Represents N analyzed, which may differ from the N randomized in some studies.
† The active comparator for this analysis is the combined 600 mg and 1,200 mg calcium study groups.

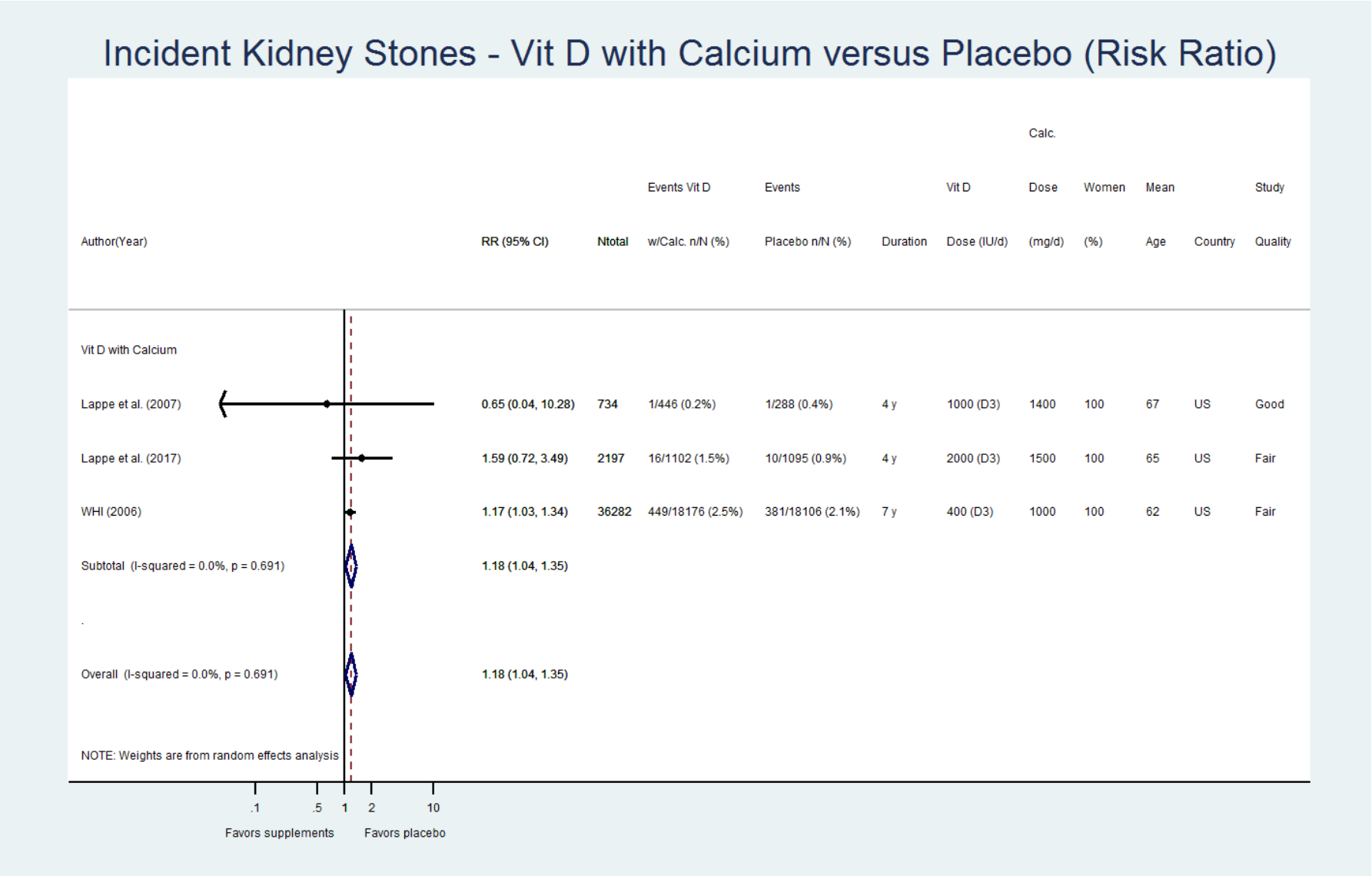
Abbreviations: Calc=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RR=relative risk ratio; US=United States; y=year.

Appendix F Figure 17. Impact of Vitamin D With Calcium on Incident Kidney Stones, as Measured by Absolute Risk Difference



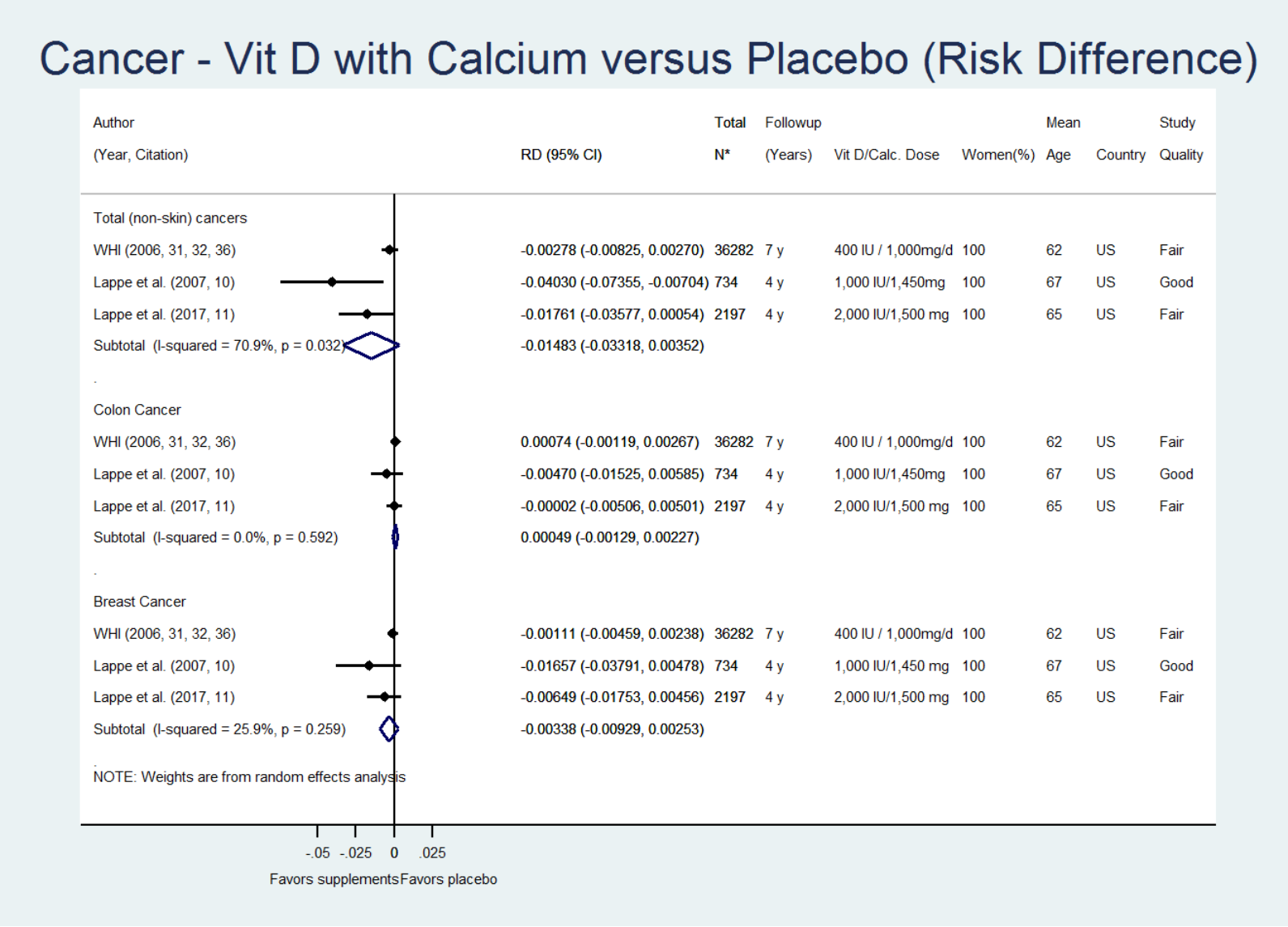
Abbreviations: Calc.=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RD= risk difference; US=United States; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

Appendix F Figure 18. Impact of Vitamin D With Calcium on Incident Kidney Stones, as Measured by Relative Risk Ratio



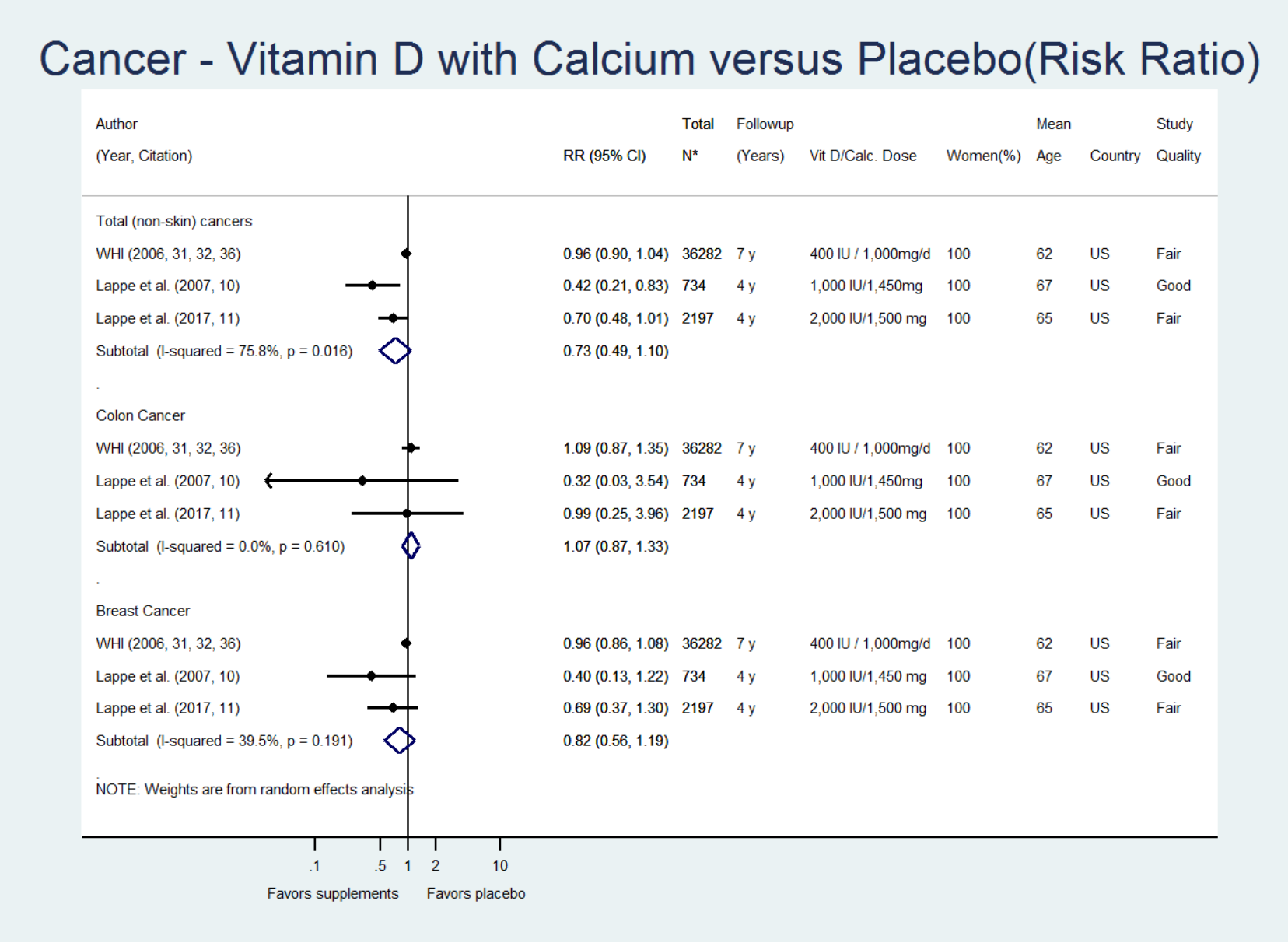
Abbreviations: Calc.=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RR=relative risk ratio; US=United States; y=year.

Appendix F Figure 19. Impact of Vitamin D With Calcium on Incident Cancer, as Measured by Absolute Risk Difference



Abbreviations: Calc.=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RD= risk difference; US=United States; y=year.
Note: Risk difference estimates in this forest plot are differences in proportions; multiply by 100 to obtain the percentage incidence. For example, -0.0081 is a risk decrease of 0.81%.

Appendix F Figure 20. Impact of Vitamin D With Calcium on Incident Cancer, as Measured by Relative Risk Ratio



Abbreviations: Calc.=calcium; CI=confidence interval; d=day; mg=milligrams; n or N=number of participants; RR=relative risk ratio; US=United States; y=year.

Appendix G. Summary of Trials in Progress

This appendix summarizes the details of seven ongoing trials of vitamin D supplementation.

The *Finnish Vitamin D Trial (FIND)* randomized men ages 65 or older and women ages 60 or older to one of three groups (daily 1,600 IU D_3, daily 3,200 IU D_3, or daily placebo) for 5 years.[192] The originally planned sample size was 18,000, but due to difficulties with funding and recruitment, the current study size is 2,500 participants. This study, which will complete final data collection in June 2018, includes cancer and cardiovascular outcomes; fracture outcomes are not included as outcomes in its trial registry listing.

The *Vitamin D and Omega-3 (VITAL)* trial is a study of 25,874 U.S. men ages 50 years or older and women ages 55 years or older who were randomized to one of four groups (daily vitamin D_3 2,000 IU supplement with fish oil placebo, vitamin D_3 placebo with fish oil supplement, vitamin D_3 and fish oil supplements, or double placebo).[193, 194] The primary study outcomes are incident cardiovascular and cancer outcomes; fracture outcomes are also being collected.[195] This 5-year study will complete final data collection in December 2020.

The *D-Health* trial is a parallel-group RCT among a population-based sample of community-dwelling adults between 60 and 84 years in Australia and is comparing 60,000 IU vitamin D_3 monthly to placebo.[196] The intervention duration and active study followup is planned for 5 years, with additional followup for an additional 5 years. The primary study outcome is all-cause mortality; secondary outcomes include total and colorectal cancer incidence. Fractures are a tertiary outcome will be ascertained through self-report in annual surveys. The planned sample size was 25,000; to date 21,315 participants are enrolled. The intervention will end in 2019, with additional followup planned through 2024.

The *DO-Health* trial is a 2 X 2 X 2 factorial design trial that recruited community-dwelling adults 70 years and over from 5 European countries.[197] It is evaluating the individual and combined benefit of vitamin D_3 (2,000 IU daily), omega-3 fatty acids, and a simple home exercise program. Five primary end-points are specified, including incident nonvertebral fractures confirmed with medical records or x-rays at 3 years. Incident total and hip fractures are secondary endpoints. The planned sample size was 2,152 and 2,159 participants are enrolled to date. The last data collection was scheduled for November 2017.

The *Vitamin D and Longevity (VIDAL)* Trial is a feasibility study in the UK that involves adults between age 65 and 84 years recruited from participating practices.[198] Some practices are participating in a double-blind intervention comparing vitamin D_3 (100,000 IU monthly) with placebo, while other practices are participating in an open-label intervention comparing vitamin D with placebo. This study will inform the design of a larger future trial assessing the impact of vitamin D supplementation on morbidity and mortality. In this feasibility trial, mortality and cancer incidence are the primary outcomes of interest. This trial is reported as ending in 2013, but we did not identify any published results.

The *Vitamin D and Type 2 Diabetes (D2d)* study includes 2,382 U.S. men and women ages 30 years and older at risk for diabetes; the study will evaluate whether 4,000 IU oral daily vitamin D_3 delays the onset of type 2 diabetes. This study will collect and report fracture outcomes as adverse events; final data collection is projected to be completed in December 2018.[199]

Appendix G. Summary of Trials in Progress

The *Vitamin D in Older People (VDOP)* study is a single-center RCT in 375 community-dwelling adults over age 70 years in the United Kingdom to evaluate the impact of three oral doses of monthly vitamin D_3 (12,000 IU; 24,000 IU; and 48,000 IU) BMD after 1 year.[200] The study does not include a placebo group and information on clinical fractures during the study will be collected as a safety measure. This study finished recruiting in 2013; findings have been presented in conferences but have not been published to date.