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Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Falls and Fractures in Community-Dwelling Adults: A Draft Evidence Update for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
[To be included in the final version of the report.]

Investigators:
[To be included in the final version of the report.]

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The information in this draft report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This draft report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Structured Abstract

Purpose: To review the evidence on supplementation with vitamin D, calcium, or both to prevent fractures and falls in community-dwelling adults for populations and settings relevant to primary care in the United States.

Data Sources: MEDLINE, the Cochrane Library, and trial registries through December 15, 2023; bibliographies from retrieved articles, outside experts, and surveillance of the literature through July 31, 2024.

Study Selection: Two investigators independently selected English-language studies using a priori defined criteria. We included randomized, controlled trials (RCTs) that evaluated supplementation with vitamin D, calcium, or both compared with placebo or no treatment among community-dwelling adults without known deficiency, bone conditions including osteoporosis, or prior fracture. Eligible outcomes included fractures, falls, all-cause mortality, healthcare utilization, quality of life, disability, adverse events, and kidney stones. Cohort studies with concurrent comparison groups were also eligible for harm outcomes. We excluded studies with poor methodological quality and studies conducted in developing countries.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated methodological quality for all included studies using predefined criteria. When at least two similar studies were available, we conducted meta-analyses.

Data Synthesis: We included 20 unique RCTs (in 54 publications). Three RCTs evaluated vitamin D with calcium compared with placebo, one RCT evaluated vitamin D with calcium compared with no treatment, one RCT evaluated vitamin D with calcium compared with calcium alone as the control, 13 RCTs evaluated vitamin D alone compared with placebo, and two RCTs evaluated calcium alone compared with placebo. Twelve RCTs evaluated daily doses of vitamin D3 that ranged from 300 to 4,000 international units (IU) and six RCTs evaluated weekly, monthly, or quarterly dosages of vitamin D3 with a daily dose equivalent ranging from 833 IU to 3,333 IU. Eight RCTs were conducted exclusively among postmenopausal women; the rest were conducted among mixed populations of men (age 50 years or older) and postmenopausal women where the proportion of women ranged from 24 to 74 percent. Two trials from the United States enrolled a racially diverse population. The followup across studies ranged from 9 months to 7 years, with one exception.

The pooled risk ratio (RR) for vitamin D (with or without calcium) supplementation compared with control on hip fracture was 0.99 (95% confidence interval [CI], 0.86 to 1.13; 7 RCTs; 88,364 participants) corresponding to an absolute risk difference (ARD) of zero fewer participants with hip fractures per 1,000 supplemented (95% CI, from 1 fewer to 1 more). The pooled RR for vitamin D supplementation alone compared with control on major osteoporotic fracture (MOF) was 0.93 (95% CI, 0.78 to 1.10; 3 RCTs; 48,883 participants) corresponding to an ARD of two fewer participants with MOF per 1,000 supplemented (95% CI, from 6 fewer to 3 more). The pooled RR for vitamin D (with or without calcium) supplementation compared with control on any fracture was 0.96 (95% CI, 0.92 to 1.00; 5 RCTs; 85,429 participants) corresponding to an ARD of three fewer participants with fractures per 1,000 supplemented (95% CI, from 7 fewer to 0 more). The pooled RR for vitamin D (with or without calcium)

supplementation compared with control on incidence of one or more falls was 0.99 (95% CI, 0.97 to 1.01; 8 RCTs; 36,744 participants) corresponding to an ARD of five fewer participants with one or more falls per 1,000 supplemented (95% CI, from 15 fewer to 5 more). The pooled RR for vitamin D (with or without calcium) supplementation compared with control on all-cause mortality was 0.96 (95% CI, 0.91 to 1.02; 16 RCTs; 109,782 participants) corresponding to an ARD of two fewer deaths per 1,000 supplemented (95% CI, from 4 fewer to 1 more). Only one RCT reported on quality of life or disability (no benefit of supplementation) and only one study reported on transition to nursing home (no benefit of supplementation).

Fewer than half of included studies systematically reported on adverse events (AEs) or serious AEs (SAEs); however, zero to very few SAEs were reported among included studies. For kidney stones, we calculated the pooled RR for vitamin D (with or without) supplementation compared with control as 1.11 (95% CI, 1.03 to 1.21; 10 RCTs; 99,036 participants) corresponding to an ARD of two more participants with kidney stones per 1,000 supplemented (95% CI, from 1 more to 5 more). Two RCTs comparing calcium supplementation alone with placebo reported the incidence of participants with kidney stones, but events were rare, so estimates were imprecise (pooled RR, 1.07 [95% CI, 0.17 to 6.77]; 2 RCTs; 969 participants).

Limitations: There was heterogeneity in some outcome specifications and ascertainment, and few trials that assessed the impact of supplementation with calcium alone.

Conclusions: Among community-dwelling populations of postmenopausal women and older men without known vitamin D deficiency, bone conditions, or prior fracture, the evidence suggests no reduction in fractures, falls, or mortality from supplementation with vitamin D (with or without calcium) compared with placebo. The evidence also suggests no difference in serious adverse events; however, a very small absolute increase in the incidence of kidney stones from vitamin D supplementation (with or without calcium) was observed. The evidence on supplementation with calcium alone was limited for all outcomes reported.

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Chapter 1. Introduction

Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2018 recommendation on empiric supplementation with vitamin D, calcium, or both to prevent falls and fractures in adults.[1] In 2018, the USPSTF assigned a D recommendation for vitamin D supplementation with dosages of 400 international units (IU) or less and for calcium supplementation with doses of 1,000 mg or less for community-dwelling postmenopausal women.[1] The USPSTF considered the evidence insufficient for empiric supplementation with higher doses of vitamin D and calcium and for supplementation in men or premenopausal women.[1] These recommendations were based on a 2018 evidence review that was primarily focused on fracture outcomes.[2] In a separate recommendation, the USPSTF assigned a D recommendation[3] for empiric vitamin D supplementation to prevent falls in older adults based on evidence[4] suggesting no benefit in preventing falls and small to moderate harms, particularly with a regimen that uses a high (500,000 IU) annual dosage. The USPSTF has assigned I grades to two related recommendations: screening for vitamin D deficiency[5, 6] and empiric supplementation with vitamin D to prevent cancer and cardiovascular disease.[7, 8]

Condition Definition

Empiric supplementation refers to the use of dietary supplements, without assessment of an individual's diet, nutritional status, serum levels, or fracture risk. This is in contrast to repletion, which is targeted use of vitamin D in persons with known low serum levels. Vitamin D, a fat-soluble prohormone, is one of several hormones that regulate calcium and phosphorus levels, which is critical to bone mineralization.[9] Calcium, a dietary micronutrient, forms the mineral hydroxyapatite, which deposits into the organic skeletal matrix to provide bone structure and strength.[9] In addition to its role in bone metabolism, inadequate vitamin D levels may cause muscle weakness and increased postural imbalance contributing to falls, which may also increase the risk of fracture.[10] The World Health Organization (WHO) defines falls as "an event that results in a person coming to rest inadvertently on the ground or floor or other lower level."[11] Fragility fractures, also known as "osteoporotic," "low-energy," or "low-trauma," are defined as fractures that are sustained during a fall from standing height or less and that would not give rise to a fracture in most healthy individuals.[12] The definition of an injurious fall varies, but typically refers to falls requiring medical attention.

Etiology, Natural History, and Risk Factors

Calcium and vitamin D are nutrients essential to bone health and along with an array of hormones contribute to bone metabolism. Bone health, specifically bone mass, is influenced by genes, hormones, underlying medical conditions, physical activity, and diet and evolves across life stages. Genes are thought to be the chief determinant of "peak" bone mass, but any of these other factors can negatively influence the development and maintenance of strong bones.

Individuals make most of their required vitamin D through biosynthesis in the skin resulting from sun (i.e., ultraviolet light) exposure. 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 not common, 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.[13] Three hormones—parathyroid, calcitonin, and calcitriol (the physiologically active form of vitamin D)—regulate calcium homeostasis. Because of vitamin D production in the skin and the fortification of food and beverages with vitamin D, clinical vitamin D deficiency manifested as osteomalacia in adults is rare. Considerable debate exists about the relevance of subclinical vitamin D deficiency (i.e., deficiency based on serum levels alone) and the serum levels associated with optimum health.[14-16]

Calcium absorption in the gastrointestinal system is facilitated by calcitriol, which also helps to maintain serum levels of calcium and phosphate to prevent hypocalcemic tetany.[10] Clinically overt calcium deficiency is rare; 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.[9] No accurate serum measure of whole-body calcium exists. Calcium ion concentration is exquisitely regulated in extracellular fluid so that serum levels do not increase in response to increases in intake; therefore, identifying individuals who are "calcium deficient" is not currently feasible.

Vitamin D and calcium are common adjunctive treatments used in people with osteoporosis. Osteoporosis is more common among certain races and ethnicities, specifically those who self-identify as White or Asian. It is unclear whether serum vitamin D levels considered "optimal" for bone and mineral metabolism in White populations are the same as those in non-White populations. The National Institutes of Health convened an expert panel in 2017 to discuss the vitamin D paradox in Black Americans.[17] The nature of this paradox is that despite lower measures of vitamin D status in Black persons, the incidence of falls, fractures, and osteopenia and osteoporosis are lower than in White persons.[17] Proposed factors thought to be related to this finding were adiposity, skin pigmentation, and vitamin D binding protein polymorphisms, though no one biologic factor explains the entire paradox.[17] Further, findings from a nested case-control study within the Women's Health Initiative Observational Study reported a paradoxical increase in fractures among Black women with serum vitamin D levels equal or greater than 20 ng/ml as compared to those with serum levels less than 20 ng/ml.[18] This poses a potential equity concern with recommendations for widespread vitamin D supplementation.

Fragility fractures occur as a result of bone fragility from bone loss or structural changes,[19] though not all fragility fractures are directly attributable to deficiencies in vitamin D or calcium or osteoporosis. Fragility fractures of the hip, proximal humerus (shoulder), distal forearm, and vertebra are considered major osteoporotic fractures (MOF), though fragility fractures can occur at other sites such as the clavicle. Nonhip fragility fractures are more common than hip fractures but typically result in less morbidity. Vertebral fractures are estimated to occur at 10 times the rate of hip fractures, and unlike most nonvertebral fragility fractures, vertebral fractures may occur without a fall.[20]

Risk Factors

Risks of Low Serum Vitamin D Levels

Several types of risk factors exist for low serum vitamin D levels. These include risks related to reduced skin synthesis (dark skin, residence at high latitudes, aging, seasonal reduction in sunlight, time spent indoors vs. outdoors), decreased bioavailability (fat malabsorption, decreased absorption following gastrointestinal surgery, sequestration in body fat of obese individuals), increased catabolism (anticonvulsants, antiretrovirals), and decreased conversion (liver or kidney disease).[10, 21]

As previously discussed, serum calcium is not a measure of whole-body calcium stores and thus cannot be used to determine risk because it is exquisitely maintained to preserve cellular functions. However, chronic inadequate calcium intake may be more common among the following populations: postmenopausal women, individuals with lactose intolerance or a cow's milk allergy, and vegens.[22, 23]

Risks for Falls

Several risk factors have been identified for falls, including living alone, dependence in instrumental activities of daily living, prior falls, being underweight, cognitive impairment, certain medications, impaired balance, poor vision, and heart disease.[20, 24] Advancing age and falls are the major risk factors for incident (i.e., first) fragility fractures, although the precise contribution of each factor to fracture risk is difficult to determine as these factors are often confounded by comorbid conditions and increased incidence of falls among the elderly.[19, 20] Recent data from the National Health and Aging Trends Study identified several social and environmental characteristics associated with recurrent falls including lower education, lower income, financial hardship, home disrepair, neighborhoods without sidewalks or with high social deprivation, living in nonmetropolitan counties, and financial hardship.[25]

Risks for Fractures

Fractures occur in 10 to 15 percent of falls,[19] and more than 90 percent of hip fractures are related to falls.[26] Although bone mineral density (BMD) is an important risk factor for fragility fractures in both men and women, advancing age is a more critical determinant.[20, 27] Older adults have much higher fracture rates than younger adults with the same bone density because of concurrent increasing risk from declining bone quality and an increasing tendency to fall.[28] The risk of fracture increases 1.5- to 2.5-fold for every standard deviation decrease in BMD.[19, 29, 30] However, the majority of fragility fractures actually occur in persons with bone density in the osteopenic (T-score between -1.0 and -2.5) or normal range (T-score $\geq$ -1.0).[31-34]

Prevalence and Burden of Disease

The National Academy of Medicine (NAM, formerly the Institute of Medicine) selected bone health and calcium metabolism to serve as the basis for establishing dietary reference intakes for vitamin D and calcium (**Appendix A Table 1**).[9, 10] The recommended dietary allowances, which range from 600 IU to 800 IU vitamin D and 1,000 mg to 1,200 mg calcium based on age, refer to

all dietary sources, including food, beverages, and dietary supplements.[10] Further, these allowances assume minimal sun exposure.[10]

Serum 25-hydroxyvitamin D, also referred to as 25(OH)D, is considered the main biomarker of total body vitamin D status and reflects intrinsic production within the skin and vitamin D obtained through food, beverages, and dietary supplements.[10] The serum 25(OH)D level that is optimal for skeletal and extraskeletal health is controversial. Serum 25(OH)D concentrations can also vary depending on the assay method used. No single serum level is associated with vitamin D deficiency in all individuals. As a result, the optimal level for the general population or specific groups continues to be actively investigated. Based on data before 2011, NAM described the relationship between serum 25(OH)D levels and health based on four categories (**Appendix A Table 2**).[9] It is important to note that these levels were established based on population data and individual needs may vary. Serum levels less than 12 ng/mL is considered "at risk" for deficiency, and serum levels between 12 and 20 ng/mL may be considered inadequate for bone and overall health in healthy individuals.[9]

Data from the 2015–2018 U.S. National Health and Nutrition Examination Survey (NHANES) regarding the usual intake of vitamin D and calcium from food and beverages suggests that most adults (males and females) do not meet the estimated average requirement for vitamin D from dietary sources and that many adults age 50 years or older do not meet the estimated average requirements for calcium (**Appendix A Table 3**).[35] However, because most vitamin D is produced by the skin through exposure to ultraviolet light such as the sun, rather than obtained through dietary sources, it is challenging to estimate the proportion of individuals who do not have an adequate daily dietary intake of vitamin D.[35, 36] Serum 25(OH)D levels in individuals are typically higher than those predicted based on intake alone because of the vitamin D synthesized through sun exposure.[35]

Burden of Disease

Although data suggest that many adults may not be getting adequate vitamin D or calcium intake, age-standardized incidence rates of fragility fractures have been decreasing.[37] Experts hypothesize that this decline is due to increasing rates of obesity, increasing use of antiresorptive agents, and birth cohort effects.[38] However, recent studies suggest that the decline in age-standardized fracture rates may have plateaued in the last 5 to 7 years (**Appendix A Table 4**).[39-41] Despite the decrease in age-standardized fracture incidence rates, the absolute incidence of fragility fractures is increasing because the population is aging; the mean age for hip fractures is 80 years.[20] The number of Medicare beneficiaries with at least one new fragility fracture in 2016 was 1,794,700, for an overall incidence of 332 new fractures per 10,000 beneficiaries.[42] Further, the morbidity and mortality associated with hip fractures is high; between 20 to 30 percent of patients die within 1 year of a hip fracture, with men experiencing a significantly higher mortality after fracture than women.[39] Nearly 40 percent of those who experience a hip fracture are unable to walk independently at 1 year, and 60 percent require assistance with at least one essential activity of daily living.[30]

As previously discussed, most serious fractures result from falls. About 14 million adults age 65 years or older (27.6%) reported falling at least once in the previous year according to 2020 data from the Center for Disease Control's Behavioral Risk Factor Surveillance System.[43] Further, 78

deaths per 100,000 people were attributed to unintentional falls in 2021, making falls the leading cause of unintentional injury among older adults.[43]

Interventions/Treatment

Treatment for symptomatic calcium deficiency or vitamin D deficiency is outside the scope of this review, which will focus on supplemental vitamin D or calcium or both, among generally healthy populations without knowledge of existing diet, serum vitamin D levels, or underlying medical conditions associated with bone metabolism. In other words, the focus is on supplementation in unselected general adult populations without known metabolic bone disease.

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 literature generally supports that D_3 is more effective at increasing serum 25(OH)D levels as compared to D_2, but there is considerable debate about the clinical significance with respect to health outcomes.[44-51] Nearly all studies included in the prior update for this topic used D_3, and no professional societies recommend using one formulation over the other. The relationship between increased vitamin D intake through supplements and increased serum levels of vitamin D is well established.[2, 52] Higher dosages of supplements lead to higher serum levels; however, the relationship is not linear.[9]

Calcium supplements are typically formulated as oral salts; calcium carbonate and calcium citrate are the most common preparations, and dosing is based on the amount of elemental calcium present.

Current Clinical Practice

Vitamin D and calcium—either alone or in combination—are often recommended for optimizing "bone health." They are often used as adjuncts for the prevention and treatment of osteoporosis and 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, and are often used by people with higher risk for fracture (e.g., postmenopausal women, elderly people).

In 2024, the Endocrine Society recommended empiric vitamin D supplementation (defined as vitamin D intake that exceeds Dietary Reference Intakes and is implemented without testing for 25(OH)D) in the general population aged 75 years and older because of the potential to lower the risk of mortality.[53] No other medical or specialty organizations have recommendations for universal supplementation. Further, most organizations do not distinguish between recommendations for total dietary intake of these nutrients vs. recommendations for supplemental intake beyond what is obtained through daily food and beverages. **Appendix A Table 5** summarizes recommendations of professional organizations related to the use of vitamin D and calcium supplementation.

Based on NHANES 2017–2018 data, vitamin D is the most common single supplement used in the United States and the second most commonly used supplement after multivitamins.[54] In these data, the use of single vitamin D supplements was 36.9 percent among adults age 60 years or older.[54] Use among younger adults was lower (24% among those ages 20 to 39 years; 30% among those ages 40 to 59 years). Calcium was used by 19.2 percent of adults age 60 years or older, with less frequent use by younger adults.[54] It is unclear how much the use of these supplements is provider recommended vs. self-prescribed.

Chapter 2. Methods

Key Questions and Analytic Framework

The Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and key questions (KQs) for this review. This update builds on previous evidence reviews for the USPSTF.[2, 55] This update also now includes fall-related outcomes and updates a portion of a previous USPSTF review on interventions to prevent falls in older adults.[4]

The analytic framework illustrates the KQs that guided the review (**Figure 1**).

1. Does supplementation with vitamin D, calcium, or both prevent fractures and falls or reduce fracture- and fall-related morbidity and mortality?

2. What are the harms of supplementation with vitamin D, calcium, or both?

Data Sources and Searches

In consultation with the review team, our information specialist searched PubMed/MEDLINE and the Cochrane Library for English-language articles. The search for fracture-related outcomes was limited to September 9, 2016, through December 15, 2023, to build on the search from the previous review.[2] The search for fall-related outcomes was not limited by date. We used Medical Subject Headings and keywords as search terms when appropriate to describe relevant populations, interventions, outcomes, and study designs and applied additional limits on the completed search to remove selected publication types. The complete search strategy for all data sources is detailed in **Appendix B.1**. The PubMed/MEDLINE and Cochrane Library searches were peer-reviewed by another information specialist following the 2015 Peer Review of Electronic Search Strategies (PRESS) guidelines.[56] We also searched the ClinicalTrials.gov registry from March 21, 2017, to December 15, 2023. In addition to database searches, we reviewed reference lists of relevant systematic review articles. Since September 2022, we conducted ongoing surveillance through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on July 31, 2024.

Study Selection

We developed inclusion and exclusion criteria for populations, interventions, comparators, outcomes, settings, and study designs with input from the USPSTF (**Appendix B.2**). We included good- or fair-quality, English-language studies focused on community-dwelling adults with no known disorders related to vitamin D, calcium, or bone metabolism in countries categorized as *very high* on the United Nations Human Development Index.[57] We excluded studies that enrolled participants based on low serum vitamin D levels or known deficiency (as

defined by the study); 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. However, we included studies with up to 20 percent of such participants in our analysis.

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 vitamin D analogs 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. We selected studies for which the comparator groups were no treatment or placebo. 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, physical activity, or environmental interventions. We excluded studies that utilized dietary interventions, rather than supplementation, to increase vitamin D and/or calcium intake.

For KQ 1, we selected studies that reported incident fractures, fracture-related morbidity and mortality, incident falls, injurious falls, recurrent falls, fall-related morbidity and mortality, all-cause mortality, disability as measured by instrumental activities of daily life, quality life as measured by validated instruments, hospitalization for fall-related injuries, emergency department visits for fall-related injuries, and institutionalization. For KQ 2, we selected studies that reported on several prespecified harms including symptomatic acute or chronic vitamin D or calcium toxicity, incident symptomatic kidney stones, and serious adverse events (SAEs). For this update, we did not include incident cancer or cardiovascular outcomes as had been included in the prior report because a related review in support of the USPSTF's recommendation on Vitamin, Mineral, and Multivitamin Supplementation to Prevent Cardiovascular Disease and Cancer comprehensively addresses these outcomes.[8]

RCTs were eligible for KQ 1 and KQ 2; prospectively conducted nonrandomized studies of interventions (NRSIs) with concurrent comparison groups with a primary study aim to evaluate the use of vitamin D or calcium supplementation were also eligible for KQ 2 to cast a wider net for studies reporting on harms.

Two team members independently reviewed titles, abstracts, and full-text articles using study selection criteria to determine inclusion or exclusion from this update. Disagreements were resolved by discussion or review by a third reviewer. We reassessed studies included in the prior 2018 report on fractures[2] and the prior 2018 report on falls in older adults[4] against the updated study selection criteria for this update. We screened all citations using the DistillerSR platform (DistillerSR, Inc.) and managed citations using EndNote Version 9.2 (Clarivate™).

Data Abstraction and Quality Assessment

One reviewer abstracted relevant information for each included study into a structured form in DistillerSR including design, population, intervention, comparator, outcomes, timing, and

setting. A second person reviewed all data abstractions for accuracy. We considered data from the same study population or cohort but reported in separate publications as one study. We contacted study authors to clarify study data when needed.

Two reviewers independently assessed each study's quality. We assessed the risk of bias (RoB) for each included RCT using RoB 2.[58] We also reevaluated previously included studies using RoB 2 to ensure consistency in RoB assessments across the body of evidence. We translated RoB ratings from these instruments to methodological quality ratings using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B.3**).

Data Synthesis and Analysis

We synthesized findings for each KQ in tabular and narrative format. When at least two similar studies were available, we conducted meta-analyses in Stata 17 (StataCorp) using random effects models with the inverse-variance method described by DerSimonian and Laird to generate pooled estimates of the relative risk (RR), which were reexpressed as absolute risk differences (ARDs) per 1000 persons screened or treated.[59] For our main analyses, we pooled data across dosage groups for studies with more than one active intervention arm and considered each dosage separately in sensitivity analyses. Where possible, we stratified analyses by dosage of vitamin D (400 IU or less vs greater than 400 IU) to align with the structure of the 2018 USPSTF's recommendation. We also stratified findings by personal use of supplements during the study where possible. We also conducted sensitivity analyses using alternative methods of pooling (Mantel-Haenszel fixed effects and Peto odds ratio) for outcomes with rare (<1%) or zero events in either study arm.[60] Findings from these sensitivity analyses were very similar to our main analyses and are not reported here. We considered pooled summary estimates that excluded a null effect from the 95 percent confidence interval (CI) as statistically significant. Statistical heterogeneity was assessed by the I^2 statistic.[61, 62]

We assessed the strength of evidence for fracture outcomes, mortality, SAEs, and kidney stones for vitamin D (with or without calcium) compared with placebo or control and for calcium alone compared with placebo. We used the guidance from the AHRQ Effective Health Care Program[63] for assessing strength of evidence and incorporated recent guidance from Grading of Recommendations Assessment, Development and Evaluation (GRADE) related to assessing precision. Specifically, we used the minimally contextualized approach.[64] We considered an ARD of less than 0.5 percent as evidence for trivial to no effect for the incidence of hip fractures, major osteoporotic fractures, clinical vertebral fractures, and kidney stones. For total fractures and falls, we considered an ARD below 1 percent as evidence of trivial to no effect, because these outcomes are more common and encompass a range of severity from mild to serious. We used visual inspection of CI overlap and the I^2 statistic to assess consistency. For the study limitations domain, we downgraded strength of evidence (SOE) if more than half of the studies were not good quality. Two reviewers independently developed SOE assessments; disagreements were resolved through discussion.

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF website for public comment from January 12, 2023, to February 8, 2023. In response to comments, the USPSTF added specificity to the fall outcomes eligible for inclusion, removed population exclusions based on cancer or cardiovascular disease, and clarified eligibility of studies enrolling mixed populations that include some persons with excludable conditions. The draft evidence review was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and revised based on comments received, as appropriate. Revisions included additional analyses stratified by personal supplement use, clarification on age groups in sub-analyses, and additional discussion regarding excluded studies. The draft evidence review will also be posted for public comment. Revisions will be made based on comments received, and any references suggested by experts or public reviewers will be evaluated for inclusion and exclusion.

USPSTF and AHRQ Involvement

Members of the USPSTF helped develop the scope of work, including the analytic framework and KQs, and reviewed the evidence synthesis. AHRQ staff provided project oversight, conducted reviews of the draft report, and helped facilitate an external review of the evidence synthesis.

Chapter 3. Results

Literature Search

We screened 2,668 records from database searches, 59 additional citations from other sources, and 26 studies included in the previous USPSTF review[2] for a total of 2,753 records. We excluded 2,558 references at title and abstract review and 195 references at full-text review. Studies excluded at full-text review are listed in **Appendix C**; we note that a study could have been excluded for multiple reasons, but we only recorded a single reason.

We included 20 unique RCTs published in 54 articles for this update review (**Figure 2**). Ten RCTs were new to this update.[65-74] We did not identify any NRSI. Nineteen RCTs published in 51 articles reported direct evidence for KQ 1.[65-102] Fifteen RCTs published in 45 publications reported direct evidence for KQ 2.[65, 66, 68-71, 73, 74, 84, 85, 89-116] A brief summary of included study and population characteristics is in **Table 1**. Additional study-level details are in **Appendix D Tables 1 to 8** and study quality ratings are in **Appendix E Tables 1 to 7**. We excluded two studies comparing calcium alone to placebo that had been included in the previous review because they did not meet eligibility criteria for this update.[117, 118] We also excluded four studies that had been included in the previous falls prevention review for the USPSTF because they did not meet eligibility for this update.[44, 119-121]

Results by Key Question

KQ 1. Does Supplementation With Vitamin D, Calcium, or Both Prevent Fractures and Falls or Reduce Fracture- and Fall-Related Morbidity and Mortality?

Nineteen 19 RCTs (in 52 publications) reported fracture, fall, or mortality outcomes with outcomes ranging from 9 months to 7 years.[65-108, 110-116, 122] One study also reported outcomes at 22 years followup for a subset of participants. Across various fracture types (hip, major osteoporotic, clinical vertebral, nonvertebral, any fracture), we observed no effect of vitamin D supplementation (with or without calcium) compared with placebo. We observed similar findings for fall and mortality outcomes. Only one RCT[72] reported quality of life outcomes or functional activity measures, and no statistically significant differences were observed for supplementation with vitamin D alone compared with placebo. One RCT reported no difference between vitamin D alone and placebo with respect to the number of participants transferred to a nursing home after 3 years.[65] Only one RCT compared calcium alone with placebo and reported no difference in nonvertebral fractures between groups.[80]

Study Characteristics

Nineteen RCTs (in 52 publications) reported fracture, fall, or mortality outcomes (**Table 1**).[65-108, 110-116, 122] Of these, 10 studies were new to this update.[65-74, 122] Three RCTs evaluated vitamin D with calcium compared with placebo,[75, 76, 82] one RCT evaluated vitamin D with calcium compared with no treatment,[67] one RCT evaluated vitamin D with calcium compared with

calcium alone,[78] and 13 RCTs evaluated vitamin D alone compared with placebo.[65, 66, 68-74, 77, 79, 81, 83] One RCT evaluated calcium alone compared with placebo.[80] With respect to fall outcomes, which were new to this update, we identified falls outcomes in two previously included RCTs,[76, 77, 108] both of which had also been included in the previous falls prevention review for the USPSTF.[4] In addition, we carried forward an additional RCT from the falls prevention review which also met inclusion criteria for this update.[72] We did not include the other four RCTs that had been previously included in the falls prevention review for the USPTF[4] because they did not evaluate vitamin D_2 or D_3 (Dukas et al,[119] Gallagher et al[120]) or the population studies did not meet our eligibility criteria because a significant proportion of the enrolled participants had a history of fracture (Porthouse et al,[121] Sanders et al[44]).

Twelve RCTs[65, 67, 68, 70, 72-76, 78, 79, 82] evaluated daily doses of vitamin D_3 that ranged from 300 to 4,000 IU, and six RCTs[66, 69, 71, 77, 81, 83] evaluated weekly, monthly, or quarterly dosages of vitamin D_3 with a daily dose equivalent ranging from 833 IU to 3,333 IU. Several studies allowed for the use of personal vitamin D supplements during the study but restricted the maximum allowable dosage (range of maximum allowable outside dosage 400 IU to 2,000 IU per day), while several studies prohibited the use of personal supplements during the study, and others did not report on whether the use of personal vitamin D or calcium supplements was allowed. Further, most studies did not measure dietary intake or sun exposure at baseline; however, appropriate randomization should mitigate the potential for bias because of baseline differences in these factors. The duration of intervention and followup ranged from 9 months to 22 years across trials.

We judged seven RCTs as good quality;[65, 68-70, 72, 73, 83] the rest were fair quality. We excluded fall-related outcomes from one included study[67] and fracture outcomes from one included study[77] because of high risk of measurement bias for those outcomes in those studies. Six RCTs were conducted in the United States[68, 70, 75, 76, 80, 82] and the rest were conducted in Australia,[69, 77] Finland,[67, 72, 73, 78] the United Kingdom,[71, 74, 81] Norway,[66] Netherlands,[79] New Zealand,[83] and multiple countries in Europe.[65] Across studies, the mean age of enrolled participants ranged from 53 to 80 years. Eight RCTs were conducted exclusively among postmenopausal women;[67, 72, 74, 75, 77, 78, 80, 82] the rest were conducted among mixed populations of men and women where the proportion of women ranged from 24 to 74 percent. Two trials enrolled a racially diverse population (VITamin D and OmegA-3 Trial [VITAL],[68] Vitamin D and Type 2 Diabetes Trial [D2d][70]); the vast majority of participants enrolled in the other seven trials reporting race or ethnicity were White or of European background, and the rest of the studies did not report the race or ethnicity of enrolled participants. Although vitamin D deficiency was not a criterion for enrollment in any included studies, 14 RCTs did measure serum 25(OH)D levels at baseline[65-68, 70, 72-74, 76, 77, 79, 80, 82, 83]; however, some studies only measured serum levels in a random subset of the enrolled population. Mean serum 25(OH)D levels ranged from 10.4 to 32.8 ng/mL among the studies that measured serum levels at baseline; with all but two studies[74, 79] reporting mean levels of 20 ng/ml or higher. Few studies reported whether enrolled participants had a history of fracture. One study exclusively enrolled persons with a previous fall,[72] and five trials[65, 68, 75, 77, 83] reported the proportion enrolled with a previous fall, which ranged from 6 percent with a fall in the previous month to 42 percent with a fall in the previous year.

Hip Fracture Results

Seven RCTs reported on participants with hip fracture (**Table 1**).[68, 69, 75, 76, 78, 79, 81] Of these, two studies were new to this update.[68, 69] Four RCTs[68, 69, 79, 81] evaluated vitamin D compared with placebo, one RCT[78] compared vitamin D with calcium to calcium alone, and two RCTs[75, 78] evaluated vitamin D with calcium compared with placebo.

Two studies[75, 79] specified that hip fracture reduction was a primary study aim; however, only one study was powered specifically based on hip fracture outcomes.[75] Study authors ascertained hip fractures through medical claims, death certificates, or participant questionnaires (with verification using medical records or radiographs in most studies). We calculated the pooled RR for vitamin D with or without calcium compared with control as 0.99 (95% CI, 0.86 to 1.13; 7 RCTs; 88,364 participants; I^2=0%; **Figure 3**) over a 3- to 7-year followup. This RR corresponds to an ARD of zero fewer per 1,000 supplemented (95% CI, from 1 fewer to 1 more). Our analysis suggests no significant heterogeneity between the pooled estimates for the RCTs with and without the use of calcium (**Figure 3**). We also conducted analyses stratified by vitamin D dosage (400 IU or less daily dose equivalent vs. greater than 400 IU) and personal supplement use during study (allowed, prohibited, not reported) and observed no significant differences among strata (**Appendix F Figures 1 and 2**). The Women's Health Initiative (WHI) Calcium Vitamin D trial (N=36,282), which reported initial results after 7 years of followup (hazard ratio [HR], 0.88 (95% CI, 0.72 to 1.08), recently reported followup after a median of 13 years for 82 percent of the study sample. At this longer-term followup, the HR was 1.01 (95% CI, 0.90 to 1.14).[122]

Findings in Special Populations

Three studies reported findings stratified by sex (**Appendix F Figure 3**).[68, 69, 81, 91] Trivedi et al[81] (N=2,686) reported an age-adjusted RR of 0.98 (95% CI, 0.41 to 2.36) in women and 0.76 (95% CI, 0.35 to 1.67) in men but did not report any statistical testing for effect modification.[81] Authors of the Vitamin D Health (D-Health) Trial (N=21,310 analyzed) reported no statistically significant effect modification (P=0.26); the HR in women was 1.28 (95% CI, 0.90 to 1.83) and was 0.94 (95% CI, 0.63 to 1.39) in men.[69] VITAL authors reported an HR of 1.34 95% CI, 0.83 to 2.15) in women and 0.62 (95% CI, 0.33 to 1.17) in men with no statistically significant effect modification (P-value NR).[68, 91]

Two studies reported findings by race or ethnicity (**Appendix F Figure 4**) and no significant effect modification was observed in either study.[68, 75, 91]Authors of the WHI Calcium Vitamin D trial (N=36,282) reported the HR comparing vitamin D and calcium with placebo as 0.89 (95% CI, 0.72 to 1.09) in White participants, 0.73 (95% CI, 0.16 to 3.32) in Black participants, and 2.98 (95% CI, 0.33 to 27.01) in Asian or Pacific Islander participants.[75] There were not enough Native American participants with hip fracture events in this trial to provide an estimate for that subgroup. Authors of the VITAL study reported the HR in White participants as 1.01 (95% CI, 0.68 to 1.5) and the HR in Black participants as 0.25 (95% CI, 0.03 to 2.24).[91]

Three studies reported findings stratified by age (**Appendix F Figure 5**).[68, 69, 91] The WHI Calcium Vitamin D trial reported a borderline statistically significant treatment effect by age (p=0.05). The HR comparing vitamin D and calcium to placebo in women ages 50 to 59 years (all postmenopausal) showed increased risk of hip fracture (HR, 2.17; 95% CI, 1.13 to 4.18), while women ages 60 to 69 years (HR 0.74) and women ages 70 to 79 years (HR 0.82) had an HR similar to the overall main trial effect (HR, 0.88), and both age-stratified estimates included the null effect.[75] Authors of the D-Health Trial reported results stratified by younger than age 70 years or greater than or equal to age 70 years, and no statistically significant effect modification was observed (P=0.06). The HR in the younger group was 1.58 (95% CI, 1.00 to 2.50) and the HR in the older group was 0.93 (95% CI, 0.67 to 1.29).[69] Lastly, the VITAL study reported findings stratified by the less or more than the median study population age (66.7 years), but no significant effect modification was observed (P-value NR). The HR in participants younger than age 66.7 years was 0.61 (95% CI, 0.22 to 1.66), and the HR in participants age 66.7 years or older was 1.09 (95% CI, 0.73 to 1.63).[68, 91]

Major Osteoporotic Fracture Results

Three RCTs reported on participants with MOF (**Table 1**).[68, 69, 81] Of these, two studies were new to this update.[68, 69] All three RCTs evaluated vitamin D compared with placebo.

No studies specified primary study aims related to MOF. Study authors ascertained MOF through medical claims in one study,[69] through medical records or radiographs in one study,[68] and via participant questionnaire or death certificates in the third study.[81] We calculated the pooled RR for vitamin D compared with control as 0.93 (95% CI, 0.78 to 1.10; 3 RCTs; 48,883 participants; I^2=56.7%; **Figure 4**) over 5 to 5.3 years. This RR corresponds to an ARD of two fewer per 1,000 supplemented (95% CI, from 6 fewer to 3 more). We could not fully explain the heterogeneity in this estimate, which appeared largely driven by results from the smaller trial by Trivedi et al (N=2,686). Authors observed a favorable effect of vitamin D compared with placebo in this study (RR 0.69 [95% CI, 0.50 to 0.65]). The daily dose equivalent was the lowest of the three studies included for this outcome, so we do not think dosage is an explanation for the heterogeneity. A significant proportion of the study population came from the British Doctor's Study; however, adherence to study intervention was similar between the doctors and general practice participants, and adherence in this study overall was similar to adherence observed in the other included trials (76% of participants had at least 80% adherence).[81] In Trivedi et al, fractures were ascertained by participant questionnaire and death certificates; and unlike the other trials, authors did not verify fractures with medical records or radiographs. However, given masking of the intervention in this study, this method of ascertainment should only impact the absolute incidence of fractures in both the vitamin D and placebo groups and should not impact the relative effect of vitamin D compared with placebo. Thus, we are left without an adequate explanation for the heterogeneity observed in our pooled estimate for this outcome.

Clinical Vertebral Fracture Results

Two RCTs (total N=38,968 participants) reported on the outcome of participants with clinical vertebral fracture (**Table 1**).[75, 81] One study[75] compared vitamin D3 with calcium to placebo over

7 years, and the other study[81] compared vitamin D_3 alone to placebo over 5 years. No new studies were included in this update.

Clinical vertebral fractures reported by participants were verified by review of imaging by blinded adjudicators in the U.S. study and by self-report via survey (or death certificate review when relevant) in the U.K. study.[75, 81] We calculated the pooled RR as 0.86 (95% CI, 0.65 to 1.12; 38,968 participants; 2 studies; I^2=21%; **Figure 5**) over 5 to 7 years. This corresponds to an ARD of two fewer per 1,000 supplemented (95% CI, from 4 fewer to 1 more).

Findings in Special Populations

With respect to sex, Trivedi et al[81] (N=2,686) reported an age-adjusted RR of 0.65 (95% CI, 0.18 to 2.30) in women and 0.62 (95% CI, 0.32 to 1.22) in men but did not report any statistical testing for effect modification (**Appendix F Figure 3**).[81]

Nonvertebral Fracture Results

Eight RCTs (N=54,584 participants) reported on the outcome of participants with nonvertebral fractures (**Table 1**).[65, 68, 69, 74, 76, 78, 80, 83] Of these, four were new to this update.[65, 68, 69, 74] Five RCTs compared vitamin D alone with placebo[65, 68, 69, 74, 83], one RCT compared vitamin D and calcium with placebo,[76] one RCT compared calcium alone with placebo,[80] and one RCT compared vitamin D and calcium with calcium alone.[78]

Six RCTs[65, 68, 69, 76, 78, 83] verified self-reports of nonvertebral fractures via medical record, radiologic review, or via diagnosis codes on claims data, and two studies[74, 80] did not report how nonvertebral fractures were defined or ascertained. We calculated the pooled RR for vitamin D (with or without calcium) compared with control as 0.96 (95% CI, 0.86 to 1.09; 6 RCTs; 52,191 participants; I^2=37.9%; **Figure 6**) over 1 to 5.7 years. This RR corresponds to an ARD of two fewer per 1,000 treated (95% CI, from 8 fewer to 5 more). One study included two dosage groups (400 IU per day and 1,000 IU per day).[74] Our main analysis combined both dosage groups and the pooled estimates were similar when each dosage group was considered separately in sensitivity analyses (data not shown). We also conducted analyses stratified by vitamin D dosage (400 IU or less daily dose equivalent vs. greater than 400 IU) and observed no differences between dosage strata (**Appendix F Figure 6**). We also conducted analyses stratified by personal supplement use; we observed mild heterogeneity across strata (I^2=37.9%) but this was not statistically significant (**Appendix F Figure 7**).

We excluded the multisite European study from the pooled estimate because the authors only reported the number and rate of fractures and not unique participants with fractures.[65] However, findings from this study (adjusted incidence rate ratio [IRR], 1.03; 99% CI, 0.75 to 1.43 at 3 years followup) were consistent with our pooled estimate.[65]

Finally, in the one RCT comparing calcium alone with placebo, 11 (9.2%) participants had nonvertebral fractures in the calcium group compared with 12 (10.3%) participants in the placebo group (calculated RR, 0.90; 95% CI, 0.41 to 1.96; ARD 10 fewer per 1,000 participants [from 61 fewer to 98 more]).[80]

Findings in Special Populations

With respect to sex (**Appendix F Figure 3**), no statistically significant effect modification by sex was observed in two trials.[68, 69, 91] The D-Health Trial (N=21,310 analyzed) authors reported the HR in women as 1.02 (95% CI, 0.87 to 1.20) and 0.89 (95% CI, 0.74 to 1.06) in men.[69] Authors of the VITAL trial (N=25,871) reported the HR as 0.92 (95% CI, 0.81 to 1.04) in women and 1.07 (95% CI, 0.90 to 1.29) in men.[68, 91]

With respect to race or ethnicity (**Appendix F Figure 4**), VITAL authors reported HRs as 0.98 (95% CI, 0.88 to 1.04), 0.86 (95% CI, 0.59 to 1.25), and 0.86 (0.57 to 1.29) for non-Hispanic White participants, Black participants, and other participants, respectively. with no statistically significant effect modification observed.[68]

With respect to age (**Appendix F Figure 5**), two studies reported no statistically significant effect modification.[68, 69] The authors of the D-Health Trial reported the HR in participants younger than age 70 years was 1.03 (95% CI, 0.85 to 1.23) and the HR in participants older than age 70 years was 0.91 (95% CI, 0.77 to 1.07).[69] The VITAL trial (N=25,871) authors reported an HR of 0.99 (95% CI, 0.83 to 1.77) in those age younger than age 66.7 years (the median study population) and 0.95 (95% CI, 0.84 to 1.08) in participants age 66.7 years or older.[68, 91]

Any Fracture Results

Seven RCTs reported on participants with any fracture (**Table 1**).[66, 68, 69, 74, 75, 81, 83] Of these, three studies were new to this update.[68, 69, 74] One RCT evaluated vitamin D and calcium compared with placebo,[75] and six RCTs evaluated vitamin D compared with placebo.[66, 68, 69, 74, 81, 83]

Only one study specified a primary study aim related to fracture.[81] Fractures were most commonly ascertained through review of hospital records, often in combination with participant questionnaires.[68, 69, 75, 83] One trial ascertained total fractures through participant questionnaires and death certificates.[81] Two trials did not report ascertainment methods, one was likely self-report,[66] and one assessed fracture as an adverse event (AE) and reported no additional details.[74] We calculated the pooled RR for vitamin D with or without calcium compared with control as 0.96 (95% CI, 0.92 to 1.00; 5 RCTs; participants 85,429; I^2=0%; **Figure 7**) over 1 to 7 years. This RR corresponds to an ARD of three fewer per 1,000 supplemented (95% CI, from 7 fewer to 0 more). One study included two dosage groups (400 IU per day and 1,000 IU per day).[74] The main analysis combined both dosage groups and the pooled estimates were similar when each dosage group was considered separately (data not shown). We also conducted analyses stratified by vitamin D dosage (400 IU or less daily dose equivalent vs. greater than 400 IU) and personal supplement use and observed no differences between strata (**Appendix F Figures 8 and 9**).

Two studies were not included in the pooled estimate.[66, 83, 100] Jorde et al[66, 100] did not report the number of total fractures in the overall sample but reported that there was no difference between the vitamin D and placebo groups (P=0.868).[66, 100] In the ViDA study, nonvertebral fractures and spinal fractures were reported separately.[83] However, the authors did not report the 13 spinal fractures by group. To estimate total fractures in a sensitivity analysis, we included this study in

our pooled estimate with all 13 additional fractures in the control group and then in the intervention group and found it had minimal effect on the pooled estimate (results not shown).

Findings in Special Populations

Three studies reported results stratified by sex (**Appendix F Figure 3**).[68, 69, 91] In the D-Health Trial (N=21,310 analyzed), the HR in men was 0.85 (95% CI, 0.71 to 1.01) and in women was 1.03 (95% CI, 0.88 to 1.20) with no statistically significant effect modification (P=0.098).[69] Authors of the VITAL trial (N=25,871) reported the HR as 0.94 (95% CI, 0.83 to 1.06) in women and 1.07 (95% CI, 0.90 to 1.28) in men and also reported no statistically significant effect modification (P-value NR).[68] Trivedi et al[81] (N=2,686) reported an age-adjusted RR of 0.68 (95% CI, 0.46 to 1.01) in women and an age-adjusted RR of 0.83 (95% CI, 0.61 to 1.13) in men but did not report any statistical testing for effect modification between the two subgroup estimates.[81]

With respect to race or ethnicity (**Appendix F Figure 4**), VITAL authors reported HRs as 0.99 (95% CI, 0.89 to 1.11), 0.89 (95% CI, 0.62 to 1.30), and 0.90 (0.61 to 1.35) for non-Hispanic White participants, Black participants, and other participants, respectively, with no statistically significant effect modification observed.[68]

With respect to age (**Appendix F Figure 5**), two studies reported results stratified by age and no statistically significant effect modification was observed.[68, 69, 91] Authors of the D-Health Trial reported the HR in participants younger than age 70 years as 1.02 (95% CI, 0.85 to 1.21) and 0.89 (95% CI, 0.55 to 0.93) in participants age 70 years or older.[69] VITAL authors reported an HR of 0.99 (95% CI, 0.84 to 1.18) in participants younger than age 66.7 years (the median age of the study population) and 0.97 (95% CI, 0.86 to 1.1) in participants age 66.7 years or older.[68, 91]

Fallers and Fall Rates Results

Fall-related outcomes are new to this update and nine RCTs reported a fall-related outcome (**Table 1**).[65, 68, 69, 72, 74, 76, 77, 81, 83] One RCT evaluated vitamin D and calcium compared with placebo,[76] and eight RCTs evaluated vitamin D alone compared with placebo.[65, 68, 69, 72, 74, 77, 81, 83] One RCT targeted recruitment to ensure at least 40 percent of the enrolled population had a history of falling in the prior year, but a prior fall was not a requirement for study entry.[65] One RCT required a history of falling in the previous 12 months for study entry.[72] The other seven RCTs did not specify any study entry criteria related to a history of falling or risks for falling. We excluded one RCT from this update for poor quality concerning falls outcomes.[67] Across the included studies, outcomes were reported over 9 months to 5 years of followup.

Only two studies specified primary study aims related to falls.[72, 77] Authors ascertained falls through annual questionnaires,[68, 69, 81] monthly questionnaires,[83] fall diaries,[65, 72, 77] and study visits,[74] or by sending a postcard after a fall.[76] For the incidence of participants with one or more falls, we calculated the pooled RR for vitamin D with or without calcium compared with placebo as 0.99 (95% CI, 0.97 to 1.01; 8 RCTs; 36,744 participants; I^2=0%; **Figure 8**) over 9 months to 5.3 years. This RR corresponds to an ARD of five fewer per 1,000 treated (95% CI, from 15 fewer to 5 more). One study included two dosage groups (400 IU per day and 1,000 IU per day).[74] The main analysis combined both dosage groups; pooled estimates were similar when

each dosage group was considered separately in the pooled analysis. We did not include the D-Health Trial[69] in the pooled analysis because the method of fall ascertainment varied substantively from the other studies in the analysis. However, the results of this study were consistent with our pooled analysis (odds ratio [OR], 1.07 [95% CI, 0.84 to 1.36]; 2,093 participants). We also conducted analyses stratified by vitamin D dosage (400 IU or less daily dose equivalent vs. greater than 400 IU) and by personal supplement use and observed no differences between dosage or supplement use strata (**Appendix F Figures 10 and 11**). No studies reported on falls specifically resulting in fracture; however, four RCTs reported on participants with an injurious fall, which was ascertained through diaries in three RCTs.[65, 72, 83] and an annual questionnaire in one RCT.[68] We calculated the pooled RR for vitamin D compared with placebo as 1.02 (95% CI, 0.97 to 1.08; 3 RCTs; 7,412; participants; I^2=3.6%; **Figure 8**). This RR corresponds to an ARD of nine more per 1,000 treated (95% CI, from 13 fewer to 35 more).We did not have data from one of the RCTs to include in the pooled analysis; however, the effect reported in this study was consistent with our pooled estimate (OR, 1.03; 95% CI, 0.94 to 1.13).[90, 120]

Two RCTs reported the number of participants with a recurrent fall.[72, 77] People with a recurrent fall were ascertained through a fall diary in one RCT[72] and an annual questionnaire in the other.[77] We calculated the pooled RR for vitamin D compared with placebo as 1.14 (95% CI, 0.78 to 1.66; 2 RCTs; 885 participants; I^2=32.9%; **Figure 8**). This RR corresponds to an ARD of 20 more per 1,000 treated (95% CI, from 31 fewer to 92 more).

Five RCTs reported the rate of falls, which includes first falls and recurrent falls.[65, 68, 69, 72, 74] We calculated a pooled IRR for vitamin D (with or without calcium) compared with placebo as 0.98 (95% CI, 0.94 to 1.03; 4 RCTs; 28,519 participants; I^2=0%; **Figure 9**). We again did not include the D-Health Trial [69] in pooled analysis because fall ascertainment varied substantively from the other trials. Authors of D-Health reported an IRR of 1.13 (95% CI, 0.89 to 1.43), which is similar to our pooled estimate. One trial (Vitamin D and Exercise in Fall Prevention [DEX][72]) also reported rates of injurious falls, injurious recurrent falls, and total recurrent falls and reported IRRs that were consistent with other falls outcomes (**Appendix F Figure 12**).

Findings in Special Populations

Three studies reported findings for participants with one or more falls stratified by sex (**Appendix F Figure 2**).[69, 76, 81] Dawson-Hughes et al (N=389) reported an OR of 0.54 (95% CI, 0.30 to 0.97) in women and an OR of 0.93 (95% CI, 0.50 to 1.72) in men for vitamin D and calcium compared with placebo but did not report any statistical testing for effect modification.[76] Authors of the D-Health Trial (N=17,616 analyzed) reported no significant effect modification with vitamin D compared with placebo for women vs. men (P for effect modification = 0.69; actual HRs not reported).[99] Lastly, Trivedi et al (N=2,038 analyzed) reported sex-stratified results comparing vitamin D with placebo: age-adjusted RR 1.03 (95% CI, 0.72 to 1.48) in women and RR 0.87 (95% CI, 0.68 to 1.12) in men but no statistical testing for effect modification was reported.[81]

No studies reported findings stratified by age or race or ethnicity.

Mortality Results

Seventeen RCTs reported mortality outcomes.[65-73, 75-79, 81-83] Of these, nine studies were new in this update.[65-73] Three RCTs evaluated vitamin D and calcium compared with placebo,[75, 76, 82] one RCT compared vitamin D and calcium with no treatment,[67] one RCT evaluated vitamin D and calcium compared with calcium alone,[78] and 12 RCTs evaluated vitamin D alone compared with placebo.[65, 66, 68-73, 77, 79, 81, 83]

No studies specified primary study aims related to mortality or were powered to evaluate mortality. Mortality was ascertained through linkages to national death registries, death certificates, medical records, and reports from participants' general practitioner or previously identified proxy. One RCT (N=686) reported four deaths overall, but these deaths were not reported by group, so it could not be included in the quantitative synthesis.[77] We calculated the pooled RR for vitamin D (with or without calcium) compared with control as 0.96 (95% CI, 0.91 to 1.02; 16 RCTs; 109,782 participants, I^2=0%; **Figure 10**) over 2 to 7 years. This RR corresponds to an ARD of two fewer deaths per 1,000 supplemented (95% CI, from 4 fewer to 1 more). The pooled estimates were similar among the RCTs with and without the use of calcium and we observed no differences between dosage strata (400 IU or less daily dose equivalent vs. greater than 400 IU (**Appendix F Figure 13**) or personal supplement use (**Appendix F Figure 14**). The WHI Calcium Vitamin D trial (N=36,282), which reported initial results after 7 years of followup, recently reported followup after a median of 22.3 years. At this longer-term followup, the HR was 1.00 (95% CI, 0.97 to 1.03).[122]

Findings in Special Populations

Three studies reported findings for vitamin D compared with placebo stratified by sex (**Appendix F Figure 3**).[68, 69, 81] The authors of the VITAL trial (N=25,871) reported no significant effect modification by sex (P=0.90). The HR in women was 1.00 (95% CI, 0.83 to 1.20) and in men was 0.98 (95% CI, 0.83 to 1.16).[68] Authors of the D-Health Trial (N=21,310 analyzed) also reported no statistically significant effect modification by sex (P=0.82). The HR was 1.07 (95% CI, 0.86 to 1.32) in women and 1.03 (95% CI, 0.90 to 1.19) in men.[69] Trivedi et al (N=2,686) reported sex-stratified estimates (women RR, 0.92 [95% CI, 0.54 to 1.55]; men RR, 0.90 [95% CI, 0.76 to 1.07]) but did not report any statistical testing for effect modification.[81]

With respect to race or ethnicity (**Appendix F Figure 4**), authors of the WHI Calcium D trial (N=36,282) reported no statistically significant effect modification comparing vitamin D and calcium with placebo by race or ethnicity (P=0.30). The HRs were 0.89 (95% CI, 0.80 to 0.99), 0.91 (95% CI, 0.67 to 1.23), 2.28 (95% CI, 1.07 to 4.87), 0.84 (95% CI, 0.16 to 4.48), and 1.60 (95% CI, 0.75 to 3.43) for White, Black, Hispanic, American Indian, Asian/Pacific Islander participants, respectively.[75] Similarly, VITAL authors also reported no statistically significant effect modification across race/ethnic groups for vitamin D compared with placebo (P=0.56; HRs not reported).[68]

With respect to age (**Appendix F Figure 5**), two trials reported no statistically significant effect modification.[69, 75] The WHI Calcium D Trial (N=36,282) reported no statistically significant effect modification for vitamin D with calcium compared with placebo for participants younger

than age 70 years (HR 0.89 [95% CI, 0.79 to 1.01]) vs. participants age 70 years or older (HR, 0.95 [95% CI, 0.80 to 1.12]).[75] Authors of the D-Health Trial reported an HR of 1.15 (95% CI, 0.92 to 1.44) for participants younger than age 70 years and 1.00 (95% CI, 0.87 to 1.15) for participants age 70 years or older.[69]

Quality of Life and Disability Results

One RCT[72] reported quality of life and disability outcomes and it was new to this update. This RCT (N=204) compared 800 IU of vitamin D daily with placebo. After 2 years, study authors reported no statistically significant differences between study groups as measured by the Leipad quality of life instrument (P=0.30), but findings with respect to the WHO-Five Well-Being Index suggested a small but statistically significant decrease in mental health well-being for vitamin D compared with placebo (P=0.04).[72] Study authors reported no statistically significant differences between study groups as measured by the activities of daily living disability score or by the instrumental activities of daily living score (actual values not reported).[72]

Healthcare Utilization and Transition to Institutional Care Results

No RCTs reported on outcomes related to emergency department use or hospitalization outside of the context of SAEs (see KQ 2). One RCT,[65] which was new to this update, reported on the number of participants that transitioned to a nursing home. This trial compared 2,000 IU of vitamin D with placebo. Thirteen participants (1.2%) in the vitamin D group compared with nine participants (0.8%) in the placebo group transferred to a nursing home by 3 years of followup (P=0.39).[65]

KQ 2. What Are the Harms of Supplementation With Vitamin D, Calcium, or Both?

Fewer than half of the studies included for KQ 1 systematically reported on AEs or SAEs and ascertainment methods and reporting of AEs were limited; however, we observed no differences in AEs or SAEs between vitamin D (with or without calcium) and control groups. Ten RCTs reported on the incidence of kidney stones from vitamin D (with or without calcium) supplementation, and our pooled estimates suggests a trivial but statistically significant increase (ARD 2 more per 1,000 supplemented; 95% CI, from 1 more to 5 more). The magnitude of association is higher among trials of combined vitamin D and calcium (ARD 4 more, 95% CI, from 1 more to 7 more)[75, 82, 123] compared with the trials evaluating vitamin D alone[65, 66, 68-70, 73, 83] (ARD 2 more per 1,000, from 1 fewer to 4 more). Only two RCTs[80, 123] compared calcium alone with placebo and reported no differences in the incidence of participants with kidney stones; however, these events were rare, so estimates were imprecise.

Study Characteristics

Fifteen RCTs (in 46 publications) reported on 16 comparisons for one or more harm outcome.[65, 66, 68-71, 73-76, 78, 80, 82, 83, 123] All but one of these RCTs[123] also reported a KQ 1 outcome and thus are described in the previous section and in **Table 1**. The RCT that only reported harm (KQ 2) outcomes was included in the previous review and evaluated 1,000 IU of vitamin D with 1,400 mg calcium, calcium alone, and placebo among 1,180 postmenopausal women with a mean age

of 67 in the United States.[123] We did not identify any eligible cohort studies that reported on harms.

Findings Organized by Outcome

In this section we report on AE, SAE, withdrawals due to AE, and kidney stones. We note that because adverse events, serious adverse events, and withdrawals due to adverse events were reported by a minority of studies and because of heterogeneity of outcome ascertainment, we were not able to quantitatively synthesize findings for these outcomes. Further, no studies reported results for any harm outcomes by subgroups defined by age, sex, or race and ethnicity.

Participants With Adverse Events

Seven RCTs[66, 68-70, 74, 83, 123] reported the number of participants with one or more AEs; however, the details about method of ascertainment (i.e., passive surveillance, regular patient prompting, clinical or laboratory examination) and AE classification scheme (i.e., researcher defined, established taxonomy) were often not reported. Three studies reported no increased AEs with vitamin D supplementation alone compared with control (adjusted HR,1.03 [95% CI, 0.90 to 1.18] after 3.3 years of followup;[83] IRR, 0.94 [95% CI, 0.90 to 0.98] after 3 years of followup;[70] IRR, 0.99 [95% CI, 0.93 to 1.04] after 3 years of followup[69]). One RCT evaluating vitamin D with calcium did not report actual data and only reported "no patterns of adverse events were seen among the three groups"[123] and another evaluating vitamin D alone reported "no significant differences between the two groups with respect to adverse events."[68] The remaining two RCTs[66, 74] did not report measures of effect, but the frequency of adverse events was similar in vitamin D alone groups compared with control groups.

Participants With Serious Adverse Events

Nine RCTs reported the number of participants with SAEs.[66, 69-71, 74, 76, 78, 82, 123] Similar to the reporting of AEs, few studies provided details regarding method of ascertainment or definition of what was considered as an SAE. Three RCTs[76, 82, 123] all evaluating vitamin D with calcium compared to control reported zero SAEs among participants. Two RCTs reported measures of effect suggesting no increase in SAEs for vitamin D alone compared with control (IRR, 0.96 [95% CI, 0.81 to 1.14] over 3 years followup[70] and IRR, 0.91 [95% CI, 0.83 to 1.00] over 3 years followup).[69] The remaining four RCTs[66, 71, 74, 78] did not report measures of effect, but the frequency of SAEs was similar in vitamin D and control groups. Three of these four studies evaluated vitamin D alone[66, 71, 74] and one evaluated vitamin D with calcium.[78]

Participants With Withdrawals Due to Adverse Events

Three RCTs reported the number of participants with withdrawals due to AEs.[70, 76, 80] One RCT evaluating vitamin D alone compared with control reported no differences in the frequency of participants with withdrawals due to AEs (IRR, 0.96 [95% CI, 0.81 to 1.14] over 3 years followup).[70] One study evaluating vitamin D with calcium reported total number of participants with withdrawals due to AEs but did not report data by study group.[76] Lastly, one study comparing calcium alone with placebo reported a similar frequency of participants with withdrawals due to AEs between study groups but did not report a measure of effect.[80]

Participants With Kidney Stones

Eleven RCTs reported 12 comparisons for the incidence of participants with kidney stones (**Table 1**).[65, 66 , 68-70, 73, 75, 80, 82, 83, 123] Six studies were new to this update.[65, 66 , 68-70, 73] Three RCTs[75, 82, 123] evaluated vitamin D and calcium compared with placebo, two RCTs evaluated calcium alone compared with placebo,[80, 123] and seven RCTs[65, 66, 68-70, 73, 83] evaluated vitamin D alone compared with placebo. Six RCTs evaluated daily doses of vitamin D_3 that ranged from 400 to 4,000 IU. The other five RCTs evaluated weekly or monthly dosages of vitamin D_3 with a daily dose equivalent ranging from 400 IU to 4,000 IU.

No studies specified primary study aims related to kidney stones or were powered to evaluate kidney stones. For the studies that did identify how outcomes were was ascertained, self-report was used.[69, 70, 75, 82, 83] We calculated the pooled RR for vitamin D with or without calcium compared with placebo as 1.11 (95% CI, 1.03 to 1.21; 10 RCTs, 99,036 participants; I^2=0%; **Figure 11**) over 2.5 to 7 years. This RR corresponds to an ARD of two more participants with stones per 1,000 treated (95% CI, from 1 more to 5 more). Although no statistical heterogeneity was present between the studies of vitamin D with and without calcium, the pooled estimate for the studies evaluating vitamin D alone included the null effect (RR, 1.08 [95% CI, 0.97 to 1.19]), while the pooled estimate for the studies evaluating vitamin D with calcium was numerically higher (RR, 1.18 [95% CI, 1.04 to 1.35]) and excluded the null effect (**Figure 11**). The overall pooled estimate was similar when the two vitamin D dosage groups used in one of the trials[73] were considered separately.

Two RCTs[80, 123] compared calcium alone with placebo but the sample sizes were small and events were rare, so the pooled estimate was imprecise (pooled RR, 1.07 [95% CI, 0.17 to 6.77]; 2 RCTs; 969 participants; I^2=0%; ARD, 0 more, from 3 fewer to 20 more).

Chapter 4. Discussion

Summary of Evidence

A summary of findings, strength of evidence, and applicability is presented in **Table 2**, which is organized by KQ and then by outcome. Several new, good-quality, large trials with racially diverse populations that include men and that evaluated higher dosages of vitamin D as compared with the previous report were available for this update. As a result, our SOE ratings in this update largely reflect an increase in our certainty (from low to moderate) regarding a trivial to no effect of empiric vitamin D supplementation (at low or high dosages and with or without calcium) across most fractures, incidence of falls, all-cause mortality, incidence of kidney stones and serious adverse events. As compared with the previous report, two RCTs of calcium alone compared with placebo were excluded because of changes in study selection criteria for this update. We continue to judge the SOE for calcium supplementation alone as insufficient.

Summary of Benefits and Harms of Supplementation From Evidence in This Review

We evaluated the SOE as moderate (MOF, hip, clinical vertebral, or any fracture) or low (nonvertebral fracture) for trivial to no effect of vitamin D supplementation (with or without calcium) across the various fracture types (**Table 2**). For these fracture types, the ARDs ranged from three fewer to zero fewer people with fractures per 1,000 participants supplemented compared with control groups, which were almost all placebo. All CIs around effect estimates included the null effect, and the lower bounds of the CI suggest at the most, a trivial benefit from supplementation (8 fewer per 1,000 for nonvertebral fractures to 1 fewer per 1,000 for hip fractures). Similar findings of trivial to no effect were observed for fall rate (high SOE) and for the incidence of participants with falls (moderate SOE), where the ARD was five fewer participants with one or more falls per 1,000 people supplemented compared with control. With respect to mortality, we evaluated the SOE as moderate for trivial to no effect for vitamin D supplementation with an ARD of two fewer deaths per 1,000 participants supplemented compared with control.

We rated the SOE for SAEs as moderate for trivial to no effect. Although the evidence was not suitable for a quantitative synthesis, the evidence suggests that SAEs are rare and generally not different in frequency between vitamin D supplemented groups compared with control. The relative effect of vitamin D supplementation (with or without calcium) on the incidence of kidney stones was not meaningfully different from the previous report (ARD 2 more per 1,000 participants) despite the addition of seven new trials in this update. However, evolution in methods for assessing the precision domain of SOE,[124] including a focus on assessing ARDs rather than RRs and guidance for using a contextualized approach, resulted in a change in our SOE rating for this outcome from *moderate for harm* to *moderate for trivial to no effect* based on the ARD observed, which, although excludes a null effect, is a magnitude that we consider trivial.

We did not evaluate the impact of supplementation on cardiovascular events or incident cancer because a recent systematic review conducted for the USPSTF evaluated these outcomes and reported low to moderate SOE for no effect of vitamin D or calcium supplementation and cardiovascular events or incident cancer.[8]

Applicability

This update review was focused on studies that enrolled participants without respect to baseline serum level of vitamin D; thus, some participants with low serum 25(OH)D levels were likely included. Among the 14 studies that measured serum 25(OH)D at baseline, the mean levels ranged from 10.4 to 32.8 ng/mL and all but two studies[74, 79] reported mean levels of 20 ng/ml or higher. However, studies did not report findings by baseline serum levels, precluding us from making conclusions about benefits and harms in populations with low serum 25 (OH)D based on the evidence in this update review. However, a related review on screening for vitamin D deficiency for the USPSTF includes evidence focused on populations with known low serum levels and also found no effect of vitamin D use on fractures, falls, or all-cause mortality as compared with placebo.[6]

Based on Sex

The 2018 USPSTF recommendation found insufficient evidence to make a recommendation for dosages of vitamin D higher than 400 IU in postmenopausal women and at any dosages in men and premenopausal women.[1] Although women have a higher absolute risk of falls and fracture, presumably because of differences in BMD and bone size and geometry,[125, 126] the evidence in this update suggests no difference in the relative effect of vitamin D supplementation in men and postmenopausal women with respect to fall or fracture outcomes. Four of the included trials enrolled both men and women and reported some outcomes stratified by sex.[65, 68, 69, 76, 81, 85, 89, 91] Effect estimates for fractures, falls, and mortality were generally similar for women and men, with no discernible pattern with respect to fracture, falls, or mortality. Two of the four studies that were new to this update reported no statistically significant effect modification by sex for these outcomes.[65, 68, 69, 85, 89, 91] Based on the current evidence, we conclude that results are applicable to both men and postmenopausal women. We did not identify any eligible evidence in premenopausal women.

Based on Race or Ethnicity

One of the previously included studies (WHI Calcium Vitamin D[75]) reported effects by race or ethnicity, and two of the new trials in this update (VITAL[68] and D2d[70]) enrolled racially diverse study populations. Results from VITAL and the WHI trial did not suggest any difference by race or ethnicity in fractures, falls, or mortality.[75, 89, 91] The D2d trial did not report results for eligible outcomes by race or ethnicity.[93] Based on the current evidence, we conclude that results are possibly applicable to people from diverse racial or ethnic groups; however, additional evidence would offer more certainty related to this conclusion.

Based on Age

The evidence in this update is applicable to postmenopausal women of any age. With respect to applicability to men, the mean age in the studies that enrolled men ranged from ages 60 to 80 years; two trials enrolled men as young as age 50 or 55 years. Two trials reported findings stratified by age with mixed findings. The newly included D-Health Trial, which included both men and women, suggested no difference in effect for participants younger than age 70 years compared with older participants on fracture and mortality outcomes.[69] In contrast, the WHI Calcium D trial suggested an increased risk for hip fracture among women ages 50 to 59 years compared with women ages 60 to 79 years, where a null effect was observed.[75] However, a similar effect was not observed for mortality in the WHI trial.[75] Overall, we have limited evidence to draw conclusions about how effectiveness of vitamin D with or without calcium might vary by age in the studied populations (postmenopausal women and older men) and no evidence for premenopausal women or men younger than 60 years.

Based on Dosage

This update offers good-quality evidence from several large trials evaluating dosages of vitamin D greater than 400 IU, which was a gap in evidence from the prior review. The daily doses evaluated in this update ranged from 300 to 4,000 IU and the daily dose equivalents for the weekly, monthly, or quarterly dosages ranged from 833 IU to 3,333 IU. When we stratified based on vitamin D dosages of 400 IU or less compared to higher doses, we did not see any meaningful differences in effects for the outcomes where at least one study was available for each strata.

The 2018 review on falls prevention for the USPSTF[4] included an RCT (Sanders et al[44]) of annual high dosage vitamin D (500,000 IU, corresponding to a 1,370 IU daily dose equivalent) that reported statistically significant increases in falls and nonstatistically significant increases in fractures. This study was not included in this update or in the previous update[2] because it enrolled people at higher risk for fracture and 35 percent of the enrolled study population had a history of fracture. No included trials in the present update evaluated annual dosages or dosages as high as what was used in the Sanders et al[44] trial. The trials included in the present update used 1-, 3- or 4- month bolus dosages of vitamin D ranging from 60,000 IU to 150,000 IU and all reported trivial to no effect, similar to the trials using weekly or daily dosages. Based on evidence included in this review, we conclude that monthly bolus dosages of up to 100,000 IU (or at less frequent intervals) probably do not convey harm with respect to increased fractures, falls, or mortality. A recent 2023 systematic review by Myung et al included 15 RCTs of intermittent or single high dosages of vitamin D including the Sanders et al trial.[127] This review also included several trials that we included in the present update,[69, 77, 81, 83] but also included trials in populations not eligible for this update (e.g., long-term care residents, people with known vitamin D deficiency or prior fracture).[127] The Myung et al review reported no statistically significant difference for falls (RR, 1.03 [95% CI, 0.98 to 1.09]; 11 RCTs) or fractures (RR, 0.99 [95% CI, 0.87 to 1.14]; 11 RCTs).[127]

Findings in Context

Many systematic reviews evaluating the impact of supplementation with vitamin D on various health outcomes are published, but direct comparison of findings across these reviews is challenging because of different study selection criteria with respect to study design, population, and outcomes resulting in discordant results.[128] For example, many reviews include studies with populations in long-term care settings or with known deficiency, which were populations out of scope in this update. Thus, findings from other reviews with respect to falls or fractures may be different than our findings because of differences in the populations of the studies that we included or excluded in this review.

For this update, we dropped previously included cardiovascular events and incident cancer as "harm" outcomes because the impact of vitamin D and calcium on these outcomes was more thoroughly addressed in the 2022 O'Connor et al review for the USPSTF.[8] Some experts have expressed concerns that calcium supplementation beyond standard dietary consumption may be associated with adverse cardiovascular events based on findings from observational studies such as the NIH-AARP Diet and Health study,[129] which reported excess CVD deaths associated with supplemental calcium in men (but not in women), and the Multi-Ethnic Study of Atherosclerosis study, which found that calcium supplementation was associated with increased coronary artery calcium scores, which may increase CVD.[130, 131] In the O'Connor et al review, pooled analyses demonstrated no association between calcium supplementation and CVD events (5 trials)[8] and in a separate meta-analysis (11 RCTs, 8,634 participants) by Huo et al, no association between calcium supplements (with or without vitamin D) was not associated with increased risk for CHD or stroke.[132] In contrast, A 2021 systematic review of calcium supplementation in postmenopausal women that included 14 RCTs reported that calcium supplements significantly increased the risk of CVD (RR, 1.15; 95% CI, 1.06 to 1.25).[133]

With respect to all-cause mortality, a recently published 2023 review by Cao et al examined the association between vitamin D supplementation and all-cause mortality in people with various and different health conditions (e.g., people with COVID-19 infection, chronic kidney disease, type 2 diabetes mellitus, or liver cirrhosis) as well as the general population.[134] Among the 116 RCTs included in this review, 43 RCTs assessed the impact of vitamin D supplementation in the general population (the subgroup most similar to the population considered in the present update). In this population, vitamin D had no association with all-cause mortality (pooled RR, 0.99; 95% CI, 0.96 to 1.03).[134] Similarly, the O'Connor et al review for the USPSTF and the Huo et al review also reported no association between supplementation with vitamin D or calcium with or without vitamin D with all-cause mortality.[8, 132]

Limitations of the Literature and Future Research Needs

The evidence included in this review has several limitations. Few trials explicitly limited the use of personal vitamin D, calcium, or multivitamin/mineral supplements outside of the trial protocol. For example, 57 percent of participants in the WHI Calcium D trial were taking vitamin D, calcium, or both supplements at the time of randomization, and personal supplementation up to 1,000 IU of vitamin D and up to 1,000 mg of calcium were permitted during the trial, which by protocol examined daily dosages of 400 mg IU of vitamin D and 1,000

mg of calcium.[103] In the VITAL trial, which examined a dosage of 2,000 IU daily, authors asked study participants to limit personal use of vitamin D supplements to dosages of less than 800 IU including multivitamins.[68] This design feature (the allowing of personal supplement use) results in a bias toward a null effect in intention-to-treat analyses and may partially explain the lack of any clinically meaningful effect.[135] However, in our stratified analyses, we saw no differences in effect when stratified by personal supplement use (**Appendix F Figures 2, 7, 9, 11, and 14**). Further, it may not be ethically feasible to limit personal use of supplements given NAM's existing recommended dietary allowances and participant or provider concerns about the ability to meet those recommendations through sun exposure and diet alone.

Mortality, some types of fractures, and serious harms are rare events and most included studies were not sufficiently powered for these outcomes. We note many differences in methods that authors used to ascertain fall outcomes, and many studies simply lack any information about the methods used to ascertain adverse events from supplements. The study duration of some studies may not have been long enough to ascertain impact on falls, fractures, and mortality.

The evidence base has a limited number of studies to assess the impact of calcium alone. The evidence is also limited for drawing direct comparisons between different dosages of vitamin D because few studies evaluated multiple dosage arms. We did not observe any visible patterns in outcomes based on daily dose equivalent above or below 400 IU per day, the dosage by which the 2018 USPSTF recommendation is stratified. However, studies evaluating multiple dosage arms and frequency (e.g., daily, weekly, monthly, yearly, or other) would better assess the impact of different dosages and dosing regimens on fracture and fall outcomes. Finally, no studies address supplementation in premenopausal women, men younger than 50 years, or in transgender populations.

The ongoing trials that we identified in the prior report are now completed and are reflected in this update. These studies addressed many of the limitations in the evidence base that we noted in the previous report.[2] The evidence in this update provides more certainty for concluding that vitamin D supplementation (with or without calcium) has trivial to no effect in unselected populations across a wide range of dosages in postmenopausal women and men (generally age 60 or older). Thus, continued evaluation of vitamin D supplementation in unselected and general populations may not be warranted. Future trials of vitamin D supplementation could focus on higher-risk populations (e.g., oldest ages, high fall risk, frailty, medical conditions increasing risk), limit the use of personal supplements, ensure adequate power for important clinical outcomes, and use robust methods of ascertainment for fractures, falls, and harms. Whether supplemental vitamin D and calcium would be beneficial when started at younger ages (i.e., premenopause in women or in men younger than 50 to 60 years) is not known and would require a large and lengthy trial given the low incidence of fractures, falls, and mortality in younger populations. Such a trial is likely not feasible and may deter research resources from other potential strategies for prevention. Interventions designed to prevent falls may be a more promising strategy for fracture prevention than empiric vitamin D or calcium supplementation in unselected populations. The USPSTF recently issued an updated B recommendation for exercise interventions to prevent falls among adults at high risk for falls.[136]

Limitations of This Review

This review was limited to studies on community-dwelling adults not known to have vitamin D deficiency, osteoporosis, a prior fragility fracture, or metabolic bone disease. Although some people with these conditions may have been included in studies, our review does not directly address the effect of supplementation in these higher-risk, selected populations, including people in institutional settings. We did not include vitamin D analogs or formulations typically dispensed with a prescription, and we did not evaluate the impact of supplementation on intermediate bone outcomes (e.g., BMD). We only included studies published in English and conducted in countries categorized as *very high* on the United Nations Human Development Index.

The evolution in methods for assessing RoB and SOE compared with the previous report on this topic may have introduced some inconsistencies; however, with the exception of the change in SOE rating for kidney stone incidence, these inconsistencies are trivial and have no substantive impact on our conclusions. The pooled estimate of effect in this update for kidney stone incidence was similar to the previous report, even with additional new evidence. However, when we applied new guidance from GRADE for assessing the precision domain of SOE for this outcome, our assessment of the SOE changed. Whereas our prior assessment was largely focused on the RR and its relationship to the null effect, the SOE rating in this update applied a contextualized approach focusing on the ARD and its relationship to an effect size commensurate with more than a trivial harm.[64]

This review includes a limited perspective on harms because we did not include all trials evaluating vitamin D supplementation, only those that reported use in unselected populations without metabolic bone disease and that reported outcomes we prespecified as eligible (e.g., falls, fractures, mortality, harms). Although current guidance for conducting systematic reviews recommends the inclusion of both benefit and harm outcomes to allow for a balanced perspective, a limited perspective on harms occurs in reviews that only focus on a subset of the evidence for interventions that are studied across many different populations and settings, like vitamin D and calcium.[137] Different benefits and outcomes are relevant for different populations or settings, but it is unlikely that harms will vary. At the same time, conducting a systematic review that includes every trial of vitamin D or calcium supplementation to thoroughly assess harms is not feasible and perhaps not warranted given the widespread availability of these agents without a prescription for many decades, suggesting overall safety of these supplements when taken at recommended doses when diet alone is insufficient for achieving recommended dietary allowances.

Conclusion

Among community-dwelling populations of postmenopausal women and older men without known vitamin D deficiency, bone conditions including osteoporosis, or prior fracture, the evidence suggests no reduction in fractures, falls, or mortality from supplementation with vitamin D (with or without calcium) compared with placebo. The evidence also suggests no difference in serious adverse events; however, a very small absolute increase in the incidence of

kidney stones from vitamin D supplementation (with or without calcium) was observed. The evidence on supplementation with calcium alone was limited for all outcomes reported.

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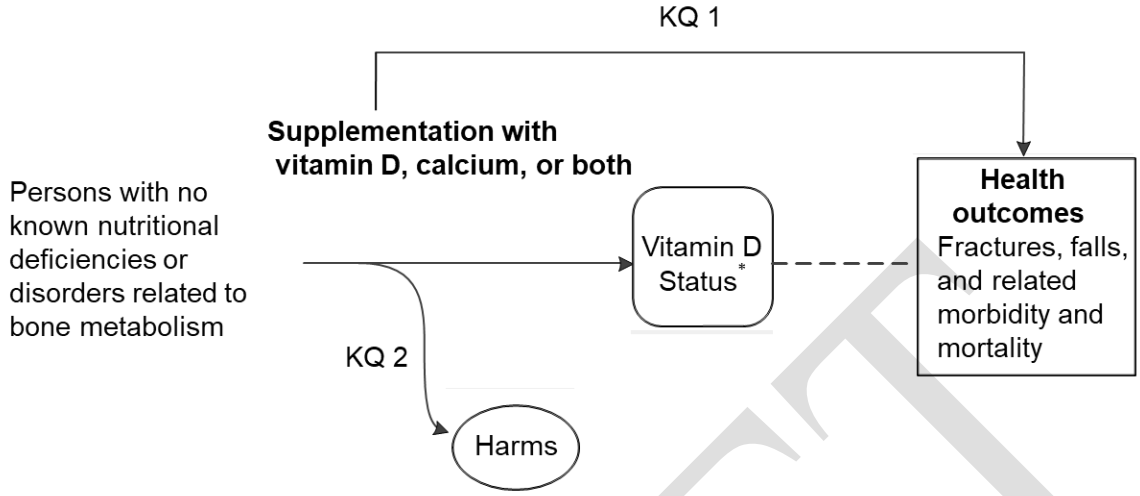
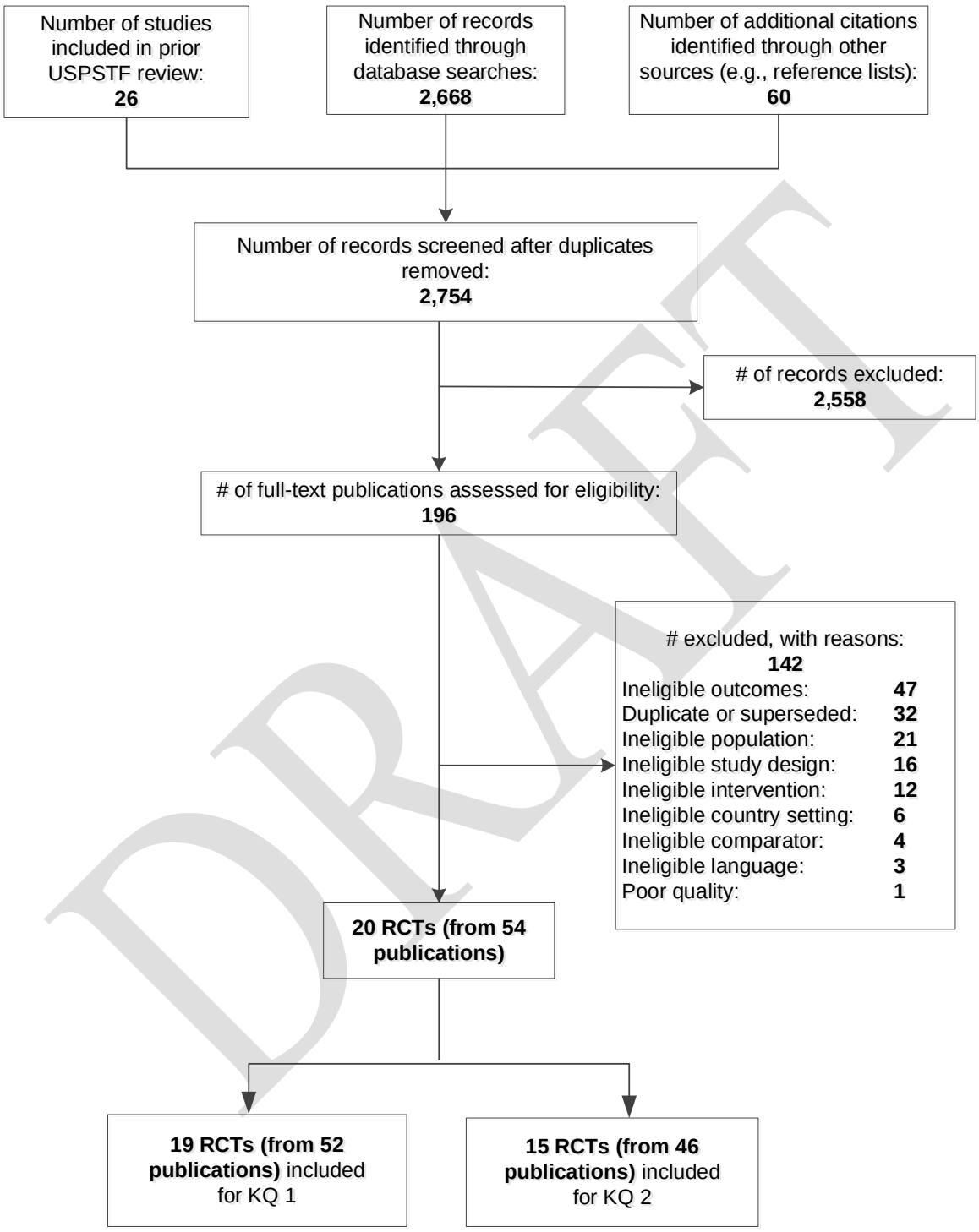
Figure 1. Analytic Framework



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

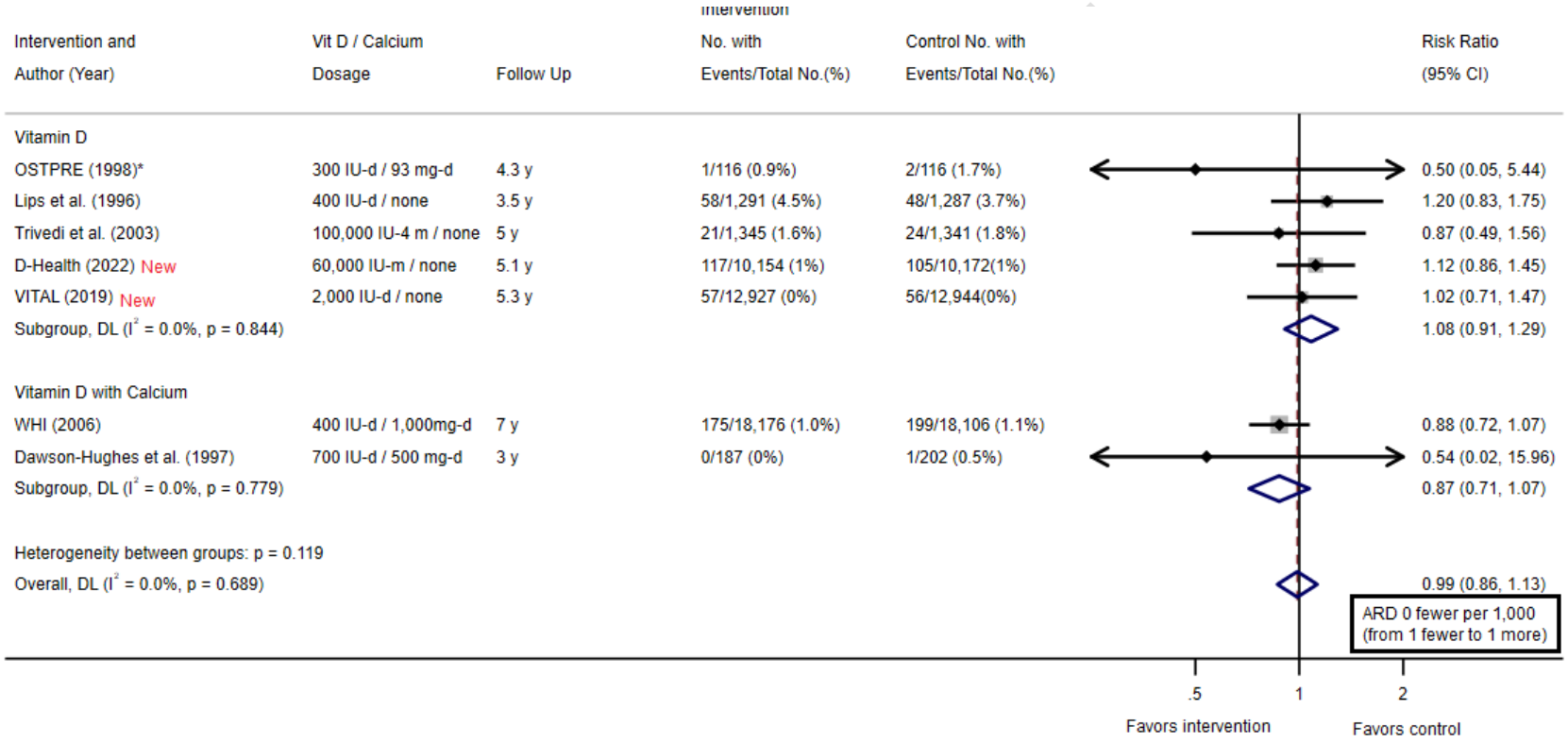
Abbreviation: KQ=key question.

Figure 2. Literature Flow Diagram



Abbreviations: KQ=key question; RCT=randomized, controlled trial; USPSTF=U.S. Preventive Services Task Force.

Figure 3. Effect of Vitamin D Supplementation on Hip Fracture (KQ 1)

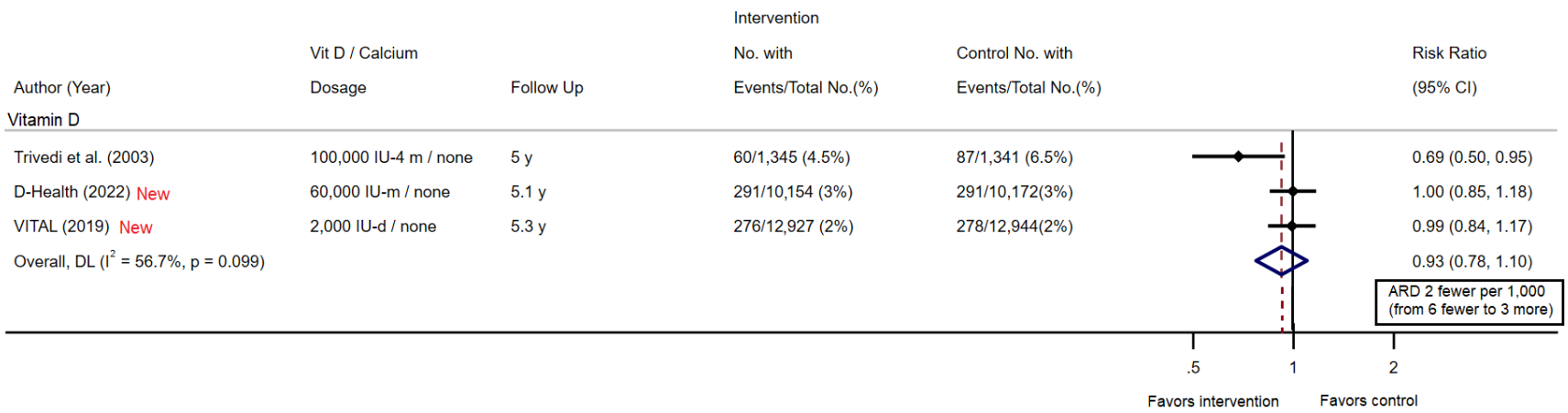


* Comparator is 93 mg per day of calcium and not placebo.

Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; d=day; D-Health=Vitamin D Health; IU=international units; KQ=key question; m=month; OSTPRE=Osteoporosis Risk Factor and Prevention Study; RCT=randomized, controlled trial; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

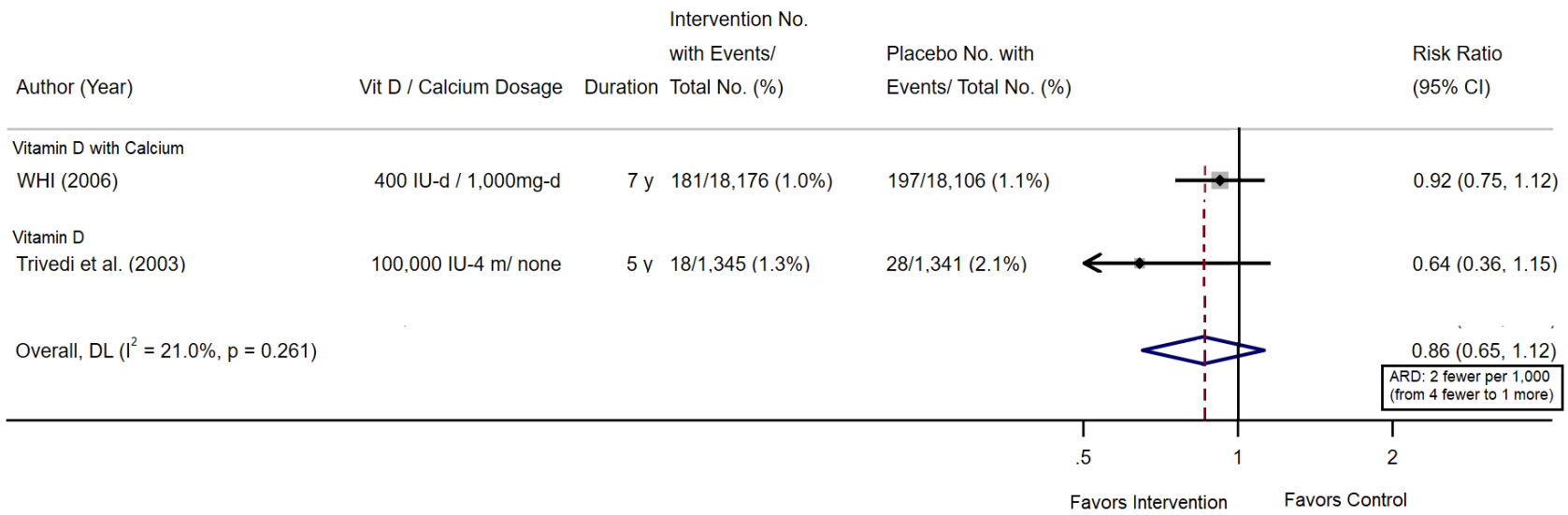
Figure 4. Effect of Vitamin D Supplementation on Major Osteoporotic Fracture (KQ 1)



Note: Studies are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; d=day; D-Health=Vitamin D Health; IU=international units; KQ=key question; m=month; RCT=randomized, controlled trial; VITAL=The VITamin D and OmegA-3 Trial; y=year.

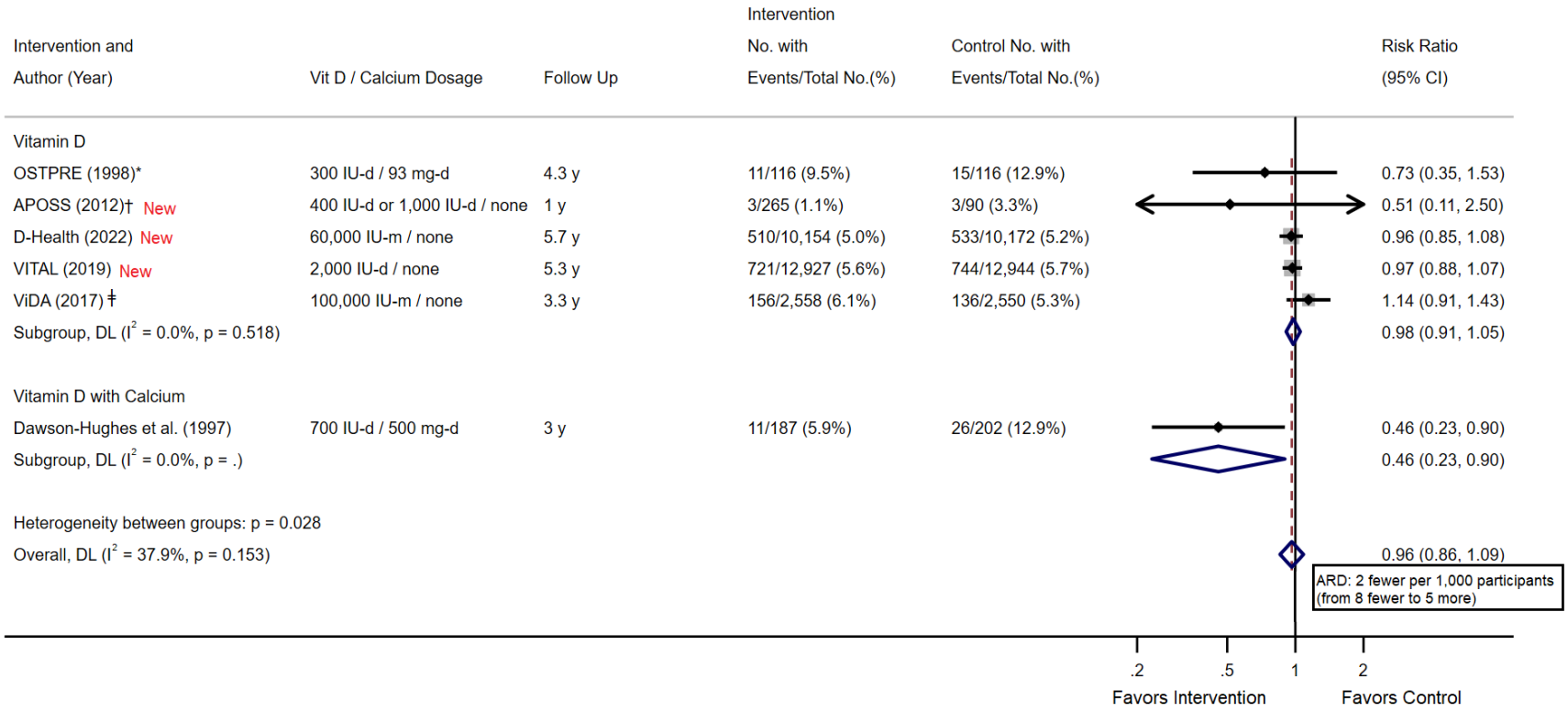
Figure 5. Effect of Vitamin D Supplementation on Clinical Vertebral Fracture (KQ 1)



Note: Studies are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; d=day; IU=international units; KQ=key question; m=month; RCT=randomized, controlled trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Figure 6. Effect of Vitamin D Supplementation on Nonvertebral Fracture (KQ 1)



* Comparator is 93 mg-d of calcium and not placebo.

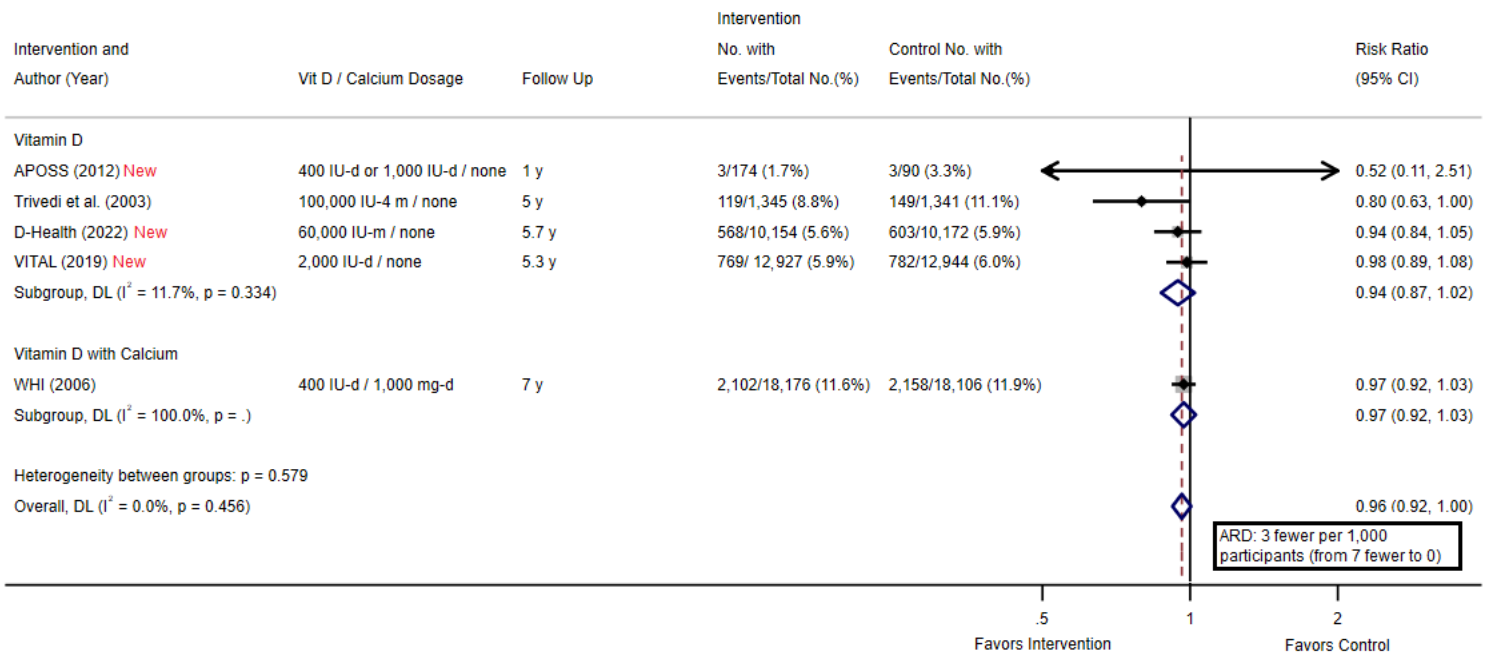
† Combined 400 IU-d and 1,000 IU-d dose groups for analysis.

ǂ 200,000 IU loading dose used.

Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; ARD=absolute risk difference; CI=confidence interval; d=day; D-Health=Vitamin D Health; IU=international units; KQ=key question; m=month; OSTPRE=Osteoporosis Risk Factor and Prevention Study; RCT=randomized, controlled trial; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; y=year.

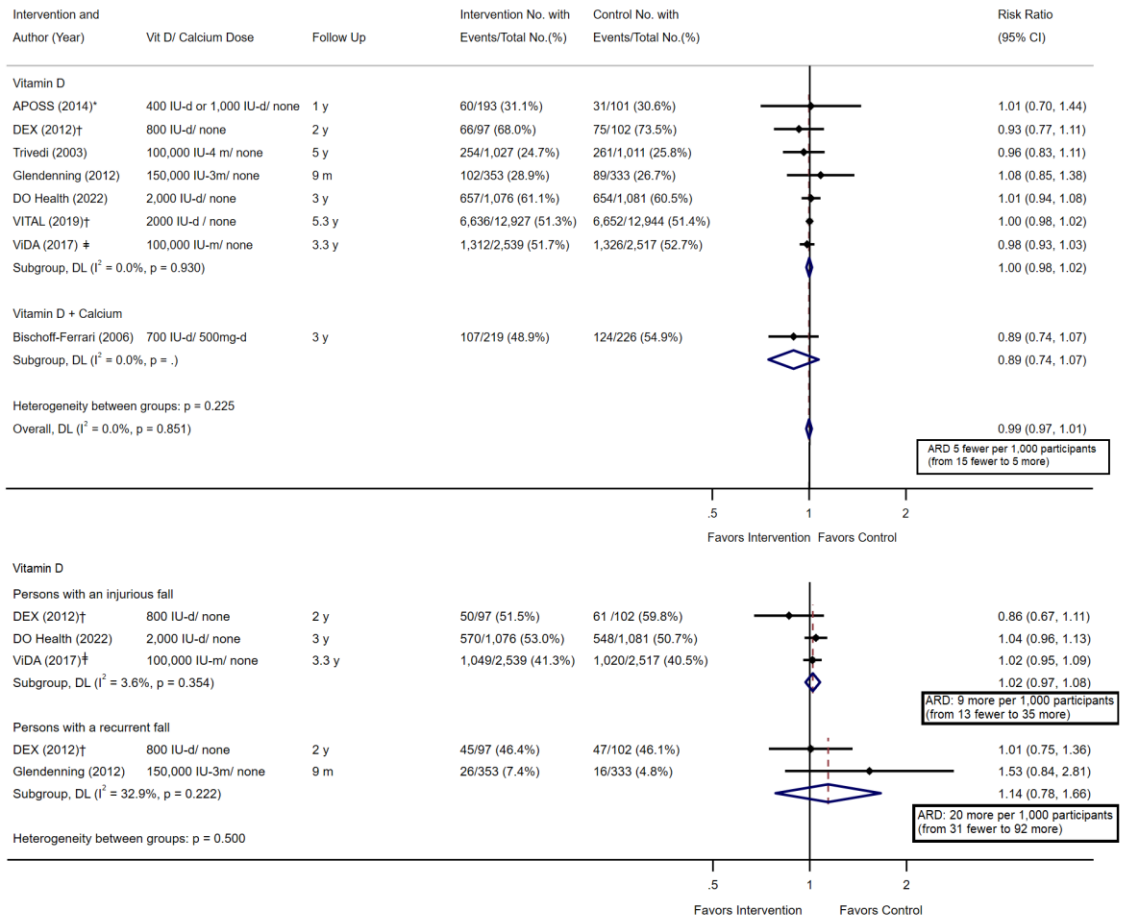
Figure 7. Effect of Vitamin D Supplementation on Any Fractures (KQ 1)



Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; ARD=absolute risk difference; CI=confidence interval; d=day; D-Health=Vitamin D Health; IU=international units; KQ=key question; m=month; RCT=randomized, controlled trial; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Figure 8. Effect of Vitamin D Supplementation on Participants With Incident Falls (KQ 1)



* 400 IU-d and 1,000 IU-d dosage groups are combined for analysis.

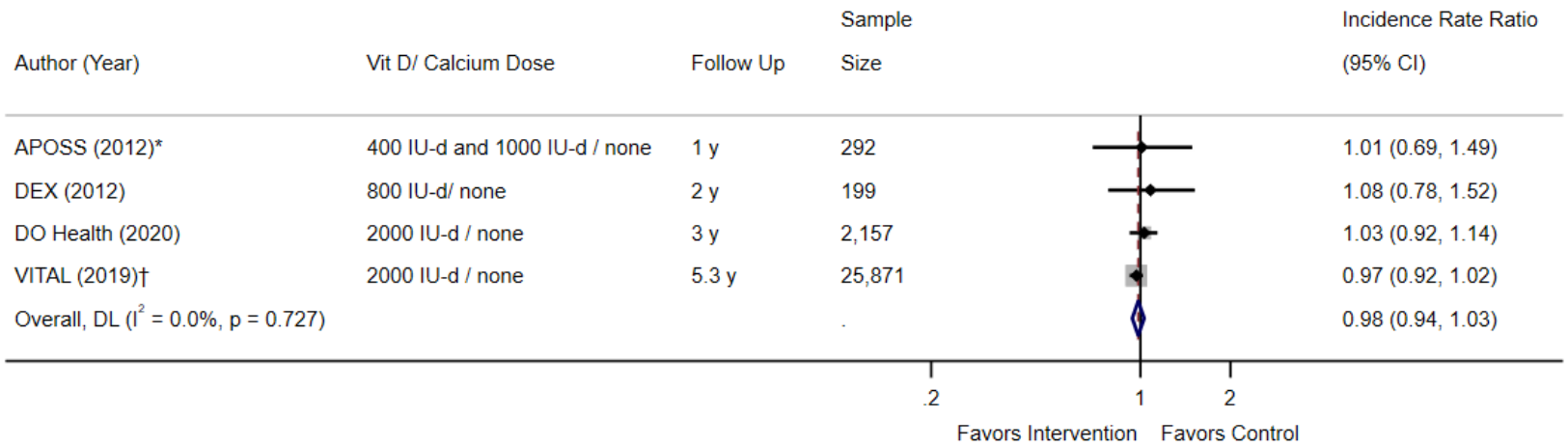
† Data obtained from a request to the authors.

ǂ 200,000 IU loading dose used.

Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; ARD=absolute risk difference; CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; IU=international units; KQ=key question; m=month; RCT=randomized, controlled trial; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; y=year.

Figure 9. Effect of Vitamin D Supplementation on Fall Rate (KQ 1)



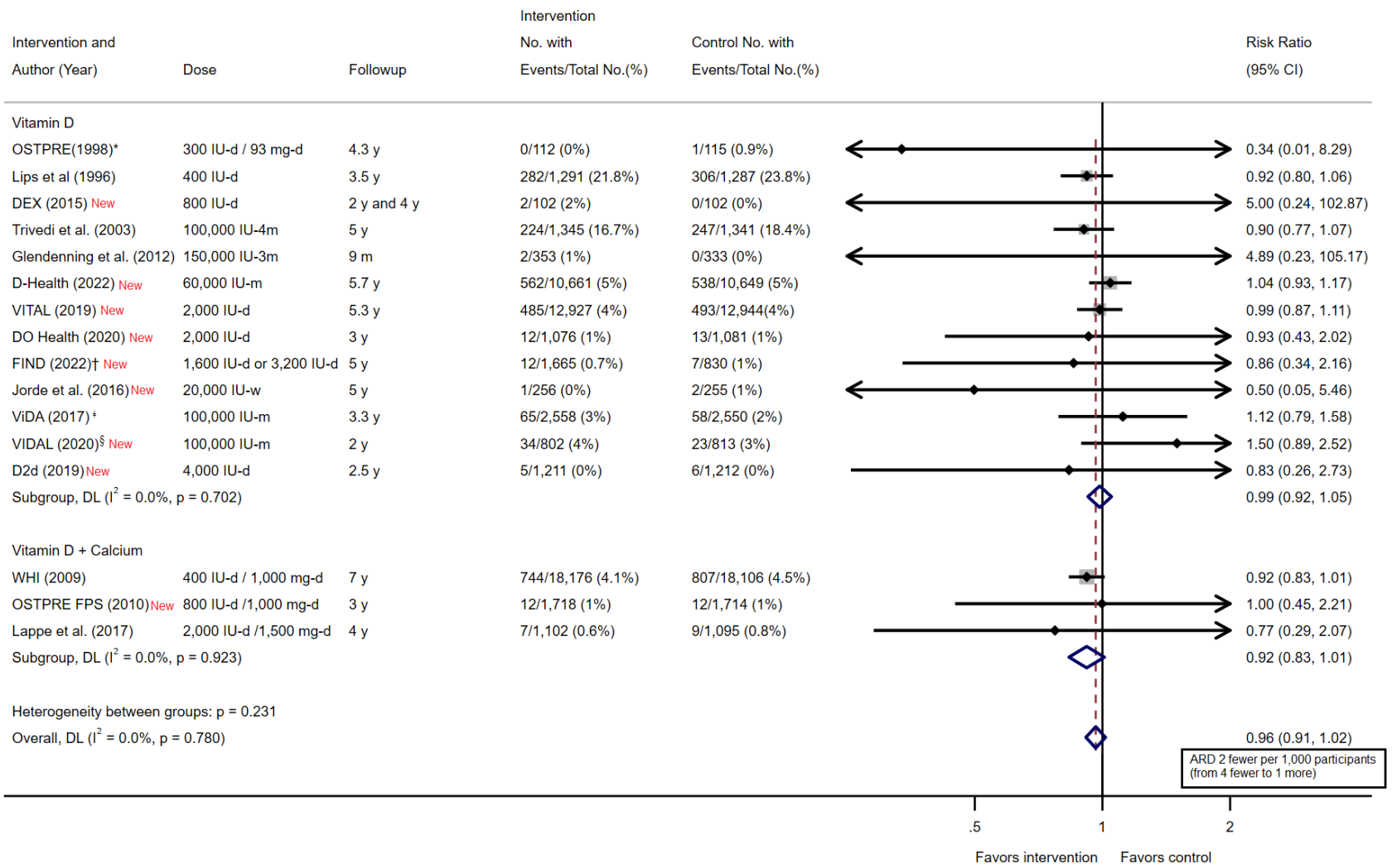
* 400 IU-d and 1,000 IU-d dosage groups are combined for analysis.

† Author-reported data.

Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; IU=international units; KQ=key question; RCT=randomized, controlled trial; VITAL= The VITamin D and OmegA-3 Trial; y=year.

Figure 10. Effect of Vitamin D Supplementation on Mortality (KQ 1)



* Comparator is 93 mg-d of calcium and not placebo.

† Data for the 1,600 IU-d and 3,200 IU-d dose groups are combined.

ǂ 200,000 IU loading dose used.

Figure 10. Effect of Vitamin D Supplementation on Mortality (KQ 1)

§ Data for the open-label and blinded components of the study are combined.

Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; d=day; D2d=Vitamin D and Type 2 Diabetes Trial; DEX= Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; IU=international units; m=month; OSTRPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; w=week; y=year.

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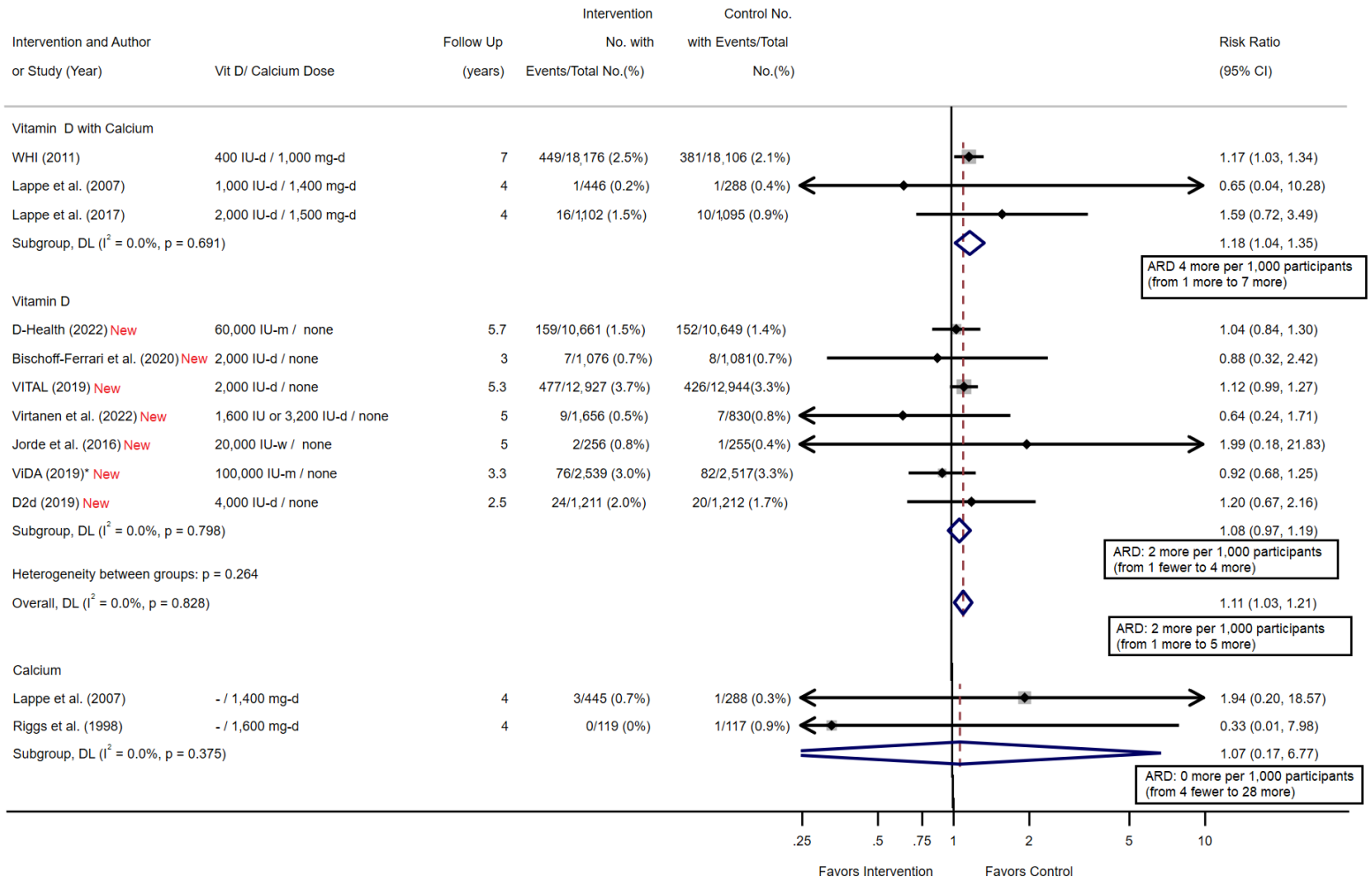
Figure 11. Effect of Vitamin D Supplementation on Kidney Stones (KQ 2)



Note: Studies within each stratum are sorted from lowest to highest daily dose equivalent of vitamin D.

* 200,000 IU loading dose used.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; d=day; D2d=Vitamin D and Type 2 Diabetes Trial; D-Health=Vitamin D Health; IU=international units; KQ=key question; m=month; RCT=randomized, controlled trial; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D Trial; w=week.

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
APOSS, 2012[74, 101, 102]	Fair/ Fair	U.K.	Postmenopausal women, nonsmokers without severe disease or on vascular medications or abnormal blood biochemistry	305	63.8 (2.2)	305 (100)	Caucasian: 305 (100)	D_3 400 or 1,000 IU daily; Placebo; 1 year	• Nonvertebral fracture • Any fracture • Falls • AE, SAE, withdrawals due to AE • Kidney stones
D2d, 2019[70, 93-95]	Good/ Good	U.S.	Persons at least age 30 years, BMI 24 to 42 kg/m2 with 2 of 3 glycemic criteria for prediabetes	2,423	60.0 (9.9)	1086 (44.8)	Asian: 130 (5.4) Black: 616 (25.4) White: 1,616 (66.7) Other: 61 (2.5) Hispanic: 225 (9.3)	D_3 4,000 IU daily; Placebo; 2.5 years	• Mortality • AE, SAE • Kidney stones
Dawson-Hughes et al, 1997[76, 108]	Fair/ Fair	U.S.	Healthy, ambulatory people at least age 65 years who were living at home recruited through direct mailings and community presentations	445	71.5 (NR)	213 (55)*	White: 430 (96.6) Black: 11 (2.5) Asian: 4 (0.9)	D_3 700 IU with calcium 500 mg daily; Placebo; 3 years	• Hip fracture • Nonvertebral fracture • Falls • SAE, withdrawals due to AE
DEX, 2012[72, 86-88]	Good/NA	Finland	Community-dwelling women ages 70 to 80 years who had fallen at least once during the previous 12 months	409†	74 (NR)	204 (100)	NR	D_3 800 IU daily; Placebo; 2 years	• Falls • Mortality • Quality of life • Disability

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
D-Health, 2022[69, 96-99]	Good/ Good	Australia	People ages 60 to 84 years recruited from electoral rolls	21,315	69.3 (5.5)	9,780 (45.9)	British or European: 19,450 (91.3) Australian or New Zealander: 726 (3.4) Asian: 242 (1.1) Indigenous: 151 (0.7) Other: 365 (1.7) Missing data: 376 (1.8)	D_3 60,000 IU monthly (2,000 IU daily dose equivalent); Placebo; 5 years	• Hip fracture • MOF • Nonvertebral fracture • Any fracture • Falls • Mortality • AE, SAE • Kidney stones
DO-HEALTH, 2020[65, 84, 85]	Good/ Good	Switzerland, France, Germany, Austria, Portugal	Community-dwelling people at least age 70 years; recruitment targeted at least 40% of participants with a fall in the last year	2,157	74.9 (4.4)	1,331 (61.7)	NR	D_3 2,000 IU daily; Placebo; 3 years	• Nonvertebral fracture • Falls • Mortality • Transition to nursing home • Kidney stones
FIND, 2022[73]	Good/ Good	Finland	Men at least age 60 years and postmenopausal women at least age 65 years recruited from the general population	2,495	68.2 (4.5)	1,069 (42.8)	Reports all participants White	D_3 1,600 or 3,200 IU daily; Placebo; 5 years	• Mortality • Kidney stones
Glendenning et al, 2012[77]	Fair/ NA	Australia	Community-dwelling women at least age 70 years recruited from 4 general practice clinics and electoral rolls	686	76.7 (4.1)	686 (100)	Caucasian: NR (96.5) Asian: NR (3.2) Other: NR (0.4)	D_3 150,000 IU every 3 months (1,667 IU daily dose equivalent); Placebo; 9 months	• Falls • Mortality

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
Jorde, R et al, 2016,[66] Larsen et al, 2018[100]	Fair/ Fair	Norway	Adults with prediabetes diagnosed with an oral glucose tolerance test as part of the Tromsø Study 2007–2008 were included	511	62 (NR)	197 (38.5)	NR	D_3 20,000 IU weekly (2,857 daily dose equivalent); Placebo; 5 years	• Any fracture • Mortality • AE, SAE, withdrawals due to AE • Kidney stones
Lappe et al, 2007 [123] Lappe et al, 2006 [109]	NA/ Fair	U.S.	Community-dwelling, postmenopausal women at least age 55 years in rural areas of a single state recruited through random digit dialing	1,180	66.7 (7.3)	1,180 (100)	White: 1,180 (100)	D_3 1,000 IU daily with calcium 1,400 or 1,500 mg daily; Calcium alone; Placebo; 4 years	• AE, SAE • Kidney stones
Lappe et al, 2017[82]	Fair/ Fair	U.S.	Community-dwelling, postmenopausal women at least age 55 years from rural areas of a single state recruited from the population through mailings and advertisements	2,303	65.2 (NR)	2,303 (100)	White: 2,291 (99.5) American Indian or Alaska Native: 8 (0.3) Asian, Black, or unknown: 4 (0.4) Hispanic: 11 (0.5)	D_3 2,000 IU with calcium 1,500 mg daily; Placebo; 4 years	• Mortality • SAE • Kidney stones
Lips et al,1996[79]	Fair/ NA	The Nether-lands	Persons at least age 70 years recruited from general practitioners or from apartment houses or homes for the elderly‡	2,578	80 (6.0)	1,916 (74.3)	NR	D_3 400 IU daily; Placebo; 3 to 3.5 years	• Hip fracture • Mortality

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
OSTPRE-FPS, 2010[67]	Varied by outcome (poor for falls and fair for mortality)/ NA	Finland	Women at least age 65 years living in a single province who were enrolled in an existing population-based cohort study on bone health	3,139	67 (NR)	3,139 (100)	NR	D_3 800 IU with calcium 1,000 mg daily; No treatment; 3 years	• Falls • Mortality
OSTPRE, 1998 [78, 110]	Fair/ NA	Finland	Postmenopausal women ages 52 to 61 years from a single province who were enrolled in an existing population-based cohort study on bone health	232	52.7 (NR)	232 (100)	NR	D_3 300 IU with calcium 93 mg daily; Calcium alone; 5 years	• Hip fracture • Nonvertebral fracture • Mortality • SAE
Riggs et al, 1998[80]	Fair/ Fair	U.S.	Postmenopausal ambulatory women ages 61 to 70 years identified through a medical record review from a single health system	236	66.3 (NR)	236 (100)	NR, but county where women were recruited is a largely White population	Calcium 1,600 mg daily; Placebo; 4 years	• Nonvertebral fractures • Withdrawals due to AE • Kidney stones
Trivedi et al, 2003[81]	Fair/ NA	U.K.	Community-dwelling men and women ages 65 to 85 years; 83% recruited from the British Doctors Study and 17% recruited from the register of a general practice	2,686	74.7 (4.6)	649 (24.0)	NR	D_3 100,000 IU every 4 months (833 IU daily dose equivalent); Placebo; 5 years	• Hip fracture • MOF • Clinical vertebral fracture • Any fracture • Falls • Mortality

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
ViDA, 2017[83, 111-116]	Good/ Good	New Zealand	People ages 50 to 84 years recruited from 55 family practices in a single large city	5,108	65.9 (8.3)	2,139 (41.9)	Maori: 272 (5.3) Pacific Islander: 334 (6.5) South Asian: 249 (4.9) European or other: 4,253 (83.3)	D_3 100,000 IU monthly[§] (3,333 IU daily dose equivalent); Placebo; 3.3 years	• Nonvertebral fracture • Any fracture • Falls • Mortality • AE • Kidney stones
VIDAL, 2020[71]	Fair/ Fair	U.K.	People ages 65 to 84 years recruited from general practitioner offices	Total: 1,615 Double-blind phase: 787 Open-label phase: 828	Age group,N (%) 65–69: 624 (38.6) 70–74: 510 (31.6) 75–79: 325 (20.1) 80–84: 156 (9.7)	758 (46.9)	White British: 1,563 (96.8) White Irish: 11 (0.7) White other: 26 (1.6) Caribbean: 6 (0.4) Asian: 6 (0.4) Mixed: 3 (0.2)	D_3 100,000 IU monthly (3,333 IU daily dose equivalent); Placebo; 2 years	• Mortality • SAE

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
VITAL, 2019[68, 89-92]	Good/ Good	U.S.	Men and women at least ages 50 and 55 years, respectively, without cancer or cardiovascular disease at baseline and recruited from the national population via mailings and advertisments, with targeted recruitment of persons from the Black community	25,871	67.1 (7.1)	13,085 (50.6)	Non-Hispanic White: 18,046 (71.3) Black: 5,106 (20.2) Non-Black Hispanic: 1013 (4.0) Asian or Pacific Islander: 388 (1.5) Native American or Alaskan Native: 228 (0.9) Other or unknown: 523 (2.1)	D_3 2,000 IU daily; Placebo; 5 years	• Hip fracture • MOF • Nonvertebral fracture • Any fracture • Falls • Mortality • AE • Kidney stones

Table 1. Randomized, Controlled Trials Included for Key Questions 1 and 2

Study Identifier	Study Quality (Benefits/ Harms)	Country	Population	Sample Size	Mean (SD) Age	N (%) Women	Race/ Ethnicity N(%)	Intervention; Comparator; Duration	Outcomes Reported
WHI CaD, 2006[75, 103-107, 122]	Fair/ Fair	U.S.	Postmenopausal women ages 50 to 79 years participating in either the WHI Dietary Modification or Hormone Therapy trials at 40 clinical sites	36,282	62.4 (NR)	36,282 (100)	White: 30,153 (83.1) Black: 3,317 (9.1) Hispanic: 1,507 (4.2) American Indian or Native American: 149 (0.4) Asian or Pacific Islander: 722 (2.0) Unknown or not identified: 434 (1.2)	D_3 400 IU with calcium 1,000 mg daily; Placebo; 7 years	• Hip fracture • Clinical vertebral fracture • Any fracture • Mortality • Kidney stones

***** Based on the 389 participants included in the ITT analyses.

† For all study arms, some of which were not relevant to our review.

‡ Participants recruited from practitioners lived independently and 93% of participants recruited from apartment homes for the elderly were able to walk independently.

§ After an initial loading dose of 200,000 IU.

Abbreviations: AE=adverse event; APOSS=Aberdeen Prospective Osteoporosis Screening Study; BMI=body mass index; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; IU=international units; MOF=major osteoporotic fracture; NA=not applicable; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; SAE=serious adverse event; SD=standard deviation; U.K.=United Kingdom; U.S.=United States; ViDa=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial.

Table 2. Summary of Evidence

Key Question	Outcome	No. of Studies (No. of Participants)	Summary of Findings*	Consistency and Precision	Limitations	Strength of Evidence	Applicability
1	Participants with hip fracture	7 RCTs[68, 69, 75, 76, 78, 79, 81] (88,364)	Followup 3 to 7 years Pooled RR, 0.99 (95% CI, 0.86 to 1.13); ARD, 0 fewer participants with hip fracture per 1,000 supplemented (95% CI, from 1 fewer to 1 more)	Consistent, precise	Most studies, were fair quality; none were designed to assess hip fracture alone as a primary outcome	Moderate for trivial to no effect (downgraded 1 level for study limitations)	Men and women without known vitamin D deficiency; interventions with or without calcium; vitamin D doses ranged from 300 IU to 2,000 IU daily (or daily equivalent from weekly or monthly dosages)
1	Participants with MOF	3 RCTs[68, 69, 81] (48,833)	Followup 5 to 5.3 years Pooled RR, 0.93 (95% CI, 0.78 to 1.10) ARD, 2 fewer participants with MOF per 1,000 supplemented (from 6 fewer to 3 more)	Inconsistent, precise	1 study was fair quality and 2 studies were good quality	Moderate for trivial to no effect (downgraded 1 level for study limitations and 1 level for inconsistency) *not graded down for imprecision due to being related to inconsistency	Men and women without known vitamin D deficiency; interventions without calcium; vitamin D doses ranged from 833 IU to 2,000 IU daily (or daily equivalent from weekly or monthly dosages)
1	Participants with clinical vertebral fracture	2 RCTs[75, 81] (38,968)	Followup 5 to 7 years Pooled RR, 0.86 (95% CI, 0.65 to 1.12); ARD, 2 fewer participants with vertebral fractures per 1,000 supplemented (from 4 fewer to 1 more)	Consistent; precise	Both studies were fair quality; meaningful contamination in the larger of the 2 studies	Moderate for trivial to no effect (1 level for study limitations)	Men and women; vitamin D doses were 300 IU and 400 IU daily; 1 study also included calcium in the intervention arm

Table 2. Summary of Evidence

Key Question	Outcome	No. of Studies (No. of Participants)	Summary of Findings*	Consistency and Precision	Limitations	Strength of Evidence	Applicability
1	Participants with nonvertebral fracture	Vitamin D (with or without calcium) 7 RCTs[65, 68, 69, 74, 76, 78, 83] (54,348)	Followup 1 to 5.7 years Pooled RR from 6 studies, 0.96 (95% CI, 0.86 to 1.09); ARD, 2 fewer participants with nonvertebral fractures per 1,000 supplemented (from 8 fewer to 5 more)	Consistent; imprecise	Four studies were good quality and 3 were fair quality; among these studies, the most common concerns were for bias due to randomization, allocation concealment, and adherence	Low for trivial to no effect (2 levels for imprecision)	Men and women; vitamin D dosages ranged from 300 to 3,300 IU daily equivalent; 1 study included calcium in the intervention arm
		Calcium only 1 RCT[80] (236)	Followup 4 years Calculated RR, 0.90 (95% CI, 0.41 to 1.96); ARD 10 fewer participants with nonvertebral fractures per 1,000 supplemented (from 61 fewer to 98 more).	Consistency NA; very imprecise	Fair quality due to lack of information about about randomization or allocation concealment	Insufficient for calcium alone (2 levels for imprecision, 1 level for study quality)	Women only; calcium dosage 1,600 mg daily.
1	Participants with any fracture	7 RCTs [66, 68, 69, 74, 75, 81, 83] (91,048)	Followup 1 to 7 years Pooled RR, 0.96 (95% CI, 0.92 to 1.00) based on 5 RCTs ARD, 3 fewer per 1,000 participants (from 7 fewer to 0 more) Results from 3 RCTs that could not be included in the pooled estimate were consistent	Consistent, precise	Three studies were good quality and 4 were fair quality; among these studies, risk of bias was most frequently associated with randomization, missing outcome data, and departures from the intervention; only 1 study was designed to assed fracture as a primary outcome	Moderate for trivial to no effect (downgraded 1 level for study limitations)	Men and women without known vitamin D deficiency; interventions with or without calcium; vitamin D doses ranged from 400 IU to 3,333 IU daily (or daily equivalents from weekly or monthly dosages)

Table 2. Summary of Evidence

Key Question	Outcome	No. of Studies (No. of Participants)	Summary of Findings*	Consistency and Precision	Limitations	Strength of Evidence	Applicability
1	Participants with 1 or more falls	9 RCTs).[65, 68, 69, 72, 74, 76, 77, 81, 83] (38,837)	Followup 9 months to 5.3 years Pooled RR, 0.99 (95% CI, 0.97 to 1.01) based on 8 RCTs ARD, 5 fewer per participants with falls per 1,000 supplemented (95% CI, from 15 fewer to 5 more)	Consistent, imprecise	5 good and 4 fair quality RCTs; only 2 were designed to assess falls as a primary outcome	Moderate for trivial to no effect (downgraded 1 level for imprecision)	Men and women without known vitamin D deficiency; one study included calcium; vitamin D dosages ranged from 400 IU to 3,333 IU daily (or daily equivalent from weekly or monthly dosages)
1	Fall rate	5 RCTs.[65, 68, 69, 72, 74] (49,834)	Followup 1 to 5.3 years Pooled IRR 0.98 (95% CI, 0.94 to 1.03) based on 4 RCTs (N=28,519)	Consistent, precise	4 good quality and 1 fair quality RCT; only 1 was designed to assess falls as a primary outcome	High for trivial to no effect	Men and women without known vitamin D deficiency; no studies included calcium; vitamin D doses ranged from 400 IU to 2,000 IU daily
1	Mortality	16 RCTs[65-73, 75, 77-79, 81-83] (109,782)	Followup 2 to 7 years Pooled RR, 0.96 (95% CI, 0.91 to 1.02) ARD, 2 fewer deaths per 1,000 supplemented (from 4 fewer to 1 more)	Consistent, precise	Most studies, were fair quality; none were designed to assess mortality as a primary outcome	Moderate for trivial to no effect (downgraded 1 level for study limitations)	Men and women without known vitamin D deficiency; interventions with or without calcium; vitamin D doses ranged from 300 IU to 4,000 IU daily (or daily equivalent from weekly or monthly dosages)
2	Participants with SAE	9 RCTs[66, 69-71, 74, 76, 78, 82, 123] (29,445)	Three RCTs[76, 82, 123] reported zero SAEs among participants; 2 RCTs reported measures of effect suggesting no increase in SAEs for vitamin D compared with control; [69, 70] the remaining 4 RCTs[66, 71, 74, 78] did not report measures of effect but the frequency of SAEs was similar in vitamin D (with or without calcium) and control groups	Consistent; imprecise	Methods for ascertainment not well described in most studies; studies not powered for this outcome	Moderate for trivial to no effect for vitamin D with or without calcium (downgraded 1 level for imprecision)	Men and women without known vitamin D deficiency; interventions with or without calcium; vitamin D doses ranged from 300 IU to 4,000 IU daily (or daily equivalent from weekly or monthly dosages)

Table 2. Summary of Evidence

Key Question	Outcome	No. of Studies (No. of Participants)	Summary of Findings*	Consistency and Precision	Limitations	Strength of Evidence	Applicability
2	Participants with kidney stones	10 RCTs [65, 66, 68-70, 73, 75, 82, 83, 123] (99,036)	Followup 2.5 to 7 years Vitamin D with or without calcium (10 RCTs): Pooled RR, 1.11 (95% CI, 1.03 to 1.21) ARD, 2 more (from 1 more to 5 more)	Consistent, imprecise	Six studies were good quality and the rest were fair quality; none were designed to assess kidney stones as a primary outcome	Moderate for trivial to no effect for vitamin D with or without calcium (downgraded 1 level for imprecision)	Men and women without known vitamin D deficiency; interventions with or without calcium; vitamin D doses ranged from 400 IU to 4,000 IU daily (or daily equivalent from weekly or monthly dosages).
		2 RCTs[80, 123] (969)	Followup 4 years Calcium alone (2 RCTs): Pooled RR, 1.07 (95% CI, 0.17 to 6.77) ARD, 0 more (from 3 fewer to 20 more)	Consistent, very imprecise	Both studies were fair quality and neither designed to assess kidney stones as a primary outcome; events were very rare	Insufficient for calcium alone (downgraded 2 levels for imprecision and 1 level for study limitations)	Women without known vitamin D deficiency; doses of 1,400 and 1,600 mg daily, respectively

* Represents findings for supplementation using vitamin D with or without calcium unless otherwise specified.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; IU=international units; MOF=major osteoporotic fracture; N=number; NA=not applicable; RCT=randomized, controlled trial; RR=risk ratio; SAE=serious adverse event.

Appendix A. Additional Background

Appendix A Table 1. NAM Recommended Dietary Allowances, Estimated Average Requirement, and Tolerable Upper Intake Level[9]

Age	Dietary Reference Intakes for Vitamin D and Calcium (per day)		
	RDA	EAR	UL
19 to 50 years*	600 IU/1,000 mg	400 IU/800 mg	4,000 IU/2,500 mg
51 to 70 years (males)	600 IU/1,000 mg	400 IU/800 mg	4,000 IU/2,000 mg
51 to 70 years (females)	600 IU/1,200 mg	400 IU/1,000 mg	4,000 IU/2,000 mg
70 years or older	800 IU/1,200 mg	400 IU/1,000 mg	4,000 IU/2,000 mg

* Pregnant and lactating adults have the same dietary reference intakes as healthy adults who are not pregnant or lactating.

Abbreviations: EAR=estimated average requirement (meets needs of 50% of healthy adults); IU=international units; NAM=National Academy of Medicine; RDA=recommended dietary allowance (meets needs of 97.5% of healthy adults); UL=tolerable upper intake level (maximum dose above which potential for harm exists).

Appendix A Table 2. Serum 25(OH)D Level and Relationship to Health, NAM (2010)[9]

ng/ml*	nmol/*L	Health Status
<12	<30	At risk for deficiency (levels lower than this may lead to rickets in children and osteomalacia in adults)
12 to <20	30 to <50	May be inadequate for bone and overall health in healthy individuals
≥20	≥50	Probably adequate for bone and overall health in healthy individuals
>50	>125	Potential for adverse effects

* 1 nmol/L is equivalent to 0.4 ng/ml. For consistency, this evidence review will discuss serum levels using ng/ml units.

Abbreviations: NAM=National Academy of Medicine.

Appendix A Table 3. Usual Nutrient Intake From Food and Beverages for Adults; National Health and Nutrition Examination, 2015–2018[35]

Age	Males, Median (SE)	% With Intake <EAR	Females, Median (SE)	% With Intake <EAR
	*Vitamin D intake per day (IU)**			
19 to 30 years	160 (8)	95	136 (4)	>97
31 to 50 years	160 (4)	95	140 (8)	>97
51 to 70 years	176 (8)	93	140 (4)	>97
70 years or older	212 (12)	89	152 (8)	97 (0.6)
	Calcium intake per day (mg)			
19 to 30 years	1,071 (25)	22	844 (20)	44
31 to 50 years	1,056 (22)	23	860 (19)	41
51 to 70 years	1,000 (22)	28	806 (14)	75
70 years or older	925 (20)	58	749 (22)	82

* Reported in microgram (μg) and converted to IU (1 μg=40 IU).[10]

Abbreviations: EAR=estimated average requirement; SE=standard error.

Appendix A Table 4. Age-Standardized Hip Fracture Incidence in a Large Cohort (N=1,841,263), Medicare Advantage Enrollees*

Year	Age Strata	Overall	Males	Females
2007	50 to 64 years	5.90	4.32	7.39
	65 years or older	20.51	12.00	27.49
2013	50 to 64	5.67	4.20	7.09
	65 years or older	17.01	10.72	22.08
2017	50 to 64 years	6.03	4.33	7.73
	65 years or older	19.35	12.04	24.92

* Rates expressed as number of hip fractures per 1,000 person-years.[41]

Abbreviation: N=number.

Appendix A. Additional Background

Appendix A Table 5. Summary of Recommendations for Vitamin D and Calcium for the Primary Prevention of Fractures

Organization, Year	Recommendation
American Academy of Family Physicians, 2017[138]	Endorses the USPSTF recommendation on this topic from 2013, which is the same as the 2018 recommendation.
American Congress of Obstetricians and Gynecologists, 2021[139]	Has no universal supplementation recommendation. Recommendation is in the guideline for prevention and treatment of osteoporosis: • Counsel patients to consume the recommended daily allowance of dietary calcium and vitamin D for bone health and general health
American Association of Clinical Endocrinologists, 2020[140]	Has no universal supplementation recommendations. Recommendations are in the guideline for prevention and treatment of osteoporosis: • Measure serum 25(OH)D; supplement with vitamin D_3 (1,000 to 2,000 IU per day) if needed to maintain an optimal serum level (30 to 50 ng/ml) • Counsel patients to maintain adequate dietary intake of calcium, to a total intake (including diet plus supplement, if needed) of 1,200 mg per day for women age 50 years or older
American College of Rheumatology, 2017[141]	Has no universal supplementation recommendation. Recommendation for supplementation is specific to the prevention of glucocorticoid-induced osteoporosis: • Vitamin D: 400 to 1,000 IU per day depending on age • Calcium: 1,000 to 1,200 mg per day from diet or supplements depending on age
Bone Health and Osteoporosis Foundation, 2022[142] (formerly National Osteoporosis Foundation)	Has no universal supplementation recommendation. Recommendations are in the guidance for prevention and treatment of osteoporosis: • Monitor serum 25(OH)D levels, prescribe supplemental vitamin D (800 to 1,000 IU per day) as needed for individuals age 50 years or older to achieve a sufficient vitamin D level • Recommend a diet with adequate total calcium intake (1,000 mg per day for men ages 50 to 70 years; 1,200 mg per day for women age 51 years or older and men age 71 years or older), incorporating calcium supplements if dietary intake is insufficient
Endocrine Society, 2024[53]	Reccomends empiric vitamin D supplementation for those aged 75 years and older, which defined as Vitamin D intake that exceeds DRI and is implemented without testing for 25(OH)D.
National Institute for Clinical Excellence and U.K. Public Health Authorities, 2017 [143, 144]	Recommends routine vitamin D supplementation for the following special populations: • People older than age 65 years • People who have low or no exposure to the sun; for example, those who cover their skin for cultural reasons, who are housebound, or who are confined indoors for long periods • People who have dark skin, for example, people of African, African Caribbean, and South Asian origin
Osteoporosis Canada, 2022[145-147] (national advocacy and educational organization)	Recommends routine vitamin D supplementation year-round: • Healthy adults ages 19 to 50 years: 400 to 1,000 IU per day • Adults older than age 50 years or those who are younger but at high risk: 800 to 2,000 IU per day Recommends calcium (from all sources including diet and supplements): • Adults ages 19 to 50 years: 1,000 mg per day • Adults older than age 50 years: 1,200 mg per day • No more than 500 to 600 mg at one time

Abbreviations: DRI = Dietary Reference Intakes; IU=international units; U.K.=United Kingdom; USPSTF=U.S. Preventive Services Task Force.

B.1 Update Search Strategies

Appendix B Table 1. PubMed Benefits

Fracture-Related Terms: September 21, 2016, through September 15, 2022

Fall-Related Terms: Inception through September 15, 2022

Search Number	Query	Filters	Results
1	"Vitamin D"[Mesh] OR "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcium"[tw] OR "Vitamin D"[tw] OR Cholecalciferol[tw] OR Ergocalciferol*[tw]		716,589
2	"Vitamin D"[Mesh] OR "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcium"[tw] OR "Vitamin D"[tw] OR Cholecalciferol[tw] OR Ergocalciferol*[tw]	English	660,036
3	"Vitamin D"[Mesh] OR "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcium"[tw] OR "Vitamin D"[tw] OR Cholecalciferol[tw] OR Ergocalciferol*[tw]	English, Adult: 19+ years	102,391
4	#2 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])		640,149
5	#2 NOT (child*[tiab] OR children[tiab] kindergarten*[tiab] OR preschool*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR adolescen*[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR boys[tiab] OR girls[tiab] OR youth[tiab] OR youths[tiab]) NOT (Adult[Mesh] OR adult*[tiab] OR Aged[Mesh] OR patient*[tiab] OR senior*[tiab] OR elder*[tw] OR geriatric*[tw] OR women[tw] OR men[tw])		476,399
6	#3 OR #4 OR #5		649,548
7	"Fractures, Bone"[Mesh] OR fracture[tw] OR fractures[tw]		341,969
8	#6 AND #7		14,300
9	"Accidental Falls"[Mesh] OR falls[tiab] OR faller[tiab] OR fallers[tiab] OR fall[ti] OR falling[ti]		73,743
10	#6 AND #9		2,200
11	#8 AND #10		990
12	#8 AND #10	from 2016/9/21 - 2022/9/15	289
13	"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] OR "Pragmatic Clinical Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "randomized"[tiab] OR "trial"[tiab]		3,381,380
14	#8 AND #13		2,855
15	#8 AND #13	from 2016/9/21 - 2022/9/15	556

Appendix B. Additional Methods

Search Number	Query	Filters	Results
16	(cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR "Prospective Studies"[Mesh] OR "Observational Study" [Publication Type]) NOT (comment[pt] OR editorial[pt] OR review[pt] OR meta analysis[pt] OR case report[tw] OR consensus[mh] OR guideline[pt] OR history[sh])		5,375,661
17	#8 AND #16		4,853
18	#8 AND #16	from 2016/9/21 - 2022/9/15	1,426
19	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murine[tw] OR murinae[tw]		8,993,985
20	#15 NOT #19		520
21	#18 NOT #19		1,241
22	"Systematic Reviews as Topic"[Mesh] OR "cochrane database syst rev"[ta] OR "systematic literature review"[ti] OR "systematic review"[ti] OR ("systematic review"[tiab] AND review[pt]) OR "this systematic review"[tw] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analyses"[tiab] OR "meta-analysis"[tiab] OR meta synthesis[tiab] OR "Umbrella Review"[tiab]		393,428
23	#8 AND #22		521
24	#23 NOT #19 (limited to 2016-2022)		216
25	#10 NOT #19		1,702
26	#25 AND #13		465
27	#25 AND #16		585
28	#25 AND #22		137

Appendix B. Additional Methods

Appendix B Table 2. PubMed Harms

Fracture-Related Terms: September 21, 2016, through September 15, 2022

Fall-Related Terms: Inception through September 15, 2022

Search Number	Query	Filters	Results
1	"Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Dietary Supplements/adverse effects"[Mesh] OR "Dietary Supplements/toxicity"[Mesh] OR "Mortality"[Mesh] OR "Urinary Calculi"[Mesh] Or "Nephrolithiasis"[Mesh] OR "kidney stones"[tw] OR "bladder stones"		10,858
2	"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 "Vitamin D toxicity"[tw] OR "hypervitaminosis D"[tw] OR "vitamin D poison*"[tiab] OR "vitamin d toxic*"[tiab] OR ("vitamin d"[tiab] AND adverse[tiab]) OR ("vitamin d"[tiab] AND harm*[tiab]) 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] OR "Cholecalciferol/adverse effects"[Mesh] OR "Cholecalciferol/poisoning"[Mesh] OR "Cholecalciferol/therapeutic use"[Mesh] OR "Cholecalciferol/therapy"[Mesh] OR "Cholecalciferol/toxicity"[Mesh] OR "calcium poison*"[tiab] OR "Calcium toxic*"[tiab] OR (calcium[tiab] AND adverse[tiab]) OR (calcium[tiab] AND harm*[tiab])		56,971
3	#1 AND #2		299
4	#1 AND #2	English	268
5	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "Case Reports" [Publication Type] OR "case report*"[tiab] OR "case series"[tiab] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murine[tw] OR murinae[tw]		9,224,069
6	#4 NOT #5		219
7	#4 NOT #5	from 2019/9/21 - 3000/12/12	36
8	"Systematic Reviews as Topic"[Mesh] OR "cochrane database syst rev"[ta] OR "systematic literature review"[ti] OR "systematic review"[ti] OR ("systematic review"[tiab] AND review[pt]) OR "this systematic review"[tw] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analyses"[tiab] OR "meta-analysis"[tiab] OR meta synthesis[tiab] OR "Umbrella Review"[tiab]		394,204
9	#7 AND #8		7
10	#7 NOT #9		29

Appendix B. Additional Methods

Appendix B Table 3. Cochrane Library Benefits

Fractures: 2016 through September 29, 2022

Falls: Inception through September 29, 2022

Search Number	Query	Results
#1	[mh "Vitamin D"] OR [mh Calcium] OR [mh "Calcium Compounds"] OR [mh Cholecalciferol] OR [mh Ergocalciferols] OR Calcium:ti,ab,kw OR "Vitamin D":ti,ab,kw OR Cholecalciferol:ti,ab,kw OR Ergocalciferol*:ti,ab,kw	41252
#2	#1 NOT (([mh Adolescent] OR [mh Child] OR [mh Infant]) NOT [mh Adult])	39638
#3	#1 NOT ((child*:ti,ab OR ("children" OR kindergarten*):ti,ab OR preschool*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR adolescen*:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR boys:ti,ab OR girls:ti,ab OR youth:ti,ab OR youths:ti,ab) NOT ([mh Adult] OR adult*:ti,ab OR [mh Aged] OR patient*:ti,ab OR senior*:ti,ab OR elder*:ti,ab,kw OR geriatric*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw))	39458
#4	#2 OR #3	40504
#5	[mh "Fractures, Bone"] OR fracture:ti,ab,kw OR fractures:ti,ab,kw	26148
#6	#4 AND #5	2900
	#6 limiting to Trials, 2016-2022, and removing results from WHO ICTRP and ClinicalTrials.gov	**261**
#7	[mh "Accidental Falls"] OR falls:ti,ab OR faller:ti,ab OR fallers:ti,ab OR fall:ti OR falling:ti	9435
#8	#1 AND #7	604
#9	#8 NOT (([mh Adolescent] OR [mh Child] OR [mh Infant]) NOT [mh Adult])	604
#10	#8 NOT ((child*:ti,ab OR ("children" OR kindergarten*):ti,ab OR preschool*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR adolescen*:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR boys:ti,ab OR girls:ti,ab OR youth:ti,ab OR youths:ti,ab) NOT ([mh Adult] OR adult*:ti,ab OR [mh Aged] OR patient*:ti,ab OR senior*:ti,ab OR elder*:ti,ab,kw OR geriatric*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw))	602
#11	#9 OR #10	604
	#11 limiting to Trials, and removing results from WHO ICTRP and ClinicalTrials.gov	**240**

Appendix B Table 4. Cochrane Library Harms

Fractures: 2016 through September 29, 2022

Falls: Inception through September 29, 2022

Search Number	Query	Results
#1	[mh "Drug-Related Side Effects and Adverse Reactions"] OR [mh "Dietary Supplements"/AE] OR [mh "Dietary Supplements"/TO] OR [mh Mortality] OR [mh "Urinary Calculi"] OR [mh Nephrolithiasis] OR "kidney stones":ti,ab,kw OR "bladder stones":ti,ab,kw	20678
#2	[mh "Vitamin D"/AE] OR [mh "Vitamin D"/DT] OR [mh "Vitamin D"/PO] OR [mh "Vitamin D"/TU] OR [mh "Vitamin D"/TH] OR [mh "Vitamin D"/TO] OR "Vitamin D toxicity":ti,ab,kw OR "hypervitaminosis D":ti,ab,kw OR ("vitamin D" NEXT poison*):ti,ab OR ("vitamin d" NEXT toxic*):ti,ab OR ("vitamin d" AND adverse):ti,ab OR ("vitamin d":ti,ab AND harm*:ti,ab) OR [mh "Calcium"/AE] OR [mh Calcium/PO] OR [mh "Calcium"/TU] OR [mh Calcium/TH] OR [mh Calcium/TO] OR [mh "Calcium Compounds"/AE] OR [mh "Calcium Compounds"/PO] OR [mh "Calcium Compounds"/TU] OR [mh "Calcium Compounds"/TH] OR [mh "Calcium Compounds"/TO] OR [mh "Cholecalciferol"/AE] OR [mh Cholecalciferol/PO] OR [mh "Cholecalciferol"/TU] OR [mh Cholecalciferol/TH] OR [mh Cholecalciferol/TO] OR ("calcium" NEXT poison*):ti,ab OR ("calcium" NEXT toxic*):ti,ab OR (calcium:ti,ab AND adverse:ti,ab) OR (calcium:ti,ab AND harm*:ti,ab)	6980

Appendix B. Additional Methods

Search Number	Query	Results
#3	#1 AND #2	214
#4	#3 NOT (([mh Adolescent] OR [mh Child] OR [mh Infant]) NOT [mh Adult])	202
#5	#3 NOT ((child*:ti,ab OR ("children" OR kindergarten*):ti,ab OR preschool*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR adolescen*:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR boys:ti,ab OR girls:ti,ab OR youth:ti,ab OR youths:ti,ab) NOT ([mh Adult] OR adult*:ti,ab OR [mh Aged] OR patient*:ti,ab OR senior*:ti,ab OR elder*:ti,ab,kw OR geriatric*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw))	210
#6	#4 OR #5	210
#7	#6 Limited to remove WHO ICTRP and ClinicalTrials.gov results	**105**

Appendix B. Additional Methods

Appendix B Table 5. PubMed Benefits Bridge Search

Fracture-Related Terms: March 15, 2022, through December 14, 2023

Fall-Related Terms: March 15, 2022, through December 14, 2022

Search Number	Query	Results
#1	Search: "Vitamin D"[Mesh] OR "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcium"[tw] OR "Vitamin D"[tw] OR Cholecalciferol[tw] OR Ergocalciferol*[tw]	743,753
#2	Search: "Vitamin D"[Mesh] OR "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcium"[tw] OR "Vitamin D"[tw] OR Cholecalciferol[tw] OR Ergocalciferol*[tw] Filters: English	686,788
#3	Search: "Vitamin D"[Mesh] OR "Calcium"[Mesh] OR "Calcium Compounds"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcium"[tw] OR "Vitamin D"[tw] OR Cholecalciferol[tw] OR Ergocalciferol*[tw] Filters: English, Adult: 19+ years	104,268
#4	Search: #2 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])	665,919
#5	Search: #2 NOT (child*[tiab] OR children[tiab] kindergarten*[tiab] OR preschool*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR adolescen*[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR boys[tiab] OR girls[tiab] OR youth[tiab] OR youths[tiab]) NOT (Adult[Mesh] OR adult*[tiab] OR Aged[Mesh] OR patient*[tiab] OR senior*[tiab] OR elder*[tw] OR geriatric*[tw] OR women[tw] OR men[tw])	493,374
#6	Search: #3 OR #4 OR #5	675,616
#7	Search: "Fractures, Bone"[Mesh] OR fracture[tw] OR fractures[tw]	363,678
#8	Search: #6 AND #7	15,019
#9	Search: "Accidental Falls"[Mesh] OR falls[tiab] OR faller[tiab] OR fallers[tiab] OR fall[ti] OR falling[ti]	79,214
#10	Search: #6 AND #9	2,295
#11	Search: #8 AND #10	1,033
#12	Search: address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murine[tw] OR murinae[tw]	9,320,533
#13	Search: #10 NOT #12	1,788
#14	Search: #11 NOT #12	960
#15	Search: #10 NOT #12 Filters: from 2022/3/15 - 2023/12/31	125
#16	Search: #11 NOT #12 Filters: from 2022/3/15 - 2023/12/31	56
#17	Search: "Systematic Reviews as Topic"[Mesh] OR "cochrane database syst rev"[ta] OR "systematic literature review"[ti] OR "systematic review"[ti] OR ("systematic review"[tiab] AND review[pt]) OR "this systematic review"[tw] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analyses"[tiab] OR "meta-analysis"[tiab] OR meta synthesis[tiab] OR "Umbrella Review"[tiab]	457,700

Appendix B. Additional Methods

Search Number	Query	Results
#18	Search: #15 AND #17	12
#19	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] OR "Pragmatic Clinical Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "randomized"[tiab] OR "trial"[tiab]	3,501,801
#20	Search: #15 AND #19	35
#21	Search: (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR "Prospective Studies"[Mesh] OR "Observational Study" [Publication Type]) NOT (comment[pt] OR editorial[pt] OR review[pt] OR meta analysis[pt] OR case report[tw] OR consensus[mh] OR guideline[pt] OR history[sh])	5,791,470
#22	Search: #15 AND #21	43
#23	Search: #16 AND #17	8
#24	Search: #16 AND #19	17
#25	Search: #16 AND #21	16

Appendix B. Additional Methods

Appendix B Table 6. PubMed Harms Bridge Search

Fracture-Related Terms: March 15, 2022, through September 14, 2023

Fall-Related Terms: March 15, 2022, through September 14, 2023

Search Number	Query	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 "Urinary Calculi"[Mesh] Or "Nephrolithiasis"[Mesh] OR "kidney stones"[tw] OR "bladder stones"	11,823
#2	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 "Vitamin D toxicity"[tw] OR "hypervitaminosis D"[tw] OR "vitamin D poison*"[tiab] OR "vitamin d toxic*"[tiab] OR ("vitamin d"[tiab] AND adverse[tiab]) OR ("vitamin d"[tiab] AND harm*[tiab]) 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] OR "Cholecalciferol/adverse effects"[Mesh] OR "Cholecalciferol/poisoning"[Mesh] OR "Cholecalciferol/therapeutic use"[Mesh] OR "Cholecalciferol/therapy"[Mesh] OR "Cholecalciferol/toxicity"[Mesh] OR "calcium poison*"[tiab] OR "Calcium toxic*"[tiab] OR (calcium[tiab] AND adverse[tiab]) OR (calcium[tiab] AND harm*[tiab])	58,988
#3	Search: #1 AND #2	315
#4	Search: #1 AND #2 Filters: English	284
#5	Search: address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "Case Reports" [Publication Type] OR "case report*"[tiab] OR "case series"[tiab] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murine[tw] OR murinae[tw]	9,521,304
#6	Search: #4 NOT #5	232
#7	Search: #4 NOT #5 Filters: from 2022/3/15 - 2023/12/31	22
#8	Search: "Systematic Reviews as Topic"[Mesh] OR "cochrane database syst rev"[ta] OR "systematic literature review"[ti] OR "systematic review"[ti] OR ("systematic review"[tiab] AND review[pt]) OR "this systematic review"[tw] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analyses"[tiab] OR "meta-analysis"[tiab] OR meta synthesis[tiab] OR "Umbrella Review"[tiab]	457,700
#9	Search: #7 AND #8	6
#10	Search: #7 NOT #9	16

Appendix B. Additional Methods

Appendix B Table 7. Cochrane Library Benefits Bridge Search

Fractures: March 15, 2022, through December 15, 2023

Falls: March 15, 2022, through December 15, 2023

Search Number	Query	Limits	Results
#1	[mh "Vitamin D"] OR [mh Calcium] OR [mh "Calcium Compounds"] OR [mh Cholecalciferol] OR [mh Ergocalciferols] OR Calcium:ti,ab,kw OR "Vitamin D":ti,ab,kw OR Cholecalciferol:ti,ab,kw OR Ergocalciferol*:ti,ab,kw		44348
#2	#1 NOT (([mh Adolescent] OR [mh Child] OR [mh Infant]) NOT [mh Adult])		42351
#3	#1 NOT ((child*:ti,ab OR ("children" OR kindergarten*):ti,ab OR preschool*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR adolescen*:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR boys:ti,ab OR girls:ti,ab OR youth:ti,ab OR youths:ti,ab) NOT ([mh Adult] OR adult*:ti,ab OR [mh Aged] OR patient*:ti,ab OR senior*:ti,ab OR elder*:ti,ab,kw OR geriatric*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw))		42428
#4	#2 OR #3		43433
#5	[mh "Fractures, Bone"] OR fracture:ti,ab,kw OR fractures:ti,ab,kw		28763
#6	#4 AND #5		3092
#7	#6	with Publication Year from 2022 to 2023, in Trials	199
#8	#6	with Cochrane Library publication date from Sep 2022 to Dec 2023, in Trials	159
#9	#7 OR #8		214
	#9 Removing results from ClinicalTrials.gov and WHO ICTRP		**172**
#10	[mh "Accidental Falls"] OR falls:ti,ab OR faller:ti,ab OR fallers:ti,ab OR fall:ti OR falling:ti		10443
#11	#1 AND #10		642
#12	#11 NOT (([mh Adolescent] OR [mh Child] OR [mh Infant]) NOT [mh Adult])		641
#13	#11 NOT ((child*:ti,ab OR ("children" OR kindergarten*):ti,ab OR preschool*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR adolescen*:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR boys:ti,ab OR girls:ti,ab OR youth:ti,ab OR youths:ti,ab) NOT ([mh Adult] OR adult*:ti,ab OR [mh Aged] OR patient*:ti,ab OR senior*:ti,ab OR elder*:ti,ab,kw OR geriatric*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw))		640
#14	#12 OR #13		642
#15	#14	with Publication Year from 2022 to 2023, in Trials	46
#16	#14	with Cochrane Library publication date from Sep 2022 to Dec 2023, in Trials	32
#17	#15 OR #16		49
	#17 Removing results from ClinicalTrials.gov and WHO ICTRP		**45**

Appendix B. Additional Methods

Appendix B Table 8. Cochrane Library Harms Bridge Search

Fractures: March 15, 2022, through December 15, 2023

Falls: March 15, 2022, through December 15, 2023

Search Number	Query	Results
#1	[mh "Dietary Supplements"/TO] OR [mh Mortality] OR [mh "Urinary Calculi"] OR [mh Nephrolithiasis] OR "kidney stones":ti,ab,kw OR "bladder stones":ti,ab,kw	24350
#2	[mh "Drug-Related Side Effects and Adverse Reactions"]	5432
#3	#1 OR #2	29647
#4	[mh "Vitamin D"/AE] OR [mh "Vitamin D"/DT] OR [mh "Vitamin D"/PO] OR [mh "Vitamin D"/TU] OR [mh "Vitamin D"/TH] OR [mh "Vitamin D"/TO] OR "Vitamin D toxicity":ti,ab,kw OR "hypervitaminosis D":ti,ab,kw OR ("vitamin D" NEXT poison*):ti,ab OR ("vitamin d" NEXT toxic*):ti,ab OR ("vitamin d" AND adverse):ti,ab OR ("vitamin d":ti,ab AND harm*:ti,ab) OR [mh "Calcium"/AE] OR [mh Calcium/PO] OR [mh "Calcium"/TU] OR [mh Calcium/TH] OR [mh Calcium/TO] OR [mh "Calcium Compounds"/AE] OR [mh "Calcium Compounds"/PO] OR [mh "Calcium Compounds"/TU] OR [mh "Calcium Compounds"/TH] OR [mh "Calcium Compounds"/TO] OR [mh "Cholecalciferol"/AE] OR [mh Cholecalciferol/PO] OR [mh "Cholecalciferol"/TU] OR [mh Cholecalciferol/TH] OR [mh Cholecalciferol/TO] OR ("calcium" NEXT poison*):ti,ab OR ("calcium" NEXT toxic*):ti,ab OR (calcium:ti,ab AND adverse:ti,ab) OR (calcium:ti,ab AND harm*:ti,ab)	7757
#5	#3 AND #4	196
#6	#5 NOT (([mh Adolescent] OR [mh Child] OR [mh Infant]) NOT [mh Adult])	191
#7	#5 NOT ((child*:ti,ab OR ("children" OR kindergarten*):ti,ab OR preschool*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR adolescen*:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR boys:ti,ab OR girls:ti,ab OR youth:ti,ab OR youths:ti,ab) NOT ([mh Adult] OR adult*:ti,ab OR [mh Aged] OR patient*:ti,ab OR senior*:ti,ab OR elder*:ti,ab,kw OR geriatric*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw))	195
#8	#6 OR #7	195
#9	#8 with Publication Year from 2022 to 2023, in Trials	10
#10	#8 with Cochrane Library publication date Between Sep 2022 and Dec 2023	10
#11	#9 OR #10	13
	Limited to Trials and Removing results from ClinicalTrials.gov and WHO ICTRP	**8**

Clinicaltrials.gov Search

Date range: March 21, 2017, to October 14, 2022

Benefits

Conditions or disease box: fracture OR fractures OR fall OR falls OR faller OR fallers OR falling

Age check boxes: Adult, and Older Adult

Study Type box: All Studies

Recruitment: Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, and Completed

Intervention / treatment box: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Last update posted from: 03/21/2017 to 10/14/2022

103 Studies found for: fracture OR fractures OR fall OR falls OR faller OR fallers OR falling | "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol* | Adult, Older Adult | Last update posted from 03/21/2017 to 10/14/2022

Harms

Other Terms box: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi”

Age check boxes: Adult, and Older Adult

Study Type box: All Studies

Recruitment: Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, and Completed

Intervention / treatment box: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Limited to last update posted: 03/21/2017 – 10/14/20222

351 Studies found for: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi” | "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol* | Adult, Older Adult | Last update posted from 03/21/2017 to 10/14/2022

ClinicalTrials.gov Bridge Search August 2, 2023

Date Range: October 14, 2022, to August 2, 2023

Benefits

Conditions or disease box: fracture OR fractures OR fall OR falls OR faller OR fallers OR falling

Age check boxes: Adult, and Older Adult

Study Type box: All Studies

Recruitment: Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, and Completed

Intervention / treatment box: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Last update posted from: 10/14/2022 to 08/02/2023

32 Studies found for: fracture OR fractures OR fall OR falls OR faller OR fallers OR falling | "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol* | Adult, Older Adult | Last update posted from 10/14/2022 to 08/02/2023

Harms

Other Terms box: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi”

Age check boxes: Adult, and Older Adult

Study Type box: All Studies

Recruitment: Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, and Completed

Intervention / treatment box: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Limited to last update posted: 10/14/2022 to 08/02/2023

124 Studies found for: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi” | "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol* | Adult, Older Adult | Last update posted from 10/14/2022 to 08/02/2023

Clinicaltrials.gov Bridge Search December 15, 2023

Date Range: October 8, 2022, to December 15, 2023

Benefits

Conditions or disease box: fracture OR fractures OR fall OR falls OR faller OR fallers OR falling

Age check boxes: Adult, and Older Adult

Study Type box: All Studies

Recruitment: Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, and Completed

Intervention / treatment box: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

45 Studies found.

Harms

Other Terms box: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi”

Age check boxes: Adult, and Older Adult

Study Type box: All Studies

Recruitment: Not yet recruiting, Recruiting, Enrolling by invitation, Active, not recruiting, and Completed

Intervention / treatment box: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

171 Studies found.

WHO International Clinical Trials Registry Platform Search

Date range: March 21, 2017, to October 14, 2022

Benefits

Condition: Intervention / treatment box: fracture OR fractures OR fall OR falls OR faller OR fallers OR falling

Intervention: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Recruitment dropdown box: ALL

Date of registration is between: March 21, 2017 – October 14, 2022

Harms

Harms putting harms terms in condition box:

Intervention: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Condition: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi”

Recruitment dropdown box: ALL

Date of registration is between: March 21, 2017 – October 14, 2022

And harms search putting Condition terms in title:

Intervention: "Vitamin D" OR Calcium OR Cholecalciferol* OR Ergocalciferol*

Title: “bladder stones” OR “hypervitaminosis D” OR “kidney stones” OR mortality OR Nephrolithiasis OR “urinary calculi”

Recruitment dropdown box: ALL

Date of registration is between: March 21, 2017 – October 14, 2022

B.2 Detailed Eligibility Criteria

Appendix B Table 5. Detailed Eligibility Criteria

Category	Include	Exclude
Population	Community-dwelling adults with no known disorders related to vitamin D, calcium, or bone metabolism Mixed populations will be included if no more than 20% of the study population has any of the excluded conditions	Children or adolescents age 18 years or younger; pregnant or lactating persons; 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 those who take antiresorptive agents, 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) • 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) • Nephrolithiasis or nephrocalcinosis
Setting	Community and primary care–relevant settings, including assisted and independent living facilities	Inpatient, skilled nursing facilities; postacute care and rehabilitation facilities
Interventions	• Vitamin D_2 or D_3; any dose given orally or intramuscularly at any frequency • Calcium; any dose given orally at any frequency • Vitamin D and calcium in combination	Short-term supplementation use (less than 1 month); vitamin D preparations or metabolites designed for treatment not supplementation (e.g., calcitriol, alphacalcidiol, 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

Appendix B. Additional Methods

Category	Include	Exclude
Comparators	Placebo or no treatment	Alternative dosages of vitamin D, calcium, or both Intervention and comparison arms that do not allow for the evaluation of the independent contribution of vitamin D, calcium, or both (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)
Outcomes	**KQ 1:** • Incident fractures, including all-cause, all-fragility, fall-related, major osteoporotic fractures, hip, and clinical vertebral; fracture-related morbidity and mortality • Incident first falls, including all-cause, low-trauma, and injurious falls (i.e., requiring hospitalization or ED visit), incident recurrent falls, fall rate, and fall-related morbidity and mortality • All-cause mortality • Disability as measured by instrumental activities of daily life • Quality of life as measured by validated instruments; hospitalization for fall-related injuries; ED visits for fall-related injuries; and institutionalization **KQ 2:** Symptomatic acute or chronic vitamin D or calcium toxicity, incident symptomatic nephrolithiasis, and serious adverse events	**KQ 1:** Morphometric vertebral fractures; BMD; laboratory or functional measures of bone or muscle strength or quality; fall efficacy measures; and basic activities of daily living **KQ 2:** Incident cancer or cardiovascular disease or events; asymptomatic renal outcomes (soft tissue calcification, nephrocalcinosis, artery calcification, hypercalcemia, hypercalciuria); and nonserious adverse events
Study design	**KQ 1:** RCTs, controlled clinical trials **KQ 2:** RCTs; prospective cohort studies with contemporaneous comparison groups with a primary study aim to evaluate the use of vitamin D or calcium supplementation	Study designs not listed as specifically included (e.g., case reports, case series, case-control studies, studies without a comparison group). Recent systematic reviews will not be included but will be hand searched to ensure that no relevant studies have been missed
Timing	**KQ 1:** Intervention duration of 1 month or longer **KQ 2:** Intervention of any duration	**KQ 1:** Intervention duration of less than 1 month **KQ 2:** No exclusions
Country setting	Studies conducted in countries categorized as “very high” on the Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries not categorized as “very high” on the Human Development Index (as defined by the United Nations Development Programme)
Language	Full-text articles published in English	Full-text articles not published in English
Quality	Fair or good quality according to design-specific criteria	Poor quality according to design-specific criteria

Abbreviations: BMD=bone mineral density; ED=emergency department; KQ = Key Question; RCT=randomized, controlled trial.

B.3 U.S. Preventive Services Task Force Quality Rating Criteria

Criteria for Randomized, Controlled Trials and Cohort Studies

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; 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, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria Randomized, Controlled Trials and Cohort Studies

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 the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains regarding whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and are 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 lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: 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.

Appendix C. Excluded Studies

List of Exclusion Codes:

X1 Ineligible population
X2 Ineligible setting
X3 Ineligible or no intervention
X4 Ineligible or no comparator
X5 Ineligible or no outcome
X6 Ineligible study design or timing
X7 Ineligible timing
X8 Not in very high HDI country
X9 Not published in English
X10 Study superseded by new evidence or duplicate
X11 Poor quality

1. Exercise useful for elderly women. *Prescrire Int*. 2016 Oct;25(175):246. PMID: 30645834. Exclusion Code: X10.
2. Albert CM, Cook NR, Pester J, et al. Effect of marine omega-3 fatty acid and vitamin D supplementation on incident atrial fibrillation: a randomized clinical trial. *JAMA*. 2021 Mar 16;325(11):1061-73. doi: 10.1001/jama.2021.1489. PMID: 33724323. Exclusion Code: X5.
3. Anek A, Bunyaratavej N, Jittivilai T. Effects of short-term vitamin D supplementation on musculoskeletal and body balance for prevention of falling in postmenopausal women. *J Med Assoc Thai*. 2015 Sep;98 Suppl 8:S26-31. PMID: 26529811. Exclusion Code: X1.
4. Appel LJ, Michos ED, Mitchell CM, et al. The effects of four doses of vitamin D supplements on falls in older adults: a response-adaptive, randomized clinical trial. *Ann Intern Med*. 2021;174(2):145-56. doi: 10.7326/M20-3812. PMID: CN-02211502. Exclusion Code: X10.
5. Appel LJ, Michos ED, Mitchell CM, et al. The effects of four doses of vitamin D supplements on falls in older adults: a response-adaptive, randomized clinical trial. *Ann Intern Med*. 2021 Feb;174(2):145-56. doi: 10.7326/m20-3812. PMID: 33284677. Exclusion Code: X1.
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9. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*. 2009 Apr 15(2):Cd000227. doi: 10.1002/14651858.CD000227.pub3. PMID: 19370554. Exclusion Code: X6.

Appendix C. Excluded Studies

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28. Brunner RL, Wactawski-Wende J, Caan BJ, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. *Nutr Cancer*. 2011;63(6):827-41. doi: 10.1080/01635581.2011.594208 [doi]. PMID: 21774589. Exclusion Code: X5.

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39. Dawson-Hughes B, Staten MA, Knowler WC, et al. Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the Vitamin D and Type 2 Diabetes (D2d) study. *Diabetes Care*. 2020 Dec;43(12):2916-22. doi: 10.2337/dc20-1765. PMID: 33020052. Exclusion Code: X5.

40. de Boer IH, Zelnick LR, Ruzinski J, et al. Effect of vitamin D and omega-3 fatty acid supplementation on kidney function in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2019 Nov 19;322(19):1899-909. doi: 10.1001/jama.2019.17380. PMID: 31703120. Exclusion Code: X5.

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42. Dhaliwal R, Islam S, Mikhail M, et al. Effect of vitamin D on bone strength in older African Americans: a randomized controlled trial. *Osteoporos Int*. 2020 Jun;31(6):1105-14. doi: 10.1007/s00198-019-05275-1. PMID: 31938818. Exclusion Code: X1.

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54. Gillespie WJ, Avenell A, Henry DA, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*. 2001(1):Cd000227. doi: 10.1002/14651858.Cd000227. PMID: 11279685. Exclusion Code: X1.

55. Gillespie WJ, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*. 2000(2):Cd000227. doi: 10.1002/14651858.Cd000227. PMID: 10796331. Exclusion Code: X6.

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58. Guralnik JM, Sternberg AL, Mitchell CM, et al. Effects of vitamin D on physical function: results from the STURDY trial. *J Gerontol A Biol Sci Med Sci*. 2021doi: 10.1093/gerona/glab379. PMID: CN-02360631. Exclusion Code: X1.

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61. Hiemstra T, Lim K, Thadhani R, Manson JE. Vitamin D and atherosclerotic cardiovascular disease. *J Clin Endocrinol Metab*. 2019 Apr 4doi: 10.1210/jc.2019-00194. PMID: 30946457. Exclusion Code: X6.

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64. Hsia DS, Rasouli N, Pittas AG, et al. Implications of the Hemoglobin Glycation Index on the diagnosis of prediabetes and diabetes. *J Clin Endocrinol Metab*. 2020 Mar 1;105(3):e130-8. doi: 10.1210/clinem/dgaa029. PMID: 31965161. Exclusion Code: X5.

65. Hsieh KL, Speiser JL, Neiberg RH, et al. Factors associated with falls in older adults: a secondary analysis of a 12-month randomized controlled trial. *Arch Gerontol Geriatr*. 2023 May;108:104940. doi: 10.1016/j.archger.2023.104940. PMID: 36709562. Exclusion Code: X1.

66. Hu Z, Zhi X, Li J, et al. Effects of long-term vitamin D supplementation on metabolic profile in middle-aged and elderly patients with type 2 diabetes. *J Steroid Biochem Mol Biol*. 2023;225:106198. doi: 10.1016/j.jsbmb.2022.106198. PMID: CN-02470496. Exclusion Code: X8.

67. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *QJM*. 2007;100(4):185-92. doi: 10.1093/qjmed/hcm005. PMID: CN-01752395. Exclusion Code: X6.

68. Jorde R, Stunes AK, Kubiak J, et al. Effects of vitamin D supplementation on bone turnover markers and other bone-related substances in subjects with vitamin D deficiency. *Bone*. 2019 Jul;124:7-13. doi: 10.1016/j.bone.2019.04.002. PMID: 30959189. Exclusion Code: X6.

69. Joseph P, Pais P, Dans AL, et al. The International Polycap Study-3 (TIPS-3): design, baseline characteristics and challenges in conduct. *Am Heart J*. 2018 Dec;206:72-9. doi: 10.1016/j.ahj.2018.07.012. PMID: 30342297. Exclusion Code: X8.

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72. Karkkainen M, Tuppurainen M, Salovaara K, et al. Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS). *Osteoporos Int*. 2010 Dec;21(12):2047-55. doi: 10.1007/s00198-009-1167-8. PMID: 20204604. Exclusion Code: X5.

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79. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents severe falls in elderly community-dwelling women: a pragmatic population-based 3-year intervention study. *Aging Clin Exp Res*. 2005 Apr;17(2):125-32. doi: 10.1007/bf03324585. PMID: 15977461. Exclusion Code: X10.

80. Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing*. 2006 Sep;35(5):482-6. doi: 10.1093/ageing/afj080. PMID: 16641143. Exclusion Code: X10.

81. LeBoff MS, Chou SH, Murata EM, et al. Effects of supplemental vitamin D on bone health outcomes in women and men in the VITamin D and OmegA-3 TriaL (VITAL). *J Bone Miner Res*. 2020 May;35(5):883-93. doi: 10.1002/jbmr.3958. PMID: 31923341. Exclusion Code: X5.

82. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental vitamin D and incident fractures in midlife and older adults. *N Engl J Med*. 2022;387(4):299-309. doi: 10.1056/NEJMoa2202106. PMID: CN-02428557. Exclusion Code: X10.

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Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Bischoff-Ferrari et al, 2020 [65] Bischoff-Ferrari et al, 2022 [85] Bischoff-Ferrari et al, 2021 [84] DO-HEALTH	Switzerland, France, Germany, Austria, Portugal Seventh Framework Program of the European Commission, University of Zurich, DSM Nutritional Products, Roche, NESTEC, Pfizer, and Streuli	2,157 Community-dwelling people at least age 70 years ; recruitment targeted at least 40% of participants to have had a fall in the last year, but a prior fall was not a requirement for study entry.	74.9 (4.4)	1,331 (61.7)	NR	Primary study aim was to test whether vitamin D, omega-3 fatty acids, and a strength training exercise program, alone or in combination, improved health outcomes among older adults.	Benefits: Good Harms: Good
Dawson-Hughes et al, 1997 [76] Bischoff-Ferrari et al, 2006[108]	U.S. National Institutes of Health	445 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.	Placebo: Women 72 (5) Men 71 (5) Vitamin D + calcium: Women 71 (4) Men 70 (4)	213 (55) Based on the 389 participants included in the ITT analyses	White: 430 (96.6) Black: 11 (2.5) Asian: 4 (0.9)	Primary study aim was to examine the effects of combined calcium and vitamin D supplementation on bone loss, bone metabolism, and nonvertebral fracture incidence.	Benefits: Fair Harms: NA

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Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Glendenning et al, 2012[77]	Australia; Department of Health, Western Australia State Health Research Advisory Council Research Translation Project Grant, Sir Charles Gairdner Hospital Research Advisory Committee Grant, and Royal Perth Hospital Medical Research Foundation Grant	686 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 investigator's opinion, would not be suitable for the study.	76.7(4.1)	686 (100)	Placebo Caucasian: 96.0% Asian: 3.4% Other: 0.6% Vitamin D Caucasian: 96.9% Asian: 2.9% Other: 0.3%	Primary study aim was to examine the effects of vitamin D supplementation on falls, muscle strength, and mobility.	Benefits: Poor for fractures; Fair for falls and mortality Harms: NA

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Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Jackson et al, 2006[75] Prentice et al, 2013[106] Bolland et al, 2011[103] Wallace et al, 2011[107] LaCroix et al, 2009[105] Jackson et al, 2003[104] Thomson et al, 2024[122] WHI CaD	U.S. National Heart, Lung, and Blood Institute and the General Clinical Research Center program of the National Center for Research Resources, Department of Health and Human Services	36,282 The number of participants included in analyses related to secondary analyses varied because some participants with prevalent conditions at baseline may have been excluded. 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.	Placebo: 62.4 (7.0) Vitamin D with calcium: 62.4 (6.9)	Placebo: 18,106 (100) Vitamin D with calcium: 18,176 (100)	Placebo White: 15,106 (83.4) Black: 1,635 (9.0) Hispanic: 718 (4.0) American Indian or Native American: 72 (0.4) Asian or Pacific Islander: 353 (1.9) Unknown or not identified: 222 (1.2) Vitamin D with calcium White: 15,047 (82.8) Black: 1,682 (9.3) Hispanic: 789(4.3) American Indian or Native American: 77 (0.4) Asian or Pacific Islander: 369 (2.0) Unknown or not identified: 212 (1.2)	Primary study aim was to assess the impact of vitamin D with calcium supplementation on risk of hip fractures.	Benefits: Fair Harms: Fair

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Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Jorde, R et al, 2016,[66] Larsen et al, 2018[100]	Norway Novo Nordisk Foundation, the North Norway Regional Health Authorities, UiT The Arctic University of Norway, the Norwegian Diabetes Association	511 Adults (mean age 62 years, 314 males) with prediabetes diagnosed with an oral glucose tolerance test as part of the Tromsø Study 2007–2008 were included. Subjects with primary hyperparathyroidism, granulomatous disease, history of urolithiasis, cancer diagnosed in the past 5 years, unstable angina pectoris, myocardial infarction, or stroke in the past year were excluded. Pregnant or lactating women, or women of fertile age with no use of contraception, were not included.	62 (NR)	197 (38.5)	NR	Primary study aim was to test whether supplementation with vitamin D in subjects with prediabetes would prevent progression to type 2 diabetes mellitus.	Benefits: Fair Harms: Fair
Kärkkäinen et al, 2010[67] OSTPRE-FPS	Finland Finnish Cultural Foundation	3,139 Women age 65 years or older at the end of November 2002 who were living in Kuopio Province and who were enrolled in the OSTPRE cohort study but not enrolled in the OSTPRE bone densitometry substudy.	No supplementation: 67.3 (1.8) Vitamin D with calcium: 67.4 (1.9)	No supplementation: 1,573(100) Vitamin D with calcium: 1,566 (100)	No supplementation: NR Vitamin D with calcium: NR	Primary study aim was to determine whether vitamin D and calcium supplementation would be effective for fall prevention in postmenopausal women.	Benefits: Poor for falls; Fair for mortality Harms: Fair

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	Finland NR	232 Women ages 52 to 61 years from Kuopio Province who were enrolled in the OSTPRE cohort study and who were between 6 and 24 months postmenopause. Exclusion criteria included contraindications to hormone therapy, history of breast or endometrial cancer, thromboembolic disease, and medication-resistant hypertension, baseline BMD less than 2 SD of the mean of the whole study population.	Calcium only: 52.6 (95% CI, 52.2 to 53.0) Vitamin D with calcium: 52.8 (95% CI, 52.4 to 53.2)	Calcium only: 116 (100) Vitamin D with calcium: 116 (100)	NR	Primary study aim was to examine the effects of menopausal hormone therapy with low-dose vitamin D supplementation on BMD. (hormone therapy groups were not eligible for this review).	Benefits: Fair Harms: NA

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Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Lappe et al, 2007[123] Lappe et al, 2006[109]	U.S. Department of Health and Human Services	1,180 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.	Total: 66.7 (7.3)	Total: 1,180 (100)	Total: 100% White	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 in December 2016. Secondary aim was to evaluate changes in serum vitamin D, parathyroid activity, bone density, falls, and cancer.	Benefits: NA Harms: Fair
Lappe et al, 2017[82]	U.S. National Cancer Institute	2,303 Community-dwelling, postmenopausal women age 55 years or older from rural areas of Nebraska who were at least 4 years past menses. Persons with history of malignancies or chronic kidney disease were excluded.	65.2 (NR)	2,303 (100)	White: 2,291 (99.5) American Indian or Alaska Native: 8 (0.3) Asian, Black, or unknown: 4 (0.4) Hispanic: 11 (0.5)	Primary study aim was to examine the effects of vitamin D with calcium supplementation on the risk of cancer.	Benefits: Fair Harms: Fair

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Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Lips et al, 2018[79]	The Netherlands Praeventiefonds (government); tablets provided by Solvay-Duphar and Weesp	2,578 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. Participants recruited from practitioners lived independently. Other participants were 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: total hip arthroplasty, hip fracture, hypercalcemia, sarcoidosis, kidney stones within past 5 years; diseases or medications that influence bone metabolism were not excluded..	80 (6.0)	1,916 (74.3)	NR	Primary study aim was to reduce incidence of hip and other osteoporotic fractures.	Benefits: Fair Harms: Fair

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Lips et al, 2018[79] (continued)		This study was included in the prior reviews for the USPSTF and was considered a community-dwelling population. We retained the study for this update because 93% of participants recruited from apartment homes for the elderly were able to walk independently, and the baseline measures reported suggested a higher level of physical function than other studies among institutionalized and nursing home populations					
Manson et al, 2019[68] LeBoff et al, 2022 [91] Bassuck et al, 2021 [89] LeBoff et al, 2020 [90] Manson et al, 2012[92] VITAL	U.S. National Instiutes of Health	25,871 Men age 50 or older and women age 55 years or older with no history of cancer (except nonmelanoma skin cancer) or cardiovascular disease at trial entry and who agreed to limit vitamin D from all supplemental sources. Exclusion criteria included renal failure or dialysis, cirrhosis, history of hypercalcemia, or other serious conditions that would preclude participation.	67.1 (7.1)	13,085 (50.6)	Non-Hispanic White: 18,046 (71.3) Black: 5,106 (20.2) Non-Black Hispanic: 1013 (4.0) Asian or Pacific Islander: 388 (1.5) Native American or Alaskan Native: 228 (0.9) Other or unknown: 523 (2.1)	Primary study aims of the trial were to test whether supplementation with vitamin D_3 or marine omega-3 fatty acid or both reduced the risk for total cancer and major cardiovascular disease events; additional aims included impact on falls, fractures, and adverse events.	Benefits: Good Harms: Good

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health	Australia National Health and Medical Research Council	21,315 Australians ages 60 to 84 years recruited from across the country from electoral rolls (enrollment to the electoral roll is compulsory in Australia) using mailed invitations or who voluneered and were not taking more than 500 IU of supplemental vitamin D per day and had no self-reported history of kidney stones, hypercalcemia, hyperparathyroidism, osteomalacia, or sarcoidosis.	69.3 (5.5)	9,780 (45.9)	Placebo: British or European: 9,714 (92.9) Australian or New Zealander: 362 (3.5) Asian: 127 (1.2) Indigenous: 71 (0.7) Other: 186 (1.8) Missing data: 188 (1.8) Vitamin D: British or European: 9,736 (93.0) Australian or New Zealander: 364 (3.5) Asian: 114 (1.1) Indigenous: 80 (0.8) Other: 179 (1.7) Missing data: 188 (1.8)	Trial aims were to determine if monthly high-dose vitamin D supplementation of the general older population can prevent cancer and premature mortality.	Benefits: Good Harms: Good

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	U.S. National Institute of Diabetes and Digestive and Kidney Diseases	2,423 Adults age 30 years or older (age 25 years or older for people of the following groups: American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander), BMI 24 to 42 kg/m^2, with 2 of 3 glycemic criteria for prediabetes (fasting plasma glucose 100 to 125 mg/dL; 2-h postload glucose after 75-g glucose load 140 to 199 mg/dL; or hemoglobin A1c 5.7% to 6.4%. Persons with diabetes or taking hypogylcemics or weight loss medications were excluded; persons using supplements at doses more than 1,000 IU per day (vitamin D) or 600 mg per day (calcium) were excluded.	60.0 (9.9)	1,086 (44.8)	Asian 130 (5.4) Black 616 (25.4) White 1,616 (66.7) Other 61 (2.5) Hispanic 225 (9.3)	Primary study aim was to assess whether oral daily vitamin D_3 supplementation in participants with prediabetes could reduce the rate of progression from prediabetes to diabetes.	Benefits: Good Harms: Good

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Rake et al, 2020[71] VIDAL	U.K. National Institute for Health Research Health Technology Assessment programme	1,615 Double-blind study: 787 Open-label study: 828 People ages 65 to 84 years attending a general practitioner with GP notes available for the previous year. Exclusion criteria included vitamin D intolerance, plans to move from the GP practice within 5 years, baseline corrected blood calcium level of >2.65 mmol/l, taking dietary supplements or other medication containing >400 IU of vitamin D per day, taking select concomitant therapy, taking treatment with any other investigational medical product or device up to 4 months before first dose of the investigational medicinal product.	Age group in years, N (%) 65 to 69: 624 (38.6) 70 to 74: 510 (31.6) 75 to 79: 325 (20.1) 80 to 84: 156 (9.7)	758 (46.9)	White British: 1,563 (96.8) White Irish: 11 (0.7) White other: 26 (1.6) Caribbean: 6 (0.4) Asian: 6 (0.4) Mixed: 3 (0.2)	Primary aim was to demonstrate the feasibility of a large trial of high-dose vitamin D conducted through general practices.	Benefits: Fair Harms: Fair

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Riggs et al, 1998[80]	U.S. National Institutes of Health	236 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 or more, history of kidney stones, impaired renal function, hypercalcemia or hypercalciuria, or diseases known to impact bone or calcium metabolism.	66.3 (NR)	236 (100)	NR, but county from which women were recruited has a largely White population	Primary study aim was to assess the impact of calcium supplementation on bone loss, serum PTH, and markers of bone turnover.	Benefits: Fair Harms: Fair

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Scragg et al, 2017[83] Malihi et al, 2019 [112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA	New Zealand The Health Research Council of New Zealand	5,108 People ages 50 to 84 years with anticipated residence in New Zealand for the 4-year study period. Exclusion criteria included diagnosis of psychiatric disorders that limit ability to comply with protocol, history of hypercalcemia, sarcoidosis, parathyroid disease, gastric bypass, nephrolithiasis.	65.9 (8.3)	2,139 (41.9)	Maori: 272 (5.3) Pacific Islander: 334 (6.5) South Asian: 249 (4.9) European or other: 4,253 (83.3)	Primary study aim was to examine the effects of vitamin D supplementation on cardiovacular disease incidence. Fractures and fall were designated as secondary outcomes.	Benefits: Good Harms: Good
Trivedi et al, 2003[81]	U.K. The Medical Research Council	2,686 Community-dwelling men and women ages 65 to 85 years, 83.0% (2,907 out of 3,504) of whom were recruited from the British Doctors Study (thus were physicians); 17.0% (597 out of 3,504) were 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.	74.7 (4.6)	649 (24.0)	NR	Primary study aim was to assess the 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).	Benefits: Fair Harms: NA

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Uusi-Rasi et al, 2015[72] Uusi-Rasi et al, 2017[88] Patil et al, 2015[86] Uusi-Ras et al, 2012[87] DEX	Finland Academy of Finland, Ministry of Education and Culture, Competitive Research Fund of Pirkanmaa Hospital District, and Juho Vainio Foundation	409 (including all study arms; only 204 were in eligible study arms) Community-dwelling women ages 70 to 80 years who had fallen at least once during the previous 12 months, did not use vitamin D supplements, and had no contraindications to exercise. Individuals who participated in moderate to vigorous exercise for more than 2 hours per week or had a history of fracture within the prior year were excluded from the study.	Placebo: 73.8 (3.1) Vitamin D: 74.1 (3.0)	Total: 204 (100)	NR	Primary study aim was to determine the effectiveness of targeted exercise training and vitamin D supplementation in reducing falls and injurious falls among older women.	Benefits: Good Harms: NA
Virtanen et al, 2022[73] FIND	Finland Academy of Finland, University of Eastern Finland, Juho Vainio Foundation	2,495 Men age 60 years or older and postmenopausal women age 65 years or older without history of cancer (except nonmelanoma skin cancer) or cardiovascular disease. Exclusion criteria included a history of kidney stones, renal failure, hypercalcemia, parathyroid disease, cirrhosis, and granulomatous disease.	68.2 (4.5)	1,069 (42.8)	White: 2,495 (100)	Primary study aim was to determine the effects of vitamin D supplementation on cardiovascular disease and cancer incidence.	Benefits: Good Harms: Good

Appendix D Table 1. Sample Characteristics

Author, Year Trial Name, No. of Participants, Quality	Country; Funder	Sample Size Population	Mean (SD) Age, Years	Women No. (%)	Race or Ethnicity No. (%)	Study Aims	Quality
Wood et al, 2012[74] Wood et al, 2014[102] Macdonald et al, 2013[101] APOSS	U.K. U.K. Department of Health	305 Caucasian postmenopausal women who were nonsmokers and were without severe disease or on vascular medications or Vitamin D-containing supplements, or with abnormal blood biochemistry.	63.8 (2.2)	305 (100)	Caucasian: 305 (100)	Primary study aim was to assess the impact of vitamin D on conventional markers of cardiovascular disease risk in postmenopausal women.	Benefits: Fair Harms: Fair

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; BMD=bone mineral density; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; GP=general practitioner; ITT=intention to treat; IU=international units; N=number of participants; NA=not applicable; NR=not reported; No.=number; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; U.K.=United Kingdom; U.S.=United States; USPSTF=U.S. Preventive Services Task Force; ViDa=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative; WHI CaD=Women's Health Initiative Calcium and vitamin D.

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Bischoff-Ferrari et al, 2020 [65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Total: 2,157 Benefits: Good Harms: Good	Total: NR Placebo: 22.4 (8.5) (n=1,074) Vitamin D: 22.4 (8.4) (n=1,066)	NR	NR	Total:0 (0)	Dose: >800 IU per day Total: 236 (10.9) Placebo: 126 (11.7) Vitamin D: 110 (10.2)	NR	Within past year Total: 903 (41.9) Placebo: 457 (42.3) Vitamin D: 446 (41.4)
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108] Total: 445 Benefits: Fair Harms: NA	Total: NR Placebo: Women: 24.5 (10.3) Men: 33.6 (12.7) Vitamin D with Calcium: Women: 28.6 (13.3) Men: 33.0 (16.3) (Based on the 313 participants who completed the study interventions.)	NR	Total: NR Placebo: Women: 0.81 g/cm2 (0.11) Men: 0.95 g/cm2 (0.12) Vitamin D with Calcium: Women: 0.80 g/cm2 (0.11) Men: 0.99 g/cm2 (0.14)	Total: 0 (0)	Total: 0 (0)	Total: 0 (0)	NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Glendenning et al, 2012[77] Total: 686 Benefits: Varies Harms: NA	Total: 26.3 (9.1) Placebo: 26.6 (10.8) Vitamin D: 26 (7.1) Based on subsample of 40 participants, 20 from each study arm; assay used was the automated Liaison method (DiaSorin, Stillwater, MN).	NR	NR	NR	NR	NR	Within past year Total: NR Placebo: 82 (24.5) Vitamin D: 118 (33.4)

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Jackson et al, 2006[75] Prentice et al, 2013[106] Bolland et al, 2011[103] Wallace et al, 2011[107] LaCroix et al, 2009[105] Jackson et al, 2003[104] Thomson et al, 2024[122] WHI CaD Total: 36,282 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. Benefis: Fair Harms: Fair	NR	Total: NR Placebo: Fracture at any age: 6,228 (34.4) Fracture after age 55 or older: 1,968 (10.9) Vitamin D with calcium: Fracture at any age: 6,311 (34.7) Fracture after 55 or older: 1,948 (10.7)	Total: Reported by study groups only and only for the subgroup of participants in whom BMD was measured. Placebo: N=1,201 subsample Total hip BMD Mean (SD): -0.77 (1.05) Vitamin D with Calcium: N=1,230 subsample Total hip BMD Mean (SD): -0.65 (1.03)	NR	Vitamin D and calcium[103] 16,100 (44) Calcium only [103] 3,464 (10) Vitamin D only[103] 1,072 (3) Multivitamin use (with or without minerals)[104] 23,354 (64.4) Calcium as a single supplement[104] 27,626 (76.1) Single supplement other than Vitamin C or E or calcium[104] 24,147 (66.6)	Total: 97 (3.9) Based on subsample of 2,529 participants who underwent bone density testing Placebo: N=1,201 Subsample: 48 (4) Vitamin D with Calcium: N=1,230 Subsample: 37 (3)	Within past year 13,889 (38.3) Placebo: NR Vitamin D with Calcium: NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Jorde, R et al, 2016[66] Larsen et al, 2018[100] Total: 511 Benefits: Fair Harms: Fair	Total: NR Placebo:24.4 (8.5) Vitamin D: 24.0 (8.8)	NR	NR	NR	NR	NR	NR
Karkkainen et al, 2010[67] OSTPRE-FPS Total: 3,139 Benefits: Varies Harms: Fair	Total: NR No supplementation: 19.7 (7.1) Vitamin D with calcium: 20.0 (7.5)	NR	NR	NR	Total: NR No supplementation: Calcium: 283 (18.0) Vitamin D with calcium: Calcium: 254 (16.2)	NR	NR
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE Total: 232 Benefits: Fair Harms: NA	NR	Fracture within the past 15 years Total: 35 (15.0) Calcium only: 15 (12.9) Vitamin D with calcium: 20 (17.2)	Total: NR Calcium only: 0.95 g/cm2 (95% CI, 0.93 to 0.97) Vitamin D with calcium: 0.93 g/cm2 (95% CI, 0.91 to 0.95)	NR	NR	Total: 0 (0)	NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Lappe et al, 2007[123] Lappe et al, 2006[109] Total: 1,180 Benefits: NA Harms: Fair	Total: 28.7 (8.1) Placebo:28.8 (8.3) Calcium: 28.6 (8.2) Vitamin D with calcium: 28.7 (8.0) Assay used was radioimmunoassay, Immunodiagnostic kit (Fountain Hills, AZ).	NR	NR	NR	Total: NR (59.3)	NR	NR
Lappe et al, 2017[82] Total: 2,303 Benefits: Fair Harms: Fair	Total: 32.8 (NR) Placebo:32.6 (NR) Vitamin D with calcium: 33.0 (NR) (Diasorin, Liaison Analyzer)	NR	NR	0 (0)	NR	NR	NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Lips et al, 1996[79] Total: 2,578 Benefits: Fair Harms: Fair	Total: 10.4 (IQR 7.6 to 14.8) Based on a nonrandom sample of participants in a substudy selected from among the participants recruited from apartment houses/homes for the elderly. Assay used was competitive protein binding assay after purification by gradient high-pressure	Total: NR (prior hip fracture excluded)	NR	Total: NR (59) The authors described that participants received 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.	Total: 133 (5.1*)	NR	NR
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Total: 25,871 Benefits: Good Harms: Good	Total: 30.7 (10.0) For a subgroup of 16,757 participants who had blood samples that could be analyzed.	Total: 2578 (10.0)	NR	NR	Total: Vitamin D: 11,030 (42.6) Calcium: 5,166 (20.0)	NR	Within past year: 6,605 (23.4)

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Total: 21,315 Benefits: Good Harms: Good	NR	NR	NR	NR	NR	NR	NR
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d Total: 2,423 Benefits: Good Harms: Good	Total: 28.0 (10.2) Placebo:28.2 (10.1) Vitamin D: 27.7 (10.2)	NR	NR	NR	Total: Vitamin D: 1,037 (42.8) Calcium: 804 (33.2) Placebo: Vitamin D: 529 (43.6) Calcium: 419 (34.6) Vitamin D: Vitamin D: 508 (41.9) Calcium: 385 (31.8)	Total: 78 (3.2)	NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Rake et al, 2020[71] VIDAL Total: Total: 1,615 Double-blind study: 787 Open-label study: 828 Benefits: Fair Harms: Fair	Total: NR Placebo: <30, N (%) Open-label control: 344 (81.7) Blinded study control: 318 (81.8) ≥30, N (%) Blinded study control: 77 (18.3) Blinded study control: 71 (18.3) Vitamin D: <30, N (%) Open-label vitamin D: 333 (82.0) Blinded study vitamin D: 334(85.2) ≥30, N (%) Blinded study vitamin D: 73 (18.0) Blinded study vitamin D: 58 (14.8)	NR	NR	NR	NR	NR	NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Riggs et al, 1998[80] Total: 236 Benefits: Fair Harms: Fair	Total: NR Placebo:29.6 (10.3) Calcium: 30.4 (10.5) Serum 25-hyroxyvitamin D level measured by the methods of Eisman et al[148] and Kumar et al [149].	Total: 0 (0)	Total: NR Placebo: Median: 0.81 g/cm2 (NR) Calcium: Median: 0.81 g/cm2 (NR)	Total: 0 (0)	Total: NR, but persons taking low dose daily supplements were eligible for inclusion (D <800 IU, calcium <500 mg) Placebo: NR Calcium: NR	Total: 0 (0)	NR
Scragg et al, 2017[83] Malihi et al, 2019[112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA Total: 5,108 Benefits: Good Harms: Good	Total: 25.3 (9.5) Placebo:25.5 (9.5) Vitamin D: 25.2 (9.4)	NR	NR	NR	Total: 408 (8.0) Placebo: 200 (7.8) Vitamin D: 208 (8.1)	Total: NR Placebo: 29 (1%) Vitamin D: 42 (2%)	Total: NR Placebo: 161 (6%) (in last 4 weeks) Vitamin D: 147 (6%) (in last 4 weeks)

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Trivedi et al, 2003[81] Total: 2,686 Benefits: Fair Harms: NA	NR	NR	NR	NR	NR	NR	NR
Uusi-Rasi et al, 2015[72] Uusi-Rasi et al, 2017[88] Patil et al, 2015[86] Uusi-Ras et al, 2012[87] DEX Total: 409 (including all study arms) Benefits: Good Harms: NA	Total: NR Placebo:27.0 (7.5) Vitamin D: 26.3 (6.8)	NR	Total: NR Placebo: 0.87 (0.14) Vitamin D: 0.82 (0.11)	Total:0 (0) Placebo: 0 (0) Vitamin D: 0 (0)	NR	NR	Total: 204 (100) Placebo: 102 (100) Vitamin D: 102 (100)
Virtanen et al, 2022[73] FIND Total: 2,495 Benefits: Good Harms: Good	Total: NR Placebo:29.5 (NR) 1,600 IU vitamin D: 30.2 (NR) 3,200 IU vitamin D 30.0 (NR)	NR	NR	NR	Vitamin D (other supplments NR) Total: 825 (33.1) Placebo: 295 (35.5) 1,600 IU vitamin D: 266 (32) 3,200 IU vitamin D 264 (31.7)	NR	NR

Appendix D Table 2. Relevant Conditions or Risks at Baseline

Author, Year Trial Name, No. of Participants, Quality	Mean (SD)25[OH]D ng/mL	No. (%) Prior Osteoporotic Fractures	Means (SD) Femoral Neck BMD	No. (%) Institutionalized	No. (%) Taking Vitamin D or Calcium at Baseline	No. (%) with Osteoporosis	No. (%) with Prior Falls
Wood et al, 2012[74] Wood et al, 2014[102] Macdonald et al, 2013[101] APOSS Total: 305 Benefits: Fair Harms: Fair	Total: NR Placebo:14.5 (6.8) 400 IU vitamin D: 13.1 (5.2) 1,000 IU vitamin D 13.0 (5.5)	NR	NR	Total:0 (0)	Total: 0 (0)	NR	NR

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; BMD=bone mineral density; CI=confidence interval; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; g/cm2=gram-square centimeter; IQR=interquartile range; IU=international unit; N=number of participants; NA=not applicable; ng/mL=nanograms per milliliter; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; USPSTF=U.S. Preventive Services Task Force; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=Vitamin D and Omega-3 Trial; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Total: 2,157 Benefits: Good Harms: Good	3 years	Vitamin D_3 2,000 IU per day po	Vitamin D: 1,076	Placebo	1,081	Subjects who agreed to limit their intake to 800 IU per day of vitamin D and 500 mg per day of calcium were not excluded from enrollment. Subjects taking more than 1,000 IU per day were required to undergo a 3- or 6-month washout period (depending on dose) in which they limited dose to 800 IU per day prior to trial entry.
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108] Total: 445 Benefits: Fair Harms: NA	3 years	Vitamin D_3 700 IU per day Calcium citrate malate 500 mg per day	Vitamin D with calcium: 187	Placebo tablets	202	Excluded participants with dietary calcium intake exceeding 1,500 mg per day; advised participants to maintain their usual diets and to avoid taking supplemental calcium and vitamin D on their own for 2 months before and throughout the study.
Glendenning et al, 2012[77] Total: 686 Benefits: Varies Harms: NA	9 months	Vitamin D_3 150,000 IU orally at baseline, 3 months and 6 months Cointerventions: Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outdoors) and consuming 1,300 mg calcium per day using diet and/or supplements.	Vitamin D: 353	Placebo Cointerventions: Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outdoors) and consuming 1,300 mg calcium per day using diet and/or supplements.	333	Participants were encouraged to consume 1,300 mg calcium per day using diet and/or supplements.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Jackson et al, 2006[75] Prentice et al, 2013[106] Bolland et al, 2011[103] Wallace et al, 2011[107] LaCroix et al, 2009[105] Jackson et al, 2003[104] Thomson et al, 2024[122] WHI CaD Total: 36,282 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. Benefits: Fair Harms: Fair	Mean 7.0 years	Vitamin D_3 400 IU orally plus 1,000 mg elemental calcium (as carbonate salt) in 2 divided doses	Vitamin D with calcium: 18,176	Placebo	18,106	Personal supplemental calcium (up to 1,000 mg per day) and vitamin D (up to 600 IU per day) were allowed. In 1999, after the publication of reports from the Institute of Medicine, the upper limit of personal vitamin D intake was raised to 1,000 IU. The calcium with vitamin D trial permitted the use of bisphosphonates and calcitonin. Use of estrogen with or without progestin was per randomization in the WHI trial. Estrogen and Selective Estrogen Receptor Modulators were permitted for participants in the dietary modification trial.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Jorde, R et al, 2016[66] Larsen et al, 2018[100] Total: 511 Benefits: Fair Harms: Fair	5 years	Vitamin D_3 20,000 IU per week for 5 years	Vitamin D: 256	Placebo	255	Not allowed to take >400 IU per day of vitamin D; proportion NR
Karkkainen et al, 2010[67] OSTPRE-FPS Total: 3,139 Benefits: Varies Harms: Fair	3 years	Vitamin D_3 800 IU per day plus calcium 1,000 mg (as carbonate salt) per day in 2 divided doses.	Vitamin D with calcium: 1,566	Received no supplementation	1,573	NR
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE Total: 232 Benefits: Fair Harms: NA	5 years	Vitamin D_3 300 IU plus elemental calcium 93 mg per day (as lactate salt) No intake during June through August. Dose reduced to 100 IU during the fifth treatment year because of observed adverse lipid change during vitamin D treatment.	Vitamin D with calcium: 116	Elemental calcium 93 mg (as lactate salt) per day (no vitamin D placebo)	116	NR
Lappe et al, 2007[123] Lappe et al, 2006[109] Total: 1,180 Benefits: NA Harms: Fair	4 years	Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D placebo 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	Calcium: 445 Vitamin D with alcium: 446	Placebo	288	Taking supplements containing vitamin D at baseline: 59.3% (includes multivitamin, paired supplements (with calcium), and single supplements). Unclear whether off-study supplements were allowed to be used during the trial.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Lappe et al, 2017[82] Total: 2303 Benefits: Fair Harms; Fair	4 years	Vitamin D_3 2,000 IU orally daily with 1,500 mg calcium per day (as carbonate salt)	Vitamin D with calcium: 1,156	Placebo	1,147	Outside supplements were limited to 800 IU vitamin D and 1,500 mg calcium per day.
Lips et al, 2018[79] Total: 2,578 Benefits: Fair Harms: Fair	3 to 3.5 years	Vitamin D_3 400 IU orally per day	Vitamin D: 1,291	Placebo	1,287	Use of Vitamin D supplements and multivitamins was discouraged; participants who used vitamin D or multivitamin supplements other than the trial medication in the analyses were excluded. During the study, 73 participants (37 in the placebo group and 36 in the vitamin D group) were found to be taking a vitamin or multivitamin supplement that contained vitamin D at two or more followup visits and were excluded.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Total: 25,871 Benefits: Good Harms: Good	5 years	Vitamin D_3 2,000 IU orally per day	Vitamin D: 12,927	Placebo	12,944	Participants were required to limit their consumption of supplemental vitamin D to no more than 800 IU per day from all supplemental sources combined (stand-alone vitamin D supplements, calcium with vitamin D supplements, medications containing vitamin D [e.g., Fosamax Plus D] and multivitamins) to limit consumption of supplemental calcium to no more than 1,200 mg per day from all supplemental sources combined and to forego the use of fish oil supplements during the run-in and randomized treatment periods.
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Total: 21,315 Benefits: Good Harms: Good	5 years	60,000 IU vitamin D_3 orally per month	Vitamin D: 10,661	Placebo	10649	Up to 2,000 IU per day were allowed; participants who reported taking more than 2,000 IU of vitamin D per day outside of the trial were withdrawn. The proportion taken off trial vitamin D was 23% in year 1 and 27% in year 5.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d Total: 2,423 Benefits: Good Harms: Good	2.5 years	Vitamin D_3 4,000 IU po per day	Vitamin D: 1,211	Placebo	1,212	Patients were encouraged to meet IOM-recommended amounts of supplemental vitamin D for their age (600 IU or 800 IU per day) but to limit daily supplementation to no more than 1,000 IU per day (vitamin D) and 600 mg per day (calcium) from all supplements including multivitamins.
Rake et al, 2020[71] VIDAL Total: 1,615 Double-blind study: 787 Open-label study: 828 Benefits: Fair Harms: Fair	2 years	Vitamin D_3 100,000 IU (2.5 mg) po per month	Double-blind study: 395 Open-label study: 407	Placebo monthly	Double-blind study: 392 Open-label study: 421	Study excluded those who were randomized to control groups who began taking Vitamin D. At 24 months, current consumption of any medication or supplement containing vitamin D was recorded to assess contamination.
Riggs et al, 1998[80] Total: 236 Benefits: Fair Harms: Fair	4 years	1,600 mg per day in 4 divided doses; serum and urinary calcium measured annually and dose decreased per algorithm when a serum calcium value grater than 10.4 mg/dl or a urinary calcium value greater than 350mg/24 h was found	119	Placebo	117	Women taking supplementary calcium at less than or equal to 500 mg per day and/or vitamin D at less than or equal to 800 IU per day at baseline were eligible for inclusion in the trial. Participants prescribed calcium by local personal physicians during the study were excluded.

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Scragg et al, 2017[83] Malihi et al, 2019[112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA Total: 5,108 Benefits: Good Harms: Good	3.3 years	Initial dose of vitamin D_3 200,000 IU followed by doses of 100,000 IU po per month	Vitamin D: 2,558	Placebo monthly	2,550	NR; participants were not eligible for study if they were taking more than 600 IU per day if ages 50 to 70 years, or more than 800 IU per day if ages 71 to 84.
Trivedi et al, 2003[81] Total: 2,686 Benefits: Fair Harms: NA	5 year	Vitamin D_3 100,000 IU orally every 4 months	Vitamin D: 1,345	Placebo	1,341	No

Appendix D Table 3. Intervention Description

Author, Year Trial Name, No. of Participants	Intervention Duration	Intervention Description	Intervention Sample Size	Comparator Description	Comparator Sample Size	Use of Supplemental Vitamin D or Calcium During Study
Uusi-Rasi et al, 2015[72] Uusi-Rasi et al, 2017[88] Patil et al, 2015[86] Uusi-Ras et al, 2012[87] DEX Total: 409 (including all study arms) Benefits: Good Harms: NA	2 years	Vitamin D_3 800 IU po per day	Vitamin D: 102	Placebo	102	No regular use of vitamin D supplements was an exclusion criterion, but use of outside supplements during the study was NR.
Virtanen et al, 2022[73] FIND Total: 2,495 Beneftis: Good Harms : Good	5 years	1,600 IU vitamin D_3 per day 3,200 IU vitamin D_3 per day	1,600 IU vitamin D: 832 3,200 IU vitamin D: 833	Daily placebo	830	Participants were excluded for use of vitamin D if they were taking more than 800 IU per day or for use of calcium if they were taking more than 1,200 mg per day from all supplemental sources combined unless they were willing to decrease intake during the the trial; does not clarify if study used a washout period for supplement users.
Wood et al, 2012[74] Wood et al, 2014[102] Macdonald et al, 2013[101] APOSS Total: 305 Benefits: Fair Harms: Fair	1 year	Vitamin D_3 400 IU per day orally Vitamin D_3 1,000 IU per day orally	400 IU Vitamin D: 102 1,000 IU Vitamin D: 101	Placebo	102	Outside study supplements were not allowed.

Appendix D Table 3. Intervention Description

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D TrialIOM=Institutes of Medicine; IU=international units;NA=not applicable; N=number; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; po=per os; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial.

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Randomized: 2,157 Analyzed: 2,157	3	NR	NR	Placebo: 127 (5.8*) Vitamin D: 129 (5.9*) Crude IRR, 1.02 (99% CI, 0.74 to 1.40) Adjusted IRR, 1.03 (99% CI, 0.75 to 1.43)	NR	NR
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108] Randomized: 445 Analyzed: 389	3	NR	Placebo: 1 (0.5*) Vitamin D with calcium: 0 (0*) Calcualted ARD, -0.50% (-1.88% to 0.89%); Calculated RR, 0.36 (0.01 to 8.78)	Placebo: 26 (12.9) Vitamin D with calcium: 11 (5.9) Calculated ARD, -6.99% (95% CI, -12.71% to -1.27%) Calculated RR, 0.46 (95% CI, 0.23 to 0.90, P=0.02) Reported RR, 0.5 (95% CI, 0.2 to 0.9) Fractures resulting from minimal or no trauma: 28 (7.2) RR, 0.40 (95% CI, 0.2 to 0.8)	NR	NR
Glendenning et al, 2012[77] Randomized: 686 Analyzed: 686	9 months	Placebo: 10 (3.0) Vitamin D: 10 (2.8) Calculated ARD, -0.17% (95% CI, -2.69% to 2.35%) Calculated RR, 0.94 (95% CI, 0.40 to 2.24)	NR	NR	NR	NR

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Jackson et al, 2006[75] Prentice et al, 2013[106] Bolland et al, 2011[103] Wallace et al, 2011[107] LaCroix et al, 2009[105] Jackson et al, 2003[104] Thomson et al, 2024[122] WHI CaD Randomized: 36,282 Analyzed: 36,282	Mean 7 years (SD 1.4) Longer follow-up for a subset of participants[122]	At 7 years: Placebo: 2,158 (11.9) Vitamin D with calcium: 2,102 (11.6) Caculated ARD, -0.35% (95% CI, -1.02% to 0.31%) HR, 0.96 (95% CI, 0.91 to 1.02) Calculated RR, 0.97 (95% CI, 0.92 to 1.03) Subgroups HR (95% CI) By personal use of calcium or vitamin D supplements at baseline[106] Nonusers: 0.97 (0.88 to 1.07) HR for users NR By personal use of supplements at baseline[103] Nonusers: 0.98 (0.89 to 1.07) Users: 0.96 (0.89 to 1.04) P for interaction between treatment allocation and use of personal supplements at baseline: 0.72	At 7 years Placebo: 199 (1.1) Vitamin D with calcium: 175 (1.0) Calculated ARD, -0.14% (95% CI, -0.34% to 0.07%) HR, 0.88 (95% CI, 0.72 to 1.08) Calculated RR, 0.88 (95% CI, 0.72 to 1.07) Subgroups[75] HR (95% CI) By age in years 50 to 59: 2.17 (1.13 to 4.18) 60 to 69: 0.74 (0.52 to 1.06) 70 to 79: 0.82 (0.62 to 1.08) P for interaction: 0.05 By race or ethnicity White: 0.89 (0.72 to 1.09) Black: 0.73 (0.16 to 3.32) Hispanic: NR American Indian: NR Asian or Pacific Islander: 2.98 (0.33 to 27.01) Unknown or not identified: NR P for interaction: 0.87 Prior fracture P for interaction: 0.71 Sunlight exposure	NR	At 7 years Placebo: 197 (1.1) Vitamin D with calcium: 181 (1.0) Calculated ARD, -0.09% (95% CI, -0.30% to 0.12%) HR, 0.90 (95% CI, 0.74 to 1.10) Calcualted RR, 0.92 (0.75 to 1.12)	At 7 years Placebo: Lower arm or wrist: 557 (3.1) Vitamin D with calcium: Lower arm or wrist: 565 (3.1) Calculated 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 4. Fracture-Related Outcomes

			P for interaction: 0.73 Hormone therapy (never, past, current) P for interaction: 0.23 No. of falls in prior 12 months Zero: 0.74 (0.56 to 0.98) One: 0.96 (0.62 to 1.49) Two: 1.16 (0.63 to 2.16) Three or more: 2.51 (0.97 to 6.48) P for interaction: 0.05 Personal use of calcium supplements at baseline[75] 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[106] Nonusers HR, 0.86 (95% CI, 0.62 to 1.20) HR for users NR			

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
			Personal use of calcium or vitamin D supplements at baseline[103] Nonusers HR 0.85 (95% CI, 0.61 to 1.17) Any use HR 0.93 (95% CI, 0.71 to 1.21) P for interaction = 0.65 Censoring data from participants after their first recorded use of osteoporosis medication (alendronate [n=3,890], risedronate [n=654], raloxifene [n=1,094], calcitonin [n=451]). HR 0.87 (95% CI, 0.69 to 1.09) At median 13.2 years (IQR: 11.3 to 19.6)[122] Placebo: 668 (0.26) Vitamin D with Calcium: 676 (0.26) HR, 1.01 (95% CI, 0.90 to 1.14) [Based on 82% followup of the sample randomized]			

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Jorde, R et al, 2016[66] Larsen et al, 2018[100] Randomized: 511 Analyzed: 414	4.9	Value NR, but reported as not significant (p=0.868)	NR	NR	NR	NR
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE Randomized: 232 Analyzed: 232	Mean: 4.3 years	NR	Calcium only: 2 (1.7*) Vitamin D with calcium: 1 (0.9*) At mean 4.3 years followup ARD*, -0.86% (95% CI, -3.77% to 2.04%) RR* 0.50 (95% CI, 0.05 to 5.44)	Calcium only: 15 (12.9*) Vitamin D with calcium: 11 (9.5*) At mean 4.3 years followup ARD*, -3.45% (95% CI, -11.55% to 4.66%) Unadjusted RR, 0.72, (95% CI, 0.33 to 1.56); P=0.405 Adjusted RR, 0.64 (95% CI, 0.29 to 1.42) 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	NR	NR

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Lips et al, 2018[79] Randomized: 2,578 Analyzed: 2,578	4 (maximum); 3.5 (median)	NR	Placebo: 48 (3.7) Vitamin D: 58 (4.5) At median 3.5 years followup: ARD*, 0.76% (95% CI, -0.77% to 2.30%) Unadjusted HR, 1.18 (95% CI, 0.81 to 1.71); P=0.39 RR*, 1.20 (95% CI, 0.83 to 1.75) (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.)	NR	NR	Placebo: 74 (5.8) Vitamin D: 77 (6.0) At median 3.5 years followup: ARD*, 0.21% (95% CI, 1.60% to 2.03%); unadjusted HR, 1.03 (95% CI, 0.75 to 1.40); P=0.86 RR*, 1.04 (95% CI, 0.76 to 1.41)

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Manson et al, 2019[68] LeBoff et al, 2022 [91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Randomized: 25,871 Analyzed: 25,871	Median 5.3	Placebo: 782 (6.0*) Vitamin D: 769 (5.9*) HR, 0.98 (95% CI, 0.89 to 1.08) Total excluding toe, finger, skull, periprosthetic, and pathologic fractures: HR, 0.99 (95% CI, 0.89 to 1.10) Subgroups:[91] Authors stated no effect modification by age, sex, race or ethnicity, or omega-3 fatty acid allocation. HR (95% CI) By sex: Female: 0.94 (0.83 to 1.06) Male: 1.07 (0.90 to 1.28) By race or ethnicity: Non-Hispanic White: 0.99 (0.89 to 1.11) Black: 0.89 (0.62 to 1.30) Other: 0.90 (0.61 to 1.35)	Placebo: 56 (0.4*) Vitamin D: 57 (0.4*) Total confirmed incident hip Fractures HR, 1.01 (95% CI, 0.70 to 1.47) Total excluding pathologic fractures: HR, 1.03 (95% CI, 0.70 to 1.52) By race/ethincity: Non-Hispanic White: 1.01 (95% CI, 0.68 to 1.50) Black: 0.25 (95% CI, 0.03 to 2.24) Other: 2.84 (95% CI, 0.55 to 14.73)	Placebo: 744 (5.7*) Vitamin D: 721 (5.6*) Total Confirmed Incident Nonvertebral Fractures HR, 0.97 (95% CI, 0.87 to 1.07) Total excluding toe, finger, skull, periprosthetic, and pathologic fractures HR, 0.97 (95% CI, 0.87 to 1.08) By race or ethnicity: Non-Hispanic White: 0.98 (0.88 to 1.10) Black: 0.86 (0.59 to 1.25) Other: 0.86 (95% CI, 0.57 to 1.29)	NR	Placebo: Pelvic: 29 (0.2) Wrist: 132 (1.0*) Vitamin D: Pelvic: 29 (0.2) Wrist: 132 (1.0*)

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020 [90] Manson et al, 2012[92] VITAL Randomized: 25,871 Analyzed: 25,871 (continued)		By age <66.7 years (median): 0.99 (0.84 to 1.18) ≥66.7 years: 0.97 (0.86 to 1.10)	By age: <66.7 years (median): 0.61 (0.22 to 1.66) ≥66.7 years: 1.09 (0.73 to 1.63)	By age <66.7 years (median) 0.99 (0.83 to 1.17) ≥66.7 years: 0.95 (0.84 to 1.08)		
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Randomized: 21,315 Analyzed: 21,310	Median 5.7	Placebo: 603 (5.9) Vitamin D: 568 (5.6) HR, 0.94 (95% CI, 0.84 to 1.06); P=0.32 ARD: 0.33% (95% CI, -0.31% to 0.97%) NNT: 303 Subgroups HR (95% CI) By sex Male: 0.85 (0.71 to 1.01) Female: 1.03 (0.88 to 1.20) P for interaction: 0.098 By age < 70 years:1.02 (0.85 to 1.21) ≥ 70 years: 0.89 (0.77 to 1.04) P for interaction: 0.27	Placebo: 105 (1.0) Vitamin D: 117 (1.2) HR, 1.11 (95% CI, 0.86 to 1.45) Subgroups HR (95% CI) By sex Male: 0.94 (0.63 to 1.39) Female: 1.28 (0.90 to 1.83) P for interaction: 0.26 By age <70 years: 1.58 (1.00 to 2.50) ≥ 70 years or older: HR 0.93(95% CI, 0.67 to 1.29) P for interaction by age: 0.06	Placebo: 533 (5.2) Vitamin D: 510 (5.0) HR 0.96 (95% CI, 0.85 to 1.08) Men: HR 0.89 (95% CI, 0.74 to 1.06) Women: HR 1.02 (95% CI, 0.87 to 1.20) P for interaction by sex: 0.25 < Younger than age 70 years: HR 1.03 (95% CI, 0.85 to 1.23) >=70 years: HR 0.91 (95% CI, 0.77 to 1.07) P for interaction by age: 0.33	NR	NR

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Riggs et al, 1998[80] Randomized: 236 Analyzed: 177	4	NR	NR	Placebo: 12 (10.3) Calcium: 11 (9.2) ARD*, -1.01% (95% CI, -8.58% to 6.56%) RR*, 0.90 (95% CI, 0.41 to 1.96)	NR	NR
Scragg et al, 2017[83] Malihi et al, 2019 [112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA Randomized: 5,110 Analyzed: 5,108	3.3	Placebo: NR (only total across groups reported) Vitamin D: NR (only total across groups reported) Adjusted HR 1.14 (95% CI, 0.91 to 1.42) Adjusted for age, sex, and ethnic origin.	NR	Placebo: 136 (5.3) Vitamin D: 156 (6.1) ARD*, 0.77% (95% CI, -0.51% to 2.04%); Adjusted HR, 1.19 (95% CI, 0.94 to 1.50) Adjusted for age, sex, ethnic origin, history of recent fall, physical activity, and baseline serum 25OH)D level	NR	NR

Appendix D Table 4. Fracture-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Fractures No. (%) Treatment Effect	Hip Fractures No. (%) Treatment Effect	Nonvertebral Fractures No. (%) Treatment Effect	Clinical Vertebral Fractures No. (%) Treatment Effect	Other Fractures No. (%) Treatment Effect
Trivedi et al, 2003[81] Randomized: 2,686 Analyzed: 2,686	5	Placebo: 149 (11.1*) Subgroups: Women: 58 (18.0*) Men: 91 (8.9*) Vitamin D: 119 (8.8*) Subgroups: Women: 42 (12.9*) Men: 77 (7.6*) Calculated ARD, -2.26% (95% CI, 4.53% to 0.00%) Age-adjusted RR, 0.78 (95% CI, 0.61 to 0.99) Calculated RR, 0.80 (95% CI, 0.63 to 1.00) Subgroups RR (95% CI) By sex Female: Age-adjusted 0.68 (0.46 to 1.01) Male: Age-adjusted 0.83 (0.61 to 1.13)	Placebo: 24 (1.8*) Subgroups: Women: 10 (3.1*) Men: 14 (1.4*) Vitamin D: 21 (1.6*) Subgroups: Women: 10 (3.1*) Men: 11 (1.1*) Calculated ARD, -0.23% (95% CI, -1.20% to 0.74%) Age-adjusted RR, 0.85 (95% CI, 0.47 to 1.53) Calculated RR, 0.87 (95% CI, 0.49 to 1.56) Subgroups RR (95% CI) By sex Female: Age-adjusted 0.98 (0.41 to 2.36) Male: Age-adjusted 0.76 (0.35 to 1.67)	NR	Placebo: 28 (2.1*) Subgroups: Women: 6 (1.9*) Men: 22 (2.2*) Vitamin D: 18 (1.3*) Subgroups: Women: 4 (1.2*) Men: 14 (1.4*) Calculated ARD, -0.75% (95% CI, -1.73% to 0.23%) Age-adjusted RR, 0.63 (95% CI, 0.35 to 1.14) Calculated RR, 0.64 (95% CI, 0.36 to 1.15) Subgroups: RR (95% CI) By sex Female: Age-adjusted 0.65 (0.18 to 2.30) Male: Age-adjusted 0.62 (0.32 to 1.22)	NR
Wood et al, 2012[74] Wood et al, 2014[102] Macdonald et al, 2013[101] APOSS Randomized: 305 Analyzed: 265	1	Placebo: 3(3) 400 IU Vitamin D: 3(4) 1,000 IU Vitamin D: 0(0) Summary effect NR	NR	Placebo: 3(3) 400 IU Vitamin D: 3(4) 1,000 IU Vitamin D: 0(0)	NR	NR

***** Calculated value.

Appendix D Table 4. Fracture-Related Outcomes

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; ARD=absolute risk difference; BMD=bone mineral density; CI=confidence interval; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; HR=hazard ratio; IRR=incidence rate ratio; IU=international units; NNT=number needed to treat; n=number; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; po=per os; RR=risk ratio; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial.

Appendix D Table 5. Persons With Fall-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Persons with a Fall No. (%) Treatment Effect	Persons with Recurrent Falls No. (%) Treatment Effect	Persons with Injurious Falls No. (%) Treatment Effect	Persons with an Injurious Recurrent Fall No. (%) Treatment Effect
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Total: 2,157 Analyzed: 2,157	3	Placebo: 654 (60.4) Vitamin D: 657 (61.0) Calculated RR, 1.01 (95% CI, 0.94 to 1.08)	NR	Placebo: 548 (50.7) Vitamin D: 570 (53.0) Calculated RR, 1.04 (95% CI, 0.96 to 1.13)	NR
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108] Total: 445 Analyzed: 389	3	Placebo: 124 Vitamin D with calcium: 107 At 3 years: OR, 0.77 (95% CI, 0.51 to 1.15) (n=416) Subgroups OR (95% CI) By sex Female: 0.54 (0.30 to 0.97) (n=229) Less active: 0.35 (0.15 to 0.81) (n=130) More active: 1.06 (0.42 to 2.66) (n=99) Male: 0.93 (0.50 to 1.72) (n = 187)) Less active: 0.96 (0.34 to 2.67) (n=74) More active: 1.01 (0.43 to 2.40) (n=113)	NR	NR	NR

Appendix D Table 5. Persons With Fall-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Persons with a Fall No. (%) Treatment Effect	Persons with Recurrent Falls No. (%) Treatment Effect	Persons with Injurious Falls No. (%) Treatment Effect	Persons with an Injurious Recurrent Fall No. (%) Treatment Effect
Glendenning et al, 2012[77] Total: 686 Analyzed: 686	9 months	Placebo: 89 (26.7) Vitamin D: 102 (28.9) OR, 1.11 (95% CI, 0.80 to 1.56) Adjusted OR, 1.06 (95% CI, 0.75 to 1.49) Adjusted for age, falls in prior 12 months, and length of followup	Placebo: 16 (4.8) Vitamin D: 26 (7.4) OR, 1.58 (95% CI, 0.83 to 2.99) Adjusted OR, 1.35 (95% CI, 0.70 to 2.59) Adjusted for age, falls in prior 12 months, and length of followup	NR	NR
Karkkainen et al, 2010[67] OSTPRE-FPS Total: 3,432 Analyzed: 3,139	3	No supplementation: 833 (53.0) Vitamin D with calcium: 812 (51.9) RR, 0.98 (95% CI 0.92, 1.05), P=0.160 OR, 1.05 (0.91 to 1.20)	No supplementation: 500 (31.8*) Vitamin D with calcium: 457 (29.2*) OR, 1.13 (95% CI, 0.97 to 1.32)	No supplementation: 299 (19.0*) Vitamin D with calcium: 258 (16.5*) Falls requiring medical attention: OR, 0.84 (95% CI, 0.70 to 1.01)	No supplementation: 107 (6.8*) Vitamin D with calcium: 78 (5.0*) Multiple falls requiring medical attention: OR, 0.72 (95% CI, 0.53 to 0.97), P<0.05
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Total: 25,871 Analyzed: 25,871	5.3 (median)	Placebo: 6,652 (51.4) Vitamin D: 6,636 (51.3) OR, 0.97 (95% CI, 0.92 to 1.02, P=0.26) (Author-reported data)	Percentage of participants with 2 or more falls per year[90] Baseline: Placebo: 10.5% Vitamin D: 11.0% Average over 5-year followup period: Placebo: 11.1% Vitamin D: 11.4% OR, 0.97 (95% CI, 0.90 to 1.05, P=0.50)	Persons with an injurious fall[90] OR, 1.03 (95% CI, 0.94 to 1.13, P=0.46) Persons with falls resulting in a hospital visit[90] OR, 1.04 (95% CI, 0.90 to 1.19) Both are the odds ratio comparing the average percentage with an injurious fall over followup compared with baseline in the vitamin D vs. placebo groups.	NR

Appendix D Table 5. Persons With Fall-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Persons with a Fall No. (%) Treatment Effect	Persons with Recurrent Falls No. (%) Treatment Effect	Persons with Injurious Falls No. (%) Treatment Effect	Persons with an Injurious Recurrent Fall No. (%) Treatment Effect
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Total: 21,315 Analyzed: 17,616	Varied depending on ascertainment method	Placebo: 2,106 (5.8) Vitamin D: 2,174 (6.0) Fall within month prior to annual survey Analyzed by repeated measures over the duration of followup and for each year separately Repeated measures: OR, 1.02 (95% CI, 0.95 to 1.10) Falling at least once based on diary (subset of participants ascertained with this method): Vitamin D: 159/1045 (15.2) Placebo: 153/1048 (14.6) OR, 1.07 (95% CI, 0.84 to 1.36) Subgroups By sex: Men: Vitamin D: 70/509 (13.8) Placebo: 69/533 (12.9) Women: Vitamin D: 89/536 (16.6) Placebo: 84/515 (16.3) P for interaction: 0.69	NR	NR	NR

Appendix D Table 5. Persons With Fall-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Persons with a Fall No. (%) Treatment Effect	Persons with Recurrent Falls No. (%) Treatment Effect	Persons with Injurious Falls No. (%) Treatment Effect	Persons with an Injurious Recurrent Fall No. (%) Treatment Effect
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d Analyzed: 2,423 Total: 2,423	3	NR	NR	NR	NR
Scragg et al, 2017[83] Malihi et al, 2019 [112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA Total: 5,110 Analyzed: 5,056	3.3	Placebo: 1,326 Vitamin D: 1,312 Adjusted HR, 0.99 (95% CI, 0.92 to 1.07) Adjusted for age, sex, ethnic origin, history of recent fall, baseline physical activity, and baseline serum 25(OH)D level	NR	Placebo: 1,020 Vitamin D: 1,049 Adjusted HR, 1.03 (95% CI 0.95 to 1.13) Adjusted for age, sex, ethnic origin, history of recent fall, baseline physical activity, and baseline serum 25(OH)D level	NR
Trivedi et al, 2003[81] Total: 2,686 Analyzed: 2,038	5	Placebo: 261 (25.8) Subgroups: Women: 92 (36.1) Men: 169 (22.4) Vitamin D: 254 (24.7) Women: 100 (37.0) Men: 154 (20.3) ARD: NR Age-adjusted RR: 0.93 (95% CI, 0.76 to 1.14) Subgroups By sex, RR (95% CI) Female: 1.03 (0.72 to 1.48) Male: 0.87 (0.68 to 1.12)	NR	NR	NR

Appendix D Table 5. Persons With Fall-Related Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Persons with a Fall No. (%) Treatment Effect	Persons with Recurrent Falls No. (%) Treatment Effect	Persons with Injurious Falls No. (%) Treatment Effect	Persons with an Injurious Recurrent Fall No. (%) Treatment Effect
Uusi-Rasi et al, 2015[72] Uusi-Rasi et al, 2017[88] Patil et al, 2015[86] Uusi-Ras et al, 2012[87] DEX Total: 204 Analyzed: 199	2 and 4	Placebo: 75 (73.5) Vitamin D: 66 (68.0) (Author-reported data) At 2 years: HR, 0.77 (95% CI, 0.54 to 1.11) At 4 years: HR, 0.86 (95% CI, 0.63 to 1.19)	Placebo: 47 (46.0) Vitamin D: 45 (46.4) (Author-reported data) At 2 years: HR, 1.07 (95% CI, 0.71 to 1.62)	Placebo: 61 (59.8) Vitamin D: 50 (51.5) (Author-reported data) At 2 years: HR, 0.89 (0.47 to 1.69) At 4 years: HR, 0.62 (95% CI, 0.39 to 1.00)	Placebo: 27 (26.5) Vitamin D: 26 (26.8) (Author-reported data)
Wood et al, 2012[74] Wood et al, 2014[102] Macdonald et al, 2013[101] APOSS Total: 305 Analyzed: 293	1	Placebo: 31 (31.0) 400 IU vitamin D: 33 (34.4) 1,000 IU vitamin D: 27 (28.1) Self-reported falls ascertained every 2 months at a study visit; fall outcome defined as "ever fallen during study": NR; P=0.65 across groups	NR	NR	NR

***** Calculated value.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; ARD=absolute risk difference; CI=confidence interval; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; HR=hazard ratio; IU=international units; NR=not reported; OR=odds ratio; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RR=risk ratio; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial.

Appendix D Table 6. Fall Rate Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Falls No. and Treatment Effect	Total Recurrent Falls No. and Treatment Effect	Total Injurious Falls No. and Treatment Effect
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Total: 2,157 Analyzed: 2,157	3	3 years Placebo: 1,673 Adjusted IR, 0.51 per person-year (95% CI, 0.47 to 0.55) Vitamin D: 1,660 Adjusted IR, 0.52 (95% CI, 0.48 to 0.56) Crude IRR, 1.00 (95% CI, 0.90 to 1.12) Adjusted IRR, 1.03 (95% CI, 0.92 to 1.14) Subgroups stratified by sex: Men: adjusted IRR, 1.20 (95% CI, 1.00 to 1.45) Women: adjusted IRR, 0.92 (95% CI, 0.81 to 1.04) Authors report no effect modification for any subgroup.	NR	3 years Placebo: 1,068 Adjusted IR, 0.33 (95% CI, 0.31 to 0.36) Vitamin D: 1,073 Adjusted IR, 0.34 (95% CI, 0.31 to 0.37) Crude IRR, 1.01 (95% CI, 0.90 to 1.13) Adjusted IRR, 1.03 (95% CI, 0.92 to 1.14)
Karkkainen et al, 2010[67] OSTPRE-FPS Total: 3,432 Analyzed: 3,139	3	No supplementation: 1,944 Vitamin D with calcium: 1,832	NR	No supplementation: 444 Vitamin D with calcium: 377
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Total: 25,871 Analyzed: 25,871	5.3 (median)	Placebo: 13,182 Vitamin D: 13,533 (Author-reported data) Over a median of 5.3 years of followup, there were 15,161 participants who reported a total of 51,260 falls. No significant interaction by sex or race or ethnicity[89]	NR	NR

Appendix D Table 6. Fall Rate Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration (Years)	Total Falls No. and Treatment Effect	Total Recurrent Falls No. and Treatment Effect	Total Injurious Falls No. and Treatment Effect
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Total: 21,315 Analyzed: 17,616	Varied depending on ascertainment method	Placebo: Based on diary data: 820 per 1,000 person-years Vitamin D: Based on diary data: 728 per 1,000 person-years	NR	NR
Uusi-Rasi et al, 2015[72] Uusi-Rasi et al, 2017[88] Patil et al, 2015[86] Uusi-Ras et al, 2012[87] DEX Total: 204 Analyzed: 0	2 and 4	Placebo: 229 IR, 118.2/100person-years Vitamin D: 228 IR, 132.1/100 person-years IRR, 1.08 (95% CI, 0.78 to 1.52) At 4 years: IRR, 0.78 (95% CI, 0.53 to 1.14)	Placebo: NR Vitamin D: NR IRR, 1.05 (95% CI, 0.60 to 1.86)	Placebo: 127 Vitamin D: 100 (Author-reported data) At 2 years: 0.84 (95% CI, 0.45 to 1.57) At 4 years: 0.45 (95% CI, 0.23 to 0.87)
Wood et al, 2012[74] Wood et al, 2014[102] Macdonald et al, 2013[101] APOSS Total: 305 Analyzed: 293	1	Placebo: 40 400 IU vitamin D: 48 1,000 IU vitamin D: 30	NR	NR

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; IRR=incidence rate ratio; IU=international units; NR=not reported; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; VITAL=The VITamin D and OmegA-3 Trial.

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Analyzed: 2,157 Total: 2,157	3 years	Placebo: 13 (1.2%) Vitamin D: 12 (1.1%)	Transition to institutional care: 3 year Placebo: 9 (0.8%) Vitamin D: 13 (1.2%) P=0.39
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108] Analyzed: 389 Total: 445	3 years	4 died but were not reported by group	NR
Glendenning et al, 2012[77] Analyzed: 686 Total: 686	9 months	Placebo: 0 (0) Vitamin D: 2 (0.6)	NR

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Jackson et al, 2006[75] Prentice et al, 2013[106] Bolland et al, 2011[103] Wallace et al, 2011[107] LaCroix et al, 2009[105] Jackson et al, 2003[104] Thomson et al, 2024[122] WHI CaD Analyzed: 36,282 Total: 36,282 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.	7 years (SD, 1.4)	At 7 years Placebo: 807 (4.5) Vitamin D with calcium: 744 (4.1) ARD*, -0.36 (95% CI, -0.78% to 0.05%) HR, 0.91 (95% CI, 0.83 to 1.01)[105] RR*, 0.92 (95% CI, 0.83 to 1.01) Subgroups HR (95% CI) By age[105] < 70 years: 0.89 (0.79 to 1.01) ≥ 70 years: 0.95 (0.80 to 1.12); P for interaction: 0.10 By race or ethnicity[105] White: 0.89 (0.80 to 0.99) Black: 0.91 (0.67 to 1.23) Hispanic: 2.28 (1.07 to 4.87) American Indian: 0.84 (0.16 to 4.48) Asian/Pacific Islander 1.60 (0.75 to 3.43) Other/unknown: 0.90 (0.45 to 1.80) P for interaction: 0.30 Personal supplement use at baseline:[103] No use: N=7,755 placebo, N=7,891 for CaD HR, 0.94 (95% CI, 0.81 to 1.10) P for interaction: 0.44 Any Use Placebo: N=10,351 placebo CaD: N=10,285 HR, 0.88 (95% CI, 0.77 to 1.01) P for interaction: 0.44 At median 22.3 years (IQR 18.0 to 23.5) Placebo: 7,748 (2.1) Vitamin D with Calcium: 7,834 (2.2) HR, 1.00 (95% CI, 0.97 to 1.03)[122]	NR

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Jorde, R et al, 2016[66] Larsen et al, 2018[100] Analyzed: 511 Total: 511	5 years	Placebo: 2 (0.8) Vitamin D: 1 (0.4)	NR
Karkkainen et al, 2010[67] OSTPRE-FPS Analyzed: 3,432 Total: 3,139	3 years	No supplementation: 12 (0.7) Vitamin D with Calcium: 12 (0.7)	NR
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE Analyzed: 232 Total: 232	4.3 years	Calcium only: 1 (0.9*) Vitamin D with calcium: 0 (0*) ARD*, -0.87% (-3.26% to 1.52%) RR*, 0.34 (0.01 to 8.31)	NR
Lappe et al, 2007[123] Lappe et al, 2006[109] Analyzed: 1,180 Total: 1,180	4 years	NR	NR
Lappe et al, 2017[82] Analyzed: 2,303 Total: 2,303	4 years	Placebo: 9 (0.8%) Vitamin D with calcium: 7 (0.6%) ARD*, -0.19% (-0.90% to 0.52%); RR*, 0.77 (0.29 to 2.07)	NR
Lips et al, 2018[79] Analyzed: 2,578 Total: 2,578	3 years	Placebo: 306 (23.8) Vitamin D: 282 (21.8) ARD*, -1.93% (95% CI, -5.17% to 1.31%) RR*, 0.92 (95% CI, 0.80 to 1.06)	NR

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Analyzed: 25,871 Total: 25,871	5.3 years	Placebo: 493 (3.8) Vitamin D: 485 (3.8) HR, 0.99 (95% CI, 0.87 to 1.12)[68] Subgroups [89]: HR (95% CI) By sex Male: 0.98 (0.83 to 1.16) Female:1.00 (0.83 to 1.20) P for interaction: 0.90 By race or ethnicity HRs not reported P for interaction: 0.56	NR
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Analyzed: 21,310 Total: 21,315	5.7 years	Placebo: 538 (5.1) Vitamin D: 562 (5.3) HR, 1.04 (95% CI, 0.93 to 1.18); P=0.47 Subgroups HR (95% CI) By sex Male: 1.03 (0.90 to 1.19) Female: 1.07 (0.86 to 1.32) P for interaction: 0.82 By age < 70 years: 1.15 (0.92 to 1.44) ≥ 70 years: 1.00 (0.87 to 1.15) P for interaction: 0.29	NR
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d Analyzed: 2,423 Total: 2,423	3 years	Placebo: 6 (0.5) Vitamin D: 5 (0.4) IRR, 0.83 (95% CI, 0.25 to 2.71)	Hospitalizations: IRR, 0.94 (95% CI, 0.79 to 1.12) Vitamin D: 7.18/100 person-years Placebo: 7.65/100 person-years

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Rake et al, 2020[71] VIDAL Analyzed: 787 Total: 1,615 Double-blind study: 787 Open-label study: 828	2 years	Placebo: 23 (2.8*) Vitamin D: 34 (4.2*) Effect size NR, but comparison between groups reported as P=0.12. (Study was not powered to detect clinical effects or mortality differences.)	NR
Riggs et al, 1998[80] Analyzed: 236 Total: 236	4 years	NR; reported that 1 person died in motor vehicle accident but did not report which group	NR
Scragg et al, 2017[83] Malihi et al, 2019 [112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA Analyzed: 5,108 Total: 5,108	3.3 years	Placebo: 58 (2.3) Vitamin D: 65 (2.5) ARD, -0.33% (-1.16% to 0.51%)* RR, 0.87 (0.61 to 1.24)	NR

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Trivedi et al, 2003[81] Analyzed: 2,686 Total: 2,686	5 years	Placebo: 247 (18.4) Women: 27 (8.4) Men: 220 (21.6) Vitamin D: 224 (16.7) Women: 25 (7.7) Men: 199 (19.5) Calculated ARD, -1.76% (95% CI, -4.64% to 1.11%); Age-adjusted RR, 0.88 (95% CI, 0.74 to 1.06); Calculated RR, 0.90 (95% CI, 0.77 to 1.07) Subgroups Female Calculated ARD, -0.69% (95% CI, -4.87% to 3.49%); Calculated RR, 0.92 (95% CI, 0.54 to 1.55) Male Calculated ARD, -2.08% (95% CI, -5.59% to 1.43%); Calcualted RR, 0.90 (95% CI, 0.76 to 1.07)	NR

Appendix D Table 7. Mortality, Quality of Life, and Utilization Outcomes

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration	All-Cause Mortality Risk or No. (%)	Quality of Life, Disability, Healthcare Utilization or Other Measures
Uusi-Rasi et al, 2015[72] Uusi-Rasi et al, 2017[88] Patil et al, 2015[86] Uusi-Ras et al, 2012[87] DEX Analyzed: 204 Total: 409 (including all study arms)	2 and 4 years	Placebo: 0 (0) Vitamin D: 2 (2.0)	Quality of Life: Change at 2 years Leipad QOL measure (Range 0 to 87) Vitamin D: 5.3 (95% CI, -6.3 to 18.3) Placebo: -0.9 (95% CI, -11.7 to 11.2) P=0.30 WHO-5 Well-Being Index (Range 0 [lower well-being] to 25 [higher well-being]) Vitamin D: -7.1 (95% CI, -12.0 to -1.8) Placebo: -1.1 (-6.2 to 4.4) P=0.04 Disability measures: Change at 2 years ADL disability score (Range 6 to 36): Vitamin D: NR Placebo: NR No significant difference IADL disability score (Range 8 to 48): Vitamin D: NR Placebo: NR No significant difference ED visits: NR Hospitalizations: NR Transition to institutional care: NR Other utilization measures: NR
Virtanen et al, 2022[73] FIND Analyzed: 2,495 Total: 2,495	5 years	Placebo: 7 (0.8) 1,600 IU vitamin D: 7 (0.8) 3,200 IU vitamin D 5 (0.7) Combined vitamin D dose HR (95% CI): 0.81 (0.32 to 2.06), P=0.66	NR

***** Calculated value.

Abbreviations: ADL=Activities of Daily Living; ARD=absolute risk difference; CI=confidence interval; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; ED=emergency department; FIND=Finnish Vitamin D Trial; HR=hazard ratio; IADL=Instrumental Activity of Daily Living; IRR=incidence rate ratio; IU=international units; N=number; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; QOL=quality of life; RR=risk ratio; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial; WHO=World Health Organization.

Appendix D Table 8. Harms

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration of Followup (Years)	Incident Kidney Stones	Adverse Events	Withdrawal Due to Adverse Events	Serious Adverse Events	Other Harms
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2022[85] Bischoff-Ferrari et al, 2021[84] DO-HEALTH Analyzed: 2,157	3	Placebo: 8 (0.7%) Vitamin D: 7 (0.7%)	NR	NR	NR	NR
Dawson-Hughes et al, 1997 [76] Bischoff-Ferrari et al, 2006[108] Analyzed: 389	3	NR	NR	Vitamin D with calcium group: 6 (3 constipation, 1 epigastric distress, 1 sweating, 1 hypercalciuria) Placebo group: 3 (2 epigastric distress, 1 flank pain) 11 additional subjects discontinued because of difficulty swallowing the pills, but this was not reported by study group.	0 (0)	NR

Appendix D Table 8. Harms

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration of Followup (Years)	Incident Kidney Stones	Adverse Events	Withdrawal Due to Adverse Events	Serious Adverse Events	Other Harms
Jackson et al, 2006[75] Prentice et al, 2013[106] Bolland et al, 2011[103] Wallace et al, 2011[107] LaCroix et al, 2009[105] Jackson et al, 2003[104] Thomson et al, 2024[122] WHI CaD Analyzed: 36,282 Placebo: 18,106 Vitamin D with calcium: 18,176	7 (SD, 1.4)	Placebo: 381 (2.1) Vitamin D with calcium: 449 (2.5)	NR	NR	NR	NR
Jorde, R et al, 2016[66] Larsen et al, 2018[100] Analyzed: 511 Placebo: 255 Vitamin D: 256	5	Placebo: 1 (0.4) Vitamin D: 2 (0.8)	Summary effect: NR Total nonserious adverse events: Placebo: 1,849 events Vitamin D: 1,787 events	NR	(Defined as requiring hospitalization) Summary effect: NR Placebo: 134 events Vitamin D: 115 events	NR
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE Analyzed: 232 Calcium only: 116 Vitamin D with calcium: 116	5	NR	NR	NR	Vitamin D: 5 (4.5*) Placebo: 4 (3.5*)	NR

Appendix D Table 8. Harms

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration of Followup (Years)	Incident Kidney Stones	Adverse Events	Withdrawal Due to Adverse Events	Serious Adverse Events	Other Harms
Lappe et al, 2007[123] Lappe et al, 2006[109] Analyzed: 1,180 Placebo: 288 Calcium: 445 Vitamin D with calcium: 446	4	Placebo: 1 (0.3) Calcium: 3 (0.7) Vitamin D with calcium:1 (0.2)	No patterns of adverse events were seen among the 3 groups.	NR	No SAEs were reported.	NR
Lappe et al, 2017[82] Analyzed: 0 Placebo: 1,095 Vitamin D with calcium: 1,102	4	Placebo: 10 (0.9) Vitamin D with calcium: 16 (1.5)	NR	NR	0 events	NR
Manson et al, 2019[68] LeBoff et al, 2022[91] Bassuck et al, 2021[89] LeBoff et al, 2020[90] Manson et al, 2012[92] VITAL Analyzed: 25,871 Placebo: 12,944 Vitamin D: 12,927	5.3 (median)	Placebo: 426 (3.3) Vitamin D: 477 (3.7)	There were no significant differences between the 2 groups with respect to adverse events (data not reported).	NR	NR	NR

Appendix D Table 8. Harms

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration of Followup (Years)	Incident Kidney Stones	Adverse Events	Withdrawal Due to Adverse Events	Serious Adverse Events	Other Harms
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[98] Waterhouse et al, 2019[97] Neale et al, 2016[96] D-Health Analyzed: 21,315 Placebo: 10,649 Vitamin D: 10,661	3	Placebo: 152 Vitamin D: 159	Total AE IRR, 0.99 (95% CI, 0.93 to 1.04) Vitamin D: 2,568 per 1,000 person-years Placebo: 2,555 per 1,000 person-years	NR	IRR, 0.91 (95% CI, 0.83 to 1.00) Vitamin D: 884 per 1,000 person-years Placebo: 950 per 1,000 person-years	NR
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d Analyzed: 2,423 Placebo: 1,212 Vitamin D: 1,211	3	Placebo: 20 Vitamin D: 24	IRR 0.94 (95% CI, 0.90 to 0.98) Vitamin D: 116.1 per 100 person-years Placebo: 123.6 per 100 person-years	IRR 1.25 (95% CI, 0.85 to 1.84) Vitamin D: 1.67 per 100 person-years Placebo: 1.33 per 100 person-years	IRR 0.96 (95% CI, 0.81 to 1.14) Vitamin D: 260 (21.4) Placebo: 269 (22.2)	NR
Rake et al, 2020[71] VIDAL Analyzed: 787	2	NR	NR	NR	Blinded study vitamin D: 46 (12*) Blinded study control: 45 (12*) No SAEs judged to be associated with treatment.	NR
Riggs et al, 1998[80] Analyzed: 236 Placebo: 117 Calcium: 119	4	Placebo: 1 (0.9) Calcium: 0 (0)	Gastrointestinal symptoms Calcium group: 9 (7.6) Placebo group: 2 (1.7)	Discontinuations due to side effects: 16 (6.8) Calcium group: 10 (8.4) Placebo group: 6 (5.1)	NR	Arthralgia and depression: Calcium group: 0 (0) Placebo group: 1 (0.9)

Appendix D Table 8. Harms

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration of Followup (Years)	Incident Kidney Stones	Adverse Events	Withdrawal Due to Adverse Events	Serious Adverse Events	Other Harms
Scragg et al, 2017[83] Malihi et al, 2019[112] Malihi et al, 2019[113] Scragg et al, 2019[115] Scragg et al, 2019[116] Khaw, et al, 2017[111] Scragg et al, 2016[114] ViDA Analyzed: 5,108 Placebo: 2,517 Vitamin D: 2,539	3.3	Placebo: 82 (3.3) Vitamin D: 76 (3.0)	Any adverse event that patients attributed to the study capsule: Vitamin D: 419 (16.5) Placebo: 399 (15.8) Adjusted HR 1.03 (95% CI, 0.90 to 1.18) Any adverse event: Vitamin D: 604 (54.5) Placebo: 504 (45.5) P=0.01	NR	NR	NR
Virtanen et al, 2022[73] FIND Analyzed: 2,495 Placebo: 830 1,600 IU vitamin D: 832 3,200 IU vitamin D: 833	5	Placebo: 7 (0.8) 1,600 IU vitamin D: 3 (0.4) 3,200 IU vitamin D:6 (0.7)	NR	NR	NR	NR

Appendix D Table 8. Harms

Author, Year, Quality, Sample Size Analyzed Overall and by Study Group	Duration of Followup (Years)	Incident Kidney Stones	Adverse Events	Withdrawal Due to Adverse Events	Serious Adverse Events	Other Harms
Wood et al, 2012[74] Wood et al, 2014,[102] Macdonald et al, 2013[101] APOSS Analyzed: 305 Placebo: 102 400 IU vitamin D: 102 1,000 IU vitamin D: 101	NA	NR	Placebo: 24 400 IU vitamin D: 24 1,000 IU vitamin D: 23	NR	Defined as life-threatening or requiring inpatient hospitalization Number of events 400 IU vitamin D: 7 1,000 IU vitamin D: 8 Placebo: 4	NR

***** Calculated value.

Abbreviations: AE=adverse event; APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; D2d=Vitamin D and Type 2 Diabetes Trial; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; HR=hazard ratio; IRR=incidence rate ratio; IU=international units; NA=not applicable; NR=not reported; OSTPRE= OSTPRE=Osteoporosis Risk Factor and Prevention Study; SAE=serious adverse event; SD=standard deviation; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; WHI CaD=Women's Health Initiative Calcium and Vitamin D Trial.

Appendix E Table 1. Risk of Bias From Randomization or Selection

Author, Year Trial Name	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	RoB: Randomization or Selection	Comments on Bias Arising From Randomization or Selection
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Yes	Yes	Yes	Low	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	No information	No information	Yes	Uncertain because no information available	No information about randomization or allocation concealment
Glendenning et al, 2012[77]	Yes	Yes	Yes	Low	None
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	Yes	No information	Yes	Low	No information about allocation concealment
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	No information	No information	Yes	Some concerns	No information about randomization or allocation concealment
Karkkainen et al, 2010[67] OSTPRE-FPS	Yes	Probably yes	Yes	Low	None
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	Yes	Yes	Yes	Low	None
Lappe et al, 2017[82]	Yes	Yes	Yes	Low	None
Lappe et al, 2007[123] Lappe et al, 2006[109]	Yes	No information	Probably yes	Low	Allocation concealment NR
Lips et al,2018[79]	Yes	Yes	Yes	Low	None

Appendix E Table 1. Risk of Bias From Randomization or Selection

Author, Year Trial Name	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	RoB: Randomization or Selection	Comments on Bias Arising From Randomization or Selection
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020[90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	Yes	Probably yes	Yes	Low	None
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	Yes	Yes	Yes	Low	None
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	Yes	Yes	Yes	Low	Reported in trial protocol supplement
Rake et al, 2020[71] VIDAL	Probably yes	Yes	No information	Some Concerns	Methods of randomization and allocation concealment seem adequate, but no information about baseline characteristics by study arm so cannot assess adequacy of randomization
Riggs et al, 1998[80]	No information	No information	Yes	Some concerns	No information about randomization or allocation concealment
Sakalli, 2012[151]	No information	No information	No information	High	No information about method of randomization or allocation concealment and differences among groups at baseline that could be meaningful

Appendix E Table 1. Risk of Bias From Randomization or Selection

Author, Year Trial Name	Was method of randomization adequate?	Was allocation concealment adequate?	Were group characteristics balanced at baseline?	RoB: Randomization or Selection	Comments on Bias Arising From Randomization or Selection
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	Yes	Yes	Yes	Low	None
Trivedi et al, 2003[81]	No information	No information	Yes	Some concerns	No information about randomization or allocation concealment
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	Yes	Probably yes	Yes	Low	None
Virtanen et al, 2022[73] FIND	Yes	Yes	Yes	Low	None
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	No information	No information	Yes	Some concerns	No information about method of randomization or allocation concealment
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Yes	Yes	Yes	Low	None

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RoB=risk of bias; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

Appendix E Table 2. Risk of Bias From Missing Data

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 missing data similar across interventions?	For benefits and outcomes, was intent to treat analysis used?	Were appropriate statistical methods used?	RoB: Missing Outcome Data	Comments on Bias Arising From Missing Data
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Followup data missing for 9.6%. Vitamin D group: 21 had no followup, 105 had partial followup, and 12 died. All randomized were included in primary analysis. Placebo group: 21 had no followup, 110 had partial followup, and 13 died. All randomized were included in primary analysis. Post hoc analysis using imputed data showed stable estimates.	Yes	Yes	Yes	Yes	Low	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	Overall: 56/445=12.6% Placebo: NR Vitamin D with calcium: NR	Probably yes	No information	Yes	Probably yes	Low	Attrition by groups was NR.
Glendenning et al, 2012[77]		Yes	Yes	Yes	No information	Low	None

Appendix E Table 2. Risk of Bias From Missing Data

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 missing data similar across interventions?	For benefits and outcomes, was intent to treat analysis used?	Were appropriate statistical methods used?	RoB: Missing Outcome Data	Comments on Bias Arising From Missing Data
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	Overall: 2,531/36,282=7.0% Placebo: 1,291/18,106=7.1% Vitamin D with calcium: 1,240/18,176=6.8%	Yes	Yes	Yes	Yes	Low	None
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	45 subjects were excluded post randomization and did not receive the study drug for unclear reasons. Of those who received the study drug (n=511), overall attrition varied after each year of followup. After 1 year: 27/511=5.3% After 2 years: 54/511=10.6% After 3 years: 72/511=14.1% After 4 years: 85/511=16.6% After 5 years: 95/511=18.6% Attrition did not vary by group.	Probably no	Yes	Yes	Probably no	Some concerns	Post randomization exclusions without explanation; given that these occurred prior to the study drug administration, there was likely minimal bias and probably reflected lack of clarity on study eligibility. Used last observation carried forward method to account for missing data.

Appendix E Table 2. Risk of Bias From Missing Data

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 missing data similar across interventions?	For benefits and outcomes, was intent to treat analysis used?	Were appropriate statistical methods used?	RoB: Missing Outcome Data	Comments on Bias Arising From Missing Data
Karkkainen et al, 2010[67] OSTPRE-FPS	3,432 randomized 3,139 analyzed (91.4%) 293 not included (8.6%) 152 not included in intervention arm (8.8%) 141 not included in control arm (8.2%)	Yes	Yes	Yes	No information	Low	None
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	Overall: 6/232=2.6% Calcium: 3/116=2.6% Vitamin D with calcium: 3/116=2.6%	Yes	Yes	Yes	Probably yes	Low	None
Lappe et al, 2017[82]	Overall:106/2,303=4.6% Placebo:52/1,147=4.5% Vitamin D with calcium: 54/1,156=4.7%	Yes	Yes	Yes	No information	Low	None
Lappe et al, 2007[123] Lappe et al, 2006[109]	Overall: 156/1,180=13.2% Attrition by group NR	Yes	No information	NA	Yes	Low	None
Lips et al, 2018[79]	Placebo: 7/1287=0.5% Vitamin D: 7/1291=0.5%	Yes	Yes	Yes	Yes	Low	Loss to followup 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.

Appendix E Table 2. Risk of Bias From Missing Data

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 missing data similar across interventions?	For benefits and outcomes, was intent to treat analysis used?	Were appropriate statistical methods used?	RoB: Missing Outcome Data	Comments on Bias Arising From Missing Data
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020[90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	0% for ITT analysis.	Yes	Yes	Yes	Probably yes	Low	None
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	5/21,315	Yes	Yes	Yes	NA	Low	None
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	0% for ITT analysis	Yes	Yes	Yes	Yes	Low	None
Rake et al, 2020[71] VIDAL	Range 7% to 13% across the 4 study arms	Yes	Probably yes	Yes	NA	Low	Mortality measured through linkage to death registry.

Appendix E Table 2. Risk of Bias From Missing Data

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 missing data similar across interventions?	For benefits and outcomes, was intent to treat analysis used?	Were appropriate statistical methods used?	RoB: Missing Outcome Data	Comments on Bias Arising From Missing Data
Riggs et al, 1998[80]	Overall: 59/236=25.0% Placebo: 28/117=23.9% Calcium: 30/119=25.2%	No	No information	Yes	No information	Some concerns	Modest attrition overall and no information about how missing data were handled regarding fractures for participants with incomplete followup.
Sakalli, 2012[151]	NR; no CONSORT diagram provided	No information	No information	No Information	NA	Uncertain because no information	None
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	Placebo: 2/2552=0.1% Vitamin D: 0/2558=0%	Yes	Yes	Yes	Yes	Low	None
Trivedi et al, 2003[81]	Overall: 631/2,686=23.5% Placebo: 324/1,341=24.2% Vitamin 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 was 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 followup.

Appendix E Table 2. Risk of Bias From Missing Data

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 missing data similar across interventions?	For benefits and outcomes, was intent to treat analysis used?	Were appropriate statistical methods used?	RoB: Missing Outcome Data	Comments on Bias Arising From Missing Data
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	At 2 years: 8.3% At 4 years: 15.2%	Yes	Yes	Yes	No information	Low	Reports ITT analysis, but no information about how participants with missing data at 2 and 4 years were handled.
Virtanen et al, 2022[73] FIND	0%	Yes	NA	Yes	NA	Low	Used national registry data to assess outcomes.
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	12/305	Yes	Yes	Yes	Yes	Low	None

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CONSORT=Consolidated Standards of Reporting Trials; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; ITT=intention to treat; NA=not applicable; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RoB=risk of bias; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

Appendix E Table 3. Risk of Bias From Departures From Intended Interventions

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?	RoB: Departures From Intended Interventions	Comments on Bias Arising From Departure From Intended Interventions
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Yes	Yes	Yes	Yes	Probably yes	Low	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	Yes	Yes	Yes	Yes	Yes	Some concerns	Participants were 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 followup.
Glendenning et al, 2012[77]	Yes	Yes	Yes	Yes	Yes	Low	None
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	Yes	Yes	Yes	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 per day) and vitamin D (up to 600 IU per day) was allowed throughout the intervention.
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	Probably yes	Probably yes	No information	Yes	No information	Some concerns	Outcome assessor blinding NR; personal use of supplements up to 400 IU per day were allowed.
Karkkainen et al, 2010[67] OSTPRE-FPS	No	No	No Information	Probably Yes	Probably Yes	Some Concerns	Intervention was not blinded and no information about whether outcome assessors were blinded. Given that falls were self-reported, there is a high risk for bias in reporting of falls.

Appendix E Table 3. Risk of Bias From Departures From Intended Interventions

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?	RoB: Departures From Intended Interventions	Comments on Bias Arising From Departure From Intended Interventions
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	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 the study medication.
Lappe et al, 2017[82]	Yes	Yes	Yes	Probably yes	Probably no	Some concerns	Only moderate levels of adherence, and personal supplement use was allowed during the study.
Lappe et al, 2007[123] Lappe et al, 2006[109]	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).
Lips et al,2018[79]	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 2 or more followup visits.
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020[90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	Yes	Yes	Yes	Yes	Probably yes	Low	Mean adherence was 81% to 82%. Personal supplement use outside of study protocol up to 800 IU per day was allowed.

Appendix E Table 3. Risk of Bias From Departures From Intended Interventions

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?	RoB: Departures From Intended Interventions	Comments on Bias Arising From Departure From Intended Interventions
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	Yes	Yes	Yes	Yes	Probably no	Low	By year 2, the number of participants taking more than 500 IU in off-study use was 10% in the placebo group and 7% in the vitamin D group, and by year 5 was 16% and 9%, respectively. 122 participants were withdrawn for taking more than 2,000 IU of vitamin D per day of off-study supplements.
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	Yes	Yes	Yes	Probably Yes	Probably Yes	Low	Overall adherence reported as 85.8% of prescribed pills taken; 5.2% of participants in the placebo group took outside supplements.
Rake et al, 2020[71] VIDAL	Yes	Yes	No information	Probably yes	Probably yes	Some concerns	Two parallel studies, one of which was conducted blinded, while the other was conducted open label. Given that mortality was assessed via the national death registry, it is unlikely to be biased based on whether outcome assessors were blinded.
Riggs et al, 1998[80]	Yes	Yes	No information	Yes	No information	Some concerns	Mean dose based on tablet count was 1,234 mg per day; there was approximately 75% adherence.
Sakalli, 2012[151]	Yes	Yes	No information	No information	No information	Some concerns	QOL outcome assessment was presumably masked because patients were unaware of treatment status. However, there is no information about adherence or contamination.

Appendix E Table 3. Risk of Bias From Departures From Intended Interventions

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?	RoB: Departures From Intended Interventions	Comments on Bias Arising From Departure From Intended Interventions
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	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.
Trivedi et al, 2003[81]	Yes	Yes	Probably yes	Probably yes	No information	Some concerns	76% of participants took at least 80% of study drugs. There is 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 per day, they discontinued the trial intervention but continued to be followed.
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	Yes	Yes	Yes	Yes	Probably yes	Low	None
Virtanen et al, 2022[73] FIND	Yes	Yes	No information	Yes	Yes	Low	Outcome assessment masking was not specifically reported, but national registries used and outcomes of mortality and kidney stones were likely not influenced by any knowledge of group assignment.

Appendix E Table 3. Risk of Bias From Departures From Intended Interventions

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?	RoB: Departures From Intended Interventions	Comments on Bias Arising From Departure From Intended Interventions
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	Yes	Yes	No information	Yes	No information	Low	Study investigators were blinded but does not specifically mention outcome assessors.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; IU=international units; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; QOL=quality of life; RoB=risk of bias; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

Appendix E Table 4. Risk of Bias From Outcome Measurements for Benefits

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?	RoB: Benefit Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Benefits
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Yes	Yes	Yes	Low	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	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[77]	No	Yes	Probably no	Varies by outcome Poor for fractures; fair for falls and mortality	Fractures were not defined as to site or type; no mention of whether they were verified with X-rays or medical records; 9 months may not be long enough to ascertain benefits with respect to fracture and falls.

Appendix E Table 4. Risk of Bias From Outcome Measurements for Benefits

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?	RoB: Benefit Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Benefits
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	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.
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	Probably no	Probably yes	Probably yes	Some concerns	Definition of fractures and method of ascertainment NR.
Karkkainen et al, 2010[67] OSTPRE-FPS	Probably Yes	Yes	Yes	Low	None
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	Yes	Yes	Yes	Low	Self-reported fractures were validated by medical record.
Lappe et al, 2017[82]	Yes	Yes	Yes	Low	None
Lappe et al, 2007[123] Lappe et al, 2006[109]	NA	NA	NA	NA	NA
Lips et al, 2018[79]	Probably yes	Yes	Yes	Varies by outcome: Low for hip fracture; high for other fractures because they were based on self-report and not clinically validated.	None

Appendix E Table 4. Risk of Bias From Outcome Measurements for Benefits

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?	RoB: Benefit Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Benefits
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020[90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	Yes	Yes	Yes	Low	None
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	Yes	Yes	Yes	Low	None
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	Yes	Yes	Yes	Low	None
Rake et al, 2020[71] VIDAL	Yes	Yes	Yes	Low	None
Riggs et al, 1998[80]	Yes	Yes	Yes	Low	None
Sakalli, 2012[151]	Yes	Yes	Probably no	High	Only 30 days of followup
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	Yes	Yes	Yes	Low	None

Appendix E Table 4. Risk of Bias From Outcome Measurements for Benefits

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?	RoB: Benefit Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Benefits
Trivedi et al, 2003[81]	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.
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	Yes	Yes	Yes	Low	None
Virtanen et al, 2022[73] FIND	Yes	Yes	Yes	Low	None
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	Probably no	Yes	Probably yes	Some concerns.	Only 1 year of followup; fractures were assessed as adverse events; no specific definitions or method for systematic ascertainment was described

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; NA=not applicable; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RoB=risk of bias; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

Appendix E Table 5. Risk of Bias From Outcome Measurements for Harms

Author, Year Trial Name	Were harm outcomes adequately described, valid, and reliable?	Were similar techniques used among groups to ascertain harm outcomes?	Was the duration of followup adequate to assess harm outcomes?	RoB: Harms Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Harms
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Yes	Yes	Yes	Low	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	Probably no	Yes	Yes	Some concerns	Poor specification of harms and ascertainment methods for harms.
Glendenning et al, 2012[77]	NA	NA	NA	NA	No harms were reported.
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	Yes	Yes	Yes	Low	Kidney stone incidence was based on self-report[107] and was not validated by clinical records.
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	Probably no	Yes	Yes	Some concerns	Definition of adverse events NR, though study indicates that adverse events were ascertained at every study visit.
Karkkainen et al, 2010[67] OSTPRE-FPS	NA	NA	NA	NA	No harms were reported.
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	Probably no	Yes	Yes	Some concerns	No information about whether harms measured were clinically verified or based on self-report.

Appendix E Table 5. Risk of Bias From Outcome Measurements for Harms

Author, Year Trial Name	Were harm outcomes adequately described, valid, and reliable?	Were similar techniques used among groups to ascertain harm outcomes?	Was the duration of followup adequate to assess harm outcomes?	RoB: Harms Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Harms
Lappe et al, 2017[82]	Probably No	Yes	Yes	Some Concerns	No information about how kidney stones were ascertained.
Lappe et al, 2007[123] Lappe et al, 2006[109]	Yes	Yes	Yes	Some Concerns	No information about how kidney stones outcome was specified or ascertained; thus, there are some concerns for this outcome.
Lips et al, 2018[79]	NA	NA	NA	NA	No harms were reported.
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020[90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	Yes	Yes	Yes	Low	None
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	Yes	Yes	Yes	Low	None
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	Yes	Yes	Yes	Low	None
Rake et al, 2020[71] VIDAL	Yes	Yes	Yes	Low	SAEs from open-label portion were not eligible as was not blinded.
Riggs et al, 1998[80]	No information	Yes	Yes	Low	None

Appendix E Table 5. Risk of Bias From Outcome Measurements for Harms

Author, Year Trial Name	Were harm outcomes adequately described, valid, and reliable?	Were similar techniques used among groups to ascertain harm outcomes?	Was the duration of followup adequate to assess harm outcomes?	RoB: Harms Outcome Measurement	Comments on Bias Arising From Measurement of Outcomes for Harms
Sakalli, 2012[151]	NA	NA	NA	NA	No harms were reported.
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	Probably yes	Yes	Yes	Low	None
Trivedi et al, 2003[81]	NA	NA	NA	NA	No harms were reported.
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	NA	NA	NA	NA	No harms were reported.
Virtanen et al, 2022[73] FIND	Probably yes	Yes	Yes	Low	None
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	Probably yes	Yes	Yes	Low	None

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; NA=not applicable; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RoB=risk of bias; SAE=serious adverse event; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

Appendix E Table 6. Risk of Bias From Selection of Reported Results

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?	RoB: Selection of Reported Results	Comments on Bias Arising From Selection of Reported Results
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Yes	Low	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	Yes	Low	None
Glendenning et al, 2012[77]	Yes	Low	None
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	Yes	Low	Rationale and biologic bases for the post hoc subgroup analyses seem sound.[103]
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	Yes	Low	Trial was registered.
Karkkainen et al, 2010[67] OSTPRE-FPS	Probably no	Some concerns	Study methods describe study as being powered based on the incidence of fractures, but fractures are not reported.
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	Yes	Low	None
Lappe et al, 2017[82]	Yes	Low	None

Appendix E Table 6. Risk of Bias From Selection of Reported Results

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?	RoB: Selection of Reported Results	Comments on Bias Arising From Selection of Reported Results
Lappe et al, 2007[123] Lappe et al, 2006[109]	Probably yes	Low	Primary study 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.
Lips et al, 2018[79]	Yes	Low	None
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020[90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	Yes	Low	None
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	Yes	Low	Published statistical analysis plan and trial was registered.
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	Yes	Low	None
Rake et al, 2020[71] VIDAL	Yes	Low	None
Riggs et al, 1998[80]	Yes	Low	None
Sakalli, 2012[151]	Probably no	Uncertain because no information	Trial was not registered; no published protocol.

Appendix E Table 6. Risk of Bias From Selection of Reported Results

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?	RoB: Selection of Reported Results	Comments on Bias Arising From Selection of Reported Results
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	Yes	Low	None
Trivedi et al, 2003[81]	Probably no	Some concerns	No trial registry or designation of primary endpoint and multiple fracture types were reported.
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	Yes	Low	None
Virtanen et al, 2022[73] FIND	Yes	Low	None
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	Yes	Low	Trial was registered.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RoB=risk of bias; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

Appendix E Table 7. Overall Risk of Bias

Author, Year Trial Name	Overall Rating Benefits	Benefits Overall Rating Justification/Comments	Harms Rating	Harms Overall Rating Justification/Comments
Bischoff-Ferrari et al, 2020[65] Bischoff-Ferrari et al, 2021[84] Bischoff-Ferrari et al, 2022[85] DO-HEALTH	Good	None	Good	None
Dawson-Hughes et al, 1997[76] Bischoff-Ferrari et al, 2006[108]	Fair	Some concerns over selection of participants because of lack of information about randomization and allocation concealment and fidelity to intended intervention as there was only modest adherence at final followup.	Fair	Harms were poorly specified and method of harms ascertainments not described.
Glendenning et al, 2012[77]	Varies by outcome: Poor for fractures; fair for falls and mortality	High risk of bias in outcome measurement domain for fractures. Some risk of bias in outcome measurement domain for falls and mortality because length of followup (9 months) may not be adequate for these outcomes.	NA	NA
Jackson et al, 2006[75] Jackson et al, 2003[104] Wactawski-Wende et al, 2006[150] LaCroix et al, 2009[105] Wallace et al, 2011[107] Prentice et al, 2013[106] Bolland et al, 2011b[103] Thomson et al, 2024[122] Women's Health Initiative	Fair	Some concerns for bias as adherence to study intervention was modest and personal use of supplements was allowed throughout the trial.	Fair	Some concerns for bias in harms outcomes due to limited information on outcome specification/ ascertainment.

Appendix E Table 7. Overall Risk of Bias

Author, Year Trial Name	Overall Rating Benefits	Benefits Overall Rating Justification/Comments	Harms Rating	Harms Overall Rating Justification/Comments
Jorde, R et al, 2016[66] Larsen et al, 2018[100]	Fair	Method of randomization and allocation concealment NR; post randomization exclusion with modest attrition and use of last observation carried forward to account for missing data; no information about masking of outcome assessors; no definition of fractures reported or method of ascertainment.	Fair	Same rationale as for benefits.
Karkkainen et al, 2010[67] OSTPRE-FPS	Varies by outcome: Poor for falls; some concerns for mortality	Open label with no blinding; thus, high risk of bias for self-reported outcomes such as falls. No information about outcome assessor blinding; some baseline imbalances at baseline.	NA	No harms were reported.
Komulainen et al, 1998[78] Komulainen et al, 1999[110] OSTPRE	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).	NA	NA
Lappe et al, 2017[82]	Fair	None	Fair	Some concerns related to departures from intended intervention (personal supplement use was allowed), there was modest adherence, and there is no information about methods of ascertainment for kidney stones.
Lappe et al, 2007[123] Lappe et al, 2006[109]	NA	NA	Fair	Some risk of bias in measurement domain for kidney stone outcome.

Appendix E Table 7. Overall Risk of Bias

Author, Year Trial Name	Overall Rating Benefits	Benefits Overall Rating Justification/Comments	Harms Rating	Harms Overall Rating Justification/Comments
Lips et al, 2018[79]	Fair	Some concerns due to contamination and modest adherence for both benefits and harms outcomes. Peripheral fractures were self-reported and not clinically validated.	NA	No harms were reported.
Manson et al, 2019[68] Manson et al, 2012[92] LeBoff et al, 2020 [90] Bassuck et al, 2021[89] LeBoff et al, 2022[91] VITAL	Good	Low risk of bias across all domains	Good	Low risk of bias across all domains.
Neale et al, 2022[69] Waterhouse et al, 2021[99] Waterhouse et al, 2019[97] Waterhouse et al, 2023[98] D-Health	Good	None	Good	None
Pittas et al, 2019[70] Johnson et al, 2022[93] LeBlanc et al, 2018[94] Pittas et al, 2014[95] D2d	Good	None	Good	None
Rake et al, 2020[71] VIDAL	Fair	Some concerns given that there was no presentation of baseline characteristics by group at baseline.	Fair	Some concerns given that there was no presentation of baseline characteristics by group at baseline.

Appendix E Table 7. Overall Risk of Bias

Author, Year Trial Name	Overall Rating Benefits	Benefits Overall Rating Justification/Comments	Harms Rating	Harms Overall Rating Justification/Comments
Riggs et al, 1998[80]	Fair	Some concerns because of modest attrition and no information about how missing data for those with incomplete data were handled. Also, some concerns due to modest adherence.	Fair	Same rationale as for benefits.
Sakalli, 2012[151]	Poor	High risk of bias because of baseline differences and no information about randomization or allocation concealment; also, some concerns for bias because duration was not long enough to assess benefit; no information about adherence, no CONSORT flow diagram to assess attrition, trial was not registered and there is no published protocol to evaluate potential for selective reporting.	NA	No harms were reported.
Scragg et al, 2017[83] Khaw et al, 2017[111] Scragg, 2020[115] Scragg, 2019[116] Malihi et al, 2019[113] Scragg et al, 2016[114] Malihi et al, 2019[112] ViDA	Good	Low risk of bias across all domains	Good	Low risk of bias across all domains.

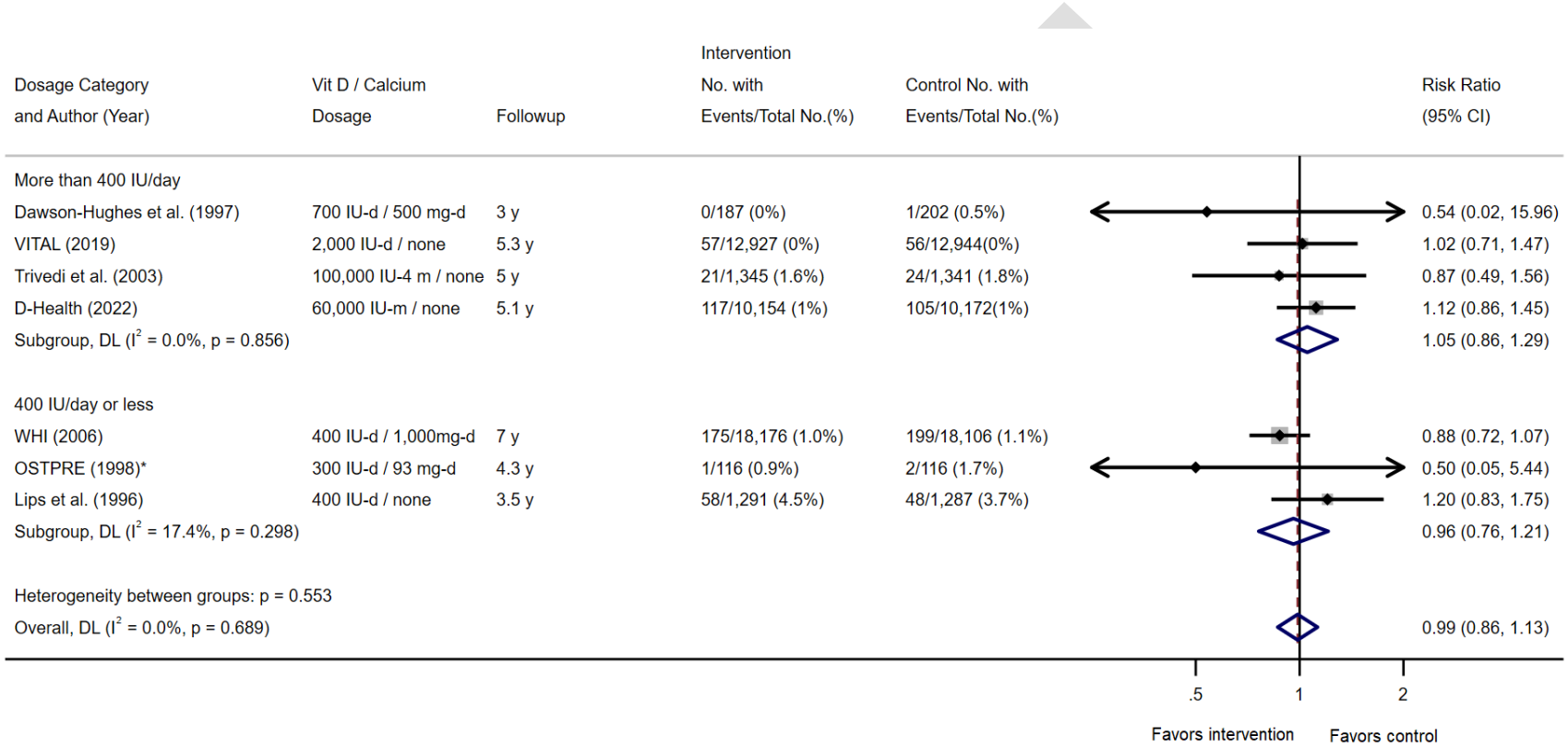
Appendix E Table 7. Overall Risk of Bias

Author, Year Trial Name	Overall Rating Benefits	Benefits Overall Rating Justification/Comments	Harms Rating	Harms Overall Rating Justification/Comments
Trivedi et al, 2003[81]	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.	NA	No harms were reported.
Uusi-Ras et al, 2012[87] Uusi-Ras et al, 2012[72] Patil et al, 2015[86] Uusi-Rasi et al, 2017[88] DEX	Good	None	NA	No harms were reported.
Virtanen et al, 2022[73] FIND	Good	None	Good	None
Wood et al, 2012[74] Macdonald et al, 2013[101] Wood et al, 2014[102] APOSS	Fair	No information about randomization or allocation concealment; some risk of bias because fractures were only assessed as an adverse event.	Fair	No information about randomization or allocation concealment.

Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CONSORT=Consolidated Standards of Reporting Trials; D2d=Vitamin D and Type 2 Diabetes Trial; DEX=Vitamin D and Exercise in Fall Prevention; D-Health=Vitamin D Health; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; NA=not applicable; NR=not reported; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial.

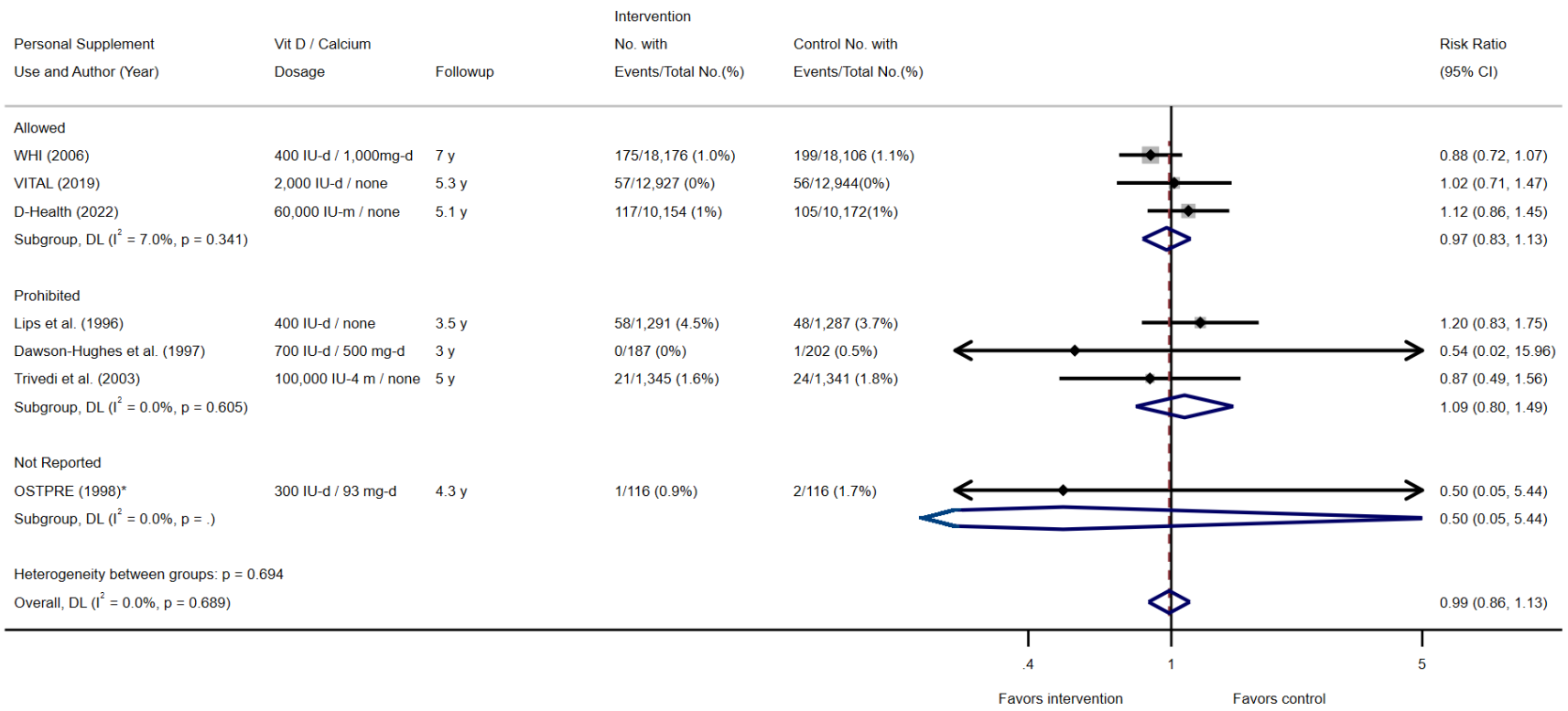
Appendix F. Additional Results

Appendix F Figure 1. Effect of Vitamin D Supplementation on Hip Fracture Stratified by Dosage Among Included RCTs



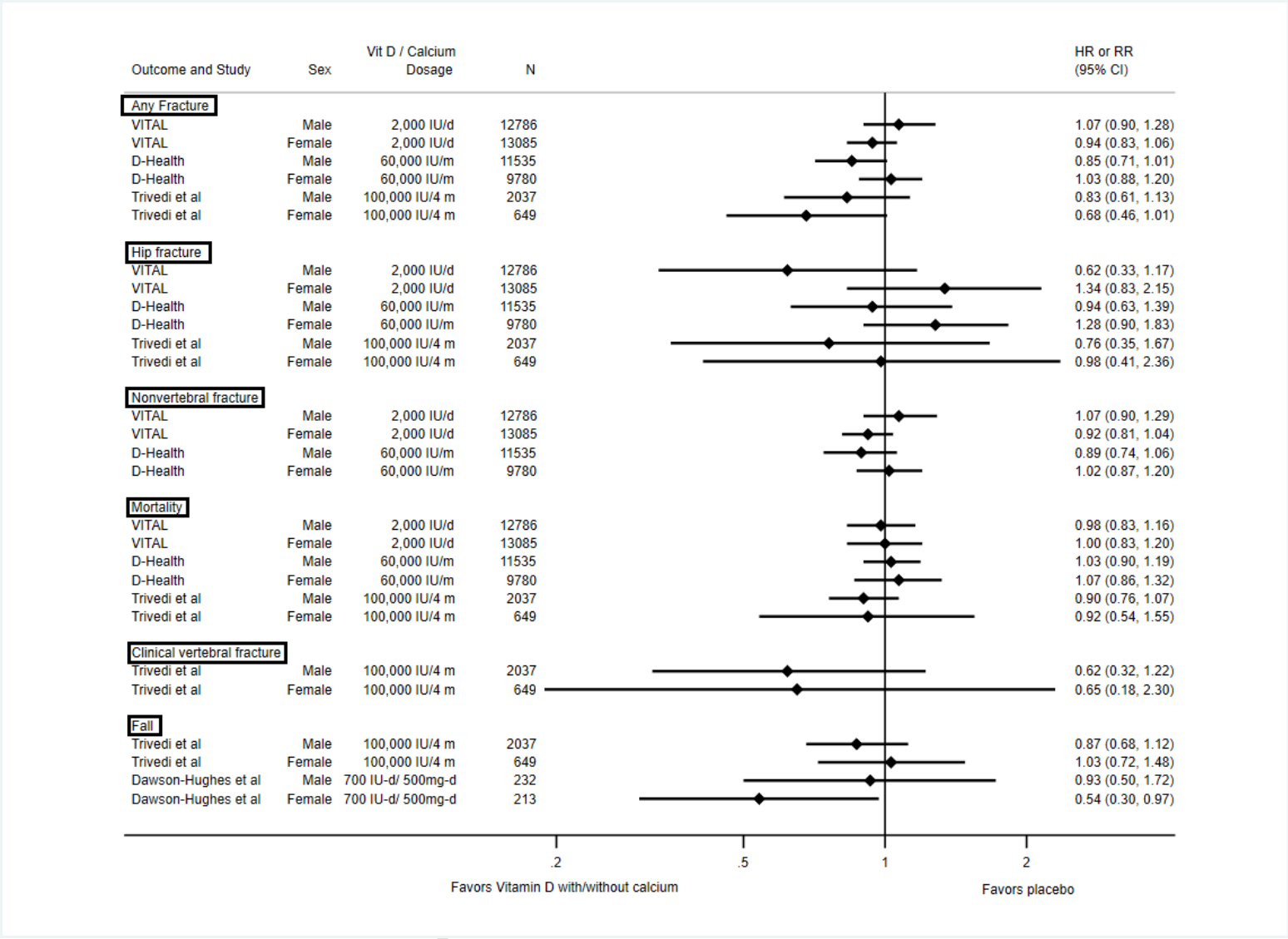
Abbreviations: CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; IU=international units; m=month; OSTPRE=Osteoporosis Risk Factor and Prevention Study; RCT=randomized, controlled trial; RR=relative risk; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Appendix F Figure 2. Effect of Vitamin D Supplementation on Hip Fracture Stratified by Personal Supplement Use Among Included RCTs



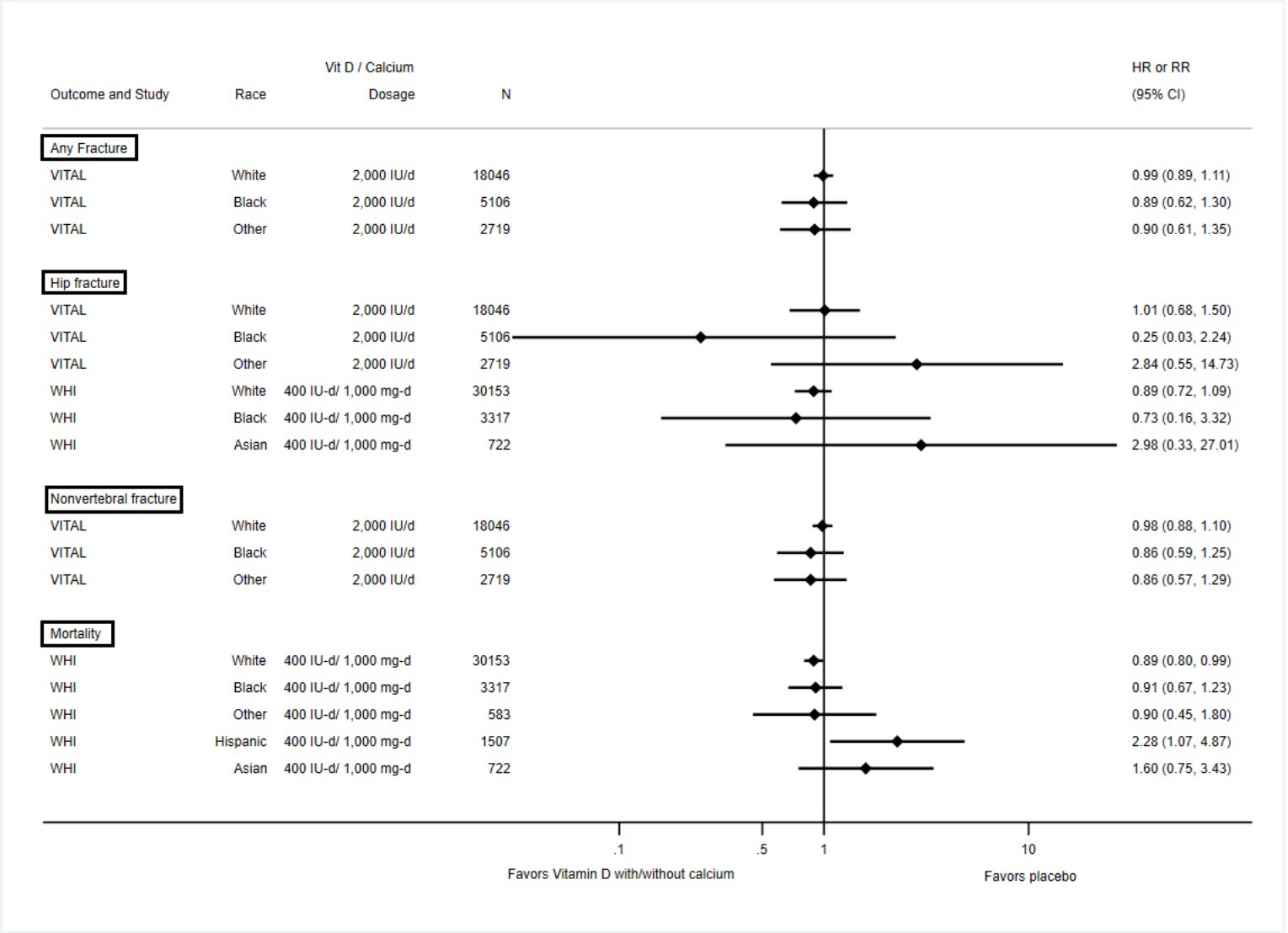
Abbreviations: CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; IU=international units; m=month; OSTPRE=Osteoporosis Risk Factor and Prevention Study; RCT=randomized, controlled trial; RR=relative risk; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Appendix F Figure 3. Effect of Vitamin D Supplementation on Fracture Stratified by Sex Among Included RCTs



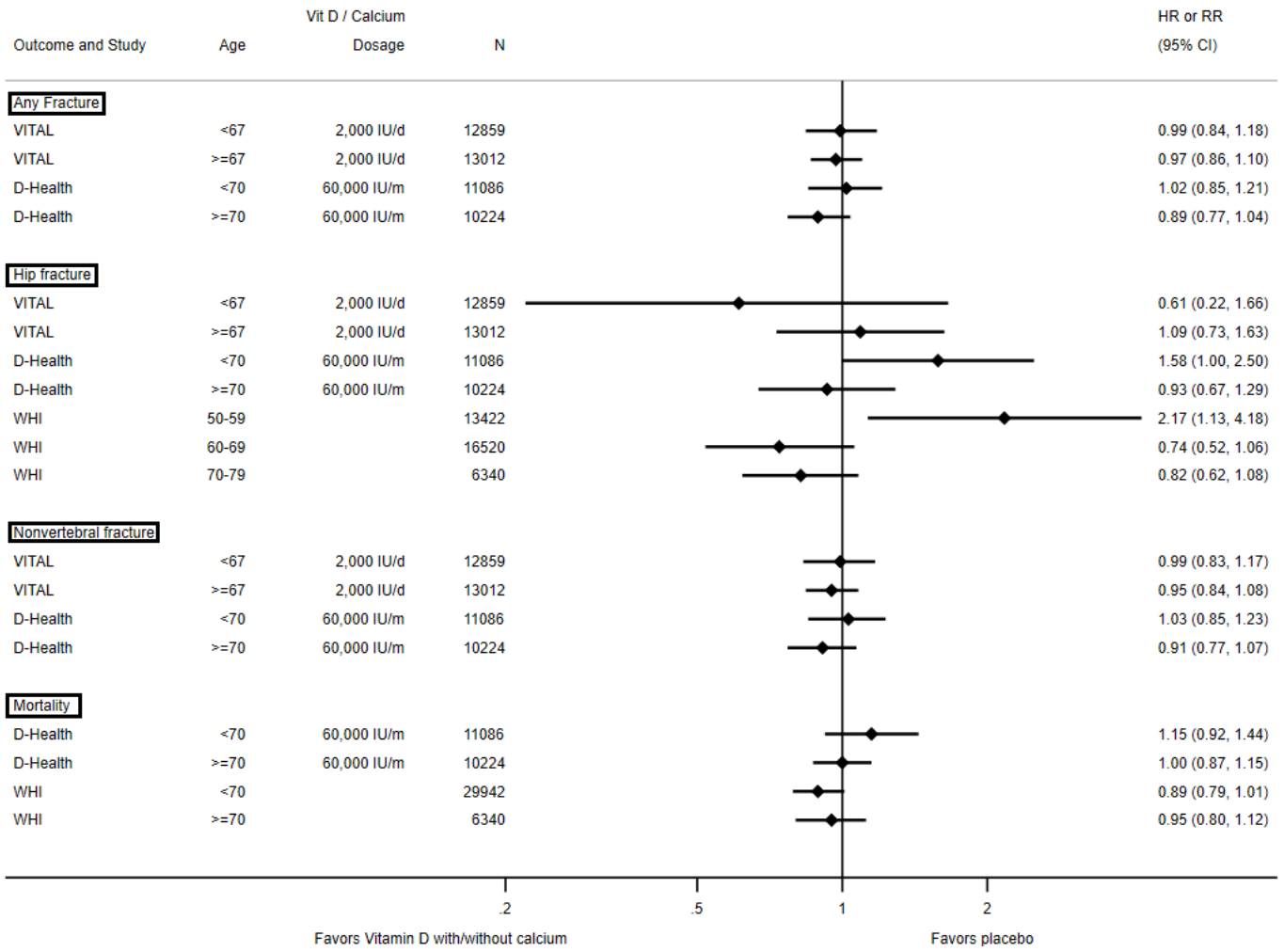
Abbreviations: CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; HR=hazard ratio; IU=international units; m=month; N=number; RCT=randomized, controlled trial; RR=relative risk; VITAL=The VITamin D and OmegA-3 Trial.

Appendix F Figure 4. Effect of Vitamin D Supplementation on Outcomes Stratified by Race Among Included RCTs



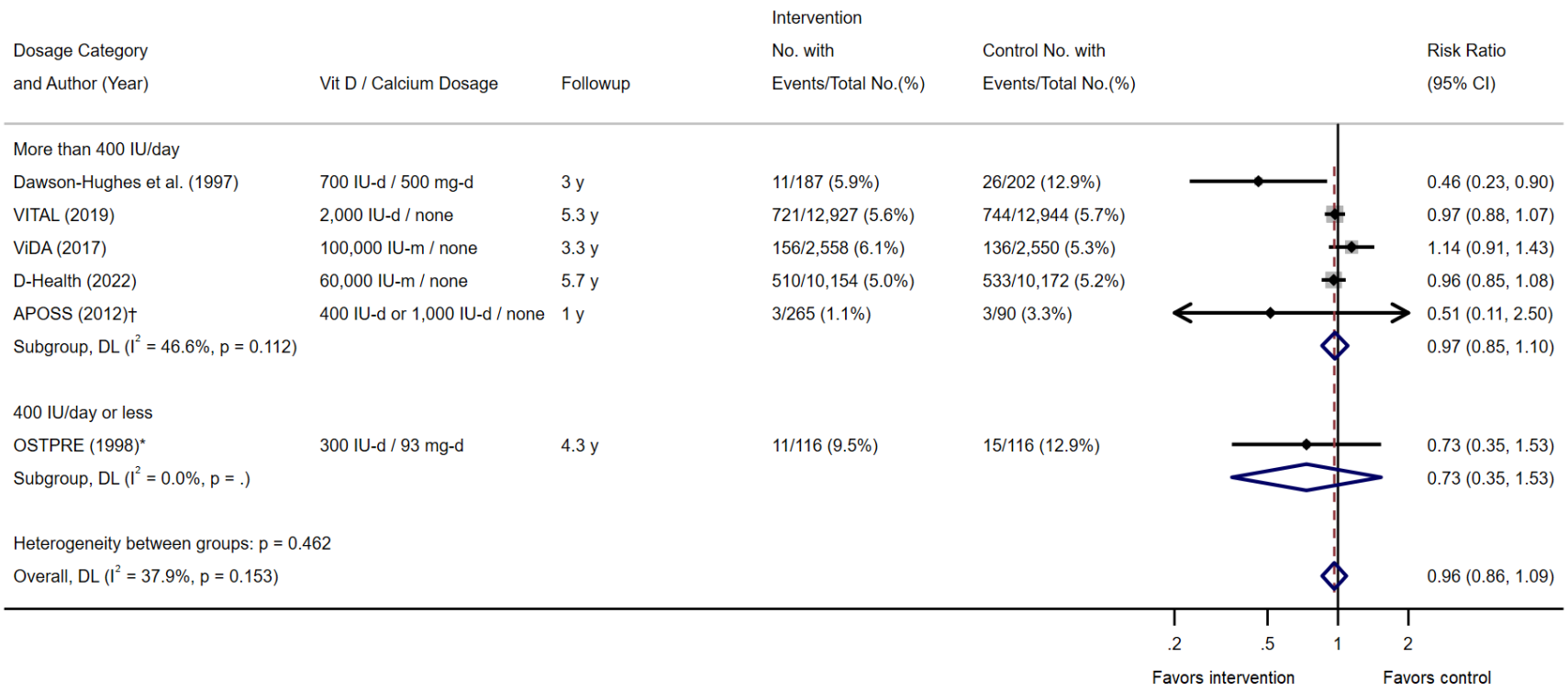
Abbreviations: CI=confidence interval; d=day; HR=hazard ratio; IU=international units; N=number; RCT=randomized, controlled trial; RR=relative risk; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial.

Appendix F Figure 5. Effect of Vitamin D Supplementation on Outcomes Stratified by Age Among Included RCTs



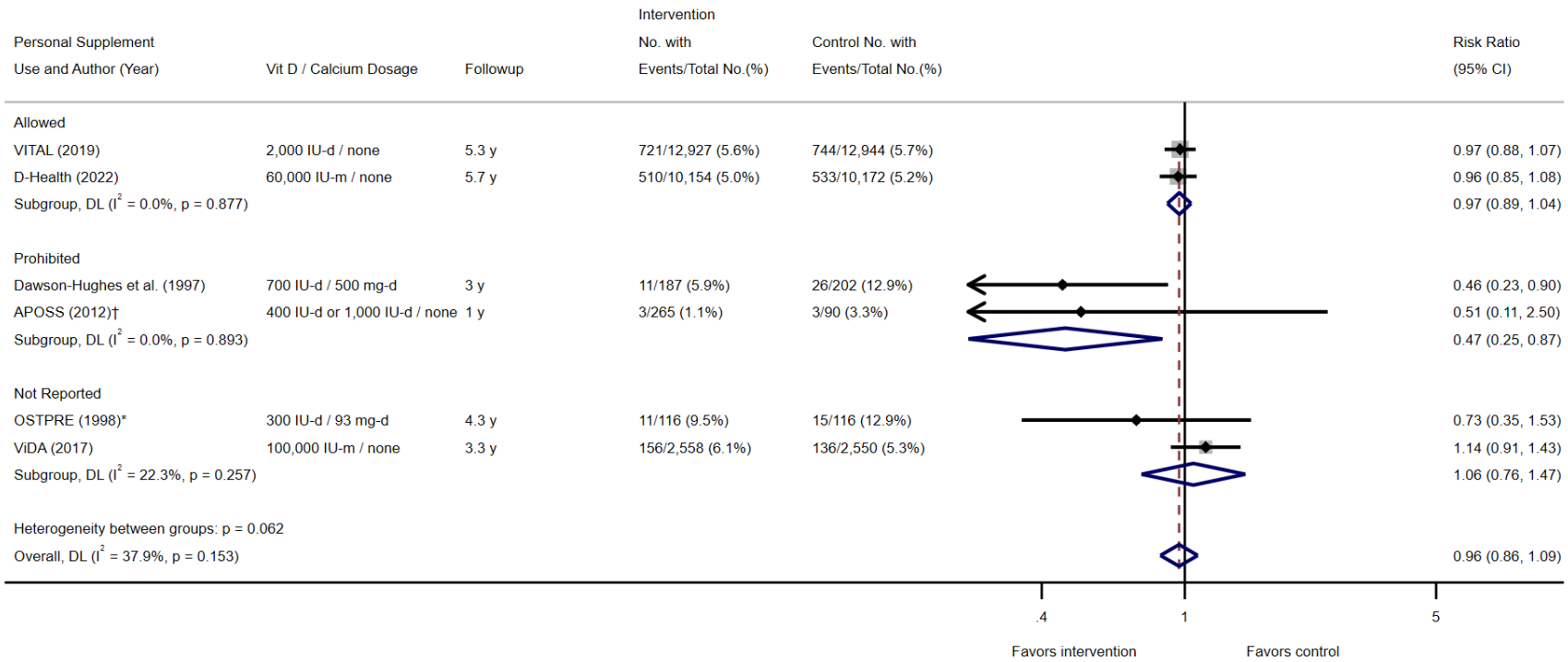
Abbreviations: CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; HR=hazard ratio; m=month; IU=international units; N=number; RCT=randomized, controlled trial; RR=relative risk; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial.

Appendix F Figure 6. Effect of Vitamin D Supplementation on Nonvertebral Fracture Stratified by Dosage Among Included RCTs



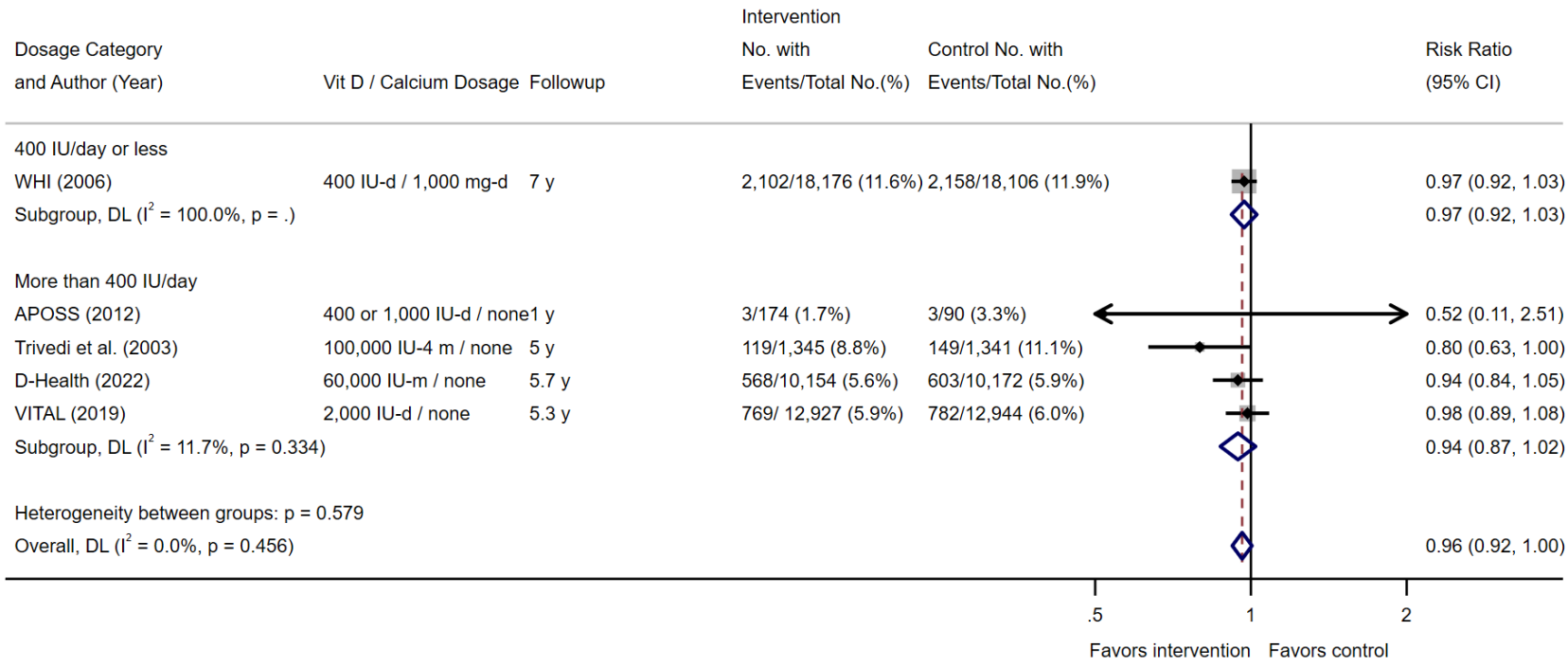
Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; IU=international units; m=month; OSTRPE=Osteoporosis Risk Factor and Prevention Study; RCT=randomized, controlled trial; y=year; RR=relative risk; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; y=year.

Appendix F Figure 7. Effect of Vitamin D Supplementation on Nonvertebral Fracture Stratified by Personal Supplement Use Among Included RCTs



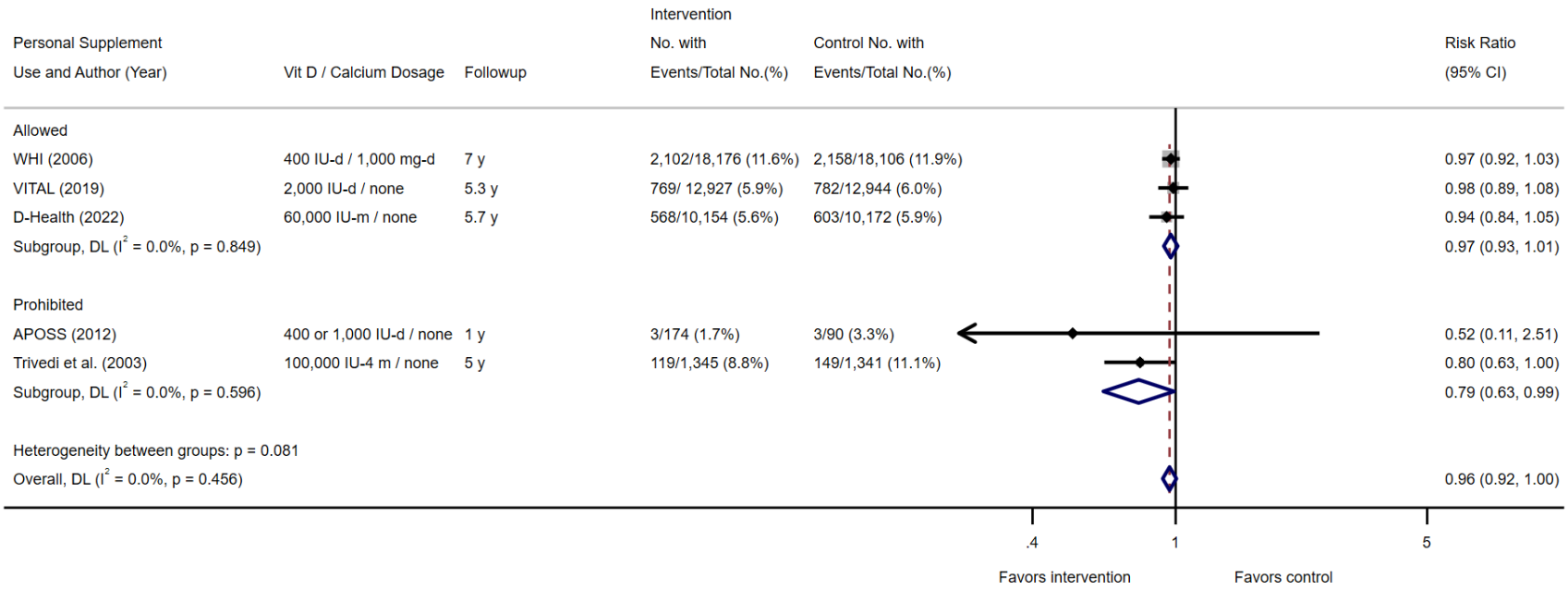
Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; IU=international units; m=month; OSTRPE=Osteoporosis Risk Factor and Prevention Study; RCT=randomized, controlled trial; RR=relative risk; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; y=year.

Appendix F Figure 8. Effect of Vitamin D Supplementation on Any Fracture Stratified by Dosage Among Included RCTs



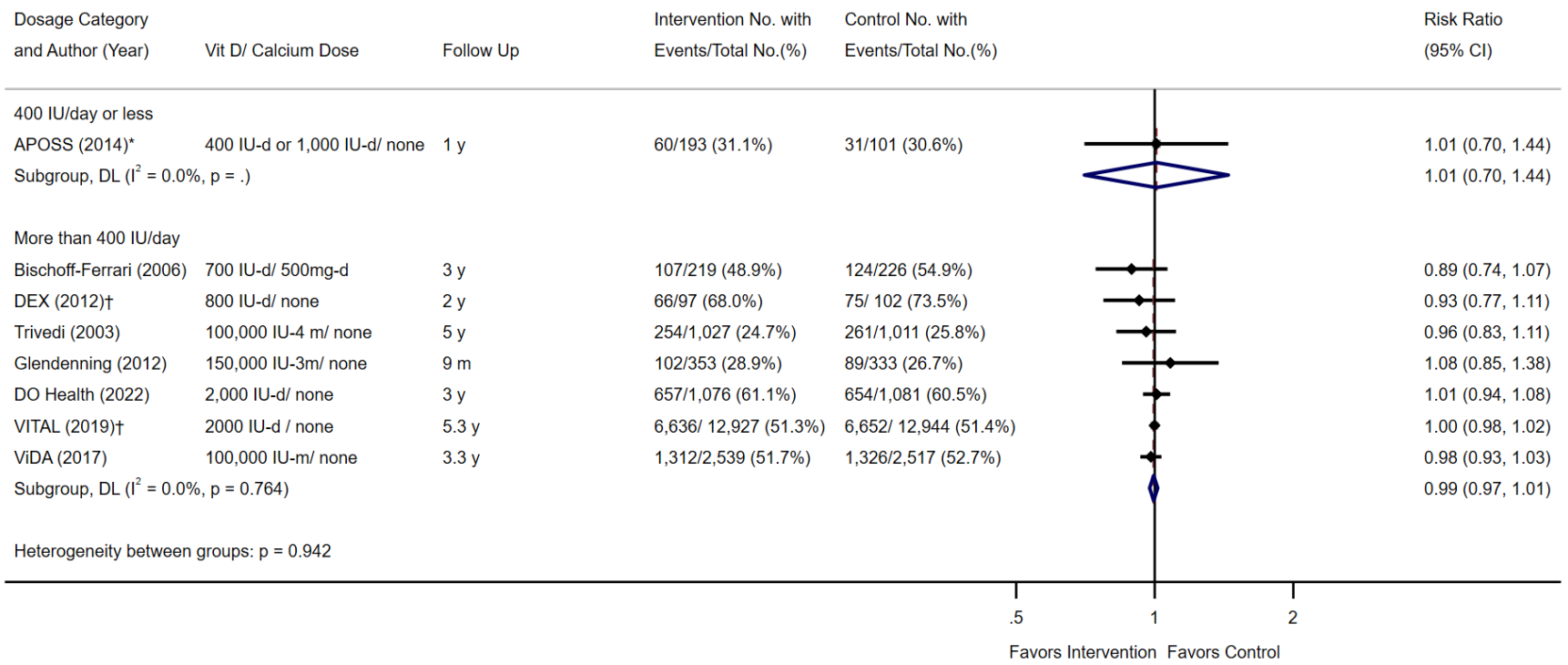
Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; IU=international units; m=month; RCT=randomized, controlled trial; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Appendix F Figure 9. Effect of Vitamin D Supplementation on Any Fracture Stratified by Personal Supplement Use Among Included RCTs



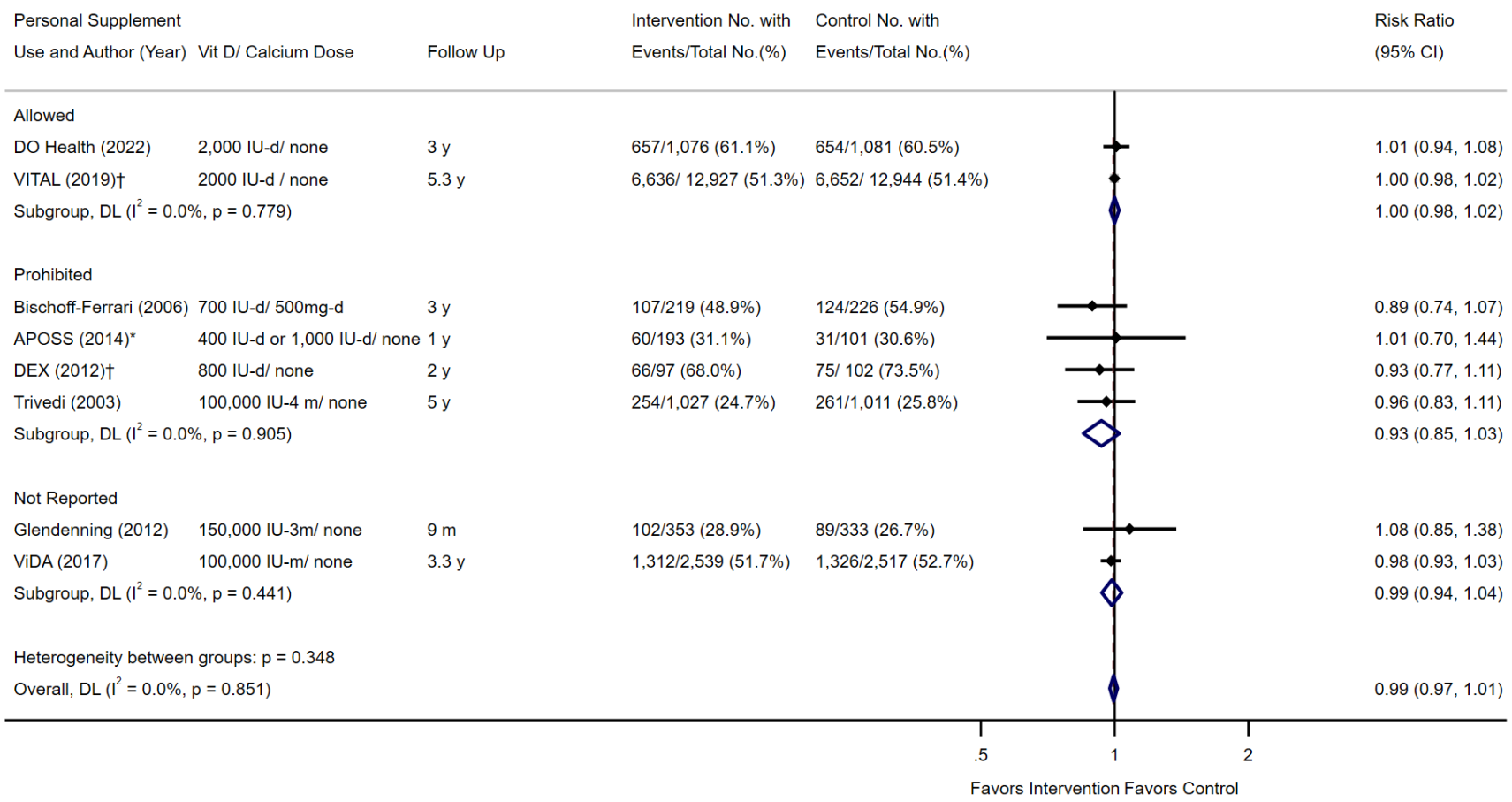
Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; D-Health=Vitamin D Health Trial; IU=international units; m=month; RCT=randomized, controlled trial; y=year; VITAL=The VITamin D and OmegA-3 Trial; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Appendix F Figure 10. Effect of Vitamin D Supplementation on Incidence of One or More Falls Stratified by Dosage Among Included RCTs



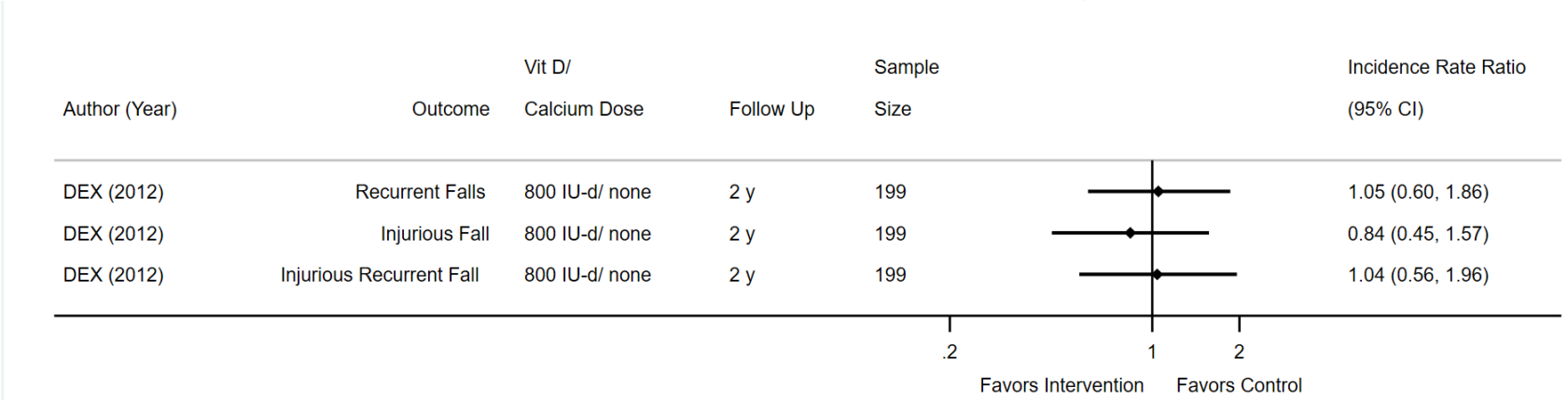
Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; IU=international units; m=month; RCT=randomized, controlled trial; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; y=year.

Appendix F Figure 11. Effect of Vitamin D Supplementation on Incidence of One or More Falls Stratified by Personal Supplement Use Among Included RCTs



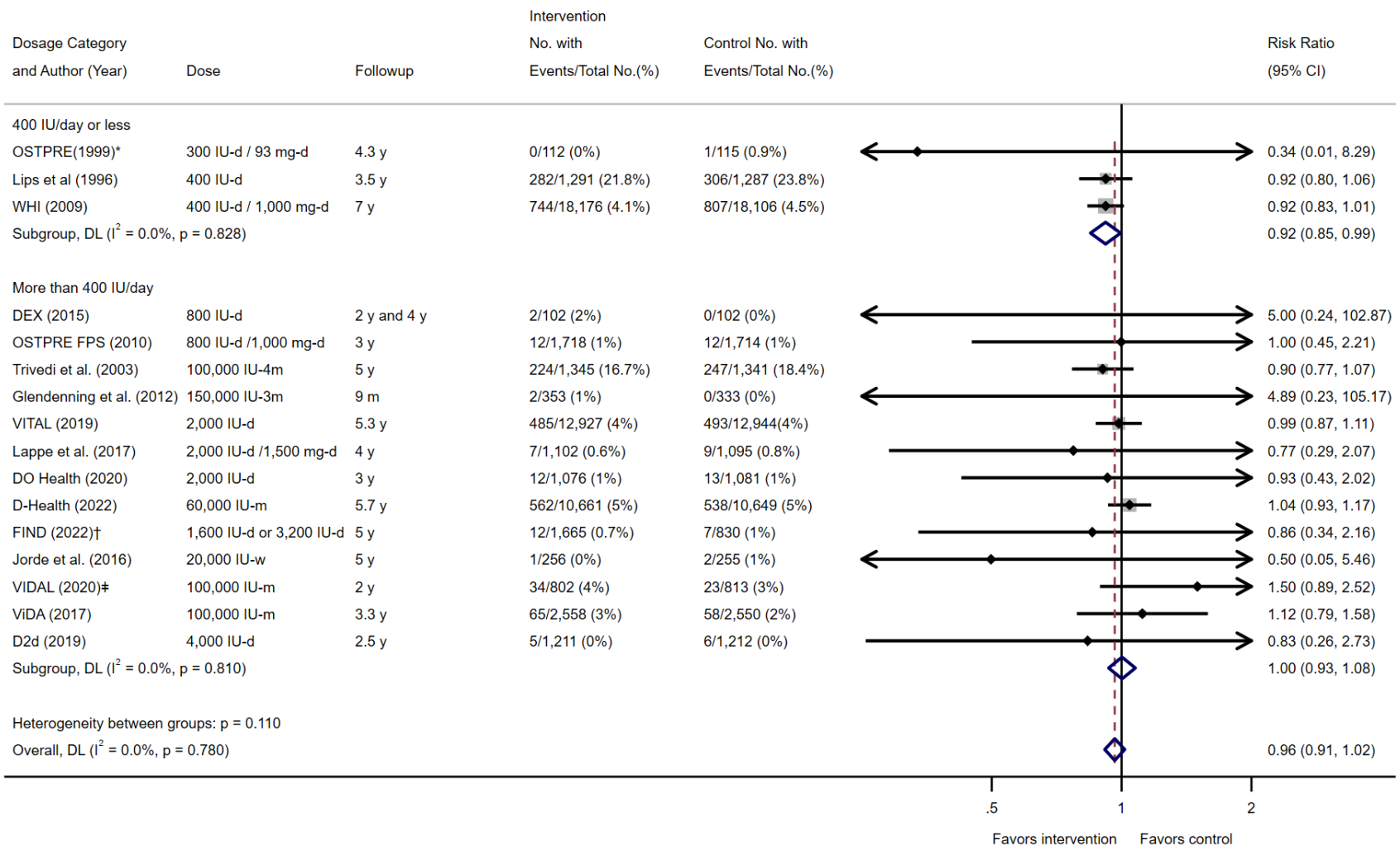
Abbreviations: APOSS=Aberdeen Prospective Osteoporosis Screening Study; CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention; DO-HEALTH=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; IU=international units; m=month; RCT=randomized, controlled trial; ViDA=The Vitamin D Assessment study; VITAL=The VITamin D and OmegA-3 Trial; y=year.

Appendix F Figure 12. Effect of Vitamin D Supplementation on Recurrent and Injurious Fall Rates Among Included RCTs



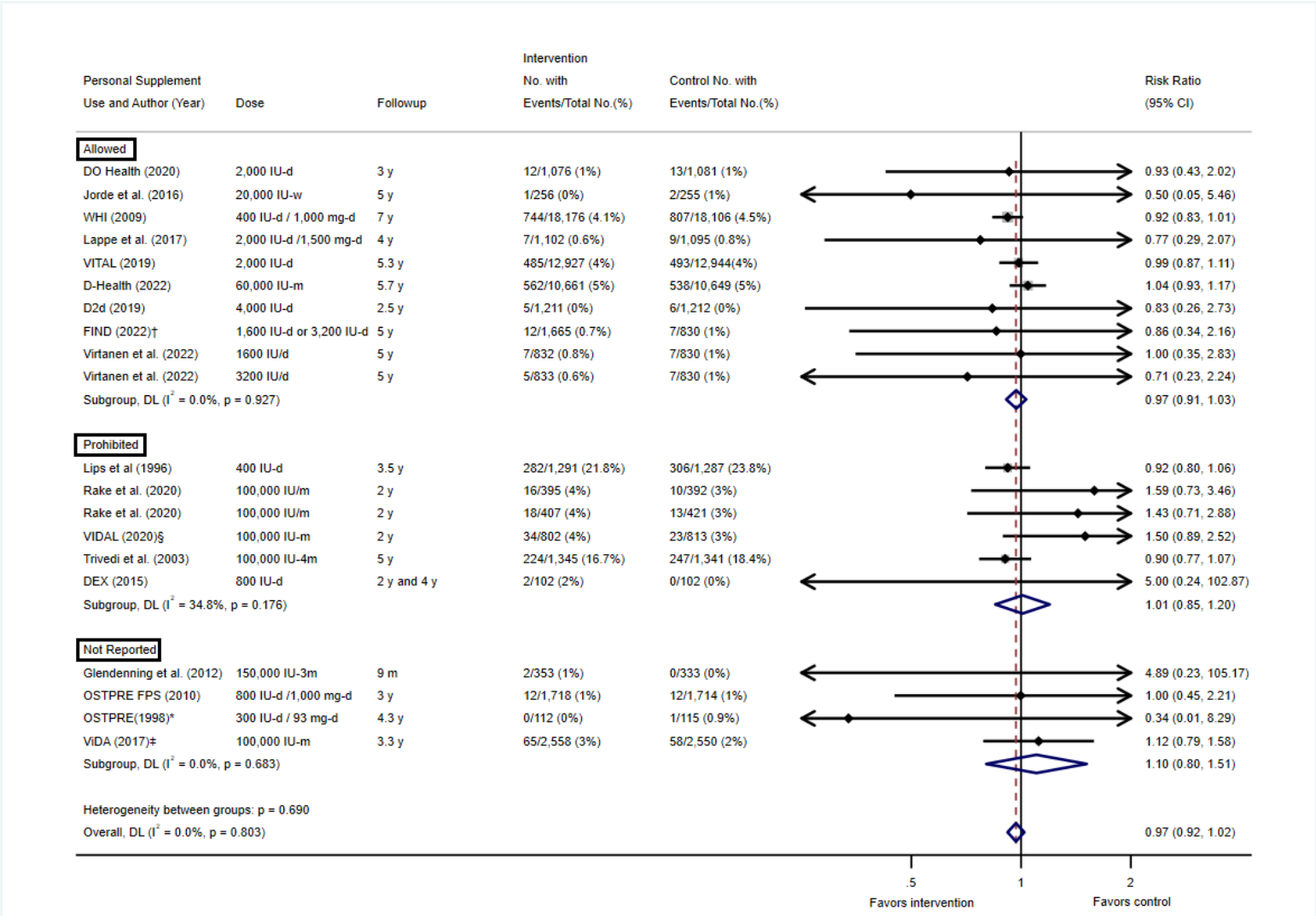
Abbreviations: CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention; IU=international units; RCT=randomized, controlled trial; y=year.

Appendix F Figure 13. Effect of Vitamin D Supplementation on Mortality Stratified by Dosage Among Included RCTs



Abbreviations: CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention ; D2d=Vitamin D and Type 2 Diabetes Trial; D-Health=Vitamin D Health Trial; DO Health=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; m=month; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSPTRE FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RCT=randomized, controlled trials; RR=relative risk; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial; w=week; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.

Appendix F Figure 14. Effect of Vitamin D Supplementation on Mortality Stratified by Personal Supplement Use Among Included RCTs



Abbreviations: CI=confidence interval; d=day; DEX=Vitamin D and Exercise in Fall Prevention ; D2d=Vitamin D and Type 2 Diabetes Trial; D-Health=Vitamin D Health Trial; DO Health=Vitamin D3 – Omega3 – Home Exercise –HeALTHy Ageing and Longevity Trial; FIND=Finnish Vitamin D Trial; IU=international units; m=month; OSTPRE=Osteoporosis Risk Factor and Prevention Study; OSPTRE FPS=Osteoporosis Risk Factor and Prevention Study—Fracture Prevention Study; RCT=randomized, controlled trial; RR=relative risk; ViDA=The Vitamin D Assessment study; VIDAL=Vitamin D and Longevity; VITAL=The VITamin D and OmegA-3 Trial w=week; WHI=Women's Health Initiative Calcium Vitamin D trial; y=year.