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Screening for Vitamin D Deficiency in Adults: An Evidence Review for the U.S. Preventive Services Task Force

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Prepared by:
RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center
Research Triangle Park, NC 27709

Investigators:
Leila C. Kahwati, MD, MPH
Erin LeBlanc, MD, MPH
Rachel Palmieri Weber, PhD
Kayla Giger, BS
Rachel Clark, BA
Kara Suvada, BS
Amy Guisinger, BS
Meera Viswanathan, PhD

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Structured Abstract

Purpose: To review the evidence about screening for vitamin D deficiency in adults.

Data Sources: MEDLINE, Embase, the Cochrane Library, trial registries, and other sources through March 12, 2020; bibliographies from retrieved articles, outside experts, and surveillance of the literature through June 30, 2020.

Study Selection: Two investigators independently selected studies using a priori inclusion and exclusion criteria. We selected randomized, controlled trials (RCTs) that evaluated the benefits or harms of screening or treatment of vitamin D deficiency in adults; observational studies were also eligible for selection if they reported eligible harms. For treatment, we selected studies for which at least 90 percent of the population had serum vitamin D levels less than 30 ng/ml. We excluded studies with poor methodological quality and studies conducted in developing countries.

Data Extraction and Analysis: 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 three similar studies were available, meta-analyses were conducted.

Data Synthesis: We did not identify any studies directly evaluating health benefits or harms of screening. We included 46 studies (45 RCTs and 1 nested case-control study within a RCT) that evaluated various doses, frequency, and duration of treatment with vitamin D (with or without calcium). We assessed 13 studies as good quality; the rest were fair quality.

Twenty-six RCTs and one nested case-control study reported on the effectiveness of treatment on health outcomes; half enrolled or reported on participants with serum vitamin D levels less than 20 ng/ml. Overall, the evidence suggests treatment with vitamin D (with or without calcium) had no effect on most health outcomes, though the evidence is limited for some outcomes. Among community-dwelling populations, treatment had no effect on mortality (pooled absolute risk difference [ARD] 0.3% [95% confidence interval [CI], -0.6% to 1.1%]; 8 RCTs), fractures (pooled ARD -0.3% [95% CI, -2.1% to 1.6%]; 6 RCTs), incidence of diabetes (pooled ARD 0.1% [95% CI, -1.3% to 1.6%]; 5 RCTs), incidence of cardiovascular disease (2 RCTs, relative risk 1.00 [95% CI, 0.74 to 1.35] and 1.09 [95% CI, 0.68 to 1.76]), incidence of cancer (2 RCTs, hazard ratio 0.97 [95% CI, 0.68 to 1.39] and 1.01 [95% CI, 0.65 to 1.58] , or depression (2 RCTs, various measures reported). The evidence for the impact of treatment on falls was inconclusive. The pooled ARD for incidence of participants with one or more falls was -4.3% (95% CI, -11.6% to 2.9%; 6 RCTs), and the pooled incidence rate difference for the total number of falls per group was -0.10 (95% CI, -0.19 to -0.002). The evidence was mixed for the impact of treatment on physical functioning (2 RCTs) and limited for the impact on infection (1 RCT).

The incidence of total adverse events, serious adverse events, discontinuations due to adverse events, kidney stones, and other harms was similar between active treatment and control groups.

Limitations: Only English-language studies were included. Most studies were primarily designed to assess intermediate health outcomes; some studies were conducted in nondeficient populations but reported on subgroups with deficiency. We did not assess comparative effectiveness or harms of various doses or formulations of vitamin D or assess the impact of vitamin D treatment for specific clinical conditions.

Conclusions: No studies have evaluated the direct benefit or harms of screening for vitamin D deficiency. Among asymptomatic, community-dwelling populations with low vitamin D levels, the evidence suggests that treatment with vitamin D (with or without calcium) has no effect on mortality; fractures; depression; or the incidence of diabetes, cardiovascular disease, cancer, or adverse events. The evidence is inconclusive about the impact of treatment on falls, physical functioning, and infection.

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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 2014 statement on screening for vitamin D deficiency in adults.[1] The 2014 USPSTF statement was informed by a 2014 systematic review conducted by the Pacific Northwest Evidence-based Practice Center (EPC).[2] The 2014 statement is summarized as follows:

- The USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults (I statement).

Condition Definition

Vitamin D is a fat-soluble compound that performs a critical role in calcium homeostasis and bone metabolism and affects many other cellular regulatory functions outside the skeletal system.[3-5] Vitamin D needs are met through synthesis of vitamin D in the skin after sun exposure and through foods that naturally contain vitamin D or that are fortified with vitamin D.[6]

Vitamin D deficiency refers to serum levels of vitamin D [serum total hydroxyvitamin D, or 25(OH)D] that are inadequate to support bodily needs and historically have been defined based on serum level of vitamin D at which an increase in circulating level of parathyroid hormone (PTH) was observed. No consensus exists regarding the precise serum levels of vitamin D that represent optimal health or deficiency. The National Academy of Medicine (formerly the Institute of Medicine [IOM]) defined the recommended dietary allowance for adults corresponding to a serum level of 20 ng/ml, which is the serum level they estimated would cover vitamin D requirements for 97.5% of the population.[3, 7] The IOM also reported that a serum level of 16 ng/ml covers the vitamin D requirements for half of the population.[3, 7] Relative to bone health, the IOM also reported that persons are at risk of deficiency at serum levels below 12 ng/ml, though some persons may be at risk between serum levels of 12 ng/ml and 20 ng/ml.[3] The Endocrine Society considers serum vitamin D levels of 20 ng/ml or less as deficient and considers levels between 21 and 29 ng/ml as insufficient.[8] Because vitamin D requirements vary across individuals, it is not possible to define a precise threshold below which deficiency is present; thus, thresholds used may more accurately reflect thresholds for which individuals may be at “at risk” for deficiency.

Prevalence and Burden of Disease/Illness

The prevalence of vitamin D deficiency varies based on the serum level used to define deficiency. According to the National Health and Nutrition Examination Survey (NHANES), which used the liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay to measure 25(OH)D levels during 2011 to 2014 survey, 5 percent of the population age 1 year or older had levels less than 12 ng/mL, 18 percent had levels between 12 ng/ml and 19 ng/mL, 73

percent had levels between 20 ng/ml and 50 ng/ml, and 4 percent had levels greater than 50 ng/ml.[9] The Institute of Medicine (IOM) developed a statistical procedure to derive group prevalence estimates of nutritional inadequacy. This statistical model found that 19 percent of the population was at risk of 25(OH)D levels less than 20 ng/ml.[10]

The prevalence of vitamin D deficiency is 1.3 to 3 times higher in winter than summer months.[11] The prevalence also varies by race and ethnicity. Depending on the serum threshold used to define deficiency, the prevalence of deficiency is 2 to 10 times higher in non-Hispanic black than in non-Hispanic white individuals. Hispanic individuals have a prevalence of deficiency that is 1.5 to 3 times the rate of non-Hispanic white individuals.[11-14] However, these prevalence estimates are based on total 25(OH)D levels, and controversy remains about whether this is the best measure of vitamin D status among different racial and ethnic groups. More research is needed to determine the best indicator of vitamin D deficiency as it relates to clinical outcomes (i.e., bone health), especially in nonwhite populations.

In the most recent NHANES analyses examining 25(OH)D levels over time (as measured by or calibrated to the LC-MS/MS assay), mean 25(OH)D showed no changes from 1988 to 2006, but during 2007 to 2010, the mean measured 25(OH)D was modestly higher.[11] The groups that showed the largest 25(OH)D increases included those who were older, female, non-Hispanic white, and those who used vitamin D supplements.

Etiology and Risk Factors

Vitamin D is synthesized in the skin under the influence of ultraviolet (UV) light and can also be obtained from dietary sources and supplements. In the United States, the main dietary sources of vitamin D are fortified foods such as milk, milk products, orange juice, and cereals, as well as supplements. Naturally occurring foods that contain vitamin D include fatty fish, egg yolk, and mushrooms that have been exposed to sunlight or UV radiation. In healthy individuals, vitamin D deficiency most often results from either decreased dietary intake, reduced sun exposure, and/or reduced ability to produce vitamin D (e.g., due to increased skin pigmentation, aging, or both).[15]

Vitamin D has a variety of actions on calcium, phosphate, and bone metabolism. Low 25(OH)D concentrations are associated with impaired intestinal calcium and phosphate absorption, negative calcium balance, phosphaturia, and a compensatory rise in PTH, which results in excessive bone resorption. Severe vitamin D deficiency causes a mineralization defect in the skeleton.[15] In children, vitamin D deficiency results in skeletal deformities classically called "rickets." In adults, severe vitamin D deficiency can result in osteomalacia, which is associated with decreased bone mineral density (BMD), diffuse bone and joint pain, muscle weakness, and difficulty walking.[16] Although rickets and osteomalacia are now uncommon in the United States, concern exists about subclinical vitamin D deficiency (i.e., low serum levels in the absence of overt symptoms), which may affect musculoskeletal health. Whether there is an association between subclinical deficiency and extraskeletal health is an area of active research.[6, 17-21]

Little or no UVB exposure (e.g., due to winter season, high latitude, and sun avoidance) is also associated with an increased risk for low vitamin D levels.[12, 13, 22-24] Although sunscreen reduces

the skin's ability to produce vitamin D in response to UVB in controlled research settings,[25] this association has not been found in population-based studies.[11, 22, 26] This finding in population-based studies is likely due to incomplete sunscreen application[27] or because subjects who use sunscreen are more likely to be exposed to the sun for extended periods, or both.[28] Low dietary vitamin D intake and/or lack of vitamin D supplements may also be associated with lower 25(OH)D levels,[11] with a 2- to 5-fold increased risk of vitamin D deficiency when defined as serum levels less than 20 ng/mL.[12-14]

Obesity is associated with lower 25(OH)D levels,[11, 29] translating into a 1.3- to 2-fold increased risk of being vitamin D deficient depending on threshold used to define deficiency.[12-14, 29] The exact mechanism for this finding is not completely understood. Older theories speculated that it was due to sequestration of vitamin D in fat cells[7] or due to lifestyle differences (e.g., lower physical activity levels or lower dietary vitamin D intake); however, newer theories suggest possibly altered metabolism of 25(OH)D in the liver. Little physical activity,[12, 13, 23] low education attainment,[30] and low health status[14, 22] are modestly associated with lower vitamin D levels in some studies. Differences in diet, supplement use, and UV exposure, however, could be mediating factors.

Cross-sectional studies have reported inconsistent findings on the association between older age and prevalence of vitamin D deficiency, although there may be an increased risk in persons age 85 years or older, but this may be related to less sun exposure, decreased dietary consumption, or both.[12-14, 23, 24] The prevalence of deficiency by sex is also mixed.[11, 13, 14, 24]

A significant proportion of the variability in 25(OH)D levels among persons is not explained by traditional risk factors, which seem to account for only 20 to 30 percent of the variation in 25(OH)D levels.[23, 31] Genetic factors may influence serum 25(OH)D concentrations, including genetic variants of vitamin D–metabolizing genes.[32]

Rationale for Screening/Screening Strategies

The rationale for screening for vitamin D among asymptomatic adults is to identify a deficiency early and offer treatment before potential adverse clinical outcomes (e.g., falls, fractures, other outcomes) occur. Testing vitamin D levels in individuals with conditions known to be associated with low vitamin D levels (e.g., chronic kidney disease) is not within the scope of this review.

Screening Tests

Total 25(OH)D is currently considered the best marker of vitamin D status because it incorporates endogenous synthesis from UV exposure and dietary intake from food or supplements or both.[7, 33] Total 25(OH)D is defined as the sum of 25 $(OH)_2$ and $25(OH)_3$ and is measured by both binding and chemical assays. Binding assays include competitive protein binding assays, radioimmunoassays, and chemiluminescence immunoassays. Chemical assays include HPLC (liquid chromatography [LC] with UV detection), liquid chromatography–mass spectrometry (LC-MS), and LC-MS/MS. Historically, it has been difficult to measure 25(OH)D accurately, which has resulted in assay variability and bias with likely misclassification of vitamin D status, especially for levels close to a threshold, in both research studies and clinical

practice. Currently, LC-MS/MS is considered a reference method; however, it is complex to perform and can still be subject to variation and error. Since the establishment of the Vitamin D Standardization Program (VDSP) in 2010, great strides have been made toward standardizing vitamin D assays. However, there are limited data on how quickly this standardization is being adopted by small and large commercial laboratories and as part of previous and ongoing research studies. Although several vitamin D metabolites are under active investigation as markers of vitamin D status, their association with clinical outcomes is much less studied than 25(OH)D, and the research on alternative assays suffers from the same assay standardization issues that have plagued 25(OH)D research until the recent development of the VDSP. Findings from a contextual question (CQ 1), located in **Appendix A,** provide additional information about vitamin D assays and other vitamin D measures proposed as potential markers of vitamin D status.

Interventions/Treatment

For healthy individuals not known to be vitamin D deficient, the recommended dietary allowance for vitamin D is 600 international units (IU) per day for adults ages 18 to 70 years and 800 IU per day for adults over 70 years of age.[7] Other expert bodies, however, suggest that the daily intake of vitamin D may need to be higher (e.g., 1,000 to 2,000 IU per day) to avoid vitamin D deficiency, especially in high-risk individuals.[8, 34-38] Vitamin D deficiency can be treated by increased dietary intake, vitamin D supplementation, and increased UV exposure. UV exposure is usually not recommended because of increased skin cancer risk. Although few foods naturally contain vitamin D, several food products (e.g., milk, cereals) are available that are fortified with vitamin D. A 2014 evidence report commissioned by the Agency for Healthcare Research and Quality (AHRQ) for the Effective Healthcare Program that assessed the effect of vitamin D and calcium intake on various health outcomes concluded that there was "good" evidence that dietary intake of vitamin D increases serum 25(OH)D levels among adults.[39]

Primary care physicians often treat vitamin D deficiency with oral vitamin D supplementation. There are two commonly available forms: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) available as either a prescription or as an over-the-counter supplement. Although a 2012 meta-analysis of seven randomized trials concluded that vitamin D_3 treatment increased serum 25(OH)D more efficiently than vitamin D_2,[40-43] there was significant between-study heterogeneity, and the difference was of uncertain clinical significance. Although more recent trials have also found that vitamin D_3 may be more efficient in raising total 25(OH)D levels than vitamin D_2 treatment,[44-46] the clinical significance on health outcomes remains unclear. Neither the Endocrine Society nor the IOM recommends using vitamin D_3 over vitamin D_2.[7, 8]

There are multiple forms (e.g., tablet, gel capsule, injectables), dosages (e.g., 200 to 500,000 IU), and dosing regimens (e.g., daily, weekly, monthly, yearly) for vitamin D treatment. In those with normal absorption, every additional daily equivalent of 100 IU of vitamin D_3 is estimated to increase serum 25(OH)D concentrations by approximately 0.7 to 1.0 ng/mL.[47, 48] However, these effects vary depending on study participants' characteristics such as baseline serum 25(OH)D status, body mass index (BMI), and the duration of treatment.[39, 49] Despite the variability in effect, evidence from 26 randomized, controlled trials (RCTs) summarized in the previously discussed AHRQ evidence review reported a definitive dose-response between supplemental vitamin D use and increased serum vitamin D levels.[21] In practice, injectable vitamin D is rarely

used and is mainly reserved for patients with gastrointestinal conditions or malabsorptive syndromes.

The amount of vitamin D required to effectively treat vitamin D deficiency also depends on an individual's vitamin D absorptive capacity, their capacity to convert vitamin D to 25(OH)D in the liver, their baseline serum level, and genetic determinants. Because of these factors, many different dosages and dosage patterns are used clinically, but there are little data on the optimal regimen. The Endocrine Society, for example, recommends that adults with serum levels less than 30 ng/mL be treated with 50,000 IU of vitamin D once a week or 6,000 IU per day for 8 weeks followed by maintenance therapy of 1,500 to 2,000 IU per day. In obese people, the Endocrine Society recommends increasing the dose 2- or 3-fold.[8] Other experts recommend using high weekly dosing for those with 25(OH)D levels of less than 12 ng/mL and suggest daily dosing of 600 IU to 1,000 IU per day for those with levels between 12 and 30 ng/mL. Some recommend caution when prescribing intermittent high-dose vitamin D (e.g., monthly and yearly dosing) because of evidence from some studies that it may be associated with increased risk of falls and fractures;[41-43, 50] however, not all studies have not noted such adverse effects,[20] so more research is needed. Although optimal monitoring strategies during vitamin D treatment are also not well studied, most experts recommend measuring 25(OH)D levels after 2 to 4 months of high-dose therapy.[51] Symptoms of vitamin D intoxication are unlikely below serum levels of 150 to 200 ng/ml, although some believe serum concentrations greater than 50 ng/mL may be associated with potential adverse effects.[7, 52-55]

Vitamin D is often administered with oral calcium. Although some meta-analyses have suggested possible differences in health outcomes and harms between vitamin D alone and vitamin D with calcium,[20, 56, 57] the previously discussed AHRQ systematic review concluded the addition of calcium to vitamin D had inconsistent associations with health outcomes.[21] A 2016 clinical guidelines statement from the National Osteoporosis Foundation and the American Society for Preventive Cardiology stated that taking calcium amounts not exceeding 2,000 to 2,500 mg/day with vitamin D was safe.[58] A recent systematic review in support of the USPSTF's recommendation on supplementation using vitamin D with or without calcium for fracture prevention among nondeficient adults also found no differences between vitamin D alone or with calcium on fractures, cardiovascular disease, or cancer.[59]

Current Clinical Practice

The prevalence of vitamin D deficiency screening by primary care clinicians in the United States is not known; however, evidence from other countries suggests increasing incidence of screening over the past several decades.[60-62] **Table 1** summarizes the recommendations of professional organizations related to screening for vitamin D deficiency in adults or vitamin D supplementation. Two organizations (Endocrine Society, American Association of Clinical Endocrinologists) recommend screening serum vitamin D levels in individuals at risk for deficiency, and one organization (American Society for Clinical Pathology) recommends against population-based laboratory screening. The rest of the organizations listed in Table 1 have recommendations related to vitamin D intake but are not specific to laboratory screening for deficiency.

Chapter 2. Methods

Key Questions and Analytic Framework

The EPC investigators, USPSTF members, and AHRQ Medical Officers developed the scope and key questions (KQs) for this review. The analytic framework illustrates the KQs that guided the review (**Figure 1**). The KQs for this update were similar to the KQs used in the previous review for the USPSTF and were as follows:

1. a. Does screening for vitamin D deficiency improve health outcomes?
   b. Does screening efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (e.g., persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?
2. What are the harms of screening for vitamin D deficiency?
3. a. Does treatment of vitamin D deficiency with vitamin D improve health outcomes?
   b. Does treatment efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (e.g., persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?
4. a. What are the harms of treatment of vitamin D deficiency with vitamin D?
   b. Do harms vary among patient subpopulations at higher risk for vitamin D deficiency (e.g., persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?

In addition to our KQs, we looked for evidence related to three CQs.

1. What are the various assays for measuring serum vitamin D (including total and free 25-hydroxyvitamin D and 1,25-dihydroxycholecalciferol), and what is known about the intermethod and interlaboratory variability of these assays?
2. In observational studies, what is the association between vitamin D use or serum vitamin D levels and the incidence of selected health outcomes (i.e., mortality, fractures, falls, cardiovascular disease, cancer, diabetes, dementia, autoimmune disease, and infections)?
3. In RCTs, what is the effect of vitamin D treatment on selected intermediate outcomes (i.e., bone mineral density, blood pressure, glucose levels, lipid levels, and measures of physical or muscle strength)?

We do not show these CQs in the analytic framework because they were not analyzed using the same systematic review process as the KQs. Findings related to the CQs are summarized in **Appendix A**.

Data Sources and Searches

Data Sources

We searched the following electronic bibliographic databases for this review: MEDLINE® via PubMed, Embase, the Database of Abstracts of Reviews of Effects, the National Institutes of

Health (NIH) Research-Health Technology Assessment database, and Health Services Research Project database. We searched the following clinical trial registries: Cochrane Central Register of Controlled Trials, clinical trials.gov, and the World Health Organization International Clinical Trials Registry Platform, which consolidates many non-U.S. clinical trials registries. Our literature search also included the National Institute for Health and Care Excellence Web site, the NIH Web site, the Centers for Disease Control and Prevention (CDC) Web site, the National Institute for Health Research (United Kingdom), and Web sites of relevant professional societies.

Search Strategy

We searched MEDLINE (via PubMed), Embase, and the Cochrane Library for English-language articles from January 1, 2013, through March 12, 2020, building on the literature included in the prior 2014 evidence review for the USPSTF. We used Medical Subject Headings (MeSH) terms when available and keywords to describe relevant screening and treatment interventions, populations, and study designs. The complete search terms and limits are detailed in **Appendix B1**. We also searched the clinicaltrials.gov registry and the World Health Organization International Clinical Trials Registry Platform and Health Services Research Projects in Process. To supplement the electronic database searches, we screened relevant systematic reviews and reference lists of included articles. We conducted surveillance of the literature through June 30, 2020.

Study Selection

We developed inclusion and exclusion criteria for selecting studies based on populations, interventions, comparators, outcomes, timing, settings, and study designs; these are described in detail in **Appendix B2**. For all KQs, we selected systematic reviews similar in scope, controlled trials (randomized or nonrandomized), or case-control studies nested within an RCT that were conducted in nonpregnant adults. For the KQs on harms (KQs 2 and 4), controlled observational studies were also eligible for selection. Only studies conducted in the 51 countries categorized as *very high* on the 2016 Human Development Index were selected.[63] For the KQs on treatment benefit or harms (KQs 3 and 4), we required 90 percent or more of study participants to have serum levels of less than 30 ng/ml or for study results to be reported stratified by vitamin D level. For all KQs, we excluded studies for which participants were selected for a specific clinical condition to assess the benefit of adding vitamin D to existing therapy for that condition. For example, we excluded studies that selected participants with asthma to evaluate the impact of adding vitamin D to an existing asthma regimen. For the KQs on the benefits and harms of screening (KQs 1 and 2), we selected studies that compared screening with a serum vitamin D assay with no screening. For the KQs on treatment benefit or harms (KQs 3 and 4), we selected studies that compared vitamin D_2 or D_3 treatment (with or without calcium) with placebo or no treatment. For the KQs on the benefits of screening or treatment (KQs 1 and 3), we selected studies that reported mortality, quality of life, self-reported physical functioning, or the incidence of specific morbidities including fractures, falls, diabetes, cardiovascular events, cancer, autoimmune disease, dementia, or infection and required outcomes to be measured after at least 8 weeks. For the KQs on the harms of screening or treatment (KQs 2 and 4), we selected studies that reported on harms of screening (e.g., anxiety, labeling) or treatment (e.g., toxicity, renal harms, adverse events), and we did not restrict study duration.

Two independent reviewers screened titles and abstracts and then full-text articles for selection; disagreements were resolved by discussion or by a third reviewer. We included English-language studies that met all study selection criteria and that were fair or good methodological quality. We reassessed studies included in the prior 2014 review[2] against the study selection and methodological quality criteria for this update.

Quality Assessment and Data Extraction

For each included study, one reviewer abstracted relevant study characteristics (i.e., population, intervention, comparator) and data for eligible outcomes into a structured form. A second reviewer checked all data for completeness and accuracy, and the lead investigator reviewed all abstracted information for consistency across included studies. We contacted study authors to clarify study data when needed.

Two senior reviewers independently assessed each study's methodological quality using the Cochrane ROB 2.0 instrument[64] and the predefined criteria developed by the USPSTF (**Appendix B3**), which uses study methodological quality ratings of poor, fair, and good. In addition to assessing the methodological quality of any newly identified studies, we reassessed the methodological quality of all previously included studies. Studies reporting multiple outcomes may have been assigned different quality ratings for different outcomes. Disagreements in study quality ratings were resolved through discussion.

Data Synthesis and Analysis

We synthesized data in tabular and narrative formats. For each KQ, we assessed whether a quantitative synthesis was appropriate by evaluating the number of studies available and the clinical and methodological heterogeneity present among available studies based on established guidance, which includes evaluating the similarities in study population, medication, dose, and frequency and similarities in timing and specification of outcomes.[65] When at least three similar studies were available, we performed a quantitative synthesis to generate pooled estimates of the absolute risk difference (ARD), the relative risk (RR), the incidence rate difference (IRD), or the incidence rate ratio (IRR). Specifically, we generated separate pooled analyses based on study population (community-dwelling vs. institutionalized) when at least three studies were available for each population. We used random effects models with the inverse-variance weighted method of DerSimonian and Laird in Stata (Version 16).[66] For rare event outcomes, such as mortality, we also conducted sensitivity analyses using other estimators and models with and without continuity corrections to assess robustness of our main findings. We assessed statistical heterogeneity of findings with the I^2 statistic; an I^2 between 0 and 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, and 50 to 90 percent may represent substantial heterogeneity.[67] We did not have enough studies for any single outcome to formally assess publication bias through visual inspection of a funnel plot.

We assessed the strength of evidence (SOE) based on AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, which specifies the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major

outcome of interest.[68] Two senior reviewers independently developed initial SOE assessments for each relevant outcome; discrepancies were resolved through discussion and consultation with a third senior reviewer. We considered all outcomes to be direct because they were health outcomes selected by the USPSTF as important and relevant for consideration. For the benefits of treatment (KQ 3), we conducted SOE assessments focused on the studies with community-dwelling populations where possible. We evaluated the consistency domain by visually inspecting the forest plot and with the I^2 statistic for pooled outcomes and by assessing the range of estimates and confidence intervals of individual studies where pooling was not possible. We also assessed whether any inconsistency could be explained by study population (e.g., community-dwelling vs. institutionalized populations, serum levels used to define deficiency [20 ng/ml vs. 30 ng/ml]), intervention (vitamin D with or without calcium), or study design characteristics. We evaluated the precision domain by calculating the optimal information size (i.e., sample size needed in a single adequately powered trial required to generate a precise estimate) and by evaluating whether the confidence intervals around pooled estimates crossed clinically meaningful thresholds of benefit or harm.

U.S. Preventive Services Task Force Involvement

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

Expert Review and Public Comment

The draft research plan was posted for public comment on the USPSTF Web site from October 25, 2018, to November 21, 2018. In response to public comments, the USPSTF modified KQs 1b, 3b, and 4b to include race/ethnicity as a characteristic of interest. The USPSTF also added dementia, autoimmune diseases, and infections to the list of eligible health outcomes. In addition to these changes in scope, we clarified our analytic approach for KQ 3 with respect to stratifying analyses by threshold used to define deficiency (20 ng/mL vs. 30 ng/mL) and by population (community dwelling vs. institutionalized). A final research plan was posted on the USPSTF's Web site in January 2019.

A draft version of this report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate. A draft version of this report will be posted for public comment on the USPSTF Web site.

Chapter 3. Results

We screened 1,616 titles and abstracts and 211 full-text articles and identified 46 studies from 75 publications for inclusion (**Figure 2**). The list of articles excluded during full-text review is in **Appendix C**. We did not identify any direct evidence for benefits (KQ 1) or harms (KQ 2) of screening. We identified 27 studies reporting on the benefits of treatment (KQ 3); ten of these studies are new to this update. We identified 36 studies reporting on the harms of treatment (KQ 4); 17 of these studies are new to this update.

Benefits of Screening (Key Question 1)

We did not identify any studies that evaluated the benefits of screening for vitamin D deficiency.

Harms of Screening (Key Question 2)

We did not identify any studies that evaluated the harms of screening for vitamin D deficiency.

Benefits of Treatment (Key Question 3)

We identified 46 publications describing the results from 26 RCTs and one nested case-control study from the Women's Health Initiative (WHI) Calcium-Vitamin D RCT. Ten RCTs were new since the 2014 evidence report. Included studies reported on the effect of various doses of vitamin D with or without calcium compared with a control group across a range of health outcomes. Key findings are the following:

- Among community-dwelling participants with low vitamin D levels (i.e., <20 or 30 ng/mL), treatment with vitamin D, with or without calcium, likely has no association with mortality; fractures; and the incidence of diabetes, cardiovascular disease, cancer, or depression compared with control.
- The evidence was inconclusive for drawing conclusions about the association of vitamin D with or without calcium on falls in community-dwelling populations; findings were mixed between the two fall outcomes reported (incidence of participants with one or more falls vs. total falls) and across the individual studies reporting fall outcomes.
- The evidence was insufficient to draw conclusions about the effect of vitamin D on physical functioning and infection. Few studies reported these outcomes, findings were inconsistent and imprecise, and the studies reporting these outcomes had limitations.
- Treatment effects may vary by population setting (community dwelling vs. institutionalized) for some outcomes (e.g., mortality), but outcomes were similar in studies using a 20 ng/ml versus a 30 ng/ml threshold for deficiency. The evidence was limited for drawing conclusions about other subpopulations.

Study Characteristics

The studies included for the benefits of treatment (KQ 3) were conducted over the years 1990 to 2019; 17 were included in the prior Evidence Report and 10 are new to this update.[69-78] All but one study were RCTs. The one non-RCT was a nested case-control study from the WHI Calcium-Vitamin D (Cal-D) trial.[79] We assessed nine RCTs as good quality,[49, 69-73, 75, 78, 80] and the rest were assessed as fair quality.

Nine studies were conducted in the United States;[49, 69, 71, 75, 76, 78, 79, 81, 82] one was conducted in New Zealand,[72] and one was a multicountry study conducted in Canada, United States, Germany, the Netherlands, and Mexico.[83] The rest were conducted in various European countries. Twelve studies reported at least some industry funding;[73-75, 78, 81, 83-89] the rest were funded through government or foundation sponsorship. **Table 2** describes the characteristics of included studies, with additional details in **Appendix D Table 1** and **Table 13**. Individual study quality ratings are in **Appendix E Tables 1, 2, and 3**.

Five studies were conducted exclusively or predominantly among populations in nursing homes or homes for the elderly (i.e., "institutionalized" settings).[87, 89-91] The rest of the RCTs were conducted exclusively or predominantly among community-dwelling populations. Twelve studies were conducted exclusively among female populations,[49, 69, 70, 79, 81, 85, 87-89, 91-93] and the rest were conducted among populations of males and females. The race/ethnicity of the studied populations included multiple races and ethnicities in nine studies,[49, 69, 71, 72, 76, 78, 79, 81, 82] was exclusively Caucasian in one study,[93] was mostly Latino in one study,[75]and was not reported in the 16 remaining studies. The mean age of included populations ranged from a mean of 36 to 85, but half were conducted among study populations ages 60 to 75 years. The mean BMI ranged from 25 to 33 across studies.

The included studies varied with respect to other characteristics of the enrolled populations potentially relevant to the outcomes of interest in this review. Eleven studies excluded participants with osteoporosis or who were taking osteoporosis medications (e.g., bisphosphonates).[49, 69, 70, 73, 81, 83-85, 87-89] One study reported that 15 to 17 percent of enrolled participants had osteoporosis;[70] the rest of the studies did not report whether participants with osteoporosis were included. Five studies excluded participants with a recent history of fracture;[49, 84-86, 89] one study reported that between 15 and 30 percent of participants had a history of fracture in adulthood,[70] and the rest of the studies did not specify fracture history of enrolled participants. No studies excluded participants based on a previous history of falling, and all but four studies did not specify whether enrolled participants had a history of falling. Two of the studies that did specify whether participants had a history of falls were conducted among institutionalized populations; the percentage of enrolled participants with a fall in the 6 weeks before enrollment was 23 to 24 in one study[89] and was 15 to 18 percent within the previous 3 months in the other study.[87] Other characteristics known to be associated with vitamin D levels (e.g., UV exposure) were variably measured or reported.

Nine studies enrolled participants with serum vitamin D levels less than 20 ng/ml.[49, 70, 77, 78, 81, 83, 85, 88, 90] Five studies enrolled participants using a higher serum vitamin D threshold (<25 ng/ml,[82] <27 ng/ml,[69] <22 ng/ml,[80] <30 ng/ml,[75] or <31.2 ng/ml[84]). Eight studies did not require participants to meet specific serum vitamin D–level criteria for enrollment, but the mean baseline

serum vitamin D levels reported among the enrolled populations suggested that 90 percent or more of the enrolled participants had baseline levels less than 20 ng/ml in three studies[86, 87, 93] and less than 30 ng/ml in five studies.[73, 89, 91, 92, 94] Five studies did not require participants to be vitamin D deficient for study enrollment but reported results separately for the subgroup of participants with serum levels less than 20 ng/ml.[71, 72, 74, 76, 79] Vitamin D assays used by studies varied (e.g., radioimmunoassay, competitive-binding protein assay, LC-MS/MS).

All studies used vitamin D_3 as part of the active treatment intervention. Most studies used daily doses, which varied from as low as 400 IU to as high as 4,000 IU . Two studies used a high initial loading dose, followed by lower monthly doses;[69, 72] one of these studies also titrated the dose to reach a target serum level of 30 ng/ml.[69] One study titrated the weekly dose to achieve a target serum level between 65 ng/ml and 90 ng/ml, resulting in an average weekly dose of 88,865 IU.[75] The rest of the studies used weekly, twice weekly, twice monthly, or monthly doses. Two studies used a no-intervention control group;[91, 92] the rest used placebo controls. Four studies included various doses of oral calcium as part of the active treatment intervention.[87, 88, 91, 92] Six studies provided calcium to both the active vitamin D treatment group and control group.[49, 81, 83-85, 89] The rest of the included studies did not include any calcium as part of the active or control intervention. Treatment duration ranged from 8 weeks to 7 years.

Findings

All-Cause Mortality

We identified 13 studies (12 RCTs[49, 69, 73, 81, 83, 86-88, 90-92, 94] and 1 nested case control study[79]) that reported mortality. Two RCTs are new to this update.[69, 73] Seven RCTs were good quality;[49, 69-73, 80] the rest of the studies were fair quality. Four RCTs were conducted exclusively[87, 90, 91] or predominantly[86] in institutionalized populations; the rest were conducted exclusively or predominantly in community-dwelling populations. Four RCTs used calcium as part of the active vitamin D intervention,[87, 88, 91, 92] and three studies used calcium in both the active treatment and control groups.[49, 81, 83] The treatment duration ranged from 16 weeks to 7 years. No studies specifically evaluated mortality as a primary study aim.

The pooled ARD in the eight RCTs conducted among community-dwelling populations was 0.3 percentage points (95% CI, -0.6% to 1.1%; 2,006 participants; I^2=0%). The RR was 1.13 (95% CI, 0.39 to 3.28) (**Figure 3**). All of the RCTs individually excluded a statistically significant treatment effect; however, because events were rare, individual study estimates were imprecise. Because events were so rare, we conducted sensitivity analyses using different statistical approaches as recommended for situations with rare binary events (e.g., several approaches for continuity correction, use of Peto method). In sensitivity analyses, the ARD was stable, varying from 0% to 0.3%; however, the RR varied from 0.86 to 1.17, depending on the approach used (**Appendix F Table 1** and **Table 2**). We found minimal difference in treatment effect based on whether RCTs enrolled community-dwelling participants with serum vitamin D levels predominantly less than 20 ng/ml versus enrolling participants with levels that were predominantly less than 30 ng/ml (**Appendix F Figure 1**). Results were too imprecise to draw any definitive conclusions about the effect of calcium use on treatment effect (**Appendix F Figure 2**).

The findings from the WHI nested case-control study were consistent with the findings from the RCTs.[79, 95] In this nested case-control study of community-dwelling women, no association between treatment with vitamin D and calcium and all-cause mortality was observed among the participants with baseline vitamin D levels between 14 and 21 ng/ml or for participants with levels less than 14 ng/ml (**Appendix D Table 14**).

One of the RCTs conducted in institutional settings reported mortality (1 participant), but this was not reported by group, so it could not be included in the quantitative synthesis.[90]Among the three RCTs conducted among institutionalized populations, an absolute risk decrease ranging from 2.2 to 5.6 percentage points was observed; however, no individual study estimates were precise enough to exclude the null effect (**Figure 3**). When pooled, the ARD was -2.8 percentage points (95% CI, -5.5% to -0.2%; 3,409 participants, I^2=0%), equivalent to a decrease of 28 deaths per 1,000 participants with a number needed to treat of 35 (95% CI, 18 to 500). The RR was 0.86 (95% CI, 0.74 to 0.99). These findings suggest some beneficial treatment effect in this population.

Fractures

We identified 10 studies (9 RCTs[69, 70, 72, 73, 84-87, 90] and 1 nested case control study[79]) that reported one or more fracture outcomes. Four of the RCTs are new to this update.[69, 70, 72, 73] We assessed four studies as good quality,[69, 70, 72, 73] and the rest were fair quality. All but three RCTs[86, 87, 90] were conducted among community-dwelling populations. One study enrolled participants without regard to vitamin D level but reported findings from a subgroup analysis of vitamin D–deficient (< 20 ng/ml) participants.[72] One RCT used calcium as part of the active treatment intervention,[87] and two RCTs used calcium as part of both the active and control interventions.[84, 85] Treatment duration and followup ranged from 12 weeks to 3.5 years.

Nine studies (8 RCTs and the 1 nested case-control study) reported on any type of fractures;[69, 70, 72, 73, 79, 84-87] fracture was not a study aim in any studies except for the two studies noted in the next paragraph that designated hip fractures as a primary study aim. Two studies were conducted exclusively or predominantly in institutionalized populations;[86, 87] the rest were conducted in community-dwelling populations. Two RCTs reported nonvertebral fractures; in one of these studies, fractures were ascertained based on International Classification of Diseases Tenth Revision (ICD-10) codes from national administrative datasets[72] and in the other study from incidence reported at study visits every 3 months with systematic verification only for vertebral fractures.[87] One RCT reported peripheral fractures as ascertained through patient questionnaire with verification from the general practitioner.[86] Two RCTs reported all fractures that were verified by X-ray or medical report.[84, 85] Two RCTs reported "self-reported fractures," but location was not defined.[69, 73] One RCT did not provide any information about location of fractures or method of ascertainment.[70] The pooled ARD from RCTs for incidence of fractures among community-dwelling populations was -0.3 percentage points (95% CI, -2.1% to 1.6%; 2,186 participants; 6 RCTs; I^2=13.0%)(**Figure 4**). The pooled RR was 0.84 (95% CI, 0.58 to 1.21). We found a minimal difference in treatment effect based on whether RCTs enrolled community-dwelling participants with serum vitamin D levels predominantly less than 20 ng/ml versus enrolling participants with levels that were predominantly less than 30 ng/ml (**Appendix F Figure 3**). Data were limited, and results were too imprecise to draw any definitive

conclusions about the effect of calcium use on treatment effect on fracture incidence (**Appendix F Figure 4**).

Four RCTs and one nested case-control study reported hip fracture outcomes;[79, 85-87, 90] hip fractures were the primary study aim for two of these studies.[79, 86] Two studies were in exclusively or predominantly community-dwelling populations,[79, 85] and three were in exclusively or predominantly institutionalized populations.[86, 87, 90] One RCT reported one participant with a hip fracture but did not specify the group; these results cannot be interpreted.[90] Ascertainment methods across studies varied: hip fractures were captured as adverse events (no other information provided by authors) in one study,[90] incidence was assessed at study visits every 3 months in one study,[87] incidence was assessed with annual questionnaire with verification from the general practitioner in one study,[86] and one study required hip fractures to be verified by X-ray reports and medical records.[85] The pooled ARD for incidence of hip fractures was -0.9 percentage points (95% CI, -3.5% to 1.8%; 3,349 participants; 3 RCTs; I^2=47.4%)(**Figure 5**). The pooled RR was 0.86 (95% CI, 0.50 to 1.47). In the one RCT conducted among community-dwelling populations, only one hip fracture occurred, leading to a very imprecise effect estimate for this study. The estimates from the two studies conducted among institutionalized populations were mixed; one study estimated a decrease[87] and one study estimated an increase,[86] but neither study could exclude the null effect. All studies enrolled participants with serum vitamin D levels predominantly less than 20 ng/ml; no calcium was used in two studies, while calcium was used as part of the active treatment intervention in one study and was used as part of both the active and control groups in one study.

Findings from the WHI nested case-control study confirmed findings from the RCTs for both any fracture and hip fracture outcomes. This study reported "clinical fractures," defined as fractures at sites other than ribs, sternum, skull, fingers, toes, or cervical vertebrae.[79] Further, blinded, central physician adjudicators reviewed imaging and operative reports to ascertain the incidence of hip fracture. Over 7 years of followup, there was no association between treatment using vitamin D with calcium and clinical fracture or hip fracture incidence among study participants with serum vitamin D levels less than 24 ng/ml at baseline (**Appendix D Table 14**).

Falls

Ten RCTs reported fall outcomes;[69, 72, 73, 78, 84, 85, 87, 89, 92, 93] four are new to this update.[69, 72, 73, 78] Four were good quality[69, 72, 73, 78] and the rest were fair quality. Two RCTs were conducted in institutionalized settings;[87, 89] the rest were conducted among community-dwelling populations. Two RCTs reported that between 12 and 15 percent of the study population had a prior history of falls,[73, 87] and one RCT (conducted in an institutionalized setting) reported that 15 to 21 percent of the study population had a prior history of hip fracture.[89] One study enrolled participants without regard to vitamin D level but reported findings from a subgroup analysis of vitamin D–deficient (< 20 ng/ml) participants.[72] Calcium was used as part of the active treatment intervention in two RCTs[87, 92] and was used in both the active and control interventions in three RCTs.[84, 85, 89] Treatment duration ranged from 8 weeks to 3.3 years, though followup measures were ascertained at between 1 and 3.3 years.

Falls were indicated as the primary study outcome in three of the RCTs.[84, 89, 92] Four RCTs reported the number of participants who experienced one or more falls (i.e., incidence of

fallers),[72, 73, 78, 87] two RCTs reported the total number of falls experienced in each group,[69, 93] and four RCTs reported both outcomes.[84, 85, 89, 92] A variety of means were used to ascertain falls, most commonly self-report at in-person or telephone study followup visits. In some cases, falls were recorded as part of adverse event monitoring. One study, conducted in an institutionalized setting, recorded falls as measured by a fall protocol in use within the unit.[89]

The pooled ARD for the incidence of participants with one or more falls in the six RCTs conducted among community-dwelling populations was -4.3 percentage points (95% CI, -11.6% to 2.9%; 2,633 participants; I^2=70.1%) (**Figure 6**). The RR was 0.90 (95% CI, 0.75 to 1.08). Heterogeneity was high as indicated by the I^2 statistic, and we observed inconsistency in the direction and magnitude of effect. Two studies conducted by the same first author observed a more than 10 percentage point absolute decrease in incidence;[84, 85] however, findings were only statistically significant in one of the studies.[84] The other four studies observed smaller effects ranging from a decrease of 4.6 percentage points to an increase of 3.1 percentage points; these findings were not statistically significant.[72, 73, 78, 92] We found minimal difference in treatment effect based on whether RCTs enrolled community-dwelling participants with serum vitamin D levels predominantly less than 20 ng/ml versus enrolling participants with levels that were predominantly less than 30 ng/ml (**Appendix F Figure 5**). Data were limited and results were too imprecise to draw any definitive conclusions about the effect of calcium use on treatment effect on fall incidence (**Appendix F Figure 6**).

Among the two RCTs conducted in institutionalized settings, one study observed a decrease of 7.4 percentage points (95% CI, -23.0% to 8.2%) in the absolute risk over 12 weeks, while the other observed an increase of 1.8 percentage points (95% CI, -6.6% to 10.1%) over 2 years, but findings were not statistically significant in either study. Both studies were conducted in very elderly populations (mean age 85); the study that observed a decrease used calcium in both the active treatment and control arms,[89] while the other study only used calcium in the active treatment arm.[87]

Six RCTs reported the total number of falls by group over the duration of followup.[69, 84, 85, 89, 92, 93] Using these data, we calculated IRDs and IRRs (**Figure 7**). Among the five RCTs conducted in community-dwelling populations, participants allocated to active treatment had 0.10 fewer falls per person-year compared with placebo (95% CI, -0.19 to -0.002; 2,838 person-years; I^2=76.9%), and the IRR was 0.76 (95% CI, 0.57 to 0.94) comparing active treatment to control. Heterogeneity was high as indicated by the I^2 statistic. Three of the studies observed statistically significant decreases ranging from 0.07 to 0.32 falls per person-year.[84, 92] The other two studies observed nonsignificant findings, though one observed a decrease (-0.01)[93] and the other observed an increase (0.03).[69]

In the one RCT conducted in an institutional setting, the incident rate difference was -2.2 falls per person-year (95% CI, -3.5 to -0.98), and the incident rate ratio was 0.44 (95% CI, 0.27 to 0.70).[89]

Diabetes

Four fair-quality RCTs[74, 76, 93, 96] and one good-quality RCT,[75] all conducted among community-dwelling populations, reported the effect of vitamin D treatment on the incidence of diabetes.

Three RCTs were new to this update and enrolled participants with prediabetes or impaired fasting glucose,[74-76] and two trials specified incident diabetes as a primary study outcome.[74, 76] Three trials did not exclusively enroll vitamin D–deficient participants but reported findings among subgroups of vitamin D–deficient participants;[74, 76, 96] however, these analyses were pre-specified in only one of the studies.[76] One RCT used calcium as part of the active vitamin D intervention;[96] the rest of the RCTs did not use calcium. One of the included trials was the WHI Cal-D trial.[79, 96] Other outcomes presented from the WHI study earlier in this report were reported from a nested case-control study design; in contrast, the incidence of diabetes outcome was reported from a post hoc analysis of the WHI Cal-D trial for the subgroup of participants with measured serum vitamin D at baseline.

The studies varied in the way this outcome was ascertained. In three RCTs, incident diabetes was based on glycemic testing using established thresholds for diagnosis.[74-76] In one study, the incidence of diabetes was reported as an adverse event without any specific criteria for diagnosis listed,[93] and in the subgroup analysis from the WHI CalD trial, diabetes was based on participant self-report of a doctor prescribing medication or insulin for diabetes.[96] The pooled ARD for incident diabetes over 1 to 7 years was 0.1 percentage points (95% CI, -1.3% to 1.6%; 3,356 participants; I^2=0%). The pooled RR was 0.96 (0.80 to 1.15) (**Figure 8**).

Two studies reported subgroup analyses based on degree of baseline vitamin D deficiency.[76, 96] The hazard ratio (HR) for developing incident diabetes over 7 years of followup in the WHI trial varied by baseline vitamin D level (HR 1.60 [95% CI, 0.80 to 3.18] for participants with serum vitamin D levels between 17 and 24 ng/ml, HR 0.66 [95% CI, 0.36 to 1.23] for levels between 13 and 17 ng/ml, and HR 1.07 [95% CI, 0.62 to 1.82] for levels less than 13 ng/ml.[96] These findings were reported from a subgroup of 3,097 participants with serum vitamin D levels measured at baseline. Among the 525 participants with serum vitamin D levels less than 20 ng/ml enrolled in the D2d trial, the HR for incident diabetes was 0.87 (95% CI, 0.61 to 1.22) at a median of 2.5 years followup.[76] This finding was consistent with the findings reported in participants with serum vitamin D levels greater than 20 ng/ml.[76] However, in a post hoc subgroup analysis of participants (n=103) with serum vitamin D levels less than 12 ng/ml, an HR of 0.38 (95% CI, 0.18 to 0.80) was observed.[76]

Cardiovascular Disease

Two good-quality RCTs (Vitamin D Assessment Study [ViDA][72, 97] and VITamin D and OmegA-3 TriaL [VITAL][71]), both new to this update, enrolled community-dwelling males and females and reported the effect of vitamin D on the incidence of cardiovascular disease. These trials did not exclusively enroll participants with vitamin D deficiency but reported findings in preplanned subgroup analyses among participants with baseline serum vitamin D levels less than 20 ng/ml. VITAL specifically excluded participants with preexisting cardiovascular disease, while between 1 and 10 percent of enrolled participants had cardiovascular morbidities at baseline in the ViDA trial. In VITAL, participants were allocated to vitamin D_3 alone or in combination with omega-3 fatty acids compared with placebo in a two-by-two factorial design.[71] In ViDA, participants were allocated to vitamin D or placebo.[72, 97] Neither trial used calcium as part of the treatment intervention.

Both trials specified cardiovascular events as a primary outcome; however, the definition of cardiovascular events was somewhat broader in the ViDA trial and included venous thromboembolism, pulmonary embolism, inflammatory cardiac conditions, arrythmias and conduction disorders with ascertainment based on ICD-10 codes from administrative data. In VITAL, cardiovascular endpoints included myocardial infarction, stroke, and cardiovascular disease (CVD) mortality (primary composite) and an expanded composite that also included cardiac revascularization. These endpoints were based on established criteria and adjudicated by a committee masked to treatment assignment using all available data sources. Both trials observed no differences in cardiovascular events between active treatment groups and the placebo group among the subgroup of participants with serum vitamin D levels less than 20 ng/ml. Over a median followup of 5.3 years, the HR was 1.09 (95% CI, 0.68 to 1.76) in the VITAL trial (N=2,001 subgroup) and was 1.00 (95% CI, 0.74 to 1.35) over a mean of 3.3 years followup in the ViDA trial (N=1,270 subgroup).[71, 72, 97]

Cancer

Three studies, the good-quality VITAL[71] and ViDA[72, 97, 98] RCTs and the fair-quality WHI nested case-control study[79, 99, 100] reported the effect of vitamin D on the incidence of cancer. VITAL and ViDA are new to this update. All studies enrolled participants without a history of cancer at baseline, but no studies exclusively enrolled participants with vitamin D deficiency; rather, outcomes were reported in a preplanned subgroup analysis for participants with deficiency. In VITAL, over 25,000 participants were allocated to vitamin D_3 alone or in combination with omega-3 fatty acids compared with placebo in a two-by-two factorial design.[71] In ViDA, participants were allocated to monthly 100,000 IU doses (after an initial dose of 200,000 IU) of vitamin D_3 or placebo. In the WHI nested case-control study, participants were exposed to vitamin D_3 plus calcium versus placebo.[79, 99, 100] The VITAL study specified invasive cancer as a primary study outcome, and cancer cases were confirmed by histologic or cytologic data upon medical record review by blinded physician adjudicators. In ViDA, cases of cancer were identified through a national registry.[98] In the WHI study, cases were verified by medical record and pathology reports by blinded physician adjudicators.[99, 100]

Over a median followup of 5.3 years, the HR for incident invasive cancer (any type) was 0.97 (95% CI, 0.68 to 1.39) for vitamin D compared with placebo among the subgroup of 2,001 participants with serum vitamin D levels less than 20 ng/ml at baseline in the VITAL trial.[71] In the ViDA trial, the HR for incident cancer among the subgroup of 1,270 participants with serum vitamin D levels less than 20 ng/ml at baseline was 1.01 (95% CI, 0.65 to 1.58) over a mean of 3.3 years of followup.[98] In the WHI nested case-control study, the adjusted odds ratios (ORs) for incident breast or colorectal cancer over 7 years of followup did not demonstrate a statistically significant association between exposure to active treatment and incidence of breast or colorectal cancer among participants with vitamin D deficiency at baseline (**Appendix D Table 14**).[99, 100]

Depression

Two RCTs, both conducted in Norway, reported depression outcomes; one was fair quality[77] and one was good quality.[80] One of the RCTs was new to this update.[77] One RCT conducted with 243 participants reported on depression outcomes among community-dwelling adults ages 30 to 75 years with vitamin D levels less than 22 ng/ml who were randomized to vitamin D_3 or

placebo for 12 weeks with followup measured at 26 weeks;[80] depression was the primary study aim. Three depression measures were used (Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, Hospital Anxiety and Depression Scale). Authors observed small improvements in depression as measured by all three scales in both the active treatment and placebo groups; the difference between active treatment and placebo groups was not statistically significant for any of the three scales (**Appendix D Table 7**). The other study was conducted among 422 participants with serum levels less than 16.8 ng/ml and compared vitamin D_3 with placebo over 16 weeks;[77] depression was not the primary study aim and appeared to be an outcome assessed in a post hoc analysis. This study reported a decrease of 1.9 on the Beck Depression Inventory II scores in the placebo group compared with a decrease of 1.5 in the active treatment group, a difference that was not statistically significant.

Physical Functioning

Two RCTs reported physical functioning measures;[69, 82] one of these is new to this update.[69] Arvold et al (fair quality) evaluated a weekly dose of vitamin D_3 compared with placebo among 90 outpatients (40% female, mean age 58) at a single study center in the United States.[82] The authors reported findings with the fibromyalgia impact questionnaire, which ranges from 0 (minimal symptoms) to 100 (maximal symptoms). We note the authors stated they selected this questionnaire because it includes symptoms potentially relevant to vitamin D deficiency. The authors observed a statistically significant difference in the change in scores between active treatment and control at 8 weeks followup (-3.7 vs. 1.9, p=0.03). Hansen et al (good quality) evaluated two doses of vitamin D_3 compared with placebo among women (mean age 61) at a single study center in the United States.[69] The authors reported findings using a modified Stanford Health Assessment Questionnaire. After 1 year, no significant difference in scores was observed for either of the vitamin D doses compared with placebo (**Appendix D Table 7**).

Infection

One fair-quality RCT that was new to this update evaluated vitamin D_3 compared with placebo over 5 years of followup.[74] Participants were between the ages of 25 and 80 and had impaired fasting glucose. Participants were not enrolled based on vitamin D level; however, findings from an unplanned subgroup analysis for participants with baseline serum vitamin D levels less than 20 ng/ml were reported. The authors reported an HR of 0.53 (95% CI, 0.17 to 1.64) for incidence of first urinary tract infection for active treatment compared with placebo among the deficient participants.

Effect of Vitamin D Treatment in Patient Subgroups

In this section, we summarize findings based on patient subgroups that were specified in our final research plan.

Population/Setting

Four studies were conducted among institutionalized populations;[87, 89-91] two were conducted among mixed community-dwelling and institutionalized populations,[83, 101] and the rest were conducted exclusively in community-dwelling populations. As noted in the previous section, we identified differences in treatment effect based on setting for mortality. A lower risk of mortality

was observed for treatment compared with no treatment among institutionalized populations, while no effect of treatment was observed for community-dwelling participants. We did not observe any difference in treatment effect for fractures (all types) by setting; we did not have enough studies to draw conclusions about the influence of setting on hip fracture incidence. For falls, we did not observe any difference in the incidence of falls by treatment setting. However, when considering the total number of falls, the one study that was conducted in an institutionalized setting reported a larger decrease in the IRD and IRR for active treatment group compared with control group than what was observed among the five studies conducted in community-dwelling populations. However, only one study was conducted in institutionalized settings, which limits our ability to draw definitive conclusions.

The rest of the outcomes reported in the previous section (i.e., diabetes, cardiovascular incidence, cancer incidence, depression, physical functioning, and infection) were reported from studies conducted among exclusively community-dwelling populations, limiting our ability to determine the influence of setting on those outcomes.

Age

No studies reported benefits stratified by age. Only two studies reporting KQ 3 outcomes enrolled younger populations (mean age 30 to 40 years).[81, 102] Findings in these studies appeared similar to findings reported in studies enrolling older participants (mean age 50s, 60s, 70s, and 80s).

Race/Ethnicity

Only one study reported benefits of vitamin D treatment stratified by race or ethnicity.[49, 103] In this study, no mortality events occurred among either the white or African American populations enrolled. With the exception of one study conducted primarily among a Latino population,[75] the six other studies reporting the race/ethnicity of the enrolled population were conducted exclusively or predominantly among white populations, and 14 studies did not report race/ethnicity. Thus, our ability to determine the influence of race/ethnicity on outcomes was limited.

Sex

About half of the studies reporting KQ 3 outcomes enrolled only females; the rest enrolled both males and females, but none enrolled exclusively males. Of the studies enrolling both sexes, no studies reported harms stratified by sex. For mortality, fracture, and fall outcomes, findings were similar whether reported in female-only or mixed male and female populations. We did not have enough studies to draw conclusions about the impact of sex on treatment effect for other outcomes.

Baseline Vitamin D Level

Nineteen studies were conducted among populations with vitamin D deficiency based on a lower serum level (approximately 20 ng/ml), and eight studies used higher thresholds (greater than 20 ng/ml but less than 30 ng/ml). Outcomes for mortality, fractures, and falls were similar between studies using the lower threshold compared with studies using a higher threshold. We did not

have enough studies reporting other outcomes to draw conclusions about the impact of baseline vitamin D level on treatment effect for those outcomes.

Obesity Status

No studies reported benefits by obesity status, and the mean BMI of enrolled participants was similar across this body of evidence, precluding any assessment of the influence of obesity status on benefits.

Levels of Sun Exposure

More than half of the included studies did not provide any information about the level of sun exposure among participants at baseline. Among those that did report baseline sun exposure, no studies reported outcomes by sun exposure status. This characteristic was reported in very different ways across studies, precluding our ability to draw any conclusions about whether benefits vary by sun exposure.

Harms of Treatment (Key Question 4)

We identified 36 studies (in 52 publications) that reported adverse events from treatment with vitamin D (with or without calcium) compared with a control group (e.g., placebo or no intervention) among vitamin D–deficient adults. These studies varied with respect to how adverse events were specified and ascertained. Overall, we identified five distinct adverse event outcomes reported by studies: total adverse events, serious adverse events, discontinuations due to adverse events, kidney stones, and other harms, which refers to specific adverse events reported by studies. Key findings:

- Adverse events and related harms were similar between active treatment and control groups.
- The evidence was limited for drawing conclusions about differences in harms based on various subpopulations.

Study Characteristics

The 36 included studies were published over the years 1990 to 2019. Nineteen of these studies were included in the 2014 Evidence Report,[46, 49, 80-83, 87-94, 101, 104-107] and 17 are new to this update.[69, 70, 73, 77, 102, 108-119] Sixteen of the studies included for KQ 4 (harms of treatment) also reported KQ 3 (benefit of treatment) outcomes.[49, 69, 70, 73, 77, 80-83, 87-94] A summary of study characteristics is provided in **Table 2**. We assessed nine of the studies as good quality;[49, 69, 70, 73, 80, 109, 115, 116, 119] the rest were assessed as fair quality A common issue among studies that we assessed as fair quality was that these studies included no information about how harms were defined or ascertained. Additional study characteristics are described in **Appendix D Table 1** and **Table 13** and individual study quality ratings are in **Appendix E Tables 1, 2, and 3**.

All studies were RCTs; 11 were conducted in the United States,[49, 69, 81, 82, 104, 108, 109, 111, 113, 115, 118] and one was a multicountry study (United States, Canada, Germany, Mexico). The rest were conducted in Australia,[110, 119] Canada,[114] and various European countries.[46, 70, 73, 77, 80, 87-94, 101, 102,

[105-107, 112, 116, 117] Four studies were conducted among institutionalized populations,[87, 89-91] two were conducted among mixed community-dwelling and institutionalized populations,[83, 101] and the rest were conducted exclusively in community-dwelling populations.

Eleven studies enrolled participants with serum vitamin D levels less than 20 ng/ml.[49, 70, 77, 81, 83, 88, 90, 107, 109, 116, 118] Nine studies enrolled participants using a higher serum vitamin D threshold (<22 ng/ml,[80, 110] <25 ng/ml,[82] <26 ng/ml,[108, 114] <27 ng/ml,[69] <30 ng/ml[102, 112, 117]). Sixteen studies did not require participants to meet specific serum vitamin D level criteria for enrollment, but the baseline serum vitamin D levels reported among the enrolled populations suggested that 90 percent or more of the enrolled participants had baseline levels less than 20 ng/ml in four studies[87, 91, 93, 105] or less than 30 ng/ml in 12 studies.[46, 73, 89, 92, 94, 101, 104, 106, 111, 113, 115, 119] Vitamin D assays used by studies varied (e.g., radioimmunoassay, competitive-binding protein assay, LC-MS/MS).

Three studies evaluated vitamin D_2 as a 2,000 IU daily dose,[46] a 50,000 IU weekly dose,[109] or a single 100,000 IU dose.[106] The rest of the studies evaluated various daily, weekly, monthly, or single doses of vitamin D_3. In the studies using daily doses, the doses ranged from as low as 400 IU to as high as 4,000 IU, and the studies using weekly doses ranged from 20,000 IU to 50,000 IU weekly. One study used a loading dose of vitamin D,[69] and two studies titrated the dose of vitamin D to achieve a target serum vitamin D level.[108, 110] Three studies used a no-intervention control group;[91, 92, 101] the rest used placebo controls. Five studies included various doses of oral calcium as part of the active treatment intervention.[87, 88, 91, 92, 101] Nine studies provided calcium to both the active vitamin D treatment group and the control group.[49, 81, 83, 89, 104, 108, 110, 115, 119] The rest of the included studies did not include any calcium as part of the active or control intervention. The duration of the intervention ranged from a single, one-time dose to 3 years; however, the duration of intervention was less than 6 months in 22 of the 36 studies.

No studies specified adverse events as primary outcomes. With one exception,[92] primary outcomes included laboratory (e.g., serum vitamin D level), imaging (e.g., bone mineral density), or physical strength measures (e.g., grip strength). Seven studies collected data on adverse events at study visits,[83, 89, 107, 110, 111, 113, 116] two used followup phone calls,[94, 109] one used a toll-free call-in line available to participants to report adverse events,[119] and one study used multiple methods.[80] Fourteen studies did not report how adverse events were ascertained.[46, 70, 77, 82, 88, 90, 93, 102, 105, 106, 108, 112, 114, 118] Lastly, a consistent definition for total and serious adverse events was not used across studies.

Findings

Total Adverse Events

Twenty-four studies reported overall adverse events (**Appendix D Table 8**).[46, 70, 80, 82, 83, 88-90, 93, 94, 102, 105-114, 116, 118, 119] We assessed five as good quality;[70, 80, 109, 116, 119] the rest were fair quality. Twelve were new to this update.[70, 102, 108-114, 116, 118, 119] Three studies were conducted exclusively or predominantly among institutionalized populations.[83, 89, 90] The rest were conducted exclusively in community-dwelling populations. Three studies used vitamin D_2,[46, 106, 109] and the rest used vitamin D_3. One study used calcium as part of the active treatment intervention,[88] and five studies used calcium as part of the active and control interventions.[83, 89, 108, 110, 119] The

duration of the intervention ranged from a single, one-time dose to 3 years, and the length of followup ranged from 4 weeks to 3 years.

The incidence of adverse events highly varied by study, ranging from 0 percent to 92 percent across the treatment and control groups. However, within any given study, the incidence of adverse events was generally similar between treatment and control groups. Seven studies reported no adverse events.[82, 90, 106, 108, 112, 114, 118] However, one of the studies that reported no adverse events noted side effects (e.g., nausea) and discontinuations from the study.[90] Of the remaining 18 studies, 13 studies reported adverse events by treatment group,[80, 83, 88, 89, 93, 94, 102, 107-111, 116] whereas four studies reported total adverse events overall (i.e., not by group).[70, 105, 113, 119] Of these four studies, two reported that no significant difference in adverse events was observed between groups,[70, 119] one reported that events were "few, mild, and equally distributed between groups,"[105] and one reported the specific nonserious adverse events that were reported by one to four women in the study.[113] Of the 14 studies reporting total adverse events by group, only three conducted statistical significance testing, and all reported no significant differences between groups.[88, 107, 116] Of the 10 studies that did not conduct statistical significance testing, results appeared similar between active treatment and control groups.[80, 83, 89, 93, 94, 102, 108-111] Although many studies did not list the specific adverse events experienced by participants, those that did reported the following types of adverse events: abdominal discomfort, gastrointestinal issues, fatigue, musculoskeletal symptoms, nontoxic goiter, light-headedness, severe headaches, nausea, rash/hives, weakness, numbness, constipation, and itching.[89, 90, 107-110, 113]

Serious Adverse Events

Sixteen RCTs reported serious adverse events (**Appendix D Table 9**).[49, 70, 73, 77, 81, 83, 88, 93, 102, 104, 105, 108, 109, 113, 117, 119] We assessed five studies as good quality;[49, 70, 73, 109, 119] the rest were fair quality. Thirteen were new to this update.[69, 71, 72, 74-76, 110-112, 114-116, 118] All were conducted exclusively or predominantly among community dwelling participants. Few studies were clear about their definition of a serious adverse event. Two studies used hospitalizations as a proxy for serious adverse events,[105, 117] and one defined "serious" according to National Institute on Aging guidelines.[49] Six studies collected information about serious adverse events at study visits,[49, 73, 81, 83, 109, 113] and one study had a toll-free call-in line to report adverse events as well as a questionnaire at the end of the study.[119] Eight studies did not report how this outcome was either defined or ascertained.[70, 77, 88, 93, 102, 104, 105, 108, 117] The treatment duration and length of followup across this body of evidence ranged from 8 weeks to 3 years. One study used vitamin D_2,[109] the rest used vitamin D_3. One study used calcium as part of the active treatment intervention,[88] and six studies used calcium in both the active treatment and control interventions.[49, 81, 83, 104, 108, 119]

The incidence of serious adverse events ranged from 0% to 29.4% across the groups within the studies; the incidence appeared similar between treatment and control groups, although formal statistical significance testing was not conducted in any study. Seven studies reported zero serious adverse events overall.[70, 77, 102, 108, 109, 113, 119] Five studies reported serious adverse events but authors indicated that these were most likely unrelated to the study medication.[49, 73, 81, 93, 104] Examples of such events were knee or hip replacement, syncope, heart failure, and internal bleeding from auto collision. The remaining four studies did not specify the nature of the serious adverse events reported or whether they were thought to be related to the study medication.[83, 88, 105, 117]

Discontinuations Due to Adverse Events

Seven RCTs reported treatment discontinuations because of adverse events (**Appendix D Table 10**).[80, 83, 88, 90-92, 110] We assessed one as good quality[80] and the rest were fair quality. One RCT was new to this update.[110] Two RCTs were conducted among institutionalized populations,[90, 91] and the rest were conducted exclusively or predominantly among community-dwelling populations. Only one study described how adverse events were ascertained (at study visits every 2 months).[110] The treatment duration and length of followup ranged from 16 weeks to 3 years. All studies used vitamin D_3. Three studies included calcium as part of the active treatment intervention[88, 91, 92] and two used calcium in both the active treatment and control interventions.[83, 110]

Across the studies that reported findings by treatment group, the incidence of discontinuations due to adverse events appeared similar in treatment and placebo groups, though no studies conducted formal statistical significance testing for this outcome. The incidence ranged from 0 percent to 15.8 percent in the vitamin D treatment groups and 0 percent to 17.7 percent in the placebo groups. In one study, Krieg et al reported treatment discontinuations due to the specific adverse event of upper gastrointestinal side effects (0% in the control group, 4.8% in the vitamin D group).[91] In the one study that did not report by treatment group, Janssen et al reported 11 participants discontinued study treatment due to likely adverse events.[90]

Kidney Stones

Ten RCTs reported on kidney stones (**Appendix D Table 11**).[49, 69, 81, 83, 87, 94, 101, 102, 104, 110] We assessed two studies as good-quality[49, 69] and the rest as fair-quality. Two RCTs were new to this update.[69, 102] One study was conducted among institutionalized populations,[87] one was conducted among mixed populations of institutionalized and community-dwelling,[101] and the rest were conducted exclusively or predominantly among community-dwelling populations. Among six RCTs, the self-reported incidence of kidney stones was recorded at study visits.[49, 69, 83, 87, 101, 110] In one RCT, study nurses contacted participants to assess adverse events, including the incidence of kidney stones.[94] The remaining three RCTs did not report the method of ascertainment of kidney stones.[81, 102, 104] The duration of treatment and length of followup across this body of evidence ranged from 8 weeks to 3 years. All studies used vitamin D_3. Two studies reported the use of calcium as part of the active treatment intervention,[87, 101] five studies used calcium as part of both the active treatment and control interventions.[49, 81, 83, 104, 110]

In all but one study, the incidence of kidney stones was reported in 0 percent of both the active treatment and control groups. In the study reporting more than zero events, one participant in the lower dose vitamin D (800 IU daily) group reported a kidney stone; no kidney stones were reported in the placebo group or in the higher dose vitamin D group (50,000 IU twice monthly).[69] This study did not use calcium as part of the active treatment or control intervention.

Other Harms

Five RCTs reported on various specific harms, including gastrointestinal side effects (e.g. nausea, diarrhea, epigastric pain, constipation) and minor adverse events (**Appendix D Table 12**).[49, 87, 89, 101, 115] We assessed two studies as good quality[49, 115] and the rest were fair quality.

One RCT was new to this update.[115] Two studies were conducted among institutionalized populations,[87, 89] one study was conducted among a mixed population of both institutionalized and community-dwelling participants,[101] and the rest were conducted exclusively among community-dwelling populations. Three RCTs collected self-reported data on side effects at study visits.[49, 87, 115] Conversely, one RCT[89] continuously monitored study participants on a long-stay geriatric unit to assess for adverse events and one RCT[101] did not report how other harms were ascertained. The treatment duration and length of followup ranged from 12 weeks to 2 years. All studies used vitamin D_3. Two studies included calcium as part of the active treatment intervention,[87, 101] and three studies used calcium in both the active treatment and control interventions.[49, 89, 115]

One study reported mild gastrointestinal symptoms among nine participants (16.3%) in the active treatment group (vitamin D plus calcium); outcomes for the no-intervention group were not reported.[101] One study reported two cases of constipation in the vitamin D group compared with 0 cases in participants treated with placebo.[89] One study reported 16 (8.4%) cases of gastrointestinal disorders in the placebo group compared with 24 (6.1%) in the vitamin D with calcium group (calculated RR 0.73 [95% CI, 0.40 to 1.33]).[87] One study reported symptoms potentially attributed to hypercalcemia (pruritis, polydipsia, and polyuria) in two participants in the active treatment groups (control group not reported [NR]).[115] Lastly, one study reported minor adverse events equally distributed within all vitamin D dose groups among black participants; however, actual values and descriptions of adverse events were not described, and data for white participants were not reported.[49]

Effect of Vitamin D Treatment in Patient Subgroups

In this section, we summarize findings based on patient subgroups that were specified in our final research plan. Some harm outcomes occurred with very rare frequency, precluding any assessment of variation by subgroup.

Population/Setting

Four studies were conducted among institutionalized populations;[87, 89-91] two were conducted among mixed community-dwelling and institutionalized populations,[83, 101] and the rest were conducted exclusively in community-dwelling populations. The two studies that included mixed populations did not report harms by population setting (institutionalized vs. community dwelling). As previously noted, the incidence of adverse events varied widely across studies with no differences between active treatment and control; this finding held true whether studies were conducted among community-dwelling or institutionalized populations.

Age

No studies reported harms stratified by age. Twelve of the studies reporting KQ 4 outcomes enrolled younger populations (mean age 20s to 40s).[46, 71, 81, 102, 105, 107, 109, 111, 112, 114, 116, 118] Findings for adverse event outcomes in these studies appeared similar to findings reported in studies enrolling older participants (mean age 50s, 60s, 70s, and 80s).

Race/Ethnicity

No studies reported harms stratified by race/ethnicity. Many studies enrolled diverse racial and ethnic populations; of those, none reported harms stratified by race or ethnicity. Four studies enrolled exclusively black participants;[104, 108, 115, 118] one study enrolled a predominantly South Asian population,[106] two studies enrolled mixed black and white populations,[49, 81] and one study enrolled a mixed Asian and white population.[110] An additional six studies enrolled multiple races/ethnicities, but the majority of participants were white.[69, 111, 113, 114, 116, 119] As previously noted, the incidence of adverse events varied widely across studies with no differences between active treatment and control; this finding held true whether studies were conducted among exclusively black populations, diverse populations, or all-white populations.

Sex

The majority of the studies reporting KQ 4 outcomes enrolled only females. One study enrolled only males,[112] and the rest enrolled both males and females. Of the studies enrolling both sexes, no studies reported harms stratified by sex. As previously noted, the incidence of adverse events varied widely across studies with no differences between active treatment and control, and this finding held true whether studies were conducted among female or mixed populations.

Baseline Serum Vitamin D Level

Twelve studies were conducted among populations with deficiency defined based on a lower serum level (approximately 20 ng/ml); nine studies used higher thresholds (greater than 20 ng/ml but less than 30 ng/ml). As previously noted, the incidence of adverse events varied widely across studies with no differences between active treatment and control, and this finding held true whether studies were conducted using lower or higher thresholds for defining deficiency.

Obesity Status

No studies reported harms by obesity status, and the mean BMI of enrolled participants was similar across this body of evidence, precluding any assessment of the influence of obesity status on harms.

Levels of Sun Exposure

More than half of the included studies did not provide any information about the level of sun exposure among participants at baseline. Among those that did report baseline sun exposure, no studies reported adverse event outcomes by sun exposure status. This characteristic was reported in very different ways across studies, precluding our ability to draw any conclusions about whether adverse events vary by sun exposure.

Chapter 4. Discussion

Summary of Evidence

We identified no direct evidence evaluating the benefits (KQ 1) or harms (KQ 2) of screening for vitamin D deficiency. We did identify evidence addressing the benefits and harms of treatment with vitamin D in deficient persons (KQ 3, KQ 4); however, the evidence for variation in effectiveness of benefits or harms by specific subgroups was limited. **Table 3** summarizes the evidence synthesized in this report by KQ and provides our EPC's assessment of the SOE.

Benefits of Treatment (Key Question 3)

Among community-dwelling populations, we assessed the SOE as moderate for no benefit for mortality, any fractures, incident diabetes, cardiovascular disease, and incident cancer. For these outcomes, we downgraded the SOE for study limitations or imprecision. We assessed the evidence as low for no benefit for hip fractures and depression and downgraded these bodies of evidence for study limitations and imprecision. We assessed the SOE for falls, physical functioning, and infection as insufficient because of inconsistency, imprecision, and study limitations.

Despite a reasonable number of studies reporting on the incidence of falls, the body of evidence demonstrated inconclusive findings. Among the studies reporting the incidence of one or more falls, a numerical but not statistically significant decrease (ARD -4.3%) was observed among community-dwelling populations. Among the studies reporting total number of falls, a small but statistically significant decrease (-0.1 falls per person-year) in the total number of falls was observed. Estimates for both outcomes were inconsistent and imprecise. Some studies reported both outcomes, but others only reported one of these outcomes, raising the possibility of selective outcome reporting. One hypothesis to explain the difference between these two outcomes is that although vitamin D may not prevent a first fall, it may have some benefit in preventing repeat falls. However, a related systematic review on behalf of the USPSTF's recommendation for fall prevention in community-dwelling populations at increased risk of falls found mixed findings for vitamin D interventions.[120] There was also evidence of possible harms from high-dose vitamin D in such populations, resulting in a recommendation against vitamin D supplementation in community-dwelling adults age 65 years or older.[120, 121] The falls prevention review excluded studies conducted among vitamin D–deficient populations; thus, additional evidence specifically in vitamin D–deficient populations is needed to be able to draw definitive conclusions about the impact of screening for vitamin D deficiency on falls among community-dwelling adults.

Findings regarding benefits of treatment in this review are not directly comparable with other reviews of vitamin D supplementation because this review was focused specifically on persons with low levels of vitamin D that would place them at risk for deficiency. Despite this key difference, the findings from this review are largely consistent with findings from other reviews conducted in broader populations with respect to most outcomes. One exception to this deserves mention. Several meta-analyses have specifically focused on the effect of vitamin D

supplementation on both incident cancer and cancer mortality.[122-125] These analyses do not all include the same set of studies, but all suggest no effect on cancer incidence. However, three [122-124] of the four analyses suggest a small favorable effect of vitamin D supplementation on cancer deaths. Authors of these analyses cannot precisely identify the reason for the divergence between cancer incidence and mortality outcome but offer several biological theories that will require further research to fully elucidate.

Harms of Treatment (Key Question 4)

We assessed the SOE as low for no harm for total adverse events, serious adverse events, discontinuations due to adverse events, kidney stones, and other harms. We downgraded the SOE for these outcomes because of imprecision and study limitations. Although studies were consistent in demonstrating no difference in harms between active treatment and control groups, the absolute incidence of reported adverse events varied vastly across studies. This is likely because of different approaches to defining and ascertaining these outcomes across the studies. Some studies proactively inquired about adverse events at regular, periodic study visits, while others relied on voluntary patient self-report of adverse events, while many studies provided no information about how these outcomes were ascertained.

Limitations

Limitations of the Evidence

We found no available evidence that directly evaluated the health benefits and harms of screening (KQs 1 and 2); thus, we could only assess the evidence related to the treatment of vitamin D deficiency (KQs 3 and 4). The doses and duration of treatment varied widely across this body of evidence as did the use of calcium as part of the treatment intervention or in both the treatment and control groups. The level used to define vitamin D deficiency varied across studies; however, our analyses suggest no impact of using a lower threshold (less than 20 ng/ml) as compared with using a higher threshold (less than 30 ng/ml) on the effect of treatment.

The use of standard outcome definitions and methods of ascertainment varies widely across studies, likely reflecting the fact that vitamin D is not regulated as a prescription drug. This fact affects how studies are designed, conducted, and reported, including less rigorous and transparent methodology and incomplete reporting, particularly for older studies. We note that more recently conducted studies appear to be of higher quality and/or have better reporting. For many outcomes, the followup time periods used by studies may not have been long enough to demonstrate an effect. Results from some studies were reported based on subgroup analyses, some of which were not prespecified. Of note, two of the large trials that were included for KQ 3 (benefits of treatment) because they examined health outcomes in prespecified subgroups with low vitamin D levels did not present data on harms by subgroup and thus could not be formally included for KQ 4 (harms of treatment).[71, 76] However, we note that the data on harms reported on the overall population in these two studies are similar to the findings from studies included for KQ 4 (i.e.., no difference between treatment and placebo groups). One of these trials (VITAL) also reported findings from the overall trial (not limited to vitamin D–deficient subgroup) stratified by subgroups. In these analyses, study authors reported no interaction between age, sex,

or race and incident cancer of major cardiovascular events.[71] A significant interaction was observed for BMI for incident cancer; fewer cases of incident cancer were observed among participants with BMI less than 25 for treatment with vitamin D compared with placebo. This effect was not observed among participants with BMI 25 to less than 30 or BMI greater than or equal to 30.

We identified few to no trials for some outcomes specified in our research plan, and few studies reported outcomes for prespecified patient subgroups of interest. Lastly, we did not have enough studies to evaluate the impact of different doses on benefits and harms, specifically the impact of intermittent, high doses of vitamin D, as some evidence has suggested adverse effects of high dose, intermittent regimens in studies that are not included in the scope of this review, specifically studies comparing low to high doses of vitamin D[42, 50] and studies in populations not defined based on deficiency.[41, 43] Two of the studies included in this review used a single, high-dose regimen (100,000 IU and 250,000 IU one time) but did not report any difference in total adverse effects between active treatment and control groups.[111, 116]

Limitations of the Review

We limited this review to English-language studies conducted in very highly developed countries. We selected studies in this review to include vitamin D–deficient populations, including those in institutionalized settings. However, our synthesis and SOE assessment focused mainly on community-dwelling populations because USPSTF recommendations focus on clinical preventive services in or referred from primary care settings. Studies focused on populations with a specific clinical condition to evaluate the treatment of vitamin D deficiency for the alleviation of specific symptoms or issues associated with that condition were not included (e.g., infertility, asthma). We did not assess the comparative benefits or harms of various vitamin D doses, formulations, or durations of treatment. This review included studies that enrolled participants based on 25(OH)D levels that used various assays and that may not have been standardized according to current criteria from the VDSP; it is uncertain whether findings would be different had all studies used standardized testing.

The treatment key questions of this review focused on asymptomatic populations known to have low vitamin D levels, typically less than 20 or 30 ng/mL. For the trials enrolling participants unselected with respect to vitamin D status, we only reported findings from the vitamin D–deficient subgroups. We did not include findings from the overall population, but these would likely be eligible to be included in the next update of a related review of vitamin D supplementation conducted on behalf of the USPSTF.[59] We also note that findings from this review may not be directly comparable to other reviews of Vitamin D interventions because of differences in eligible study populations, interventions, and settings. For example, two recent meta-analyses evaluating vitamin D supplementation on the incidence of diabetes among normoglycemic and prediabetic populations reported findings suggestive of a small clinical benefit among some subgroups.[126, 127] However, these analyses were not limited to vitamin D deficient populations, included studies evaluating vitamin D analogs, or were conducted countries not considered as *very highly* developed per the UN Human Development Index.[63]

Consistent with USPSTF methods, this review focused on health outcomes and did not systematically evaluate asymptomatic benefits (e.g., effects on intermediate cardiovascular or

metabolic measures) or harms (e.g., hypercalcemia, hypercalciuria, or nephrocalcinosis), yet few studies designated hard health outcomes as the primary study aim or powered their designs based on such outcomes. Further, some findings were reported after followup times that might not be long enough to demonstrate an impact on mortality and chronic disease outcomes such as diabetes, cancer, and cardiovascular events. Findings from RCTs related to the effect of vitamin D treatment on intermediate measures of health are summarized in Contextual Question 3 in **Appendix A**. Overall, there appears to be no relationship between treatment with vitamin D and intermediate outcomes such as bone mineral density, muscle/physical strength, blood pressure, fasting glucose of HgbA1C, cholesterol, weight or BMI, or precancerous outcomes (e.g., adenoma). In terms of asymptomatic harms, findings from a 2014 AHRQ Effective Health Care Review suggest sporadic cases of hypercalcemia or hypercalciuria in RCTs of vitamin D supplementation; however, these reviews were not limited to vitamin D–deficient populations.[21] Two other reviews also not conducted solely among vitamin D–deficient populations also suggest increased risk for hypercalcemia and hypercalciruia but without any increased risk for kidney stones.[128, 129] A 2014 Cochrane review of vitamin D or vitamin D analogues with or without calcium to prevent fractures in postmenopausal women or older men described an increased risk for mild hypercalcemia (pooled RR 2.28 [95% CI, 1.57 to 3.31]; 21 RCTs; 17,124 participants).[130] This Cochrane review was also not limited to vitamin D–deficient populations.

Future Research Needs

Over the past two decades, increased recognition of the possible consequences of low vitamin D levels has resulted in increased vitamin D level screening in routine practice among community-dwelling persons,[60-62] despite no direct evidence of benefits or harms of this practice. Despite increasing standardization of vitamin D assays for measuring serum levels, the precise serum level at which any given individual is deficient may vary, and debate continues on what level should be considered as defining deficiency. Even if it is possible to screen and detect deficiency, it is not clear from the current evidence that a benefit of treatment exists for deficiency as defined by serum levels less than 20 ng/ml or less than 30 ng/ml. Future RCTs that randomize general populations of community-dwelling adults to either vitamin D screening or no screening would be needed to directly determine the benefits and harms of screening for vitamin D deficiency. In the absence of this direct evidence, rigorously designed and adequately powered placebo-controlled trials of treatment specifically in vitamin D–deficient populations would be needed to clarify the impact of vitamin D on some outcomes for which the current evidence is inconclusive (e.g., falls) or insufficient (e.g., infections, physical functioning, other outcomes), to determine optimal doses and regimens for benefits, to clarify potential harms from intermittent high dose regimens, and to further elucidate differential effects among patient subgroups (e.g., sex, race/ethnicity). Despite evidence for clinical equipoise of treatment and placebo for many outcomes, it is not clear whether conducting placebo-controlled trials would be feasible given the already widespread practice of treating low vitamin D levels.

Conclusions

No studies have evaluated the direct benefit or harms of screening for vitamin D deficiency. Among asymptomatic community-dwelling populations with low vitamin D levels, the evidence suggests that treatment with vitamin D (with or without calcium) has no effect on mortality,

fractures, depression, the incidence of diabetes, cardiovascular disease, cancer, or adverse events. The evidence is inconclusive about the impact of treatment on falls, physical functioning, and infection.

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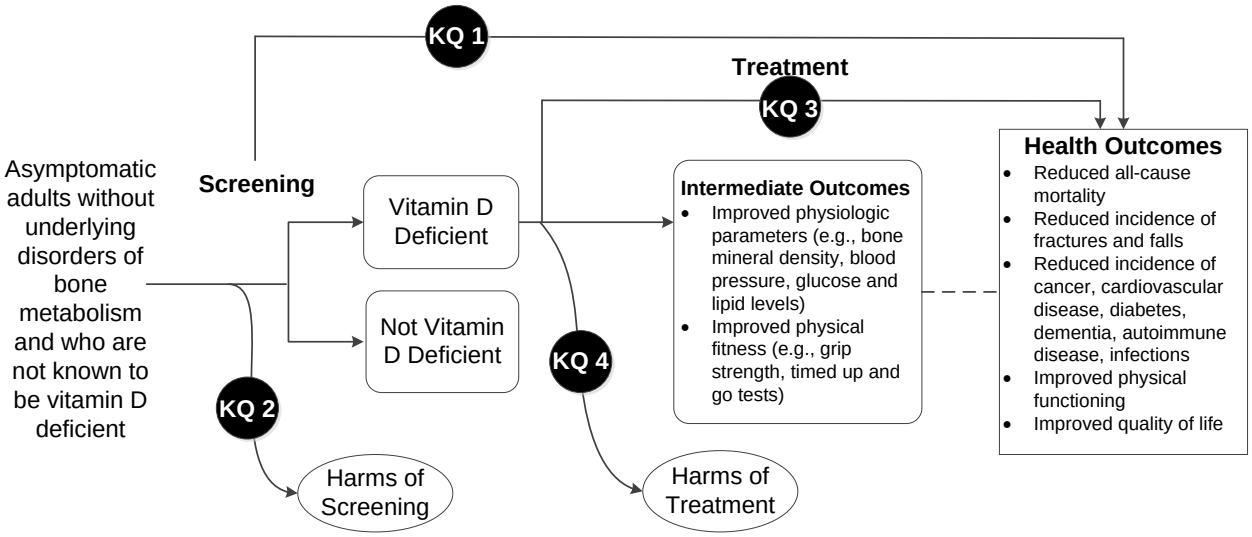
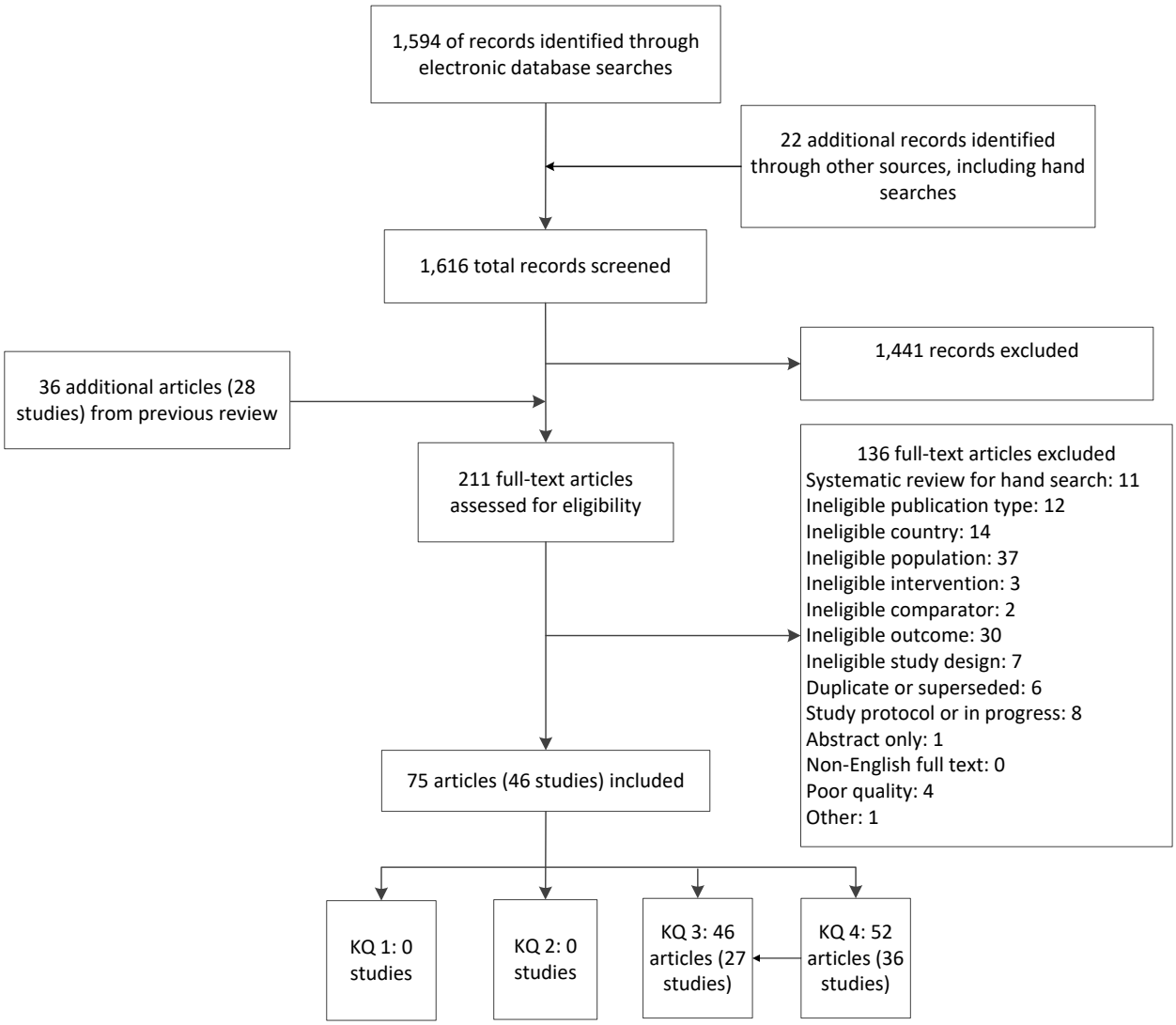
Figure 1. Analytic Framework for Systematic Review of Screening for Vitamin D Deficiency in Adults



Abbreviation: KQ=key question.

Figure 2. Literature Flow Diagram for Systematic Review of Screening for Vitamin D Deficiency in Adults



Abbreviation: KQ=key question.

Figure 3. Effect of Vitamin D Treatment on Mortality Stratified by Setting

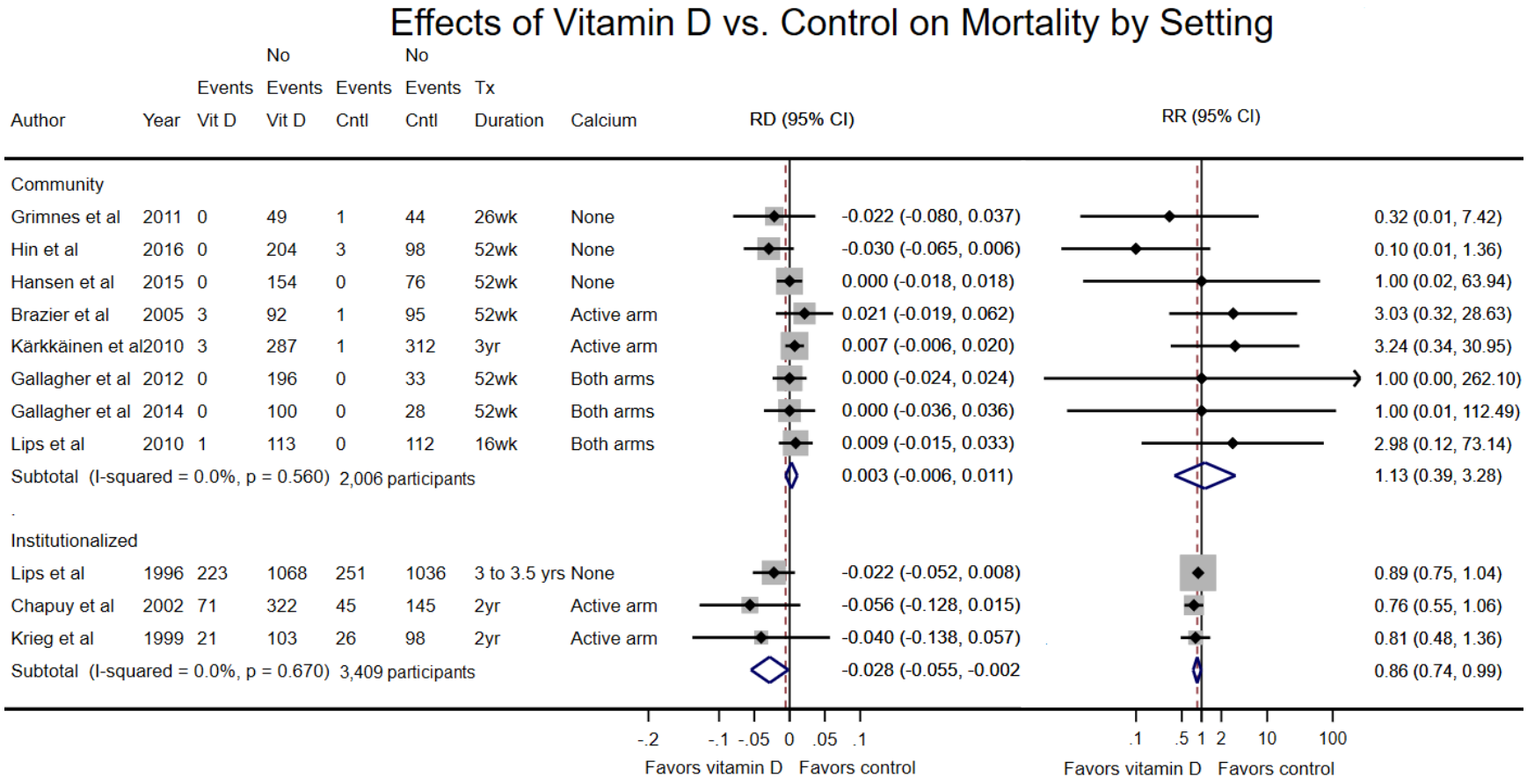


Figure Note: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=week; yr=year.

Figure 4. Effect of Vitamin D Treatment on Incidence of Any Fracture in Community-Dwelling Participants

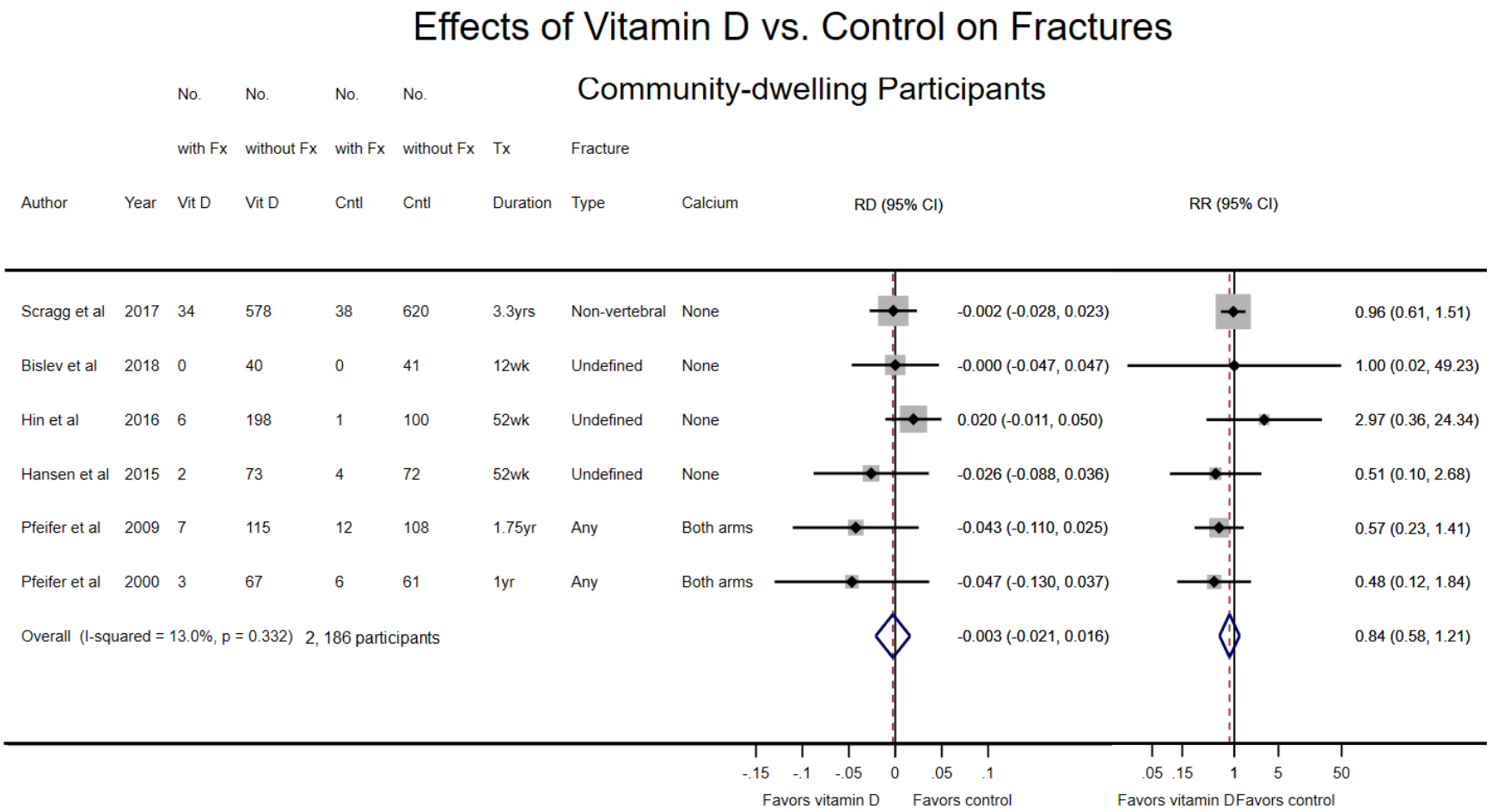


Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points)

Abbreviations: CI=confidence interval; Cntl=control; Fx=fracture, RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit = vitamin; wk=weeks; yr=years.

Figure 5. Effect of Vitamin D Treatment on Incidence of Hip Fractures

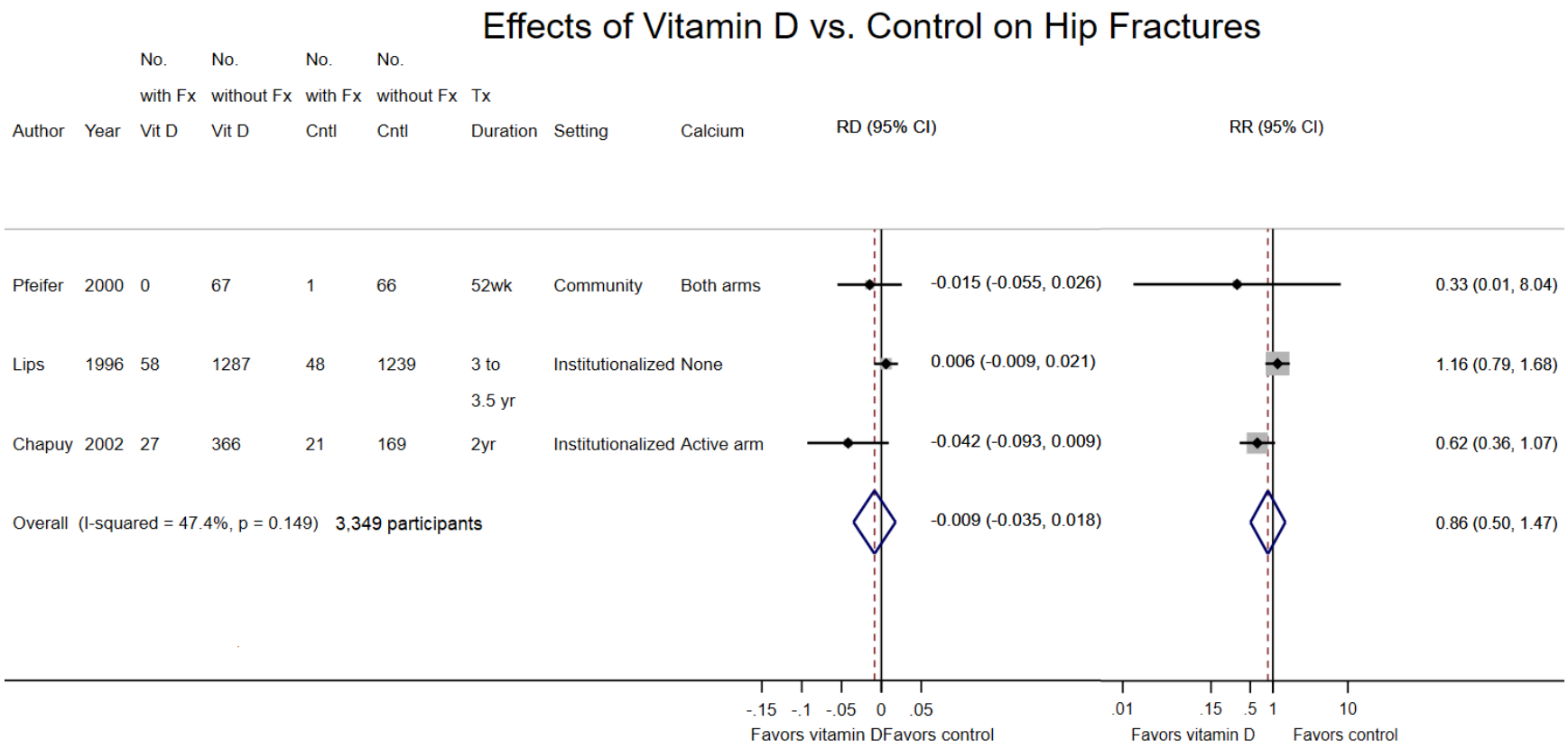


Figure Note: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; Fx=fracture; RD=absolute risk difference; RR=relative risk; Tx=treatment, wk=weeks; yr=years.

Figure 6. Effect of Vitamin D Treatment on Incidence of Falls in Community-Dwelling Participants

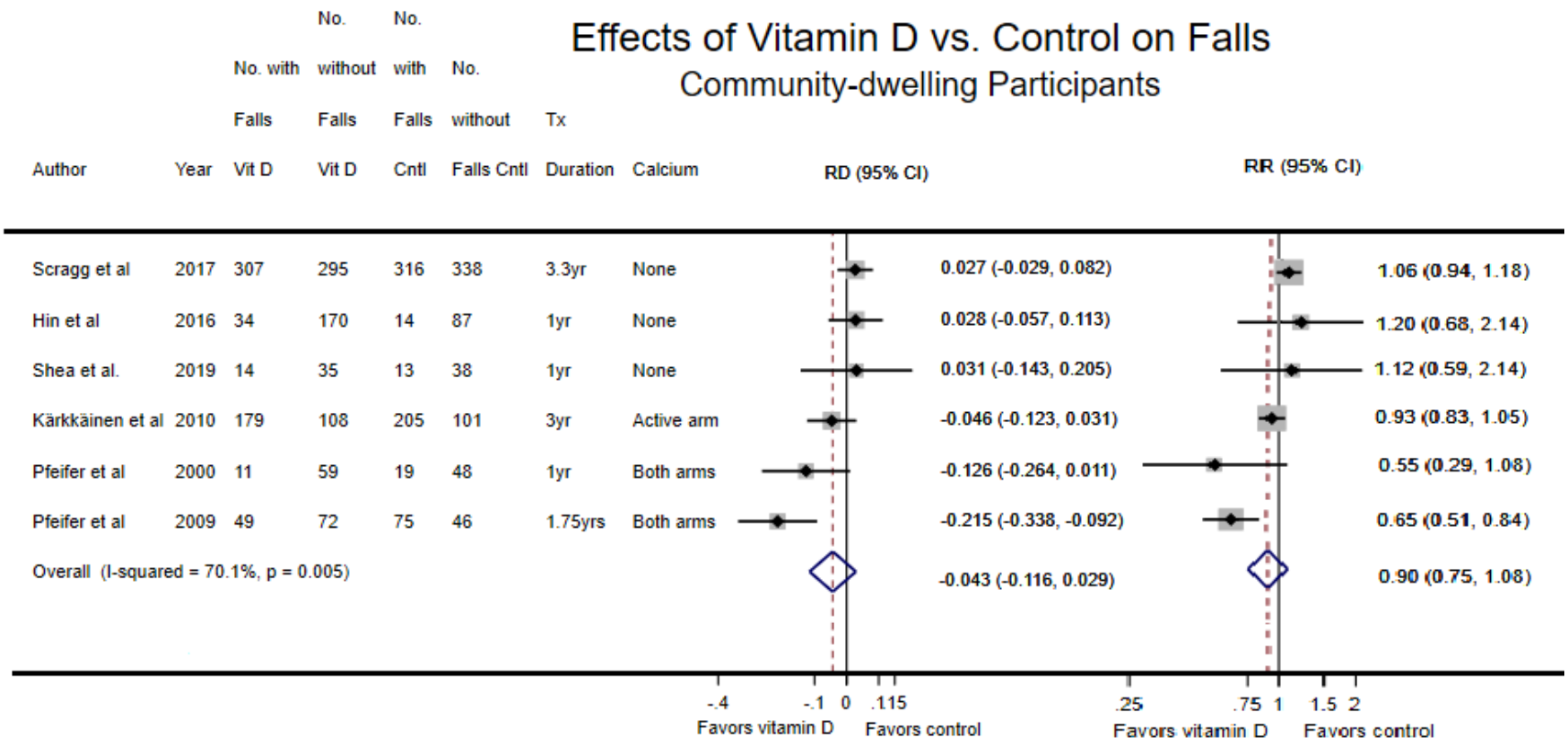


Figure Note: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=weeks; yr=years.

Figure 7. Effect of Vitamin D Treatment on Total Number of Falls in Community-Dwelling Participants

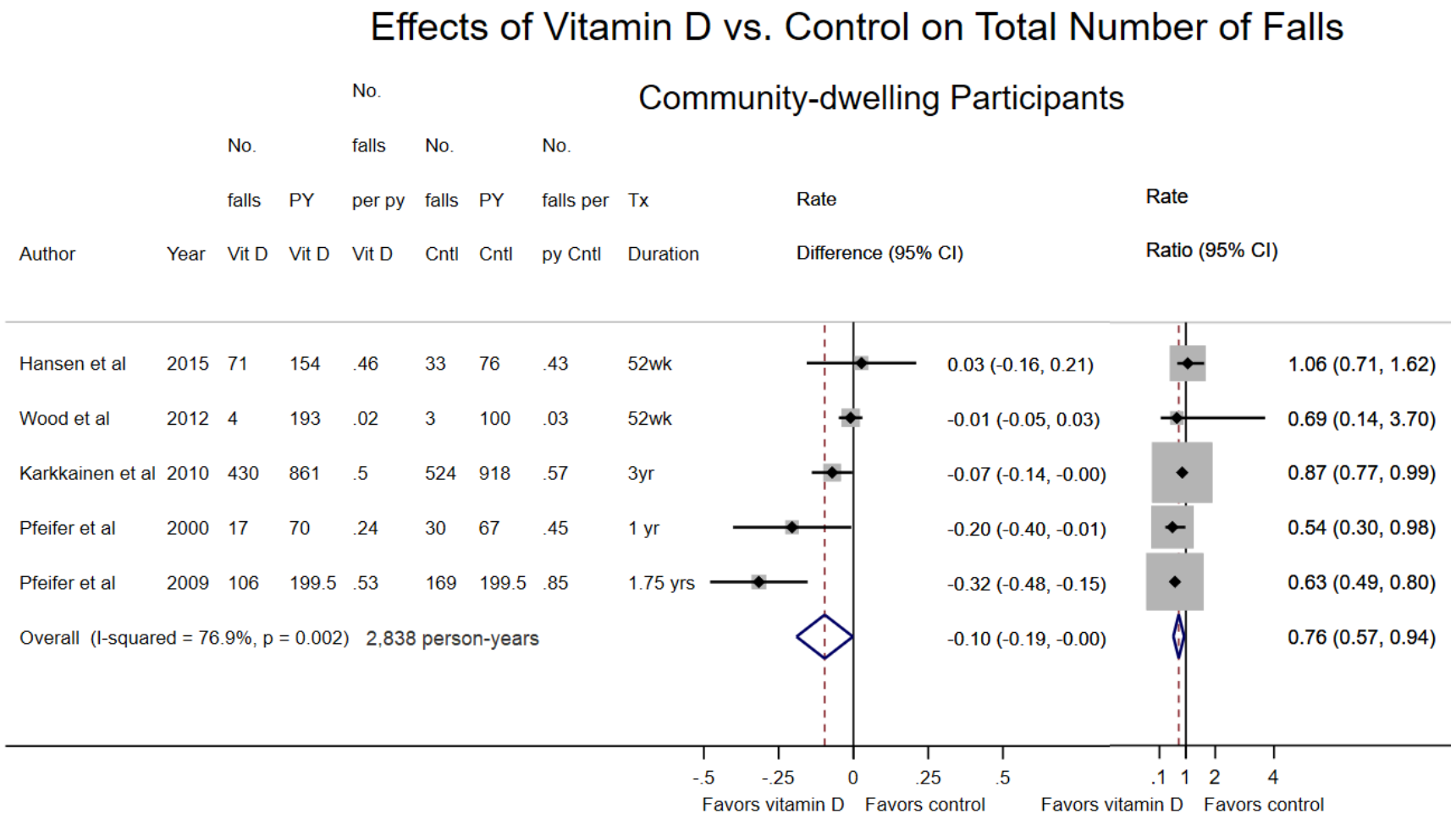


Figure Note: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; PY=person-year; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit= vitamin; wk=weeks; yr=years.

Figure 8. Effect of Vitamin D Treatment on Incidence of Type 2 Diabetes in Community-Dwelling Participants

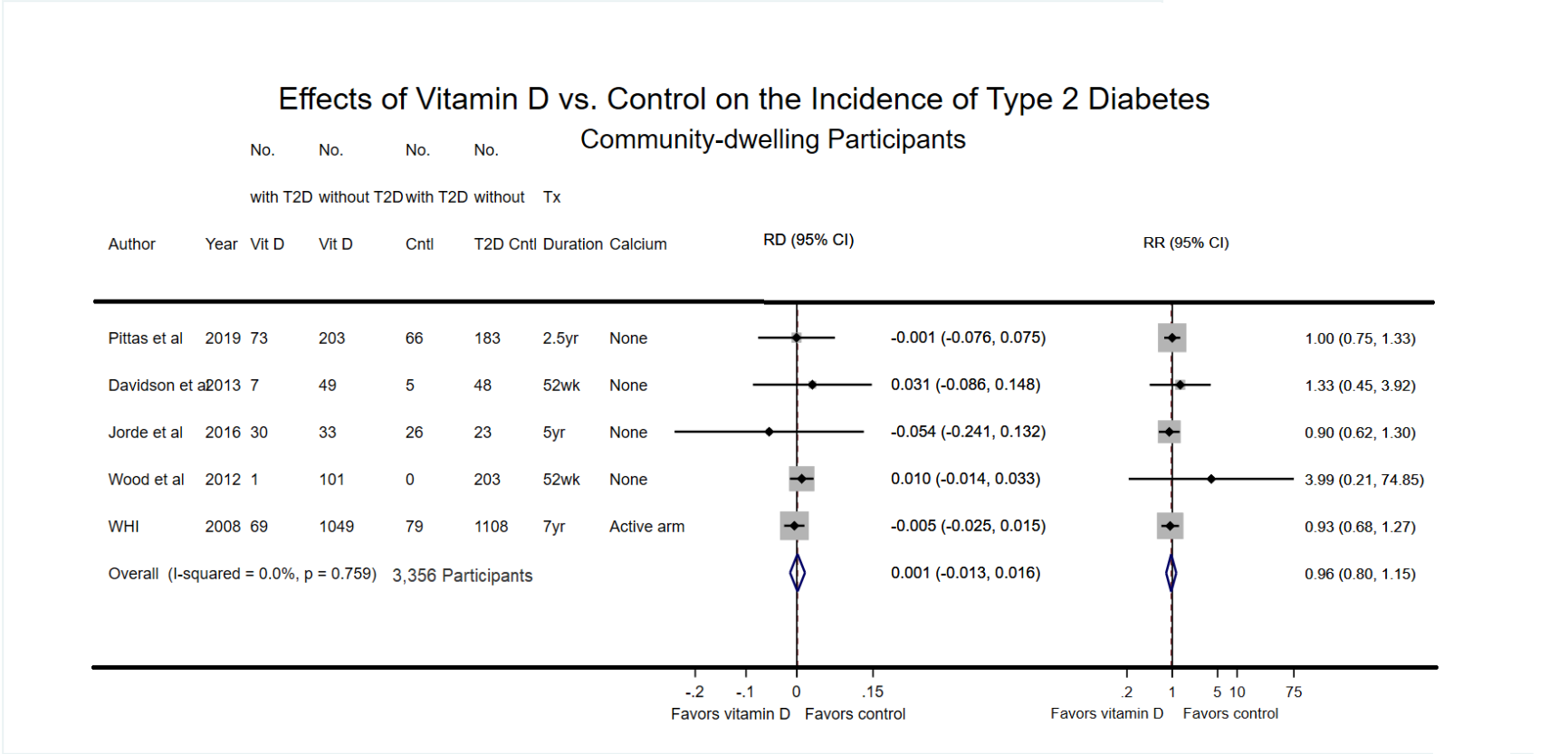


Figure Note: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points). The direction of the risk difference is positive and the direction of the relative risk is negative because of the nature of the continuity correction used in the one study with zero events in the control group.[93] A sensitivity analysis without this study confirmed consistency in the direction of effect suggesting a statistical artifact from the use of a continuity correction.

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; T2D=type 2 diabetes; Tx=treatment; Vit=vitamin; WHI=Women's Health Initiative; wk=weeks; yr=years.

Table 1. Summary of Recommendations for Screening for Vitamin D Deficiency in Adults*

Organization (Year) Title	Recommendations
American Academy of Family Physicians (2014)[131] Clinical preventive service recommendation. Vitamin D deficiency: screening.	There is insufficient evidence to recommend screening the general population for vitamin D deficiency. Treating asymptomatic individuals with identified deficiency has not been shown to improve health. Routine vitamin D supplementation in community-dwelling adults is not recommended.
American Association of Clinical Endocrinologists (2016)[132] Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis	Measure serum 25-hydroxyvitamin D (25[OH]D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis.
American Congress of Obstetricians and Gynecologists (2011)[133] Practice Bulletin No. 129. Osteoporosis	• Recommend testing for vitamin D as part of evaluation of secondary causes of osteoporosis.
American Geriatric Society (2014)[134] American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and Their Consequences	• Statement 1a: Clinicians are strongly advised to recommend vitamin D supplementation of at least 1,000 IU per day, as well as calcium supplementation, to community-dwelling older adults (>65 years of age) to reduce the risk of fractures and falls. • Statement 3: Clinicians should review older adults' vitamin D intake from all sources (diet, supplements, sunlight) and discuss strategies to achieve a total vitamin D input associated with fall and fracture prevention (30 ng/ml). A total daily intake of 4,000 IU across all sources is recommended. • Statement 4a: Routine laboratory testing for 25(OH)D serum concentrations before supplementation begins is not necessary.
American Society for Clinical Pathology (2014)[135] Choosing Wisely campaign	Do not perform population-based screening for vitamin D deficiency.
Endocrine Society (2011)[8] Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline.	• Recommend screening for vitamin D deficiency in individuals at risk for deficiency. Factors increasing risk for vitamin D deficiency include obesity, pregnancy, lactation, darker skin tone, use of sunscreen, use of anticonvulsant medications, glucocorticoids, antifungals, or other medications for AIDS as well as chronic granuloma-forming disorders, some lymphomas, and primary hyperparathyroidism. • Do not recommend population screening for vitamin D deficiency in individuals who are not at risk (strong recommendation, high-quality evidence). • Recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. • Recommend treatment and prevention for patients who are vitamin D deficient using either vitamin D_2 or vitamin D_3: All adults, treatment with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 weeks or its equivalent of 6,000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1,500–2,000 IU/day (weak recommendation, high-quality evidence).

Table 1. Summary of Recommendations for Screening for Vitamin D Deficiency in Adults*

Organization (Year) Title	Recommendations
National Academy of Medicine (formerly Institute of Medicine) (2011)[7] The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know.	No recommendations specific to screening. Recommendations specific to vitamin D intake: 600 IU/day for individuals 1 to 70 years of age 800 IU/day for individuals >70 years of age
National Osteoporosis Foundation (2018)[136] Calcium and Vitamin D	No recommendations specific to screening. Recommendations specific to vitamin D intake: Adults <50 years of age need a total of 400 to 800 IU of vitamin D every day. Adults ≥50 years of age need a total of 800 to 1,000 IU of vitamin D every day.

* We searched for both stand-alone guidelines related to vitamin D screening, but also looked for screening recommendations that may have been embedded in related clinical practice guidelines, such as those related to general bone health or osteoporosis.

Abbreviations: 25OH(D)=vitamin D; IU=international units.

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

Author Year	Country	Study Quality	Interventions (N randomized)	Calcium Use	Treatment Duration	Mean Age (SD)	N (%) Female	Setting	Outcomes Reported
Aloia et al 2005)[104]	United States	Fair	Placebo qd (104) Vitamin D3 800 IU qd, changed to 2000 IU qd at 2 yr (104)	Active and control intervention	3 yr	Placebo: 61.2 (6.3) Vitamin D: 59.9 (6.2)	208 (100)	Community dwelling	• Serious adverse events • Kidney stones
Aloia et al (2018)[108]	United States	Fair	Placebo qd titrated to match Vitamin D group (130) vitamin D_3 titrated to a serum level of 30 ng/m, dosage was adjusted every 3 months, doses provided as a single daily dose (130)	Active and control intervention	3 yr	Median age (IQR): 68.2 (65.4 to 72.5)	258 (100)	Community dwelling	• Total adverse events • Serious adverse events
Arvold et al (2009)[82]	United States	Fair	Placebo weekly (50) Vitamin D_3 50,000 IU weekly (50)	No calcium used	8 wk	Placebo: 57.8 (15.8) Vitamin D: 59.7 (14.0)	Placebo: 15 (36) Vitamin D: 21 (44)	Community dwelling	• Physical functioning • Total adverse events
Bischoff et al (2003)[89]	Switzer-land	Fair	Placebo bid (60) Vitamin D_3 400 IU bid (total daily dose 800 IU) (62)	Active and control intervention	12 wk	Placebo: 85.4 (5.9) Vitamin D: 84.9 (7.7)	122 (100)	Institution-alized	• Falls • Total adverse events • Other harms
Bislev et al (2018)[70]	Denmark	Good	Placebo qd (41) Vitamin D_3 2,800 IU qd (40)	No calcium used	12 wk	NR, all women participating were between 60 and 79 years	81 (100)	Community dwelling	• Fractures • Total adverse events • Serious adverse events
Borgi et al (2016)[109]	United States	Good	Placebo weekly (47) Vitamin D_2 50,000 unit tablets weekly (46)	No calcium used	8 wk	37 (12.3)	Placebo: 31 (66*) Vitamin D: 31 (67*)	Community dwelling	• Total adverse events • Serious adverse events
Brazier et al (2005)[88]	France	Fair	Placebo bid (97) 500 mg calcium carbonate + vitamin D_3 400 IU bid (1,000 mg/800 IU total daily dose) (95)	Active treatment intervention	52 wk	74.6 (6.9)	192 (100)	Community dwelling	• Mortality • Total adverse events • Serious adverse events • Discontinuation
Chapuy et al (2002)[87]	France	Fair	Placebo qd (NR), vitamin D_3 800 IU and 1,200 mg tricalcium phosphate as fixed combination (NR),	Active treatment intervention	2 yr	Placebo: 85.7 (7.6) Vitamin D + calcium (fixed): 84.9 (6.6) Vitamin D +	583 (100)	Institution-alized	• Mortality • Falls • Fractures • Other harms • Kidney stones

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

Author Year	Country	Study Quality	Interventions (N randomized)	Calcium Use	Treatment Duration	Mean Age (SD)	N (%) Female	Setting	Outcomes Reported
			vitamin D_3 800 IU and 1,200 mg tricalcium phosphate as separate combination (NR)			calcium (separate): 84.9 (7.0)			
Davison et al (2013)[75]	United States	Good	Placebo weekly (53); vitamin D_3 weekly, dosing based on body weight and baseline serum vitamin D level to achieve a target serum level of 65 ng/ml to 90 ng/ml.. Average weekly dose 88,865 (16,154) IU (56)	No calcium used	52 wk	Placebo: 52.5 (7.0) Vitamin D: 52.3 (8.0)	Placebo: 38* (71) Vitamin D: 36* (64)	Community dwelling	• Diabetes mellitus
Gagnon et al (2014)[110]	Australia	Fair	Placebo qd (49); 2,000 IU vitamin D_3, dose increased by 2,000 IU every 2 months if serum levels not at target (30 ng/ml) (46)	Active and control intervention	26 wk	Placebo: 55.3 (11.1) Vitamin D: 53.8 (11.9)	Placebo: 30*(67) Vitamin D: 25* (71)	Community dwelling	• Total adverse events • Discontinuation • Kidney stones
Gallagher et al (2012)[49]	United States	Good	Placebo, qd (38); vitamin D_3 400 IU qd (22) vitamin D_3 800 IU qd (45) vitamin D_3 1,600 IU qd (43) vitamin D_3 2,400 IU qd (44), vitamin D_3 3,200 IU qd (23 vitamin D_3 4,000 IU qd (24) vitamin D_3 4,800 IU qd (34)	Active and control intervention	52 wk	White women: 67 (7.3) Black women: 66.6 (7.5)	273 (100)	Community dwelling	• Mortality • Serious adverse events • Kidney stones • Other harms
Gallagher et al (2014)[81]	United States	Fair	Placebo qd (38) Vitamin D_3 400 IU qd (37) Vitamin D_3 800 IU qd (42) Vitamin D_3 1,600 IU qd (41) Vitamin D_3 2,400 mg IU qd (40)	Active and control intervention	52 wk	36.7 (5.9)	198 (100)	Community dwelling	• Mortality • Serious adverse events • Kidney stones
Grimnes et al (2011)[94]	Norway	Fair	Placebo twice per week (53) vitamin D_3 20,000 IU twice per week (weekly dose 40,000 IU) (51)	No calcium used	26 wk	52.1 (9.3)	53 (49.1)	Community dwelling	• Mortality • Total adverse events • Kidney stones
Hansen et al (2015)[69]	United States	Good	Placebo qd (76) Vitamin D_3 800 IU qd (75) Vitamin D_3 50,000 IU twice monthly after an initial loading dose of 50,000 IU qd for 15 d, women with serum levels <30 ng/ml at followup study visits had doses increased and titrated to target (79)	No calcium used	52 wk	61 (6)	230 (100)	Community dwelling	• Mortality • Falls • Fractures • Physical functioning • Kidney stones

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

Author Year	Country	Study Quality	Interventions (N randomized)	Calcium Use	Treatment Duration	Mean Age (SD)	N (%) Female	Setting	Outcomes Reported
Hin et al (2016)[73]	United Kingdom	Good	Placebo qd (101) Vitamin D_3 2,000 IU qd (102) Vitamin D_3 4,000 IU qd (102)	No calcium used	52 wk	Placebo: 72 (6) Vitamin D 2,000 IU: 72 (6) Vitamin D 4,000 IU: 71 (6)	Placebo: 49 (49) Vitamin D 2,000 IU: 51 (50) Vitamin D 4,000 IU: 50 (49)	Community dwelling	• Mortality • Falls • Fractures • Serious adverse events
Honkanen et al (1990)[101]	Finland	Fair	No intervention (63), vitamin D_3 1,800 IU with calcium 1,558 mg qd (63)	Active treatment intervention	11 wk	Mean age (SE) community dwelling Control: 69.6 (0.49) Vitamin D: 69.4 (0.54) Hospital Control: 82.8 (1.3) Vitamin D: 82.2 (1.0)	126 (100)	Mixed	• Kidney stones • Other harms
Janssen et al (2010)[90]	Nether-lands	Fair	Placebo qd (34) Vitamin D_3 400 IU qd (36)	No calcium used	24 wk	Placebo: 79.2 (6.7) Vitamin D: 82.4 (6.4)	70 (100)	Institution-alized	• Mortality • Fractures • Total adverse events • Discontinuation
Jorde et al (2016)[74, 137]	Norway	Fair	Unplanned subgroup analysis of 173 participants Placebo once weekly Vitamin D_3 20,000 IU weekly	No calcium used	5 yr	Placebo†: 61.9 (9.2) Vitamin D†: 62.3 (8.1)	Placebo†: 102 (40.0) Vitamin D: 95 (37.1) †	Community dwelling	• Diabetes mellitus • Infection
Jorde et al (2018)[77]	Norway	Fair	Post hoc outcome analysis Placebo, five-capsule loading dose followed by one capsule each week (202) Loading dose of 100,000 IU vitamin D_3 capsules followed by 20,000 IU each week (206)	No calcium used	16 wk	52.0 (8.8)	191 (46.8)	Community dwelling	• Depression • Serious adverse events
Kärkkäinen et al (2010)[92]	Finland	Fair	No intervention (313) vitamin D_3 400 IU bid (total daily dose 800 IU) with calcium 500 mg bid (total daily dose 1,000 mg) (290)	Active treatment intervention	3 yr	Control: 67.4 (1.9) Vitamin D: 67.4 (2.0)	593 (100)	Community dwelling	• Mortality • Falls • Discontinuation

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

Author Year	Country	Study Quality	Interventions (N randomized)	Calcium Use	Treatment Duration	Mean Age (SD)	N (%) Female	Setting	Outcomes Reported
Kearns et al (2015)[111]	United States	Fair	Five placebo pills by mouth at once (14) Five vitamin D_3 50,000 IU tablets by mouth once for a total single dose of 250,000 IU (14)	No calcium used	One-time dose, 1-yr of followup	Placebo: 26.5 (5.2) Vitamin D: 28.2 (6.7)	Placebo: 10 (71) Vitamin D: 12 (86)	Community dwelling	• Total adverse events
Kjaergaard et al (2012)[80]	Norway	Good	Placebo weekly (121) Vitamin D_3 40,000 IU weekly (122)	No calcium used	12 wk	Placebo: 53.3 (10.1) Vitamin D: 53.4 (10.3)	129 (56)	Community dwelling	• Depression • Total adverse events • Discontinuation
Knutsen et al (2014)[105]	Norway	Fair	Placebo qd (82) Vitamin D_3 400 IU qd (85) Vitamin D_3 1,000 IU qd (84)	No calcium used	16 wk	Placebo: 39 (7.6) Vitamin D 400 IU: 37 (7.6) Vitamin D 1,000 IU: 36 (8.2)	Placebo: 63 (77) Vitamin D 400 IU: 61 (72) Vitamin D 1,000 IU: 58 (69)	Community dwelling	• Total adverse events • Serious adverse events
Krieg et al (1999)[91]	Switzer-land	Fair	No intervention (124) Vitamin D_3 880 IU + 1,000 mg calcium qd (124)	Active treatment intervention	2 yr	Control‡: 85 (7) Vitamin D‡: 84 (8)	248 (100)	Institution-alized	• Mortality • Discontinuation
Lehmann et al (2013)[46]	Germany	Fair	Placebo qd (20) Vitamin D_2 2,000 IU qd (50) Vitamin D_3 2,000 IU qd (49)	No calcium used	8 wk	Placebo: 31.6 (9.3) Vitamin D2: 33.2 (12.4) Vitamin D3: 35.6 (13.5)	68 (63.6)	Community dwelling	• Total adverse events
Lerchbaum et al (2017)[112]	Austria	Fair	50 placebo drops weekly (50) Vitamin D_3 20,000 IU as 50 drops weekly (50)	No calcium used	12 wk	Median age (IQR): 37 (27 to 50)	0 (0)	Community dwelling	• Total adverse events
Lips et al (1996)[86]	Nether-lands	Fair	Placebo qd (1,287) Vitamin D_3 400 IU qd (1,291)	No calcium used	3 to 3.5 yr	80 (6)	1,916 (74)	Mixed§	• Mortality • Fractures
Lips et al (2010)[83]	Multi-country, Canada, Germany, Nether-lands, Mexico,	Fair	Placebo weekly (112) Vitamin D_3 8,400 IU weekly (114)	Active and control intervention	16 wk	Placebo: 77.6 (6.6) Vitamin D: 78.5 (6.2)	NR	Mixed§	• Mortality • Total adverse events • Serious adverse events • Discontinuation • Kidney stones

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

Author Year	Country	Study Quality	Interventions (N randomized)	Calcium Use	Treatment Duration	Mean Age (SD)	N (%) Female	Setting	Outcomes Reported
	United States.								
Manson et al (2019)[71]	United States	Good	Planned subgroup analysis of 2,001 participants Placebo qd Vitamin D_3 2,000 IU qd	No calcium used	NR, but median length of followup was 5.3 yr (IQR, 3.8 to 6.1)	67 (7.1)	13,085 (50.6)	Community dwelling	• Cancer • Cardiovascular
Martineau et al (2007)[106]	United Kingdom	Fair	Placebo (one-time dose) (96) Vitamin D_2 100,000 IU (onetime dose) (96)	No calcium used	NA	Median age (IQR) Placebo: 37.5 (29.8 to 45.2) Vitamin D: 30.1 (25.1 to 44.1)	67 (51.2)	Community dwelling	• Total adverse events
Mason et al (2014)[113]	United States	Fair	Placebo qd (109) Vitamin D_3 2,000 IU qd (109)	No calcium used	52 wk	59.6 (5.1)	218 (100)	Community dwelling	• Total adverse events • Serious adverse events
Moreira-Lucas et al (2017)[114]	Canada	Fair	Placebo cheese weekly (36) Vitamin D_3 28,000 IU in cheese weekly (35)	No calcium used	24 wk	Placebo: 45.6 (14.3) Vitamin D: 49.1 (13.9)	Placebo: 20 (56) Vitamin D: 18 (51)	Community dwelling	• Total adverse events
Ng et al (2014)[115]	United States	Good	Placebo qd (81) Vitamin D_3 1,000 IU qd (81) Vitamin D_3 2,000 IU qd (83) Vitamin D_3 4,000 IU qd (83)	Active and control intervention	12 wk	Median age (IQR): 51.0 (43.6 to 59.4)	222 (67.7)	Community dwelling	• Other harms
Nowak et al (2016)[116]	Switzer-land	Good	Placebo (one-time dose) (63) Vitamin D_3 100,000 IU (one-time dose) (59)	No calcium used	One-time dose (4-wk followup)	Placebo: 28 (6) Vitamin D: 29 (7)	Placebo: 33 (52) Vitamin D: 31 (53)	Community dwelling	• Total adverse events
Pfeifer et al (2000)[85]	Germany	Fair	Calcium bid (74) Vitamin D_3 400 IU bid (total daily dose 800 IU) (74)	Active and control intervention	8 wk	Calcium: 74.7 (0.5) Vitamin D: 74.8 (0.5)	148 (100)	Community dwelling	• Falls • Fractures
Pfeifer et al (2009)[84]	Multi-country, Austria, Germany.	Fair	Calcium bid (121) Vitamin D_3 400 IU bid (total daily dose 800 IU) (121)	Active and control intervention	1 yr	Calcium: 77 (4) Vitamin D: 76 (4)	Calcium: 91* (75) Vitamin D: 90* (74)	Community dwelling	• Falls • Fractures
Pilz et al (2015)[117]	Austria	Fair	Placebo qd (100) Vitamin D_3 2,800 IU qd (100)	No calcium used	8 wk	60.0 (11.1)	94* (47)	Community dwelling	• Serious adverse events
Pittas et al (2019)[76]	United States	Fair	Planned subgroup analysis of 525 participants	No calcium used	2.5 yr	60.0 (9.9)†	1,086 (44.8) †	Community dwelling	• Diabetes mellitus

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

Author Year	Country	Study Quality	Interventions (N randomized)	Calcium Use	Treatment Duration	Mean Age (SD)	N (%) Female	Setting	Outcomes Reported
			Placebo qd) Vitamin D_3 4,000 IU qd						
Raed et al (2017)[118]	United States	Fair	Placebo monthly (17) Vitamin D_3 18,000 IU monthly (equivalent to 600 IU qd) (17) Vitamin D_3 60,000 IU monthly (equivalent to 2,000 IU qd) (18) Vitamin D_3 120,000 IU monthly (equivalent to 4000 IU qd) (18)	No calcium used	16 wk	Placebo: 27.8 (9.9) Vitamin D 18,000 IU: 26.2 (9.8) Vitamin D 60,000 IU: 24.4 (8.7) Vitamin D 120,000 IU: 25.5 (9.0)	Placebo: 13 (76) Vitamin D 18,000 IU: 15 (88) Vitamin D 60,000 IU: 15 (83) Vitamin D 120,000 IU: 16 (89)	Community dwelling	• Total adverse events
Scragg et al (2017)[97] Khaw et al (2017)[72]	New Zealand	Good	Planned subgroup analysis of 1,270 participants Placebo monthly Vitamin D_3 200,000 IU initial dose followed by monthly doses of 100,000 IU	No calcium used	3.3 yr	65.9 (8.3) †	2,139 (41.9)†	Community dwelling	• Falls • Fractures • Cardiovascular • Cancer
Shea et al. (2019)[78]	United States	Good	Placebo bid (51) Vitamin D_3 858 IU daily (49)	No calcium used	52 wk	Mean age (SD): 69.6 (6.9)	36 (36*)	Community dwelling	• Falls
Tran et al (2014)[119]	Australia	Good	Placebo monthly (214) Vitamin D_3 30,000 IU monthly (215) Vitamin D_3 60,000n IU monthly (215)	Active and control intervention	48 wk	72 (NR)	288* (47)	Community dwelling	• Total adverse events • Serious adverse events
Wamberg et al (2013)[107]	Denmark	Fair	Placebo qd (26) Vitamin D_3 7,000 IU qd (26)	No calcium used	26 wk	Placebo: 41.2 (6.8) Vitamin D: 39.5 (8.0)	39 (71)	Community dwelling	• Total adverse events
Witham et al (2013)[102]	United Kingdom	Fair	Placebo once (25) Vitamin D_3 100,000 IU once (25)	No calcium used	One-time dose (8-wk followup)	Placebo: 39.4 (11.8) Vitamin D: 41.7 (13.4)	50 (100)	Community dwelling	• Total adverse events • Serious adverse events • Kidney stones
Wood et al (2012)[93]	United Kingdom	Fair	Placebo qd (102) Vitamin D_3 400 IU qd (102) Vitamin D_3 1,000 IU qd (101)	No calcium used	52 wk	Placebo: 63.9 (2.3) Vitamin D 400 IU: 63.5 (1.9) Vitamin D 1,000 IU: 64.1 (2.3)	305 (100)	Community dwelling	• Falls • Diabetes mellitus • Total adverse events • Serious adverse events

* Represents a calculated value.

Table 2. Summary of Study Characteristics of Randomized, Controlled Trials Reporting Benefits and Harms of Treatment (KQ 3 and KQ 4)

† Represents characteristic for the entire study population, not the subgroup that was vitamin D deficient.
ǂ Of those who completed the study.
§ Lips et al (1996)[86] included a majority of participants from institutionalized settings; thus, this study was considered an institutionalized setting in all stratified analyses. Lips et al (2010)[83] included a majority of participants from community-dwelling participants; thus, this study was considered community dwelling in all stratified analyses.

Abbreviations: bid=twice daily; IU=international unit; IQR= interquartile range; N=number of participants; NA=not applicable; NR=not reported; qd=every day; SD=standard deviation.

Table 3. Summary of Evidence

Key Question	No. of Studies Study Designs No. of Participants	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 3 Mortality	8 RCTs[49, 69, 73, 81, 83, 88, 92, 94] 2,006 participants 1 nested CC[79] 2,285 participants	Among community-dwelling populations, pooled ARD from RCTs 0.3% (95% CI, -0.6% to 1.1%; I^2=0%). Nested CC consistent with findings from RCTs.	Consistent, precise*	Five of the RCTs were fair quality, mortality was not a primary outcome in any study, ascertainment of mortality was heterogenous across studies, followup was of short duration in some studies (particularly considering populations were relatively healthy at the start of study), and mortality events were rare in most studies.	Moderate for no benefit	Studies included community-dwelling males and females, applicable to various doses of vitamin D with or without calcium.
KQ 3 Any Fractures	6 RCTs[69, 70, 72, 73, 84-87] 2,186 participants 1 nested CC[79] 2,982 participants	Among community-dwelling populations: Pooled ARD from RCTs -0.3% (95% CI, -2.1% to 1.6%; I^2=13.0%). Nested CC consistent with findings from the RCTs.	Consistent, precise†	Five of the RCTs were fair quality; type of fracture and methods of ascertainment heterogenous across studies and, in some cases, based on self-report without verification.	Moderate for no benefit	Community-dwelling populations, all but two studies were conducted among female and male populations, applicable to various doses of vitamin D with or without calcium.
KQ 3 Hip Fractures	4 RCTs[85-87, 90] 3,349 participants 1 nested CC[79] 714 participants	Pooled ARD from 3 RCTs -0.86% (95% CI, -3.5% to 1.8%; I^2=47.4%). Nested CC consistent with findings from the RCTs.	Consistent, imprecise‡	All studies were fair quality, outcome ascertainment methods variable across studies.	Low for no benefit	Two of the studies were conducted in institutionalized populations; two of the studies were conducted exclusively in women; mean age 75-85 in the studies. Applicable to various doses of vitamin D with or without calcium.

Table 3. Summary of Evidence

Key Question	No. of Studies Study Designs No. of Participants	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 3 Falls	Incidence of one or more falls: 6 RCTs[72, 73, 78, 84, 85, 92] 2,633 participants Total number of falls: 5 RCTs[69, 84, 85, 92, 93] 2,838 person-years	Among community-dwelling populations: Incidence of one or more falls: Pooled ARD -4.3% (95% CI, -11.6% to 2.9%; I^2=70.1%). Total number of falls: Pooled IRD -0.10 falls per person-year (95% CI, -0.19 to -0.002; I^2=76.9%).	Inconsistent,[§] imprecise[‖]	Most studies were fair quality, outcome ascertainment methods were variable across studies, potential for selective outcome reporting (total falls vs. incidence of one or more falls).	Insufficient	Community-dwelling populations; studies were predominantly in females but some included males; applicable to various doses of vitamin D with or without calcium.
KQ 3 Diabetes	5 RCTs[74-76, 79, 93, 96] 3,356 participants	Pooled ARD 0.1% (95% CI, -1.3% to 1.6%; I^2=0%).	Consistent, precise[¶]	1 good quality and 4 fair quality (2 were planned subgroup analyses and 1 was unplanned), diabetes captured as an adverse event in one study (criteria and methods of ascertainment NR).	Moderate for no benefit	Four studies included males and females and all were community-dwelling, three studies included participants with prediabetes, impaired fasting glucose, or intolerance. Applicable to various doses of vitamin D with or without calcium.
KQ 3 Cardiovascular	2 RCTs[71, 72, 97] 3,271 subgroup participants	No difference in cardiovascular events between treatment and control groups were observed in either trial over a 3- to 5-year followup (VITAL RR 1.09 [95% CI, 0.68 to 1.76], ViDA (NZ) 1.00 [95% CI, 0.74 to 1.35]).	Consistent, imprecise[#]	Findings from both good-quality RCTs were from planned subgroup analyses, a broad definition of CVD events was used by one of the trials.	Moderate for no benefit	Both RCTs included males and females, all were community-dwelling populations, uncertain applicability to participants with preexisting cardiovascular disease, applicable to use of vitamin D without calcium.

Table 3. Summary of Evidence

Key Question	No. of Studies Study Designs No. of Participants	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 3 Cancer	2 RCTs[71, 98] 3,271 subgroup participants 1 nested CC[79, 99, 100] 1,201 participants	No difference in incident cancer (HR 0.97 and 1.01 in the 2 RCTs), no significant association between active treatment exposure and incident breast or colorectal cancer in CC study.	Consistent, imprecise**	Findings from both good-quality RCT were from planned subgroup analysis, nested CC study was fair quality.	Moderate for no benefit	The RCTs included both males and females, the nested CC only included females, applicable to participants without a prior history of cancer, applicable to use of vitamin D with or without calcium.
KQ 3 Depression	2 RCTs[77, 80] 665 participants	No difference between active treatment and control groups on validated measures of depression in either study.	Consistent, imprecise††	1 good-quality RCT and 1 fair quality RCT, duration of intervention was 12 weeks, with measurement at 26 weeks in one study and only 16 weeks in the other study, unclear whether study enrolled participants with prevalent depression.	Low for no benefit	Both RCTs included males and females, findings not applicable to patients with serious depression, applicable to use of vitamin D without calcium.
KQ 3 Physical Functioning	2 RCTs[69, 82] 320 participants	1 trial showed small, but statistically significant improvement on the fibromyalgia impact questionnaire at 8 weeks for active treatment group compared with control, the other trial showed no difference in change on the modified Stanford Health Assessment Questionnaire after 1 year.	Inconsistent, imprecise††	1 good-quality RCT, the fair quality RCT had differential attrition and unclear randomization and allocation concealment methods and was only conducted over 8 weeks, different measures used by the two trials.	Insufficient	1 of the trials included both males and females, the other trial only included females, both studies conducted at single centers, applicable to use of vitamin D without calcium.

Table 3. Summary of Evidence

Key Question	No. of Studies Study Designs No. of Participants	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 3 Infection	1 RCT[74, 137] 173 subgroup participants	Lower incidence of urinary tract infection over 5 years for active treatment compared with control group (HR 0.53 (95% CI, 0.17 to 1.64).	Consistency cannot be evaluated (single study body of evidence) Imprecise††	Unplanned subgroup analysis from a fair-quality RCT with possible selective outcome reporting.	Insufficient	Study included both men and women, all had prediabetes.
KQ 4 Total Adverse Events	25 RCTs 3,938 participants	Incidence was similar between active treatment and control groups.	Consistent, imprecise††	5 good-quality studies, the rest were fair-quality. Methods of ascertainment varied greatly among studies likely leading to widely differing estimates of incidence.	Low for no harm	Studies included males and females, most of the evidence was from community-dwelling populations, applies to various doses of vitamin D with or without calcium.
KQ 4 Serious Adverse Events	16 RCTs 3,636 participants	Incidence was similar between active treatment and control groups.	Consistent, imprecise††	5 good-quality studies, the rest were fair-quality. Definitions of serious adverse events and methods of ascertainment varied greatly among studies likely leading to widely differing estimates of incidence.	Low for no harm	Studies included males and females, most of the evidence was from community-dwelling populations, applies to various doses of vitamin D with or without calcium.
KQ 4 Discontinuations due to Adverse Events	7 RCTs 1,677 participants	Incidence reported and was similar between active treatment and control groups.	Consistent, imprecise††	1 good-quality study, the rest were fair-quality. Methods of ascertaining adverse events varied greatly among studies likely leading to widely differing estimates of discontinuations.	Low for no harm	All but 3 studies conducted exclusively in females, most of the evidence was from community-dwelling populations, applies to vitamin D with or without calcium.
KQ 4 Kidney Stones	10 RCTs 2,120 participants	Only 1 event reported in the low-dose vitamin D group in 1 study.	Consistent, imprecise††	2 good-quality studies, the rest were fair quality. Most studies did not report how this outcome was ascertained.	Low for no harm	Most of the evidence was from female community-dwelling populations, applies to various doses of vitamin D with or without calcium.

Table 3. Summary of Evidence

Key Question	No. of Studies Study Designs No. of Participants	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ 4 Other Harms	5 RCTs 1,459 participants	No difference between active treatment and control groups for various other specific harms reported (e.g., specific GI side effects).	Consistent, imprecise††	2 good-quality studies, the rest were fair quality. Most studies did not report how these outcomes were ascertained, potential for selective outcome reporting (nonstandardized selection of outcomes and various approaches to reporting used).	Low for no harm	All but 1 study was conducted exclusively in females, applies to both community-dwelling and institutionalized populations, applies to various doses of vitamin D with or without calcium.

* Although this estimate could be considered imprecise based on strict interpretation of optimal information size criteria, the event rates were very low, resulting in excessively wide CIs around the relative effect measure, which was 1.13 (95% CI, 0.39 to 3.28). Because of this, we prioritized evaluation of the ARD and determined that the CI was precise enough to exclude a clinically meaningful benefit or harm. This approach is consistent with current GRADE recommendations for assessing precision.[138]

† The pooled RR was 0.84 (9% CI, 0.58 to 1.21); although this estimate could be considered imprecise based on strict interpretation of optimal information size criteria, we prioritized evaluation of the ARD and determined that the confidence interval was precise enough to exclude a clinically meaningful absolute benefit or harm. This approach is consistent with current GRADE recommendations for assessing precision.[138]

‡ The pooled RR was 0.86 (95% CI, 0.50 to 1.47). Required sample size would be 13,658 assuming 5% control group risk, 80% power, alpha=0.05 for detecting effect size of RR 0.8.

§ Findings are inconsistent between outcomes (incidence of one or more falls vs. total falls). For incidence of falls, two studies among community-dwelling populations both conducted by the same author showed a larger beneficial effect compared with the other three studies that had findings close to and on both sides of the null effect. For total falls, a small, statistically significant benefit of treatment was observed among community-dwelling populations.

‖ Required sample size 834 for RR 0.8, control risk 50%, so OIS criteria are met, but CI does not exclude the null and the 95% CI cannot rule out a clinically meaningful effect.

¶ Required sample size 2,944 for RR 0.8, control risk 20%, so OIS criteria are met. Pooled RR 0.96 (95% CI, 0.80 to 1.15); however, CIs around ARD exclude a clinically meaningful effect.

Required sample size 9,920, 7% control risk, 0.8 RR, alpha= 0.05. Data to calculate ARD not provided; cannot exclude a clinically meaningful treatment effect based on the RR alone.

** Required sample size 11,476, 6% control risk, 0.8 RR, alpha= 0.05 in order to meet OIS criteria. Data not provided in order to calculate ARDs.

†† OIS criteria will vary depending on outcome used but sample size combined with rare events means that OIS criteria are unlikely to be met.

Abbreviations: ARD=absolute risk difference; CC=case-control; CI=confidence interval; CVD=cardiovascular disease; GI=gastrointestinal; HR=hazard ratio; IRD=incidence rate difference; IRR=incidence rate ratio; KQ=key question; No.=number; NR=not reported; OIS=optimal information size; RCT=randomized, controlled trials; RR=relative risk; SAE=serious adverse event; ViDA (NZ)=Vitamin D Assessment Study; VITAL= VITamin D and OmegA-3 TriaL.

Contextual Questions (CQs) 1, 2, and 3 were designed to provide the USPSTF with additional information about vitamin D assays and the relationship between vitamin D deficiency and selected outcomes. CQ 1 was designed to provide the USPSTF with the historical context surrounding vitamin D assays. CQ 2 was designed to provide the USPSTF information about the association between vitamin D and health outcomes from observational studies, building on a previous 2014 AHRQ Effective Health Care (EHC) review.[21] Finally, CQ 3 was designed to provide the USPSTF with information about the effect of vitamin D treatment on selected intermediate outcomes, again building on the previous 2014 AHRQ EHC review.

CQ 1. What Are the Various Assays for Measuring Serum Vitamin D, Including Total 25(OH)D, Free 25(OH)D, and 1,25 (OH)2D, and What Is Known About Intermethod and Interlaboratory Variability of the Various Assays?

Key Points:

- Historically, it has been difficult to measure 25(OH)D accurately, which has resulted in assay variability and bias with likely misclassification of vitamin D status, especially for levels close to a threshold, in both research studies and clinical practice.
- LC-MS/MS is considered the gold-standard assay. But it is complex to perform and can still be subject to variation and error.
- Since the establishment of the VDSP in 2010, great strides have been made toward standardizing vitamin D assays. However, there are limited data on how quickly this standardization is being adopted by small and large commercial laboratories and as part of previous and ongoing research studies.
- Although several vitamin D metabolites are under active investigation as markers of vitamin D status, their association with clinical outcomes is much less studied than 25(OH)D, and the research suffers from the same assay standardization issues that have plagued 25(OH)D research until the recent development of the VDSP standardization program.

Assays for Measuring Total 25 Hydroxyvitamin D (25(OH)D)

25(OH)D is currently considered the best marker of vitamin D status.[33] 25(OH)D is defined as the sum of 25 $(OH)_2$ and $25(OH)_3$. Total 25(OH)D is measured by both binding and chemical assays. Binding assays include competitive protein binding assays, radioimmunoassays, and chemiluminescence immunoassays. Automated immunoassays are popular in clinical laboratories because they are available in kit form and can be automated to process hundreds of samples per hour.[139] Chemical assays include HPLC (LC with UV detection), LC-MS, and LC-MS/MS. Traditionally, chemical assays have been more technically involved requiring more expertise. Although traditionally a much smaller number of samples could be run at a time using chemical assays, advancing technology is allowing an increasing number of samples to be processed per day with these types of assays.[139]

Serum total 25(OH)D is difficult to measure accurately because of several issues.[33] First, total 25(OH)D assays need to recognize both $25(OH)_2$ and $25(OH)_3$. In immunoassays, the antibodies used to measure 25(OH)D can have a low affinity for $25(OH)_2$, leading to low estimates of total 25(OH)D. Conversely, some 25(OH)D assays measure vitamin D metabolites, leading to an overestimation of 25(OH)D. For example, some immunoassays cross-react with $24,25(OH)_2D$, which can account for up to 20% of the measured total vitamin D. 25(OH)D is also a very hydrophobic molecule that circulates bound to vitamin D binding protein (DBP), albumin, and lipoproteins; it is therefore mandatory that 25(OH)D is completely dissociated from its carriers prior to measurement. The dissociation step is complicated because $25(OH)_2$ and $25(OH)_3$ have different affinities for the carriers. Also, immunoassays use different sample preparations, resulting in variable release of DBP and other binding proteins from 25(OH)D, leading to discrepant results, especially in those with high or low DBP concentrations.[33] All of these issues can lead to misclassification of vitamin D status, especially if levels are close to the thresholds for defining vitamin D status.

LC methods offer the advantage of being able to individually quantify 25(OH)2 and 25(OH)3 and remove interfering substances.[140] Adding MS and particularly, tandem mass spectrometry (MS/MS) can account for protein binding and provide structure-specific information on the molecules. As a result, LC-MS/MS is considered the gold-standard assay. Despite its benefits, LC-MS/MS is still subject to variation and error, including interference from other chemical compounds (such as the 3-epimers of 25(OH)D).[33] In addition, performing LC-MS/MS is complex, requiring extensive experience and training and extensive validation of both the LC-MS/MS and sample preparation methods.

Reliability of Measurement

Given these assay issues, the Vitamin D External Quality Assessment Scheme (DEQAS) was established in 1989 with the objective of ensuring the reliability of measurements of serum total 25(OH)D. DEQAS distributes human serum samples for analysis of 25(OH)D to participating laboratories in multiple countries. As of January 2017, DEQAS was distributing five human serum samples quarterly to approximately 1,000 laboratories in 56 countries that were using 30 different assay methods. The participating laboratories receive summary reports about their laboratory's results (both overall and by individual method used). Until late 2012, these reports compared each laboratory's result to a consensus value based on the all-laboratory trimmed mean (ALTM) of the results of the participating laboratories. However, use of the ALTM rather than a "true" value limited the ability of the DEQAS program to evaluate the true performance of laboratory assays because the results were influenced by the dominance of the most popular assays, the changing mix of assays, and biases of the assays.

In 2010, the U.S. National Institutes of Health (NIH) Office of Dietary Supplements (ODS) initiated the VDSP in collaboration with CDC, the U.S. National Institute of Standards and Technology (NIST), Ghent University (Belgium), national nutrition survey laboratories in eight countries, and vitamin D researchers worldwide.[141, 142] The primary goal of the VDSP has been to promote the standardized measurement of 25(OH)D to enhance patient care and facilitate the research study of vitamin D. A key part of the VDSP has been the establishment of a reference measurement system, including reference measurement procedures developed by multiple collaborators including NIST, Ghent University, and CDC. These reference measurement

systems were developed to provide a true value of 25(OH)D that could be used as the gold standard for comparison to vitamin D results obtained from routine assays in research and clinical care. The NIST reference measurement procedures are based on isotope dilution LC-MS/MS, which is considered the most accurate and precise method to determine $25(OH)_2$ and $25(OH)_3$.[143]

VDSP and its collaborators (CDC, NIST) have developed cost-effective tools and methods to standardize 25(OH)D measurement prospectively in current and future vitamin D research as well as retrospectively from past studies with banked samples.[144] The development of the VDSP and reference measurement procedures have therefore allowed the first unbiased evaluation of 25(OH) assay variation.[33] As part of the VDSP, all DEQAS samples have been analyzed (since late fall 2012) using the NIST reference measurement procedures in addition to the consensus value based on ALTM. When the results of using the NIST-assigned target were compared with the ALTM, there was evidence that significant bias occurred when the ALTM value was used as the reference point. There was a great deal of sample-to-sample variation within laboratories using the same assay and also between different assay platforms.[33] For example, in a recent study coordinated by the VDSP group,[145] a set of 50 samples from healthy individuals was analyzed by 16 different laboratories to provide results for total 25(OH)D using both immunoassays and LC-MS/MS methods. The results were compared with those obtained by two reference methods: NIST and a similar reference method from the Ghent University.[146] Results showed that only 50 percent of immunoassays achieved the VDSP criteria of performance (namely coefficient of variation ≤10% and mean bias ≤5%); however, 80 percent of LC-MS/MS assays met the VDSP criteria.[145] Results would likely have been even worse if samples from patients with chronic kidney disease or other health conditions, pregnant women, or different ethnic groups were used.[147]

Researchers have been retrospectively rerunning previously banked samples using the standardized methods developed as part of the VDSP and comparing updated results with previously reported data measured using unstandardized methods. Standardization of these databases have resulted in both upward and downward reporting of 25(OH)D levels,[33, 148, 149] indicating that standardization may lead to an increase or decrease in observed 25(OH)D levels depending on the original assay that was used. In NHANES data, standardization of serum total 25(OH)D values has led to a narrower range of 25(OH)D values,[150] resulting in a dramatic difference in the prevalence of low vitamin D status in samples analyzed by unstandardized and standardized methods.[149] For example, although NHANES originally reported that 25(OH)D levels in the U.S. population had declined, after rerunning the samples using standardized methods, there was no change in vitamin D levels between 1988 and 2006.[11] In another reanalysis of NHANES data, a previously noted reverse J-shaped association between 25(OH)D concentration and risk of death was no longer present; using standardized procedures to measure vitamin D status, only 25(OH)D concentrations <16 ng/ml were associated with an increased risk of death.[150]

CDC, in collaboration with the VDSP, has also developed the Vitamin D Standardization-Certification Program (VDSCP), a program to standardize commercial assay systems and large commercial or research laboratories. The certification program is conducted over a 1-year period and requires laboratories to develop a reference system, establish metrological traceability, and verify "end user" test performance.[139] When participants pass four consecutive surveys, they are

awarded certification for 1 year. Renewal is annual, which means that maintenance of certification requires continuous participation in the program. Laboratories that are certified by this program are listed on the CDC website. As of November 2019, 19 certificates had been issued in the previous 12 months (26% to research laboratories, 32% to clinical laboratories, and 42% to assay/kit manufacturers) and 57 in the previous 36 months (27% research, 20% clinical, and 53% assay/kit manufacturers).[151]

Other Measurements of Vitamin D Status

Other vitamin D metabolites are under active investigation to determine if they can help inform a person's vitamin D status. Potential markers include free 25(OH)D, DBP, 1-alpha $25(OH)_2D$, 24, $25(OH)_2D_3$, and PTH. There are no standardization programs for these metabolites, so research of these metabolites is at risk of bias from assay variation, similar to research using unstandardized 25(OH)D assays.[33] Each metabolite is described briefly below.

Free 25(OH)D. It is hypothesized that the unbound fraction (<1%) of vitamin D, free 25(OH)D, drives many of vitamin D's effects. Free 25(OH)D can be measured directly or can be calculated. There is no certified reference material for directly measuring free 25(OH)D, and development of a certified reference material for directly measuring free 25(OH)D will be very difficult because the concentration of free 25(OH)D is at the limit of current LC-MS/MS technology.[33]

DBP. Because vitamin D is transported primarily by DBP and albumin, it can also be calculated using total 25(OH)D, DBP, and albumin levels. However, DBP and albumin concentrations vary in different clinical conditions and according to the assay used. For example, persons with particular DBP genotypes have lower measured concentrations of DBP when measured by monoclonal assays compared with LC-MS/MS or polyclonal assays.[152] This assay variation likely explains the varying findings regarding levels of DBP in black versus white patients.[153] NIST has recently developed an assay for DBP that may eventually lead to the development of reference measurement procedures and eventual standardization of DBP. Such standardization could lead to improvements in calculation of "free" 25(OH)D.

1-alpha $25(OH)_2D$. This compound is the active, hormone form of vitamin D. It has a relatively short half-life and is tightly controlled by PTH, calcium, and phosphate, so is not considered a useful measurement of vitamin D status. It should only be measured in association with other vitamin D metabolites. DEQAS does run a program for 1-alpha $25(OH)_2D$, but there are no reference measurement procedures, limiting the ability of this program to lead to improved 1-alpha $25(OH)_2D$ assay accuracy.

$24,25(OH)_2D_3$. This compound results from the degradation of 25(OH)D, and its expression has been shown to be increased when there is increased binding and activation of the vitamin D receptor (VDR) in response to 1-alpha $25(OH)_2D$.[154] $24,25(OH)_2D_3$ concentration may therefore reflect VDR activity. As a result, there is growing interest in measuring $24,25(OH)_2D_3$ and calculating the $25(OH)D/24,25(OH)_2D_3$ ratio, which is known as the Vitamin D Metabolism Ratio (VMR).[155] Studies have reported that VMR predicts vitamin D_3 supplementation[33] and that lower $24,25(OH)_2D_3$ concentration and lower VMR are associated with increased hip fracture risk in community-living older people. Of particular interest given the paradox that more blacks carry a diagnosis of vitamin D deficiency than whites yet do not have a higher risk for fractures than whites, VMR was shown to be similar in black and white Americans, unlike 25(OH)D levels, which were lower among blacks.[156] NIST has developed a reference measurement

procedure for $24,25(OH)_2D_3$, which could lead to improved standardization of $24,25(OH)_2D_3$ measurements.[33]

PTH. The tight connection between calcium, 1-alpha 25(OH)D, and PTH makes PTH another possible marker of vitamin D status. However, the threshold at which PTH rises when 25(OH)D levels are physiologically low is inconsistent across individuals.[33] Other barriers to using PTH include differences in standardization of the PTH assays and other analytical issues.

CQ 2. In Observational Studies, What Is the Association Between Vitamin D Use or Serum Vitamin D Levels and the Incidence of Selected Health Outcomes (i.e., Mortality, Fractures, Falls, Cardiovascular Disease, Cancer, Diabetes, Dementia, Autoimmune Disease, Infections)?

Though KQ 3 and CQ 2 in this review are both focused on the relationship between vitamin D and health outcomes, it is important to note three important differences between them. First, evidence synthesized in KQ 3 comes from trials, while evidence described in CQ 2 comes from observational studies. Second, KQ 3 is focused on vitamin D–deficient adult populations; the data in support of CQ 2 come from studies that are not limited to vitamin D–deficient populations (and include people with all levels of vitamin D). Finally, all the trials included in KQ 3 evaluate treatment with vitamin D, while almost all the observational studies in CQ 2 assess the relationship between serum vitamin D levels (usually measured at the study baseline) and health outcomes. It is important to note the numerous limitations of the evidence from observational studies that should be considered when evaluating the potential relationships between vitamin D and health outcomes: observational studies are meant to generate hypotheses about potential associations and do not reflect causal relationships; residual confounding remains an issue; time between serum vitamin D levels at study entry and incidence of diagnosis may or may not make sense biologically; and potential outcome misclassification due to self-reported outcome measures are problematic in the observational body of evidence regarding vitamin D.

To describe the evidence from observational studies on the association between vitamin D levels and health outcomes published before 2014, we relied primarily on the 2014 AHRQ evidence report/health technology assessment titled "Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)," which was sponsored by the NIH Office of Dietary Supplements to support the updating of the IOM's Dietary Reference Intakes.[21] Observational studies of the association between vitamin D and health outcomes (e.g., bone health, all-cause mortality, cardiovascular mortality, cancer) were eligible for this 2014 report. The authors of the evidence report concluded that results from observational studies, if consistent with each other, were not consistent with the results from RCTs, and no firm conclusions could be drawn from the combined RCT and observational body of evidence. Additionally, we identified 21 primary observational studies and 14 systematic reviews or meta-analyses from our systematic literature search, published since the 2014 AHRQ review,[21] that could further address this question.

Overall, the findings are:

Lower serum vitamin D levels may be associated with a higher incidence of mortality, cardiovascular disease and deaths, diabetes, and dementia; the evidence, however, is somewhat inconsistent both among the observational studies and is inconsistent with the evidence from trials.

Conclusions about an association between serum vitamin D levels and the incidence of cancer, fractures, falls, autoimmune disease, and infections cannot be determined because of mixed or sparse evidence.

Details of the findings from the 2014 AHRQ review and results from studies published since then are in Table A1 (noncancer health outcomes) and Table A2 (cancer health outcomes).

CQ 3. What Is the Relationship Between Vitamin D Use and Selected Intermediate Outcomes (i.e., Bone Mineral Density, Blood Pressure, Measures of Physical or Muscle Strength)?

To address this question, we relied on the 2014 AHRQ evidence report/health technology assessment titled "Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)" sponsored by the NIH Office of Dietary Supplements to support the updating of the IOM's Dietary Reference Intakes.[21] We note that this report was not restricted to included studies among vitamin D–deficient populations. To identify relevant studies published since 2014 that could further address this question in vitamin D–deficient populations, we identified 29 RCTs included for either KQ 3 or KQ 4 in our current update that also reported intermediate outcomes. In addition to these 29 studies, we identified seven additional RCTs reporting intermediate outcomes that were excluded from the KQ portion of this update because "hard" health outcomes were not reported by these studies. Thus, a total of 36 new RCTs were used to supplement the findings from the 2014 AHRQ review regarding the relationship between treatment with vitamin D and intermediate outcomes.

Overall, treatment with vitamin D (with or without calcium) appears to have no effect on any intermediate outcomes. A summary of findings organized by outcomes is provided in **Appendix A Table A3**.

Table A1. Summary of Relationship Between Serum Vitamin D Levels and Selected Health Outcomes Among Observational Studies

Health Outcome	Results From 2014 AHRQ Systematic Review[21]*	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
Mortality	29 observational studies • 10 studies reported no association • 17 studies reported an inverse association (i.e., lower serum levels are associated with higher mortality) • 2 studies reported a U-shaped association	8 observational studies • 1 IPD MA of 8 observational studies in a Northern European consortium reported a significant inverse association between vitamin D levels and mortality over a median followup of 10.5 years; participants with vitamin D concentrations of <30 nmol/L had an adjusted HR of 1.67 (95% CI, 1.44 to 1.89) for all-cause mortality compared with participants with levels of 75 to 99.9 nmol/L.[157] • 1 IPD MA of 8 European and U.S.-based prospective cohort studies in the CHANCES consortium (plus NHANES III) reported a significant inverse association between vitamin D levels and all-cause mortality (RR 1.57 [95% CI, 1.36 to 1.81]) when comparing the bottom to the top quartile of vitamin D levels.[158] • 1 SR of 9 studies (24,297 participants) reported a significant inverse association between vitamin D levels and all-cause mortality; the association was stronger among older adults (pooled HR 1.25 [95% CI, 1.14 to 1.36]) than younger participants (pooled HR 1.12 [95% CI, 1.01 to 1.24]).[159] • 3 cohort studies (ESTHER, NHANES III, NESDO) reported inverse associations between vitamin D levels and all-cause mortality;[160] association was only significant among vitamin D–insufficient or –deficient participants[161] and may be modified by vitamin A supplementation.[162] • The Whitehall study among older men reported an HR of 0.78 (95% CI, 0.72 to 0.85) for all-cause mortality associated with a 2-fold higher measured vitamin D level[163] ○ Significant inverse association was replicated in an MA of 18 studies performed by the same authors; individuals in the top quarter of serum vitamin D levels had 28% lower all-cause mortality (95% CI, 24% to 32%) compared with individuals in the bottom quarter	Possible inverse association, but the evidence is not entirely consistent.

Table A1. Summary of Relationship Between Serum Vitamin D Levels and Selected Health Outcomes Among Observational Studies

Health Outcome	Results From 2014 AHRQ Systematic Review[21]*	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
Fractures	23 observational studies • Hip: 3 studies showed mixed results and 1 study reported an inverse association • Nonvertebral: 2 studies showed no association and 1 study reported an association • Total fragility: 2 studies showed mixed results • Fractures, not otherwise defined: 10 studies reported an inverse association	1 observational study • 1 case-cohort analysis of men enrolled in the MrOS reported mixed results:[164] o No association with nonvertebral fractures o Significant increase in risk of hip fracture when comparing the lowest quartile of serum vitamin D levels to the rest of the participants; the significant protective effect of higher vitamin D levels was, however, restricted to the second quartile (20.91 to 25.90 ng/mL)	Cannot be determined
Falls	5 observational studies • 2 cohort studies reported an inverse association • 2 cohort studies and 1 case-control study reported mixed results or no association	1 observational study • 1 MA of 18 observational studies (10 cross-sectional and 8 cohort studies) reported an inverse association between serum vitamin D levels and risk of falls (summary OR 0.97 [95% CI, 0.96 to 0.99]); the association between falls and vitamin D deficiency varied depending on the threshold used for deficiency[165]	Cannot be determined
Cardiovascular disease	28 observational studies 1 good-quality SR of 17 prospective studies,† 2 cohort studies, and 1 nested case-control study reported an inverse association • 2 cohort studies and 1 nested case-control study reported mixed effects • 3 cohort studies and 2 nested-case control studies reported no association	6 observational studies • 1 SR of 27 studies reported an inverse association between vitamin D and total CVD events (pooled RR per 10 ng/mL increase in vitamin D 0.90 [95% CI, 0.86 to 0.94])[166] • 1 cohort study (MrOS) reported no association between vitamin D levels and all CVD or CHD events combined, and a significant increased risk of cerebrovascular events among vitamin D–deficient men after excluding supplement users (HR 1.70 [95% CI 1.02 to 2.83])[167]	Possible inverse association, but the evidence is not entirely consistent.
Cardiovascular disease (continued)		• The Copenhagen City Heart Study reported a stepwise increased risk of ischemic stroke with stepwise decreased vitamin D levels; the HR for ischemic stroke was 1.36 (95% CI, 1.09 to 1.70) for vitamin D–deficient participants (<10 ng/mL) compared with vitamin D–optimized participants (≥30 ng/mL). There was no association with hemorrhagic stroke.[168] o Authors of the Copenhagen City Heart Study also performed an MA of 10	

Table A1. Summary of Relationship Between Serum Vitamin D Levels and Selected Health Outcomes Among Observational Studies

Health Outcome	Results From 2014 AHRQ Systematic Review[21]*	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
		prospective studies and reported an HR of 1.46 (95% CI, 1.35 to 1.58) for the lowest versus highest quartile of vitamin D levels[168] • Over a median followup of 21 years, there was no association between vitamin D levels and incident atrial fibrillation in the ARIC study except for among younger participants (HR 1.35 [95% CI 1.05 to 1.73]) when comparing deficient (<20 ng/mL) to optimal levels (≥30 ng/mL) of vitamin D.[169] ○ Authors of the ARIC study also performed an MA of 5 prospective studies and reported no association	
Cardiovascular disease deaths	18 observational studies • 7 cohort studies and 1 nested case-control study reported mixed results • 10 cohort studies reported no association	4 observational studies • 1 SR of 27 studies reported an inverse association between vitamin D and CVD mortality (pooled RR per 10 ng/mL increase in vitamin D 0.88 [95% CI 0.80 to 0.96])[166] • 2 IPD MA of prospective studies in Europe and the United States reported significant inverse associations between vitamin D levels and cardiovascular mortality[157, 158] • 1 cohort study (NHANES III: 1988-1994) reported an inverse association between vitamin D and CHD death,‡ but it was only significant when comparing the lowest to the highest quartile in adjusted models[170]	Possible inverse association but the evidence is not entirely consistent.

Table A1. Summary of Relationship Between Serum Vitamin D Levels and Selected Health Outcomes Among Observational Studies

Health Outcome	Results From 2014 AHRQ Systematic Review[21]*	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
Diabetes	Not included in 2014 SR	3 observational studies • The Copenhagen City Heart Study (9,841 participants, 29 years of followup) reported a significant increased risk of type 2 diabetes when comparing the lowest to the highest quartile of 25(OH)D levels (HR 1.35 [95% CI, 1.09 to 1.66])[171] ○ Authors of the Copenhagen City Heart Study also performed an MA of 16 cohort and nested case-control studies (including theirs) and reported the same association (OR 1.50 [95% CI, 1.33 to 1.70] for bottom compared with top quartile)[171] • The ESTHER cohort study in Germany reported a significant inverse association between serum vitamin D levels and incident type 2 diabetes among women but not men[172]	Possible inverse association
Dementia	Not included in 2014 SR	5 observational studies • 1 MA of 26 observational studies reported significantly poorer cognition among participants with low vitamin D status (OR 1.24 [95% CI 1.14 to 1.35]); the effect was stronger among cross-sectional than longitudinal studies[173] • 3 cohort studies, 2 among the general population and 1 among elderly men, reported mixed results depending on domains of cognitive performance[174, 175] or no association[176] • 1 cohort of Swedish men (mean age 71 years) reported no association between baseline vitamin D status and long-term (i.e., 18 year period of time) risk of dementia or cognitive impairment[177]	Possible inverse association, but the evidence is not entirely consistent.

Table A1. Summary of Relationship Between Serum Vitamin D Levels and Selected Health Outcomes Among Observational Studies

Health Outcome	Results From 2014 AHRQ Systematic Review[21]*	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
Autoimmune disease	2 observational studies • 1 nested case-control study reported mixed results for type 1 diabetes mellitus • 1 nested case-control study reported mixed results for multiple sclerosis	2 observational studies • 1 MA of 27 case-control studies reported that Crohn's disease patients had significantly lower levels of serum vitamin D (pooled mean difference-3.99 [95% CI, -5.91 to -2.08]) than healthy controls; there was substantial heterogeneity of effects.[178] • 1 analysis of the Hospital Episode Statistics database in England from 1999 to 2011 reported significantly higher rates of autoimmune disease (e.g., Crohn's disease, rheumatoid arthritis, celiac disease) among people admitted for vitamin D deficiency[179]	Possible inverse association specifically for Crohn's disease, evidence inconclusive or not available for other conditions.
Infections	4 observational studies • 1 cohort study reported an inverse association with acute respiratory illness • 1 cohort study reported no association with respiratory mortality • 1 cohort study reported no association with infectious disease mortality • 1 cohort study reported an inverse association with pneumonia; only the comparison between the 1st and 3rd tertile was significant.	1 observational study • 1 cohort of over 6,000 middle-aged and elderly participants in the Norwegian Tromsø Study reported no association between baseline serum vitamin D levels and presence or duration of self-reported symptoms of respiratory tract infection within 28 days of baseline[180]	Cannot be determined

* Results from the 2014 AHRQ review include all results reported in the 2006 and 2009 AHRQ reviews and results from eligible studies published since the 2009 AHRQ review.

† The SR included 16 prospective studies that were included in either the original AHRQ report or the 2014 update[21] and one prospective study that was excluded from the 2014 update.[21]

ǂ Underlying causes of CHD death included acute myocardial infarction, other acute ischemic heart diseases, atherosclerotic cardiovascular disease, and all other forms of chronic ischemic heart diseases.

Abbreviations: 25(OH)D=vitamin D; AHRQ=Agency for Healthcare Quality and Research; ARIC=Atherosclerosis Risk in Communities; CHANCES=Consortium on Health and Aging: Network of Cohorts in Europe and the United States; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ESTHER=German Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung; HR=hazard ratio; IPD=individual patient data; MA=meta-analysis; MrOS=Osteoporotic Fractures in Men Study; NESDO=Netherlands Study on Depression in Older Adults; NHANES=National Health and Nutrition Examination Survey; OR=odds ratio; RR=relative risk; SR=systematic review.

Table A2. Summary of Relationship Between Serum Vitamin D Levels and Cancer Outcomes Among Observational Studies

Cancer Outcome	Results From 2014 Systematic Review Update[21]	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
All cancer	3 observational studies • 1 cohort study reported an inverse association • 1 cohort study reported mixed results • 1 cohort study reported no association	No additional studies identified by our search	Cannot be determined
Cancer mortality	11 observational studies • 2 cohort studies reported inverse association • 1 cohort study reported U-shaped association • 3 cohort studies and 1 nested case-control study reported mixed results • 4 cohort studies reported no association	No additional studies identified by our search	Cannot be determined
Prostate cancer	19 observational studies • 1 cohort study reported no association • 1 nested case-control study reported an increased risk of prostate cancer with increased vitamin D levels while 1 nested case-control study reported an inverse association • 5 nested case-control studies reported mixed results or a U-shaped association • 11 nested case-control studies reported no association	2 observational studies • 1 nested case-control study reported an inverse association between serum vitamin D levels and risk of prostate cancer (OR 0.30 [95% CI, 0.12 to 0.77] for highest versus lowest quartile; p trend 0.007)[181] • 1 nested case-control study from the Prostate Cancer Prevention Trial reported mixed results by stage of cancer; authors concluded that higher vitamin D levels may increase risk of lower stage prostate cancer and may decrease risk of higher stage prostate cancer[182]	Cannot be determined
Colorectal cancer	9 observational studies • 2 nested case-control studies reported inverse association • Among women, 3 nested case-control studies reported inverse association and 1 nested case-control study reported no association • Among men, 4 nested case-control studies reported no association	1 observational study • 1 case-control study, nested within the Women's Health Study, reported that mean prediagnostic levels of vitamin D were significantly lower in cases (21.9 ng/mL) than controls (23.9 ng/mL) and that there was a significant inverse association between vitamin D and both incident colorectal cancer and colorectal cancer-related mortality[183]	Cannot be determined
Breast cancer	11 observational studies • 2 cohort studies reported no association • 2 nested case-control studies reported inverse association • 7 case-control studies reported no association	1 observational study • 1 nested case-control study reported mixed results that were mediated by BMI status and alcohol intake[184]	Cannot be determined

Table A2. Summary of Relationship Between Serum Vitamin D Levels and Cancer Outcomes Among Observational Studies

Cancer Outcome	Results From 2014 Systematic Review Update[21]	Results From Studies Published Since 2014 Review[21]	Conclusion About the Vitamin D–Health Outcome Relationship
Pancreatic cancer	3 observational studies • 1 pooled case-control study based on 8 cohort studies reported increased risk when comparing 6th to 1st sextile of vitamin D levels • 1 nested case-control study reported increased risk when comparing 5th to 1st quintile • 1 nested case-control study reported mixed results based on UVB exposure status	No additional studies identified by our search	Cannot be determined

Abbreviations: BMI=body mass index; CI=confidence interval; OR=odds ratio; UVB=type B ultraviolet.

Table A3. Summary of Relationship Between Treatment With Vitamin D and Intermediate Outcomes

Intermediate Outcome	Results From 2014 Systematic Review	Results From Studies Published Since 2014 Review Among Vitamin D–Deficient Populations	Impression About the Vitamin D–Intermediate Outcome Relationship
Bone mineral density	10 RCTs of vitamin D supplementation in adults, 9 showed no effect and 1 showed reduced loss of BMD at hip but not at spine in postmenopausal women. 7 RCTs of vitamin D and calcium supplementation, 2 showed positive effects and 4 showed mixed effects in postmenopausal women, 1 showed no effect in men.	9 RCTs of vitamin D with or without calcium, one reported mixed effects depending on method of measurement (broadband ultrasound attenuation vs. speed of sound); the rest measured BMD using DXA at the hip or spine and reported no differences between active treatment and control groups.	No relationship
Muscle/-physical strength	2 RCTs of vitamin D supplementation, both showed positive effect but only one of the RCTs was conducted in participants with low vitamin D levels; 4 cohort studies, 3 showed inverse association between vitamin D levels and muscle strength 2 RCTs of vitamin D and calcium supplementation, no effects reported.	11 RCTs reporting on various measures of muscle/physical strength including timed up and go test, balance tests, chair rise tests, 3-meter walk, jump height, handgrip strength, with the exception of one RCT, no differences between active treatment and control group was observed.	Probably no relationship
Hypertension/ blood pressure	No RCTs of vitamin D supplementation; 4 observational studies; 3 show an inverse relationship between vitamin D levels and risk of hypertension (i.e., lower levels means high risk), 1 shows a J-shaped association. 1 RCT of vitamin D and calcium supplementation, no effects reported.	None identified.	No relationship
Blood pressure	13 RCTs of vitamin D supplementation, 7 reported no effect, inconsistent findings (increases or decreases in diastolic or systolic blood pressure) in the other 6. 2 RCTs of vitamin D and calcium supplementation, no effects reported.	12 RCTs reporting systolic and diastolic blood pressure, no differences between active treatment and control groups.	No relationship
Cancer intermediate outcomes (colorectal adenoma, aberrant cryptic, breast mammographic density)	No RCTs. 1 nested case-control study found no association between vitamin D levels and risk of polyps.	Not evaluated as part of this contextual questions.	Cannot be determined
Weight and BMI	Not assessed in the 2014 update, previous versions of the review identified 3 RCTs of vitamin D with or without calcium, no difference in weight change was reported.	6 RCTs reporting weight and 9 RCTs reporting BMI all reporting no differences between active treatment and control groups.	No relationship
Fasting glucose and HgbA1C	Not reported	7 RCTs reporting on fasting glucose and 2 RCTs reporting on HgbA1C, no differences between active treatment and control groups	No relationship

Table A3. Summary of Relationship Between Treatment With Vitamin D and Intermediate Outcomes

Intermediate Outcome	Results From 2014 Systematic Review	Results From Studies Published Since 2014 Review Among Vitamin D–Deficient Populations	Impression About the Vitamin D–Intermediate Outcome Relationship
Cholesterol	Not reported	11 RCTs reporting on total cholesterol, 10 RCTs reporting on LDL cholesterol, 12 RCTs reporting on HDL cholesterol. No differences between active treatment and control groups for total, LDL, or HDL cholesterol.	No relationship

Abbreviations: BMD=bone mineral density; BMI=body mass index; DXA=dual energy x-ray absorptiometry; HDL=high-density lipoprotein; HbA1C=hemoglobin A1c; LDL=low-density lipoprotein; RCT=randomized, controlled trial.

Appendix B1. Search Strategy

PubMed Search Strategy

Appendix B Table B1. Combined KQs PubMed (January 1, 2013 through March 12, 2020)

Screening and Treatment

#1	Search "Vitamin D"[Mesh] OR "Vitamin D Deficiency"[Mesh] Sort by: Best Match
#2	Search ("Mass Screening"[Mesh]) OR "Diagnostic Tests, Routine"[Mesh] Sort by: Best Match
#3	Search (#1 AND #2) Sort by: Best Match
#7	Search (#1 AND #2) Sort by: Best Match Filters: Publication date from 2013/01/01; Humans; English; Adult: 19+ years
#8	Search ((("Administration, Oral"[Mesh]) OR "Parenteral Nutrition"[Mesh]) OR "Prescriptions"[Mesh]) OR "Diet"[Mesh] Sort by: Best Match
#9	Search ("Vitamin D/administration and dosage"[Mesh] OR "Vitamin D/adverse effects"[Mesh] OR "Vitamin D/contraindications"[Mesh] OR "Vitamin D/poisoning"[Mesh] OR "Vitamin D/therapeutic use"[Mesh] OR "Vitamin D/toxicity"[Mesh]) Sort by: Best Match
#10	Search (#8 OR #9) Sort by: Best Match
#11	Search "Vitamin D Deficiency"[Mesh] Sort by: Best Match
#12	Search (#10 AND #11) Sort by: Best Match
#19	Search (#10 AND #11) Sort by: Best Match Filters: Publication date from 2013/01/01; Humans; English; Adult: 19+ years
#41	Search (#7 OR #19) Sort by: Best Match

Harms

#1	Search "Vitamin D"[Mesh] OR "Vitamin D Deficiency"[Mesh] Sort by: Best Match
#2	Search ("Mass Screening"[Mesh]) OR "Diagnostic Tests, Routine"[Mesh] Sort by: Best Match
#3	Search (#1 AND #2) Sort by: Best Match
#4	Search (#1 AND #2) Sort by: Best Match Filters: Humans
#5	Search (#1 AND #2) Sort by: Best Match Filters: Humans; English
#6	Search (#1 AND #2) Sort by: Best Match Filters: Humans; English; Adult: 19+ years
#7	Search (#1 AND #2) Sort by: Best Match Filters: Publication date from 2013/01/01; Humans; English; Adult: 19+ years
#8	Search (((((("Risk"[Mesh]) OR "Morbidity"[Mesh]) OR "Comorbidity"[Mesh]) OR "adverse effects" [Subheading]) OR ("Mortality"[Mesh] OR "mortality" [Subheading]) OR harms[tw]) Sort by: Best Match
#9	Search (#1 AND #8) Sort by: Best Match
#10	Search (#4 OR #9) Sort by: Best Match
#11	Search (("Epidemiologic Studies"[Mesh]) OR "Outcome and Process Assessment (Health Care)"[Mesh]) OR "Vital Statistics"[Mesh] Sort by: Best Match
#12	Search (#10 AND #11) Sort by: Best Match
#13	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline
#14	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis
#15	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial
#16	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews
#17	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Humans

#18	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Humans; English
#19	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Humans; English; Adult: 19+ years
#20	Search (#10 AND #11) Sort by: Best Match Filters: Controlled Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Publication date from 2013/01/01; Humans; English; Adult: 19+ years

Combined PubMed=1,395 (three were included in prior report and not considered as having been identified through the electronic search)

Other Data Sources

Cochrane Reviews=21 total, 1 unique
Cochrane Controlled Clinical Trials Registry=143 total, 78 unique
Embase=167 total, 127 unique
ClinicalTrials.gov=24 total,18 unique
Health Services Research Projects in Process (HSRProj)=8 total, 4 unique
World Health Organization International Clinical Trials Registry Platform=7 total, 4 unique

Appendix B2. Study Selection Criteria

	Include	Exclude
Population	**KQs 1, 2:** Nonpregnant adults age ≥18 years without known vitamin D deficiency **KQs 3, 4:** Nonpregnant adults enrolled in studies based on a vitamin D level <30 ng/mL; studies in which at least 90% of the study population have serum vitamin D levels below this threshold will also be included	• Pregnant women • Persons with clinical signs of vitamin D deficiency • Studies in which participants are selected for a condition (e.g., osteoporosis, malabsorption, chronic kidney disease) that is associated with altered vitamin D levels or bone metabolism • Studies in which participants are selected for a specific clinical condition (e.g., depression, diabetes, infertility, multiple sclerosis) to assess the benefit of adding vitamin D to existing treatment
Intervention	**KQs 1, 2:** Screening with serum 25-hydroxyvitamin D assay **KQs 3, 4:** Treatment with oral or injectable vitamin D_2 or D_3, with or without calcium	**KQs 1, 2:** Vitamin D−binding protein; 1,25-dihydroxycholecalciferol assay **KQs 3, 4:** Food-based interventions; vitamin D analogs, multivitamins with a vitamin D component, sun, or ultraviolet exposure
Comparison	**KQs 1, 2:** No screening **KQs 3, 4:** Placebo or no treatment, or usual care	**KQs 1, 2:** Head-to-head comparisons of different serum vitamin D assays **KQs 3, 4:** Head-to-head comparisons of different vitamin D doses or formulations
Outcomes	KQs 1, 3: • All-cause mortality • Incidence of falls • Incidence of fractures • Incidence of other health outcomes, such as diabetes, cardiovascular disease, cancer, dementia, autoimmune disease, and infections • Quality of life, as measured by a validated instrument • Self-reported physical functioning, as measured by a validated instrument **KQ 2:** Anxiety and labeling **KQ 4:** Toxicity, renal harms (e.g., nephrolithiasis), and other adverse events	**KQs 1, 3:** Changes in serum vitamin D levels, intermediate physiologic outcomes (bone mineral density, osteoporosis, blood pressure, cholesterol, glucose, muscle mass), behavioral outcomes (changes in diet or physical activity), or physical fitness/muscle strength measures (e.g., grip strength, timed up and go test, distance walked test, step test, balance test) **KQs 2, 4:** None
Timing	**KQ 1:** Outcomes measured at 8 weeks or longer after screening **KQ 3:** Treatment intervention lasting at least 8 weeks; outcomes measured at 8 weeks or longer after start of treatment **KQs 2, 4:** Any duration and any timing of measurement	**KQ 1:** Outcomes measured at less than 8 weeks after screening **KQ 3:** Treatment intervention lasting less than 8 weeks or outcomes measured at less than 8 weeks after start of treatment **KQs 2, 4:** None
Settings	Countries categorized as "very high" on the 2016 Human Development Index (as defined by the United Nations Development Programme);[63] primary care settings and settings generalizable to primary care institutional settings (e.g., nursing homes)	Countries categorized as less than "very high" on the Human Development Index
Study design	**KQs 1, 3:** CCTs, RCTs, and nested case-control studies within RCTs; systematic reviews of CCTs or RCTs with a similar scope to this review **KQs 2, 4:** CCTs, RCTs, cohort studies, case-control studies, and systematic reviews with a similar scope to this review	Editorials, narrative reviews, letters to the editor, and study designs not listed as specifically included (e.g., case reports, case series, studies without a comparison group)

Appendix B2. Study Selection Criteria

	Include	Exclude
Language	English language	Languages other than English
Study quality	Good- and fair-quality studies (i.e., studies with low risk of bias or some concerns for bias)	Poor-quality studies (i.e., studies with high risk of bias)

Abbreviations: CCT=controlled clinical trial; KQ=key question; RCT=randomized, controlled trial.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- 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: 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

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 on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is 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.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:

Good:	Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair:	Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor:	Has a fatal flaw, such as using inappropriate reference standard, improperly administering screening test, using biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

Sources: Harris et al, 2001[185] and U.S. Preventive Services Task Force, Procedure Manual, Appendix VI Criteria for Assessing Internal Validity of Individual Studies. Available at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix C. Excluded Studies

List of Exclusion Codes:

X1: Systematic review for hand search
X2: Ineligible publication type
X3: Ineligible country
X4: Ineligible population
X5: Ineligible intervention
X6: Ineligible comparator
X7: Ineligible outcome
X8: Ineligible study design
X9: Duplicate or superseded
X10: Study protocol or in progress
X11: Abstract only
X12: Non-English full text
X13: Other
X14: Poor quality

1. Effect of omega-3 and vitamin D on women with pre- diabetes and hypo vitaminosis D. Cochrane Central Register of Controlled Trials (CENTRAL). 2019PMID: CN-01949034. Exclusion Code: X10.
2. To study effect of Vitamin D supplementation on atherosclerotic risk factors (endothelial dysfunction) in post-renal transplant patients. Cochrane Central Register of Controlled Trials (CENTRAL). 2019PMID: CN-01970623. Exclusion Code: X7.
3. Acibucu F, Dokmetas HS, Acibucu DO, et al. Effect of vitamin D treatment on serum sclerostin level. Exp Clin Endocrinol Diabetes. 2017 Oct;125(9):634-7. doi: 10.1055/s-0035-1559790. PMID: 28938476. Exclusion Code: X3.
4. Adebayo FA, Itkonen ST, Ohman T, et al. Vitamin D intake, serum 25-hydroxyvitamin D status and response to moderate vitamin D3 supplementation: a randomised controlled trial in East African and Finnish women. Br J Nutr. 2018;119(4):431-41. doi: 10.1017/S000711451700397X. PMID: CN-01464054. Exclusion Code: X7.
5. Akyuz G, Sanal-Toprak C, Yagci I, et al. The effect of vitamin D supplementation on pain, quality of life, and nerve conduction studies in women with chronic widespread pain. Int J Rehabil Res. 2017 Mar;40(1):76-83. doi: 10.1097/mrr.0000000000000211. PMID: 28005440. Exclusion Code: X3.
6. Aloia JF, Dhaliwal R, Shieh A, et al. Calcium and vitamin d supplementation in postmenopausal women. J Clin Endocrinol Metab. 2013 Nov;98(11):E1702-9. doi: 10.1210/jc.2013-2121. PMID: 23595003. Exclusion Code: X4.
7. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr. 2008;87(6):1952-8. Exclusion Code: X7.
8. Ammann EM, Drake MT, Haraldsson B, et al. Incidence of hematologic malignancy and cause-specific mortality in the Women's Health Initiative randomized controlled trial of calcium and vitamin D supplementation. Cancer. 2017 Nov 1;123(21):4168-77. doi: 10.1002/cncr.30858. PMID: 27049526. Exclusion Code: X7.
9. Aoki K, Sakuma M, Endo N. The impact of exercise and vitamin D supplementation on physical function in community-dwelling elderly individuals: A randomized trial. J Orthop Sci. 2018 Jul;23(4):682-7. doi: 10.1016/j.jos.2018.03.011. PMID: 30087216. Exclusion Code: X4.
10. Barengolts E, Manickam B, Eisenberg Y, et al. Effect of high-dose vitamin D repletion on glycemic control in African-American males with prediabetes and hypovitaminosis D. Endocr Pract. 2015 Jun;21(6):604-12. doi: 10.4158/ep14548.Or. PMID: 25899914. Exclusion Code: X6.
11. Beilfuss J, Jorde R, Kamycheva E. High-sensitivity CRP is associated with serum 25-hydroxyvitamin D levels, but is not affected by 5-year supplementation with cholecalciferol. J

Appendix C. Excluded Studies

Nutrition Health Food Sci. 2017;5(5):1-8. Exclusion Code: X4.

12. Berlin T, Emtestam L, Björkhem I. Studies on the relationship between vitamin D3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D3. Scand J Clin Lab Invest. 1986;46(8):723-9. Exclusion Code: X14.
13. Bischoff-Ferrari HA, Dawson-Hughes B, John Orav E, et al. Monthly high-dose Vitamin D treatment for the prevention of functional decline a randomized clinical trial. JAMA Internal Medicine. 2016;176(2):175-83. doi: 10.1001/jamainternmed.2015.7148. Exclusion Code: X4.
14. Bislev LS, Langagergaard Rodbro L, Bech JN, et al. The effect of vitamin D3 supplementation on markers of cardiovascular health in hyperparathyroid, vitamin D insufficient women: a randomized placebo-controlled trial. Endocrine. 2018 Oct;62(1):182-94. doi: 10.1007/s12020-018-1659-4. PMID: 29699378. Exclusion Code: X9.
15. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014;1:CD007470. doi: 10.1002/14651858.CD007470.pub3. PMID: 24414552. Exclusion Code: X1.
16. Bjelakovic G, Nikolova D, Bjelakovic M, et al. Vitamin D supplementation for chronic liver diseases in adults. Cochrane Database Syst Rev. 2017 Nov 3;11:Cd011564. doi: 10.1002/14651858.CD011564.pub2. PMID: 28291696. Exclusion Code: X4.
17. Blair K. Making the case for universal vitamin D supplementation. J Fam Health. 2016 Sep;26(5):14-7. PMID: 27470251. Exclusion Code: X2.
18. Blann A. An update on vitamin D deficiency and at risk groups. J Fam Health. 2015 May-Jun;25(3):16-9. PMID: 25900732. Exclusion Code: X2.
19. Bogdanou D, Penna-Martinez M, Filmann N, et al. T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: a randomized controlled trial with sequential crossover. Diabetes Metab Res Rev. 2017 Mar;33(3)doi: 10.1002/dmrr.2865. PMID: 27995499. Exclusion Code: X4.
20. Bolland MJ, Avenell A, Grey A. Should adults take vitamin D supplements to prevent disease? BMJ. 2016 Nov 23;355:i6201. doi: 10.1136/bmj.i6201. PMID: 27402012. Exclusion Code: X2.
21. Bolland MJ, Grey A, Gamble GD, et al. Concordance of results from randomized and observational analyses within the same study: a re-analysis of the women's health initiative limited-access dataset. PLoS One. 2015;10(10):e0139975. doi: 10.1371/journal.pone.0139975. PMID: 26246241. Exclusion Code: X4.
22. Brady SRE, Naderpoor N, de Courten MPJ, et al. Vitamin D supplementation may improve back pain disability in vitamin D deficient and overweight or obese adults. J Steroid Biochem Mol Biol. 2019 Jan;185:212-7. doi: 10.1016/j.jsbmb.2018.09.005. PMID: 30044160. Exclusion Code: X7.
23. Brenner H, Jansen L, Saum KU, et al. Vitamin D supplementation trials aimed at reducing mortality have much higher power when focusing on people with low serum 25-hydroxyvitamin D concentrations. J Nutr. 2017 Jul;147(7):1325-33. doi: 10.3945/jn.117.250191. PMID: 28468770. Exclusion Code: X8.
24. Bressendorff I, Brandi L, Schou M, et al. The effect of high dose cholecalciferol on arterial stiffness and peripheral and central blood pressure in healthy humans: a randomized controlled trial. PLoS One. 2016;11(8):e0160905. doi: 10.1371/journal.pone.0160905. PMID: 27026331. Exclusion Code: X7.
25. Bubshait DA, Al-Dakheel DA, Alanii FM. Topical vitamin D3: a randomized controlled trial (RCT). Clin Nutr ESPEN. 2018 Oct;27:16-9. doi: 10.1016/j.clnesp.2018.05.009. PMID: 29288249. Exclusion Code: X7.
26. Cameron ID, Dyer SM, Panagoda CE, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2018(9)doi: 10.1002/14651858.CD005465.pub4. PMID: CD005465. Exclusion Code: X1.
27. Carrara D, Bruno RM, Bacca A, et al. Cholecalciferol treatment downregulates renin-angiotensin system and improves endothelial function in essential hypertensive patients with hypovitaminosid D. J Hypertens. 2016 Nov;34(11):2199-205. doi: 10.1097/hjh.0000000000001072. PMID: 26970588. Exclusion Code: X8.
28. Castro JP, Penckofer S. The role of vitamin D in the health of Hispanic adults with diabetes. Hisp Health Care Int. 2014;12(2):90-8. doi: 10.1891/1540-4153.12.2.90. PMID: 24847674. Exclusion Code: X2.
29. Castro M, King TS, Kunselman SJ, et al. Effect of vitamin D3 on asthma treatment failures in

adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. JAMA. 2014 May;311(20):2083-91. doi: 10.1001/jama.2014.5052. PMID: 23995795. Exclusion Code: X4.

30. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health (Larchmt). 2013 Nov;22(11):915-29. doi: 10.1089/jwh.2013.4270. PMID: 23883271. Exclusion Code: X7.
31. Cefalo CMA, Conte C, Sorice GP, et al. Effect of vitamin D supplementation on obesity-induced insulin resistance: a double-blind, randomized, placebo-controlled trial. Obesity (Silver Spring). 2018 Apr;26(4):651-7. doi: 10.1002/oby.22132. PMID: 29442353. Exclusion Code: X7.
32. Chacko SJ, Pauwaa S, Barengolts E, et al. Vitamin D attenuates left atrial volume changes in African American males with obesity and prediabetes. Echocardiography. 2016 May;33(5):681-5. doi: 10.1111/echo.13159. PMID: 26547147. Exclusion Code: X6.
33. Chandler PD, Buring JE, Manson JE, et al. Circulating vitamin D levels and risk of colorectal cancer in women. Cancer Prev Res (Phila). 2015 Aug;8(8):675-82. doi: 10.1158/1940-6207.Capr-14-0470. PMID: 28486474. Exclusion Code: X8.
34. Chaney A, Heckman MG, Diehl NN, et al. Effectiveness and outcomes of current practice in treating vitamin D deficiency in patients listed for liver transplantation. Endocr Pract. 2015 Jul;21(7):761-9. doi: 10.4158/ep14416.Or. PMID: 26067469. Exclusion Code: X4.
35. Close GL, Russell J, Cobley JN, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci. 2013;31(4):344-53. doi: 10.1080/02640414.2012.733822. PMID: 22975529. Exclusion Code: X4.
36. Cutillas-Marco E, Marquina-Vila A, Grant WB, et al. Vitamin D and cutaneous lupus erythematosus: effect of vitamin D replacement on disease severity. Lupus. 2014 Jun;23(7):615-23. doi: 10.1177/0961203314522338. PMID: 25112048. Exclusion Code: X4.
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Appendix C. Excluded Studies

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135. Zuk A, Fitzpatrick T, Rosella LC. Effect of vitamin D3 supplementation on inflammatory markers and glycemic measures among overweight or obese adults: a systematic review of randomized controlled trials. PLoS One. 2016;11(4):e0154215. doi: 10.1371/journal.pone.0154215. PMID: 27094871. Exclusion Code: X7.
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Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Aloia et al (2005)[104] & Talwar et al (2007)[186]	United States	National Institute of Aging	Recruited from the community using direct mail Single center (all participants enrolled and participate at a single study center) Number approached: 50,000 Number screened: 385 Number eligible: 233 Number randomized: 208	Healthy ambulatory postmenopausal African American women not receiving hormone therapy	Previous treatment with bisphosphonates or fluoride; use of estrogen, calcitonin, glucocorticoids, androgens, phosphate, anabolic steroids, or 400 IU/d vitamin D 6 months before entry; history of previous hip fracture; uncontrolled diabetes, anemia, or thyroid disease; history of current liver, renal, neurologic, or malignant disease; malabsorption or alcoholism; history of hypercalciuria, nephrolithiasis, or active sarcoidosis; smoking 10 cigarettes a day; unexplained weight loss; use of medications known to interfere with calcium or vitamin D absorption or metabolism, such as anticonvulsants; severe osteoarthritis; and participation in weight training or elite athletic training.
Aloia et al (2018)[108] PODA	United States	National Institutes of Health (NIH), Office of Dietary Supplements, Nutrition and Obesity Research Center at the University of Washington	Recruited from the community by direct mail, e-mail to hospital employees, and presentations at black churches and events Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 625 Number eligible: NR Number randomized: 260	African American women older than 60, ambulatory, serum vitamin D levels between 8 ng/mL and 26 ng/mL	Serum vitamin D < 8 ng/ml

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Arvold et al (2009)[82]	United States	St. Luke's Foundation	Recruited adult patients seen for medical care at the outpatient clinic Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 610 Number eligible: 244 Number randomized: 100	Adult outpatients with mild (20 to 25 ng/mL) or moderate (10 or 19 ng/mL) vitamin D deficiency	History of vitamin D deficiency, known previous hypercalcemia, primary hyperparathyroidism, severe renal disease (defined as a creatinine concentration greater than 3 mg/dL), or sarcoidosis
Bischoff et al (2003)[89]	Switzerland	Strathmann AG, Germany, International Foundation for the Promotion of Nutrition Research and Nutrition Education, Swiss Orthopedic Society, and Swiss Foundation for Nutrition Research	Elderly women who are not able to live independently and awaiting placemen in long-stay geriatric care units in hospitals Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: NR Number eligible: 130 Number randomized: 122	Women age 60 or older in long-stay geriatric care units awaiting placement who were not living independently but with the ability to walk 3 meters with or without a walking aid	Primary hyperparathyroidism, hypocalcemia, hypercalciuria, renal insufficiency (creatinine >117 uM), fracture or stroke within the last 3 months, received any treatment with hormone replacement therapy, calcitonin, fluoride, or bisphosphonates during the previous 24 months
Bislev et al (2018)[70]	Denmark	Aarhaus University, Augustinis Foundation, Toyota Foundation, A.P. Moller and wife, Chastine MC Kinney Mollers Foundation, PA Messerschimidt and wife Foundation, Orkla Health	Letter invitation to randomly selected women from a nationwide civil registry living in the vicinity of the hospital Single center (all participants enrolled and participate at a single study center) Number approached: 32,321 Number screened: 1,580 Number eligible: 109 Number randomized: 81	Women ages 60 to 79 with serum vitamin D deficiency (<20 ng/ml and PTH >6.9 pmol/L), plasma ionized calcium and creatinine below upper limit of the reference interval	Current treatment with antihypertensives, diuretics, systemic glucocorticoids, nonsteroidal anti-inflammatory drugs, or lithium; current or previous treatment with antiosteoporotic drugs; planned travel to sunny destinations or using sunbeds on a regular basis

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Borgi et al (2016)[109] & McMullan et al (2017)[187]	United States	NIH, Harvard Clinical and Translational Science Center	Electronic and print community advertisements, recruitment within large health care systems Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 489 Number eligible: 93 Number randomized: 93	Age 18 years or older, BMI ≥25, vitamin D deficiency (<20 ng/ml)	Hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease, active malignancy (except nonmelanoma skin cancer), history of kidney stones, osteoporosis. pregnancy, hypocalcemia or hypercalcemia, hypophosphatemia or hyperphosphatemia; taking vitamin D supplements and unwilling to stop for the trial
Brazier et al (2005)[88]	France	Innothera Laboratories	Community-dwelling women who spontaneously consulted a practitioner Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 360 Number eligible: 192 Number randomized: 192	Community-dwelling, ambulatory women >65 years, serum vitamin D ≤12ng/ml	Hypercalcemia, primary hyperparathyroidism, renal insufficiency, hepatic insufficiency, women receiving treatment acting on bone metabolism (e.g., bisphosphonate, calcitonin, vitamin D) in the last 6 months
Chapuy et al (2002)[87] Decalyos II	France	MERCK KGaA	Recruited from 55 apartment houses for elderly people Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: NR Number eligible: NR Number randomized: 610	Women who were ambulatory (able to walk indoors with a cane or a walker) and had a life expectancy of at least 24 months	Intestinal malabsorption, hypercalcemia (serum calcium >2.63 mmol/l), chronic renal failure (serum creatinine >150 mmol/l), received drugs known to alter bone metabolism within the past year, treatments with fluoride salts (>3 months), bisphosphonates, calcitonin (>1 month), calcium (4,500 mg/day) and vitamin D (4,100 IU/day) during the last 12 months

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Davison et al (2013)[75]	United States	American Diabetes Association, National Institutes of Health, Bayer HealthCare, LLC/Bayer Diabetes Care	Individuals with risk factors for prediabetes were evaluated at churches, health fairs, and other community events or after referral from clinics or responding to flyers distributed in the community Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 15,51 Number eligible: 755 Number randomized: 117	Prediabetes, serum vitamin D level <30 ng/ml, less than 40 years old. The following four criteria were used to identify subjects who may have prediabetes: 1) waist circumference measured at the umbilicus of 40 inches in men and 35 inches in women, 2) family history of diabetes in first-degree relatives, 3) hypertension (either being treated or newly diagnosed at screening of 140/90 mmHg), and 4) history of gestational diabetes mellitus.	NR
Gagnon et al (2014)[110]	Australia	Diabetes Australia Research, Department of Medicine, University of Melbourne	Recruitment through newspaper and radio advertisements, flyers posted in hospitals and medical clinics, presentations to local community Single center (all participants enrolled and participate at a single study center); Number approached: 885 Number screened: 510 Number eligible: 95 Number randomized: 95	BMI between 25 and 40; serum vitamin D ≤ 22 ng/ml, diagnosis of prediabetes or high risk for diabetes as determined by a score of 15 or more on the AUSDRISK	HbA1c ≥ 6.5%, pregnancy or breast-feeding, creatinine clearance <60 ml/min, cirrhosis, malabsorption or elevated antitissue transglutaminase antibody, hypercalcemia, hypercalciuria, history of nephrolithiasis, previous nontraumatic fractures, serum vitamin D <5.2 ng/ml, active or chronic inflammation, medications known to affect glucose and mineral metabolism over the last 3 months, pharmacologic treatment of obesity, commencement of physical activity ≥3 times/week or >5% change in weight in last 3 months

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Gallagher et al (2012)[49], Gallagher et al (2013)[103], & Smith et al (2017)[54] VIDOS	United States	National Institute on Aging	Recruitment of local population by advertising in local newspapers, church bulletins Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: 2,639 Number screened: 936 Number eligible: NR Number randomized: 273	Women ages 57 to 90 who were at least 7 years postmenopausal; serum vitamin D levels <20 ng/mL	Substantial comorbid condition, history of cancer other than skin in past 10 years, terminal illness, previous hip fracture, hemiplegia, uncontrolled diabetes, active or history of kidney stones, chronic renal or liver failure, physical conditions severe enough to prevent reasonable physical activity, serum vitamin D <5.2 ng/ml, BMI >45, elevated serum or urine calcium, T-score <-3 at the spine or hip, current or prior use of bone sparing medications, use of steroids for more than 6 months, antiepileptic drug use

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Gallagher et al (2014)[81] VITADAS	United States	U.S. Department of Defense, Bayer Pharmaceuticals provided calcium tablets	Recruitment in local community through advertising in newspaper, church bulletins, hair salons, and social media Single center (all participants enrolled and participate at a single study center) Number approached: 1,514 Number screened: 558 Number eligible: 305 Number randomized: 198	Women ages 25 to 45 with serum vitamin level D ≤ 20 ng/ml	Pregnant, significant comorbidities, history of cancer except skin cancer within last 10 years, uncontrolled type 1 diabetes ± significant proteinuria or fasting blood sugar >140 mg in type 2 diabetes, active kidney stone disease or history of >2 kidney stones, chronic renal failure, evidence of chronic liver disease, alcoholism, severe vitamin D deficiency (serum vitamin D level <5 ng/mL), BMI >45, serum calcium level >2.57 mmol/L on 2 baseline tests, 24-hour urinary calcium level >7.3 mmol/day on 2 baseline tests, BMD T-score <-3 at the spine or hip (specific to race), and use of bone-active drugs such as fluoride, PTH or derivatives, calcitonin, estrogen during past 6 months, chronic high-dose corticosteroid therapy (>10 mg/d), bisphosphonates for >3 months in the past, anticonvulsants, or high-dose thiazide therapy

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Grimnes et al (2011)[94]	Norway	Norwegian Council of Cardiovascular Disease	Persons previously participating in the sixth Tromsø Study (ongoing longitudinal population-based study) were invited to participate Single center (all participants enrolled and participate at a single study center) Number approached: 1,028 Number screened: 337 Number eligible: 108 Number randomized: 104	Subjects ages 30 to 75 years previously participating in the sixth Tromsø Study with serum vitamin D between 5th and 10th percentiles or 80th and 95th percentiles. We only abstracted data and results related to the participants with serum vitamin D levels < 10th percentile, as this was the group randomized to placebo or vitamin D.	Current smokers, diabetes, heart attack or stroke during the past 12 months, cancer during the past 5 years, steroid use, kidney disease, hyperparathyroidism, sarcoidosis, high blood pressure, and pregnancy, lactation, or fertile age and no contraception use in women
Hansen et al (2015)[69]	United States	National Institute on Aging, Office of Dietary Supplements	Recruitment through local advertisements (newspaper advertisements, letters of invitation sent to female faculty and to registrants on an aging Registry, website posting) Single center (all participants enrolled and participate at a single study center) Number approached: 2,521 Number screened: 886 Number eligible: NR Number randomized: 230	Women 5 years or more past menopause or oophorectomy or 60 years or older if they had undergone a prior hysterectomy without oophorectomy, vitamin D levels between 14 ng/mL and 27 ng/mL	Women older than 75 years, hypercalcemia, nephrolithiasis, cancer within 5 years (excluding skin cancer), diabetes mellitus, inflammatory bowel disease, malabsorption, celiac sprue, chronic diarrhea, glomerular filtration rate less than 45 mL/min, adult fragility, fracture of the hip, spine, or wrist, use of bone-active medications within the past 6 month, total-body BMD T scores of -2.5 or less
Hin et al (2016)[73] BEST-D	United Kingdom	Tishcon Corporation, The British Heart Foundation, British Heart Foundation for Research Excellence; UK Medical Research Council, Cancer Research UK	Recruitment by a postal letter from a single general practice Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 1,122 Number eligible: 932 Number randomized: 305	Community-dwelling men and women age 65 or older and not currently taking more than 400 IU of vitamin D daily	Nursing home residents; prescription of calcium, biphosphonates, PTH, or calcitonin; hypercalemia; dementia; hyperparathyroidism, lymphoma, sarcoidosis; active tuberculosis; renal calculus; history of alcohol abuse; terminal illness

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Honkanen et al (1990)[101]	Finland	Academy of Finland, the Remeda Pharmaceutical Company, Sandoz Pharmaceutical Company	A consecutive series of women independently living at home were selected during routine health screening for 67- and 72-year-old residents of the city and female inpatients age 65 years or older were selected from the long-term geriatric wards of the City Hospital Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 203 Number eligible: NR Number randomized: 126	Community-dwelling women ages 67 and 72 years, female inpatients age 65 years or older in the long-term geriatric wards of the City Hospital	Patients unable to eat or drink without help and with active malignant disease, recent or concurrent holiday trip to the south
Janssen et al (2010)[90]	Netherlands	Prevention Program of ZonMw	Women recruited from those attending an outpatient geriatric medicine clinic, most lived in residential homes for the elderly Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: NR Number eligible: 91 Number randomized: 70	Age > 65, ambulatory, able to follow simple instructions, serum vitamin D levels between 8 and 20 ng/ml	Treatment with vitamin D or steroids in the previous 6 months, a history of hypercalcemia or renal stones, liver cirrhosis, serum creatinine >200 micromol/L, malabsorptive bowel syndrome, primary hyperparathyroidism, uncontrolled thyroid disease, anticonvulsant drug therapy, and/or presence of any other condition that would probably interfere with the patient's compliance (i.e., surgery planned)

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Jorde et al (2016)[74] & Jorde et al (2016)[137]	Norway	Novo Nordisk Foundation, North Norway Regional Health Authorities, UiT the Arctic University of Norway, Norwegian Diabetes Association, Research Council of Norway	Recruited from sixth Tromsø Study Single center (all participants enrolled and participate at a single study center) Number approached: NA-subgroup analysis Number screened: NA-subgroup analysis Number eligible: NA-subgroup analysis Number randomized: NA-subgroup analysis	Ages 25 to 80 with impaired fasting glucose (108 mg/dl to 124 mg/dl), or impaired glucose tolerance (2-hour value 140 to 198 mg/dl)	Not previously diagnosed with diabetes, primary hyperparathyroidism, granulomatous disease, history of urolithiasis, cancer diagnosed in the past 5 years, unstable angina pectoris, myocardial infarction or stroke in the last 5 years, pregnant or lactating women, women of fertile age with no use of contraception, serum calcium >10.2 mg/dL, renal stones
Jorde et al (2018)[77]	Norway	North Norway Regional health Authorities, UiT, The Arctic University of Norway	Participants from the Tromsø study invited to participate by mail Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 639 Number eligible: 422 Number randomized: 422	Ages 40 to 80 years, serum vitamin D level < 16.8 ng/ml	NR
Kärkkäinen et al (2010)[92] & Karkkainen et al (2010)[188] OSTPRE-FPS	Finland	Finnish Cultural Foundation (Hulda Tossavainen Foundation), Sigrid Juselius Foundation, Academy of Finland, and Kuopio University Hospital EVO-grant	Postal invitation sent to eligible women from the OSTRPE-FPS cohort study Single center (all participants enrolled and participate at a single study center) Number approached: NA Number screened: NA Number eligible: 750 Number randomized: 603	Postmenopausal women from the OSTPRE cohort of 13,100 women born in 1932 to 1941 who were (1) age 65 years or older at the end of November 2002, (2) living in the area at the onset of the trial, and (3) not belonging to the former OSTPRE bone densitometry sample	NR

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Kearns et al (2015)[111]	United States	NIH	Flyer advertisements on a university campus and email Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 29 Number eligible: 29 Number randomized: 28	Ages 18 to 65 and good health status (self-reported)	Pregnancy, breast-feeding, granulomatous conditions, kidney or liver disease, diabetes, certain medications (anticonvulsants, barbiturates, steroids, >1,000 mg/day calcium supplementation), calcium or bone abnormalities (hyperparathyroidism, Paget's disease, osteoporosis), thyrotoxicosis, history of malignancy or complete immobilization
Kjaergaard et al (2012)[80] Tromo Study	Norway	Northern Norway Regional Health Authority	Eligible participants from the sixth Tromsø study were invited by mail Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 1,351 Number eligible: NR Number randomized: 243	Adults ages 30 to 75 years with serum vitamin D levels below the 20th percentile (22 ng/ml) in the sixth Tromsø study	Participants with a history of known diabetes, hypertension, coronary heart disease or stroke in the past 12 months, cancer, kidney stones, pregnant or lactating women, fertile women below the age of 50 years without adequate contraception, primary hyperparathyroidism, elevated serum creatinine levels, SBP>174 mm Hg, DBP>104 mm Hg, high depression scores or serious depression in clinical interview, participants reporting use of vitamin D supplements, antidepressants or other mood stabilizing medication, serious depression, participants stating regular use of a solarium, and participants reporting a planned trip to a sunny location in the trial period

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Knutsen et al (2014)[105]	Norway	Institute of Health and Society, University of Oslo, Norwegian Women's Public Health Association, Furst Medical Laboratory, Nycomed Pharma AS, Furst medical Laboratory, Nycomed Pharma AS	Recruited through local immigrant web sites or through local radio Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 301 Number eligible: 253 Number randomized: 251	Healthy immigrants ages 18 to 50 years, born in or had parents born in the Middle East, Africa, or South Asia	Regularly used vitamin D supplements, receiving treatment for vitamin D deficiency, pregnant or breastfeeding, malabsorption, medication interfering with vitamin D metabolism, kidney disease, cancer, tuberculosis, sarcoidosis, osteoporosis, recent fracture, use strong painkillers
Krieg et al (1999)[91]	Switzerland	NR	Women recruited from 19 nursing homes Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: NR Number eligible: NR Number randomized: 248	Women living in nursing homes	NR
Lehmann et al (2013)[46]	Germany	German Ministry of Education and Research	Participants were recruited through newspaper advertisements, personal contacts, and information in public institutions Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: NR Number eligible: NR Number randomized: 119	NR	Use of vitamin D and calcium supplements, history of chronic illness and elevated serum creatinine (in females, 1.1 mg/dL; in males, 1.3 mg/dL), elevated serum calcium, pregnancy or lactation, and vacations in areas with abundant UVB irradiation in the course of the study

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Lerchbaum et al (2017)[112] Graz Vitamin D&TT-RCT	Austria	Austrian National Bank	Conversations, telephone calls, and written information posted in outpatient internal medicine and urology clinics; targeted patients, hospital staff, family members of hospital staff Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 500 Number eligible: NR Number randomized: 100	Males ages 18 to 70, vitamin D deficiency (<30 ng/ml), total testosterone levels >10.4 nmol/L	Hypercalcemia; oral, transdermal, IM testosterone supplementation use within prior 2 to 6 months; vitamin D supplement use; diabetes; thyroid disease; endocrine disturbances; sarcoidosis; tuberculosis; Wegener granulomatosis; vasculitis; inflammatory bowel disease; intake of medicine influencing endocrine parameter; PSA level >4 ng/mL; hematocrit >50%; untreated, severe obstructive sleep apnea; urinary tract symptoms; uncontrolled heart failure; history of cancer, chromosomal disorders
Lips et al (1996)[86] & Ooms et al (1995)[189]	Netherlands	The Praeventiefonds, the Hague, the Netherlands, Solvay-Duphar, Inc. supplied the tablets.	Participants were recruited from general practitioners, from apartment houses for elderly persons, and from homes for elderly persons within the vicinity. Participants recruited from apartment houses and homes were receiving some care but less than they would have received in a nursing home Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: NR Number eligible: NR Number randomized: 2,578 (348 in a substudy focused on BMD)	Age 70 or older	Persons requiring nursing home care, history of hip fracture or total hip arthroplasty, known hypercalcemia, sarcoidosis, or recent urolithiasis (<5 years earlier)

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Lips et al (2010)[83]	Multicountry, Canada, Germany, Netherlands, Mexico, United States	Merck & Co Inc..	Recruitment approach: NR; Multicenter (participants enroll and participate at one of multiple study centers conducting the study); Number approached: NR Number screened: 593 Number eligible: NR Number randomized: 226	Age 70 or older, vitamin D levels between 6 ng/ml and 20 ng/ml, walk 10 feet without walking aid, mentally competent. For participants with serum vitamin D levels between 6 and 9 ng/ml, a 24-hour urine calcium concentration must be > or equal to 50 mg/d and bone-specific alkaline phosphatase concentrations must be below upper bound of normal limits, ambulatory.	Primary hyperparathyroidism, active thyroid disease, impaired renal function, osteomalacia, neurologic impairment, peripheral neuropathy, myocardial infarction within 6 months of screening, uncontrolled hypertension, postural hypotension, malabsorption syndrome, alcohol abuse, cancer, treatment with oral glucocorticoids, anabolic steroids, or growth hormone within 12 months of screening, treatment with >800 IU vitamin D or its metabolites within 6 months of screening; treatment with any drug that might affect vitamin D metabolism or interfere with postural stability at screening

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Manson et al (2019)[71], Manson et al (2019)[190], Manson et al (2012)[191], Donlon et al (2018)[192], & Bassuk et al (2016)[193] VITAL	United States	National Institutes of Health	Mail recruitment materials nationwide and through local health fairs Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 41,605 Number eligible: 39,430 Number randomized: 25,871	Males age 50 or older, females age 55 or older, minimally a high school education	History of cancer (except nonmelanoma skin cancer); history of cardiovascular disease; anticoagulant use at baseline; history of kidney stones, renal failure, or dialysis; hypercalcemia; hypo- or hyperparathyroidism; severe liver disease (cirrhosis); sarcoidosis or other granulomatous diseases; fish allergy; serious illnesses that would preclude participation; current vitamin D supplement use greater than 800 IU/day at baseline or those unwilling to forego vitamin D supplements during the trial; current calcium supplement use greater than 1,200 mg/day; and current fish oil supplement use
Martineau et al (2007)[106]	United Kingdom	Wellcome Trust, the Department of Environmental Health; London Borough of Newham; Newham University Hospital NHS Trust Research Fund; Northwick Park Hospital Tropical Research Fund	Recruited from tuberculosis contact clinics at hospitals Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 364 Number eligible: NR Number randomized: 192	Age 18 or older who had been exposed to a patient with active tuberculosis	Symptoms, clinical signs, or radiographic evidence of active tuberculosis, HIV infection, renal failure, sarcoidosis, or hyperparathyroidism, taking corticosteroids, thiazide diuretics, or supplementary vitamin D (either alone or as part of a multivitamin preparation), breastfeeding or pregnant

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Mason et al (2014)[113] ViDA (US)	United States	None listed	Media publicity and mass mailings, invitation letters to women who participated in previous studies Single center (all participants enrolled and participate at a single study center) Number approached: 6,461 Number screened: 264 Number eligible: 230 Number randomized: 218	Postmenopausal women ages 50 to 75 who were overweight or obese (BMI > or equal to 25) and serum vitamin D levels ≥10 ng/mL and ≤32 ng/mL	Current use of >400 IU vitamin D, osteoporosis, diabetes, renal disease, kidney stones, severe heart failure, history of breast cancer or other invasive cancer, use of hormone replacement therapy within past 6 mo., alcohol intake >2 drinks per day, current smoking, current participation in another diet/nutrition lifestyle change program, history of bariatric surgery, use of weight loss medications
Moreira-Lucas et al (2017)[114]	Canada	Dairy Farmers of Canada, Genomic Research and Development Initiative Program (Public Health Agency of Canada)	Participants were recruited via flyers and newspaper advertisements. Participants who responded were then screened for eligibility at one of three research centers Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: 1,101 Number screened: 241 Number eligible: 88 Number randomized: 71	Men and women ages 18 to 75, Finnish Diabetes Risk score of >10 for whites and greater than 6 for all other races and/or had metabolic syndrome, BMI < 40, serum vitamin D levels ≤ 20 ng/ml (changed to 26 ng/ml during study), plasma glucose of 2.4 to 2.8 ng/mL or HbA1c of 5.5% to 6.4%	Pregnant or breastfeeding, history of renal or liver disease, granulomatous disease, hypercalcemia, medication for diabetes, steroid use, pancreatic enzyme use, diagnosed with any condition affecting nutrient absorption, intolerance to cheese, allergy to vitamin D
Ng et al (2014)[115], Chandler et al (2014)[194] & Chandler et al (2013)[195]	United States	National Cancer Institute at NIH, Department of Defense Prostate Cancer Research Program, American Society of Clinical Oncology, Pharmavite LLD	Recruitment through a community-based public-housing cancer prevention study in Boston Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 763 Number eligible: 366 Number randomized: 328	Ages 30 to 80, self-identified as black or African American, and participating in Open Doors to Health study	Pregnancy, parathyroid/thyroid disorder, calcium disorder, sarcoidosis, calcium channel blocker use, type I diabetes, malignancies

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Nowak et al (2016)[116]	Switzerland	EMDO Foundation	Participants were recruited through informational boards and the intranet of the university Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 286 Number eligible: 128 Number randomized: 122	Ages 20 to 50, fatigue, BMI between 18 and 25 kg/m^2, serum vitamin D level < 20 ng/ml	Intake of vitamin D 8 weeks prior to study, pregnancy or lactation, hypersensitivity to vitamin D, cardiovascular/pulmonary/ renal/hepatic diseases, anemia, hypercalcemia, hypocalcemia, muscle/bone disease, severe infection, sleep disorders, chronic intake of concurrent medications (excluding contraceptives), chronic kidney disease, mental disorders, or concurrent enrollment in another therapeutic trial
Pfeifer et al (2000)[85]	Germany	Strathmann AG	Recruitment through newspaper advertisements in the community Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 208 Number eligible: 151 Number randomized: 148	Healthy, ambulatory women age 70 years or older with serum vitamin D < 20 ng/ml	Hypercalcemia or primary hyperparathyroidism; fractures of the extremities caused by osteoporosis; therapy with a bisphosphonate, calcitonin, vitamin D and vitamin D metabolites, estrogen, tamoxifen in the past 6 months, or fluoride in the past 2 years; chronic renal failure; history of drug, alcohol, nicotine, or caffeine abuse; increased scheduled holiday in geography with more UV exposure, diabetes; and medications possibly interfering with postural stability and balance; anticonvulsant use

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Pfeifer et al (2009)[84]	Multicountry; Austria, Germany	Meda Pharma Inc.	Individuals recruited by newspaper advertisements and mailing lists Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 315 Number eligible: 242 Number randomized: 242	Healthy ambulatory women and men age 70 or older with vitamin D deficiency (<31.2 ng/ml)	Hypercalcemia; primary hyperparathyroidism; fractures of the extremities due to osteoporosis; therapy with a thiazide, bisphosphonate, calcitonin, vitamin D and vitamin D metabolites, estrogen, anti-estrogen in the past 6 months or fluoride treatment in the past 2 years; known intolerance to study medication, chronic renal failure (serum creatinine above 20% of the upper limit of the reference range), history of drug or alcohol abuse, nicotine abuse (more than 20 cigarettes per day), more than 7 cups of coffee daily, scheduled holidays along the geographic longitude during the study period, diabetes mellitus and severe cardiovascular disease

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Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Pilz et al (2015)[117], Grubler et al (2016)[196], Grubler et al (2016)[197] & Grubler et al (2018)[198] Styrian Vitamin D Hypertension Trial	Austria	Austrian National Bank	Participants were recruited from outpatient clinics from the Department of Internal Medicine, Division of Endocrinology and Metabolism at a University Medical Center Single center (all participants enrolled and participate at a single study center) Number approached: 1,700 Number screened: 518 Number eligible: NR Number randomized: 200	Age 18 or older, arterial hypertension or ongoing antihypertensive treatment, serum vitamin D level < 30 ng/mL	Hypercalcemia, pregnant or lactating, drug intake as a part of another clinical trial, acute coronary syndrome, cerebrovascular event in past 2 weeks, low glomerular filtration rate; 24-hr systolic BP > 160 mmHg or diastolic BP > 100 mmHg, change in hypertensive treatment within 4 weeks of study, planned change in hypertensive treatment during study, life expectancy of <1 yr, clinically significant acute disease requiring drug treatment or radiation; regular intake of vitamin D > 880 IU in 4 previous weeks
Pittas et al (2019)[76] D2d	United States	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Intramural Research Program of the NIDDK, Office of Dietary Supplements of the NIH, American Diabetes Association, National Diabetes Education Program	Recruitment through screening of electronic health records and research volunteer databased, community advertising, mailings to primary care physicians, social media, and press releases Multicenter (participants enroll and participate at one of multiple study centers conducting the study) Number approached: NR Number screened: 7,133 Number eligible: NR Number randomized: 2,423	Two of three glycemic criteria for prediabetes; age 30 years or older (age 25 years or older for American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders); BMI of 24 to 42 (22.5 to 42 for Asians)	

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Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Raed et al (2017)[118] & Bhagatwala et al (2015)[199]	United States	The Diabetes and Obesity Discovery Institute (Augusta University), Bio-Tech Pharmacal	Participants were recruited through flyers and word of mouth in local community Single center (all participants enrolled and participate at a single study center) Number approached: Number screened: 129 Number eligible: 96 Number randomized: 70	African American race, age 13 to 45 years, BMI ≥ 25 or ≥ 85% for age and sex for adolescents, serum vitamin D ≤ 20 ng/mL	Pregnant, taking medications/dietary supplements, medical status that could affect nutritional status or metabolism
Scragg et al (2017)[97] Scragg et al (2018)[98] Khaw et al[72] ViDA (NZ)	New Zealand	Health Research Council of New Zealand, Accident Compensation Corporation of New Zealand	Recruited from 55 different family practices through letter mailed to potential participants home Single center (all participants enrolled and participate at a single study center) Number approached: NA-subgroup analysis Number screened: NA-subgroup analysis Number eligible: NA-subgroup analysis Number randomized: NA-subgroup analysis	Age 50 to 84 years, resident of local community	Current use of vitamin D supplements, psychiatric disorders that would limit compliance with study protocol, history of hypercalcemia, nephrolithiasis, sarcoidosis, parathyroid disease, gastric bypass surgery, enrolled in another study that would affect participation, serum calcium level > 10.0 mg/dL

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Shea et al (2019)[78]	United States	Pfizer, U.S. Department of Agriculture	Direct mailings and advertisements Single center (all participants enrolled and participate at a single study center) Number approached: 2,289 Number screened: 120 Number eligible: 100 Number randomized: 100	Healthy, community-dwelling men or postmenopausal women, >60 years, vitamin D serum levels between 8 and 20 ng/mL	Vitamin D supplement use >600 IU/d (for ages 60–70 years) or >800 IU/d (for age ≥71 years); vitamin D injection within the past 3 months; >2 falls or 1 fall with injury within the last year; use of cane, walker, or other indoor walking aid; history of kidney stones within the last 3 years; history of liver disease, sarcoidosis, lymphoma, dysphagia, or other gastrointestinal disorder; neuromuscular disorder affecting lower-extremity function; hip replacement within the last year; cancer treatment in the last 3 years, treatment with thiazide diuretics >37.5 months; teriparatide, denosumab, or bisphosphonates (within the past 2 years); oral steroids (for >3 weeks in the last 6 months); fat-malabsorption products; anticonvulsant therapy; and alcohol intake > 2 drinks/day; GFR < 30 L/min, urine calcium: creatinine ratio > 0.325, or serum calcium > 10.8 mg/d.
Tran et al (2014)[119] & Tran et al (2012)[200] D-Health	Australia	Sanofi-Aventis Healthcare provided the study drug	Electoral rolls Single center (all participants enrolled and participate at a single study center) Number approached: 6,535 Number screened: 1,180 Number eligible: 747 Number randomized: 644	Ages 60 to 84	Taking > 400 IU vitamin D, history of kidney stones, hyperparathyroidism, osteomalacia, osteoporosis, sarcoidosis

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Author (Year) Trial Name	Country	Sponsor	Recruitment Approach, Study Setting, Sample Size	Inclusion Criteria	Exclusion Criteria
Wamberg et al (2013)[107] & Wamberg et al (2013)[201]	Denmark	NR	Participants were recruited through announcements in local newspapers Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 88 Number eligible: 55 Number randomized: 52	Healthy males and females ages 18 to 50 with a BMI > 30 and serum vitamin D levels < 20 ng/mL	History of diabetes, body weight > 125 kg, a fasting plasma glucose > 7.0 mmol/L, hypercalcemia, or impaired renal (plasma creatinine > 130 mol/L) or hepatic function (alanine aminotransferase > 135 U/L), treated with vitamin D within the last 3 months, recent major weight changes, history of sarcoidosis, osteomalacia, or alcohol or substance abuse. Women were excluded if they were planning pregnancy or did not report use of safe contraception
Witham et al (2013)[102]	United Kingdom	HeartResearch UK: NHS Support for Science, University of Dundee	In-person recruitment by research team visiting local community centers/groups, study information leaflets Single center (all participants enrolled and participate at a single study center) Number approached: 82 Number screened: 54 Number eligible: 52 Number randomized: 50	Age 18 or older, female, vitamin D deficiency (< 30 ng/ml), self-defined South Asian origin	Previous symptomatic cardiovascular disease, vitamin D supplementation use, eGFR < 40 mL/min, abnormal liver function tests, adjusted serum calcium > 2.60 or < 2.15 mmol/L, history of renal calculi, sarcoidosis, metastatic malignancy, pregnancy, participants of childbearing age and not taking reliable contraception
Wood et al (2012)[93] & Macdonald et al (2017)[202]	United Kingdom	UK Department of Health	Women recruited from prior osteoporosis screening study which randomly selected from the Community Health Index records Single center (all participants enrolled and participate at a single study center) Number approached: NR Number screened: 424 Number eligible: 327 Number randomized: 305	Caucasian females age 60 to 70, healthy, postmenopausal	Preexisting cardiovascular disease, diabetes, asthma, malabsorption, hypertensive blood pressure measurements, difficulty swallowing tablets or capsules, medications or supplements known to affect any dependent variable, smokers, abnormal blood chemistry

Appendix D Table 1. Detailed Study Characteristics of Included RCTs

Abbreviations: AUSRISK=Australian Type 2 Diabetes Risk Assessment tool; BMD=bone mineral density; BMI=body mass index; BP=blood pressure; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; IU=international units; NA=not applicable; NDDK=National Institute of Diabetes and Digestive and Kidney Disease; NHS=National Health Service; NR=not reported; OSTRPE-FPS=Osteoporosis Risk Factor and Prevention-Fracture Prevention Study; PODA= physical performance, osteoporosis prevention, and vitamin D in older African Americans; PTH=parathyroid hormone; RCT=randomized, controlled trial; SBP=systolic blood pressure; VIDOS=Vitamin D Supplementation in Older Subjects; VITADAS=not defined by authors.

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Aloia et al (2005)[104]	Mean age (SD) Placebo: 61.2 (6.3) Vitamin D: 59.9 (6.2) N (%) female: 208 (100)	African American: 208 (100)	Mean (SD) Placebo: 30 (4) Vitamin D: 29 (4)	Osteoporosis: 0 (0) Hip fracture: 0 (0) Other comorbidities NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 17.2 (6.6) Vitamin D: 19.3 (8.4) Assay: Radioimmunoassay (DiaSorin), laboratory participates in DEQAS	Mean (SD) calcium intake mg/day Placebo: 756 (541) Vitamin D: 762 (623); Mean (SD) dietary vitamin D intake IU/day Placebo: 184 (168) Vitamin D: 184 (192) UV exposure: NR N (%) with use of bone-sparing medication: 0 (0)
Aloia et al (2018)[108] PODA	Median age (IQR): 68.2 (65.4 to 72.5); N (%) female: 258 (100)	Black: 258 (100)	Median (IQR): 30.0 (26.5 to 34.0)	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 21.9 (6.7) Assay: Immunochemiluminometric (DiaSorin Liaison)	Mean calcium intake (IQR) in mg/day: 826.5 (614 to 1,157); Vitamin D intake: NR UV exposure: NR N (%) with use of bone-sparing medication: NR
Arvold et al (2009)[82]	Mean age (SD) Placebo: 57.8 (15.8) Vitamin D: 59.7 (14.0); N (%) female Placebo: 15 (36) Vitamin D: 21 (44)	Nonwhite Placebo: 2 (5) Vitamin D: 2 (4)	NR	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 18.1 (4.0) Vitamin D: 17.9 (3.5) Assay: LC-MS/MS	Calcium intake: NR; N (%) use of over-the-counter supplements, including multivitamin, vitamin D, or calcium with vitamin D Placebo: 13 (31) Vitamin D: 15 (31) UV exposure: Participants identified and study started in midwinter N(%) with use of bone-sparing medication: NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Bischoff et al (2003)[89]	Mean age (SD) Placebo: 85.4 (5.9) Vitamin D: 84.9 (7.7); N (%) female: 122 (100)	NR	Mean (SD) Placebo: 24.7 (5.6) Vitamin D: 24.7 (5.3)	Stroke: 19 (15.6) Myocardial infarction/congestive heart failure: 61 (50.0) Hypertension: 37 (30.3) Anemia: 15 (12.3) Diabetes: 18 (14.8) Peptic ulcer disease: 20 (16.4) Depression: 30 (24.6) Dementia: 67 (54.9) Fracture at any site: 66 (54.1); Number (%) with falls in 6 weeks prior to intervention Placebo: 14 (23.3) Vitamin D: 15 (24.2)	Median (IQR) serum vitamin D level in ng/ml Placebo: 11.6 (9.2 to 22.0) Vitamin D: 12.3 (9.2 to 22.0); Assay: Radioimmunoassay (Nichols)	Mean (SD) dietary calcium intake mg/day: 600 to 700 (NR) N (%) taking vitamin D supplements before study entry: Placebo: 11* (18) Vitamin D: 12* (19) UV exposure: Study was done during the winter months (November 1999 and March 2000) N (%) with use of bone-sparing medication: 0 (0)
Bislev et al (2018)[70]	Mean age (SD): NR, all women participating were between 60 and 79 years N (%) female: 81 (100)	NR	Mean (SD) Placebo: 26.6 (1.16) Vitamin D: 27.7 (1.23)	History of fractures in adulthood Placebo: 6 (15) Vitamin D: 12 (30) Osteoporosis Placebo: 7 (17) Vitamin D: 6 (15) Other comorbidities: NR History of falls: NR	Mean serum vitamin D level in ng/ml: 13.2 (3.7) Assay: LC-MS/MS (Chromsystems)	Mean (SD) dietary calcium intake/day Placebo: 840 (1.39) Vitamin D: 800 (1.30) Vitamin D intake: NR UV exposure: The study was conducted in the winter season (November-April) during two consecutive winters (years). Additionally, women planning on travelling to sunny destinations or using tanning/sunning beds were excluded from the study. N (%) with use of bone-sparing medication: 0 (0)

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Borgi et al (2016)[109]	Mean age (SD): 37 (12.3) N (%) female Placebo: 31 (66*) Vitamin D: 31 (67*)	Nonwhite Placebo: 31* (66*) Vitamin D: 24* (52*)	Mean (SD): 33.9 (5.6)	Diabetes: 0 (0) HTN: 0 (0) Cardiovascular disease: 0 (0) Osteoporosis: 0 (0) History of cancer: 0 (0) History of falls: NR	Median (IQR) serum vitamin D level in ng/mL: 15.4 (11.4 to 17.5) Assay: Radioimmunoassay (Diasorin Corporation)	Calcium intake: NR; Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication: NR
Brazier et al (2005)[88]	Mean age (SD): 74.6 (6.9) N (%) female: 192 (100)	NR	Mean (SD): 26.7 (4.3)	Comorbidities: NR History of falls: NR	Median serum vitamin D level in ng/ml: 7.0 Assay: Competitive protein-binding assay after ethanol extraction followed by chromatographic purification.	Mean (SD) dietary calcium intake mg/day: 736.0 (369.6) Mean (SD) dietary vitamin D intake IU/day: 84.4 (70.4) UV exposure: NR N (%) with use of any bone-sparing/anabolic prescription agent: 0 (0)
Chapuy et al (2002)[87] Decalyos II	Mean age (SD): Placebo: 85.7 (7.6) Vitamin D + calcium (fixed): 84.9 (6.6) Vitamin D + calcium (separate): 84.9 (7.0); N (%) female: 583 (100)	NR	Mean (SD) NR	Comorbidities: NR N (%) with history of falls within previous 3 months Placebo: 30* (15.8) Vitamin D + calcium (fixed) serum: 29* (14.1) Vitamin D + calcium (separate) serum: 36* (18.6)	Mean (SD) serum vitamin D level in ng/ml Placebo: 9.1 (6.9) Vitamin D + calcium (fixed): 8.5 (5.3) Vitamin D + calcium (separate): 9.0 (6.6) Assay: Competitive protein-binding assay (Incstar)	Mean (SD) calcium intake mg/day Placebo: 556 (246.1) Vitamin D + calcium (fixed): 565 (230.1) Vitamin D + calcium (separate): 551 (238.0); Mean (SD) vitamin D intake IU/day: Placebo: 41 (28.8) Vitamin D + calcium (fixed): 42 (28.3) Vitamin D + calcium (separate): 40 (27.3) UV exposure: NR N (%) with use of any bone-sparing medication: 0 (0)
Davison et al (2013)[75]	Mean age (SD) Placebo: 52.5 (7.0) Vitamin D: 52.3 (8.0) N (%) female Placebo: 38* (71) Vitamin D: 36* (64)	Latino Placebo: 44* (83) Vitamin D: 51* (91)	Mean (SD) Placebo: 32.9 (4.3) Vitamin D: 32.1 (4.7)	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 22.0 (4.8) Vitamin D: 22.0 (4.5) Assay: High-performance LC-MS/MS	Calcium intake: NR; Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Gagnon et al (2014)[110]	Mean age (SD) Placebo: 55.3 (11.1) Vitamin D: 53.8 (11.9) N (%) female Placebo: 30*(67) Vitamin D: 25* (71)	European background Placebo: 31*(69) Vitamin D: 24*(69) Asian Placebo: 13*(29) Vitamin D: 8*(23) Other Placebo: 1*(2) Vitamin D: 3*(9)	Mean (SD) Placebo: 31.9 (62) Vitamin D: 31.1 (5.7)	Diabetes: 11 (14) Other comorbidities: NR N (%) with history of falls: 0 (0)	Mean (SD) serum vitamin D level in ng/ml Placebo: 17.2 (5.2) Vitamin D: 18.8 (5.2) Assay: Automated chemiluminescent immunoassay (DiaSorin)	Mean (SD) dietary calcium intake mg/day Placebo: 563 (275) Vitamin D: 689 (419) Mean (SD) dietary vitamin D intake IU/day Placebo: 108 (60) Vitamin D: 132 (76) UV exposure: N (%) with season of recruitment spring/summer Placebo: 30* (67) Vitamin D: 33* (94) Sun index, hours/week/m^2 Placebo: 152 (218) Vitamin D 158 (233) N (%) sunscreen use < 50% of the time Placebo: 31*(69) Vitamin D: 23* (66) N (%) with use of bone-sparing/anabolic prescription agents: 0 (0)
Gallagher et al (2012)[49] VIDOS	Mean age (SD) White women: 67 (7.3) Black women: 66.6 (7.5) N (%) female: 273 (100)	White: 163 (59.7*) Black: 110 (40.3*)	Mean (SD): White women: 30.2 (5.7) Black women: 32.7 (7.0)	Severe osteoporosis: 0 (0) Diabetes: 0 (0) History of cancer in last 10 years (except skin): 0 (0) Other comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: White women: 15.2 (3.8) Black women: 13.2 (4.3) Assay: Radioimmunoassay (Diasorin), laboratory participates in DEQAS	Mean (SD) dietary calcium intake mg/day White women: 685 (259) Black women: 551 (221) Mean (SD) dietary vitamin D intake mg/day White women: 114 (69) Black women: NR UV exposure: NR N (%) with use of bone-sparing medication: 0 (0)
Gallagher et al (2014)[81] VITADAS	Mean age (SD): 36.7 (5.9) N (%) female: 198 (100)	African American: 79 (40) White: 119 (60)	Mean (SD): 30.2 (6.6)	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 13.4 (4.5) Assay: Radioimmunoassay, laboratory participates in DEQAS	Mean dietary vitamin D intake/day (mg): 100

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Grimnes et al (2011)[94]	Mean age (SD): 52.1 (9.3) N (%) female: 53 (49.1)	NR	Mean (SD): 26.5 (3.1)	Diabetes: 0 (0) Cardiovascular disease: 0 (0) History of cancer: 0 (0) Other comorbidities NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 16.1 (5.1) Assay: Electrochemilumin-escence immunoassay (Modular E170, Roche Diagnostics) and an in-house–developed LC-MS/MS.	Calcium intake NR: N (%) with vitamin D supplement use: 26 (24.1) UV exposure: N (%) sun bed use past year: 6 (5.6) N (%) sunny holiday past 3 months: 8 (7.4) N (%) with use of bone-sparing medication use: NR
Hansen et al (2015)[69]	Mean age (SD): 61 (6; n (%) female: 230 (100)	White: 207 (90) Black: 14 (6.1) Asian: 5 (2.2) American Indian/Alaskan: 2 (0.9) Hispanic/Latina: 2 (0.9)	Mean (SD): 30.8 (6.8)	Diabetes: 0 (0) History of cancer (within 5 yr): 0 (0) Osteoporosis: 0 (0) Other comorbidities NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 21 (3) Assay: High-performance liquid chromatography assay	Median (IQR) total calcium intake mg/day: 967 (752 to 1,215) Median (IQR) dietary vitamin D intake IU/day: 196 (115 to 266) UV exposure: all participants were asked to apply high potency sunscreen between April and October N (%) with use of bone-sparing medication: 0 (0)

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Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Hin et al (2016)[73] BEST-D	Mean age (SD) Placebo: 72 (6) Vitamin D 2,000 IU: 72 (6) Vitamin D 4,000 IU: 71 (6) N (%) female Placebo: 49 (49) Vitamin D 2,000 IU: 51 (50) Vitamin D 4,000 IU: 50 (49)	NR	Mean (SD) Placebo: 28 (5) Vitamin D 2,000 IU: 27 (4) Vitamin D 4,000 IU: 27 (5)	Heart diseases (heart attack, angina, heart failure) Placebo: 11 (11) Vitamin D 2,000 IU: 11 (11) Vitamin D 4,000 IU: 20 (20) Fracture Placebo: 30 (30) Vitamin D 2,000 IU: 30 (29) Vitamin D 4,000 IU: 31 (30); N (%) with fall in the past 6 months Placebo: 12 (12) Vitamin D 2,000 IU: 15 (15) Vitamin D 4,000 IU: 13 (13)	Mean (SD) serum vitamin D level in ng/ml: Placebo: 19.6 (6.4) Vitamin D 2,000 IU: 22 (8.9) Vitamin D 4,000 IU: 18.8 (6.0) Assay: Access 2 immunoassay (Beckman Coulter, Ltd.), laboratory participates in DEQAS	Mean (SD) dietary calcium intake (mg/day) Placebo: 713 (302) Vitamin D 2,000 IU: 695 (292) Vitamin D 4,000 IU: 724 (287) N (%) with vitamin D intake=400 IU/day Placebo: 13 (13) Vitamin D 2,000 IU: 10 (10) Vitamin D 4,000 IU: 12 (12) UV exposure: NR N (%) with use of bone-sparing medication: NR
Honkanen et al (1990)[101]	Mean age (SE) Community dwelling Control: 69.6 (0.49) Vitamin D: 69.4 (0.54) Hospital Control: 82.8 (1.3) Vitamin D: 82.2 (1.0) N (%) female: 126 (100)	NR	NR	Comorbidities: NR; History of falls: NR	Mean (SE) serum vitamin D level in ng/ml Community-dwelling Control: 14.5 (1.1) Vitamin D: 17.1 (1.4) Hospital Control: 9.6 (1.0) Vitamin D: 9.6 (0.8) Assay: NR	Calcium intake: NR Vitamin D intake: NR Recruitment during winter months, November and December. All hospital patients were exposed to open air and sun to some extent during the summer. Excluded participants with a recent or concurrent holiday trip to the south. N (%) with use of bone-sparing medication: NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Janssen et al (2010)[90]	Mean age (SD) Placebo: 79.2 (6.7) Vitamin D: 82.4 (6.4) N (%) female: 70 (100)	NR	Mean (SD) Placebo: 26.7 (4.6) Vitamin D: 26.2 (4.9)	Mean (SD) Number of Comorbidities Placebo: 2.1 (1.1) Vitamin D: 2.7 (1.5) Comorbidities defined as cardiovascular disease, chronic obstructive pulmonary disease, cerebrovascular disease, dizziness, peripheral neuropathy, lower extremity arthritis, visual impairment, mini-mental status exam score < 24, depression; History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 13.7 (4.6) Vitamin D: 13.0 (4.6) Assay: NR	Calcium intake: NR; Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication: NR
Jorde et al (2016)[74] and Jorde et al (2016)[137]	Mean age (SD) † Placebo: 61.9 (9.2) Vitamin D: 62.3 (8.1) N (%) female† Placebo: 102 (40.0) Vitamin D: 95 (37.1)	NR	Mean (SD)† Placebo: 29.8 (4.4) Vitamin D: 30.1 (4.1)	Osteoporosis: NR Diabetes: 0 (0) Cardiovascular Disease: 0 (0) History of cancer: 0 (0) Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml NR for the subgroup of vitamin D–deficient participants (subgroup defined as serum level <20 ng/ml) Assay: LC-MS/MS	Calcium intake: NR N (%) vitamin D supplementation use# Placebo: 92 (36.1) Vitamin D: 87 (34.0) #Represents characteristic for the entire study population, not the subgroup that was vitamin D deficient UV exposure: NR N (%) with use of bone-sparing medication: NR
Jorde et al (2018)[77]	Mean age (SD): 52.0 (8.8); N (%) female: 191 (46.8)	NR	Mean (SD): 27.8 (4.8)	Diabetes: 0 (0%) History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 13.5 (5.0) Assay: LC-MS/MS	Calcium intake: NR Vitamin D intake: NR Regular use of solarium and participants with planned "sunny" holidays excluded from study. No difference in participant recruited in various seasons. N (%) with any use of bone-sparing medication: NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Mean age (SD) Control: 67.4 (1.9) Vitamin D: 67.4 (2.0); N (%) female: 593 (100)	NR	Mean (SD) Control: 27.4 (3.9) Vitamin D: 27.5 (4.5)	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Control: 19.7 (7.1) Vitamin D: 20.0 (7.5) Assay: Radioimmunoassay (DiaSorin)	Mean (SD) total calcium intake mg/day Control: 965 (489) Vitamin D: 988 (490); Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication Control: NR (6.9) Vitamin D: NR (11.1)
Kearns et al (2015)[111]	Mean age (SD) Placebo: 26.5 (5.2) Vitamin D: 28.2 (6.7) N (%) female Placebo: 10 (71) Vitamin D: 12 (86)	Nonwhite Placebo: 5* (36*) Vitamin D: 5* (36*)	Mean (SD) Placebo: 22.3 (2.2) Vitamin D: 23.7 (2.9)	Osteoporosis: 0 (0) Diabetes: 0 (0) Cardiovascular disease: NR History of cancer: 0 (0) Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/mL Placebo: 16.5 (NR) Vitamin D: 16.6 (NR) Assay: IDS-iSYS immunoassay (Immunodiagnostic Systems, Inc.), participates in DEQAS	Mean (SD) dietary calcium intake mg/day Placebo: 0 (0) Vitamin D: 0 (0); N of study participants receiving daily vitamin D supplementation at baseline (400 to 1,000 IU) Placebo: 1 (7.1*) Vitamin D: 4 (28.5*) UV exposure: study administered dose of in November to evaluate impact over winter months. N (%) with use of any bone-sparing medication: NR
Kjaergaard et al (2012)[80] Tromo Study	Mean age (SD) Placebo: 53.3 (10.1) Vitamin D: 53.4 (10.3) N (%) female: 129 (56)	NR	Mean (SD) Placebo: 28.0 (4.2) Vitamin D: 27.5 (4.0)	Diabetes: 0 (0) Cancer: 0 (0) Other comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D3 level in ng/ml Placebo: 19.1 (6.2) Vitamin D: 19.0 (6.3) Assay: Isotope dilution tandem mass spectrometry	Calcium intake: NR; Vitamin D intake: NR UV exposure: Participants reporting a planned trip to a sunny location in the trial period were excluded. N (%) with use of any bone-sparing medication: NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Knutsen et al (2014)[105]	Mean age (SD) Placebo: 39 (7.6) Vitamin D 400 IU: 37 (7.6) Vitamin D 1,000 IU 36 (8.2) N (%) female Placebo: 63 (77) Vitamin D 400 IU: 61 (72) Vitamin D 1,000 IU: 58 (69)	NR	Mean (SD) Placebo: 27.8 (5.0) Vitamin D 400 IU: 27.5 (5.2) Vitamin D 1,000 IU: 27.0 (5.2)	Osteoporosis: 0 (0) Diabetes: NR Cardiovascular disease: NR History of cancer: 0 (0) Dementia: NR Recent fractures: 0 (0) History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 10.8 (6.0) Vitamin D 400 IU: 10.8 (6.0) Vitamin D 1,000 IU: 10.8 (6.8) Assay: High performance LC-MS/MS, laboratory participates in DEQAS	Calcium intake: NR; Vitamin D intake: NR UV exposure: assessments were done in spring and winter, times with minimal sun exposure N (%) with use of bone-sparing medication NR
Krieg et al (1999)[91]	Mean age (SD)‡ Control: 85 (7) Vitamin D: 84 (8) (N=103) N (%) female: 248 (100)	NR	Mean (SD)‡ Control: 23.8 (5.4) Vitamin D: 25.7 (4.8) (N=103)	Comorbidities: NR History of falls: NR	Mean (SEM) serum vitamin D level in ng/ml Control: 11.7 (1.2) Vitamin D: 11.9 (1.2) Assay: Protein binding assay (Amersham Life Science)	Calcium intake: NR; Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication NR
Lehmann et al (2013)[46]	Mean age (SD) Placebo: 31.6 (9.3) Vitamin D_2: 33.2 (12.4) Vitamin D_3: 35.6 (13.5) N (%) female: 68 (63.6)	NR	Mean BMI (SD) kg/m^2 Placebo: 23.7 (4.9) Vitamin D_2: 23.7 (3.8) Vitamin D_3: 24.0 (4.2)	Comorbidities: NR; History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 16.1 (7.2) Assay: LC-MS	Calcium intake: NR; Vitamin D intake: NR UV exposure: Study conducted during January, February, and March when virtually no UVB irradiation is measurable in the surrounding region. Participants with vacations in areas with abundant UVB irradiation in the course of the study were excluded. Bone-sparing medication: NR
Lerchbaum et al (2017)[112] Graz Vitamin D&TT-RCT	Median age (IQR): 37 (27 to 50) N (%) female: 0 (0)	NR	Median (IQR): 25.1 (22.8 to 26.8)	Osteoporosis: 0 (0) Diabetes: 0 (0) Cardiovascular disease: NR History of cancer: 0 (0) Dementia: NR Fractures: NR History of falls: NR	Median (IQR) serum vitamin D level in ng/mL: 20.8 (16.8 to 26.4) Assay: Immunoassay and isotope-dilution LC-MS/MS	Calcium intake: NR Vitamin D intake: NR UV exposure: participants recruited throughout the year, seasonal variation analyzed N (%) with use of any bone-sparing medication NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Lips et al (1996)[86]	Mean age (SD): 80 (6); N (%) female: 1,916 (74)	NR	Mean (SD)[§] Placebo: 28.6 (4.0) Vitamin D: 28.1 (4.1)	Hip fractures: 0 (0) Other comorbidities: NR History of falls: 0 (0)	Median (IQR) serum vitamin D level in ng/ml at baseline:[¶] Placebo: 10.4 (7.6 to 14.8) Vitamin D: 10.8 (7.6 to 14.4) Assay: Competitive protein binding assay	Median (IQR) supplement calcium intake mg/day Placebo: 859 (644 to 1,099) Vitamin D: 876 (638 to 1,101) N (%) with vitamin D supplement use at baseline: 133 (5.2*) UV exposure: outdoor and sunshine scores similar between placebo and active treatment group. N (%) with use of any bone-sparing medication NR
Lips et al (2010)[83]	Mean age (SD) Placebo: 77.6 (6.6) Vitamin D: 78.5 (6.2) N (%) female: NR	NR	NR	Osteoporosis: NR Diabetes: NR Cardiovascular disease: NR History of cancer: 0 (0%) Dementia: NR Fractures: NR 14% were residents of a nursing home History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 14.1 (5.5) Vitamin D: 13.7 (4.4) Assay: Reverse phase HPLC, laboratory participates in DEQAS	Calcium intake: NR; Vitamin D intake: NR UV exposure: instructed participants to avoid direct sunlight, participants agreed to apply sunscreen (SPF 15 or greater) when time in direct sunlight was greater than 15 minutes N (%) with use of any bone-sparing medication NR
Manson et al (2019)[71] VITAL	Mean age (SD): 67 (7.1) N (%) female: 13,085 (50.6)	Black: 5,106 (20.2) Nonblack Hispanic: 1,013 (4.0) Asian or Pacific Islander: 388 (1.5) Native American or Alaska Native: 228 (0.9)	Mean (SD): 28.1 (5.7)	Osteoporosis: NR Diabetes: 3,549 (13.7) Cardiovascular disease: 0 (0) History of cancer: 0 (0) Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 30.8 (10.0) Percent between 20-30 ng/ml: 32.2 Assay: LC-MS/MS (Quest Diagnostics), participated in the CDC Vitamin D Standardization Program	N (%) with current use of supplemental calcium (<1,200 mg/d): 5,166 (20.0) N (%) with current use of supplemental vitamin D (<800 mg/d): 11,030 (42.6) UV exposure: NR N (%) with any use of bone-sparing medication: NR
Martineau et al (2007)[106]	Median age (IQR) Placebo: 37.5 (29.8 to 45.2) Vitamin D: 30.1 (25.1 to 44.1); N (%) female: 67 (51.2)	White: 18 (13.7) Black African: 17 (12.9) South Asian: 90 (68)	NR	Comorbidities: NR History of falls: NR	N (%) with serum vitamin D level < 8 ng/ml Placebo: 30 (46.9) Vitamin D: 23 (34.3) Assay: Isotope-dilution LC-MS, laboratory participates in DEQAS	Calcium intake: NR Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Mason et al (2014)[113] ViDA (US)	Mean age (SD): 59.6 (5.1) N (%) female: 218 (100)	Non-Hispanic white: 188 (86.2) Non-Hispanic black: 13 (6.0) Hispanic: 5 (2.3) American Indian, Asian, or unknown: 12 (5.5)	Mean (SD): 32.4 (5.8)	Osteoporosis: 0 (0) Diabetes: 0 (0) Cardiovascular disease: NR History of cancer: 0 (0) Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 21.4 (6.1) Assay: Chemiluminescence immunoassay (DiaSorin)	Mean total calcium intake (diet and supplement) in mg/day: 1,120 (600) Mean dietary vitamin D intake (ug) per day: 6.6 (4.6) Mean vitamin D supplement intake (IU) per day: 332.4 (106.2) UV exposure: sun exposure (hours/week): 2.4 (1.3) N (%) with use of bone-sparing medication NR
Moreira-Lucas et al (2017)[114]	Mean age (SD) Placebo: 45.6 (14.3) Vitamin D: 49.1 (13.9) N (%) female Placebo: 20 (56) Vitamin D: 18 (51)	White Placebo: 19 (54) Vitamin D: 12 (34)	Mean (SD) Placebo: 31.7 (4.9) Vitamin D: 30.1 (3.9)	Osteoporosis: NR Diabetes: 0 (0) Cardiovascular disease: NR History of cancer: NR Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 19.0 (5.7) Vitamin D: 19.2 (5.7) Assay: High performance LC-MS/MS, laboratory participates in DEQAS.	Mean (SD) dietary calcium intake (mg/day) Placebo: 817 (370) Vitamin D: 678 (352) Mean (SD) dietary vitamin D intake (IU/day) Placebo: 144 (118) Vitamin D: 138 (123) UV exposure: NR N (%) with use of any bone-sparing medication NR
Ng et al (2014)[115]	Median age (IQR): 51.0 (43.6 to 59.4) N (%) female: 222 (67.7)	Black: 328 (100)	Median (IQR): 31.2 (26.8 to 36.3)	Comorbidities: NR History of falls: NR	Median (IQR) serum vitamin D level in ng/ml: 15.3 (10.4 to 22.8) Assay: Radioimmunoassay (Diasorin Inc.)	Median (IQR) calcium intake (mg/day): 356.6 (188.6 to 693.8) Median (IQR) dietary vitamin D intake (IU/day): 167.5 (72.3 to 291.8) N (%) with vitamin D supplementation: 24 (7.3) UV exposure: enrollment occurred over winter/spring months to minimize confounding due to UVB radiation N (%) with use of any bone-sparing medication NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Nowak et al (2016)[116]	Mean age (SD) Placebo: 28 (6) Vitamin D: 29 (7) N (%) female Placebo: 33 (52) Vitamin D: 31 (53)	White 110 (92) Black: 1 (1) Asian: 6 (5) Indian: 3 (3)	Median (IQR) Placebo: 22 (21 to 24) Vitamin D: 22 (21 to 24)	Comorbidities: NR; History of falls: NR	Median (IQR) serum vitamin D level in ng/ml Placebo: 14 (10 to 17) Vitamin D: 13 (10 to 18) Assay: Automated immunoassay Cobas 8000 Analyzer (Roche Diagnostics)	Calcium intake: NR; Vitamin D intake: NR UV exposure: the allocation of treatment groups did not differ by season N (%) with use of any bone-sparing medication
Pfeifer et al (2000)[85]	Mean age (SD) Calcium: 74.7 (0.5) Vitamin D: 74.8 (0.5) N (%) female: 148 (100)	NR	Mean (SD) Calcium: 24.6* (NR) Vitamin D: 24.8* (NR) *Calculated from reported mean weight and height	Osteoporosis: 0 (0) Diabetes: 0 (0) Cardiovascular disease: NR History of cancer: NR Dementia: NR Fractures from osteoporosis: 0 (0) History of falls NR	Mean (SD) serum vitamin D level in ng/ml Calcium: 9.8 (4.9) Vitamin D: 10.3 (5.5) Assay: Radioimmunoassay (Nichols Institute)	Calcium intake: NR; Vitamin D intake: 0 (0) UV exposure: exclusion criteria included scheduled holiday along the geographic longitude during the study period, study enrolled participants in March. N (%) with use of any bone-sparing medication: 0 (0)
Pfeifer et al (2009)[84]	Mean age (SD) Calcium: 77 (4) Vitamin D: 76 (4) N (%) female Control: 91* (75) Vitamin D: 90* (74)	NR	Mean (SD) Calcium: 27.4* (NR) Vitamin D: 27.0* (NR) *Calculated from reported mean weight and height	Osteoporosis: 0 (0) Diabetes: 0 (0) Severe cardiovascular disease: 0 (0) History of cancer: NR Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Calcium: 21.6 (7.6) Vitamin D: 22.0 (7.2) Assay: Radioimmunoassay (Immunodiagnostic Systems)	Mean (SD) nutritional calcium intake mg/day Calcium: 628 (42) Vitamin D: 608 (38); Mean (SD) supplement vitamin D intake: 0 (0) UV exposure: exclusion criteria included scheduled holidays along the geographic longitude during the study period. The study commenced in May 2001 and terminated in March 2003. N (%) with use of any bone-sparing medication NR
Pilz et al (2015)[117] Styrian Vitamin D Hypertension Trial	Mean age (SD): 60.0 (11.1) N (%) female: 94* (47)	NR	Mean (SD): 30.4 (5.4)	Osteoporosis: NR Diabetes: 73 (36.5) Cardiovascular disease: NR History of cancer: NR Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 21.1 (5.6) Assay: ChemiLuminescence assay (Immunodiagnostics Systems, Ltd.)	N (%) taking calcium supplements: 16* (8) N (%) taking vitamin D supplements: 14 (7) UV exposure: NR N (%) with use of any bone-sparing medication NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Pittas et al (2019)[76] D2d	Mean age (SD) : 60.0 (9.9)† N (%) female: 1,086 (44.8) †	Asian: 130 (5.4)† Black: 616 (25.4)† White: 1,616 (66.7)† Other: 61 (2.5)†	Mean (SD): 32.1 (4.5)†	Diabetes: 0 (0) Other Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml: 28.0 (10.2)† Assay: LC-MS/MS, laboratory participates in DEQAS	Calcium intake: NR; Vitamin D intake: NR UV Exposure: NR N (%) with use of any bone-sparing medication NR
Raed et al (2017)[118]	Mean (SD) age Placebo: 27.8 (9.9) Vitamin D 18,000 IU: 26.2 (9.8) Vitamin D 60,000 IU: 24.4 (8.7) Vitamin D 120,000 IU: 25.5 (9.0) N (%) female Placebo: 13 (76) Vitamin D 18,000 IU: 15 (88) Vitamin D 60,000 IU: 15 (83) Vitamin D 120,000 IU: 16 (89)	African American: 70 (100)	Mean (SD) Placebo: 36.2 (8.3) Vitamin D 18,000 IU: 34.6 (5.4) Vitamin D 60,000 IU: 37.1 (8.0) Vitamin D 120,000 IU: 34.4 (7.2)	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D in ng/ml Placebo: 15.9 (3.9) Vitamin D 18,000 IU: 14.0 (3.9) Vitamin D 60,000 IU: 15.9 (3.7) Vitamin D 120,000 IU: 13.3 (4.4) Assay: Enzyme immunoassay (Immunodiagnostics Systems), laboratory participates in DEQAS	Calcium intake: NR; Vitamin D intake: NR UV exposure: season of recruitment was adjusted for in the analyses. About three-quarters of participants were recruited in the winter or spring N (%) with use of any bone-sparing medication NR
Scragg et al (2017),[97] Scragg et al (2018)[98] Khaw et al (2017)[72] ViDA (NZ)	Mean age (SD): 65.9 (8.3) † N (%) female: 2,139 (41.9)†	European or other: 4,253 (83.3)† Polynesian or South Asian: 855 (16.7)†	Mean (SD) † Placebo: 28.5 (5.1) Vitamin D: 28.4 (5.1)	Diabetes† Placebo: 239 (9.4) Vitamin D: 265 (10.4) Myocardial infarction† Placebo: 162 (6.4) Vitamin D: 168 (6.6) Stroke† Placebo: 31 (1.2) Vitamin D: 50 (2.0) Osteoporosis: NR Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml† Placebo: 25.2 (9.4) Vitamin D: 25.5 (9.5) Assay: LC-MS/MS (ABSciex API 4000), laboratory participates in DEQAS	N (%) using calcium supplements† Placebo: 127 (5.0) Vitamin D: 125 (4.9) N (%) using vitamin D supplements† Placebo: 200 (7.8) Vitamin D: 208 (8.1) UV exposure: self-reported sun exposure recorded at baseline N (%) with use of any bone-sparing medication: NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Shea et al (2019)[78]	Mean age (SD): 69.6 (6.9) 36 (36%*) female	Nonwhite: 21 (21*) White: 79 (79*)	Mean (SD): 28.2 (7.0)	Comorbidities: NR N (%) with fall within last 2 months Placebo: 2 (3.9*) Vitamin D: 3 (6.1*)	Mean (SD) serum vitamin D level in ng/ml: 20.2 (6.7) Assay: LC-MS/MS (ZRT Laboratory)	Mean (SD) calcium intake mg/day Placebo: 815 (424) Vitamin D: 926 (439); Mean (SD) vitamin D intake ug/day Placebo: 160 (168) Vitamin D: 192 (208); UV exposure: NR N(%) with use of any bone-sparing medication: 0
Tran et al (2014)[119] D-Health	Mean age (SD): 72 (NR); N (%) female: 288* (47)	Nonwhite Placebo: 8 (3.9) Vitamin D 30,000 IU: 9 (4.3) Vitamin D 60,000 IU: 14 (6.8)	N (%) with BMI <25 Placebo: 63.0 (31.0) Vitamin D 30,000 IU: 76 (36.2) Vitamin D 60,000 IU: 64 (31.2)	Osteoporosis: 0 (0) Diabetes: NR Cardiovascular disease: NR History of cancer: NR Dementia: NR Fractures: NR; History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 16.8 (5.3) Vitamin D 30,000 IU: 16.6 (5.1) Vitamin D 60,000 IU: 16.6 (5.6); Assay: Chemiluminescent immunoassay (LIAISON, DiaSorin, Inc.), laboratory participates in DEQAS	NR; N (%) with > 100 IU/day Placebo: 86 (41.9) Vitamin D 30,000 IU: 74 (35.2) Vitamin D 60,000 IU: 68 (33.2) UV exposure: participants were recruited during summer months N (%) with use of any bone-sparing medication NR
Wamberg et al (2013)[107]	Mean age (SD) Placebo: 41.2 (6.8) Vitamin D: 39.5 (8.0) N (%) female: 39 (71)	NR	Mean (SD) Placebo: 35.0 (3.2) Vitamin D: 36.1 (3.4)	Comorbidities: NR History of falls: NR	Mean (SD) vitamin D level in ng/ml Placebo: 13.8 (4.1) Vitamin D: 13.8 (4.3) Assay: Isotope dilution LC-MS	Mean (SD) dietary calcium intake mg/day Placebo: 936 (389) Vitamin D: 992 (400) Median (IQR) dietary vitamin D intake IU/day Placebo: 68 (56 to 124) Vitamin D: 84 (60 to 160) UV exposure: participants recruited from February 2010 to May 2011 N (%) with use of any bone-sparing medication NR

Appendix D Table 2. Population Characteristics of Included RCTs

Author (Year) Trial Name	Age and Sex	N (%) Race and Ethnicity	Body Mass Index	N (%) Comorbidities	Vitamin D Status and Assay Used	Other Baseline Characteristics
Witham et al (2013)[102]	Mean age (SD) Placebo: 39.4 (11.8) Vitamin D: 41.7 (13.4) N (%) female: 50 (100)	Nonwhite: 50 (100)	Mean (SD) Placebo: 28.7 (5.5) Vitamin D: 24.9 (3.3)	Comorbidities: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/mL Placebo: 10.8 (6.0) Vitamin D: 10.8 (5.2) Assay: ELISA (IDS Ltd)	Calcium intake: NR; Vitamin D intake: NR UV exposure: NR N (%) with use of any bone-sparing medication NR
Wood et al (2012)[93]	Mean age (SD) Placebo: 63.9 (2.3) Vitamin D 400 IU: 63.5 (1.9) Vitamin D 1,000 IU: 64.1 (2.3) N (%) female: 305 (100)	Caucasian: 305 (100)	Mean (SD) Placebo: 26.6 (4.4) Vitamin D 400 IU: 26.6 (4.2) Vitamin D 1,000 IU: 26.8 (4.2)	Osteoporosis NR Diabetes NR Cardiovascular disease: 0 (0%) History of cancer: NR Dementia: NR Fractures: NR History of falls: NR	Mean (SD) serum vitamin D level in ng/ml Placebo: 14.5 (6.8) Vitamin D 400 IU: 13.1 (5.2) Vitamin D 1,000 IU: 13.0 (5.5) Assay: High-pressure LC-MS	Dietary calcium intake in mg/day Placebo: 1,327 (441) Vitamin D 400 IU: 1,242 (741) Vitamin D 1,000 IU: 1,269 (630) Total vitamin D intake (dietary and supplement) in IU/day Placebo: 220 (144) Vitamin D 400 IU: 244 (136) Vitamin D 1,000 IU: 268 (176) UV exposure: UVB exposure measured using UVB light badges pinned to the lapel of study participants' outside coats for 1 wk after each study visit. Weekly standard erythemal dose (SED) were calculated. Questions were asked about the extent of skin exposure to sunlight including the body surface area exposed. N (%) with use of any bone-sparing medication: 0 (0)

* Represents calculated values.

† Represents characteristic for the entire study population, not the subgroup that was vitamin D deficient.

ǂ Of those who completed the study.

§ measured in a subset of 348 women participating in a substudy focused on BMD.

¶ Serum levels were only measured on a subset of 270 participants who were residents of apartments and homes for the elderly; the serum level in the larger population is NR.

Abbreviations: BMD=bone mineral density; BMI=body mass index; CDC=Centers for Disease control and Prevention; DEQAS=Vitamin D External Quality Assessment Scheme; HPLC=high performance liquid chromatography; HTN=hypertension; IQR=interquartile range; IU=international units; LC-MS=liquid chromatography mass spectrometry; LC-MS/MS=liquid chromatography tandem mass spectrometry; N=number; NR=not reported; OSTPRE-FPS=Osteoporosis Risk Factor and Prevention-Fracture Prevention Study; PODA= physical performance, osteoporosis prevention, and vitamin D in older African Americans; SD=standard deviation; SE=standard error; SED=standard erythemal dose; UV=ultraviolet light; UVB=type B ultraviolet.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Aloia et al (2005)[104]	Placebo, presumably qd (104) Vitamin D3 800 IU qd, changed to 2,000 IU qd at 2 yr (104)	3 yr	Supplemental calcium was given to both groups based on food frequency assessment at baseline to achieve a total daily calcium intake of 1,200 to 1,500 mg per day	NR	Mean pill count compliance was 87%. Serum vitamin D levels increased in treatment group relative to placebo group.
Aloia et al (2018)[108] PODA	Placebo capsule qd titrated to match distribution of vitamin D group (130) Vitamin D_3 titrated to maintain a serum level of 30 ng/mL. Dosage adjusted every 3 months to the nearest 30 ug to maintain the target. Doses were provided as a single capsule taken daily (130)	3 yr	Calcium supplements, if needed based on dietary recall, provided to achieve a total dietary intake of 1,200 mg/day	NR	Compliance reported at 85% as measured by pill count. Serum vitamin D levels increased in treatment group relative to placebo group.
Arvold et al (2009)[82]	Placebo, presumably weekly (50) Vitamin D_3 50,000 IU weekly (50)	8 wk	NR	NR	Serum vitamin D level increased in treatment group compared with placebo group.
Bischoff et al (2003)[89]	Placebo, bid (60) Vitamin D_3 400 IU bid (total daily dose 800 IU) (62)	12 wk	1,200 mg calcium per day	NR	NR Serum vitamin D levels increase in active treatment group compared with placebo.
Bislev et al (2018)[70]	Placebo qd (41) Vitamin D_3 2,800 IU qd(40)	12 wk	None	NR, however, no participants were using calcium or vitamin D supplements at enrollment	Compliance reported at 99.2% as measured by pill count and no differences between groups. Serum vitamin D levels increased in treatment group relative to placebo group.
Borgi et al (2016)[109]	Placebo, presumably weekly (47) Vitamin D_2 50,000 IU tablets weekly (46)	8 wk	NR	Not allowed (part of exclusion criteria)	Pill counts at 4-wk outpatient checkup and study staff contacted subjects weekly to ascertain compliance. Serum vitamin D levels increased in treatment group relative to placebo group.

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Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Brazier et al (2005)[88]	Placebo bid (97) 500 mg calcium carbonate + Vitamin D_3 400 IU bid (1,000 mg/800 IU total daily dose) (95)	52 wk	NR	Not explicitly reported but women taking vitamin D within the past 6 months at baseline were excluded from enrollment.	Adherence monitored by pill counts at each visit. Compliance was 92.0% in the calcium + vitamin D group and 92.5% in the placebo group. Active treatment group had increased serum vitamin D level compared with placebo group after 12 months of treatment.
Chapuy et al (2002)[87] Decalyos II	Placebo qd (NR) Vitamin D_3 800 IU and 1,200 mg tricalcium phosphate as fixed combination qd (NR) Vitamin D_3 800 IU and 1,200 mg tricalcium phosphate as separate combination qd (NR)	2 yr	NR	NR	Treatments administered at lunchtime during a meal in presence of a nurse, the mean compliance was more than 95% in the treatment groups. Serum vitamin D levels were higher at followup in active treatment groups compared with placebo group.
Davison et al (2013)[75]	Placebo weekly (53) Vitamin D_3 weekly, dosing based on body weight and baseline serum vitamin D level to achieve a target serum vitamin D level of 65 ng/ml to 90 ng/ml. Average weekly dose 88,865 (16,154) IU with a range of (64,731-134,446) (56)	52 wk	None	Participants were allowed to continue any current vitamin/mineral supplements they were taking.	Syringes returned at each visit. 100% compliance. Participants in the vitamin D group achieved much higher vitamin D levels as compared with the placebo group.
Gagnon et al (2014)[110]	Placebo qd (49) 2,000 IU vitamin D_3, vitamin D dose increased by 2,000 IU every 2 months if serum vitamin D levels not at target (30 ng/ml) (46)	26 wk	1,200 mg calcium carbonate qd	NR	Method of measuring adherence NR: compliance for calcium tablets was 76% in placebo group and 81% in vitamin D group, compliance for vitamin D was 80% in placebo group, and 85% in vitamin D group. Serum vitamin D group increased in active treatment group compared with placebo group.

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Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Gallagher et al (2012)[49], Gallagher et al (2013)[103] VIDOS	Placebo, qd (38) Vitamin D_3 400 IU qd (22) Vitamin D_3 800 IU qd (45) Vitamin D_3 1,600 IU qd (43) Vitamin D_3 2,400 IU qd (44) Vitamin D_3 3,200 IU qd (23) Vitamin D_3 4,000 IU qd (24) Vitamin D_3 4,800 IU qd (34)	52 wk	Calcium supplements administered to achieve a total daily intake of 1,200 mg to 1,400 mg daily, based on baseline food diary.	Participants were not allowed to take other vitamin D supplements during the study; those who wanted to take multivitamins were provide multivitamins without vitamin D.	Measured with pill counts. White women: 94% for vitamin D and 91% for calcium Black women: range 81% to 91% for vitamin D, range 70% to 79% for calcium Serum vitamin D levels higher in active treatment groups at followup compared with placebo.
Gallagher et al (2014)[81] VITADAS	Placebo qd (38) Vitamin D_3 400 IU qd (37) Vitamin D_3 800 IU qd (42) Vitamin D_3 1,600 IU qd (41) Vitamin D_3 2,400 IU qd (40)	52 wk	Calcium supplements were given to maintain a total calcium intake between 1,000 and 1,200 mg, based on dietary record at baseline.	Use of vitamin D not allowed; participants were provided with multivitamins without vitamin D upon request.	Pill counts at study visits at 3, 6, 9, and 12 months, mean compliance for vitamin D in white women was 88% and in African American women was 84%. Serum vitamin D increased more in active treatment groups relative to placebo groups.
Grimnes et al (2011)[94]	Placebo capsules twice per week (53) Vitamin D_3 20,000 IU twice per week (weekly dose 40,000 IU) (51)	26 wk	None	NR	A study nurse contacted the participants by phone after 1 and 3 months to ensure that the study medication was taken correctly. Unused study medication was returned and counted. Compliance was 97-98% in both groups, all but 1 subject in each group had compliance >80%. Serum levels increased in the treatment group compared with the placebo group.
Hansen et al (2015)[69]	Placebo qd (76) Vitamin D_3 800 IU qd (75) Vitamin D_3 50,000 IU twice monthly after an initial loading dose of 50,000 IU qd for 15d, women with serum levels < 30 ng/ml at followup study visits had doses increased and titrated to target (79)	52 wk	Participants consuming less than 600 mg or more than 1,400 mg/d of calcium were counseled to consume 600 to 1,400 mg/d by modifying their dietary and/or supplemental calcium intake.	Participants asked to refrain from ingestion of vitamin D outside of the study.	Adherence to therapy was approximately 100% across all arms. Serum levels were higher in participants on active treatment relative to the placebo group at all timepoints after baseline.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Hin et al (2016)[73] BEST-D	Placebo qd (101) Vitamin D_3 2,000 IU qd (102) Vitamin D_3 4,000 IU qd (102)	52 wk	None	Not explicitly reported, but participants who were taking ≤ 400 IU/day were allowed to enroll in the study.	6-month compliance (%): Placebo: 87 2,000 IU: 93 4,000 IU: 93 12-month compliance (%): Placebo: 85 2,000 IU: 92 4,000 IU: 90 Mean (SD) serum vitamin D level in active treatment groups elevated compared with placebo at both 6 and 12 months
Honkanen et al (1990)[101]	No intervention (63) Vitamin D_3 1,800 IU with calcium 1,558 mg qd (63)	11 wk	NR	NR	NR Serum vitamin D level increased in active treatment group compared with control group.
Janssen et al (2010)[90]	Placebo qd (34) Vitamin D_3 400 IU qd (36)	24 wk	NR	Use of vitamin D supplementation at baseline was excluded.	Subjects were contacted at 3 months to answer questions, compliance ranged from 59% to 100%, mean compliance was 94.8%. Active treatment group had increased serum vitamin D level compared with placebo group at 24 weeks.
Jorde et al (2016)[74] and Jorde et al (2016)[137]	Unplanned subgroup analysis Placebo once weekly (85) Vitamin D_3 20,000 IU weekly (88)	5 yr	NR	The subjects were not allowed to take vitamin D supplements exceeding 400 IU/d.	New medication was supplied every 6 months and unused capsules were returned and counted. The compliance rate was between 95% and 99% at all visits for both groups in the overall study population; Serum vitamin D level increased in active treatment group compared with placebo group.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Jorde et al (2018)[77]	Placebo, five capsule loading dose followed by one capsule each week (202) Loading dose of 100,000 IU vitamin D_3 capsules followed by 20,000 IU each week (206)	16 wk	NR	Vitamin D supplementation over 800 IU daily excluded.	Unused medication was returned and counted. Compliance was measure by number of unused pills and time between second and fourth visit, 86% had 100% compliance and the rest had compliance rate between 8$% and 100%. Mean serum vitamin D levels increased in active treatment group and decreased in placebo group, confirming adherence to treatment.
Kärkkäinen et al (2010)[92] OSTPRE-FPS	No intervention (313) Vitamin D_3 400 IU bid (total daily dose 800 IU) with Calcium 500 mg bid (total daily dose 1,000 mg) (290)	3 yr	None	Participants were asked to continue with their previous diet.	Adherence calculated based on tablets dispensed, the mean compliance in the trial was 79%. Serum vitamin D levels were higher in the treatment group as compared with the control group.
Kearns et al (2015)[111]	Five placebo pills by mouth at once (14) Five vitamin D_3 50,000 IU tablets by mouth once for a total single dose of 250, 000 IU (14)	One-time dose, 1 yr of followup	NR	Calcium: dose > 1,000 mg/day was not allowed, 0 subjects reported intake of calcium during study Vitamin D: 5 subjects were receiving vitamin D supplementation at baseline (400 to 1,000 IU)	Participants were directly observed to take either vitamin D or placebo. Plasma vitamin D levels were measured at 5 days and demonstrated difference in serum levels between vitamin D and placebo groups.
Kjaergaard et al (2012)[80] Tromo Study	Placebo, weekly (121) Vitamin D_3 40,000 IU weekly (122)	12 wk	None	NR	Method of adherence measurement was NR; the adherence rate was reported by study authors as 94% in both groups. Vitamin D serum levels were higher in active treatment group compared with placebo group.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Knutsen et al (2014)[105]	Placebo qd (82) Vitamin D_3 400 IU qd (85) Vitamin D_3 1,000 IU qd (84)	16 wk	NR	Participants advised to maintain their usual diet during intervention; vitamin D supplementation use excluded at baseline.	Adherence maximized by reminder text messages twice per week during study period. Active treatment groups had increased serum vitamin D level compared with placebo group at 16 weeks. Dosing effect observed between two active treatment groups.
Krieg et al (1999)[91]	No intervention (124) Vitamin D_3 880 IU + 1,000 mg calcium qd (124)	2 yr	NR	NR	Medications were given by nursing staff to avoid lack of compliance. Active treatment group had increased serum vitamin D level compared with placebo group at 2 years.
Lehmann et al (2013)[46]	Placebo, presumably qd (20) Vitamin D_2 2,000 IU qd (50) Vitamin D_3 2,000 IU qd (49)	8 wk	NR	NR	Compliance checked by counting the returned tablets was 97%. Serum vitamin D levels indicated adherence.
Lerchbaum et al (2017)[112] Graz Vitamin D&TT	50 oily placebo drops weekly (50) Vitamin D_3 20,000 IU as 50 oily drops weekly (50)	12 wk	NR	Not allowed (part of exclusion criteria)	Participants asked to return study medication bottles at study end. Serum vitamin D levels increased in treatment group relative to placebo group.
Lips et al (1996)[86]	One placebo tablet qd (1,287) Vitamin D_3 400 IU tablet qd (1291)	3 to 3.5 yr	All participants were also advised in writing to consume at least three servings of dairy products per day to ensure a calcium intake of at least 800 to 1,000 mg/d.	N (%) taking a vitamin or multivitamin supplement that contained vitamin D at two or more followup visits: 73 (2.8)	Compliance was considered adequate if participants reported that they took the tablets on 5 or more days per week; compliance was adequate in 85% of participants. Serum vitamin D level measures in a subset of 270 participants after 1 year; results showed an increase in the active treatment group relative to the placebo group.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Lips et al (2010)[83]	Three placebo tablets once a week (112) Vitamin D_3 8,400 IU weekly (114)	16 wk	Participants with daily dietary calcium intake under 1,000 mg were prescribed a 500 mg calcium carbonate supplement.	Participants refrained from vitamin D supplementation > 100 IU per day.	Method of ascertainment NR; authors reported that all participants who completed the trial were adherent as defined by taking ≥13 of the 16 total doses. Active treatment group had increased serum vitamin D level compared with placebo group after 16 weeks of treatment.
Manson et al (2019)[71] VITAL	Planned subgroup among N=2,001 participants Placebo pill taken by mouth once daily Vitamin D_3 2,000 IU per day taken by mouth once daily	NR, but median length of followup was reported as 5.3 yr (IQR, 3.8 to 6.1)	In this trial, participants were also randomized to omega-3 fatty acids in a 2X2 factorial design	No more than 800 IU/day of vitamin D was allowed. At 2 years, the prevalence of outside use of vitamin D (>800 IU per day) was 3.8% in the vitamin D group and 5.6% in the placebo group; at 5 years, the prevalence was 6.4% and 10.8%, respectively. Outside use of calcium: NR	Followup questionnaires to assess adherence at 6 months and 1 year after randomization and annually thereafter. The mean rate of adherence to the trial regimen (the percentage of participants who reported taking at least two-thirds of the trial capsules) was 82.0% in the vitamin D group and 80.3% in the placebo group during the 5.3-year followup period. Serum vitamin D levels increased from baseline in the active treatment group compared with the placebo group at 1-year followup.
Martineau et al (2007)[106]	Placebo (one-time dose) (96) Vitamin D_2 100,000 IU (one-time dose) (96)	NA	NR	NR	Study nurse administered medication (one-time dose) Serum vitamin D levels show increases in treatment group compared with placebo group.
Mason et al (2014)[113] ViDA (US)	Placebo sunflower oil gel capsules qd (109) Vitamin D_3 2,000 IU qd (109)	52 wk	Diet and exercise weight loss intervention, 10% reduction goal in weight loss and 225 min of moderate to rigorous physical activity per week	NR	Of participants with complete medication counts (56% of placebo participants and 54% of vitamin D participants), adherence was 97.9% in the vitamin D group and 95.8% in the placebo group. Serum vitamin D increased in vitamin D group compared with placebo.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Moreira-Lucas et al (2017)[114]	30 g of cheddar cheese per week (36) 30 g of cheese with 28,000 IU of Vitamin D_3 per week (35)	24 wk	None	Participants were instructed to avoid taking supplements during the trial.	Participants were instructed to use a log sheet to record the date each package of cheese was consumed. Compliance was assessed by counting the number of portions returned to the study researchers at each study visit. Placebo: 94% Vitamin D: 91% Serum vitamin D levels increased in the active treatment group compared with placebo.
Ng et al (2014)[115]	Placebo capsule qd (81) Vitamin D_3 1,000 IU qd + 100mg Calcium (81) Vitamin D_3 2,000 IU qd + 100 mg Calcium (83) Vitamin D_3 4,000 IU qd + 100 mg Calcium (83)	12 wk	None	NR	Electronic pill dispensers and pill counts were used to track overall compliance; study authors noted that pill compliance was "high," but nothing further is specified. Increase in serum vitamin D levels at all time points for active treatment groups compared with placebo group.
Nowak et al (2016)[116]	Placebo (mannitol) taken in one sitting as two pills (63) Vitamin D_3 50,000 IU taken twice in one sitting (total, one-time dose of 100,000 IU) (59)	4 wk	NR	Vitamin D use was not permitted outside of the study protocol. Calcium use outside of study protocol was NR.	Compliance was 100%; vitamin D or placebo taken once under the supervision of an MD. Serum vitamin D levels increased in active treatment group compared with placebo group.
Pfeifer et al (2000)[85]	Calcium qd (total daily dose 800 IU) (74) Vitamin D_3 400 IU bid (total daily dose 800 mg IU) (74)	8 wk	Calcium carbonate 600 mg bid (total daily dose 1,200 mg)	Not explicitly reported	Measured based on pill counts. Mean (SD) rate of compliance with treatment: Control: 95 (12%) Vitamin D: 96 (10%) Serum vitamin D levels higher in vitamin D group at 8 weeks compared with the control group.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Pfeifer et al (2009)[84]	Calcium tablet (121) Vitamin D_3 400 IU bid (total daily dose 800 IU) (121)	1 yr	Calcium 500 mg bid (total daily dose 1,000 mg)	The exclusion criteria included therapy with vitamin D and vitamin D metabolites in the past 6 months.	Pill counts. Eighteen subjects with an overall compliance below 80% were rated as noncompliant. Serum vitamin D levels higher in vitamin D group at 1 year (mean 84, SD 18) compared with the control group (mean 57, SD 20).
Pilz et al (2015)[117] Styrian Vitamin D Hypertension Trial	Placebo of 7 oily drops qd (100) 2,800 IU vitamin D_3 as 7 oily drops qd (100)	8 wk	None	NR	The study reports that patients were interviewed about medication use at study visits, measures of adherence were NR. Serum vitamin D level increased in active treatment group relative to control group.
Pittas et al (2019)[76] D2d	Planned subgroup of 525 participants Placebo qd Vitamin D_3 4,000 IU qd	2.5 yr (median followup)	All patients were provided with information on diabetes prevention through information sheets and twice-yearly group meetings.	Study excluded participants using vitamin D supplements over 1,000 IU daily or calcium supplements over 600 mg daily.	Pill bottles were returned at each visit; halfway between followup visits a phone call was made to promote adherence. Overall adherence was 85.8%; 11.2% in active treatment group stopped taking study medication compared with 8.9% in the placebo group. The mean serum vitamin D level was higher in the active treatment group compared with placebo at months 12 and 24.
Raed et al (2017)[118]	One placebo capsule monthly (17);18,000 IU vitamin D_3 per month (equivalent to 600 IU qd) (17) 60,000 IU vitamin D_3 per month (equivalent to 2,000 IU qd) (18) 120,000 vitamin D_3 per month (equivalent to 4,000 IU qd) (18)	16 wk	None	Not explicitly reported, but potential participants who were taking supplements at baseline were excluded from enrolling.	Dosing was supervised monthly. Mean serum vitamin D levels were higher in active treatment groups compared with placebo at 8 and 16 weeks of followup.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Scragg et al (2017)[97] Khaw et al[72] ViDA (NZ)	Planned subgroup of 1,270 participants Placebo, monthly Initial dose of 200,000 IU vitamin D_3 followed a month later by monthly doses of 100,000 IU vitamin D_3	3.3 yr	None	Use of vitamin D supplements excluded.	Capsules initially were mailed monthly to participants, along with a 1-page questionnaire (and reply-paid envelope), which recorded self-reported adherence and monitored retention. Eighty-four percent of capsules were reported taken in the vitamin D group and 82.9% in the placebo group. Serum vitamin D levels were higher in the active treatment group at followup compared with the placebo group.
Shea et al (2019)[78]	Placebo bid (51) Vitamin D_3 858 IU daily (49)	52 wk	NR	NR	Vitamin D group took 95.9% of their morning supplements and 93.1% of their afternoon supplements. Placebo group took 96.3% of their morning supplements and 92.7% of their afternoon supplements. Measured by direct remaining pill count at each visit. Serum levels of vitamin D suggest good adherence to treatment intervention.
Tran et al (2014)[119] D-Health	Placebo pill taken by mouth once monthly (214) Vitamin D_3 30,000 IU taken by mouth once monthly (215) Vitamin D_3 60,000n IU taken by mouth once monthly (215)	48 wk	NR	NR	Compliance reported as "very high" and not different among groups. Serum vitamin D levels increased in both active vitamin D groups compared with placebo.
Wamberg et al (2013)[107]	Placebo tablets qd (26) Vitamin D_3 7,000 IU qd (26)	26 wk	NR	Instructed participants to continue usual eating habits, did not report if study participants could take their own supplements during study.	All subjects who completed the trial had compliance rates above 80. Serum vitamin D levels higher in treatment group compared with placebo group.

Appendix D Table 3. Intervention and Comparator Characteristics of Included RCTs

Author (Year) Trial Name	Comparator and Intervention(s) (No. Randomized)	Duration of Intervention	Co-interventions	Use of Supplements Outside of Study Protocol	Adherence
Witham et al (2013)[102]	Placebo pill taken by mouth once (25) Vitamin D_3 100,000 IU taken by mouth once (25)	One-time dose	NR	NR	Study medication was ingested in the presence of the research team to ensure 100% adherence. Serum vitamin D levels increased in treatment group at 4 and 8 weeks compared with placebo group.
Wood et al (2012)[93]	Placebo qd (102) Vitamin D_3 400 IU qd (102) Vitamin D_3 1,000 IU qd (101)	52 wk	NR	Participants were instructed not to take any dietary supplements containing vitamin D (including cod liver oil).	Compliance was estimated every study visit by capsule count, overall compliance 95%. Active treatment groups had increased serum vitamin D level compared with placebo group at 1 year. Dosing effect observed between two active treatment groups.

Abbreviations: bid=twice a day; qd=every day; IU=international units; NA=not applicable; NR=not reported; PODA= physical performance, osteoporosis prevention, and vitamin D in older African Americans; RCT=randomized, controlled trial; SD=standard deviation; ViDAS (NZ)=Vitamin D Assessment Study; ViDA (US)=Vitamin D, Diet, and Activity Study.

Appendix D Table 4. Benefit Outcomes From Included RCTs (KQ 3)—Mortality

Author (Year) Trial Name	Mortality Outcome and Specification	Length of Followup	Results
Brazier et al (2005)[88]	Deaths, method of ascertainment NR	52 wk	N (%) deaths Placebo: 1 (1.0) Vitamin D: 3 (3.2)
Chapuy et al (2002)[87] Decalyos II	Participants were assessed every 3 months and investigators recorded their medical status	2 yr	N (%) deaths Placebo: 45* (23.9) Vitamin D (combined groups): 71* (18.1) RR* 0.75 (95% CI, 0.54 to 1.05)
Gallagher et al (2012)[49] VIDOS	Deaths, method of ascertainment NR, data obtained from author query during original 2014 SR	52 wk	N(%) deaths Placebo: 0 (0) All vitamin D groups: 0 (0)
Gallagher et al (2014)[81] VITADAS	Deaths, method of ascertainment NR, data obtain from author correspondence in the 2014 original SR	1 yr	N (%) deaths Placebo: 0 (0) Vitamin D (all groups): 0 (0)
Grimnes et al (2011)[94]	Deaths, method of ascertainment NR	26 wk	N (%) deaths Placebo 1 (2.2) Vitamin D: 0 (0)
Hansen et al (2015)[69]	Deaths, method of ascertainment NR	52 wk	N (%) deaths Placebo: 0 (0) Low-dose vitamin D: 0(0) High-dose vitamin D: 0 (0) Adjusted p=1.00
Hin et al (2016)[73]	Deaths, methods of ascertainment NR	52 wk	N (%) deaths Placebo: 3 (3.0) Vitamin D 2,000 IU: 0 (0) Vitamin D 4,000 IU: 0 (0)
Janssen et al (2010)[90]	Deaths, method of ascertainment NR	26 wk	Number of deaths: 1 (group NR)
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Method of ascertainment NR	3 yr	N (%) deaths Control: 1 (0.32) Vitamin D: 3 (1.0)
Krieg et al (1999)[91]	Deaths, method of ascertainment, NR	2 yr	N (%) deaths Control: 26 (21.0) Vitamin D: 21 (16.9) Authors report that no deaths were thought to be related to the medication.
Lips et al (1996)[86] & Ooms et al (1995)[189]	Deaths, method of ascertainment NR	3 to 3.5 yr	N (%) deaths Placebo: 251 (19.5) Vitamin D: 223 (17.2) p=0.16

Appendix D Table 4. Benefit Outcomes From Included RCTs (KQ 3)—Mortality

Author (Year) Trial Name	Mortality Outcome and Specification	Length of Followup	Results
Lips et al (2010)[83]	Deaths, method of ascertainment, NR	16 wk	N (%) deaths Placebo: 0 (0) Vitamin D: 1 (0.9)

* Represents a calculated value.

Abbreviations: CI=confidence intervals; KQ=key question; N=number; NR=not reported; OSTRPE-FPS=Osteoporosis Risk Factor and Prevention-Fracture Prevention Study; RCT=randomized, controlled trial; RR=relative risk; SR=systematic review.

Appendix D Table 5. Benefit Outcomes From Included RCTs (KQ 3)—Fractures

Author (Year) Trial Name	Fracture Outcome and Specification	Length of Followup	Results
Bislev et al (2018)[70]	NR	12 wk	No fractures reported overall.
Chapuy et al (2002)[87] Decalyos II	Hip fracture incidence as assessed at study visits every 3 months	2 yr	N (%) with hip fractures Placebo: 21 (11.1) Vitamin D (combined groups): 27 (6.9) RR* 0.62 (95% CI, 0.36 to 1.07)
Chapuy et al (2002)[87] Decalyos II	Nonvertebral fracture as assessed at study visits every 3 months	2 yr	N (%) with nonvertebral fracture Placebo: 34* (17.9) Vitamin D: 70* (17.8) RR* 1.0 (95% CI, 0.7 to 1.4)
Hansen et al (2015)[69]	Self-reported number of fractures at study visits	52 wk	Number of fractures at 1 yr Placebo: 4 Low-dose vitamin D: 2 High-dose vitamin D: 2 Adjusted p=0.92
Hin et al (2016)[73] BEST-D	Self-reported incidence of fractures collected at nurse study visits at 6 and 12 months	52 wk	N (%) incidence of self-reported fractures Placebo: 1 (1) Vitamin D (combined groups): 6 (3)
Janssen et al (2010)[90]	Hip fractures captured as adverse events	26 wk	Number of hip fractures: 1 (group NR)
Lips et al (1996)[86]	Hip fractures as ascertained by annual questionnaire and verified by the general practitioner	3 to 3.5 yr	N (%) with hip fracture Placebo: 48 (3.7) Vitamin D: 58 (4.5) p=0.39 Unadjusted HR 1.18 (95% CI, 0.81 to 1.71)
Lips et al (1996)[86]	Other peripheral fractures as ascertained by questionnaire	3 to 3.5 yr	N (%) with fractures other than hip Placebo: 74 (5.7) Vitamin D: 77 (6.0) p=0.86
Pfeifer et al (2000)[85]	All fractures were the result of falls and were verified by X-ray and medical reports	52 wk	Total number of hip fractures: Calcium: 1 Vitamin D: 0
Pfeifer et al (2000)[85]	All fractures were the result of falls and were verified by X-ray and medical reports	52 wk	Number of fractures Calcium: 6 Vitamin D: 3 p=0.14
Pfeifer et al (2009)[84]	Number of participants with fractures as the result of falls and were verified by X-rays and medical reports	1.75 yr	N (%) incidence of fractures Calcium: 12 (10.0) Vitamin D: 7 (5.7) p=0.08

Appendix D Table 5. Benefit Outcomes From Included RCTs (KQ 3)—Fractures

Author (Year) Trial Name	Fracture Outcome and Specification	Length of Followup	Results
Pfeifer et al (2009)[84]	Total number of fractures as the result of falls and verified by X-rays and medical reports	1.75 yrs	Number of fractures: Calcium: 19 Vitamin D: 12 p=0.12
Scragg et al (2017)[97] Khaw et al[72] ViDA (NZ)	Non-vertebral fractures Identified through national administrative data based on ICD-10 codes for hospital discharges with primary or secondary diagnosis code	Mean followup 3.3 yrs	N (%) with nonvertebral fracture among planned subgroup of 1,270 vitamin D–deficient participants (<20 ng/ml) Placebo: 38 (6) Vitamin D: 34 (6) HR 0.94 (95% CI, 0.58 to 1.52)

* Represents a calculated value.

Abbreviations: BEST-D=Biochemical Efficacy and Safety Trial of vitamin D; CI=confidence interval; HR=hazard ratio; ICD-10=International Classification of Disease Tenth Revision; KQ=key question; N=number; NR=not reported; RCT=randomized, controlled trial; RR=relative risk; ViDA (NZ)=Vitamin D Assessment Study.

Appendix D Table 6. Benefit Outcomes From Included RCTs (KQ 3)—Falls

Author (Year) Trial Name	Fall Outcome and Specification	Length of Followup	Results
Bischoff et al (2003)[89]	Number of falls	12 wk	Number of falls Placebo: 55 Vitamin D: 25 49% reduction in falls, p=0.01 adjusted for age, number of falls in pretreatment period, baseline serum vitamin D, and observation time during treatment
Bischoff et al (2003)[89]	Number of fallers	12 wk	N (%) participants with 1 or more falls Placebo: 18 (30) Vitamin D: 14 (23) RR 0.7 (95% CI, 0.3 to 1.5)
Chapuy et al (2002)[87] Decalyos II	Number of fallers as assessed at study visits every 3 months	2 yr	N (%) participants with 1 or more falls Placebo: 118* (62.1) Vitamin D: 251* (63.9) RR* 1.0 (95% CI, 0.9 to 1.2)
Hansen et al (2015)[69]	Self-reported number of falls at study visits	52 wk	Number of falls Placebo: 33 Low-dose vitamin D: 36 High-dose vitamin D: 35 Adjusted p=1.00
Hin et al (2016)[73] BEST-D	Self-reported incidence of falls at 6- and 12-month nurse study visits	52 wk	N (%) incidence of self-reported falls Placebo: 14 (14) Vitamin D 2,000 IU or 4,000 IU: 34 (17) p=0.53
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Number of falls requiring medical attention recorded every 4 months via telephone interviews	3 yr	Number of falls requiring medical attention Control: 159 Vitamin D: 142
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Number of fallers with falls requiring medical attention recorded every 4 months via telephone interviews	3 yr	N (%) participants with 1 or more falls requiring medical attention Control: 106 (35) Vitamin D: 95 (33)
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Number of falls recorded every 4 months via telephone interviews	3 yr	Number of falls Control: 524 Vitamin D: 430
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Number of fallers recorded every 4 months via telephone interviews	3 yr	N(%) participants with 1 or more falls Control: 205 (67) Vitamin D: 179 (62) RR 0.82 (95% CI, 0.73 to 0.92)
Pfeifer et al (2000)[85]	Number of falls recorded by questionnaires. Fall defined as falling onto the floor or ground or hitting an object like a chair or stair.	52 wk	N (%) of women with fall Calcium: 19 (28%) Vitamin D: 11 (16%) p=0.04

Appendix D Table 6. Benefit Outcomes From Included RCTs (KQ 3)—Falls

Author (Year) Trial Name	Fall Outcome and Specification	Length of Followup	Results
Pfeifer et al (2000)[85]	Number of falls recorded by questionnaires. Fall defined as falling onto the floor or ground or hitting an object like a chair or stair.	52 wk	Number of falls Calcium: 30 Vitamin D: 17 p=0.03
Pfeifer et al (2000)[85]	Mean number of falls: the number of falls was recorded by questionnaires	5 2wk	Mean (SD) number of falls Calcium: 0.45 (NR) Vitamin D: 0.24 (NR) p=0.03
Pfeifer et al (2009)[84]	Mean number of falls per group	1.75 yr	Mean number of falls Calcium: 1.41 Vitamin D: 0.63 p<0.001
Pfeifer et al (2009)[84]	Time to first fall among study participants. (Note, the study reported this outcome as a RR, but states that used a Cox regression analysis were not reported).	1.75 yr	39% decrease in number of first falls for vitamin D compared with control (RR 0.61 [95% CI, 0.34 to 0.76], p<0.01)
Pfeifer et al (2009)[84]	Time to first fall among study participants. (Note, the study reported this outcome as a RR, but states that used a Cox regression analysis were not reported).	1 yr	27% decrease in time to first fall for vitamin D compared with control (RR 0.73 [95% CI, 0.54 to 0.96], p<0.01)
Pfeifer et al (2009)[84]	Number of participants with at least one fall by 1.75 yr of followup as recorded in fall diary and as assessed at telephone interview every 2 months. The number of falls was recorded by fall diaries. Each day the participants had to make a cross depending on whether a fall had occurred or not. Every 2 months, the study subjects were also asked via telephone interviews whether a fall had happened. If so, it was clarified whether the fall was injurious or noninjurious and further diagnostic procedures like for instance X-rays had been performed or the subject had been admitted to a hospital. A fall was defined as falling onto the floor or ground or hitting an object like a chair or stair.	1.75yr	N(%) participants with 1 or more falls Calcium: 75 (62.5) Vitamin D: 49 (40.2) p<0.001

Appendix D Table 6. Benefit Outcomes From Included RCTs (KQ 3)—Falls

Author (Year) Trial Name	Fall Outcome and Specification	Length of Followup	Results
Pfeifer et al (2009)[84]	Total falls per group	1.75 yr	Number of falls Calcium: 169 Vitamin D: 106 p<0.001
Scragg et al (2017)[97] Khaw et al[72] ViDA (NZ)	Specified post hoc, assessed via mailed questionnaire with questions specific to falls and through claims data from the national accident compensation corporation, which covers residents' hospital costs from injury	Mean followup 3.3 yr	N (%) participants with 1 or more falls among preplanned subgroup (N=1,247) of vitamin D–deficient (<20 ng/ml) participants Placebo: 316 (49) Vitamin D: 307 (51) HR 1.07 (95% CI, 0.91 to 1.25
Shea et al (2019)[78]	Self-reported falls, ascertained at study visits every 2 months, including whether the fall was injurious (required medical care) or noninjurious	52 wk	Incidence of falls at 1 year Placebo: 13 (26.0*) Vitamin D: 14 (29.8*) HR 1.13 (95% CI, 0.53 to 2.41)
Wood et al (2012)[93]	Number of falls recorded as adverse events; method of ascertainment: NR	52 wk	Number of falls Placebo: 3 Vitamin D 400 IU: 4 Vitamin D 1,000 IU: 0

* Represents a calculated value.

Abbreviations: BEST-D=Biochemical Efficacy and Safety Trial of vitamin D; CI=confidence interval; HR=hazard ratio; KQ=key question; N=number; NR=not reported; OSTPRE-FPS=The Osteoporosis Risk Factor and Prevention-Fracture Prevention Study; RCT=randomized, controlled trial; RR=relative risk; ViDA (NZ)=Vitamin D Assessment Study.

Appendix D Table 7. Benefit Outcomes From Included RCTs (KQ 3)—Other Morbidity

Author (Year) Trial Name	Morbidity Outcome and Specification	Length of Followup	Results
Arvold et al (2009)[82]	Fibromyalgia impact questionnaire, overall score (range 0 to 100)	8 wk	Mean (95% CI) change Placebo: 1.91 (-2.9 to 6.7), p=0.21 Vitamin D: -3.71 (-7.5 to 0.1), p=0.03 Between-group difference NR, p=0.03
Davidson et al (2013)[75]	The criterion for the diagnosis of diabetes was an FPG less than or equal to 126 mg/dL or a 2-h value on the OGTT of less than or equal to 200 mg/dL.	52 wk	N (%) with incidence diabetes at 12 months Placebo: 5 (9) Vitamin D: 7 (12) p=0.61
Hansen et al (2015)[69]	Modified Stanford Health Assessment Questionnaire	52 wk	Mean (95% CI) between group difference Low-dose vitamin D vs placebo: −0.03 (−0.11 to 0.05), p=0.58 High-dose vitamin D vs placebo: 0.01 (−0.08 to 0.09), p=0.99
Jorde et al (2016)[74] & Jorde et al (2016)[137]	Incidence of urinary tract infection, method of ascertainment NR	5 yr	Incidence of first UTI during 5 yr among subgroup (N=173) of participants with serum vitamin D < 20 ng/ml at baseline HR 0.53 (95% CI, 0.17 to 1.64)
Jorde et al (2016)[74] & Jorde et al (2016)[137]	Measured as a fasting blood glucose greater than 126 mg/dL and/or the 2-hour value greater than 200 mg/dL or an HbA1c of 6.5% or greater consistently after one retest	5 yr	N (%) incidence of diabetes among vitamin D deficient (< 20 mg/dl) subpopulation (N=112 in subgroup) Placebo: 26 (53.1) Vitamin D: 30 (47.6) HR 0.79 (95% CI, 0.46 to 1.37)
Jorde et al (2018)[77]	Depression symptoms as measured by the Beck Depression Inventory-II Questionnaire (post hoc analysis)	16 wk	Change in mean (SD) Beck Depression Inventory-II score: Placebo: -1.9 (4.1) Vitamin D: -1.5 (4.3) Reported by study authors as no significant difference between groups
Kjaergaard et al (2012)[80] Tromo Study	Montgomery–Asberg Depression Rating Scale (range 0 to 60)	26wk	Difference in median (range) score from baseline to followup Placebo: -1.6 (4.7) Vitamin D: -1.4 (5.2) p=0.336
Kjaergaard et al (2012)[80] Tromo Study	Beck Depression Inventory (range 0 to 63)	26wk	Difference in median (range) score from baseline to followup Placebo: -0.90 (4.90) Vitamin D: -0.84 (5.66) p=0.929
Kjaergaard et al (2012)[80] Tromo Study	Hospital Anxiety and Depression Scale (range 0 to 42)	26wk	Difference in median (range) score from baseline to followup Placebo: -0.02 (3.68) Vitamin D: -0.65 (3.84) p=0.205
Manson et al (2019)[71], VITAL	Participants were asked to sign a release for medical records, which were reviewed for confirmation by a committee of physicians who were unaware of the trial-group assignments. Cancer was confirmed on the basis of histologic or cytologic data.	Median (IQR) length of followup 5.3 yr (3.8 to 6.1)	N (%) with invasive cancer of any type among subgroup (N=2,001) of vitamin D–deficient (<20 ng/ml) participants Placebo: 63 (NR) Vitamin D: 58 (NR) HR 0.97 (95% CI, 0.68 to 1.39)

Appendix D Table 7. Benefit Outcomes From Included RCTs (KQ 3)—Other Morbidity

Author (Year) Trial Name	Morbidity Outcome and Specification	Length of Followup	Results
Manson et al (2019)[71], VITAL	Participants were asked to sign a release for medical records, which were reviewed for confirmation by a committee of physicians who were unaware of the trial-group assignments. Myocardial infarction and stroke were confirmed with the use of established criteria, coronary revascularization was confirmed by medical record review, and death from cardiovascular causes was confirmed if there was convincing evidence of a cardiovascular event from all available sources.	Median (IQR) length of followup 5.3 yr (3.8 to 6.1)	N (%) with major cardiovascular event among preplanned subgroup (N=2,001) of vitamin D–deficient (<20 ng/ml) participants Placebo: 34 (NR) Vitamin D: 34 (NR) HR 1.09 (95% CI, 0.68 to 1.76)
Pittas et al (2019)[76] D2d	New-onset diabetes, based on annual glycemic testing of fasting plasma glucose, glycated hemoglobin, and 2-hour post-load plasma glucose and semiannual testing of FPG and glycated hemoglobin. If two or three of the glycemic measures met the 2010 ADA thresholds for diabetes, the participant was considered to have met the diabetes outcome.	2.5 yr (median followup)	Incidence of diabetes in planned subgroup of 525 vitamin D–deficient participants HR (95% CI): 0.87 (0.61 to 1.22)
Scragg et al (2017)[97], Khaw et al[72] ViDA (NZ)	Incidence of cardiovascular disease based on nationally available administrative data and defined by ICD-10 codes as primary reason for hospitalization or death for chronic ischemic heart disease; pulmonary embolism; inflammatory cardiac conditions; conduction disorders; cardiac arrest; arrhythmias; ill-defined heart disease; diseases of the arteries; diseases of the veins, including venous thrombosis; acute myocardial infarction; angina; and stroke.	Mean length of followup 3.3 yr	N (%) with incident CVD among planned subgroup (N=1,270) of participants with serum vitamin D levels <20 ng/ml at baseline Placebo: 88 (13.4) Vitamin D: 80 (13.1) HR 1.00 (95% CI, 0.74 to 1.35) adjusted for age, sex, and race/ethnicity
Scragg et al (2017),[97] Scragg et al (2018),[98], Khaw et al[72] ViDA (NZ)	Cancer registration on New Zealand Ministry of Health from randomization to July 31, 2015	Mean length of followup 3.3 yr	N (%) with incident cancer among planned subgroup (N=1,270) of participants with serum vitamin D levels < 20 ng/ml at baseline Placebo: 42 (6.4) Vitamin D: 37 (6.0) Adjusted HR=1.01 (95% CI, 0.65 to 1.58)
Wood et al (2012)[93]	Incidence of diabetes reported as an adverse event.	52 wk	N (%) incident diabetes Placebo: 0 (0) Vitamin D 400 IU: 1 (1.0) Vitamin D 1,000 IU: 0 (0)

Appendix D Table 7. Benefit Outcomes From Included RCTs (KQ 3)—Other Morbidity

* Represents a calculated value.

Abbreviations: ADA=American Diabetes Association; CI=confidence intervals; CVD=cardiovascular disease; FPG=fasting plasma glucose; HbA1C=glycosylated hemoglobin; HR=hazard ratio; KQ=key question; IQR=interquartile range; IU=international unit; N=number; NR=not reported; OGTT=oral glucose tolerance test; RCT=randomized, controlled trial; ViDA (NZ)=Vitamin D Assessment Study; VITAL=VITamin D and OmegA-3 TriaL.

Appendix D Table 8. Harm Outcomes From Included RCTs (KQ 4)—Total Adverse Events

Author (Year) Trial Name	Total Adverse Events Outcome and Specification	Length of Followup	Results
Aloia et al (2018)[108] PODA	Method of ascertainment was NR. AEs reported using System Organ Class (MedDra).	3 yr	Overall total number of participants with 1 or more AEs: NR. N (%) participants with AEs in the following organ systems*: Gastrointestinal disorders: Placebo: 21 (23.6); vitamin D: 20 (21.1) General disorders and administration site conditions: Placebo: 12 (13.5); vitamin D: 11 (11.6) Infections and infestations: Placebo: 82 (92.1); vitamin D: 85 (89.5) Injury, poisoning, and procedural complications: Placebo: 54 (60.7); vitamin D: 51 (53.7) Musculoskeletal and connective tissue disorders: Placebo: 57 (64.0); 49 (51.6) Nervous system disorders: Placebo: 25 (28.1); vitamin D: 21 (22.1) Respiratory, thoracic, and mediastinal disorders: Placebo: 12 (13.5); vitamin D: 17 (17.9) Surgical and medical procedures: Placebo: 29 (32.6); placebo: 23 (24.2) Vascular disorders: placebo: 6 (6.7); vitamin D: 13 (13.7) *We only extracted organ systems where 10 or more participants in either group reported an AE.
Arvold et al (2009)[82]	Outcome specification and method of ascertainment were NR.	8 wk	No participants reported AEs of the treatment.
Bischoff et al (2003)[89]	Nurses monitored side effects and reported them to the physician in charge.	12 wk	N (%) with AEs Placebo: 0 (0) Vitamin D: 2 (4.4) (increased constipation, did not lead to discontinuation)
Bislev et al (2018)[70]	Outcome specification and method of ascertainment were NR.	12 wk	There were 71 AEs reported throughout the study duration across both groups, with no significant difference by group (actual values NR).
Borgi et al (2016)[109]	Minor AEs were assessed weekly by phone and at 4-wk outpatient visit. Study staff also contacted subjects weekly to ascertain side effects of study medication.	8 wk	Number of minor AEs: Placebo: 6 Vitamin D: 6 Number of abdominal discomfort events: Placebo: 4 Vitamin D: 4 Number of other events: Placebo: 2 Vitamin D: 1

Appendix D Table 8. Harm Outcomes From Included RCTs (KQ 4)—Total Adverse Events

Author (Year) Trial Name	Total Adverse Events Outcome and Specification	Length of Followup	Results
Brazier et al (2005)[88]	AEs spontaneously reported of observed and thought by the investigators to be treatment related.	52 wk	N (%) women with AEs thought to be treatment related Placebo: 23 (24.0) Vitamin D: 21 (22.1) p=0.86
Brazier et al (2005)[88]	Spontaneously reported and observed AEs.	52 wk	Number (%) of women with at least 1 AE Placebo: 70 (72.9) Vitamin D: 69 (72.6) p=1.00
Gagnon et al (2014)[110]	Participants asked about AEs at study visits every 2 months.	26 wk	N (%) with gastrointestinal issues Placebo: 17 (37.8*) Vitamin D: 11 (31.4*) N (%) with fatigue Placebo: 3 (6.7*) Vitamin D: 2 (5.7*) N (%) with musculoskeletal symptoms Placebo: 2 (4.5*) Vitamin D: 2 (5.7*)
Grimnes et al (2011)[94]	Study nurse contacted participants by phone after 1 and 3 months to register AEs.	26 wk	Number of AEs Placebo: 46 Vitamin D: 45
Janssen et al (2010)[90]	Outcome specification and method of ascertainment NR.	2 6wk	Study authors reported “no AEs,” but then also reported that 3 participants reported nausea from the study medication (treatment groups not specified). Note, 11 participants discontinued participation for reasons that would likely be classified as AEs (death, cognitive decline, malignant lung tumor, recurrent upper urinary tract infection, acute emotional distress, hip fracture, peritonitis).
Kearns et al (2015)[111]	Participants were observed following administration of vitamin D or placebo and asked about hypercalcemia symptoms at each visit.	52 wk	No signs of hypervitaminosis following administration of the dose. One study participant in the vitamin D group developed a nontoxic goiter 11 months after receiving the treatment.
Kjaergaard et al (2012)[80] Tromo Study	AEs as collected via telephone contact at 3 months and at final study visit at 6 months.	26 wk	Number of total AEs Placebo: 158 Vitamin D: 177 The difference was reported as “not significant” by study authors.
Knutsen et al (2014)[105]	Outcome specification and method of ascertainment NR	16 wk	Reported AEs were few, mild, and equally distributed between the treatment groups and the placebo group. No further detail provided by study authors.
Lehmann et al (2013)[46]	AEs reported by participants	8 wk	No AEs were reported by the participants.

Appendix D Table 8. Harm Outcomes From Included RCTs (KQ 4)—Total Adverse Events

Author (Year) Trial Name	Total Adverse Events Outcome and Specification	Length of Followup	Results
Lerchbaum et al (2017)[112] Graz Vitamin D&TT-RCT	Outcome specification and method of ascertainment NR	12 wk	N (%) with AEs Placebo: 0 (0) Vitamin D: 0 (0)
Lips et al (2010)[83]	Number (%) of patients with one or more AEs during treatment period as recorded at each study visit and by voluntary reporting of patients at any time during the study.	16 wk	N (%) with clinical AEs Placebo: 26 (23.2) Vitamin D: 24 (21)
Martineau et al (2007)[106]	Outcome specification and method of ascertainment NR	6 wk	No study participant experienced any AE.
Mason et al (2014)[113] ViDA (US)	Participants were interviewed at months 1, 3, 6, 9, and 12 for any signs of vitamin D toxicity or AEs.	52 wk	Nonserious AEs reported by 1 to 4 women each were light-headedness, severe headaches, nausea, rash/hives, weakness/numbness, and constipation.
Moreira-Lucas et al (2017)[114]	Outcome specification and method of ascertainment NR	24 wk	The supplemental cheese was well tolerated in both groups and no participants reported difficulties consuming cheese or experienced side effects attributed to the cheese.
Nowak et al (2016)[116]	Self-reported AEs during study period or assessed by study physician at followup (4 weeks)	4 wk	N (%) reporting AE Placebo: 25 (40) Vitamin D: 16 (28) p=0.14 Number of AEs reported Placebo: 26 Vitamin D: 16 p=0.25
Raed et al (2017)[118]	Outcome specification and method of ascertainment NR	16 wk	None of the participants reported side effects.
Tran et al (2014)[119] D-Health	Participants could report AEs by contacting the study toll-free number. Additionally, the post-intervention questionnaire asked about hospitalization during the study period and reason for hospitalization.	48 wk	N (%) of participants experiencing nonserious AE: 6 (0.9) N (%) of participants hospitalized during intervention period: 104 (16.1) These instances were not significantly different between study groups (p=0.43), and all incidences were reported by authors as unlikely to have been related to the study medication.
Wamberg et al (2013)[107]	Reported number of side effects during study visits at 2, 10, and 18 weeks	26 wk	N (%) with side effects Placebo: 17 (77) Vitamin D: 13 (62) p=0.76 Reported side effects included constipation, nausea, tiredness, and headache.

Appendix D Table 8. Harm Outcomes From Included RCTs (KQ 4)—Total Adverse Events

Author (Year) Trial Name	Total Adverse Events Outcome and Specification	Length of Followup	Results
Witham et al (2013)[102]	Outcome specification and method of ascertainment NR	8 wk	N (%) with AEs Placebo: 11 (44.0) Vitamin D: 8 (32.0)
Wood et al (2012)[93]	Outcome specification and method of ascertainment NR	52 wk	N (%) with AE Placebo: 20 (20) Vitamin D 400 IU: 17 (17.5) Vitamin D 1,000 IU: 15 (15.6)

* Represents a calculated value.

Abbreviations: AE=adverse event; KQ=key question; N=number; NR=not reported; PODA=physical performance, osteoporosis prevention, and vitamin D in older African Americans; RCT=randomized, controlled trial; ViDA (US)=Vitamin D, Diet and Activity Study.

Appendix D Table 9. Harm Outcomes From Included RCTs (KQ 4)—Serious Adverse Events

Author (Year) Trial Name	Serious Adverse Events (SAEs) Outcome and Specification	Length of Followup	Results
Aloia et al (2005)[104]	Outcome specification and method of ascertainment NR	3 yr	Number of SAEs Placebo: 7 Vitamin D: 8 None were considered to be related to the study.
Aloia et al (2018)[108] PODA	Method of ascertainment NR. AEs reported using System Organ Class (MedDra).	3 yr	0 SAEs
Bislev et al (2018)[70]	Outcome specification and method of ascertainment NR.	12 wk	0 SAEs
Borgi et al (2016)[109]	AEs were assessed weekly by phone and at 4-wk outpatient visit. Study staff also contacted subjects weekly to ascertain side effects of study medication.	8 wk	0 SAEs
Brazier et al (2005)[88]	N (%) with all SAEs recorded during treatment period irrespective of relation to treatment, reported by group.	52 wk	N (%) with SAEs Placebo: 12 (12.5) Vitamin D: 14 (14.7) p=0.68
Gallagher et al (2012)[49], Gallagher et al (2013)[103] VIDOS	Data on harms were collected at each study visit, an AE was any adverse effect that occurred during the trial, definition of 'serious' was based on guidelines from the National Institute on Aging.	52 wk	N (%) with any moderate or SAE White women Placebo: 2 (9.5) (syncope, total hip replacement) Vitamin D 400 IU: 0 (0) Vitamin D 800 IU: 1 (4.8) (diverticulitis) Vitamin D 1,600 IU: 2 (10.0) (stroke, knee replacement) Vitamin D 2,400 IU: 3 (14.3) (partial thyroidectomy, tibia-fibula fracture, cholecystectomy) Vitamin D 3,200 IU: 2 (10.0) (heart failure, angina and stent) Vitamin D 4,000 IU: 0 (0) Vitamin D 4,800 IU: 1 (5.0) (COPD exacerbation) All events were thought to be unrelated to treatment Black women Placebo: 2 (9.5) Vitamin D 400 IU: 0 (0) Vitamin D 800 IU: 0 (0) Vitamin D 1,600 IU: 1 (5.5) (Cerebral hemorrhage, thought to be unrelated to study treatment) Vitamin D 2,400 IU: 0 (0) Vitamin D 3,200 IU: 0 (0) Vitamin D 4,000 IU: 0 (0) Vitamin D 4,800 IU: 0 (0)

Appendix D Table 9. Harm Outcomes From Included RCTs (KQ 4)—Serious Adverse Events

Author (Year) Trial Name	Serious Adverse Events (SAEs) Outcome and Specification	Length of Followup	Results
Gallagher et al (2014)[81] VITADAS	Data on AEs were collected at each study visit. An AE was defined as any side effect that occurred while the participant was in the trial; definition of "serious" event was NR.	52 wk	5 SAEs among 4 participants, not reported by treatment group and none were attributed to study treatment (internal bruising and bleeding due to auto collision, subarachnoid hemorrhage, maxillary hypoplasia surgery, broken ankle and tibia)
Hin et al (2016)[73] BEST-D	SAEs were recorded by study nurse at 6-month and 12-month study visits.	52 wk	N (%) with at least one SAE Placebo: 25 (24.8) 2000 IU: 30 (29.4) 4000 IU: 29 (28.4) None were considered treatment related
Knutsen et al (2014)[105]	Narrative on SAEs was defined as admissions to the hospital.	16 wk	N (%) with admissions to hospital Placebo: 1 (1.4) Vitamin 400 IU: 0 (0) Vitamin 1,000 IU: 2 (2.4)
Lips et al (2010)[83]	AEs as recorded at each study visit and by voluntary reporting of patients at any time during the study.	16 wk	N (%) with SAEs Placebo: 3 (2.7) Vitamin D: 3 (2.6)
Mason et al (2014)[113] ViDA (US)	Participants were interviewed at months 1, 3, 6, 9, and 12 for any signs of vitamin D toxicity or SAEs.	52 wk	0 SAEs
Pilz et al (2015)[117] Styrian Vitamin D Hypertension Trial	Outcome specification and method of ascertainment NR	8 wk	N (%) unplanned hospitalizations: Placebo: 4 (4.0); reasons—pneumonia (2), congestive heart failure, overdose of anticoagulation Vitamin D: 6 (6.0); reasons—fracture, fall, abdominal surgeries (2), congestive heart failure, deep venous thrombosis
Tran et al (2014)[119] D-Health	Participants could report AE by contacting the study toll-free number. Additionally, the post-intervention questionnaire asked about hospitalization during the study period and reason for hospitalization.	48 wk	0 SAEs
Witham et al (2013)[102]	Outcome specification and method of ascertainment NR	8 wk	N (%) with SAEs Placebo: 0 (0) Vitamin D: 0 (0)
Wood et al (2012)[93]	Outcome specification and method of ascertainment NR	52 wk	N (%) with SAEs Placebo: 4 (4) Vitamin D 400 IU: 7 (7.2) Vitamin D 1,000 IU: 8 (8.3) None were deemed to be related to the study medication.

* Represents a calculated value.

Abbreviations: AE=adverse event; BEST-D=Biochemical Efficacy and Safety Trial of vitamin D; COPD=chronic obstructive pulmonary disease; KQ=key question; N=number; NR=not reported; RCT=randomized, controlled trial; SAE=serious adverse event; PODA= physical performance, osteoporosis prevention, and vitamin D in older African Americans; ViDA (US)=Vitamin D, Diet and Activity Study; VIDOS=Vitamin D Supplementation in Older Subjects; VITADAS=not defined by authors.

Appendix D Table 10. Harm Outcomes From Included RCTs (KQ 4)—Discontinuations Because of Adverse Events

Author (Year) Trial Name	Discontinuations Outcome and Specification	Length of Followup	Results
Brazier et al (2005)[88]	Discontinuations because of AEs	52 wk	N (%) participants with discontinuations because of AEs: Placebo: 17 (17.7) Vitamin D: 15 (15. 8)
Gagnon et al (2014)[110]	Participants asked about side effects at study visits that occurred every 2 months	26 wk	N (%) with discontinuations because of AEs: Placebo: 0 (0) Vitamin D: 0 (0)
Janssen et al (2010)[90]	Specification NR	26 wk	11 participants discontinued participation for reasons that would likely be classified as AEs (death, cognitive decline, malignant lung tumor, recurrent upper urinary tract infection, acute emotional distress, hip fracture, peritonitis). The treatment groups of those who discontinued were not specified.
Kärkkäinen et al (2010)[92] OSTPRE-FPS	Discontinuations due to AEs	3 yr	N (%) participants with discontinuations because of AEs Control: NR Vitamin D: 17 (6)
Kjaergaard et al (2012)[80] Tromo Study	Discontinuation because of side effects or AEs	26 wk	N (%) participants with discontinuations because of AEs Placebo: 0 (0) Vitamin D: 6 (5)
Krieg et al (1999)[91]	Discontinuations because of AEs	2 yr	N (%) participants with discontinuations because of upper gastrointestinal side effects Control: 0 (0) Vitamin D: 6 (4.8)
Lips et al (2010)[83]	Discontinuations because of AEs	16 wk	N(%) participants with discontinuations because of AEs Placebo: 5 (4.5) Vitamin D: 3 (2.6)

Abbreviations: AE=adverse event; KQ=key question; N=number; NR=not reported; OSTPRE-FPS=The Osteoporosis Risk Factor and Prevention-Fracture Prevention Study; RCT=randomized, controlled trial.

Appendix D Table 11. Harms Outcomes From Included RCTs (KQ 4)—Kidney Stones

Author (Year) Trial Name	Kidney Stones Outcome and Specification	Length of Followup	Results
Aloia et al (2005)[104]	Outcome specification and method of ascertainment NR	3 yr	N (%) with kidney stones Placebo: 0 (0) Vitamin D: 0 (0)
Chapuy et al (2002)[87] Decalyos II	Medical status assessed at study visits every 3 months	2 yr	N (%) with kidney stones Placebo: 0 (0) Vitamin (combined groups): 0 (0)
Gagnon et al (2014)[110]	Participants were asked about changes in their medical condition at study visits every 2 months.	26 wk	N (%) with kidney stones Placebo: 0 (0) Vitamin D: 0 (0)
Gallagher et al (2012)[49], Gallagher et al (2013)[103] VIDOS	Data on harms were collected at each study visit.	52 wk	N (%) with kidney stones White women Placebo: 0 (0) All vitamin D groups: 0 (0) Black women: NR
Gallagher et al (2014)[81] VITADAS	Outcome specification and method of ascertainment NR	52 wk	N (%) with kidney stones Placebo: 0 (0) Vitamin D 400 IU: 0 (0) Vitamin D 800 IU: 0 0) Vitamin D 1,600 IU: 0 (0) Vitamin D 2,400 IU: 0 (0)
Grimnes et al (2011)[94]	Study nurses contacted participants after 1 and 3 months to register adverse events.	26 wk	N (%) with kidney stones Placebo: 0 (0) Vitamin D: 0 (0)
Hansen et al (2015)[69]	Self-reported incidence of kidney stones at study visits	52 wk	N (%) incidence of kidney stones Placebo: 0 (0) Low-dose vitamin D: 1 (1.4) High-dose vitamin D: 0 (0) Adjusted p=0.88
Honkanen et al (1990)[101]	Self-reported incidence of kidney stones	11 wk	N (%) with kidney stones Control: 0 (0) Vitamin D: 0 (0)
Lips et al (2010)[83]	Number of kidney stones reported as recorded at each study visit or by voluntary reporting by patients at any time during the study	16 wk	N (%) with kidney stones: Placebo: 0 (0) Vitamin D: 0 (0)
Witham et al (2013)[102]	Outcome specification and method of ascertainment NR	8 wk	N (%) with kidney stones Placebo: 0 (0) Vitamin D: 0 (0)

Abbreviations: KQ=key question; N=number; NR=not reported; RCT=randomized, controlled trial; VITADAS=not defined by authors.

Appendix D Table 12. Harm Outcomes From Included RCTs (KQ 4)—Other Harms

Author (Year) Trial Name	Other Harms Outcome and Specification	Length of Followup	Results
Bischoff et al (2003)[89]	Patients were monitored on a long-stay geriatric unit. AEs reported to physician in charge for the patient. and to 1 research physician.	12 wk	Number with constipation: Placebo: 0 Vitamin D: 2
Chapuy et al (2002)[87] Decalyos II	Gastrointestinal disorders as assessed at study visits every 3 months	2 yr	N (%) gastrointestinal disorders (nausea, diarrhea, epigastric pains) Placebo: 16 (8.4) Vitamin D (combined groups): 24 (6.1) RR* 0.73 (95% CI, 0.40 to 1.33)
Gallagher et al (2012)[49], Gallagher et al (2013)[103] VIDOS	Data on harms were collected at each study visit; an AE was any adverse effect that occurred during the trial.	52 wk	Number of minor AEs White women: NR Black women: Study authors reported that minor AEs were equally distributed within all dose groups; actual values were NR.
Honkanen et al (1990)[101]	Mild gastrointestinal symptoms	11 wk	9 community-dwelling participants in the vitamin D group reported mild gastrointestinal symptoms. Outcomes in the control group were NR.
Ng et al (2014)[115]	Self-reported symptoms of possible side effects of the intervention reported by phone every 2 weeks or in person every 4 weeks	12 wk	2 participants reported symptoms potentially attributed to hypercalcemia (pruritis, polydipsia and polyuria), 4 participants were discontinued from the study for elevated calcium (all were in one of the active treatment groups).

* Represents a calculated value.

Abbreviations: AE=adverse event; KQ=key question; N=number; NR=not reported; RCT=randomized, controlled trial; RR=relative risk; VIDOS=Vitamin D Supplementation in Older Subjects.

Appendix D Table 13. Study and Population Characteristics of the Women's Health Initiative Calcium With Vitamin D Trial

Author (Year)	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (ng/mL)	Vitamin D Level Attained (ng/mL)
Jackson et al, 2006[79] WHI Calcium with Vitamin D Trial	Mean age (years): 62* Female: 100% Race: 83.1% white, 9.1% black, 4.2% Hispanic, 0.42% American Indian or Native American, 2.0% Asian or Pacific Islander, 1.2% unknown or not identified Mean BMI (kg/m^2): 29 History of fracture at any age: 35% Number of women with falls in last 12 months: 67% with no falls, 20% with 1 fall, 9% with 2 falls, 4% with >3 falls	Inclusion: Postmenopausal women in the WHI hormone therapy and dietary modification trials age 50 to 70 years with predicted survival of >3 years and no safety, adherence, or retention risks. Exclusion: History of hypercalcemia, kidney stones, current use of corticosteroids, calcitriol, and ≥600 IU/day of vitamin D.	Chemiluminescent immunoassay	NR	NR	NR for all participants, after 2 years, in subsample (selected without regard to nonstudy supplement use or adherence to medication) of 227 women assigned to vitamin D and 221 women assigned to placebo, vitamin D levels were 28% higher (9 ng/mL) in women taking vitamin D

Abbreviations: BMI=body mass index; NR=not reported; RR=relative risk; WHI=Women's Health Initiative.

Appendix D Table 14. Findings From the Women's Health Initiative Calcium With Vitamin D Trial

Author (Year) Title	Outcome Evaluated	Cases and Sample Size	Controls and Sample Size	Findings by Baseline Serum Vitamin D Level
Jackson et al, 2006[79]	Hip fracture, total fracture Verified by review of radiology, magnetic resonance imaging, or operative reports by blinded physician adjudicators at each clinical center. Final adjudication of hip fractures performed centrally.	Participants with adjudicated cases of hip, spine, and lower arm or wrist fracture Analyzed: 357 hip, 1,491 total fracture	Participants free of fracture for the duration of study, individually matched to cases by age, latitude of clinical center, race or ethnic group, and date of venipuncture. Analyzed: 357 hip, 1,491 total fracture	OR (95% CI) over 7 years followup Hip fracture <13 ng/ml: 1.06 (0.60 to 1.86) 13 to 18 ng/ml: 0.92 (0.53 to 1.62) 18 to 24 ng/ml: 0.86 (0.48 to 1.53) ≥24 ng/ml: 0.61 (0.32 to 1.15) p=0.64 for interaction Total fracture <13 ng/ml: 1.32 (0.99 to 1.76) 13 to 18 ng/ml: 0.87 (0.66 to 1.16) 18 to 24 ng/ml: 0.87 (0.66 to 1.16) ≥24 ng/ml:1.09 (0.81 to 1.47) p=0.15 for interaction
Wactawski-Wende et al, 2006[99]	Incident invasive colorectal cancer Cases were confirmed by both local and central medical record and pathology report review by trained adjudicators who were blinded to group allocation. Tests for colorectal cancer screening were not part of the protocol and were ordered by each participant's personal physician.	Participants with confirmed invasive colorectal cancer and adequate stored serum for analysis Enrolled: 317 Analyzed: 306	Participants free of colorectal cancer for the duration of study with adequate stored serum for analysis, individually matched to cases according to age, latitude of clinical center, race or ethnic group, and date of venipuncture. Enrolled: 317 Analyzed: 306	OR (95% CI) over 7 years followup ≥23 ng/ml: 1.15 (0.58 to 2.27) 17 to 23 ng/ml:1.12 (0.59 to 2.12) 12 to 23 ng/ml: 0.99 (0.51 to 1.91) <12.4 ng/ml: 0.75 (0.39 to 1.48) p=0.54 for interaction
Chlebowski et al, 2008[100]	Incident invasive breast cancer. Confirmed by both local and central medical record and pathology report review by trained adjudicators who were blinded to group allocation.	Participants diagnosed with invasive breast cancer. Enrolled: 1,067 Analyzed: 895	Participants who were breast cancer free, matched to cases on age, latitude of clinical center, race/ethnicity, date of blood collection. Enrolled: 1,067 Analyzed: 895	Adjusted OR (95% CI) over 7 years followup ≥27 ng/ml: 0.89 (0.58 to 1.36) 22 to 27 ng/ml:1.25 (0.83 to 1.90) 18 to 22 ng/ml:1.07 (0.70 to 1.62) 13 to 18ng/ml:0.69 (0.45 to 1.06) <13 ng/ml:0.91 (0.60 to 1.39) p≥0.99 for interaction Adjusted for age, race, latitude, venipuncture date, randomization in hormone therapy and dietary modification trials, BMI, physical activity, family history of breast cancer, history of breast biopsy, and current hormone therapy use.

Appendix D Table 14. Findings From the Women's Health Initiative Calcium With Vitamin D Trial

Author (Year) Title	Outcome Evaluated	Cases and Sample Size	Controls and Sample Size	Findings by Baseline Serum Vitamin D Level
de Boer et al, 2008[96]	Incident diabetes Case-identification by self-report of a doctor prescribing medication or insulin for diabetes. Study states that accuracy of self-reported treated diabetes in WHI previously assessed using medication and laboratory data.	Participants with new physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin.	Participants with no physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin. Analyzed: 3,097	HR (95% CI) over 7 years followup ≥24 ng/ml:0.62 (0.32 to 1.20) 17 to 24 ng/ml:1.60 (0.80 to 3.18) 13 to 17 ng/ml: 0.66 (0.36 to 1.23) <13 ng/ml:1.07 (0.62 to 1.82) p=0.59 for interaction
LaCroix et al, 2009[95]	All-cause mortality For women who could not be contacted, information about vital status was sought from previously identified proxy informants, National Death Index searches, and obituary notices. Causes of death were determined based on available medical records, autopsy reports, and the death certificate in a blinded fashion by local and central physician adjudicators.	Participants with baseline serum vitamin D levels with deaths ascertained from previously identified proxy informants, National Death Index searches, and obituary notices. Causes of death determined based on medical records, autopsy reports, and death certificates. Analyzed: 323	Participants with baseline serum vitamin D levels and known to be alive. Analyzed: 1,962	Adjusted OR (95% CI) over 7 years followup ≥21 ng/ml: 1.04 (0.69 to 1.59) 14 to 21 ng/ml: 0.96 (0.64 to 1.45) <14 ng/ml: 0.79 (0.51 to 1.23) p=0.65 for interaction Adjusted for randomization to hormone therapy or diet modification, age, ethnicity, latitude of clinical center, season of blood draw, and treatment assignment.

Abbreviations: BMI=body mass index; CI=confidence interval; HR=hazard ratio; OR=odds ratio; WHI=Women's Health Initiative.

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Aloia, 2005[104]	Fair	Information related to allocation concealment, blinding, crossover, prespecification of harms, and attrition was unclear.	Yes	Unclear	Yes	Yes	No	Unclear
Aloia, 2018[108]	Fair	Moderate attrition with some lack of clarity in the numbers included in the ITT analysis. Lack of specificity in eligibility criteria. No mention of how adverse events were specified or monitored.	Yes	Yes	Yes	Yes	Unclear	Unclear
Arvold, 2009[82]	Fair	Differential attrition between groups (higher in placebo group) and unclear about both randomization methods and whether crossover occurred.	Unclear	Yes	Yes	Yes	No	Yes
Berlin, 1986[203]	Poor	Multiple deficiencies related to randomization, allocation concealment, blinding, and unknown rates of attrition or post-randomization exclusions.	No	No	Unclear	Yes	Unclear	No
Bischoff, 2003[89]	Fair	There was high overall attrition; only 73% of patients completed the study, and of those, almost a third were missing data on musculoskeletal outcomes.	Unclear	Yes	Yes	Yes	No	Yes

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Bislev, 2018[70]	Good	Good for KQ 3 outcomes; fair for KQ 4 outcomes because it is unclear how adverse events were specified or monitored.	Unclear	Yes	Yes	Yes	No	Unclear
Borgi, 2016[109]	Good	NA	Yes	Yes	Yes	Yes	Unclear	Yes
Brazier, 2005[88]	Fair	Details related to allocation concealment and blinding are unclear, though the study is described as a double-blind trial. The percentage of patients classified as withdrawn from the study is >20%; however, a large percentage of those patients withdrew after experiencing adverse events.	Yes	Unclear	Yes	Yes	Unclear	Unclear
Chapuy, 2002[87]	Fair	Methods related to randomization and allocation concealment are unclear and there is high overall attrition.	Unclear	Unclear	Yes	Yes	No	
Gagnon, 2014[110]	Fair	Some imbalances in baseline characteristics suggesting a failure of adequate randomization, borderline differential attrition (15% difference between groups).	Yes	Yes	No	Yes	No	Yes
Gallagher, 2012[49]	Good	NA	Yes	Yes	Yes	Yes	No	Yes
Gallagher, 2014[81]	Fair	High attrition	Yes	Unclear	Yes	Yes	Unclear	Yes

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Grimnes, 2011[94]	Fair	Unclear if harms were prespecified. Some differential attrition (11% difference between the groups).	Yes	Yes	Yes	Yes	No	Yes
Hansen, 2013[69]	Good	NA	Unclear	Yes	Yes	Yes	No	Yes
Harris, 1999[101]	Poor	Very small sample size, unclear if harms outcomes were prespecified, lack of blinding, unclear randomization and allocation concealment methods.	Unclear	Unclear	Yes	Yes	Yes	No
Hin, 2016[73]	Good	NA	Yes	Yes	Yes	Yes	No	Yes
Honkanen, 1990[101]	Fair	Lack of information related to randomization and treatment allocation methods. Study personnel and patients were not blind to treatment since the control group received none. Attrition was likely reasonable, but it is unclear at what point in screening/recruitment randomization occurred.	Unclear	Unclear	Yes	Yes	Unclear	No
Janssen, 2010[90]	Fair	High attrition, unclear if crossover occurred or if harms were prespecified.	Yes	Yes	Yes	Yes	No	Yes

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Jorde, 2016[74] and Jorde et al (2016)[137]	Fair	Subgroup analysis did not appear to be prespecified, also possible selective outcome reporting. Study also evaluated respiratory infections but did not report findings for that subgroup.	Yes	Yes	Yes	Yes	Unclear	Yes
Jorde, 2018[77]	Fair	Lack of information related to randomization methods, adverse events outcomes were not prespecified, analysis of depression scores appears to be a post hoc analysis, not included in the primary trial.	Unclear (probably adequate but not described)	Yes	Yes (except sig difference in baseline vitamin D levels, which was not likely clinically significant)	Yes	No	Yes
Kärkkäinen, 2010[92]	Fair	Open-label design (i.e., no blinding), unclear randomization and allocation methods, attrition between randomization and receiving treatment, and unclear whether harms were prespecified.	Unclear	Unclear	Yes	Yes	No	No
Kearns, 2015[111]	Fair	Method of randomization and allocation concealment NR, unclear whether outcome assessors were blinded, harms not prespecified as outcomes and only monitoring of serum calcium for safety was described.	Unclear	Unclear	Yes	Yes	No	Unclear

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Kjaergaard, 2012[80]	Good	NA	Yes	Yes	Yes	Yes	Yes	Yes
Knutsen, 2014[105]	Fair	Harms were not prespecified in the article and very little information is provided.	Yes	Yes	Yes	Yes	No	Yes
Krieg, 1999[91]	Fair	Attrition was high (but similar) in both groups and there was a lack of blinding, which may have affected outcomes. Information on randomization, allocation concealment, and crossover between groups was unclear.	Unclear	Unclear	Yes	Yes	No	No
Lehmann, 2013[46]	Fair	Lack of information regarding crossover and prespecification of harms outcomes.	Yes	Yes	Yes	Yes	No	Yes
Lerchbaum, 2017[112]	Fair	Harm outcomes were not prespecified and no description of how they were ascertained.	Yes	Yes	Yes	Yes	No	Yes
Lips, 1996[86]	Fair	Loss to followup was low (<1%) but 18% of randomized participants did not complete treatment. An additional 73 participants were noted as using vitamin D outside of the study protocol, but it is not clear whether they were excluded from the study after randomization.	Yes	Yes	Yes	Yes	No	Unclear
Lips, 2010[83]	Fair	Some study methods were unclear.	Unclear	Unclear	Yes	Yes	Unclear	Yes

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Manson, 2019[71]	Good	Most reporting was for the whole study population, unclear whether completely applicable to the population that was vitamin D deficient, but this subgroup was prespecified.	Yes	Unclear	Yes	Yes	No	Yes
Martineau, 2007[106]	Fair	High attrition and unclear information related to crossover and prespecification of harms/adverse events outcomes.	Yes	Yes	Yes	Yes	Yes	Yes
Mason, 2014[113]	Fair	Modest attrition	Yes	Yes	Yes	Yes	No	Yes
Moreira-Lucas, 2017[114]	Fair	Method of randomization and allocation concealment not specified and some differences in baseline characteristics, modest attrition, no mention of how adverse events were specified or monitored.	Unclear	Unclear	No	Yes	No	Yes
Ng, 2014[115]	Good	NA	Yes	Unclear	Yes	Yes	No	Yes
Nowak, 2016[116]	Good	NA	Yes	Yes	Yes	Yes	No	Unclear
Oliveri, 2015[204]	Poor	Eligibility criteria not specified, no information about allocation concealment, baseline imbalances, single blind. Harms outcomes not prespecified. This was primarily designed as a	Yes	Unclear	No	Unclear	Unclear	No

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
		pharmacokinetic study, not an intervention study.						
Osmancevic, 2016[205]	Poor	No information on randomization method or allocation concealment and baseline characteristics of treatment groups not provided, very high attrition.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Pfeifer, 2000[85]	Fair	Methods related to randomization and blinding were unclear.	Unclear	Unclear	Yes	Yes	No	Unclear
Pfeifer, 2009[84]	Fair	Unclear randomization and blinding methods.	Unclear	Unclear	Yes	Yes	No	Unclear
Pilz, 2015[117]	Fair	No mention of how adverse events were specified or monitored.	Yes	Yes	Yes	Yes	No	Yes
Pittas, 2019[76]	Fair	Methods related to randomization, allocation concealment, and blinding are minimally described, if at all.	Yes	Unclear	Yes	Yes	No	Yes
Raed, 2017[118]	Fair	No mention of how adverse events were specified or monitored.	Yes	Yes	Yes	Yes	No	Yes
Scragg, 2017;[97] Khaw, 2017[72]	Good	Subgroup analysis was prespecified.	Yes	Yes	Yes	Yes	No	Yes
Shea, 2019[78]	Good	NA	Yes	Yes	Yes	Yes	No	Unclear

Appendix E Table 1. Quality Ratings for Randomized, Controlled Trials, Part 1

Author, Year	Overall Quality Rating	Overall Rationale for Quality Rating	1. Was method of randomi-zation adequate?	2. Was allocation concealment adequate?	3. Were group characteris-tics balanced at baseline?	4. Were the eligibility criteria prespecified?	5. Were there any inappropriate post-randomization exclusions?	6. Were outcome assessors blinded?
Tran, 2014[119]	Good	Harm/safety outcomes are rated as good. Antibiotic use outcomes are rated as poor because these were defined for a post hoc analysis with serious risk of measurement bias. Further antibiotic use is a very indirect measure for incidence of infections.	Yes	Unclear	Yes	Yes	No	Yes
Wamberg, 2013[107]	Fair	Moderate attrition and unclear information about crossover.	Yes	Yes	Yes	Yes	No	Yes
Witham, 2013[102]	Fair	Baseline imbalances in BMI between groups, no specification of harms or description of harm ascertainment.	Yes	Yes	No	Yes	No	Yes
Wood, 2012[93]	Fair	Unclear whether harms were prespecified or if there was any crossover.	Yes	Yes	Yes	Yes	No	Yes

Abbreviations: BMI=body mass index; ITT=intent to treat; KQ=key question; NA=not applicable; NR=not reported.

Appendix E Table 2. Quality Ratings for Randomized, Controlled Trials, Part 2

Author, Year	7. Were care providers blinded?	8. Were participants blinded?	9. Was there acceptable attrition and no differential attrition?	10. Was there fidelity to the assigned intervention?	11. Was there crossover between groups?	12. Were participants analyzed in the groups in which they were randomized?	13. Were the outcomes prespecified?	14. Were the subgroup analyses prespecified?
Aloia, 2005[104]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	NA
Aloia, 2018[108]	Yes	Yes	Unclear	Yes	No	Yes	Unclear	NA
Arvold, 2009[82]	Yes	Yes	No	Yes	Unclear	Yes	Yes	NA
Berlin, 1986[203]	No	No	Not reported	Yes	Unclear	Yes	Yes	NA
Bischoff, 2003[89]	Yes	Yes	No	Yes	Unclear	Yes	Yes	NA
Bislev, 2018[70]	Yes	Yes	Yes	Yes	No	Yes	Unclear	NA
Borgi, 2016[109]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Brazier, 2005[88]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	NA
Chapuy, 2002[87]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	NA
Gagnon, 2014[110]	Yes	Yes	No	Yes	No	Yes	Yes	NA
Gallagher, 2012[49]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Gallagher, 2014[81]	Yes	Yes	No	Yes	No	Yes	Yes	Unclear
Grimnes, 2011[94]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	NA
Hansen, 2013[69]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Harris, 1999[101]	No	No	Yes	Unclear	Unclear	Yes	Unclear	Yes
Hin, 2016[73]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Honkanen, 1990[101]	No	No	Unclear	Yes	Unclear	Yes	Yes	Yes
Janssen, 2010[90]	Yes	Yes	No	Yes	Unclear	Yes	Unclear	NA
Jorde, 2016[74] and Jorde et al (2016)[137]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No
Jorde, 2018[77]	Yes	Yes	Yes	Yes	No	Yes	No (power calc was ad hoc)	NA
Kärkkäinen, 2010[92]	No	No	Yes	Yes	Unclear	Yes	Unclear	Yes

Appendix E Table 2. Quality Ratings for Randomized, Controlled Trials, Part 2

Author, Year	7. Were care providers blinded?	8. Were participants blinded?	9. Was there acceptable attrition and no differential attrition?	10. Was there fidelity to the assigned intervention?	11. Was there crossover between groups?	12. Were participants analyzed in the groups in which they were randomized?	13. Were the outcomes prespecified?	14. Were the subgroup analyses prespecified?
Kearns, 2015[111]	Yes	Yes	Yes	Yes	No	Yes	Unclear	NA
Kjaergaard, 2012[80]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	NA
Knutsen, 2014[105]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Krieg, 1999[91]	No	No	No	Yes	Unclear	Yes	No	NA
Lehmann, 2013[46]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	NA
Lerchbaum, 2017[112]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	No
Lips, 1996[86]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Lips, 2010[83]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	NA
Manson, 2019[71]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Martineau, 2007[106]	Yes	Yes	No	Yes	Unclear	Yes	Unclear	NA
Mason, 2014[113]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Moreira-Lucas, 2017[114]	Yes	Yes	Yes	Yes	No	Yes	Unclear	Unclear
Ng, 2014[115]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Nowak, 2016[116]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Oliveri, 2015[204]	No	Yes	Yes	Yes	No	Yes	Unclear	NA
Osmancevic, 2016[205]	Yes	Yes	No	Yes	No	Yes	Yes	NA
Pfeifer, 2000[85]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	NA
Pfeifer, 2009[84]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	NA
Pilz, 2015[117]	Yes	Yes	Yes	Yes	No	Yes	Unclear	NA
Pittas, 2019[76]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Raed, 2017[118]	Yes	Yes	Yes	Yes	No	Yes	Unclear	NA
Scragg, 2017[97] Khaw, 2017[72]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Shea, 2019[78]	Yes	Yes	Yes	Yes	No	Yes	Yes	NA
Tran, 2014[119]	Yes	Yes	Yes	Yes	No	Yes	Unclear	NA

Appendix E Table 2. Quality Ratings for Randomized, Controlled Trials, Part 2

Author, Year	7. Were care providers blinded?	8. Were participants blinded?	9. Was there acceptable attrition and no differential attrition?	10. Was there fidelity to the assigned intervention?	11. Was there crossover between groups?	12. Were participants analyzed in the groups in which they were randomized?	13. Were the outcomes prespecified?	14. Were the subgroup analyses prespecified?
Wamberg, 2013[107]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	NA
Witham, 2013[102]	Yes	Yes	Yes	Yes	No	Yes	Unclear	NA
Wood, 2012[93]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	NA

Abbreviation: NA=not applicable.

Appendix E Table 3. Quality Ratings for the Women's Health Initiative Nested Case-Control Study

Author (Year)	Can we be confident in the assessment of exposure?	Can we be confident that cases had developed the outcome of interest and the controls had not?	Can we be confident in the assessment of variable evaluated through interaction effect?	Were the cases (those who were exposed and developed the outcome of interest) properly selected?	Were the controls (those who were exposed and did not develop the outcome of interest) properly selected?	Were cases and controls matched according to important prognostic variables or was statistical adjustment carried out for those variables?	Overall Rating	Comments
Women's Health Initiative Nested Case Control Study[79, 95, 96, 99, 100]	Definitely yes	Definitely yes for mortality, fracture, colorectal cancer, and breast cancer. Probably yes for diabetes	Probably no	Definitely yes	Definitely yes	Definitely yes	Fair	Variability in vitamin D assay has potential to misclassify exposure among the various subgroups evaluated, but this is likely small. Diabetes not ascertained as rigorously as the other outcomes. Only modest adherence to study medication (59% at study end), and participants were allowed to take personal calcium and vitamin D supplements outside of the study protocol.

Appendix F Figure 1. Effect of Vitamin D Treatment on Mortality by Baseline Vitamin D Level (Community-Dwelling Participants)

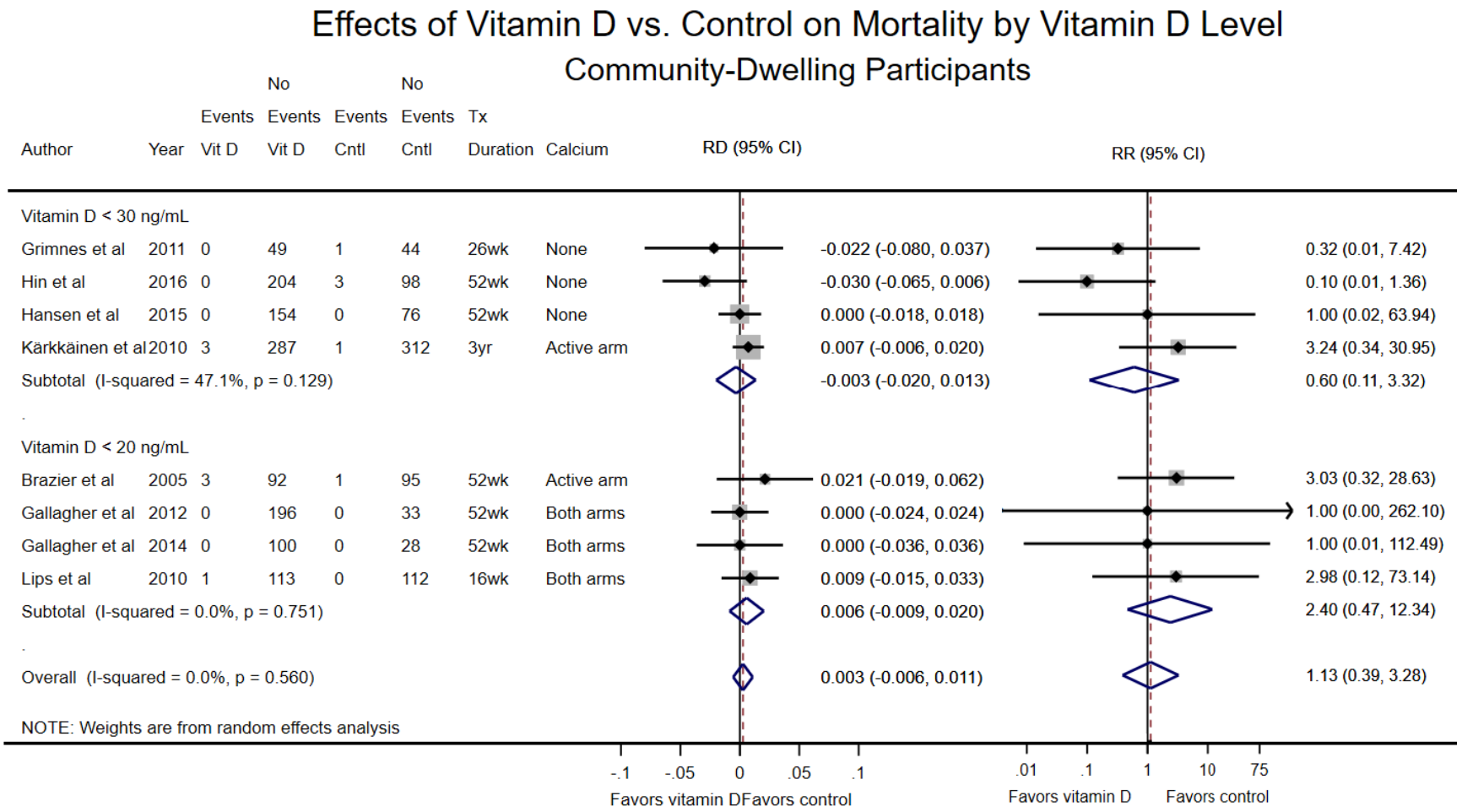

Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points)

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=weeks; yr=years.

Appendix F Figure 2. Effect of Vitamin D Treatment on Mortality by Calcium Use (Community-Dwelling Participants)

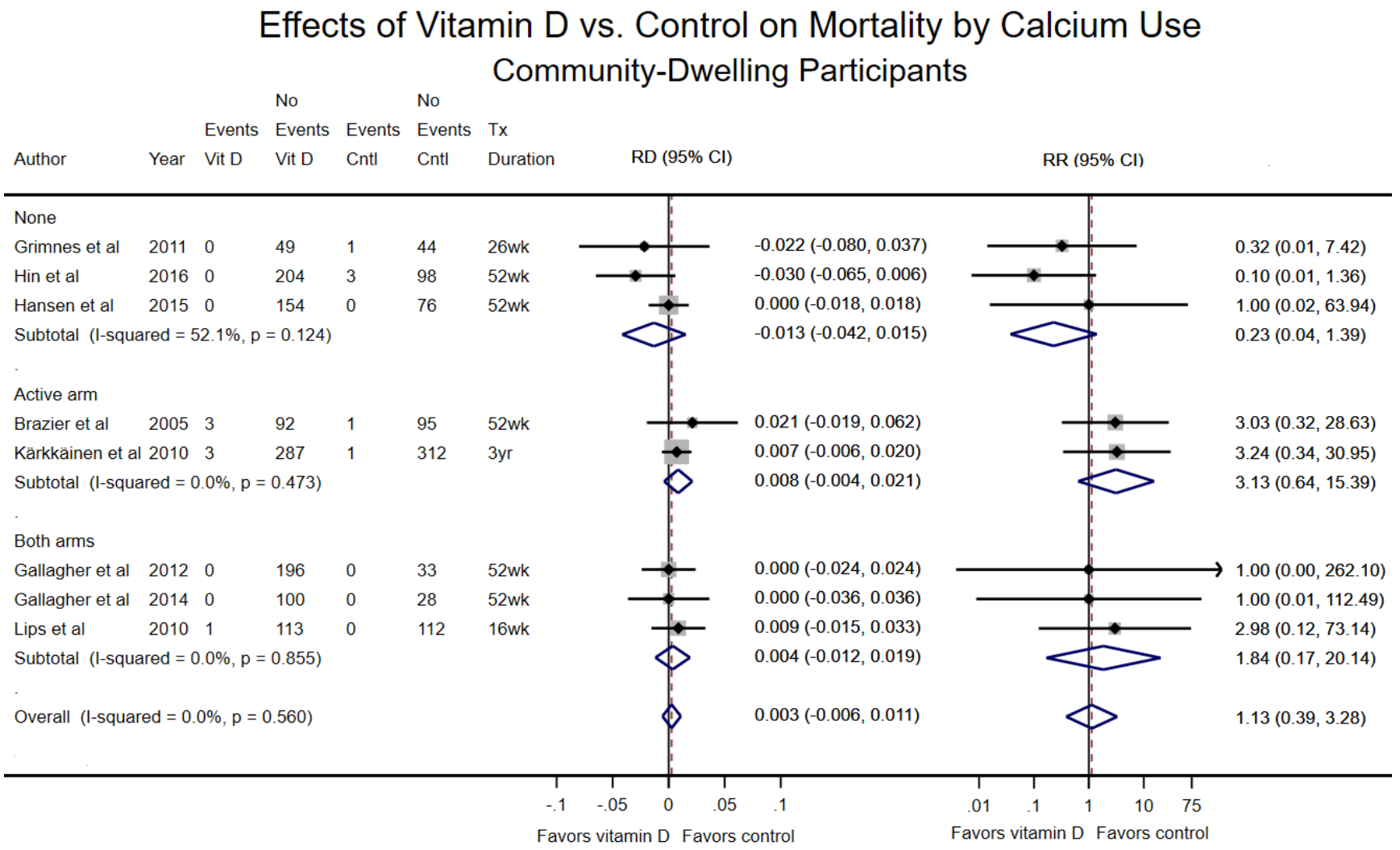

Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; Vit=vitamin; Tx=treatment; wk=weeks; yr=years.

Appendix F Figure 3. Effect of Vitamin D Treatment on Fractures by Baseline Vitamin D Status (Community-Dwelling Participants)

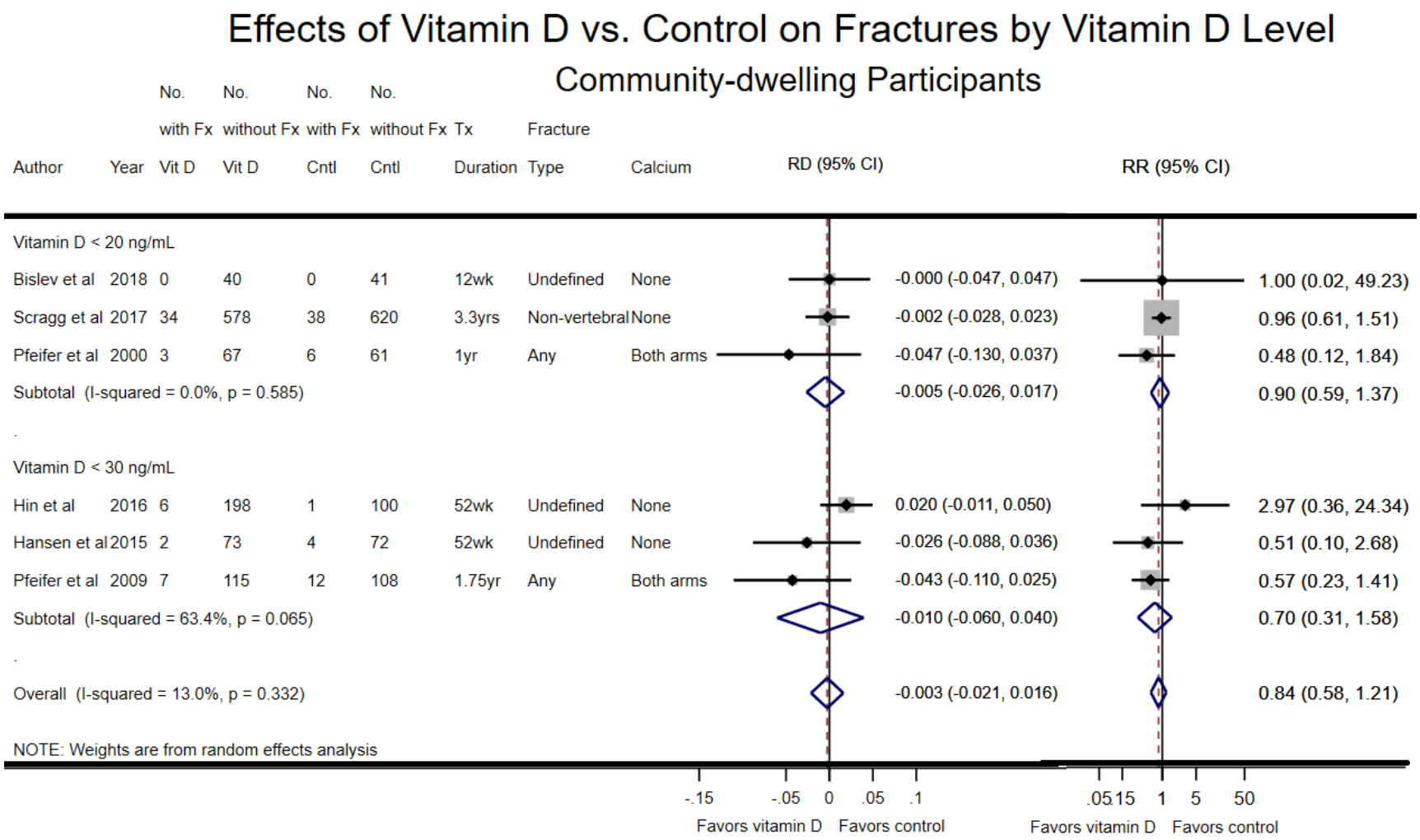

Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage point).

Abbreviations: CI=confidence interval; Cntl=control; Fx=fracture; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=weeks; yr=years.

Appendix F Figure 4. Effect of Vitamin D Treatment on Fractures by Calcium Use (Community-Dwelling Participants)

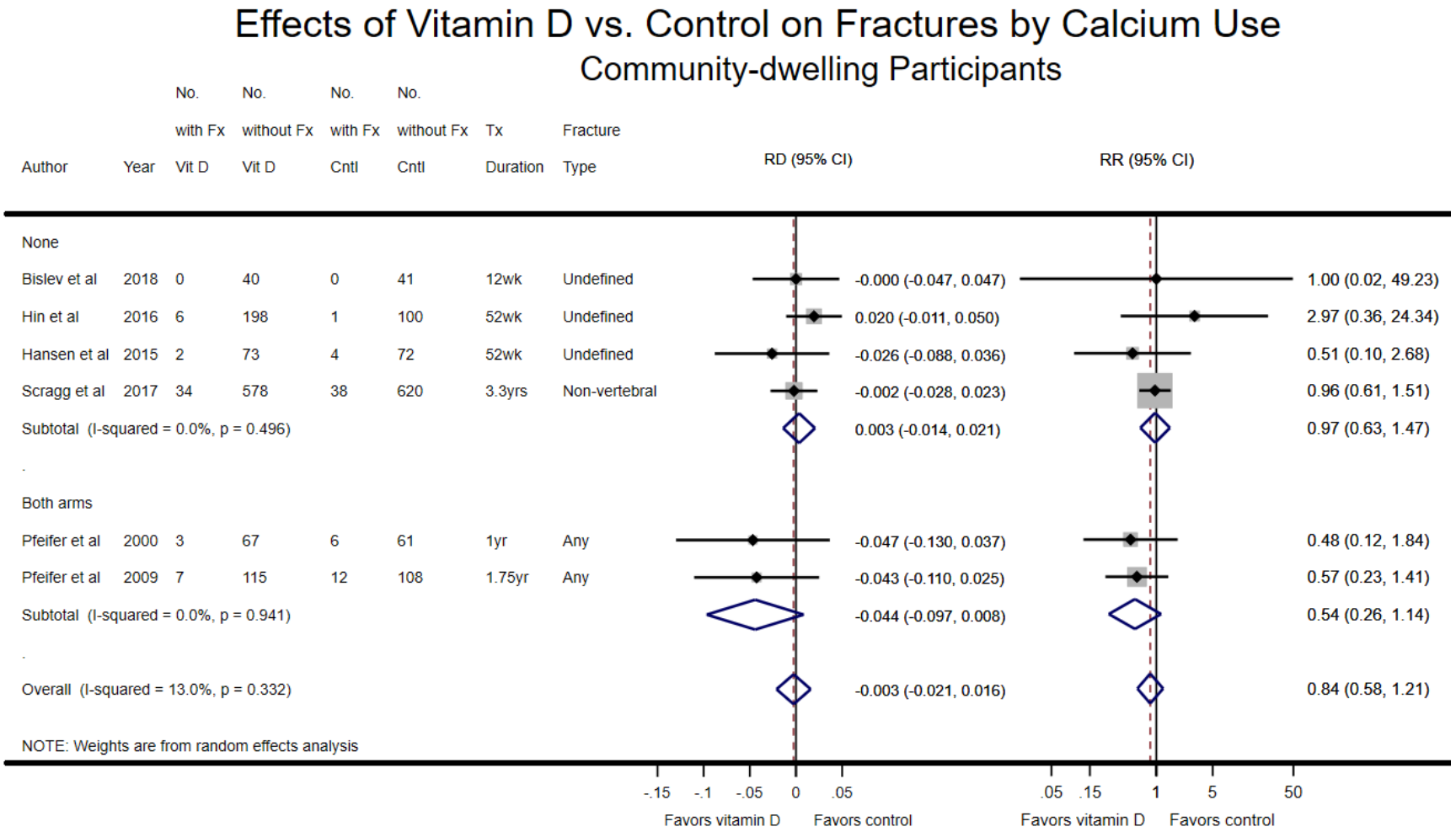

Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; Fx=fracture; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=weeks; yr=years.

Appendix F Figure 5. Effect of Vitamin D Treatment on Falls by Vitamin D Level (Community-Dwelling Participants)

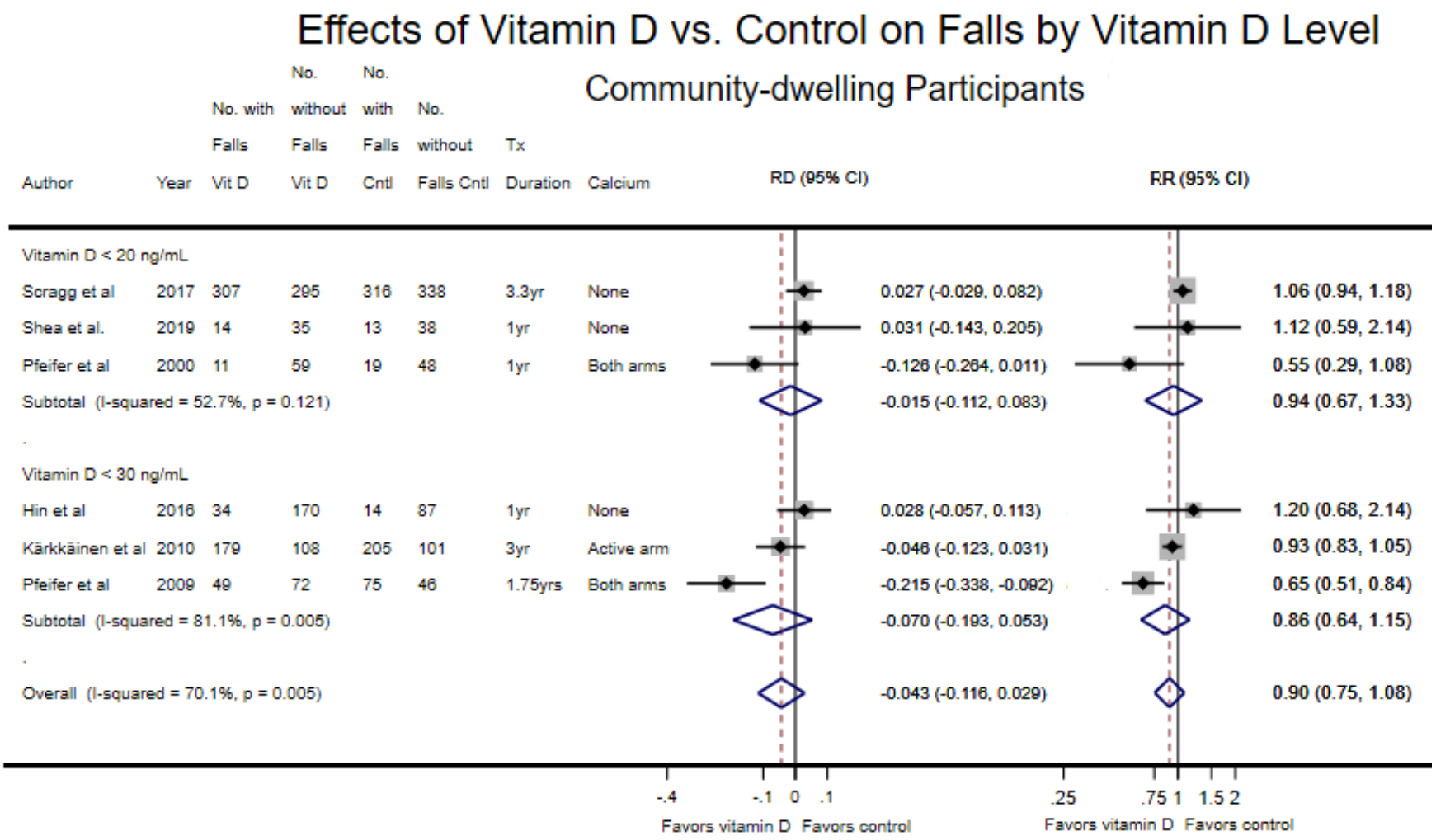

Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=weeks; yr=years.

Appendix F Figure 6. Effect of Vitamin D Treatment on Falls by Calcium Use (Community-Dwelling Participants)

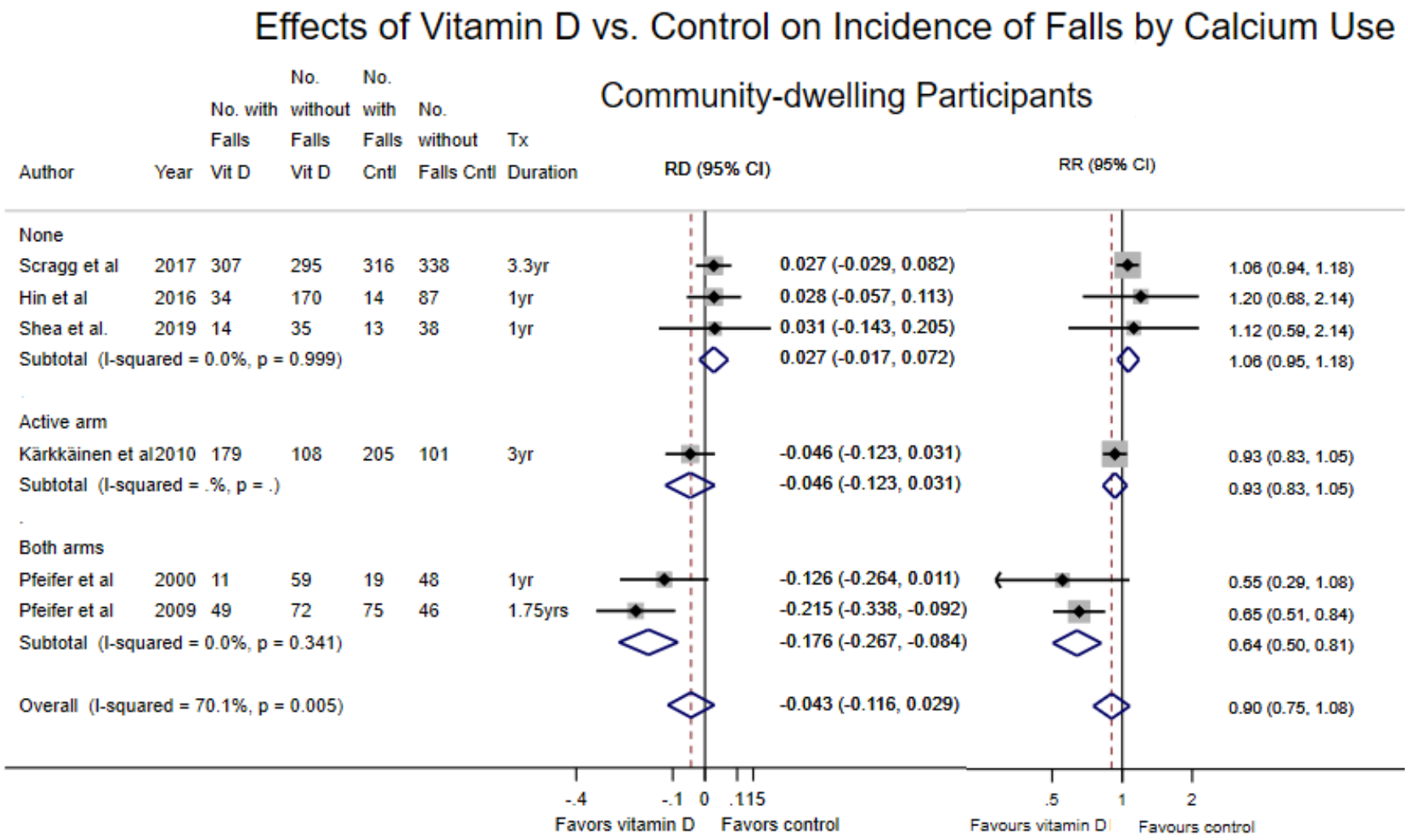

Figure Notes: To calculate the absolute risk difference in percentage points, multiply value by 100 (e.g., 0.009 multiplied by 100=0.9 percentage points).

Abbreviations: CI=confidence interval; Cntl=control; RD=absolute risk difference; RR=relative risk; Tx=treatment; Vit=vitamin; wk=weeks; yr=years.

Appendix F Table 1. Sensitivity Analysis for Pooled Estimates of Mortality Incidence—Part 1

	Main (Stata)	Sensitivity Analysis 1 (Stata)	Sensitivity Analysis 2 (Stata)	Sensitivity Analysis 3 (Stata)	Sensitivity Analysis 4 (Stata)	Sensitivity Analysis 5 (Stata)	Sensitivity Analysis 6 (Stata)
	• Random effects model using the method of DerSimonian & Laird • Studies with zero events in both treatment and control groups were included with a continuity correction for zero event cells as described by Battaggia et al (2015)[206]	Same as main analysis except studies with zero events in both treatment groups were excluded from pooling (all were in community-dwelling strata)	Same as main except a manual continuity correction of 0.5 was added to all zero event cells	Fixed effects model using M-H pooling; studies with zero events in both treatment groups were excluded	Fixed effects model using Peto method for pooling odds ratio; studies with zero events in both treatment groups were excluded	Fixed effects model using Peto method for pooling odds ratio, continuity correction for zero event cells as described by Battaggia et al (2015)[206]	Fixed effects model using Peto method for pooling odds ratio, 0.5 manual continuity correction added to all zero event cells
			Effect	**Estimate**	**(95% CI)**		
RD Overall	-0.6% (-2.2% to 1.1%)	-1.0% (-3.5% to 1.4%)	-0.8% (-2.5% to 0.8%)	-1.9% (-3.6% to -0.1%)	NA	NA	NA
RD Community-Dwelling	0.3% (-0.6% to 1.1%)	0.2% (-1.3% to 1.7%)	0.1% (-0.8% to 1.0%)	0% (-1.0% to 1.0%)	NA	NA	NA
RD Institutionalized	-2.8% (-5.5% to -0.2%)	Same as main	Same as main	Same as main	NA	NA	NA
RR Overall	0.86 (0.75 to 0.99)	Same as main	Same as main	Same as main	0.83 (0.70 to 0.99)	Same as SA2	0.83 (0.70 to 0.98)
RR Community-Dwelling	1.13 (0.39 to 3.28)	1.09 (0.25 to 4.84)	0.91 (0.31 to 2.64)	0.97 (0.39 to 2.38)	1.02 (0.34 to 3.08)	1.01 (0.40 to 2.59)	0.86 (0.32 to 2.29)
RR Institutionalized	0.86 (0.74 to 0.99)	Same as main	Same as main	Same as main	0.83 (0.69 to 0.98)	Same as SA2	Same as SA4

Abbreviations: CI=confidence interval; M-H=Mantel-Haenszel; RD=absolute risk difference; RR=relative risk.

Appendix F Table 2. Sensitivity Analysis for Pooled Estimates of Mortality Incidence—Part 2

	Main (Stata)	Sensitivity Analysis 7 (Meta Package in R)	Sensitivity Analysis 8 (Meta Package in R)	Sensitivity Analysis 9 (Meta Package in R)	Sensitivity Analysis 10 (Meta Package in R)
	• Random effects model using the method of DerSimonian & Laird • Studies with zero events in both treatment and control groups included with continuity correction for zero cell counts as described by Battaggia et al (2015)[206]	Random effects model using maximum likelihood estimator with 0.5 continuity correction for zero event cells	Random effects model using maximum likelihood estimator, studies with zero events in both treatment groups excluded	Random effects model using DerSimonian & Laird Estimator with 0.5 continuity correction for zero cell counts	Random effects using restricted maximum likelihood estimator with 0.5 continuity correction for zero cell counts
Effect Estimate (95% CI)					
RD Overall	-0.6% (-2.2% to 1.1%)	0% (-0.8% to 0.8%)	Same as SA4	-0.6% (-2.4% to 1.1%)	-0.1% (-1.1% to 0.8%)
RD Community Dwelling	0.3% (-0.6% to 1.1%)	0.3% (-0.6% to 1.2%)	Same as SA4	0.3% (-0.6% to 1.2%)	0.3% (-0.6% to 1.2%)
RD Institutionalized	-2.8% (-5.5% to -0.2%)	Same as main	Same as main	Same as main	-2.8% (-5.5% to -0.2%)
RR Overall	0.86 (0.75 to 0.99)	Same as main	Same as main	Same as main	Same as main
RR Community Dwelling	1.13 (0.39 to 3.28)	0.86 (0.29 to 2.56)	1.17 (0.33 to 4.16)	0.87 (0.29 to 2.56)	0.82 (0.25 to 2.63)
RR Institutionalized	0.86 (0.74 to 0.99)	Same as main	Same as main	Same as main	Same as main

Abbreviations: CI=confidence interval; RD=absolute risk difference; RR=relative risk.