Evidence Synthesis
Number 118

Screening for Vitamin D Deficiency: Systematic Review for the U.S. Preventive Services Task Force Recommendation

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Contract No.: HSSA 290-2007-10057-I, Task Order No.: 13

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AHRQ-Pub No. 13-05183-EF-1
June 2014

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2007-10057-1, Task Order Number 13). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment.

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements

The authors acknowledge Andrew Hamilton, MLS, MS, for conducting literature searches, Rongwei Fu, PhD, for statistical assistance, and Spencer Dandy, BS, for assistance with drafting this report at the Oregon Health & Science University. The authors also thank the AHRQ Medical Officers Robert McNellis, MPH, PA, Tina Fan, MD, MPH, and Tess Miller, DrPH, as well as the U.S. Preventive Services Task Force Leads, Linda Baumann, PhD, RN, Doug Owens, MD, MS, and Albert Siu, MD, MSPH for their contributions to this report.

Structured Abstract

Background: It is unclear if screening for vitamin D deficiency can improve health of asymptomatic individuals with this deficiency.

Purpose: The USPSTF will use this report to develop a recommendation statement on screening for vitamin D deficiency in asymptomatic adults not known to have this deficiency.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through December 2013), and MEDLINE (1946 to January 2014), and manually reviewed reference lists from applicable review articles.

Study Selection: We included systematic reviews, randomized, controlled trials (RCTs), or case-control studies nested within an RCT to examine the benefits of vitamin D treatment (with or without calcium) compared with placebo, calcium alone, or no treatment. We included systematic reviews, RCTs, and cohort or case-control studies to evaluate harms. Included study populations were asymptomatic (not selected for signs or symptoms of vitamin D deficiency or medical conditions that increase risk for deficiency), adults (aged ≥18 years) from the United States, Canada, and Europe with reported serum 25(OH)D concentrations of 30 ng/mL or less.

Data Extraction: No study examined the effect of vitamin D screening on health outcomes. In treatment studies, mortality was decreased in those randomized to vitamin D treatment (with or without calcium) (11 studies; pooled RR 0.83; 95% CI, 0.70 to 0.99). This risk reduction, however, was limited to studies of older, institutionalized persons (3 trials; pooled RR 0.72; 95% CI, 0.56 to 0.94). While vitamin D treatment (with or without calcium) was not associated with a decreased risk for falling (5 studies; pooled RR 0.84; 95% CI, 0.69 to 1.02), it was associated with fewer falls per person (5 studies; pooled RR 0.66; 95% CI, 0.50 to 0.88), suggesting decreased falls among fallers; these findings were not influenced by institutionalized status. Vitamin D treatment (with or without calcium) was not associated with decreased fracture risk (5 studies; pooled RR 0.98; 95% CI 0.82 to 1.16). Neither vitamin D dosage nor baseline level of 25(OH)D in the population influenced risk estimates. Data were limited (≤2 studies) for cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning. No trials of vitamin D treatment on risk for cardiovascular disease or immune disease met inclusion criteria. Vitamin D treatment (with or without calcium) was not associated with increased risk for harms.

Limitations: There was no direct evidence on the effect of screening for vitamin D on health outcomes. Evidence on vitamin D treatment of deficiency on health outcomes was limited. Most studies that reported harms were not designed to assess harms and lacked rigorous reporting. No study examined effects according to subgroups defined by race, age, and sex. Few studies were conducted in non-white, non-female populations. There was variability in types of assays used to measure 25(OH)D, baseline 25(OH) levels of the study population, dosages used, calcium co-supplementation, and duration of followup.

Conclusions: Treatment with vitamin D, with or without calcium, may be associated with decreased risk for mortality and falls in older or institutionalized adults. Vitamin D treatment did

not reduce fracture risk. More research is needed to determine vitamin D treatment's effects in younger, non-institutionalized adults and to clarify the subpopulations that are most likely to benefit from treatment.

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Chapter 1. Introduction

Purpose of Review

The U.S. Preventive Services Task Force (USPSTF) will use this report to develop a recommendation statement on screening for vitamin D deficiency in asymptomatic adults. While the USPSTF has not previously issued recommendations on screening for vitamin D deficiency, it has issued several recommendation statements on the effects of vitamin D supplementation on prevention of adverse health outcomes (e.g., falls, fractures, cancer, and cardiovascular disease) in populations of persons who were not necessarily vitamin D deficient (i.e., they included general populations who may or may not have been deficient).[1-4]

Condition Definition

Vitamin D is a term used to refer to a group of fat-soluble compounds that play a significant role in calcium homeostasis and bone metabolism.[5] Vitamin D is a unique "vitamin" in that it is acquired through synthesis in the skin after sun exposure in addition to through consuming food.[6] Once synthesized, vitamin D is stored in adipocytes (fat cells) and is available for conversion to its active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). In addition to its effects on calcium and bone homeostasis, vitamin D also potentially affects many other cellular regulatory functions.[7]

Vitamin D deficiency is determined by measuring serum 25-hydroxyvitamin D (25(OH)D) concentrations. 25(OH)D is the major circulating form of vitamin D and is considered the best indicator of vitamin D status.[6] Measuring the active form of vitamin D, $1,25(OH)_2D$, is generally not performed in routine clinical practice because it does not accurately reflect vitamin D status. This is because vitamin D deficiency leads to elevated parathyroid hormone (PTH), which stimulates $1,25(OH)_2D$ production in the kidneys, even when blood levels of vitamin D are low.[8] While measurement of vitamin D–binding protein levels (the major carrier protein for vitamin D) in conjunction with total 25(OH)D could possibly be a useful method for estimating bioavailable 25(OH)D,[9] more research is needed on methods for measuring and interpreting bioavailable 25(OH)D. Measuring vitamin D-binding protein is not part of current standard clinical practice.

25(OH)D assays can be subject to variability (like all clinical assays). Multiple methodologies are available commercially and for research purposes to measure 25(OH)D. The first method developed to measure 25(OH)D utilized competitive protein binding methodology. Due to the multiple limitations of this method, it has been supplanted by immunoassay methods as well as high pressure liquid chromatography (HPLC) and the combination of HPLC and mass spectrometry (LC-MS/MS).[10] The sensitivity and specificity of different assays are not available because there is not yet an internationally recognized, commutable vitamin D reference material.[11] Studies have produced evidence of inter-method and inter-laboratory variability of 10 to 20 percent, however, which could limit the ability of 25(OH)D levels to precisely define an individual's vitamin D status.[12-16] In studies comparing how different assays would classify a person's deficiency status, 4 to 32 percent of the samples would have had been considered either deficient or not deficient depending on the assay used.[17-20] The greatest risk for differential

classification occurred when an individual's measured levels were close to defined cutoffs (e.g., those with very high and low levels were unlikely to be classified differently depending on the assay used).[16,19]

Several ongoing programs are currently working to decrease assay variability. In 2009, the National Institute of Standards and Technology (NIST) produced standard reference material for 25(OH)D, which represents the first step in standardizing measurement of vitamin D. While this reference material has improved the accuracy of LC-MS/MS analyses, it has been less helpful in standardizing immunoassays.[10,11] In 2010, the Vitamin D Standardization Program (VDSP) was established to promote 25(OH)D measurements that are accurate and comparable over time, at differing locations, and using different laboratory procedure. VDSP is an international effort conducted by the Office of Dietary Supplements, National Institutes of Health (NIH) in collaboration with the Centers for Disease Control and Prevention (CDC), National Center for Environmental Health, NIST, and the Belgian Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, Ghent. VDSP has developed protocols for standardizing procedures for measuring 25(OH)D in National Health/Nutrition Surveys. These protocols, however, are not yet available for commercial use or other research laboratories. Until these protocols are available, several external accuracy-based testing systems can be used, such as the NIST-NIH Vitamin D Metabolites Quality Assurance Program, the College of American Pathologists (CAP), and the Vitamin D External Quality Assurance Scheme or DEQAS (Charing Cross Hospital, London, UK). These schemes are similar to those used in other areas of clinical chemistry and can lead to decreased variability.[21] DEQAS,[12] for example, has acted as an early warning system to alert commercial kit manufacturers when they need to modify their products and procedures or when they need to withdraw kits.[12]

The level of 25(OH)D used to define vitamin D deficiency has varied over the previous two decades. As such, there is no consensus on optimal 25(OH)D concentrations. To determine sufficiency cutoff levels, researchers have examined what level of 25(OH)D is associated with maximal suppression of PTH,[12,22-25] maximum calcium absorption,[26,27] and reduced fracture risk.[28] In fact, the actual requirements for bone health likely reflect a distribution of values rather than a specific cut point. This is problematic for the purposes of diagnosing deficiency because clinicians require a specific cut point to make a diagnosis. While experts generally agree that levels lower than 20 ng/mL (50 nmol/L) may place an individual at risk relative to bone health, disagreement exists about whether goal 25(OH)D levels should be higher than 20 ng/mL for skeletal health[29] (**Table 1**).

In 2011, the Institute of Medicine (IOM) concluded that 20 ng/mL was the level necessary for good bone health for practically all individuals.[30] Other groups suggest that 25(OH)D levels should be greater than 30 ng/mL (75 nmol/L), particularly in older adults. These groups include the Endocrine Society, National Osteoporosis Foundation, and International Osteoporosis Foundation.[13,31-34] The Endocrine Society suggests that because of variability in laboratory measurements of 25(OH)D, targeting a higher 25(OH)D than goal (such as 40 ng/mL [100 nmol/L]) better ensures that all persons meet goal levels.[13] The IOM concluded, however, there may be a potential U-shaped relationship between 25(OH)D and some outcomes with potential risks (e.g., mortality, cardiovascular disease, selected cancers, falls) above 50 ng/mL (125 nmol/L).[30] Experts do agree that optimal serum 25(OH)D concentrations for extraskeletal health

have not been established.[13,30] For this report, the term "vitamin D deficient" refers to study participants who have been diagnosed with vitamin D deficiency, regardless of the study's cutoff (as long as it was ≤30 ng/mL).

Prevalence and Burden of Disease

The prevalence of vitamin D deficiency varies based on how deficiency is defined (<20 vs. ≤30 ng/mL). According to National Health and Nutrition Examination Survey (NHANES) data, 8 percent of the population were at risk for very low 25(OH)D levels (<12 ng/mL) from 2001 to 2006, and about 25 percent were at risk for deficiency, as defined by serum 25(OH)D levels of 12 to 20 ng/mL.[5] The IOM has recently developed a statistical procedure to derive group prevalence estimates of nutritional inadequacy. According to this statistical model, 19 percent of the population is at risk for vitamin D deficiency as defined by the IOM.[35] Data on the prevalence of 25(OH)D levels of less than 30 ng/mL come from a 2009 study using 2001 to 2004 NHANES survey data, which was not corrected for assay drift per National Center for Health Statistics instructions. Between 2001 to 2004, 77 percent of noninstitutionalized U.S. participants had 25(OH)D levels below 30 ng/mL.[36]

When total 25(OH)D levels are used to define deficiency, blacks have a 2- to 9-fold greater risk for deficiency and Hispanics a 2- to 3-fold greater risk for vitamin D deficiency, compared with whites.[37-39] Additionally, one recent study found that black Americans had not only lower total 25(OH)D levels when compared with white Americans, they also had lower vitamin D-binding protein levels.[9] This resulted in similar concentrations of estimated bioavailable 25(OH)D between blacks and whites. As such, more research is needed to determine whether total versus bioavailable 25(OH)D levels are a better indication of a state of deficiency and how they correlate with clinical health outcomes (e.g., bone density and fracture risk), especially in non-white populations.

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 aged 85 years or older.[37-41] While some studies reported females had greater risk for deficiency,[37,40] not all studies confirmed this finding.[39]

In NHANES, mean 25(OH)D was lower in 2000 to 2004 than 1988 to 1994.[42] Most of the differences in 25(OH)D between these time periods appear to be an artifact of assay changes rather than an actual decline in serum 25(OH)D levels. In an adult subgroup from NHANES, however, changes in body mass index (BMI), milk intake, and sun protection appeared to contribute to a small, but real, decline in vitamin D status.[42]

Etiology and Natural History

Vitamin D is synthesized in the skin under the influence of ultraviolet (UV) light and is also obtained from dietary sources and supplements. In the United States, the primary dietary sources of vitamin D are fortified foods such as milk, milk products, fortified 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, or reduced ability to produce vitamin D (e.g., due to increased skin pigmentation or aging, or a combination of these factors).[6]

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.[6] 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.[43]

Association Between 25(OH)D Levels and Health Outcomes

The association between 25(OH)D levels of 12 to 30 ng/mL and bone and other health outcomes is controversial (**Table 1**). In 2009, an Agency for Healthcare Research and Quality (AHRQ) report (not for the USPSTF) concluded that the evidence for an association between serum 25(OH)D concentrations and fracture risk was inconsistent.[44] Prospective studies published since the 2009 review have generally shown that lower 25(OH)D levels were associated with increased fracture risk. A recent 2014 umbrella study of systematic reviews and meta-analyses of observational studies, however, concluded evidence was suggestive only for non-vertebral fractures and that no conclusions could be reached about other fractures.[45] Prospective studies finding an association have generally noted that fracture risk increases at 25(OH)D levels less than 20 ng/mL in persons of Caucasian or European descent. Low 25(OH)D levels may not be associated with increased fracture risk in non-white races.[46,47] Some have hypothesized that these findings could be due to the differences in vitamin D binding protein and levels of bioavailable 25(OH)D among different races.

In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. Most tissues in the body have vitamin D receptors, for example, and the active form of vitamin D, $1,25(OH)_2D$, influences genomic expression in many cells.[7] Therefore, researchers have hypothesized possible links between low 25(OH)D levels and muscle function, cancer, and metabolic, immune, and cardiovascular systems.[48-54]

The 2009 AHRQ review concluded there was fair evidence for an association between low serum 25(OH)D concentrations (<16 ng/mL) and increased risk for falls in institutionalized elderly.[44,55] This association, however, has not been observed in community-dwelling elderly.[56,57] Similarly, a 2014 umbrella analysis of systematic reviews and meta-analyses concluded there was insufficient evidence to draw conclusions about the association between low levels and fall risk. The review did conclude that evidence suggested that high 25(OH)D levels are linked to an increased rate of falls.[45] Evidence on the association between 25(OH)D and decline in physical function is inconsistent. [58-63]

Although the 2009 AHRQ review concluded that evidence describing the association between 25(OH)D status and cardiovascular disease was inconsistent,[44] more recent data suggest an inverse association between risk for cardiovascular disease and 25(OH)D levels, mostly from white or primarily white populations.[45,58,64-67] Several studies have suggested an association up to 24 ng/mL.[64-67] This inverse association, however, has not been observed in black individuals.[68,69]

While low 25(OH)D levels have not been associated with increased risk for breast, prostate, or pancreatic cancer,[45,58,70-74] studies suggest an association between 25(OH)D levels and risk for colorectal cancer,[45] with each 10 to 20 ng/mL increase up to a 25(OH)D level of 35 to 40 ng/mL associated with a 15 to 50 percent decreased risk.[58,71,72,75-78]

Lower 25(OH)D levels (<12 to 20 ng/mL) have been associated with an increased risk for developing diabetes[45,58,79-87] and depressed mood.[45,58,88,89] The 2014 umbrella analysis of systematic reviews and meta-analyses concluded evidence suggested a decreased risk for cognitive decline in those with high 25(OH)D levels.[45,58] Risk may increase at levels below 10 to 20 ng/mL versus those with a level greater than 30 ng/mL.[90,91] The association may vary by sex with the effect being seen more in women.[91,92]

Two 2014 systematic reviews of 31 to 73 studies concluded that lower 25(OH)D levels were associated with a significantly increased risk for death.[58,93] A 2014 umbrella review of 107 systematic reviews and 74 meta-analyses of observational studies, however, stated there was not enough evidence to make conclusions about the association between vitamin D levels and mortality.[45] Although previous studies have concluded there may be a U-shaped association where high and low 25(OH)D levels are associated with an increased risk for mortality,[94-103] this was not observed in the recent meta-analyses. In studies that included a significant proportion of nonwhite populations, lower 25(OH)D levels were associated with decreased mortality risk in black and white individuals.[98,104]

More detailed information on the association between 25(OH)D levels and health outcomes is provided in **Appendix A1**.

Risk Factors

Low dietary vitamin D intake and/or lack of vitamin D supplements are associated with a 2- to 5-fold increased risk for vitamin D deficiency (<20 ng/mL).[37-39] Little or no UVB exposure (e.g., due to winter season, high latitude, and sun avoidance) are also associated with an increased risk for vitamin D deficiency.[37,38,40,41,105] While sunscreen reduces the skin's ability to produce vitamin D in response to UVB in controlled research settings,[106] this association has not been found in population-based studies.[105,107] This finding in population-based studies is likely due to incomplete application[108] and/or because subjects who use sunscreen are more likely to be exposed to the sun for extended periods.[78]

Obesity is associated with an almost 2-fold increased risk for being vitamin D deficient.[37-39,109] This finding is possibly due to sequestration of vitamin D in fat cells[30] or due to lifestyle differences (e.g., lower physical activity levels or lower dietary vitamin D intake). Low physical

activity,[37,38,41] low education attainment,[36] and low health status[39,105] are modestly associated with vitamin D deficiency in some studies. Differences in diet, supplement use, and UV exposure, however, could be mediating factors.

A significant proportion of the variability in 25(OH)D levels does not appear to be explained by traditional risk factors, which appear to account for only 20 to 30 percent of the variation in 25(OH)D levels.[41,110] Genetic factors may influence serum 25(OH)D concentrations, including genetic variants of vitamin D-metabolizing genes.[111]

More detailed information on risk factors associated with vitamin D deficiency is detailed in **Appendix A2**.

Rationale for Screening and Screening Strategies

Vitamin D deficiency might affect one-fifth to three-fourths of the population, depending on which cutoff is used.[5,35,36,39] Despite this prevalence, many of those who have low 25(OH)D levels are unaware of their status. Screening could identify persons with deficiency prior to the development of adverse health outcomes associated with this condition, assuming thresholds for deficiency can be established. If interventions to increase 25(OH)D levels successfully decrease disease risk, screening with serum 25(OH)D levels may improve the health of individuals with low 25(OH)D levels. This potential benefit, however, would need to be weighed against the risks associated with misdiagnosis of vitamin D deficiency given current assay variability and unclear cutoffs to define deficiency. The risk for misclassification could outweigh any benefits if there are harms resulting from treatment or if diagnosis of deficiency leads to anxiety or inaccurate labeling.

Interventions and Treatment

For healthy individuals not known to be vitamin D deficient, the IOM recently revised the Recommended Dietary Allowance (RDA) for vitamin D up to 600 IU per day for adults ages 18 to 70 years and 800 IU per day for adults over the age of 70 years.[30] 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.[13,32-34,112,113]

Vitamin D deficiency can be treated by increased dietary intake, vitamin treatment, and increased UV exposure. UV exposure is usually not recommended due to increased skin cancer risk. While few foods naturally contain vitamin D, several food products (e.g., milk, cereals) are available fortified with vitamin D. A non-USPSTF, AHRQ commissioned evidence report 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.[44]

Primary care physicians often treat vitamin D deficiency with oral vitamin D treatment. There are two commonly available forms of vitamin D treatment: vitamin D3 (cholecalciferol) and

vitamin D2 (ergocalciferol). A 2012 meta-analysis of seven randomized trials concluded that vitamin D3 treatment increased serum 25(OH)D more efficiently than vitamin D2.[114] The trials in the meta-analysis, however, used varying doses, treatment time periods, and assays to measure $25(OH)D_2$ and $25(OH)D_3$. Interpreting these findings is challenging because between-study statistical heterogeneity was present and the observed difference was of uncertain clinical significance. A 2013 bioavailability study that was powered to examine the effects of vitamin D2 compared with D3 treatment concluded that vitamin D3 treatment was more effective in raising total 25(OH)D levels than vitamin D2 treatment.[115] The Endocrine Society suggests using either vitamin D2 or D3 treatment[13] based on several studies showing that physiologic doses of vitamin D2 treatment are equally as effective as vitamin D3 treatment at increasing and maintaining serum 25(OH)D levels and maintaining $1,25(OH)_2D$ levels.[116,117] The IOM does not differentiate between use of vitamin D2 or D3 supplements in its recommendations.[30]

There are multiple forms (e.g., tablet, gel capsule), dosages (e.g., 200 to 500,000 IU), and dosing regimens (e.g., daily, weekly, monthly, yearly) of vitamin D treatment. Increasing doses of vitamin D treatment are associated with greater net change in 25(OH)D concentration, although these effects vary depending on study participants' serum 25(OH)D status (e.g., ≤16 vs. >16 ng/mL) at baseline and the duration of treatment (e.g., ≤3 vs. >3 months).[44]

The amount of vitamin D required to effectively treat vitamin D deficiency also likely depends upon an individual's vitamin D absorptive capacity, their capacity to convert vitamin D to 25(OH)D in the liver, and genetic determinants. These factors lead to many different dosages and dosage patterns being used clinically. The Endocrine Society Task Force, for example, recommends that adults with vitamin D deficiency (≤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 persons with obesity, the Endocrine Society recommends increasing the dose by 2- or 3-fold.[13] The efficacy of this practice, however, has not been rigorously compared with daily, weekly, or monthly dosing. While 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.

Vitamin D supplements are often given with oral calcium, which may affect health outcomes and harms. Meta-analyses have suggested possible differences on health outcomes, such as mortality and fracture, when taking vitamin D supplementation when studies were stratified according to whether calcium was or was not given with the vitamin D supplements.[118,119]

Effect of Vitamin D Treatment on Intermediate Outcomes

In older white women with severe vitamin D deficiency (<12 ng/mL), vitamin D treatment (400 to 800 IU per day, with or without calcium) for 12 to 24 months was associated with less decline in hip and/or spine BMD than placebo in some studies,[120,121] but not all.[122] Taking vitamin D treatment (1,000 IU to 5,700 IU per day) for 6 to 36 months did not improve BMD compared with placebo in older men, postmenopausal black women, or younger, mixed sex populations.[123-126]

Among older women, our included studies found no association between vitamin D treatment (400 to 1,800 IU per day, with or without calcium) and improved hand strength,[127,128] leg strength,[127] or balance after 11 to 24 weeks,[129] versus placebo. Young persons (mean age 18 to 33 years) who were vitamin D deficient (<30 ng/mL) and given large (25,000 to >60,000 IU per week) doses of vitamin D had improvement on several strength measures when compared with those given placebo.[130,131]

Studies found no association between vitamin D treatment (400 to 7,143 IU per day, with or without calcium) and improvement in lipid, glucose, insulin sensitivity, or insulin levels among non-diabetic persons with low 25(OH)D levels (<30 ng/mL).[132-136]

Although some studies reported vitamin D treatment (800 to 4,000 IU per day) was associated with decreased systolic (but not diastolic) blood pressure when compared with placebo,[134,137] a nested case-control study of postmenopausal women with vitamin D deficiency in the Women's Health Initiative (WHI) Calcium with Vitamin D (CaD) trial found no difference between vitamin D supplementation (400 IU per day with 1,000 mg calcium) versus placebo in risk for incident hypertension over 7 years.[137]

More detailed information on the effect of vitamin D treatment on intermediate outcomes is presented in **Appendix A3**.

Adverse Effects of Vitamin D Treatment

Laboratory signs of vitamin D toxicity may appear before symptoms are evident. These symptoms can include hypercalcemia, hyperphosphatemia, suppressed PTH, and hypercalciuria that can occur after less than 4 weeks of continuous excess ingestion. These symptoms are variable and, while they are often non-specific, are mostly related to hypercalcemia and hypercalciuria.[30] Mild hypercalcemia can result in constipation, fatigue, and depression. More severe hypercalcemia can cause polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, arrhythmias, and mental status changes. Hypercalciuria can lead to increased risk for kidney stones. The toxicity level of vitamin D (most commonly defined as 25(OH)D >200 ng/mL [500 nmol/L]) is well above the level considered to be sufficient.[138,139] Acute toxicity has not been linked to vitamin D intake of less than 10,000 IU per day.[30] The IOM recommends a tolerable upper intake level (UL) of vitamin D supplementation for adults of 4,000 IU per day in order to avoid 25(OH)D levels greater than 50 ng/mL, which may be associated with potential risks (e.g., increased mortality, cardiovascular disease risk, certain cancers, and falls).[30] While the Endocrine Society recommends a maintenance regimen of UL of 4,000 IU per day, it states that 10,000 IU per day may be needed to correct deficiency for those at risk for deficiency or during treatment of deficiency.[13]

Current Clinical Practice

While we identified no reliable data on screening rates for vitamin D deficiency, available data do suggest that testing rates for vitamin D status in general are increasing. A 2009 email survey conducted among readers of Clinical Laboratory News (publication of the American Academy

for Clinical Chemistry) found that more than 50 percent of respondents reported an increase of at least 50 percent in the volume of 25(OH)D level testing in their labs over the prior year, and 27 percent reported an increase of 100 percent. Testing for $1,25(OH)_2D$ also increased over this period, which suggests possible clinician uncertainty regarding which tests to order to assess vitamin D status.[140]

While data regarding vitamin D treatment patterns are limited, these data also suggest increased use. In one large integrated health care delivery system (>3 million members), use of high-dose vitamin D (50,000 IU) increased nearly 8-fold between 2007 and 2010.[141] Use of over-the-counter supplemental vitamin D has also increased over the past decade. In 2003 to 2006, for example, NHANES data reported 56 percent of women age 60 years or older took vitamin D in one or more dietary supplements, as did 45 percent of women ages 40 to 59 years and 33 percent of women ages 20 to 39 years. This represents a significant increase from 1999 to 2002.[142] Vitamin D supplementation among men was lower than among women in the same age groups (44%, 38%, and 26%, respectively). In 2008, 60 percent of women and 46 percent of men age 50 years or older in a large integrated health system reported taking vitamin D in the form of dietary supplements, as did 76 percent of women and 47 percent of men ages 51 to 85 years. Rates of vitamin D supplement usage were generally lower among non-whites.[142,143]

Recommendations of Other Groups

In 2011, the Endocrine Society recommended screening for vitamin D deficiency in individuals at risk for deficiency. These identified groups included individuals with diseases that predispose them to deficiency, such as chronic renal disease and malabsorption syndromes; use of medications that increase the risk for deficiency, such as glucocorticosteroids and anti-epileptics; and being an at risk population, such as obese persons, black, and Hispanic persons. The Endocrine Society did not recommend screening for vitamin D deficiency in individuals who are not at risk for this condition, noting a lack of evidence demonstrating the benefit of population-level screening.[13]

The American Board of Internal Medicine Foundation's 2013 Choosing Wisely report on unnecessary medical tests included a statement from the American Society for Clinical Pathology (ASCP) that "vitamin D testing is generally unnecessary." The ASCP stated that "over-the-counter vitamin D supplements and summer sun exposure are sufficient for most otherwise healthy people." The ASCP further stated, however, that "laboratory testing is appropriate in higher risk patients–those who are obese or have chronic kidney disease, for example–when results will be used to decide whether to order more aggressive therapy."[144]

From 2009 to 2011, the IOM convened an expert panel to update the RDA for vitamin D. The panel assessed data on health outcomes associated with calcium and vitamin D in order to determine dietary reference intakes for vitamin D for the population. While the IOM did not make statements about vitamin D screening, they concluded that the average blood levels of 25(OH)D are above the level needed for good bone health in most individuals. Because national surveys show an average total intake of vitamin D that is below the recommended median requirement, the IOM concluded that sun exposure likely contributes meaningful amounts of

vitamin D to the U.S. population and that "the majority of the population is meeting its needs for vitamin D."[12] The IOM did note, however, that there were some subgroups that may be at an increased risk for getting too little vitamin D (e.g., those who are older and living in institutions or who have dark skin pigmentation).

While the USPSTF has not issued recommendations on screening for vitamin D deficiency, it has issued several recommendation statements on the effects of vitamin D supplementation on prevention of adverse health outcomes (e.g., falls, fractures, cancer, cardiovascular disease) in populations that were not necessarily vitamin D deficient (i.e., they included general populations who may or may not have been deficient). In 2012, the USPSTF recommended vitamin D supplementation for community-dwelling adults 65 years or older at increased risk for falls (i.e., history of falls and mobility problems) in order to prevent future falls (B recommendation).[1] The USPSTF examined the effects of vitamin D and calcium on fracture risk and concluded there was insufficient evidence to assess the benefits and harms of vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal adults (I statement). In noninstitutionalized postmenopausal women, there was insufficient evidence to assess the benefits and harms of daily supplementation with greater than 400 IU of vitamin D3 and 1,000 mg of calcium (I statement). The USPSTF recommended against daily supplementation with 400 IU or less of vitamin D3 and 1,000 mg calcium for the primary prevention of fractures in this population (D recommendation).[3]

The USPSTF also recently issued a draft recommendation statement on the effects of multivitamins and single vitamins on cardiovascular disease and cancer.[4] The recommendation was based on a review that included studies of vitamin D as part of multivitamins, as well as vitamin D supplementation given as a single tablet in persons who were likely receiving adequate vitamin D nutritionally. The USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of the use of vitamin D (alone or as part of a multivitamin) for the prevention of cardiovascular disease or cancer (I statement).

Chapter 2. Methods

Key Questions and Analytic Framework

The USPSTF, with input from AHRQ, set the scope and developed the key questions for this review. Based on this work, we created an analytic framework including key questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**). Key question 1 focuses on direct evidence on the effectiveness of screening for vitamin D deficiency for improving future health outcomes (e.g., mortality reduction, morbidity from selected conditions, physical and emotional functioning), compared with not screening. Such direct evidence on the effectiveness of screening interventions may be limited. Therefore, the remainder of the analytic framework (key questions 2 through 4) evaluates the chain of indirect evidence needed to link screening with improvements in important health outcomes. Links in the chain of indirect evidence include the effectiveness of vitamin D treatment for reducing the incidence of future health outcomes and the harms associated with screening and treatments in persons with vitamin D deficiency. Implicit in the indirect chain of evidence is that in order to understand benefits and harms of screening, it is not sufficient to identify individuals who are vitamin D deficient. Instead, it is necessary to show that there are effective treatments for those identified with vitamin D deficiency, which are addressed in key questions 1 and 3. Key questions 1a, 3a, and 4a address how the effectiveness of screening and treatment varies in different subgroups.

Key Questions

1. Is there direct evidence that screening for vitamin D deficiency results in improved health outcomes?
   a. Are there differences in screening efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency such as age 65 years or older; sex; race-ethnicity; body mass index; UV exposure; institutionalized status)?
2. What are the harms of screening (e.g., risk for procedure, false positives, false negatives)?
3. Does treatment of vitamin D deficiency using vitamin D lead to improved health outcomes?
   a. Are there differences in efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency such as age; sex; race-ethnicity; body mass index; UV exposure; institutionalized status)?
4. What are the adverse effects of treatment of vitamin D deficiency using vitamin D?
   a. Are there differences in adverse effects between patient subgroups (subgroups defined by risk factors for vitamin D deficiency, such as age 65 years or older; sex; race-ethnicity; body mass index; UV exposure; institutionalized status)?

We accepted different definitions of vitamin D deficiency as long as at least 90 percent of participants had a baseline 25(OH)D level of 30 ng/mL or less based on the uncertainties about what 25(OH)D level defines deficiency. However, we examined data stratified by 25(OH)D cutoff levels. For the purposes of this report, the term “vitamin D deficient” refers to populations in which at least 90 percent of individuals have 25(OH)D levels of 30 ng/mL or less.

The USPSTF also requested three contextual questions to help inform the report. Contextual questions are not reviewed using systematic review methodology. Instead, they focus on evidence from large, high-quality epidemiological and clinical studies. These contextual questions are addressed in the Introduction in the sections on Etiology and Natural History, Risk Factors, and Rationale for Screening and Screening Strategies and in more detail in **Appendixes A1-A3**.

Contextual Questions

1. What is the association between serum 25(OH) levels and health outcomes?
2. What are the risk factors associated with vitamin D deficiency?
3. What is the effect of vitamin D treatment (with or without calcium) on intermediate outcomes (e.g., blood pressure, bone mineral density, glucose tolerance, lipids)?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through December 2013), and Ovid MEDLINE (through January week 2 2014) for relevant studies and systematic reviews. Search strategies are shown in **Appendix B1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated potential studies against inclusion and exclusion criteria developed for each key question (**Appendix B2**). Articles were selected for full-text review if they evaluated the benefits or harms of screening versus no screening, or vitamin D treatment versus no treatment for our target population (see section below). We only evaluated English-language articles and excluded studies only published as abstracts. We also excluded studies of non-human subjects. All included studies reported original data. To evaluate the benefits of vitamin D screening, we included systematic reviews and randomized, controlled trials (RCTs). We also included case-control studies nested within an RCT, such as the large WHI CaD trial.[145] For evaluation of harms, we included systematic reviews, RCTs, and cohort or case-control studies. Studies had to be conducted in or relevant to primary care settings. While we included studies of persons in institutionalized settings, we performed stratified analyses in which they were examined separately from studies of community-dwelling persons.

Our target population was vitamin D deficient adults (≥18 years old) in countries generalizable to the United States. As a result, we only included studies conducted in the United States, Canada, Europe, and Australia. For key question 1, we included studies of screening for vitamin D deficiency if they enrolled a healthy, asymptomatic, study population (persons not known to have vitamin D deficiency or selected for testing for evaluation of a medical condition associated with vitamin D deficiency); described the study population (e.g., number screened, sex, age range, and setting); and reported health outcomes or harms (e.g., labeling or effects of subsequent treatments). We could not assess sensitivity, specificity, or related measures of

diagnostic accuracy (e.g., false-positives or false-negatives) due to assay variability and the absence of a recognized reference standard for vitamin D status. For key question 3, we included studies of treatment of vitamin D deficiency if they examined vitamin D deficient persons identified through screening, if participants were not selected on the basis of having symptoms or signs of vitamin D deficiency, and were not being treated with vitamin D for a specific health condition (e.g., low BMD, prior fracture, prior falls). While our review targeted asymptomatic persons, most studies did not report the presence of symptoms and symptoms of vitamin D deficiency are non-specific and may be relatively common.[146,147] Therefore, we did not require that studies screen for symptoms of deficiency or exclude all patients with conditions associated with deficiency (e.g., studies of older patients might have included some persons with osteoporosis or who had fallen in the past and were not excluded as long as the study did not purposefully select patients with these conditions). We did not examine studies that targeted populations with signs of vitamin D deficiency (e.g., osteoporosis, history of non-traumatic fracture, or history of falls) or with medical conditions that increase an individual's risk for deficiency (e.g., liver, kidney, or malabsorptive disease) because screening for vitamin D deficiency, and treating deficiency, could be a component of medical management in these conditions.

We accepted variable definitions of vitamin D deficiency as long as at least 90 percent of the participants had baseline 25(OH)D levels of 30 ng/mL or less. In addition, we included studies that did not specifically define their population as being vitamin D deficient as long as at least 90 percent of participants had baseline 25(OH)D levels of 30 ng/mL or less identified through screening. For the purposes of this report, the term "vitamin D deficient" refers to populations in which at least 90 percent of individuals have 25(OH)D levels of 30 ng/mL or less. For studies that did not restrict enrollment to persons with 25(OH)D levels of 30 ng/mL, we used the mean 25(OH)D level plus the standard deviation multiplied by 1.282 to approximate the 90th percentile and determine whether this level was at or below the 30 ng/mL threshold. To account for variability in what 25(OH)D level constitutes deficiency, we stratified studies according to whether at least 90 percent of individuals had levels less than 20 ng/mL ("<20 ng/mL" in this report) or at least 10 percent had levels greater than 20 ng/mL ("≤30 ng/mL"). We converted 25(OH)D levels reported as nmol/L to ng/mL (1 nmol/L = 0.4 ng/mL). We included interventions of vitamin D treatment (with or without calcium) if they compared vitamin D treatment with placebo, calcium alone, or no treatment. Interventions were considered to be of vitamin D alone if they examined vitamin D treatment compared with placebo or no treatment, or if they examined vitamin D and calcium compared with calcium alone. Included studies described the study population (e.g., number screened, sex, age range, setting, and baseline 25(OH)D level), had a treatment period of at least 8 weeks long for beneficial outcomes, and reported clinical health outcomes (see **Appendix B2**).

The selection of literature is summarized in the literature flow diagram (**Appendix B3**). **Appendix B4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. Two investigators independently applied USPSTF[148] criteria to rate the quality of each study as good, fair, or poor (**Appendix B5**). Poor-quality studies with a "fatal flaw" (or flaws) were excluded from the synthesis of the results. We resolved discrepancies through a consensus process. We considered the following factors to determine applicability: setting and generalizability of the setting to screening and primary care settings; enrollment criteria, and whether this resulted in a highly selected population; use of run-in and wash-out periods; and similarity of testing and interventions to current clinical practices.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("good", "fair", "poor") using USPSTF methods. This assessment was based on the number, quality, and size of studies as well as the consistency of results between studies and the directness of evidence.[148]

We conducted meta-analyses to calculate summary risk ratios (RRs) for clinical outcomes (decreased mortality and decreased morbidity from fractures, falls, and diabetes) and harms (withdrawals due to adverse events [AEs], serious AEs, and hypercalcemia) with treatment with vitamin D and/or calcium versus placebo, no treatment, or only calcium. We used the DerSimonian-Laird random effects model with RevMan software (Review Manager Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to conduct these analyses. Analyses for clinical outcomes used data from total study duration (including time following discontinuation of vitamin D treatment). For falls per person, we calculated rate ratios based on reported data and assumed mean equal length of followup between treatment groups if not reported. Rate ratios were combined using DerSimonian-Laird random effects models in the primary analyses. For all outcomes with substantial between study-heterogeneity, we conducted sensitivity analyses using profile likelihood random effects models.[149] For falls per person, one study reported an adjusted rate ratio and we also conducted a sensitivity analysis to assess the effect of the adjusted rate ratio on the summary rate ratio. Rate ratio analysis and analyses using profile likelihood model were conducted with StataIC 12.0 (StataCorp LP, College Station, TX, USA).

We assessed statistical heterogeneity using the standard χ^2test and I^2 statistic.[150] For all analyses, we stratified results by serum baseline 25(OH)D level. We performed additional analyses in which trials were stratified by institutionalized status, treatment regimen (vitamin D alone or vitamin D combined with calcium), vitamin D dose (≤400 IU vs. >400 IU per day), study duration (≤12 vs. >12 months), and participant mean age (≤70 vs. >70 years of age).

Several analyses included nested case-control studies from the WHI. We performed sensitivity analyses restricted to RCTs, excluding the results of the WHI sub-analyses. For analyses that included results from nested case-control studies from WHI, we also performed sensitivity analyses using the odds ratio (OR) rather than the RR.

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners (**Appendix B6**).

Chapter 3. Results

Key Question 1. Is There Direct Evidence That Screening for Vitamin D Deficiency Results in Improved Health Outcomes?

We found no study that addressed this key question.

Key Question 2. What are the Harms of Screening (e.g., Risk for Procedure, False-Positives, False-Negatives)?

We found no study that addressed this key question.

Key Question 3. Does Treatment of Vitamin D Deficiency Using Vitamin D Lead to Improved Health Outcomes?

Summary

Eleven studies examined the effect of vitamin D treatment on mortality,[120,122,151-159] five examined fracture,[122,160-163] six examined falls,[122,135,161,162,164,165] one examined cancer,[166,167] two examined type 2 diabetes,[135,168] two examined psychosocial function and disability,[169,170] and one examined physical function.[154] While vitamin D treatment was associated with decreased risk for mortality when compared with placebo/no treatment (pooled RR 0.83; 95% confidence interval [CI], 0.70 to 0.99; I^2=0%; 11 studies), these studies were not designed to assess mortality.[120,122,151-159] Additionally, the benefits of vitamin D treatment were confined to trials of elderly, institutionalized participants with high mortality rates.[120,122,153] The reduction no longer was significantly reduced when we only examined noninstitutionalized populations (RR 0.93; 95% CI, 0.73 to 1.18; I^2=0%; 8 studies).[151,152,154-157] Vitamin D treatment was not associated with decreased risk for fracture (pooled RR 0.98; 95% CI, 0.82 to 1.16; I^2=32%; 5 studies).[122,160-163] Falls data were mixed—while vitamin D treatment was not associated with decreased risk for experiencing a fall (our primary fall endpoint; pooled RR 0.84; 95% CI, 0.69 to 1.02; I^2=70%; 5 trials),[122,161,162,164,165] vitamin D treatment was associated with a decreased number of falls per individual (pooled rate ratio 0.66; 95% CI, 0.50 to 0.88; I^2=65%; 5 trials).[135,161,162,164,165] We found limited data (≤2 studies) on the effect of vitamin D treatment on cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning.

Evidence

We identified 16 trials and one nested case-control study that evaluated the effects of vitamin D treatment (with or without calcium) on health outcomes in vitamin D deficient populations (**Table 2** and **Appendix C1** and **C2**). Seven of these studies were conducted in populations with at least 90 percent of their participants with 25(OH)D levels of less than 20 ng/mL[122,154,156-159,161] and 10 in populations with at least 90 percent of their participants with levels of 30 ng/mL or less

(but at least 10% had levels of 20 ng/mL or more).[120,135,145,151-153,155,160,162-170] Eleven studies examined the effect of vitamin D treatment on mortality,[120,122,151-159] five examined effects on fracture,[122,160-163] six examined effects on falls,[122,135,161,162,164,165] one examined effects on cancer,[166,167] two examined effects on type 2 diabetes,[135,168] two examined effects on psychosocial function and disability,[169,170] and one examined effects of physical function.[154] The mean age of the participants ranged from 37 to 85 years and 40 to 100 percent were female. Mean BMIs ranged from 24 to 36 kg/m^2. The included studies were population-based or were conducted within outpatient clinics, academic institutions, and nursing or residential homes for the elderly (considered institutionalized) in the United States or Europe. UV exposure was not well quantified in any study. Only six[135,145,155,158,159,169] of 17 studies reported race. One study was conducted in 100 percent African Americans.[159] In the remaining studies reporting race, 83 to 100 percent of participants were white. Studies examined vitamin D3 at dosages ranging from 400 to 4,800 IU per day to 8,400 to 50,000 IU per week. Five studies examined vitamin D3 treatment co-administered with calcium (1,000 to 1,200 mg per day) and 12 examined vitamin D3 treatment alone. Study duration ranged from 2 months to 7 years. To measure 25(OH)D in participants, four studies used competitive protein binding,[122,153,156,160] eight used immunoassay methods,[145,152,155,158,159,161,162,164,165] one used HPLC,[154] and four used LC-MS/MS.[135,157,169,170] Two trials used laboratories that were participating in an external accuracy-based testing system—DEQAS.[154,155]

Two trials were rated good-quality[155,170] and 15 were rated as fair-quality[120,122,127,135,145,152-154,156-166,169] (**Appendix C3**). Methodological shortcomings in the fair-quality studies frequently included the unclear use of adequate randomization and allocation concealment methods and/or masking of outcome assessors, providers, or participants. Some studies also reported high attrition (>20%).

The WHI CaD trial was the largest study (N=36,282).[145,163,166-168] The results of the overall WHI CaD trial were not included in this evidence review because baseline levels of 25(OH)D were not measured in all participants. Instead, we included the results reported for the subset of WHI CaD participants with low 25(OH)D levels reported in several case-control studies. We quality rated the overall trial because the case-control studies were based on women originally randomized to the main WHI CaD trial (**Table 2** and **Appendix C2** and **C3**). We rated this trial as fair-quality primarily because of a potential lack of intervention fidelity. Participants in both intervention groups were allowed off-protocol supplementation of up to 600 IU per day of vitamin D initially and up to 1,000 IU per day from 1999 onward. Six years into the trial, off-protocol vitamin D use was reported by 52 percent of participants.[166] Despite this finding, those assigned to vitamin D supplementation had a 28 percent higher 25(OH)D level than those taking placebo in a random subsample of 1.2 percent of the study population at the end of year 2.[163] The baseline characteristics of the cases and controls in the WHI CaD sub-studies were also not provided, although study intervention and placebo participants had similar baseline characteristics in the overall trial.

Effects of Vitamin D Treatment on Mortality

One good-quality trial, nine fair-quality trials, and one fair-quality nested case-control study examined the effect of vitamin D3 treatment on mortality in vitamin D deficient populations

(N=4,126).[120,122,151-159] Five studies were conducted in populations with a mean age over 70 years,[120,122,153,154,156,160] three trials specifically focused on older (age >80 years) women in nursing or elderly homes,[120,122,153] and one trial specifically focused on younger (age ≥45 years) women.[158] No study had death as a primary outcome.

No individual study reported a statistically significant reduction in mortality in participants randomized to vitamin D3 treatment (dosage of 400 IU per day to 40,000 IU per week, with or without calcium) when compared with placebo, calcium alone, or no treatment. The estimates in some trials were extremely imprecise, however, due to very few events.[152,154-159] In four studies that reported at least 10 events, RR estimates ranged from 0.51 to 0.90.[120,122,151,153] When data were combined for all studies, vitamin D3 treatment (with or without calcium) was associated with decreased risk for mortality versus placebo/no treatment (pooled RR 0.83; 95% CI, 0.70 to 0.99; I^2=0%; **Figure 2**). Studies reported an absolute risk difference that ranged from a reduction of 6 percentage points to an increase of 2 percentage points with vitamin D3 treatment (with or without calcium) versus placebo/no treatment.

These results should be interpreted with caution. While the CI was very close to one, mortality was not the primary outcome in any study and mortality was usually not a prespecified outcome. In addition, in the only good-quality trial, a vitamin D treatment dose-response trial of 400 to 4,800 IU per day of vitamin D3 treatment in 163 vitamin D deficient (≤20 ng/mL) white U.S. postmenopausal women with a mean age of 67 years, no deaths were observed in any group after 12 months.[155] The largest study (n=2,185), a case-control study nested within the WHI CaD trial, also found no association between randomization to 400 IU per day of vitamin D3 and 1,000 mg per day of calcium versus placebo and risk for mortality after 7 years in vitamin D deficient (<21 ng/mL) postmenopausal women in the United States.[151] The two trials with the RR that most suggested a possible benefit of vitamin D treatment on mortality (RR 0.75; 95% CI, 0.54 to 1.05[122] and RR 0.51; 95% CI, 0.25 to 1.02[120]) examined the effects of 400 to 800 IU per day of vitamin D3 treatment (with or without calcium) in older individuals (mean age of 80 to 85 years) who were vitamin D deficient (≤30 ng/mL) institutionalized European women who experienced high mortality rates (9-20%) during followup.[120,122] When we analyzed trials of institutionalized and noninstitutionalized separately, the risk reduction was limited to studies of older, institutionalized persons (pooled RR 0.72; 95% CI, 0.56 to 0.94; I^2=0%; 3 trials; **Figure 3**); absolute risk reductions ranged from of 4 to 6 percentage points.[120,122,153] The reduction no longer was significantly reduced when we only examined noninstitutionalized populations (RR 0.93; 95% CI, 0.73 to 1.18; I^2=0%; 8 studies; **Figure 3**).[151,152,154-157] In sensitivity analyses, the reduction in mortality only occurred when studies with more than 12 months duration were pooled and in studies whose population had a mean age over 70 years. Stratification by baseline 25(OH)D level (<20 vs. ≤30 ng/mL), treatment regimen (vitamin D treatment alone vs. vitamin D treatment with calcium), or vitamin D dosage (≤400 vs. >400 IU per day) did not affect risk estimates. Excluding the WHI case-control study and pooling the ORs (instead of RRs) did not affect findings.

Effects of Vitamin D Treatment on Fracture Risk

Four fair-quality trials and one nested case-control study examined the effects of 2 months to 7 years of treatment with 400 to 800 IU per day of vitamin D3 treatment (with or without calcium)

on risk for any type of fracture in ambulatory and institutionalized vitamin D deficient persons (94% women) with a mean age of 62 to 85 years (N=3,551).[122,160-163] No individual study reported a statistically significant reduction in fracture risk in those randomized to vitamin D3 treatment versus placebo and the pooled estimate was close to one (pooled RR 0.98; 95% CI, 0.82 to 1.16; I^2=32%; **Figure 4**). This includes the largest study, which was a case-control analysis nested within the WHI CaD trial[163]. Stratifying studies by institutionalized status, baseline 25(OH)D level (<20 vs. ≤30 ng/mL), treatment regimen (vitamin D treatment alone vs. vitamin D treatment with calcium), vitamin D dosage (≤400 vs. >400 IU per day), study duration (≤12 vs. >12 months), and mean age of population (≤70 vs. >70 years) resulted in similar findings of no effect and did not decrease heterogeneity. Neither exclusion of the WHI case-control study nor examination of the pooled ORs affected findings.

In three trials and one nested case-control study that reported data separately (N=1,619),[122,160,161,163] there was also no significant reduction in hip fracture risk for vitamin D3 treatment versus placebo in any individual study and the pooled estimate was close to one (pooled RR 0.96; 95% CI, 0.72 to 1.29; I^2=46%; **Figure 5**). Only considering noninstitutionalized populations did not affect the null findings. Stratification by baseline 25(OH)D level, dosage, study duration, age, and treatment regimen did not change findings and did not decrease heterogeneity. The trial most suggestive of a possible benefit of vitamin D treatment on hip fracture risk was conducted in older, institutionalized European women given 800 IU per day of vitamin D3 with calcium over 24 months and had a population whose baseline 25(OH)D level was less than 20 ng/mL (RR 0.62; 95% CI, 0.36 to 1.07).[122]

Effects of Vitamin D Treatment on Fall Risk

Five fair-quality trials examined the effects of 2 to 36 months of 800 IU per day of vitamin D3 treatment (with or without calcium) compared with placebo, no treatment, or calcium alone on the risk for experiencing at least one fall (N=1,677; **Table 3**).[122,161,162,164,165] Although trials did not specifically recruit participants for being at high-risk for frailty or because of prior falls, the studies included persons who may have been at risk for falls based on older age (mean age >70 years),[122,161,162,164] institutionalized status,[122,164] mobility problems,[122,164] or multiple comorbidities.[122,161,164] In two studies that reported how many patients had prior falls in the past 3 to 6 months, the proportions were 16 and 34 percent.[122,164] While the overall summary RR indicated no statistically significant effect on risk for experiencing at least one fall among those given vitamin D3 treatment versus the control intervention (pooled RR 0.84; 95% CI, 0.69 to 1.02; **Figure 6**), heterogeneity was high (I^2=70%). Trials reported an absolute risk difference that ranged from a reduction of 22 percentage points to an increase of 2 percentage points with vitamin D3 treatment (with or without calcium) versus placebo/no treatment.

The only trial to report a statistically significant effect on risk for falls was a German trial conducted in an ambulatory population (75% women) with 25(OH)D levels less than or equal to 30 ng/mL and a mean age of 77 years (n=242).[162] This trial reported that 12 months of 800 IU per day of vitamin D3 treatment was associated with a 36 percent reduction in the risk for having at least one fall over 20 months (RR 0.64; 95% CI, 0.50 to 0.83), which was the trial's primary outcome. When we stratified trials by institutionalized status, the RRs did not change and heterogeneity remained high. Similarly, stratification of trials according to baseline 25(OH)D

level, vitamin D dosage, study duration , and age did not reduce heterogeneity and resulted in similar estimates. Heterogeneity was reduced to zero, however, when we excluded the two trials of co-supplementation with vitamin D and calcium[122,165] in order to separately examine the three trials of vitamin D3 treatment alone, and there was a significant reduction in risk for experiencing at least one fall (RR 0.65; 95% CI, 0.52 to 0.81; I^2=0%).[161,162,164]

Five fair-quality trials examined the effect of 400 to 1,000 IU per day of vitamin D3 treatment (with or without calcium) on the number of falls per individual (N=1,399, **Table 3**).[135,161,162,164,165] When the five trials were pooled, vitamin D treatment was associated with a significant reduction in the number of falls per individual compared with placebo (pooled rate ratio 0.66; 95% CI, 0.50 to 0.88; I^2=65%; **Figure 7**). Although there was statistical heterogeneity, all estimates favored vitamin D treatment. The trial populations were European, mostly female (88%), and had mean ages of 64 to 85 years. Only one trial studied institutionalized individuals.[164] Excluding this trial did not affect the risk estimate. Stratification by baseline 25(OH)D level, study duration, and age did not change findings, and did not decrease heterogeneity. Excluding the one trial that co-administered calcium with vitamin D did not change findings, but decreased heterogeneity. Our findings did not change when the analysis was re-run using the profile likelihood random effects model.

Four trials examined both risk for falling and rate of falls per person.[161,162,164,165] In three of these trials, the risk estimates were similar.[161,162,165] In the fourth trial, the rate ratio for falls per person (primary outcome of this trial) was lower than the risk for experiencing at least one fall (0.46; 95% CI, 0.28 to 0.76 and 0.75; 95% CI, 0.41 to 1.37, respectively).[164] This trial, conducted in an institutionalized population with a high comorbidity burden, used nurses to record falls, while other trials relied on self-report or did not report how falls were recorded. This trial also had a shorter duration than the other trials (12 weeks vs. ≥12 months). The one trial that examined only risk for falls (not rate of falls) reported no reduced risk for falls in those given vitamin D3 treatment with calcium versus placebo (RR 1.03; 95% CI, 0.90 to 1.18).[122] This trial's primary outcome was risk for fractures and the method of recording falls was not described. The trial examining only rate of falls (not risk for falls) was conducted in a younger (mean age of 64 years) population in which falls were collected as part of adverse event reporting; few falls were recorded during followup, leading to wide CIs.[135]

Effect of Vitamin D Treatment on Cancer Risk

Effects of 7 years of treatment with 400 IU per day of vitamin D3 and calcium on risk for breast cancer (n=909 cases) and colorectal cancer (n=237 cases) in women with low 25(OH)D levels was examined in case-control studies nested within the WHI CaD trial.[166,167] Compared with placebo, treatment with vitamin D3 and calcium was not associated with a decreased risk for colorectal or breast cancer among women with 25(OH)D levels in the deficiency range (OR 1.15; 95% CI, 0.58 to 2.27 for <23 vs. ≥23 ng/mL for colorectal cancer and adjusted OR 0.89; 95% CI, 0.58 to 1.36 for <27 vs. ≥27 ng/mL for breast cancer).[166,167]

Effect of Vitamin D Treatment on Type 2 Diabetes Risk

One fair-quality trial (n=305)[135] and one case-control study nested within the WHI CaD trial (cases=192)[168] examined the effects of treatment with 400 to 1,000 IU per day of vitamin D3 (with or without calcium) for 1 to 7 years in mostly (>83%) white, vitamin D deficient (<30 ng/mL) women, with mean ages of 62 to 64 years. Neither study found vitamin D treatment was associated with reduced risk for developing type 2 diabetes and the summary RR was close to one (pooled RR 0.93; 95% CI, 0.68 to 1.27; I^2=0%; **Figure 8**).

Effect of Vitamin D Treatment on Psychosocial Functioning and Disability

One good-quality trial examined the effect of 20,000 IU per week of vitamin D3 for 6 months on depression and anxiety as measured by the Beck Depression Inventory, the Montgomery-Asberg Depression Rating Scale, and the Hospital Anxiety and Depression Scale. In vitamin D deficient (<22 ng/mL) healthy persons (56% female) with a mean age of 53 years (**Table 2** and **Appendix C1**),[170] there was no difference after 6 months of treatment on any scale. There were also no significant differences between treatment groups for change from baseline when stratifying by sex, age, BMI, 25(OH)D level at baseline, or smoking status.

One small, fair-quality trial (n=90) examined the effect of 8 weekly doses of 50,000 IU vitamin D3 on psychosocial function and disability as measured by the Fibromyalgia Impact Questionnaire.[171] In vitamin D deficient (<25 ng/mL) healthy persons (40% female) with a mean age of 59 years (**Table 2** and **Appendix C1**),[169] those randomized to vitamin D3 treatment showed improvement in their overall score after 8 weeks. Individuals in the placebo group, on the other hand, experienced worsening scores (mean difference from baseline on scale from 0-100: -3.7 vs. +1.9; p<0.03 for difference between groups). Despite this result, however, vitamin D3 treatment did not beneficially affect scores on the depression or work interference subscales compared with placebo.

Effect of Vitamin D Treatment on Physical Functioning

One fair-quality trial (n=213) examined the effect of 16 weekly doses of 8,400 IU vitamin D3 on physical function in U.S. and European populations with an average age of 78 years.[154] Compared with placebo, vitamin D3 treatment did not result in greater improvement on the Short Physical Performance Battery, a validated measure of lower-extremity function.[172]

Effect of Vitamin D Treatment in Patient Subgroups

None of the included trials were designed or powered to evaluate potential subgroup effects based on age or institutionalized status. Data suggesting benefits of vitamin D treatment on mortality were limited to trials of institutionalized, European women.[120,122,153] While studies that examined fall risk with vitamin D treatment did not include participants chosen for being at high-risk for falls, baseline characteristics indicate that most of the participants were older (>70 years) and many may have had risk factors for falls. No included studies were designed to evaluate differential effects of vitamin D treatment on clinical outcomes based on factors such as sex, race, BMI, or UV exposure.

Key Question 4. What are the Adverse Effects of Treatment of Vitamin D Deficiency Using Vitamin D?

Summary

Data on the AEs of treatment of vitamin D deficiency using vitamin D treatment (with or without calcium) are limited. Trials were generally not designed to address harms and prespecified outcomes rarely included assessment of harms. In the included trials, there was no evidence that treatment with 400 to 7,000 IU per day or 8,400 to 54,000 IU per week of vitamin D3 or D2 (with or without calcium) resulted in more total AEs, serious AEs, withdrawals due to AEs, hypercalcemia, kidney stones, or gastrointestinal disturbance, when compared with control intervention over 6 weeks to 4 years.

Evidence

We identified 23 trials that examined AEs associated with vitamin D treatment (with or without calcium) in vitamin D deficient (vitamin D levels <20 ng/mL or ≤30 ng/mL) populations (N=4,471; **Table 4** and **Appendix C1**). The mean age of the participants ranged from 31 to 85 years. Seven trials were conducted in the United States,[155,158,159,169,173-176] 15 were conducted in Europe,[115,120,122,125,127,128,132,135,152,153,156,157,164,170,177,178] and one was conducted in both the United States and Europe.[154] These trials examined vitamin D3 treatment (20 trials),[120,122,125,127,128,132,135,152-159,164,169,170,173,174,176,177] vitamin D2 treatment (2 trials),[175,178] or both (1 trial)[115] and examined dosages ranging from 400 to 7,000 IU per day to 8,400 to 54,000 IU per week. Eighteen trials evaluated the effects of vitamin D treatment alone and five evaluated the effects of vitamin D treatment with calcium (1,000 to 1,200 mg per day). Trials were from 6 weeks to 4 years in duration.

Two trials were rated good-quality[155,170] and 19 were rated as fair-quality.[115,120,122,125,127,128,132,135,152-154,156-159,164,169,173,174,176,178] We excluded two poor-quality studies from the synthesis of the results[175,177] (**Appendix C2**). Methodological shortcomings in the poor- and fair-quality trials included unclear randomization procedure; inadequate or unclear masking of assessors, providers, and/or participants; high attrition; and/or no clear statement that adverse events were a prespecified outcome.

Effects of Vitamin D Treatment on Adverse Events

One good-quality and five fair-quality trials reported on total AEs in those being treated with 400 to 7,000 IU per day or 20,000 to 40,000 IU per week of vitamin D3 or D2 for 6 to 36 months (**Table 4** and **Appendix C1**; N=1,081).[125,132,135,156,157,170,174,176] No trial reported significantly more total AEs in the intervention group, compared with control group.

One good-quality and six fair-quality trials examined the effect of 400 to 4,800 IU per day or 8,400 per week of vitamin D3 treatment (with or without calcium) on serious AEs in vitamin D deficient white U.S. or European women with mean ages of 37 to 78 years (N= 1,401).[135,154-156,158,159,174,176] No trial reported a significantly increased risk for serious AEs. The summary RR

did not indicate a significantly increased risk for serious AEs in those given vitamin D treatment compared with placebo (pooled RR 1.17; 95% CI, 0.74 to 1.84; I^2=0%; **Figure 9**).

Five trials (one good- and four fair-quality) compared withdrawals due to AEs in white U.S. and European women randomized to 400 to 4,800 IU per day or 8,400 per week of vitamin D3 treatment (with or without calcium) compared with placebo or no vitamin D treatment (N=938).[153-156,159] Withdrawals were not significantly increased in the intervention group compared with controls in any trial, although the number of withdrawals was low (29 out of 568 vs. 23 out of 370). A fair-quality trial conducted in elderly, institutionalized women in Europe reported the biggest difference in withdrawals with the intervention versus controls, but the estimate was very imprecise (7 vs. 0; RR 15.00; 95% CI, 0.87 to 259.82).[153] Withdrawals were due to gastrointestinal symptoms (n=6) or hypercalcemia (n=1). When data from the five trials were combined, there was no significantly increased risk for withdrawals due to AE (pooled RR 0.90; 95% CI, 0.36 to 2.24; I^2=32%; **Figure 10**).

Two good-quality and 15 fair-quality trials examined the effects of treatment with 400 to 7,000 IU per day to 8,400 to 40,000 IU per week vitamin D3 or D2 (with or without calcium) on risk for hypercalcemia in white, black, and South Asian participants in the United States and United Kingdom with mean ages of 34 to 85 years.[115,120,122,125,128,132,135,154-159,164,170,173,174,176,178] Fifteen trials detected hypercalcemia by monitoring levels during followup. In three trials, hypercalcemia was defined as calcium levels of 10.8 mg/dL or greater.[155,156,159] One trial defined hypercalcemia as levels of 10.6 mg/dL or greater,[173] while two trials defined hypercalcemia as levels greater than 10.2 mg/dL.[157,158] The remaining trials did not report how hypercalcemia was detected or defined.[115,120,122,125,128,132,135,154,164,170,174,176,178] No individual study reported a significantly higher incidence of hypercalcemia in the intervention group when compared with the control group, although the number of events was small and seven trials reported no cases of hypercalcemia.[115,125,128,132,157,164,173,178] The nine trials with at least one participant with hypercalcemia measured calcium as part of followup.[120,122,135,155,156,158,159,170,174,176] The hypercalcemia in these trials was described as being mild, reversible, or due to an unrelated, underlying illness uncovered by vitamin D treatment. One study reported that the incidence of hypercalcemia did not differ between treatment groups, although these data were not provided.[154] Overall, in trials that provided data and reported at least one case of hypercalcemia, 32 (1.7%) of 1,939 persons randomized to vitamin D treatment (with or without calcium) were found to have hypercalcemia, versus 16 (1.3%) out of 1,233 controls (pooled RR 1.05; 95% CI 0.57 to 1.94; I^2=0%; **Figure 11**).

No kidney stones were reported in any participants in seven trials reporting this outcome (**Table 4** and **Appendix C1**).[122,128,154,155,157,158,174,176] Five fair-quality trials found no significant differences in the risk for gastrointestinal complaints in intervention compared with control participants (**Table 4** and **Appendix C1**).[122,135,156,164,170] Five trials reported no AEs among any study participants, regardless of group allocation.[115,169,175,177,178]

Effect of Vitamin D Treatment on Adverse Events in Patient Subgroups

In three trials that included non-white participants, while AEs were not increased in the vitamin D treatment group when compared with placebo, AEs were not stratified by race. Few trials

enrolled both men and women. No study evaluated risk for AEs stratified by sex. No data were available to determine risk for AEs according to BMI or UV exposure.

Chapter 4. Discussion

Summary of Review Findings

The findings of this report are summarized in **Table 5**. We did not find any studies that directly examined whether screening for vitamin D deficiency resulted in improved health outcomes or harms. While the evidence on the effects of vitamin D treatment in populations with low 25(OH) levels was available, it had limitations. For example, we identified only two good-quality studies,[155,170] relatively few trials evaluated clinical outcomes, and many studies reported few events or were otherwise underpowered to evaluate clinical outcomes. Additionally, studies were mostly conducted in white women and factors that may influence risk for deficiency, such as BMI and UV exposure were often not reported. No study specifically evaluated effects of treatment in participants with screen-detected vitamin D deficiency.

Of 11 studies that examined the association between vitamin D3 treatment and mortality, only a nested case-control analysis within the WHI CaD trial[151] was designed to assess mortality risk associated with vitamin D3 supplementation. While no individual study found vitamin D3 treatment was associated with decreased risk for mortality versus control conditions, the number of deaths in most studies was low. When results were pooled, however, vitamin D3 treatment was associated with a slight, but significant, decrease in risk for mortality among persons with 25(OH) levels of 30 ng/mL or less. Benefits were no longer seen when we excluded trials of institutionalized persons (8 studies, RR 0.93; 95% CI, 0.73 to 1.18). Some,[58,93] but not all,[45] recent systematic reviews that included studies of persons with and without deficiency have concluded that supplementation in older persons (mainly women) seemed to slightly reduce all-cause mortality

Evidence on effects of vitamin D treatment on risk for falls was somewhat inconsistent. While vitamin D treatment was not associated with a reduction in the risk for experiencing one or more falls, treatment was associated with a reduced overall burden of falls, as measured by the number of falls per vitamin D deficient individual. Four trials examined both risk for falling and rate of falls per person.[161,162,164,165] The risk estimates were similar in three of these trials.[161,162,165] In the fourth trial, the rate ratio for falls per person (primary outcome of this trial) was lower than the risk for experiencing at least one fall (0.46; 95% CI, 0.28 to 0.76 and 0.75; 95% CI, 0.41 to 1.37, respectively).[164] This trial was conducted in an institutionalized population with a high comorbidity burden and its results could account for the inconsistency between the pooled falls outcomes estimates.

Vitamin D3 treatment was not associated with decreased risk for fracture in vitamin D deficient persons. Data were limited (≤2 studies) on vitamin D3 treatment's effect on cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning in those with 25(OH) levels of 30 ng/mL or less. We did not find that baseline 25(OH)D level, vitamin D dosage, or duration of followup influenced results. No trials evaluating how vitamin D treatment affected risk for cardiovascular disease or immune disease met inclusion criteria. Recent 2014 systematic reviews that included studies of persons with and without deficiency concluded that vitamin D

supplementation did not favorably affect the health outcomes of cardiovascular disease, diabetes, and cancer, falls or fracture outcomes.[45,58]

Vitamin D (D3 or D2) treatment did not appear to be associated with harms, although few trials were designed to specifically address harms and AE reporting was often suboptimal. Given the variability of the 25(OH) assay, there is the potential for misclassification that could lead to unnecessary vitamin D treatment and mislabeling. Most misclassification, however, is likely to occur near the cutoff for sufficiency. As such, individuals with very low or very high 25(OH)D levels were probably classified correctly.

Our findings are generally consistent with previous evidence reviews for the USPSTF of vitamin D supplementation in populations not known to be deficient. A 2013 evidence review conducted by Fortmann and colleagues included three trials of noninstitutionalized populations on the effects of vitamin D supplementation (with or without calcium) on mortality. We excluded all of these trials from our review because they did not measure 25(OH)D levels in all participants at baseline.[179] None of the three trials found that vitamin D supplementation (with or without calcium) was associated with decreased mortality risk. Based on this review, the USPSTF has drafted a statement concluding that data on the effects of vitamin D supplementation (alone or with other vitamins) on mortality risk were insufficient.

A 2011 systematic review and meta-analysis by Chung, *et al.,*[70] examined 16 studies of the association of vitamin D supplementation (with or without calcium) with fracture risk. Because the review did not require populations be vitamin D deficient, we excluded 12 of these studies from our review. Chung and colleagues concluded that vitamin D combined with calcium (but not vitamin D alone) could reduce fracture risk, particularly among institutionalized elderly persons.[70] The USPSTF recommended against low-dose supplementation with vitamin D (≤400 IU) and calcium (≤1,000 mg) to reduce fracture risk in noninstitutionalized populations and concluded the data on the effects of higher doses were insufficient.[180]

A 2010 systematic review by Michael and colleagues examined nine trials evaluating the association between vitamin D supplementation (without or without calcium) and fall risk. We excluded six of these trials because they did not examine a known deficient population or examined those at high-risk for falls.[181] We included three studies not in the previous review, two because they were published after that review[135,165] and one[164] because the population was institutionalized and the 2010 review only examined noninstitutionalized populations. Michael and colleagues concluded that vitamin D supplementation (with or without calcium) was associated with a reduced risk for falling. Based on this review, the USPSTF recommended that vitamin D supplementation be given to community-dwelling adults 65 years or older who are at increased risk for falls regardless of 25(OH)D status.[1]

Two systematic reviews (in 2011 and 2013) examined whether vitamin D supplementation with or without calcium was associated with cancer risk.[70,179] The four trials included in these prior systematic reviews were excluded from our review because the study populations were not known to have low 25(OH)D levels, including the full WHI CaD trial.[145,182-184] The authors of the most recent systematic review concluded that vitamin D and/or calcium supplementation showed no overall effect on cancer.[179] The USPSTF concluded in a draft statement that data were

insufficient about the effects of vitamin D supplementation on cancer risk.

Previous systematic reviews on the effects of vitamin D and calcium supplementation on fractures, falls, and cancer in general populations (not picked for deficiency) found AE rates were generally low in both treatment and placebo groups.[70,179,181] The systematic reviews noted that the WHI CaD trial found a significantly increased risk for harm, a 17 percent increased risk for kidney stones in persons randomized to supplementation with 400 IU vitamin D, and 1,000 mg calcium per day (participants were also allowed to take up to 1,000 IU vitamin D and 1,000 mg calcium per day on their own). We did not include this evidence, however, because they derived harms data from persons with unknown vitamin D status. Harms were not given for the subgroup with 25(OH)D levels from the WHI case-control analyses.[185]

Limitations of Review Methods

We excluded non-English language articles, which could result in language bias. Some studies, however, have found empirical evidence that restricting systematic reviews of noncomplementary medicine intervention to English-language studies has little effect on the conclusions.[186,187] We did not search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods because we identified only small numbers of studies for each key question. We included the WHI nested case-control studies in the pooled trials as the event rates were low enough (≤11%) that the OR could be expected to estimate the rate ratio. In sensitivity analyses, results were unchanged when we excluded the WHI case-control analyses and when we calculated ORs for all of the studies before pooling. Some pooled analyses were based on small numbers of studies or were characterized by the presence of statistical heterogeneity. Stratification further reduced the number of studies in the pooled analyses. In such cases, CIs may be too narrow. As a result, these results should be interpreted cautiously. We also conducted sensitivity analyses based on the profile likelihood method, which did not affect conclusions.

For key questions 3 and 4, our goal was to examine the effects of vitamin D treatment for populations similar to what would be identified through a screening program. Therefore, we did not include studies that targeted populations for which vitamin D might be considered a treatment option or with particular medical conditions, even if the participants had low 25(OH)D levels. Based on these criteria, we excluded trials that required participants to have osteoporosis/osteopenia (4 studies),[188-191] risk factors for falls (5 studies),[192-196] prediabetes (1 study),[197] heart failure (2 studies),[198,199] or tuberculosis (1 study).[200] The findings from these studies of selected populations were similar to our overall results. Vitamin D treatment did not reduce risk for experiencing a compression fracture in vitamin D deficient persons with a history of a compression fracture.[188] The effects of vitamin D treatment on fall risk and functional status/physical performance were mixed. Vitamin D treatment did not reduce fall risk in those with vitamin D deficiency who had recently suffered a hip fracture[191] or who had one or more health problems or functional limitations at admission to a geriatric rehabilitation center;[194] however, vitamin D treatment did reduce falls in vitamin D deficient populations with a history of falls.[192] Although community-dwelling, homebound persons experienced an improvement in functional status with vitamin D treatment,[195] long-term inpatients and those in a rehabilitation

center with health problems or functional limitations did not experience an improvement in physical function or the ability to complete activities of daily living with vitamin D treatment.[194,196] In one trial, risk for diabetes was not reduced when vitamin D treatment was given to those with prediabetes who had low 25(OH)D levels.[197]

Limitations in the Evidence

We identified no direct evidence on the effect of vitamin D screening on health outcomes. The evidence on clinical outcomes associated with vitamin D treatment in deficient populations was relatively limited. Data on AEs was not highly reliable because most trials were not designed to assess harms and had suboptimal AE reporting. No study examined the effects of vitamin D treatment according to subgroups defined by race, age, or sex. In fact, few studies were conducted in non-white/non-European/non-female populations. While we did attempt to examine age and institutionalized status through sensitivity analyses, such sensitivity analyses are not as strong as subgroup analyses within studies. No study specifically evaluated the effect of treatment for screen-detected vitamin D deficiency, potentially limiting applicability to screening settings. There was variability in the levels of baseline 25(OH)D levels, the dosages used, the use of calcium co-supplementation, and duration of followup, all of which could have contributed to heterogeneity.

The effects of variability in vitamin D assays were difficult to assess, given the lack of a reference standard with which to estimate sensitivity, specificity, and other diagnostic parameters. In general, differential classification due to assay variability is likely to affect persons close to the threshold used to define vitamin D deficiency. In studies of treatment for vitamin D deficiency, the expected effect of misclassification due to vitamin D deficiency would be to attenuate estimates of treatment benefit, as some persons who are not vitamin D deficient would be classified and treated as such. Such persons would be subject to unnecessary treatment and any associated harms.

For the largest trial, the WHI CaD trial, we only included the results of the nested case-control studies where 25(OH)D levels were measured. Statistical power was limited for many of these stratified analyses. For the overall WHI CaD trial, however, the results were similar to the nested case-control studies; vitamin D supplementation did not significantly reduce risk for death, colorectal or breast cancer, or fractures.[145,151,163,166-168] We also were not able to include the WHI CaD trial's harms outcomes because harms outcomes were not stratified by 25(OH)D status. The WHI CaD trial did find an increased risk for kidney stones in women with unknown 25(OH)D status who were randomized to vitamin D and calcium supplementation.

Emerging Issues and Next Steps

A trial of vitamin D screening in a diverse population would be the ideal way to answer whether vitamin D screening leads to benefits or harms. Before such a trial can be conducted, however, the best method for measuring and defining vitamin D deficiency needs to be determined. A recent study noted that while total 25(OH)D levels were lower in blacks than whites, their

bioavailable 25(OH)D levels were similar.[115] This is only one study on this topic and these results require replication. This study does highlight the need for ongoing research to examine the most accurate way to measure vitamin D deficiency, especially in non-white populations.

In addition, there is a lack of consensus on what level of 25(OH)D (<20 vs. <30 ng/mL) defines deficiency. While the IOM contends that 25(OH)D concentrations of at least 20 ng/mL[30] are optimal, other expert bodies recommend that 25(OH)D levels should be greater than 30 ng/mL, including the Endocrine Society, National Osteoporosis Foundation, and International Osteoporosis Foundation.[13,31-34] Our survey of the literature on the association between 25(OH)D levels and outcomes (**Appendix A1**) found that data are still lacking about what 25(OH)D levels are associated with various health outcomes. Therefore, we stratified the results for key questions 3 and 4 according to the level of 25(OH)D in the population of study (<20 vs. ≤30 ng/mL). We did not find a clear difference in outcomes by baseline 25(OH)D level.

Relevance for Priority Populations

Certain patient subgroups appear to be at increased risk for vitamin D deficiency, including those with low UVB exposure, high BMI, and dark skin pigmentation. In addition, beneficial effects of vitamin D treatment on mortality and falls risk were primarily observed in older (e.g., >70 years of age) and/or institutionalized persons who were mainly women. Determining whether screening these high-risk populations for vitamin D deficiency would result in benefit or harm remains a critical issue. No screening studies have been conducted, however, and few trials have examined the benefits and harms of vitamin D treatment in these patient subgroups.

Future Research

Future trials of vitamin D treatment should measure 25(OH)D levels and be powered to examine effects in deficient subgroups. Trials of clinical outcomes should be adequately powered and of sufficient length to detect clinically important effects. Future trials should focus on those at higher risk and those in understudied groups. Researchers should use state-of-the-science assay methods that have acceptable performance characteristics, are comparable to currently available reference standards, and are conducted in laboratories participating in quality assurance programs. Future studies should examine vitamin D treatment alone, and vitamin D treatment combined with calcium, to separate the beneficial and harmful effects of these two nutrients.

An ongoing trial, the VITamin D and OmegA-3 TriaL (VITAL), has been designed to address many of these issues.[201] VITAL is a large randomized, double-blind, placebo-controlled trial on the effects of 5 years of supplementation with 2,000 IU per day of vitamin D3 for the primary prevention of cancer and cardiovascular disease among a multi-ethnic population of 20,000 U.S. men ages 50 years or older and women ages 55 years or older. The researchers estimate about 16,000 participants will have baseline 25(OH)D levels. Results are expected in 2017.

Conclusions

In conclusion, no study directly examined the benefits and harms of screening for vitamin D deficiency. Treatment of vitamin D deficiency with vitamin D may be associated with decreased risk for mortality in institutionalized elderly and a reduction in the average number of falls. More research is needed to reduce assay variability, determine appropriate thresholds for vitamin D deficiency, clarify the effects of screening, define the subsequent treatment, and identify the subpopulations most likely to benefit.

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Figure 1. Analytic Framework

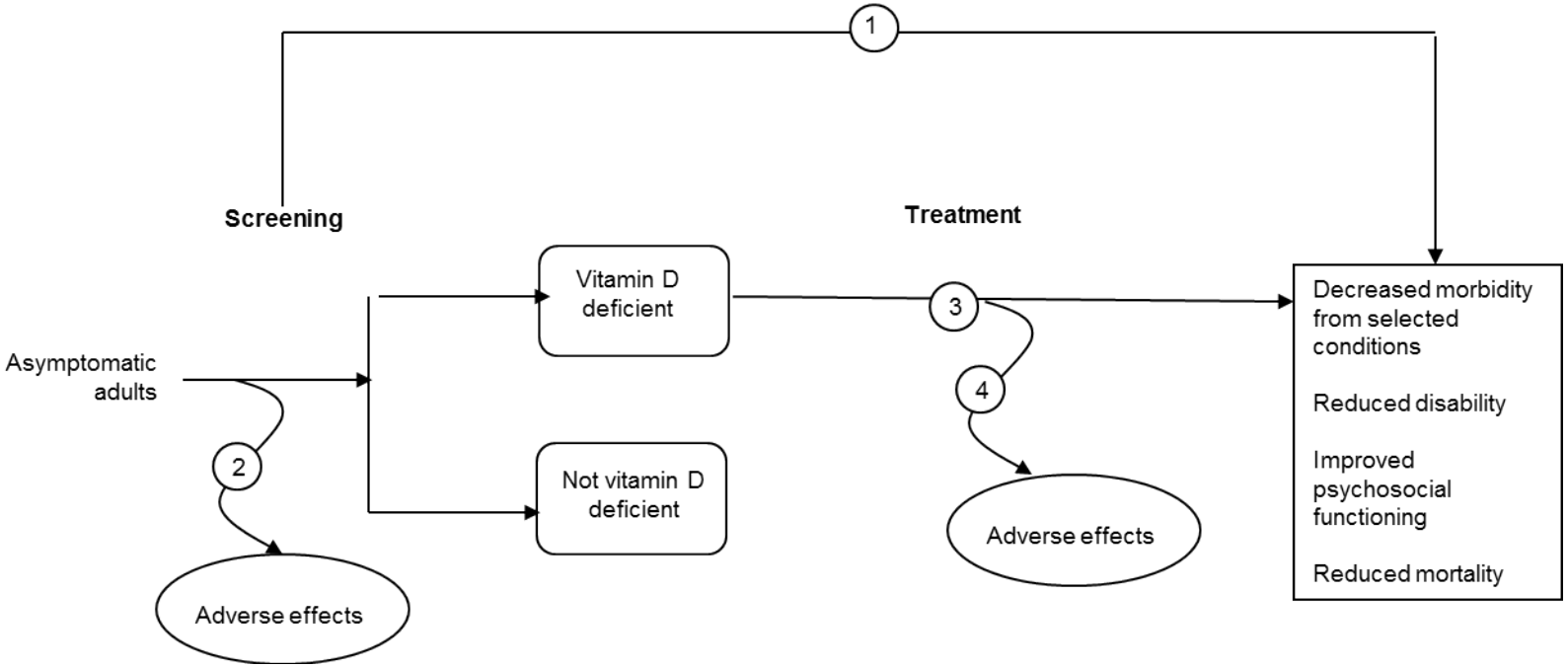
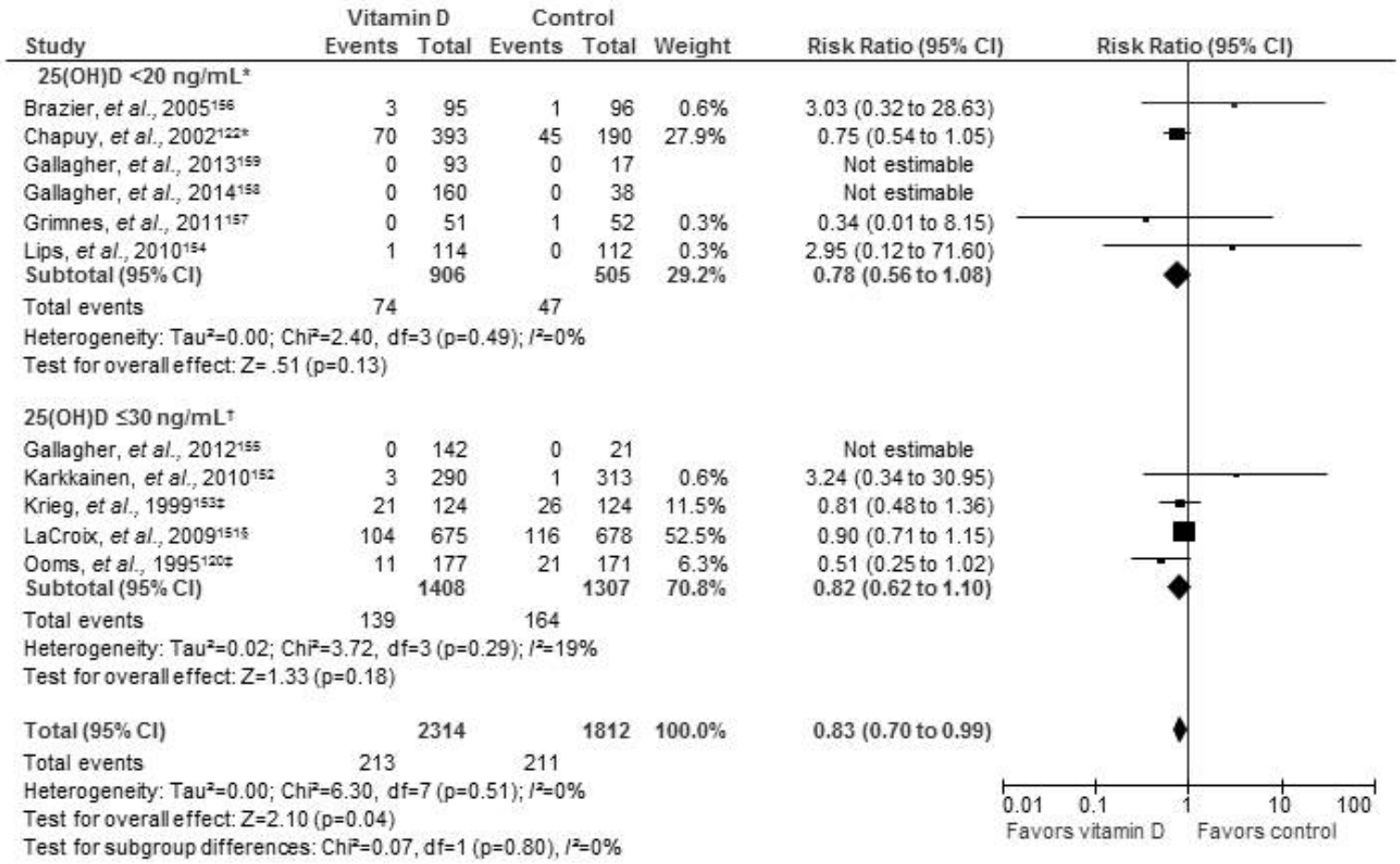


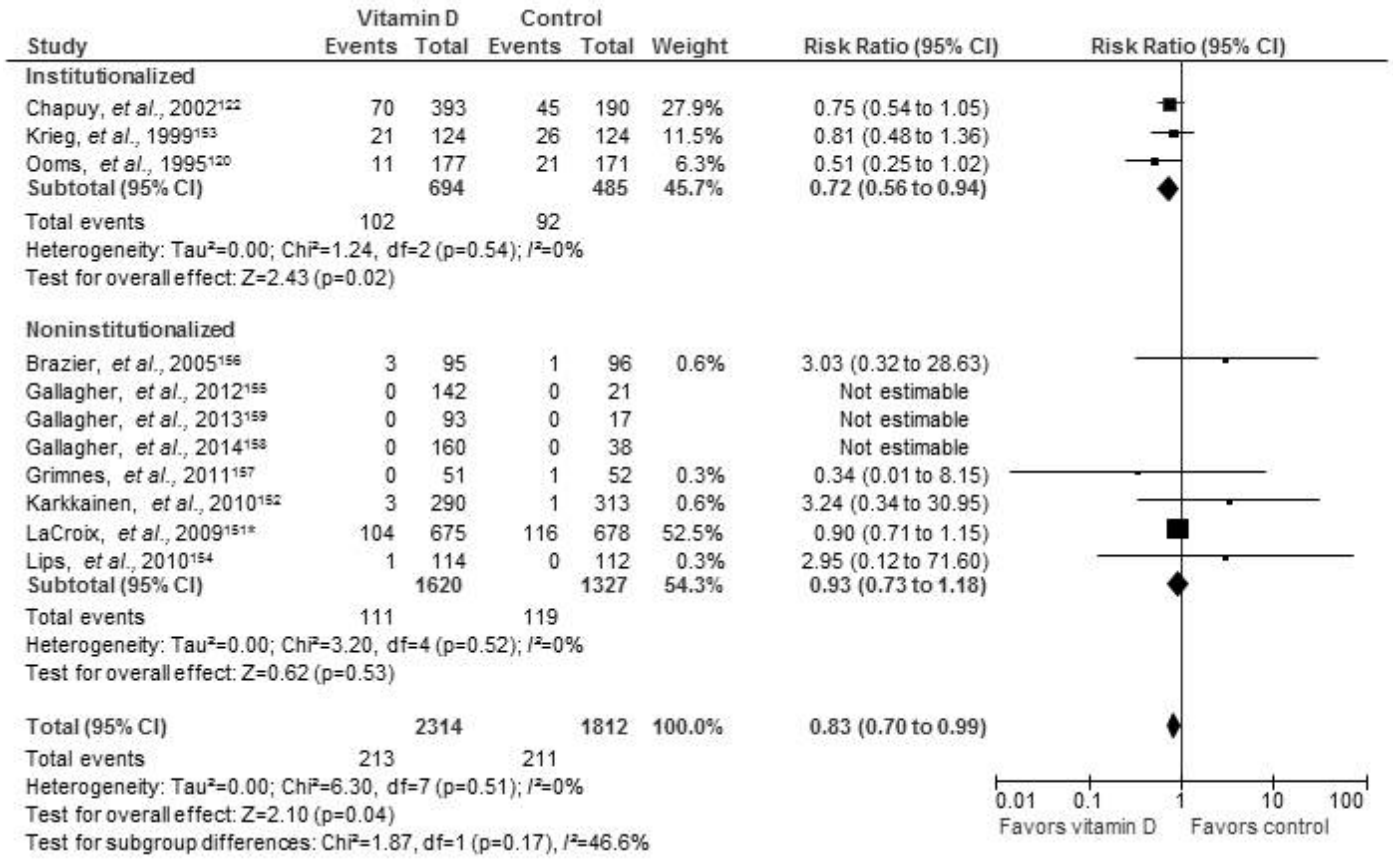
Figure 2. Meta-Analysis of Effects of Vitamin D Treatment on Mortality



* ≥90% of study participants had 25(OH)D levels <20 ng/mL.
† ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
‡Included an institutionalized population.
§This is a nested case-control study from the Women's Health Initiative Calcium with Vitamin D Trial.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

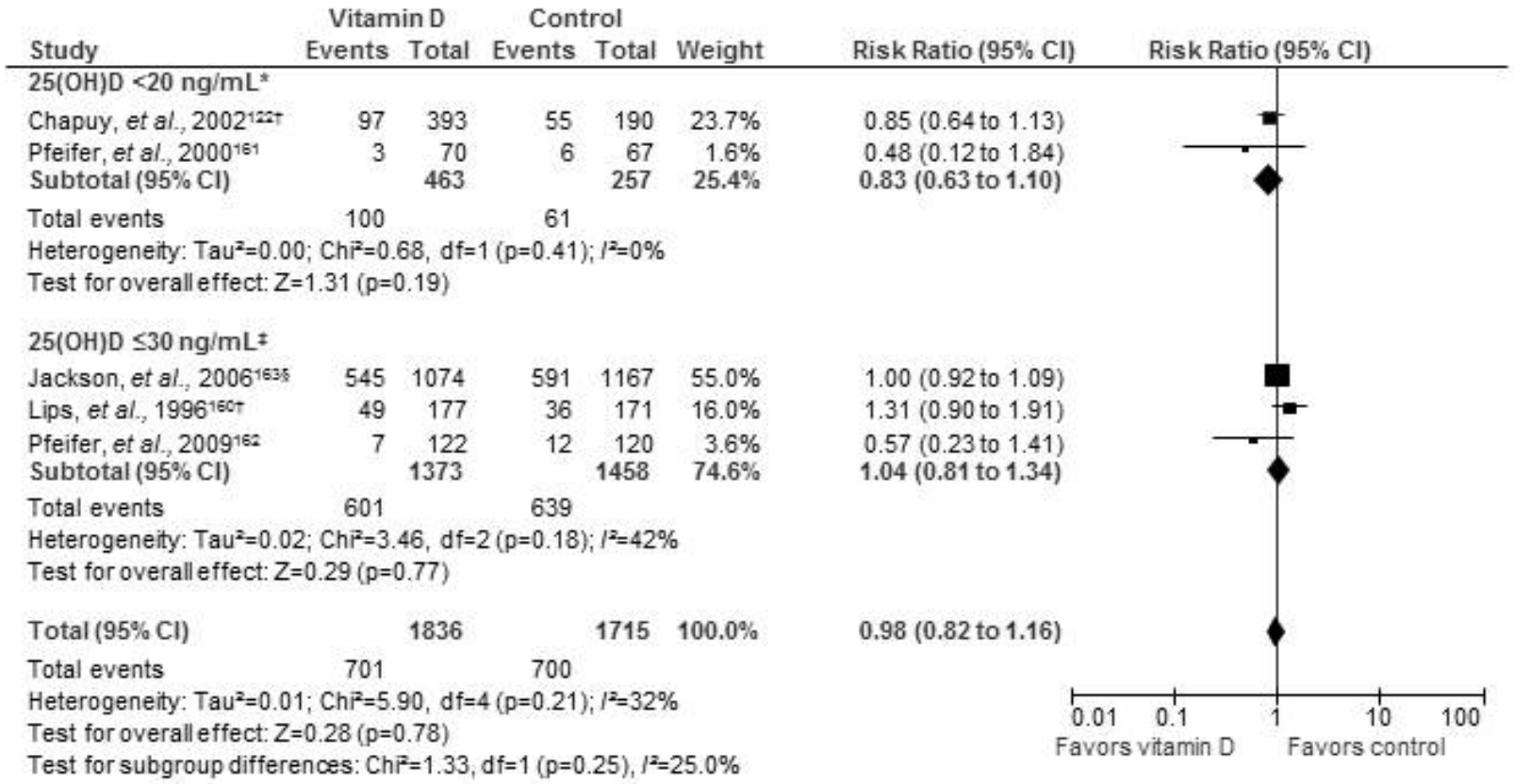
Figure 3. Meta-Analysis of Effects of Vitamin D Treatment on Mortality by Institutionalized Status



*This is a nested case-control study from the Women's Health Initiative Calcium with Vitamin D Trial.

Abbreviations: CI = confidence interval.

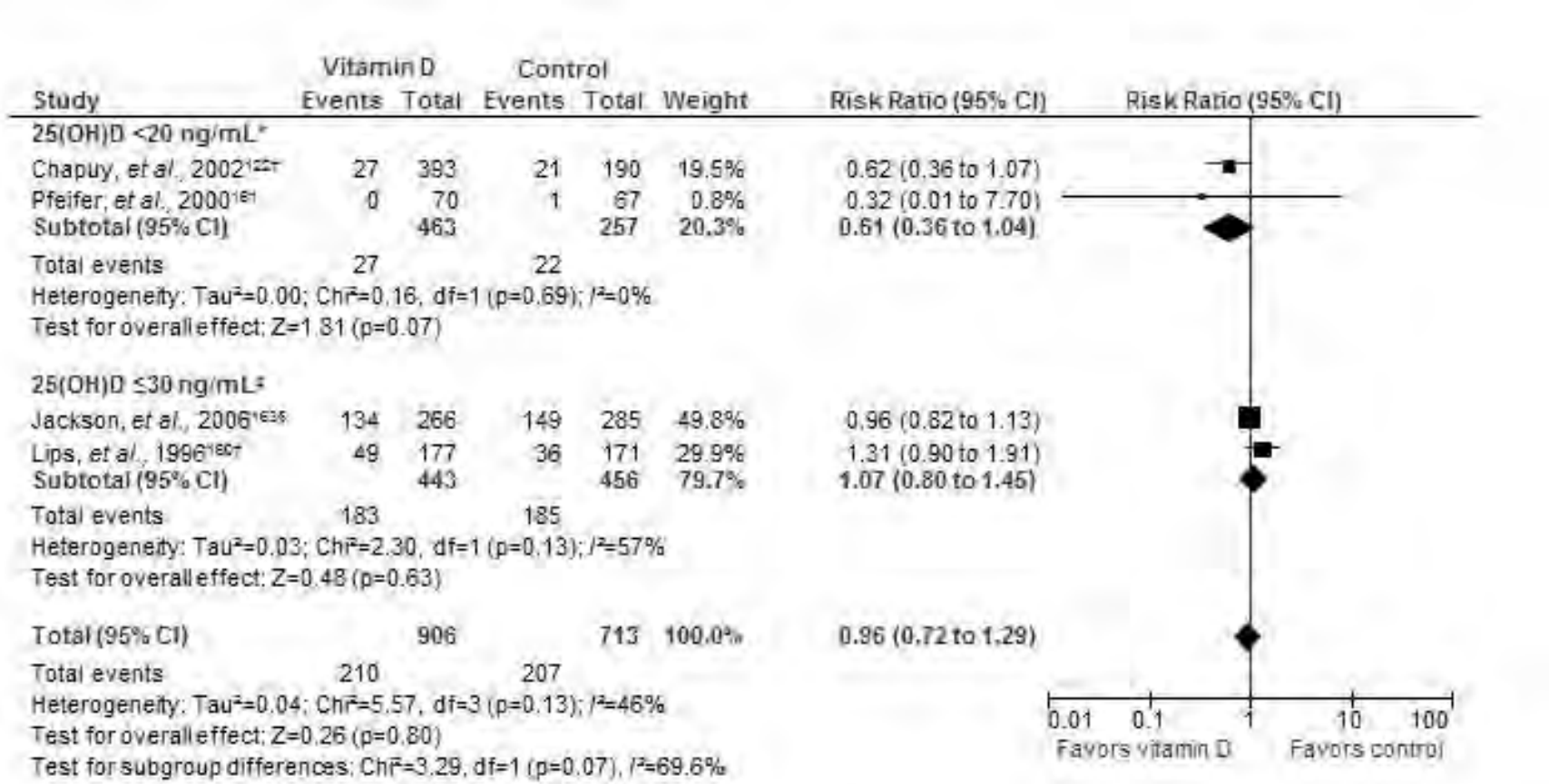
Figure 4. Meta-Analysis of Effects of Vitamin D Treatment on Any Type of Fracture Risk



* ≥90% of study participants had 25(OH)D levels <20 ng/mL.
†Included an institutionalized population.
‡ ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
§This is a nested case-control study from the Women's Health Initiative Calcium with Vitamin D Trial.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

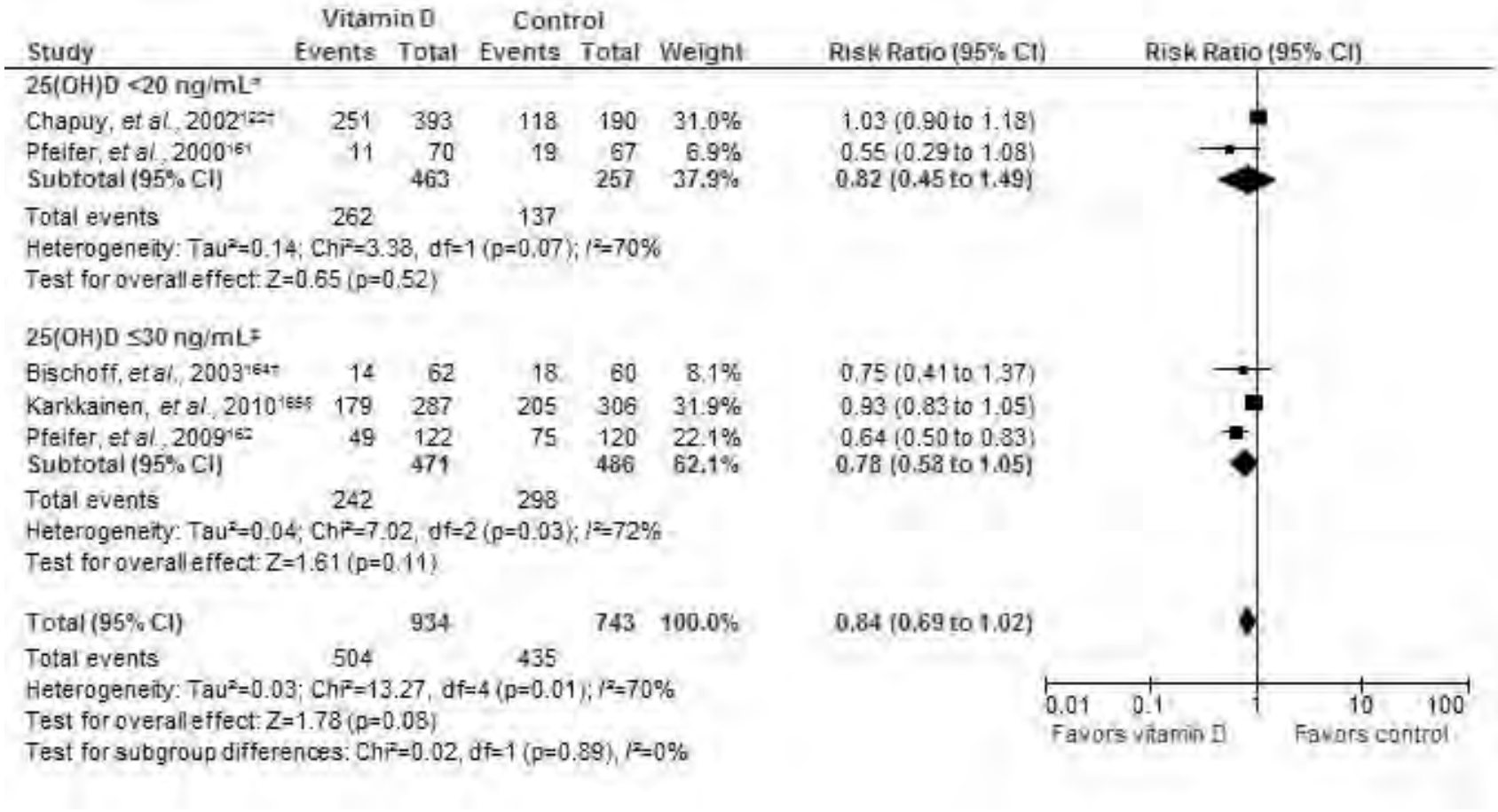
Figure 5. Meta-Analysis of Effects of Vitamin D Treatment on Hip Fracture Risk



* ≥90% of study participants had 25(OH)D levels < 20 ng/mL.
†Included an institutionalized population.
‡ ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
§This is a nested case-control study from the Women's Health Initiative Calcium with Vitamin D Trial.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval ng = nanogram; mL = milliliter.

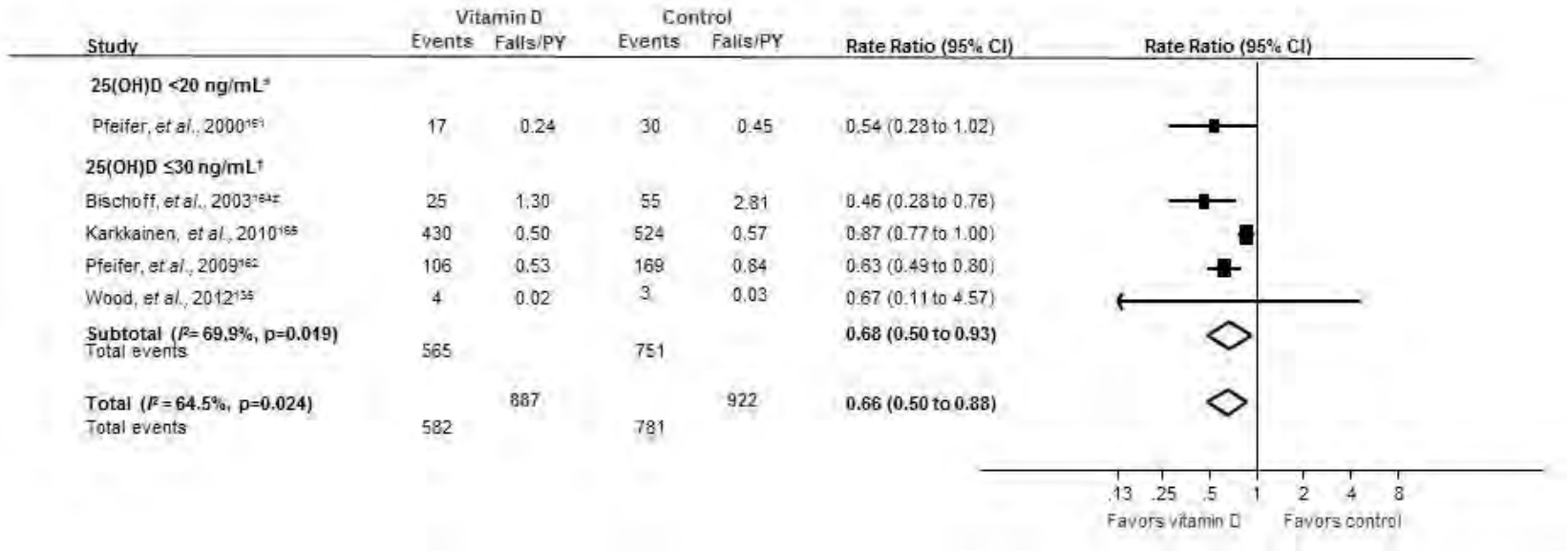
Figure 6. Meta-Analysis of Effects of Vitamin D Treatment on Risk for Falls



* ≥90% of study participants had 25(OH)D levels < 20 ng/mL.
†Included an institutionalized population.
‡ ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
§The calculated risk ratio is different than the one reported by the study.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

Figure 7. Meta-Analysis of Effects of Vitamin D Treatment on the Number of Falls per Individual



* ≥90% of study participants had 25(OH)D levels < 20 ng/mL.
† ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
‡Included an institutionalized population.

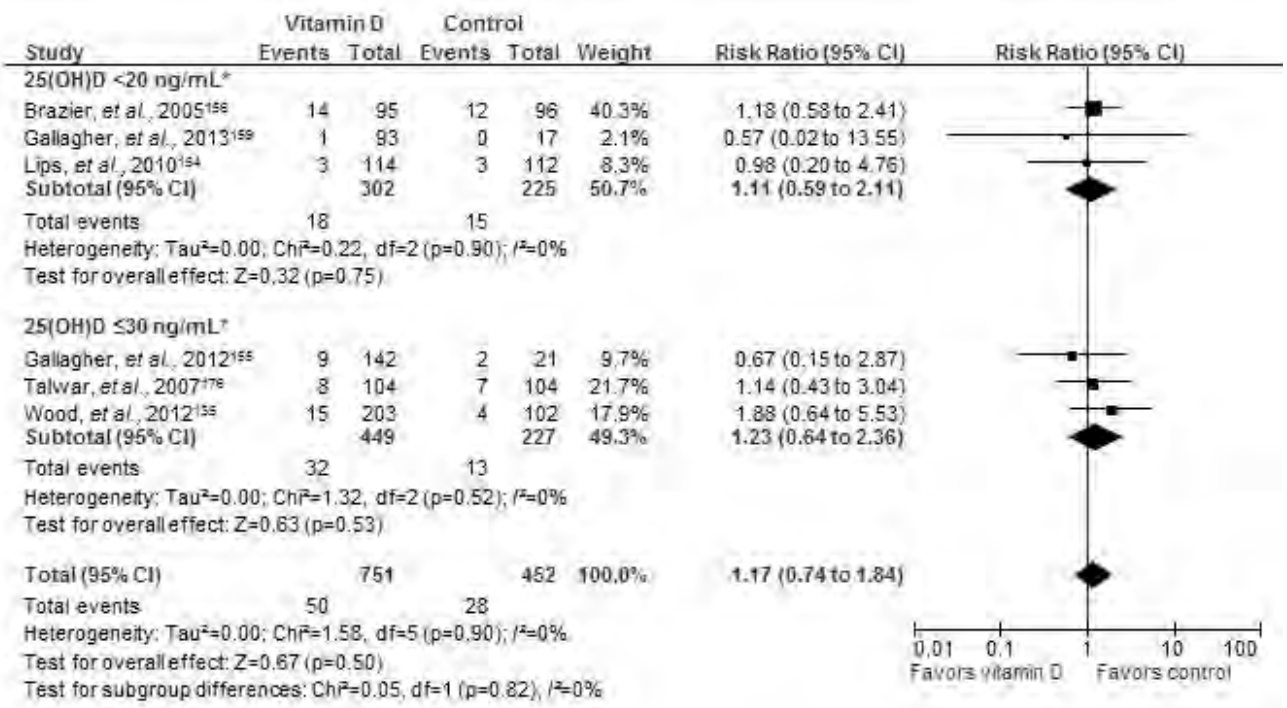
Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter; PY = person-year.

Figure 8. Meta-Analysis of Effects of Vitamin D Treatment on Type 2 Diabetes Risk

*≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
†This is a nested case-control study from the Women's Health Initiative Calcium with Vitamin D Trial.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

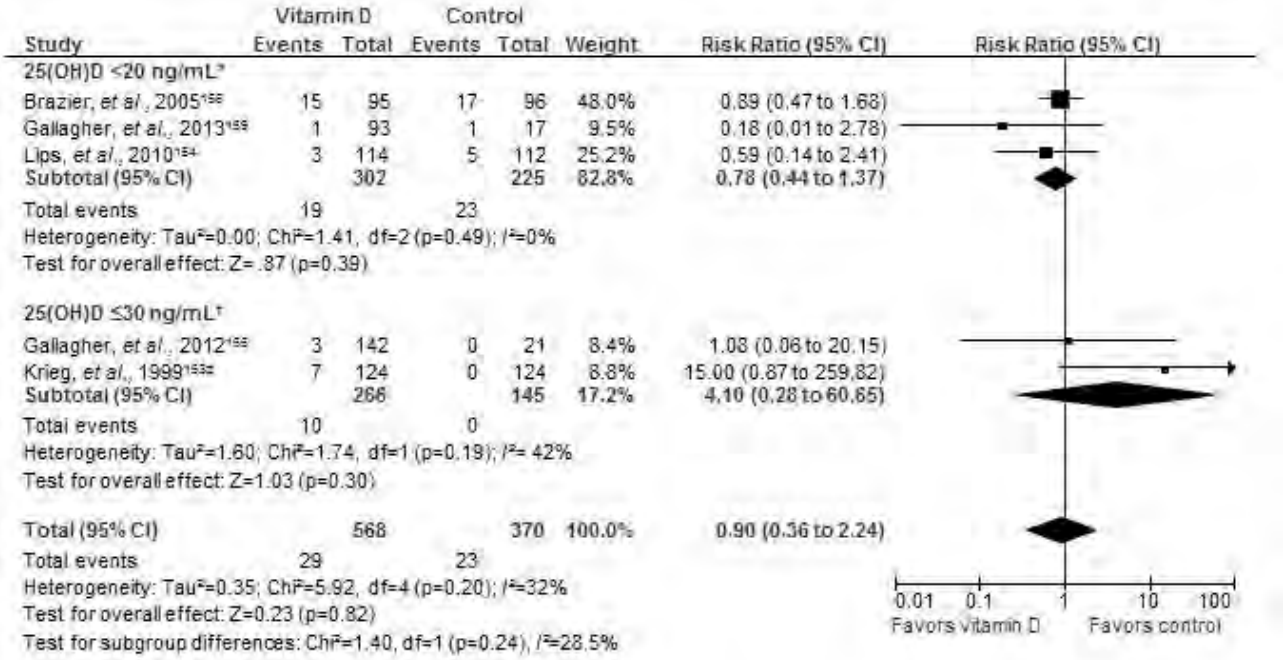
Figure 9. Meta-Analysis of Effects of Vitamin D Treatment on Serious Adverse Events



* ≥90% of study participants had 25(OH)D levels < 20 ng/mL.
† ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

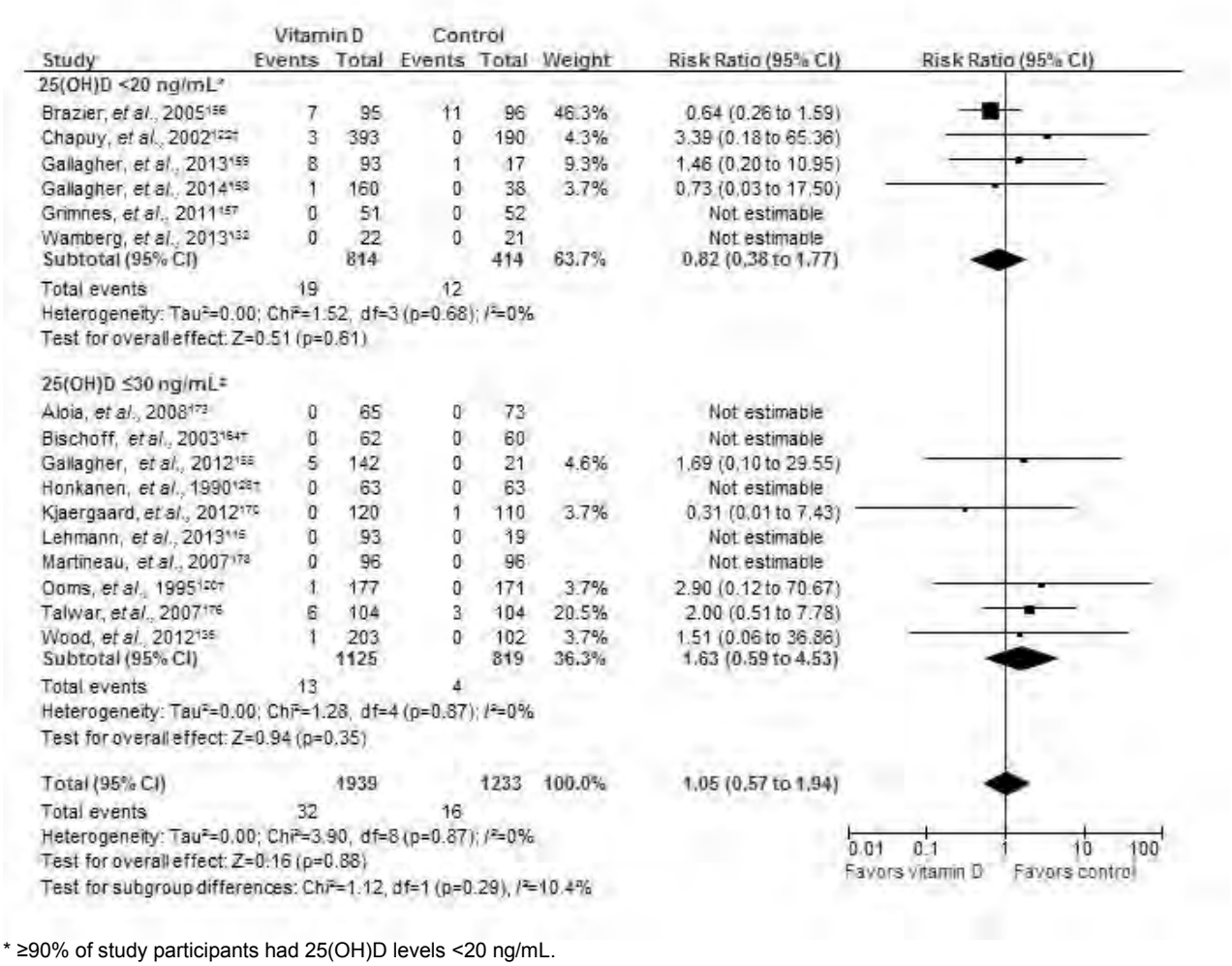
Figure 10. Meta-Analysis of Effects of Vitamin D Treatment on Withdrawals due to Adverse Events



* ≥90% of study participants had 25(OH)D levels < 20 ng/mL.
† ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
‡Included an institutionalized population.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

Figure 11. Meta-Analysis of Effects of Vitamin D Treatment on Hypercalcemia



* ≥90% of study participants had 25(OH)D levels <20 ng/mL.
† Included an institutionalized population.
‡ ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; CI = confidence interval; ng = nanogram; mL = milliliter.

Table 1. Summary of Current Opinions About Appropriate 25(OH)D Cutoffs for Defining Vitamin D Deficiency and Associations Between These 25(OH)D Cutoffs and Health Outcomes

25(OH)D Cutoff	Opinions of Expert and Professional Bodies About Cutoff Levels	Contextual Question 1 Findings on the Associations Between Level of 25(OH)D and Risk of Health Outcomes	Subgroup Differences for the Associations
<20 ng/mL	Widely used by researchers and available guidelines as indicative of deficiency.	• Levels >20 ng/mL have been associated with decreased risk of fractures, cardiovascular disease, colorectal cancer, diabetes, depressed mood, cognitive decline, mortality.	• Association with fracture and cardiovascular disease not seen in blacks. • Mortality association seen in blacks. • Associations with falls have been seen in studies of institutionalized elderly populations. • Limited data that association with cognition may be stronger in women.
20-30 ng/mL	Debate about whether 25(OH)D levels in this range represent deficiency.	• Levels >24 ng/mL associated with decreased cardiovascular disease risk. • Levels >30 ng/mL associated with decreased mortality and colorectal cancer risk. • Level >30 ng/mL mixed association with decreased fracture risk.	• Association with cardiovascular disease not seen in blacks. • Mortality association seen in blacks.
>30-40 ng/mL	General agreement that 25(OH)D levels in this range do not represent deficiency; however, some recommend targeting 25(OH)D to this range because of potential variability in laboratory testing.	• Levels up to 35-40 ng/mL may be associated with decreased risk of mortality and colorectal cancer.	No data available.
>50 ng/mL	Debate about whether 25(OH)D levels above this range are associated with adverse health outcomes.	• Possible U-shaped associated between vitamin D level and risk of mortality and pancreatic cancer.	No data available.
>200 ng/mL	25(OH)D levels above this range considered to be toxic.	No data available.	No data available.

Note: For consistency throughout the report we converted 25(OH)D levels reported as nmol/L to ng/mL by dividing the nmol/L amount by 0.4 to equal the ng/mL amount (i.e., 1 nmol/L = 0.4 ng/mL).

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; mL = milliliter; ng = nanogram.

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
25(OH)D level <20 ng/mL‡							
Brazier, *et al.,* 2005[156] Fair	France	Analyzed: 191 Age (years): 74.6 Female: 100% Co-morbidities: NR History of falls: NR Institutionalized: 0%	7 vs. 7	Median: 29 vs. 11	Vitamin D (n=95): 800 IU vitamin D_3 and 1000 mg calcium daily Control (n=97): Placebo	12 months	Mortality
Chapuy, *et al.,* 2002[122] Fair	France	Analyzed: 583 Age (years): 85 Female: 100% Co-morbidities: NR History of falls: 16.1% Use of walking device: 40.7% Institutionalized: 100%	9 vs. 9	From figure; ~ 33 vs. 5; p=0.0001 for change from baseline for vitamin D group only	Vitamin D (n=393): 800 IU of vitamin D_3 and 1200 mg calcium daily Control (n=190): Placebo	24 months	Fractures (primary outcome) Fallers Mortality
Gallagher, *et al.,* 2013[159] Fair	United States	Analyzed: 110 Age (years): 67 Female: 100% BMI (kg/m^2): 32.7 Co-morbidities: NR History of falls: NR Institutionalized: NR	Placebo: 14 Vitamin D 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14 NR for 400, 3600 or 4000 IU groups	From figure; 97.5% of those using vitamin D 800 IU reached serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D: 400 IU, 800 IU, 1600 IU, 2400 IU, 3200 IU, 4000 IU, or 4800 IU of vitamin D_3 daily Control: Placebo *All participants:* supplemented to maintain total calcium intake of 1200 to1400 mg/day	12 months	Mortality§

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
Gallagher, *et al.,* 2014[158] Fair	United States	Analyzed: 198 Age (years): 37 Female: 100% BMI (kg/m^2): 30.2 Co-morbidities: NR History of falls: NR Institutionalized: NR	Placebo: 13 Vitamin D 400 IU: 13 800 IU: 14 1600 IU: 13 2400 IU: 14	From figure; 97.5% of white women using vitamin D 400 IU reached serum 25(OH)D >20 ng/mL; 97.5% of black women using vitamin D 800 to 1600 IU reached serum 25(OH)D >20 ng/mL	Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D_3 daily Control: Placebo *All participants:* supplemented to maintain total calcium intake of 1000 to 1200 mg/day	12 months	Mortality§
Grimnes, *et al.,* 2011[157] Fair	Norway	Analyzed: 104 Age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) BMI (kg/m^2): 26.5 (27.2 vs. 26.3) History of falls: NR Institutionalized: 0%	17 vs. 16	57 vs. 17	Vitamin D (n=51): 40000 IU of vitamin D_3 weekly Control (n=52): Placebo	6 months	Mortality
Lips, *et al.,* 2010[154] Fair	Netherlands, Germany, United States	Analyzed: 213 for SPPB; 226 for mortality Age (years): 78 Female: NR BMI (kg/m^2): 27.8† Co-morbidities: NR History of falls: NR Use of walking device: 15% Institutionalized: 14%	14 vs. 14	26 vs. 12; p<0.001	Vitamin D (n=114): 8400 IU of Vitamin D3 weekly Control (n=112): Placebo *All participants:* Those with daily calcium intake <1000 mg were also given 500 mg calcium	16 weeks	Physical function Mortality

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
Pfeifer, *et al.,* 2000[161] Fair	Germany	Analyzed: 137 Age (years): 74.8† Female: 100% BMI (kg/m^2): 25.5† Co-morbidities: 39% cardiovascular; 12% central nervous, neurological; <1% psychiatric; 22% musculoskeletal History of falls: NR Use of walking device: NR Institutionalized: 0%	10 vs. 10	26 vs. 17; p<0.001	Vitamin D (n=70): 800 IU of vitamin D_3 and 1200 mg of calcium daily Control (n=67): 1200 mg of calcium daily	8 weeks treatment; 1 year followup	Falls Fallers Fractures
25(OH)D level ≤30 ng/mL ‖							
Arvold, *et al.,* 2009[169] Fair	United States	Analyzed: 90 Age (years): 58.8† Female: 40% BMI: NR Co-morbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 0%	18 vs. 18	45 vs. 22	Vitamin D (n=48): 50000 IU of vitamin D_3 weekly Control (n=42): Placebo	8 weeks	Psychosocial function Disability

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
Bischoff, *et al.,* 2003[164] Fair	Switzerland	Analyzed: 122 Age (years): 85 Female: 100% BMI (kg/m^2): 24.7 Co-morbidities: 30.3% hypertension, 15.6% stroke, 50.0% myocardial infarction or congestive heart failure, 12.3% anemia, 14.8% diabetes, 8.2% chronic obstructive pulmonary disease, 16.4% peptic ulcer disease, 24.6% depression, 9.0% malnutrition, 4.1% obesity, 54.9% dementia, 54.1% fracture at any site History of falls: 34% Use of walking device: 60% Institutionalized: 100%	Median 12 vs. 12	Median 26 vs. 11; p < 0.001	Vitamin D (n=62): 800 IU of vitamin D_3 and 1200 mg of calcium daily Control (n=60): 1200 mg calcium daily	6 weeks pretreatment; 12 weeks treatment	Falls (primary outcome) Fallers
Gallagher, *et al.,* 2012[155] Good	United States	Analyzed: 163 Age (years): 67 Female: 100% BMI (kg/m^2): 30.2 Co-morbidities: NR History of falls: NR Institutionalized: NR	Placebo: 15 Vitamin D 400 IU: 15 800 IU: 16 1600 IU: 15 2400 IU: 15 3200 IU: 16 4000 IU: 15 4800 IU: 16	From figure; 97.5% of those using vitamin D 600 IU reached serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D (n=142): Either 400 IU, 800 IU, 1600 IU, 2400 IU, 3200 IU, 4000 IU, or 4800 IU of vitamin D_3 daily Control (n=21): Placebo *All participants:* Supplemented to maintain total calcium intake of 1200 to1400 mg/day	Median: 12 months	Mortality

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
Kärkkäinen, *et al.,* 2010[165]; Kärkkäinen, et al., 2010[152] Fair	Finland	Analyzed: 593 Age (years): 67.4† Female: 100% BMI (kg/m^2): 27.5† Co-morbidities: NR History of falls: NR Ambulatory: 100% Institutionalized: NR	20 vs. 20	30 vs. 22	Vitamin D (n=290¶ and 287**): 800 IU of vitamin D_3 and 1000 mg of calcium daily Control (n=313¶ and 306**): No treatment	3 years	Falls (primary outcome) Fallers Mortality
Kjaergaard, et al., 2012[170] Good	Norway	Analyzed: 230 (per protocol) Age (years): 53.4† Female: 56% BMI (kg/m2): 27.7† Co-morbidities: NR History of falls: NR Institutionalized: NR	19 vs. 19	59 vs. 21	Vitamin D (n=120): 20,000 IU of vitamin D_3 weekly Control (n=110): Placebo	6 months	Psychosocial function (primary outcome)
Krieg, *et al.,* 1999[153] Fair	Switzerland	Analyzed: 248 Age (years): 84.5† Female: 100% BMI (kg/m^2): 24.7† History of falls: NR Institutionalized: 100%	12 vs. 12	27 vs. 6	Vitamin D (n=124): 880 IU of vitamin D_3 and 1000 mg calcium daily Control(n=124): No supplementation	2 years	Mortality

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
Lips, *et al.,* 1996[160] Ooms, *et al.,* 1995[120] Fair	Netherlands	Analyzed: 270 for fracture; 348 for mortality Age (years): 80.4† Female: 100% BMI (kg/m^2): 28.3† Co-morbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 100%††	Median: 11 vs. 10	Median: 25 vs. 9 (at 1 year)	Vitamin D (n=177): 400 IU of vitamin D_3 daily Control (n=171): Placebo	3 to 3.5 years, maximum 4 years	Fractures (primary outcome) Mortality
Pfeifer, *et al.,* 2009[162] Fair	Austria and Germany	Analyzed: 242 Age (years): 76.5 Female: 74.5% BMI (kg/m^2): 27.3 Co-morbidities: NR History of falls: NR Ambulatory: 100% Institutionalized: 0%	22 vs. 22	Month 12: 34 vs. 23 Month 20: 19 vs. 15	Vitamin D (n=122): 800 IU of vitamin D_3 and 1000 mg of calcium daily Control (n=120): 1000 mg of calcium daily	12 month treatment; 8 months post-treatment	Falls (primary outcome) Fallers Fractures
Wood, *et al.,* 2012[135] Fair	United Kingdom	Analyzed: 305 Age (years): 63.8† Female: 100% BMI (kg/m^2): 26.7† History of falls: NR Institutionalized: NR	Vitamin D 400 IU vs. 1000 IU vs. control 13 vs. 13 vs. 14	Vitamin D 400 IU vs. 1000 IU vs. control 26 vs. 30 vs. 13	Vitamin D (n=102 and 101): 400 IU or 1000 IU of vitamin D_3 daily Control (n=102): Placebo	12 months treatment; 1 month followup	Falls Type 2 diabetes

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Clinical Health Outcomes Reported
WHI calcium with vitamin D trialFairAssociated case-control studies with outcome reported: Jackson, *et al.,* 2006[163] for fracture; Wactawski-Wende, *et al.,* 2006[167] for colorectal cancer; Chlebowski, *et al.,* 2008[166] for breast cancer; de Boer, *et al.,* 2008[168] for diabetes; LaCroix, *et al.,* 2009[151] for mortality	United States	**AnalyzedEnitre trial:** 36282 **Case control studies** Fractures: 1491 cases/controls Colorectal cancer: 612 cases/controls Breast cancer: 895 cases/controls Diabetes: 192 cases/2905 controls Mortality: 323 cases/1962 controls **Entire trial characteristics** Age (years): 62 Female: 100% BMI (kg/m^2): 29 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 Co-morbidites: 35% with previous fracture; 67% with no falls, 20% with one fall, 9.0% with 2 falls, 4.0% with >3 falls in past 12 months **Case control characteristics:** NR	**Entire trial:** NR **Case control studies** Fractures: <24 Colorectal cancer: <23 Breast cancer: <27 Diabetes: <24 Mortality: <21	**Entire trial** After 2 years, in random sample of 1.2% of participants, vitamin D levels were 28% higher (9 ng/mL) in vitamin D vs. placebo group **Case control studies:** NR	Vitamin D: 400 IU of vitamin D_3 + 1000 mg calcium daily Control: Placebo **Number analyzed in case control studies per intervention (vitamin D vs. control)** Fractures: 266 vs. 285 Colorectal cancer: 237 vs. 222 Breast cancer: 909 vs. 722 Diabetes: 1118 vs. 1187 Mortality: 675 vs. 678	7 years	Fractures Mortality Type 2 diabetes Cancer

* Reported as means, unless otherwise noted.
† Calculated.
‡ ≥90% of study participants had 25(OH)D levels <20 ng/mL .

Table 2. Studies of Effectiveness of Vitamin D Treatment

§ As per author correspondence.
‖ ≥90% of study participants had 25(OH)D levels ≤30 ng/ml, with ≥10% with 25(OH)D level ≥20 ng/mL.
¶ For mortality outcome.
** For falls/fallers outcomes.
†† Received care, but not as much as nursing home.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; BMI = body mass index; IU = international unit; kg = kilogram; m = meter; mg = milligram; mL = milliliter; ng = nanogram; NR = not reported; SPPB = Short Physical Performance Battery; vs. = versus.

Table 3. Details on Studies Examining Association Between Vitamin D Treatment and Falls

Study, Setting, Age*	Fall Risk	Intervention	IRR (95% CI) for Falls per Person	RR (95% CI) for Risk of Falling	Primary Outcome of Study
Bischoff *et al.*, 2003[164] Institutionalized Age: 85	34% with falls 6 weeks prior; 30% of CG fell over 3 months	Vitamin D	0.46 (0.28 to 0.76)	0.75 (0.41 to 1.37)	Number of falls per person
Chapuy *et al.*, 2002[122] Institutionalized Age: 85	16% with falls 3 months prior. 62% of CG fell over 24 months	Vitamin D + calcium	NR	1.03 (0.90 to 1.18)	Fracture
Kärkkäinen *et al.*, 2010[165] Noninstitutionalized Age: 67	Fall history NR; 67% of CG fell over 36 months	Vitamin D + calcium	0.87 (0.77 to 1.00)	0.93 (0.83 to 1.05)	Occurrence of falls
Pfeifer *et al.*, 2000[161] Noninstitutionalized Age: 75	Fall history NR; 28% of CG fell over 12 months	Vitamin D	0.54 (0.28 to 1.02)	0.55 (0.29 to 1.08)	Body sway; biochemical measures of bone
Pfeifer *et al.*, 2009[162] Noninstitutionalized Age: 77	Fall history NR; 63% of CG fell over 20 months	Vitamin D	0.63 (0.49 to 0.80)	0.64 (0.50 to 0.83)	Occurrence of falls
Wood *et al.*, 2012[135] Noninstitutionalized Age: 64	Fall history NR; 3 falls among 227 in CG	Vitamin D	0.67 (0.11 to 4.57)	NR	Reported as adverse event

* Mean age (in years) of study population.

Abbreviations: CG = control group; CI = confidence interval; IRR = incidence rate ratio; NR = not reported; RR = risk ratio.

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
25(OH)D level <20 ng/mL‡							
Brazier, *et al.,* 2005[156] Fair	France	Analyzed: 191 Age (years): 74.6 (74.2 vs. 75.0) Female: 100% Co-morbidities: NR History of falls: NR Institutionalized: 0%	7 vs. 7	Median: 29 vs. 11	Vitamin D (n=95): 800 IU vitamin D_3 and 1000 mg calcium daily Control (n=97): Placebo	12 months	Total AEs Withdrawal due to AEs Serious AEs Any AE Hypercalcemia Gastrointestinal AEs Osteomuscular AEs Nervous system AEs Metabolic/nutritional AEs
Chapuy, *et al.,* 2002[122] Fair	France	Analyzed: 583 Age (years): 85 Female: 100% Co-morbidities: NR History of falls: 16.1% Use of walking device: 40.7% Institutionalized: 100%	9.2 vs. 9.2	From figure; roughly 33 vs. 5; p=0.0001 for change from baseline for vitamin D group only	Vitamin D (n=393): 800 IU of vitamin D_3 and 1200 mg calcium daily Control (n=190): Placebo	24 months	Withdrawal due to AEs (NR by group) Hypercalcemia Kidney stones Hypercalciuria Gastrointestinal AEs
Gallagher, *et al.,* 2013[159] Fair	United States	Analyzed: 110 Age (years): 67 Female: 100% BMI (kg/m^2): 32.7 Co-morbidities: NR History of falls: NR Institutionalized: NR	Placebo: 14 Vitamin D§ 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14	From figure; 97.5% of those using vitamin D 800 IU reached serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D: 400 IU, 800 IU, 1600 IU, 2400 IU, 3200 IU, 4000 IU, or 4800 IU of vitamin D_3 daily Control: Placebo *All participants:* supplemented to maintain total calcium intake of 1200 to1400 mg/day	12 months	Withdrawal due to AEs‖ Serious AEs Hypercalcemia

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Gallagher, *et al.,* 2014[158] Fair	United States	Analyzed: 198 Age (years): 37 Female: 100% BMI (kg/m^2): 30.2 Co-morbidities: NR History of falls: NR Institutionalized: NR	Placebo: 13 Vitamin D 400 IU: 13 800 IU: 14 1600 IU: 13 2400 IU: 14	From figure; 97.5% of white women using vitamin D 400 IU reached serum 25(OH)D >20 ng/mL; 97.5% of black women using vitamin D 800 to 1600 IU reached serum 25(OH)D >20 ng/mL	Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D_3 daily Control: Placebo *All participants:* supplemented to maintain total calcium intake of 1000 to 1200 mg/day	12 months	Serious AEs (NR by group) Hypercalcemia Kidney stones
Grimnes, *et al.,* 2011[157] Fair	Norway	Analyzed: 104 Age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) BMI (kg/m^2): 26.5 (27.2 vs. 26.3) History of falls: NR Institutionalized: 0%	17 vs. 16	57 vs. 17	Vitamin D (n=51): 40,000 IU vitamin D_3 weekly Control (n=52): Placebo	6 months	Total AEs Hypercalcemia Kidney stones
Janssen, *et al.,* 2010[127] Fair	Netherlands	Analyzed: 70 Age (years): 80.8† Female: 100% BMI (kg/m^2): 26.4† Number of co-morbidities: 2.4† Number of medications used: 5.0† History of falls: NR Institutionalized: 100%‡	13 vs. 14	31 vs. 17	Vitamin D (n=28): 400 IU of vitamin D_3 and 500 mg of calcium daily Control (n=31): Placebo and calcium 500 mg daily	6 months	Withdrawals Any AE

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Lips, *et al.,* 2010[154] Fair	Netherlands, Germany, United States	Analyzed: 226 Age (years): 78 Female: NR BMI (kg/m^2): 27.8† Co-morbidities: NR History of falls: NR Use of walking device: 15% Institutionalized: 14%	14 vs. 14	26 vs. 12; p<0.001	Vitamin D (n=114): 8400 IU of Vitamin D_3 weekly Control (n=112): Placebo *All participants:* Those with daily calcium intake <1000 mg were also given 500 mg calcium	16 weeks	Withdrawal due to AEs Serious AEs Any AE Kidney stones Hypercalcemia (data not shown)
Wamberg, *et al.,* 2013[125] Wamberg, *et al.,* 2013[132] Fair	Denmark	Analyzed: 43 Age (years): 40.5 Female: 71% BMI (kg/m^2): 35.8%† Sedentary: 35%† Lightly active: 48%† Moderately active: 17%† Co-morbidities: 2% (1/55) on lipid lowering med and 5% (3/55) on anti-hypertensive meds History of falls: NR Institutionalized: NR	14 vs. 14	44 vs. 19	Vitamin D (n=22): 7000 IU of vitamin D_3 daily Control (n=21): Placebo	26 weeks	Total AEs Hypercalcemia
25(OH)D level ≤30 ng/mL¶							

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Aloia, *et al.,* 2008[173] Fair	United States	Analyzed: 138 Age (years): 47.2† Female: 81% History of falls: NR Institutionalized: NR	19	>30 ng/mL achieved by virtually all in active group; also increased by 8 ng/mL in placebo group due to seasonal change	Vitamin D (n=65): Dosage of vitamin D_3 was dependent on 25(OH)D concentrations, mean dose: 3440 IU Control (n=73): Placebo	6 months	Hypercalcemia Hypercalcuria
Arvold, *et al.,* 2009[169] Fair	United States	Analyzed: 100 Age (years): 58.8† Female: 40% BMI: NR Co-morbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 0%	18 vs. 18	45 vs. 22	Vitamin D (n=48): 50,000 IU vitamin D_3 weekly Control (n=42): Placebo	8 weeks	Any AE
Berlin, *et al.,* 1986[177] Poor	Sweden	Analyzed: 24 Age (years): 31 (range: 22 to 47) Female: 0% History of falls: NR Institutionalized: NR	15 vs. 15	49 vs. 19	Vitamin D (n=12): 54,000 IU of vitamin D_3 weekly Control (n=12): No treatment	NR, implies 2 months	Any AE

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Bischoff, *et al.,* 2003[164] Fair	Switzerland	Analyzed: 122 Age (years): 85 Female: 100% BMI (kg/m^2): 24.7 Co-morbidities: 30.3% hypertension, 15.6% stroke, 50.0% myocardial infarction or congestive heart failure, 12.3% anemia, 14.8% diabetes, 8.2% chronic obstructive pulmonary disease, 16.4% peptic ulcer disease, 24.6% depression, 9.0% malnutrition, 4.1% obesity, 54.9% dementia, 54.1% fracture at any site History of falls: 34% Use of walking device: 60% Institutionalized: 100%	Median 12 vs. 12	Median 26 vs. 11; p<0.001	Vitamin D (n=62): 800 IU of vitamin D_3 and 1200 mg of calcium daily Control (n=60): 1200 mg calcium daily	6 weeks pretreatment/12 weeks treatment	Hypercalcemia Withdrawals Gastrointestinal AEs

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Gallagher, *et al.,* 2012[155] Good	United States	Analyzed: 163 Age (years): 67 Female: 100% BMI (kg/m^2): 30.2 Co-morbidities: NR History of falls: NR Institutionalized: NR	Placebo: 15 Vitamin D 400 IU: 15 800 IU: 16 1600 IU: 15 2400 IU: 15 3200 IU: 16 4000 IU: 15 4800 IU: 16	From figure; 97.5% of those using vitamin D 600 IU per day had serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D (n=235): Either 400 IU, 800 IU, 1600 IU, 2400 IU, 3200 IU, 4000 IU, or 4800 IU of vitamin D_3 daily Control (n=38): Placebo *All participants:* Supplemented to maintain total calcium intake of 1200 to1400 mg daily	Median: 12 months	Withdrawal due to AEs Any AE Serious AEs Kidney stones Hypercalcemia
Harris, *et al.,* 1999[175] Poor	United States	Analyzed: 20 Age (years): 31 (range: 22 to 47) Female: 0% Co-morbidities: NR History of falls: NR Institutionalized: NR	Younger men: 13 vs. 17 Older men: 16 vs. 16	Younger men: 25 vs. 13 Older men: 19 vs. 15	Vitamin D (n=11): 1800 IU of vitamin D_2 daily Control (n=7): No treatment	3 weeks	Any AE

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Honkanen, *et al.,* 1990[128] Fair	Finland	Analyzed: 126 **Home patients:** Age (years): 69.5† Female: 100% Weight (kg): 69.5† Co-morbidities: NR History of falls: NR **Hospital inpatients (52%):** Age (years): 82.5† Female: 100% Weight (kg): 61.8† Co-morbidities: NR History of falls: NR	Home patients: 17 vs. 15 Hospital inpatients: 10 vs. 10	Home patients: 32 vs. 9 Hospital inpatients: 26 vs. 4	Vitamin D (n=63): 1800 IU of vitamin D_3 and 1.558 g of calcium daily Control (n=63): No treatment	11 weeks	Hypercalcemia Kidney stones
Kärkkäinen, *et al.,* 2010[152] Fair	Finland	Analyzed: 603 Age (years): 67.4† (67.4 vs. 67.4) Female: 100% BMI: 27.4† (27.5 vs. 27.4) History of falls: NR Institutionalized: NR	20 vs. 20	30 vs. 22	Vitamin D (n=290): 800 IU of vitamin D_3 and 1000 mg calcium daily Control (n=313): No treatment	3 years	Withdrawal due to AE

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Kjaergaard, et al., 2012[170] Good	Norway	Analyzed: 230 (per protocol) Age (years): 53.4† Female: 56% BMI (kg/m2): 27.7† Co-morbidities: NR History of falls: NR Institutionalized: NR	19 vs. 19	59 vs. 21	Vitamin D (n=120): 20,000 IU of vitamin D_3 weekly Control (n=110): Placebo	6 months	Total AEs Gastrointestinal AEs Respiratory AEs Dermatological AEs Musculoskeletal AEs Urogenital AEs Circulatory AEs Neurological AEs Endocrinological AEs Other organ AEs Hypercalcemia
Krieg, *et al.,* 1999[153] Fair	Switzerland	Analyzed: 248 Age (years): 84.5† Female: 100% BMI (kg/m^2): 24.7† History of falls: NR Institutionalized: 100%	12 vs. 12	27 vs. 6	Vitamin D(n=124): 880 IU of vitamin D_3 and 1000 mg calcium daily Control(n=124): No treatment	2 years	Withdrawal due to AE
Lehmann, *et al.,* 2013[115] Fair	Norway	Analyzed: 119 Age (years): 33.8† Female: 63.5% BMI (kg/m^2): 23.8† History of falls: NR Institutionalized: NR	Overall (vitamin D_2 vs. vitamin D_3 vs. control) 16 (15 vs. 18 vs. 16)	Vitamin D_2 vs. vitamin D_3 vs. control 27 vs. 36 vs. 13	Vitamin D (n=47, 46): 2000 IU of either vitamin D_2 or D_3 daily Control(n=19): Placebo	8 weeks	Any AE Hypercalcemia
Martineau, *et al.,* 2007[178] Fair	United Kingdom	Analyzed: 192†† Median age (years): 33.7† Female: 51.2%† History of falls: NR Institutionalized: NR	14 vs. NR	27 vs. NR	Vitamin D(n=96): Single dose of 100,000 IU vitamin D_2 Control (n=96): Placebo	6 weeks	Any AE Hypercalcemia

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (Ng/Ml)*,† Vitamin D vs. Control	25(OH)D Level at Followup (Ng/Ml)*,† Vitamin D vs. Control	Interventions	Duration*	Adverse Events/Harms Reported
Ooms, *et al.*, 1995[120] Fair	Netherlands	Analyzed: 348 Age (years): 80.4† Female: 100% BMI (kg/m^2): 28.3† Co-morbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 100%**	Median: 11 vs. 10	Median: 25 vs. 9 (at 1 year)	Vitamin D (n=177): 400 IU of vitamin D_3 daily Control (n=171): Placebo	3 to 3.5 years, maximum 4 years	Any AE Hypercalcemia
Talwar, *et al.*, 2007[176] Aloia, *et al.*, 2005[174] Fair	United States	Analyzed: 208 Age (years): 60.5† Female: 100% BMI (kg/m^2): 29 vs. 30 History of falls: NR Institutionalized: NR	19 vs. 17	35 vs. 18	Vitamin D (n=104): 800 IU of vitamin D_3 daily for first 24 months, increased to 2000 IU daily Control (n=104): Placebo *All participants:* Supplements given to maintain total daily intake of 1200 to 1500 mg calcium	36 months	Total AEs (NR by group) Serious AEs Hypercalcemia Hypercalcuria Kidney stones
Wood, *et al.*, 2012[135] Fair	United Kingdom	Analyzed: 305 Age (years): 63.8† Female: 100% BMI (kg/m^2): 26.7† History of falls: NR Institutionalized: NR	Vitamin D 400 IU vs. 1000 IU vs. control 13 vs. 13 vs. 14	Vitamin D 400 IU vs. 1000 IU vs. control 26 vs. 30 vs. 13	Vitamin D (n=102 and 101): 400 IU or 1000 IU of vitamin D_3 daily Control (n=102): Placebo	12 months treatment; 1 month followup	Total AEs Serious AEs Hypercalcemia Gastrointestinal AEs Osteomuscular AEs

* Reported as means, unless otherwise noted.
† Calculated.
‡ ≥90% of study participants had 25(OH)D levels <20 ng/mL.
§ NR for 400, 3600 or 4000 IU groups.
ǁ as per author correspondence.
¶ ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.

Table 4. Studies of Harms of Vitamin D Treatment

** Received care, but not as much as nursing home.
†† Population characteristics only reported for those who finished study (n=131).

Abbreviations: 25(OH)D = serum 25-hydroxyvitamin D; AE = adverse event; BMI = body mass index; g = gram; IU = international unit; kg = kilogram; m = meter; mg = milligram; mL = milliliter; ng = nanogram; NR = not reported; vs. = versus.

Table 5. Summary of Evidence

Number/type of studies	Overall quality	Limitations	Consistency	Applicability	Summary of findings
Key Question 1. Is there direct evidence that screening for vitamin D deficiency results in improved health outcomes? Key Question 1a. Are there differences in screening efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency such as age 65 years or older; sex; race-ethnicity; body mass index; UV exposure; institutionalized status)?					
No studies	NA	NA	NA	NA	NA
Key Question 2. What are the harms of screening (e.g., risk for procedure, false-positives, false-negatives)?					
No studies	NA	NA	NA	NA	NA
Key Question 3. Does treatment of vitamin D deficiency using vitamin D lead to improved health outcomes?					
17 studies RCTs, nested case-control studies	Fair	Few studies addressing each outcome; many studies reported few events or were underpowered; variability in baseline 25(OH)D levels, doses of vitamin D treatment, use of calcium co-supplementation, and length of followup	Moderate	Studies mostly conducted in older, white U.S. or European women	• Vitamin D treatment (with or without calcium) was associated with a decreased risk of mortality (11 studies; pooled RR 0.83; 95% CI 0.70 to 0.99); risk reduction limited to studies of older, institutionalized persons (3 trials; pooled RR 0.72, 95% CI, 0.56 to 0.94) • Vitamin D treatment was not associated with decreased risk of falling (5 studies; pooled RR 0.84; 95% CI 0.69 to 1.02), but was associated with a lower rate of falls per individual (pooled rate ratio 0.66; 95% CI, 0.50 to 0.88) • Vitamin D treatment was not associated with a decreased fracture risk (5 studies; pooled RR 0.98; 95% CI 0.82 to 1.16) • Limited (≤2 studies) data on cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning but generally no associations with vitamin D treatment were seen
Key Question 3a. Are there differences in efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency such as age; sex; race-ethnicity; body mass index; UV exposure; institutionalized status)?					
No studies	NA	NA	NA	NA	NA
Key Question 4. What are the adverse effects of treatment of vitamin D deficiency using vitamin D?					

Table 5. Summary of Evidence

Number/type of studies	Overall quality	Limitations	Consistency	Applicability	Summary of findings
23 studies* RCTs, cohorts	Fair	Few studies prespecified harms outcomes; studies were not designed to address harms; variability in baseline 25(OH)D levels, doses of vitamin D treatment, use of calcium co-supplementation, and length of followup	High	Only 7 studies were conducted in the U.S. and only 3 of these U.S. studies reported populations having a significant percentage of non-white participants	Vitamin D treatment (with or without calcium) was not associated with increased adverse events
Key Question 4a. Are there differences in adverse effects between patient subgroups (subgroups defined by risk factors for vitamin D deficiency such as age 65 years or older; sex; race-ethnicity; body mass index; UV exposure; institutionalized status)?					
No studies	NA	NA	NA	NA	NA

* Includes two poor-quality trials.

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized, controlled trial; RR = risk ratio; U.S. = United States; UV = ultraviolet.

Contextual Question 1. What is the Association Between Serum 25(OH)D Levels and Health Outcomes?

The association between serum 25-hydroxyvitamin D (25(OH)D) levels and health outcomes has been evaluated in several studies (**Table 1**). For this contextual question, we included prospective cohort and nested case-control studies or systematic reviews that examined the association between pre-disease state 25(OH)D levels and health outcome, to avoid the problem of reverse causation or the health outcome influencing the 25(OH)D level (e.g., through changes in sun exposure or diet). We included studies that reported on the following health outcomes: mortality, cancer, fractures, falls, cardiovascular disease, diabetes, depression, cognitive function, and functional status.

Mortality

A 2009 Agency for Healthcare Research and Quality (AHRQ) review (not for the U.S. Preventive Services Task Force [USPSTF]) included four cohort studies on the association between 25(OH)D levels and subsequent mortality. The highest quality study found a significant trend for lower odds of death with increasing 25(OH)D concentrations, although there was a suggestion of a U-shaped relationship; the three other cohort studies did not find any association between 25(OH)D level and mortality risk.

A 2012 meta-analysis of 11 prospective cohort studies concluded that as 25(OH)D levels increased, there was a nonlinear decline in mortality risk with levels between 30 and 35 ng/mL being most clearly associated with a decreased mortality risk.[1] Similarly, three studies published soon after the review concluded that both low and high 25(OH)D levels were associated with an increased risk of mortality,[2-4] with optimal 25(OH)D level ranging from 20 to 40 ng/mL.[2-5] However, two 2014 systematic reviews of 31 to 73 studies concluded that lower 25(OH)D levels were associated with a significantly increased risk of death but did not describe a U-shaped association.[6,7] A 2014 umbrella review of 107 systematic reviews and 74 meta-analyses of observational studies stated there was not enough evidence to make conclusions about the association between vitamin D levels and mortality.[8]

In two studies that had a large enough non-white population to examine the association by race, lower 25(OH)D levels were associated with increased mortality risk in blacks.[5,9]

Cancer

We examined the 2011 systematic review and meta-analysis conducted for the USPSTF that included studies on the association between 25(OH)D levels and colorectal, breast, and prostate cancer through July 2011.[10] We also reviewed other meta-analyses and research conducted since 2011.

Colorectal Cancer

The 2011 USPSTF review reported an association between higher 25(OH)D concentrations and decreased risk of colorectal cancer in a meta-analysis of eight fair-quality nested case-control studies.[10] For each 4 ng/mL increase in blood 25(OH)D concentration, there was a 6 percent (95% confidence interval [CI], 3 to 9%) reduced risk for colorectal cancer. The direction of the association is consistent with other systematic evidence reviews, including two 2014 evidence reviews [6,8] and one conducted by the International Agency for Research on Cancer (IARC), although the magnitude of the effect was smaller; other meta-analyses have noted an increase of 10 to 20 ng/mL in 25(OH)D level decreased the risk of colorectal cancer by 15 to 50 percent, respectively.[11,12] When evaluated by 25(OH)D level, meta-analyses have shown that individuals in the highest quartile or quintile of 25(OH)D have about one-third to one-half the risk of developing colorectal cancer as those in the lowest group.[6,13-15] In its 2008 report on vitamin D and cancer, the IARC working group concluded that the dose-response was fairly linear up to a 25(OH)D level of 35 to 40 ng/mL. Some, but not all,[8] studies suggest that the association might be stronger in rectal rather than colon cancer but the numbers have been too small to draw any firm conclusions.[15]

Breast Cancer

Four meta-analyses, including the 2011 USPSTF review, have not found evidence of an association between 25(OH)D level and breast cancer risk in prospective studies.[6,8,10,16,17] Similarly, a nested case-control study not included in these meta-analyses, did not find an association between 25(OH)D levels and breast cancer in predominantly premenopausal women.[18]

Prostate Cancer

No association was reported between 25(OH)D level and risk of prostate cancer in systematic reviews and meta-analyses of prospective studies, including the 2011 USPSTF review.[6,8,10,11,16]

Pancreatic Cancer

No association between 25(OH)D level and pancreatic cancer risk was noted in two meta-analyses of prospective studies.[11,16] Both meta-analyses noted that several individual studies had observed a U-shaped association between 25(OH)D levels and pancreatic cancer, with both low and high 25(OH)D levels increasing risk of pancreatic cancer. One 2014 evidence review concluded that higher 25(OH)D levels were associated with a 24 percent increased risk of pancreatic cancer,[6] but a different systematic review concluded data were inconsistent about whether high 25(OH)D levels were associated with an increased risk of pancreatic cancer.[8]

Other Cancers

Two 2014 systematic reviews did not conclude that 25(OH)D levels were associated with risk of other cancers including esophageal and gastric, ovarian, endometrial, bladder and kidney cancer, or non-Hodgkin lymphoma.[6,8]

Fracture

A 2009 AHRQ review examined the association between 25(OH)D level and fracture risk.[19] Citing a 2007 evidence review conducted by the Ottawa Evidence-based Practice Center (EPC), the 2009 review concluded that evidence for an association between serum 25(OH)D concentrations and fracture risk was inconsistent.

While prospective studies published since the 2009 review have generally shown that lower 25(OH)D levels were associated with increased fracture risk, a recent 2014 umbrella study of systematic reviews and meta-analyses of observational studies concluded evidence was suggestive only for non-vertebral fractures and that no conclusions could be reached about other fractures.[8] Prospective studies finding an association have generally reported that risk increases at 25(OH)D levels less than 20 ng/mL in persons of Caucasian or European descent. The largest and most recent study, a prospective case-cohort study of more than 21,774 person from Norway (1,175 hip fractures), reported an inverse association between 25(OH)D level and hip fracture; those in the lowest quartile (<17 ng/mL) had a 38 percent increased risk of fracture compared with those with 25(OH)D levels greater than 27 ng/mL.[20] Similarly, two smaller Scandinavian studies found increased risk of any fracture when 25(OH)D level was below 13 to 16 ng/mL.[21,22]

In the United States, studies that have found associations between 25(OH)D and fracture risk have been done in older white men and women. In these studies, an increased risk of hip fracture occurred when 25(OH)D levels dropped below 18 to 24 ng/mL.[23-25] A 25(OH)D level of 30 ng/mL or greater was associated with a decreased risk of fracture in the Women's Health Initiative (WHI) trial,[26] but not in the National Health and Nutrition Examination Survey (NHANES) data.[24] An association between 25(OH)D level and fracture may not exist in non-white races. In the WHI trial, black women actually had a higher fracture risk at 25(OH)D levels greater than 20 ng/mL and Asians had higher risk when levels exceeded 30 ng/mL. In Hispanic and Native American women, there was no association between 25(OH)D level and fracture risk.[26] In the Health ABC study in which more than 40 percent of participants were black, there was no clear association between 25(OH)D and fracture risk, although the number of fractures in the study was low.[27]

Based on these data as well as the optimal level of 25(OH)D necessary to maximally suppress parathyroid hormone[28-32] and maximize calcium absorption,[33,34] experts generally agree that levels lower than 20 ng/mL are suboptimal for skeletal health. However, there is not general consensus about whether goal 25(OH)D levels should be higher than 20 ng/mL to protect the skeleton. The Institute of Medicine (IOM) contends that 25(OH)D concentrations above 20 ng/mL[35] are sufficient for optimal bone health. Other expert bodies like the Endocrine Society, National Osteoporosis Foundation, International Osteoporosis Foundation, suggest that 25(OH)D levels should be higher, at least 30 ng/mL, particularly in older adults.[36-40]

Falls

Appendix A1. Detailed Information on the Association Between 25(OH)D Levels and Health Outcomes

A 2009 AHRQ review cited the conclusions of a 2007 Ottawa EPC review that there was fair evidence of an association between lower serum 25(OH)D concentrations and an increased risk of falls in institutionalized elderly.[19,41] One study suggested a serum 25(OH)D concentration below 16 ng/mL was associated with an increased risk of falls. We identified one additional study published on this association since 2007. In that study of community-dwelling people, 25(OH)D levels less than 20 ng/mL were associated with increased falls in men, but not in women.[42] Of note, the one study in the 2007 Ottawa EPC review that did not find an association between 25(OH)D level and fall risk was conducted among community-dwelling women.[43] A recent 2014 umbrella analysis of systematic reviews and meta-analysis stated that evidence was inconsistent and no conclusions that could be reached about the association between lower 25(OH)D levels and fall risk; instead, the evidence was suggestive that high 25(OH)D levels are actually linked to an increased rate of falls.[8]

Cardiovascular Disease

A 2009 AHRQ review identified four prospective studies on the association between serum 25(OH)D concentrations and cardiovascular outcomes (cardiovascular events, nonfatal myocardial infarction or fatal coronary heart disease, cardiovascular death, myocardial infarction, and stroke). Results were mixed; two studies noted that levels less than 15 ng/mL were generally associated with increased cardiovascular risk, but the other two studies did not report an association.[19]

Since the 2009 AHRQ review, multiple studies on this association have been published. Recent evidence reviews and meta-analyses have concluded that among largely white or entirely white participants with 25(OH)D levels less than 24 ng/mL, lower levels may be associated with an increased risk of incident cardiovascular disease.[6,8,44-46] The association between 25(OH)D levels greater than 24 ng/mL and cardiovascular disease is not clear. Meta-analyses of seven prospective studies found that lower levels (<12 ng/mL) of 25(OH)D were associated with an increased risk of developing stroke compared with higher levels (>19 ng/mL).[6,8,47]

These associations may differ by race/ethnicity; in a recent study, lower 25(OH)D was not associated with a greater risk of incident coronary heart disease among blacks, although it was associated with cardiovascular risk among white and Chinese participants.[48] Similarly, a recent cohort study did not find that 25(OH)D levels were associated with stroke risk in blacks.[49]

Diabetes

A 2014 umbrella analysis of systematic reviews and meta-analysis concluded the evidence was suggestive for an association between 25(OH)D and diabetes risk.[8] A 2013 meta-analysis concluded that each 4 ng/mL increment in 25(OH)D was associated with a 4% decreased risk of diabetes.[50] Individual studies generally found that risk of diabetes increased in the lowest (generally less than 10-20 ng/mL) versus highest quartile or quintile of 25(OH)D. [51-58]

Depression

Two 2014 systematic reviews concluded that evidence was suggestive of a decreased risk of depression and mood disorders with high 25(OH)D concentrations.[6,8] In two prospective studies, optimal 25(OH)D levels were between 21 to 34 ng/mL..[59,60]

Cognitive Function

Two large 2014 systematic evidence reviews concluded evidence was suggestive of an association between high 25(OH)D levels and a decreased risk of cognitive decline.[6,8] A study conducted in Italian men and women found that levels less than 10 ng/mL were associated with an increased risk of cognitive decline on the Mini Mental State Examination (MMSE) versus those with a level greater than 30 ng/mL.[61] The association may vary by sex. In older American women, 25(OH)D levels less than 20 ng/mL were associated with a higher risk of incident global cognitive decline as measured by the MMSE compared with women with levels greater than 30 ng/mL.[62] However, the association was not seen in older American men.[63]

Functional Status

Results from prospective studies of community-dwelling older persons from a range of racial backgrounds (from 100% European to 50% black) are mixed.[6] Baseline 25(OH)D levels less than 20 ng/mL were associated with greater decreases in physical function measures after 3 to 6 years in some,[64-66] but not other studies.[67,68] Vitamin D deficiency was not associated with a greater risk of developing activities of daily living disability over 3 years.[65]

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Contextual Question 2. What are the Risk Factors Associated With Vitamin D Deficiency?

In the United States, the main dietary sources of vitamin D are fortified foods such as milk, milk products and cereals, as well as supplements; naturally occurring foods that contain vitamin D include fatty fish, egg yolk, and mushrooms. In large (>750 persons), population based cross-sectional studies in predominantly American populations,[1-4] low dietary vitamin D intake and/or lack of vitamin D supplements are associated with a 2- to 5-fold increased risk of vitamin D deficiency (defined as a 25-hydroxyvitamin D [25(OH)D] level <20 ng/mL).[1-3]

Vitamin D is also obtained through synthesis in the skin in response to ultraviolet B (UVB) radiation. Large population-based studies confirm that low UVB exposure is associated with an increased risk of vitamin D deficiency.[2,4-6] People who have blood drawn for a 25(OH)D level in winter have a two to three times greater risk of being vitamin D deficient than those whose level is evaluated in the fall or summer.[1,2] Avoiding sunlight by staying in the shade/indoors or wearing long sleeves is associated with increased risk of developing vitamin D deficiency.[5] Higher latitude of residence has been modestly associated with vitamin D deficiency.[2,4,5] Sunscreen, although it reduces the skin's ability to produce vitamin D in response to UVB in controlled research settings,[7] is not associated with vitamin D deficiency in population-based studies.[6,8] This discrepancy is likely due to incomplete application of sunscreen[9] and/or subjects who use sunscreen being in the sun for extended periods.[10]

Increased skin pigmentation reduces the skin's ability to produce vitamin D in response to UVB.[10]. When total 25(OH)D levels are used to define deficiency, blacks have a 2- to 9-fold greater risk and Hispanics a 2- to 3- fold greater risk of vitamin D deficiency compared with whites.[1-3] However, a recent study found that compared to white Americans, black Americans had not only lower total 25(OH)D levels but lower vitamin D-binding protein,[11] resulting in similar concentrations of estimated bioavailable 25(OH)D. This recent study has called into question previous reports of higher rates of vitamin D deficiency in blacks.

Aging also reduces the skin's ability to synthesize vitamin D and older adults may also have poor dairy and vitamin D intake and decreased sun exposure. However, studies are inconsistent about whether older age is associated with increased risk of vitamin D deficiency. In a cohort of older men (>65 years), the oldest participants (>85 years) had a 2-fold increased risk of vitamin D deficiency compared with younger men.[2] In cohorts with a smaller percentage of participants over the age of 70 years, the results are mixed with some showing significant associations between risk of vitamin D deficiency and older age,[4,5] and others not.[1,3]

Since vitamin D is stored in adipose tissue, it has been hypothesized that higher adiposity leads to greater sequestration of vitamin D. Also, obese and overweight persons may have lower physical activity levels and lower dietary vitamin D intake.[12] Obesity does appear to confer an almost 2-fold increased risk of being vitamin D deficient.[1-3,13] In addition, since females have a higher percentage of body fat compared with males, they may be at greater risk of vitamin D deficiency than males. In two large cohort studies, females were at increased risk of vitamin D

deficiency versus males.[1,5] However, in the most recent National Health and Nutrition Examination Survey (NHANES) analysis, sex did not influence risk of deficiency.[3]

Other factors have been modestly associated with vitamin D deficiency in some studies but diet, supplement use, and UV exposure may be mediating factors. For example, low physical activity was modestly associated with vitamin D deficiency in three studies.[1,2,4] In NHANES, lower education was associated with an increased risk of deficiency but this was not true in a cohort of older men who had an overall high educational background (75% had college and/or graduate education).[2] Lower health status has also been associated with an increased risk of deficiency in NHANES.[3,6]

Overall, however, these risk factors appear to account for a small percentage of the variation in 25(OH)D levels. In the Women's Health Initiative trial, a predictive model consisting of latitude of residence, total vitamin D intake from foods and supplements, waist circumference, recreational physical activity, and race-ethnicity could only explain 21 percent of the variation in 25(OH)D level.[4] Similarly, in a cohort study of male health professionals, geographic region of residence, skin pigmentation, dietary and supplement intake, body mass index, and physical activity accounted for only 28 percent of the variation in 25(OH)D level.[14]

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Contextual Question 3. What is the Effect of Vitamin D (With or Without Calcium) on Intermediate Outcomes (e.g., Blood Pressure, Bone Mineral Density, Glucose Tolerance, Lipids)?

We examined randomized controlled trials of vitamin D (with or without calcium) versus placebo on the intermediate outcomes of lipids, glucose, blood pressure, bone mineral density (BMD), and physical function/balance in persons with vitamin D deficiency (at least 90% <30 ng/mL).

Lipids

Four studies examining the effects of 400 to 5,700 IU per day of vitamin D treatment on lipid levels in persons with vitamin D insufficiency (most <23 ng/mL) found that vitamin D had no effect on lipid levels compared with placebo.[1-4]

Glucose

Three studies that examined the effects of 400 to 7.143 IU per day of vitamin D treatment found that vitamin D had no effect on glucose levels, insulin levels, insulin sensitivity, or insulin resistance in non-diabetics.[1,4,5]

Blood Pressure

We reviewed three studies examining the effect of vitamin D treatment on blood pressure in patients with vitamin D deficiency.[3,6,7] Two studies, one of elderly (≥70 years of age) women and the other of blacks ages 30 to 80 years, found that 800 to 4,000 IU per day of vitamin D resulted in decreases in systolic but not diastolic blood pressure compared with placebo.[3,7] However, in the Women's Health Initiative (WHI) study, women with vitamin D deficiency who were randomized to 1,000 mg per day of calcium and 400 IU per day of vitamin D did not have a decreased risk of incident hypertension (see main evidence review for discussion of WHI study).[7]

Bone Mineral Density

We identified seven studies that examined the effect of vitamin D treatment on BMD in persons with vitamin D deficiency.[1,2,8-13] In three European studies of older women with severe deficiency (<12 ng/mL), 400 to 800 IU per day of vitamin D (with and without calcium) had mixed results on hip BMD;[8-10] two[9,10] of three studies found less decline at the femoral neck and one[9] of two[9,10] found less decline at the trochanter while the other did not.[8] No study found that vitamin D treatment lead to less decline at the distal radius compared with placebo.[8,10] Postmenopausal black women randomized to 1000 IU per day of vitamin D for 2 years did not

have improved BMD compared to those given placebo.[13] In elderly men, 1,000 IU per day of vitamin D3 and 1,000 mg per day of calcium did not result in less loss of bone mineral content at the radius or vertebra over 3 years.[11] Results in younger, mixed sex populations given 400 to 7,000 IU per day of vitamin D for 26 to 52 weeks did not find significant effects of vitamin D on spine or hip BMD.[1,12] In a recent 2014 meta-analysis of eight studies with populations whose mean 25(OH)D level was less than 20 ng/mL, there was little evidence of an overall benefit of vitamin D supplementation on bone density.[14]

Physical Function/Balance

We reviewed four studies that evaluated the effect of vitamin D treatment on strength[15-18] and one study that examined balance.[19] Among elderly women, 400 to 1,800 IU per day of vitamin D did not improve hand strength,[15,17] leg strength,[15] or balance[19] compared with placebo. In two studies of young (mean age 18-33 years) persons that we examined, deficient (<30 ng/mL) those given large (25,000 to >60,000 IU per week) doses of vitamin D, several strength measures improved more in the vitamin D versus the placebo group.[16,18]

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Appendix B1. Search Strategies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
Search Strategy:
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1 exp Vitamin D/
2 Vitamin D Deficiency/
3 exp Mass Screening/
4 Diagnostic Tests, Routine/
5 3 or 4
6 1 or 2
7 5 and 6
8 ((take or taking or takes or give or giving or prescri$ or provid$ or oral$ or parenteral$ or diet$ or food$ or pill or pills or tablet$) adj5 supplement$ adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$)).mp.
9 (supplement$ adj5 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
10 8 or 9
11 exp Vitamin D/ad, ae, ct, po, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Poisoning, Therapeutic Use, Toxicity]
12 10 or 11
13 2 and 12
14 limit 13 to english language
15 limit 13 to abstracts
16 14 or 15
17 limit 16 to "all adult (19 plus years)"

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
Search Strategy:
---
1 exp vitamin d/
2 vitamin d deficiency/
3 1 or 2
4 exp Mass Screening/
5 Diagnostic Tests, Routine/
6 4 or 5
7 3 and 6
8 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
9 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (hypovitamin$ adj d))).mp.

10 8 or 9
11 3 and 10
12 7 or 11
13 limit 12 to english language
14 limit 12 to abstracts
15 13 or 14
16 limit 15 to "all adult (19 plus years)"
17 exp Epidemiologic Studies/
18 16 and 17
19 limit 16 to (controlled clinical trial or guideline or meta analysis or randomized controlled trial)
20 18 or 19
21 exp "Outcome and Process Assessment (Health Care)"/
22 16 and 21
23 exp Vital Statistics/
24 16 and 23
25 mo.fs.
26 pc.fs.
27 25 or 26
28 16 and 27
29 20 or 22 or 24 or 28

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
2 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 (hypovitamin$ adj d)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 or 2
4 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
5 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 (hypovitamin$ adj d)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 4 or 5

7 ((take or taking or takes or give or giving or prescri$ or provid$ or oral$ or parenteral$ or diet$ or food$ or pill or pills or tablet$) adj5 supplement$ adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$)).mp.
8 (supplement$ adj5 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
9 7 or 8

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
2 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 (hypovitamin$ adj d)).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 or 2
4 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
5 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 (hypovitamin$ adj d)).mp. [mp=title, abstract, full text, keywords, caption text]
6 4 or 5
7 ((take or taking or takes or give or giving or prescri$ or provid$ or oral$ or parenteral$ or diet$ or food$ or pill or pills or tablet$) adj5 supplement$ adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$)).mp.
8 (supplement$ adj5 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
9 7 or 8

Appendix B1. Search Strategies

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:
---
1 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
2 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 (hypovitamin$ adj d)).mp. [mp=title, full text, keywords]
3 1 or 2
4 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
5 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 (hypovitamin$ adj d)).mp. [mp=title, full text, keywords]
6 4 or 5
7 ((take or taking or takes or give or giving or prescri$ or provid$ or oral$ or parenteral$ or diet$ or food$ or pill or pills or tablet$) adj5 supplement$ adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$)).mp.
8 (supplement$ adj5 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
9 7 or 8

Database: EBM Reviews - Health Technology Assessment Search Strategy:
---
1 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
2 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 (hypovitamin$ adj d)).mp. [mp=title, text, subject heading word]
3 1 or 2
4 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 ((((low or lower or circulat$ or

blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
5 ((diagnos$ or detect$ or determin$ or find$ or found or discover$ or identif$ or undiagnos$ or undetect$ or asymptomat$ or preclinical$ or pre-clinical$ or underlying or screen$ or test or tests or testing or tested or assay$ or accura$ or predict$) adj7 (hypovitamin$ adj d)).mp. [mp=title, text, subject heading word]
6 4 or 5
7 ((take or taking or takes or give or giving or prescri$ or provid$ or oral$ or parenteral$ or diet$ or food$ or pill or pills or tablet$) adj5 supplement$ adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$)).mp.
8 (supplement$ adj5 ((((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$ or Calcifediol or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihydrotachysterol$))).mp.
9 7 or 8

Appendix B2. Inclusion and Exclusion Criteria

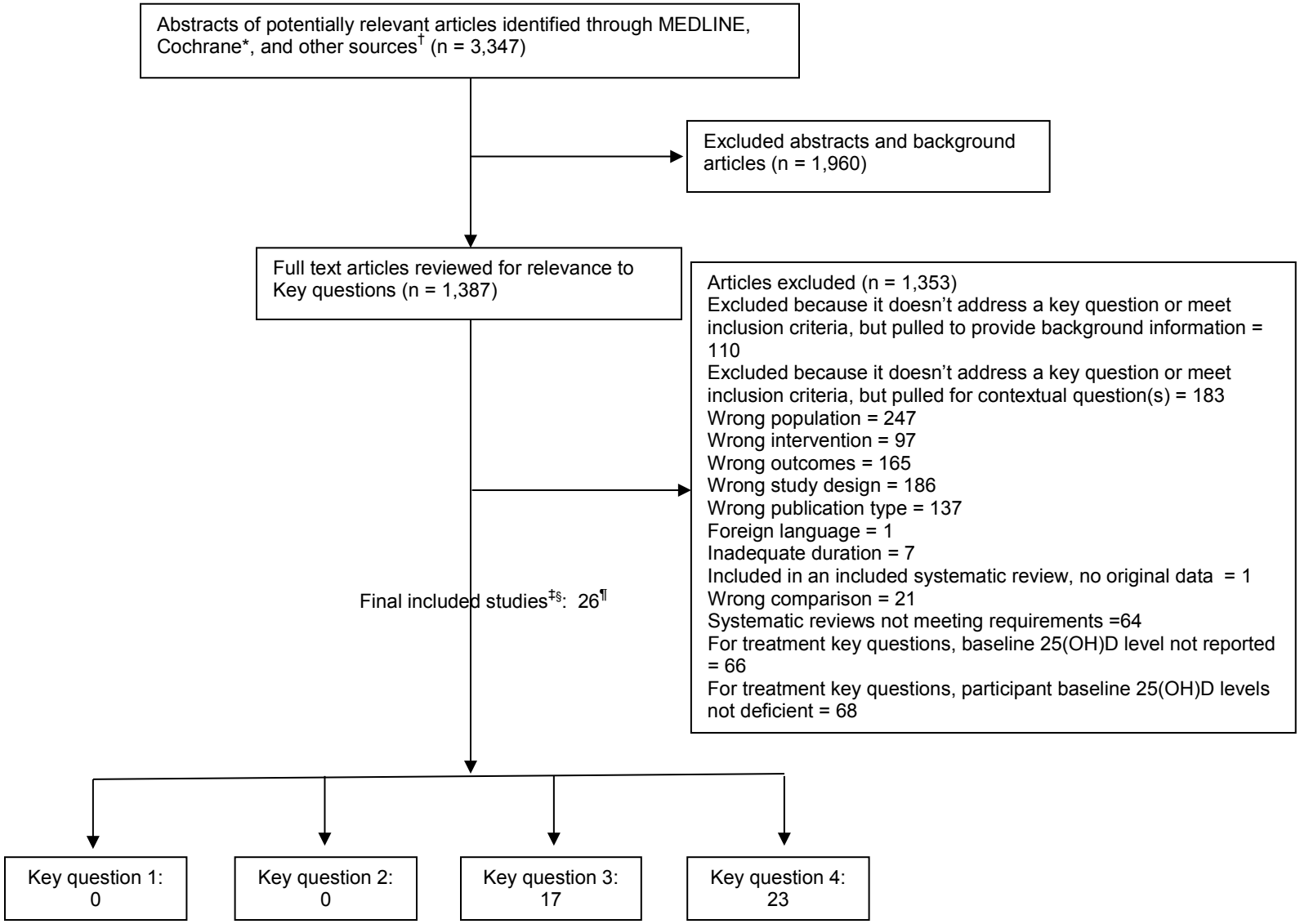
	Include	Exclude
Population	KQ 1, 3: Non-pregnant, adults ≥18 years old who are generally healthy Study participants are either: • Unselected or low-risk, OR • Selected for increased risk of vitamin D deficiency based on certain characteristics including participants who have older age or darker skin pigmentation (black or Hispanic) or are obese or institutionalized KQ 2: Non-pregnant, adults ≥18 years old who are generally healthy Study participants are either: • Unselected or low-risk, OR • Selected for increased risk of vitamin D deficiency KQ 4: Non-pregnant, adults ≥18 years old who are generally healthy with vitamin D deficiency Study participants are either: • Unselected or low-risk, OR • Selected for increased risk of vitamin D deficiency	All KQs: Selected populations with conditions including , clinical signs of vitamin D deficiency, osteoporosis, malabsorption, granuloma forming disorders, CKD, hepatic failure, cancer, CHD, diabetes/glucose intolerance, immune disorders, high-risk of falls, PCOS, multiple sclerosis
Interventions	All KQs: Vitamin D_2 or vitamin D_3 (with or without calcium); food based interventions if dose of vitamin D quantified and differences in doses between comparison groups	All KQs: Non oral routes of vitamin D delivery; dietary intake (unless a food based intervention as described under inclusion criteria); UV light exposure; multivitamins
Comparators	KQ 1, 2: Screening KQ 3, 4: Placebo, no treatment, usual care	KQ 1, 2: No screening KQ 3, 4: Different dosages of vitamin D
Outcomes	KQ 1, 3: Health outcomes include decreased morbidity from osteoporosis/fractures, falls, diabetes mellitus, cardiovascular disease, cancer, immune diseases; Improved depression; improved psychosocial functioning as measured by quality of life instruments; physical fitness capacity or performance; physical functioning as measured by scores on physical subscales of quality of life measures; disability (global measures only, such as activities of daily living); mortality; outcomes reported at ≥8 weeks after start of intervention or the baseline assessment (if the intervention start cannot be determined) (required) KQ 2, 4: Mortality; renal outcomes (e.g., stones); soft tissue calcification; adverse events (e.g., GI issues)	KQ 1, 3: Improved functioning (except as enumerated under health outcomes); intermediate physiological outcomes (examined as contextual question); behavioral changes (e.g., physical activity, diet); outcomes reported <8 weeks after start of the intervention or the baseline assessment (if time from intervention start cannot be determined); baseline vitamin D not reported or baseline vitamin D not deficient KQ 2, 4: None

Appendix B2. Inclusion and Exclusion Criteria

	Include	Exclude
Settings	All KQs: Studies conducted in primary care or feasible for conducting in primary care or feasible for referral from primary care, including institutionalized settings. In order for an intervention to be feasible for primary care *referral*, it would need to be conducted as part of a healthcare setting or be widely available in the community at a national level. U.S., Canada, UK, and other geographic settings generalizable to U.S.	All KQs: Studies performed in countries with populations not similar to the U.S.; studies conducted in schools or work-sites, unless primary-care feasible
Timing	KQ 1, 3: At least 8 weeks KQ 2, 4: Any duration	KQ 1, 3: Less than 8 weeks KQ 2, 4: None
Study types and designs	KQ 1, 3: Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials KQ 2, 4: Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials, and large cohort studies or case-control studies; studies must have an appropriate comparison group	KQ 1, 3: Non-systematic reviews, letters to the editor, cohort or case-control studies, non-comparative studies, and comparative efficacy trials; review not in English KQ 2, 4: Non-systematic reviews, letters to the editor, non-comparative studies, and comparative efficacy trials; review not in English

Abbreviations: CHD = coronary heart disease; CKD = chronic kidney disease; GI = gastrointestinal; KQ = key question; PCOS = polycystic ovary syndrome; UK = United Kingdom; U.S.= United States; UV = ultraviolet.

Appendix B3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, hand searching, suggested by experts, etc.
‡Studies that provided data and contributed to the body of evidence were considered 'included'.
§Studies may have provided data for more than one key question.
¶Studies may have more than one published article, this number indicates the number of unique studies included; there were a total of 34 articles included.

Appendix B4. Excluded Studies List

Key to exclusion codes

2	Excluded because it doesn't address a key question or meet inclusion criteria, but pulled to provide background information
3	Excluded because it doesn't address a key question or meet inclusion criteria, but pulled for contextual question(s)
4	Wrong population
5	Wrong intervention
6	Wrong outcomes
7	Wrong study design for key question
8	Wrong publication type
9	Foreign language
10	Inadequate duration
11	Included in an included systematic review, no original data
12	Wrong comparison
13	Systematic review not meeting our requirements
14	For treatment key questions, baseline 25(OH)D level not reported
15	For treatment key questions, participant baseline 25(OH)D levels not deficient

List of excluded studies

Check your vitamin D intake to avoid multiple health consequences. Three 2008 studies link low vitamin D levels to depression, hip fractures, and increased risk of death. *Duke Med Health News.* 2008;14(11):9-10
Exclusion code: 8

Do low vitamin D levels increase risk for hip fracture?.[Original report in Ann Intern Med. 2008 Aug 19;149(4):242-50; PMID: 18711154]. *Ann Intern Med.* 2008;149(4):I42
Exclusion code: 8

Study shows monthly vitamin D supplement effective in older women. *Mayo Clin Womens Healthsource.* 2009;13(5):3
Exclusion code: 8

Extra vitamin D may keep you mobile in later years. *Harv Health Lett.* 2012;37(10):8
Exclusion code: 8

Abbas S, Chang-Claude J, Linseisen J. Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study. *Int J Cancer.* 2009;124(1):250-255
Exclusion code: 6

Abbas S, Linseisen J, Chang-Claude J. Dietary vitamin D and calcium intake and premenopausal breast cancer risk in a German case-control study. *Nutr Cancer.* 2007;59(1):54-61
Exclusion code: 7

Appendix B4. Excluded Studies List

Abbas S, Linseisen J, Slanger T, et al. The Gc2 allele of the vitamin D binding protein is associated with a decreased postmenopausal breast cancer risk, independent of the vitamin D status. *Cancer Epidemiol Biomarkers Prev.* 2008;17(6):1339-1343
Exclusion code: 6

Abbas S, Linseisen J, Slanger T, et al. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer--results of a large case-control study. *Carcinogenesis.* 2008;29(1):93-99
Exclusion code: 6

Abbas S, Nieters A, Linseisen J, et al. Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. *Breast Cancer Res.* 2008;10(2):R31
Exclusion code: 6

Abbasi M, Hashemipour S, Hajmanuchehri F, Kazemifar AM. Is vitamin D deficiency associated with non specific musculoskeletal pain? *Glob J Health Sci.* 2013;5(1):107-111
Exclusion code: 4

Abnet CC, Chen W, Dawsey SM, et al. Serum 25(OH)-vitamin D concentration and risk of esophageal squamous dysplasia. *Cancer Epidemiol Biomarkers Prev.* 2007;16(9):1889-1893
Exclusion code: 7

Abnet CC, Chen Y, Chow W-H, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):94-106
Exclusion code: 4

Abrahamsen B, Masud T, Avenell A, et al. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ (Online).* 2010;340(7738):139
Exclusion code: 6

Abrams SA, Hicks PD, Hawthorne KM. Higher serum 25-hydroxyvitamin D levels in school-age children are inconsistently associated with increased calcium absorption. *J Clin Endocrinol Metab.* 2009;94(7):2421-2427
Exclusion code: 4

Abu-Mouch S, Fireman Z, Jarchovsky J, Zeina A-R, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naive patients. *World J Gastroenterol.* 2011;17(47):5184-5190
Exclusion code: 6

Adams JS, Hewison M. Hypercalcemia caused by granuloma-forming disorders. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 6 ed. Washington, D.C.: American Society for Bone and Mineral Research; 2006:200-202
Exclusion code: 8

Adams JS, Lee G. Gains in bone mineral density with resolution of vitamin D intoxication. *Ann Intern Med.* 1997;127(3):203-206
Exclusion code: 15

Adams JS, Modlin RL, Diz MM, Barnes PF. Potentiation of the macrophage 25-hydroxyvitamin D-1-hydroxylation reaction by human tuberculous pleural effusion fluid. *J Clin Endocrinol Metab.* 1989;69(2):457-460
Exclusion code: 4

Afzal S, Nordestgaard BG, Bojesen SE. Plasma 25-hydroxyvitamin D and risk of non-melanoma and melanoma skin cancer: a prospective cohort study. *J Invest Dermatol.* 2013;133(3):629-636
Exclusion code: 3

Agborsangaya CB, Surcel H-M, Toriola AT, et al. Serum 25-hydroxyvitamin D at pregnancy and risk of breast cancer in a prospective study. *Eur J Cancer.* 2010;46(3):467-470
Exclusion code: 4

Ahn J, Peters U, Albanes D, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst.* 2008;100(11):796-804
Exclusion code: 7

Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control.* 2000;11(9):847-852
Exclusion code: 3

Akhter N, Sinnott B, Mahmood K, Rao S, Kukreja S, Barengolts E. Effects of vitamin D insufficiency on bone mineral density in African American men. *Osteoporos Int.* 2009;20(5):745-750
Exclusion code: 6

Aksnes L, Aarskog D. Plasma concentrations of vitamin D metabolites in puberty: Effect of sexual maturation and implications for growth. *J Clin Endocrinol Metab.* 1982;55(1):94-101
Exclusion code: 4

Ala-Houhala M, Koskinen T, Koskinen M, Visakorpi JK. Double blind study on the need for vitamin D supplementation in prepubertal children. *Acta Paediatr Scand.* 1988;77(1):89-93
Exclusion code: 4

Albanes D, Mondul AM, Yu K, et al. Serum 25-hydroxy vitamin D and prostate cancer risk in a large nested case-control study. *Cancer Epidemiol Biomarkers Prev.* 2011;20(9):1850-1860
Exclusion code: 4

Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. *Am J Clin Nutr.* 2003;77(4):814-818
Exclusion code: 5

Alele JD, Luttrell LM, Hollis BW, Luttrell DK, Hunt KJ, Group VS. Relationship between vitamin D status and incidence of vascular events in the Veterans Affairs Diabetes Trial. *Atherosclerosis.* 2013;228(2):502-507
Exclusion code: 4

Allali F, El Aichaoui S, Saoud B, Maaroufi H, Abouqal R, Hajjaj-Hassouni N. The impact of clothing style on bone mineral density among post menopausal women in Morocco: a case-control study. *BMC Public Health.* 2006;6:135
Exclusion code: 5

Allen SH, Shah JH. Calcinosis and metastatic calcification due to vitamin D intoxication. A case report and review. *Horm Res.* 1992;37(1-2):68-77
Exclusion code: 7

Almquist M, Bondeson AG, Bondeson L, Malm J, Manjer J. Serum levels of vitamin D, PTH and calcium and breast cancer risk-a prospective nested case-control study. *Int J Cancer.* 2010;127(9):2159-2168
Exclusion code: 6

Al-oanzi ZH, Tuck SP, Raj N, et al. Assessment of vitamin D status in male osteoporosis. *Clin Chem.* 2006;52(2):248-254
Exclusion code: 7

Aloia J, Bojadzievski T, Yusupov E, et al. The relative influence of calcium intake and vitamin D status on serum parathyroid hormone and bone turnover biomarkers in a double-blind, placebo-controlled parallel group, longitudinal factorial design. *J Clin Endocrinol Metab.* 2010;95(7):3216-3224
Exclusion code: 15

Aloia JF. African Americans, 25-hydroxyvitamin D, and osteoporosis: a paradox. *Am J Clin Nutr.* 2008;88(2):545S-550S
Exclusion code: 2

Aloia JF. Clinical Review: The 2011 report on dietary reference intake for vitamin D: where do we go from here? *J Clin Endocrinol Metab.* 2011;96(10):2987-2996
Exclusion code: 8

Aloia JF, Dhaliwal R, Shieh A, et al. Vitamin D supplementation increases calcium absorption without a threshold effect. *Am J Clin Nutr.* 2013
Exclusion code: 15

Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. *Epidemiol Infect.* 2007;135(7):1095-1096; author reply 1097-1098
Exclusion code: 8

Aloia JF, Talwar SA, Pollack S, Feuerman M, Yeh JK. Optimal vitamin D status and serum parathyroid hormone concentrations in African American women. *Am J Clin Nutr.* 2006;84(3):602-609
Exclusion code: 6

Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of postmenopausal osteoporosis. *Am J Med.* 1988;84(3 PART 1):401-408
Exclusion code: 4

Aloia JF, Vaswani A, Yeh JK, Ross PL, Flaster E, Dilmanian FA. Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. *Ann Intern Med.* 1994;120(2):97-103
Exclusion code: 5

Ameri P, Bovio M, Murialdo G. Treatment for vitamin D deficiency: here and there do not mean everywhere. *Eur J Nutr.* 2012;51(2):257-259; author reply 255-256
Exclusion code: 8

American Society for Clinical Pathology. Choosing Wisely. Chicago, IL 2012
Exclusion code: 2

Amir E, Cecchini RS, Ganz PA, et al. 25-Hydroxy vitamin-D, obesity, and associated variables as predictors of breast cancer risk and tamoxifen benefit in NSABP-P1. *Breast Cancer Res Treat.* 2012;133(3):1077-1088
Exclusion code: 4

Amir E, Simmons CE, Freedman OC, et al. A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D(3) in breast cancer patients with bone metastases. *Cancer.* 2010;116(2):284-291
Exclusion code: 4

Amrein K, Sourij H, Wagner G, et al. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study. *Crit Care.* 2011;15(2):R104
Exclusion code: 4

Anagnostis P, Athyros VG, Adamidou F, Florentin M, Karagiannis A. Vitamin D and cardiovascular disease: a novel agent for reducing cardiovascular risk? *Curr Vasc Pharmacol.* 2010;8(5):720-730
Exclusion code: 7

Andersen R, Brot C, Mejborn H, et al. Vitamin D supplementation does not affect serum lipids and lipoproteins in Pakistani immigrants. *Eur J Clin Nutr.* 2009;63(9):1150-1153
Exclusion code: 3

Andersen R, Molgaard C, Skovgaard LT, et al. Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study. *Br J Nutr.* 2008;100(1):197-207
Exclusion code: 2

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Exclusion code: 7

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Exclusion code: 4

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Zwart SR, Parsons H, Kimlin M, Innis SM, Locke JP, Smith SM. A 250 mug/week dose of vitamin D was as effective as a 50 mug/d dose in healthy adults, but a regimen of four weekly followed by monthly doses of 1250 mug raised the risk of hypercalciuria. *Br J Nutr.* 2013;110(10):1866-1872
Exclusion code: 15

Randomized, Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups**:**
  - for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up 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

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup at least 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 to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below. Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; 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 done for RCTs.

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

Sources: USPSTF Procedure Manual[148]

Expert Reviewers

John F. Aloia, MD Director, Winthrop Bone Mineral Research Center, Mineola, NY; Chief Academic Officer, Winthrop University Hospital, Mineola, NY; Associate Dean, Professor of Medicine, State University of New York at Stony Brook

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Catherine Witkop MD, MPH Chief, Preventive Medicine, Air Force, Military Health Service

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
≥90% of study participants had 25(OH)D level <20 ng/mL						
Brazier, *et al.*, 2005[156] *Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study*	Mean age (years): 74.6 (74.2 vs. 75.0) Female: 100% Race: NR BMI: NR Co-morbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 736 (752 vs. 721)	France 50 centers Institutionalized: 0%	Inclusion: Community-dwelling ambulatory women ages >65 years who spontaneously consulted a practitioner and presented with vitamin D insufficiency. Exclusion: Hypercalcemia, primary hyperparathyroidism, renal insufficiency, or hepatic insufficiency; taken bisphosphonate, calcitonin, vitamin D or its metabolites, estrogen, raloxifene, fluoride, anticonvulsives, or any other treatment acting on bone metabolism in the past 6 months.	Competitive protein-binding assay	Insufficiency: serum 25(OH)D ≤12	7 vs. 7 100% <20
Chapuy, *et al.*, 2002[122] *Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The Decalyos II Study*	Mean age‡ (years): 85 (84.9† vs. 85.7) Female‡: 100% Race‡: NR Mean weight (kg): 59.2† (58.9† vs. 59.9) Mean height (cm): 155 (155 vs. 155) Falls in 3 months prior to randomization (%): 16.1† (16.3† vs. 15.8) Use of walking device (%): 40.7†(41.2† vs. 39.5†) Mean dietary calcium intake at baseline: 557.7 mg/day	France Homes for the elderly Institutionalized: 100%	Inclusion: Elderly women living in apartment houses for the elderly who were ambulatory (able to walk indoors with cane or walker) and had a life expectancy ≥24 months. Exclusion: Women with intestinal malabsorption, hypercalcemia, or chronic renal failure; women who had received drugs known to alter bone metabolism like corticosteroids, anticonvulsants, or high dose thyroxine within the previous year; women who had been treated with	Competitive-binding protein assay	Not specifically defined	9.2 vs. 9.2 100% <20

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			fluoride salts (>3 months), bisphosphonates, calcitonin (>1 month), calcium (>500 mg/day), and vitamin D (>100 IU/day) during the previous 12 months.			
Gallagher, *et al*., 2013[159] *Effects of vitamin D supplementation in older African American women*	Mean age (years): 67 Female: 100% Race: 100% Black Mean BMI (kg/m^2): 32.7 Co-morbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 551	Indiana and Nebraska University medical center; community recruitment Institutionalized: NR	Inclusion: Healthy, postmenopausal white and black women ages 57 to 90 years who were ≥7 years postmenopausal with vitamin D insufficiency. Exclusion: Substantial comorbid conditions; any history of nonskin cancer in last 10 years; terminal illness; previous hip fracture; hemiplegia; uncontrolled diabetes with or without significant proteinuria or a fasting blood glucose level <7.8 mmol/L (<140 mg/dL) in persons with type 2 diabetes; active kidney stone disease or a history of kidney stones >twice in lifetime; chronic renal failure; evidence of chronic liver disease, including alcoholism; physical conditions such as rheumatoid arthritis, osteoarthritis, and heart failure, severe enough to prevent reasonable physical activity; unwillingness to	Radioimmuno assay	Insufficiency: serum 25(OH)D ≤20	Overall: 13 Placebo: 14 Vitamin D 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14 NR for 400, 3600 or 4000 IU groups

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			discontinue therapy with vitamin D supplements after entering the study; 25(OH)D level <5 ng/mL or >20 ng/mL; BMI >45 kg/m2; serum calcium level >2.57 mmol/L (>10.3 mg/dL) on 2 baseline tests; 24-hour urinary calcium level >7.3 mmol/day (>290 mg/day) on 2 baseline tests; BMD T-score <-3 at the spine or hip; current use of bisphosphonates or prior use for >3 months; use of fluoride, PTH, or PTH derivatives in the past 6 months; use of calcitonin or estrogen in the past 6 months; current use of phenytoin or phenobarbital, high-dose thiazide therapy, or any drugs interfering with vitamin D metabolism; or inability to give informed consent.			

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
Gallagher, *et al.*, 2014[158] *Vitamin D Supplementation in Young White and African American Women*	Mean age (years): 36.7 Female: 100% Race: 60% White, 40% Black Mean BMI (kg/m^2): 30.2 Co-morbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 655	Nebraska University medical center; community recruitment Institutionalized: NR	Inclusion: Women ages 25 to 45 years old with vitamin D insufficiency Exclusion: Pregnant; significant co-morbidities; history of cancer except skin cancer within last 10 years; uncontrolled type I diabetes +/- significant proteinuria or fasting blood sugar >140 mg in type II diabetes; active kidney stones disease or history of kidney stones more than two times previously; chronic renal failure; evidence of chronic liver disease; alcoholism; severe vitamin D deficiency (serum 25(OH)D level <5 ng/mL, BMI >45 kg/m2; serum calcium level >2.57 mmol/L (>10.3 mg/dL) on 2 baseline tests; 24-hour urinary calcium level >7.3 mmol/day (>290 mg/day) on 2 baseline tests; BMD T-score <-3 at the spine or hip (specific to race); use of bone active drugs: 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	Radioimmuno assay	Insufficiency: serum 25(OH)D ≤20	Overall: 13.4 Placebo: 12.7 Vitamin D 400 IU: 13.1 800 IU: 13.8 1600 IU: 13.3 2400 IU: 14.1

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			(>37.5 mg/d)			
Grimnes, *et al.*, 2011[157] *Vitamin D, insulin secretion, sensitivity, and lipids. Results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique*	Mean age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) Race: NR Mean BMI (kg/m^2): 26.5 (27.2 vs. 26.3) Co-morbidities: NR History of falls: NR Mean dairy servings at baseline: 16/week	Norway Community Institutionalized: 0%	Inclusion: Ages 30 to 75 years with serum 25(OH)D between the 5th and 10th percentiles. Exclusion: Current smokers, diabetes, acute MI or stroke during the past 12 months, cancer during the past 5 years, steroid use, serum creatinine ≥130 µmol/L (males) or ≥110 µmol/L (females), possible primary hyperparathyroidism (plasma PTH >5.0 pmol/L combined with serum calcium >2.50 mmol/L), sarcoidosis, SBP >175 mmHg or DBP >105 mmHG, pregnancy, lactation, or fertile age and no contraception use.	Liquid chromatography double mass spectrometry	Low: serum 25(OH)D <17	17 vs. 16 100% <17

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
Janssen, *et al.,* 2010[127] *Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation*	Mean age (years): 80.8† (82.4 vs. 79.2) Female: 100% Race: NR Mean BMI (kg/m^2): 26.4† (26.2 vs. 26.7) Number of co-morbidities: 2.4† (2.7 vs. 2.1) Number of medications used: 5.0† (5.2 vs. 4.8) History of falls: NR Calcium intake: NR	Netherlands Outpatient clinics Institutionalized: most women lived in residential homes for the elderly, numbers NR	Inclusion: Ambulatory women ages >65 years, able to follow simple instructions, and a serum 25(OH)D level between 8 and 20 ng/mL. Exclusion: Treatment with vitamin D or steroids in the previous 6 months; history of hypercalcemia or renal stones, liver cirrhosis, serum creatinine >200 μmol/L, malabsorptive bowel syndrome, primary hyperparathyroidism, uncontrolled thyroid disease, anticonvulsant drug therapy, and/or presence of any other condition that would interfere with compliance.	NR	Insufficiency: serum 25(OH)D 8 to 20	13 vs. 14 90% <19
Lips, *et al.,* 2010[154] *Once-weekly dose of 8400 IU vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency*	Mean age (years): 78 (78.5 vs. 77.6) Female: NR Race: NR Mean BMI (kg/m^2): 27.8† (27.4 vs. 28.2) Co-morbidities: NR Use of walking device: 15% History of falls: NR Calcium intake: NR	Netherlands, Germany, Wisconsin, Nebraska, New Jersey, Pennsylvania Medical centers and nursing homes Institutionalized: 14%	Inclusion: Ambulatory men and women ages ≥70 years old who were vitamin D insufficient and mentally competent. Exclusion: Primary hyperparathyroidism, active thyroid disease, impaired renal function, osteomalacia, neurologic impairment, peripheral neuropathy, MI within 6 months, uncontrolled HTN, postural hypotension, malabsorption syndrome, alcohol abuse, or cancer; use of oral glucocorticoids, anabolic steroids, or growth	Reverse phase high performance liquid chomatography Lab participates in DEQAS	Insufficiency: serum 25(OH)D 6 to 20	14 vs. 14 100% <20

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			hormone within 12 months, treated with >800 IU vitamin D/day or with active metabolites of vitamin D within 6 months, treatment with drug that might affect vitamin D metabolism or interfere with postural stability.			
Pfeifer, *et al.,* 2000[161] *Effects of a short-term Vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women*	Mean age (years): 74.8† (74.8 vs. 74.7) Female: 100% Race: NR Mean BMI (kg/m^2): 25.5† (25.5 vs. 25.4) Co-morbidities: 39% cardiovascular; 12% central nervous, neurological; <1% psychiatric; 22% musculoskeletal Concomitant medication: 2.8% benzodiazepine use; 13.6% thyroidotherapy; 68% cardiovascular drugs History of falls: NR Calcium intake: NR	Germany Population-based Institutionalized: 0%	Inclusion: Healthy ambulatory women ages ≥70 years with serum 25(OH)D level <20 ng/mL. Exclusion: Hypercalcemia or primary hyperparathyroidism; fractures of the extremities from osteoporosis; therapy with bisphosphonate, calcitonin, vitamin D and vitamin D metabolites, estrogen, tamoxifen in the past 6 months, or fluoride in the past 2 years; known intolerance to study medication; chronic renal failure (serum creatinine >20% of upper limit of reference range); history of drug or alcohol abuse; nicotine abuse (>20 cigarettes daily); >7 cups of coffee daily; scheduled holiday along geographic longitude during study period; diabetes mellitus, and other diseases;	Radioimmuno assay	Not specifically defined, but study only included women with serum 25(OH)D <20	10 vs. 10 100% < 20

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			medications possibly interfering with postural stability and balance (specifically, use of anticonvulsants).			
Wamberg, *et al.,* 2013[125] *The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study*Wamberg, *et al.,* 2013[132] *Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - Results from a randomized trial*	Mean age (years): 40.5 (39.5 vs. 41.2) Female: 71% (69% vs. 73%) Race: NR Mean BMI (kg/m^2): 35.8† (36.1 vs. 35.0) Sedentary: 35%† (35% vs. 35%) Lightly active: 48%† (46% vs. 50%) Moderately active: 17%† (19% vs. 15%) Co-morbidities: NR Concomitant medications: 2% (1/55) lipid lowering; 5% (3/55) anti-hypertensive History of falls: NR Mean dietary calcium intake at baseline(mg/day): 992 vs. 936	Denmark University hospital Institutionalized: NR	Inclusion: Healthy males and females ages 18 to 50 years with BMI >30 kg/m^2 and plasma 25(OH)D level <20 ng/mL. Exclusion: Pregnant women or women planning pregnancy; history of diabetes, fasting plasma glucose >7.0 mmol/L, hypercalcemia, or impaired renal or hepatic function; subjects treated with vitamin D within the last 3 months; and history of sarcoidosis, osteomalacia, or alcohol or substance abuse; recent large weight change (+/- 3 kg); and body weight >125 kg.	Isotope dilution liquid chomatography-tandem mass spectrometry	Low: plasma 25(OH)D <20	14 vs. 14 100% <20

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL						
Aloia, *et al.,* 2008[173] *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration*	Mean age (years): 47.2† Female: 81% Black: 45% White: 55% BMI: NR Co-morbidities: NR History of falls: NR Mean dietary calcium intake at baseline: 665 mg/day	New York University hospital Institutionalized: NR	Inclusion: Healthy men and women ages 18 to 65 years. Exclusion: Baseline 25(OH)D >32 ng/mL, morbid obesity, chronic medical conditions (history of nephrolithiasis or hypercalciuria), bone disease (osteoporosis), or taking medications known to interfere with vitamin D metabolism.	Radio-receptor assay Lab participates in DEQAS	Not specifically defined, but study only included participants with 25(OH)D ≤32	Overall: 19 90% ≤30
Arvold, *et al.,* 2009[169] *Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial*	Mean age (years): 58.8† (59.7 vs. 57.8) Female: 40% (44% vs. 36%) White: 95% (96% vs. 95%) BMI: NR Co-morbidities: NR Use of over the counter supplements: 31% (31% vs. 31%) History of falls: NR Weekly milk intake ≥ 1 quart: 48% (46% vs. 50%)	Minnesota Outpatient clinic Institutionalized: 0%	Inclusion: Adult patients with mild to moderate vitamin D deficiency. Exclusion: History of vitamin D deficiency, hypercalcemia, primary hyperparathyroidism, severe renal disease (creatinine >3 mg/dL), or sarcoidosis.	Liquid chromatography-tandem mass spectrometry	Moderately deficient: 10 to 19 Mildly deficient: 20 to 25	18 vs. 18 100% <25
Berlin, *et al.,* 1986[177]** *Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3*	Mean age (years): 31 (range: 22 to 47) Female: 0% Race: NR Co-morbidities: NR History of falls: NR Mean calcium intake estimated to be 800 mg/day based on outside sources (not measured)	Sweden Department of Urology, University hospital Institutionalized: NR	Inclusion: Healthy males. Exclusion: Exposure to drugs containing vitamin D.	Isotope dilution mass spectrometry	NR	15 vs. 15 90% ≤30

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Bischoff, *et al.,* 2003[164] *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*	Mean age (years): 85 (85 vs. 85) Female: 100% Race: NR Mean BMI (kg/m^2): 24.7 (24.7 vs. 24.7) % using walking aid: 60† (58 vs. 62) % with history of falls: 34† (35 vs. 33) % with co-morbidities: 95† (98 vs. 91) % co-morbid fracture at any site: 54.1† (56.5 vs. 51.7) % using ≥ 4 medications: 70.6† (77 vs. 64) Mean dietary calcium intake at baseline (mg/day): 600 to 700	SwitzerlandLong-stay geriatric clinicInstitutionalized: 100%	Inclusion: Women ages ≥60 years being cared for in long-stay geriatric care units; able to walk 3 m with or without a walking aid. Exclusion: Primary hyperparathyroidism; hypocalcaemia; hypercalciuria; renal insufficiency (creatinine >117 μmol/L); fracture or stroke within last 3 months; those who had received treatment with HRT, calcitonin, fluoride, or bisphosphonates during the previous 24 months.	Radioimmuno assay	Not specifically defined by study; refers to different definitions such as how many of their subjects were <12, <31, or <40	Median 12.3 vs. 11.6
Gallagher, *et al.,* 2012[155] *Dose response to vitamin D supplementation in postmenopausal women: a randomized trial*	Mean age (years): 67 Female: 100% White: 100% Mean BMI (kg/m^2): 30.2 Co-morbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 685	Nebraska University medical center Institutionalized: NR	Inclusion: Healthy, postmenopausal white and African American women ages 57 to 90 years who were ≥7 years postmenopausal with vitamin D insufficiency. Exclusion: Substantial comorbid conditions; any history of nonskin cancer in last 10 years; terminal illness; previous hip fracture; hemiplegia; uncontrolled diabetes with or without significant proteinuria or a fasting blood glucose level <7.8 mmol/L (<140 mg/dL) in persons with type 2 diabetes; active kidney	Radioimmuno assay	Insufficiency: serum 25(OH)D ≤20	Overall: 15 Placebo: 15 Vitamin D 400 IU: 15 800 IU: 16 1600 IU: 15 2400 IU: 15 3200 IU: 16 4000 IU: 15 4800 IU: 16 100% ≤ 20

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			stone disease or a history of kidney stones >twice in lifetime; chronic renal failure; evidence of chronic liver disease, including alcoholism; physical conditions such as rheumatoid arthritis, osteoarthritis, and heart failure, severe enough to prevent reasonable physical activity; unwillingness to discontinue therapy with vitamin D supplements after entering the study; 25(OH)D level <5 ng/mL or >20 ng/mL; BMI >45 kg/m^2; serum calcium level >2.57 mmol/L (>10.3 mg/dL) on 2 baseline tests; 24-hour urinary calcium level >7.3 mmol/day (>290 mg/day) on 2 baseline tests; BMD T-score <-3 at the spine or hip; current use of bisphosphonates or prior use for >3 months; use of fluoride, PTH, or PTH derivatives in the past 6 months; use of calcitonin or estrogen in the past 6 months; current use of phenytoin or phenobarbital, high-dose thiazide therapy, or any drugs interfering with vitamin D metabolism; or inability to give informed consent.			

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Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
Harris, *et al.,* 1999[175‡‡] *Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D*	Mean age (years): 31 (range: 22 to 47) Female: 0% Race: NR BMI: NR Co-morbidities: NR History of falls: NR Calcium intake: NR	Massachusetts Tufts University Institutionalized: NR	Inclusion: Men with low vitamin D intakes (<200 IU/day), either younger (ages 20 to 35 years) or older (ages 60 to 75 years). Exclusion: Men who had traveled to southern locations in the previous month; used vitamin D supplement in the previous 6 months or who worked in an outdoor occupation; usual calcium intakes of ≥600 mg/day; use of a calcium supplement in the past 6 months; usual consumption of >3 alcoholic beverages a day; use of medications known to affect vitamin D absorption or metabolism in past year; any history of liver disease, kidney disease, gastrointestinal disease resulting in malabsorption syndrome, gastrointestinal surgery; a kidney stone in the past 5 years; or any current medical condition likely to affect vitamin D absorption or metabolism.	HPLC	Low: <26	Younger men: 13 vs. 17 Older men: 16 vs. 16 90% ≤24

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
Honkanen, *et al.,* 1990[128‡‡] *The necessity and safety of calcium and vitamin D in the elderly*	**Home patients** Mean age (years): 69.5† (69.4 vs. 69.6) Female: 100% Weight (kg): 69.5† (70.7 vs. 68.4) Race: NR BMI: NR Co-morbidities: NR History of falls: NR Dietary calcium intake: NR **Hospital inpatients (institutionalized)** Mean age (years): 82.5† (82.2 vs. 82.8) Female: 100% Weight (kg): 61.8† (62.1 vs. 61.5) Race: NR BMI: NR Co-morbidities: NR History of falls: NR Dietary calcium intake: NR	Finland City hospital Institutionalized (inpatients): 52%	Inclusion: Elderly women ages 67 and 72 years old, living independently at home or geriatric women inpatients aged ≥65 years. Exclusion: Use of calcium and/or vitamin D; trip to south; cancer; kidney disease; other health disorders; trip in Finland; refused to participate; unable to eat or drink without help; and active malignant disease.	NR	NR	Home patients: 17 vs. 15 Hospital inpatients: 10 vs. 10 90% ≤26

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
Karkkainen, *et al.,* 2010[165‡‡] *Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)* Karkkainen, *et al.,* 2010[152‡‡] *Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS)*	Mean age (years): 67.4† (67.4 vs. 67.4) Female: 100 % Race: NR Mean BMI (kg/m^2): 27.5† (27.5 vs. 27.4) Ambulatory: 100% Mean number of prescribed medications: 2.7† (2.8 vs. 2.5) History of falls: NR Baseline use of calcium supplements: 17%† (15% vs. 19%) Total calcium at baseline: 977† mg/day (988 vs. 965)	Finland Population-based Institutionalized: NR	Inclusion: Female members of the OSTPRE cohort born in 1932 to 1941 and ages ≥65 years at the end of November 2001; living in Kuopio province area in Finland at trial onset; not belonging to former OSTPRE bone densitometry sample; subsample with vitamin D levels included a random sample of ambulatory women from the larger study. Exclusion: NR	Radioimmuno assay	NR	20 vs. 20 90% ≤30
Kjaergaard, *et al.,* 2012[170] *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomized clinical trial*	Mean age (years): 53.4† (53.4 vs. 53.3) Female: 56% Race: NR Mean BMI (kg/m^2): 27.7† (27.5 vs. 28.0) Co-morbidities: NR History of falls: NR Mean serum calcium at baseline (mmol/L): 2.28 (2.28 vs. 2.28)	Norway Population-based Institutionalized: NR	Inclusion: Adults ages 30 to 75 years with low serum vitamin D levels from the sixth Tromso study, a population-based cohort study conducted from 2007 to 2008. Exclusion: Participants with a history of known diabetes, coronary heart disease or stroke in past 12 months, cancer, kidney stones, pregnant or lactating women, fertile women <50 years of age not using adequate contraception, those using vitamin D supplements, antidepressants or other mood stabilising	Liquid chromatography with tandem mass spectrometry	Low: <22	19 vs. 19 100% <22

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			medication, those regularly using a solarium, and those planning a trip to a sunny location during the trial period. In addition, participants with possible primary hyperparathyroidism, elevated creatinine, and elevated systolic or diastolic blood pressure, those with high scores on depression scales or serious depression indicated in interview were excluded.			
Krieg, *et al.,* 1999[153‡‡] *Effect of supplementation with vitamin D_3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study*	Mean age (years): 84.5[†] (84 vs. 85) Female: 100% Race: NR Mean BMI (kg/m^2): 24.7[†] (25.7 vs. 23.8; p=0.04) Co-morbidities: NR History of falls: NR Calcium intake: NR	Switzerland Nursing homes Institutionalized: 100%	Inclusion: Women living in 19 nursing homes in the Lausanne area. Exclusion: NR	Protein binding assay	NR	12[§§] vs. 12[§§] 90% ≤ 21
Lehmann, *et al.,* 2013[115] *Bioavailability of vitamin D_2 and D_3 in healthy volunteers, a randomized placebo-controlled trial*	Overall (vitamin D_2 vs. D_3 vs. control) Mean age (years): 33.8[†] (33.2 vs. 35.6 vs. 31.6) Female: 63.5% (67.4% vs. 61.9% vs. 57.9%) Race: NR Mean BMI (kg/m^2): 23.8[†] (23.7 vs. 24.0 vs. 23.7) Co-morbidities: NR History of falls: NR Calcium intake: NR	Norway Healthy community population Institutionalized: NR	Inclusion: Healthy adults. Exclusion: 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.	Liquid chromatography with mass spectrometry	NR	Vitamin D_2 vs. vitamin D_3 vs. control) 15 vs. 18 vs. 16 90% ≤25

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
Lips, *et al.,* 1996[160] *Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial* Ooms, *et al.,* 1995[120] *Prevention of bone loss by vitamin D supplementation in elderly women: A randomized double-blind trial*	Mean age (years): 80.4[†] (80.1 vs. 80.6) Female: 100% Race: NR Mean BMI (kg/m^2): 28.3[†] (28.1 vs. 28.6) Co-morbidities: NR History of falls: NR Median calcium intake at baseline (mg/day): NR (876 vs. 859)	The Netherlands Community Institutionalized: 100%[‖‖]	Inclusion: Elderly people ages ≥70 years; Nonrandom sample of female residents of homes for the elderly and apartments for the elderly who were mobile enough to visit the hospital for BMD measurements three times. Exclusion: History of hip fracture or total hip arthroplasty, and recent history of hypercalcemia, sarcoidosis, or urolithiasis	Competitive protein-binding assay	Not specifically defined	Median: 11 vs. 10 90% ≤20
Martineau, *et al.*, 2007[178] *A single dose of vitamin D enhances immunity to mycobacteria*	Median age[¶¶] (years): 33.7[†] (30.1 vs. 37.5) Female[¶¶]: 51.2%[†] (46.3% vs. 56.2%) Black[¶¶]: 12.9%[†] (10.4% vs. 15.6%) South Asian[¶¶]: 68%[†] (70.1% vs. 67.2%) White[¶¶]: 13.7%[†] (13.4% vs. 14.1%) BMI: NR Co-morbidities: NR History of falls: NR Calcium intake: NR	London, U.K. TB contact clinics Institutionalized: NR	Inclusion: Individuals ages >17 years who had been exposed to a patient with active TB. Exclusion: Had symptoms, clinical signs, or radiographic evidence of active TB; had HIV infection, renal failure, sarcoidosis, or hyperparathyroidism; taking corticosteroids, thiazide diuretics, or supplementary vitamin D; or were breastfeeding or pregnant.	Isotope dilution liquid chomatography-tandem mass spectrometry Lab participates in DEQAS	Deficiency: <8 Insufficiency: <30	14 vs. NR Overall Deficient: 42% (84/192) Overall Insufficient: 94% (189/192)*** 94% <30
Pfeifer, *et al.,* 2009[162] *Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals*	Mean age (years): 76.5 (76 vs. 77) Female: 74.5% (74% vs. 75%) Race: NR Mean BMI (kg/m^2): 27.3 (27.0 vs. 27.5) Co-morbidities: NR History of falls: NR	Austria and Germany Population-based Institutionalized: 0%	Inclusion: Healthy ambulatory women and men ages≥70 years with 25(OH)D serum level <31 ng/mL. Exclusion: Hypercalcemia or primary hyperparathyroidism; fractures of the extremities	Radioimmuno assay	Not specifically defined, but study only included participants with 25(OH)D <31	22 vs. 22 100% <31

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
	Mean baseline nutritional calcium intake (mg/unit time NR): 618 (608 vs. 628)		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 >20% of the upper limit of reference range); history of drug or alcohol abuse; nicotine abuse (>20 cigarettes per day), >7 cups of coffee/day; scheduled holidays along geographic longitude during study period; diabetes mellitus, severe cardiovascular disease.			
Talwar, *et al.,* 2007[176] *Dose response to vitamin D supplementation among postmenopausal African American women* Aloia, *et al.,* 2005[174] *A randomized controlled trial of vitamin D_3 supplementation in African American women*	Mean age (years): 60.5[†] (59.9 vs. 61.2) Female: 100% Black: 100% Mean BMI (kg/m^2): 29 vs. 30 Co-morbidities: NR History of falls: NR Calcium intake: NR	New York Population-based Institutionalized: NR	Inclusion: Healthy postmenopausal black women not receiving HRT. Exclusion: Previous treatment with bone active agents and any medication or illness that affects skeletal metabolism; previous treatment with bisphosphonates or fluoride; use of estrogen, calcitonin, glucocorticoids, androgens, phosphate, anabolic steroids, or >400 IU/day vitamin D 6 months before entry; history of	Radioimmuno assay Lab participates in DEQAS	Deficiency: <30	19 vs. 17 90% ≤29

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			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/day; unexplained weight loss; use of medications known to interfere with calcium or vitamin D absorption or metabolism; severe osteoarthritis or scoliosis that would interfere with bone density assessment of the spine or hip; and participation in weight training or elite athletic training.			
Wood, *et al.,* 2012[135] *Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT*	Overall (vitamin D 400 IU vs. 1000 IU vs. control) Mean age (years): 63.8[†] (63.5 vs. 64.1 vs. 63.9) Female: 100% White: 100% Mean BMI (kg/m^2): 26.7[†] (26.6 vs. 26.8 vs. 26.6) Co-morbidities: NR History of falls: NR Calcium intake: NR	U.K.CommunityInstitutionalized: NR	Inclusion: White postmenopausal women from Aberdeen Prospective Osteoporosis Screening cohort. Exclusion: Pre-existing CVD, diabetes, asthma, malabsorption, hypertensive BP measurements (≥160 mmHg systolic or ≥99 mmHg diastolic), difficulty in swallowing tablets or capsules, taking medications or	HPLC-tandem mass spectrometer	NR	Vitamin D 400 IU vs. 1000 IU vs. control13 vs. 13 vs. 14 90% ≤23

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

Author, Year, Title*	Population Characteristics Reported as: Overall (Vitamin D vs. Control)	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (Ng/Ml)	Mean Baseline 25(OH)D Level Reported as: Vitamin D vs. Control (Ng/Ml)
			supplements known to affect any dependent variable, current smokers, or abnormal blood biochemistry at screening.			

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
≥90% of study participants had 25(OH)D level <20 ng/mL						
Brazier, *et al.,* 2005[156] *Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study*	Median: 29 vs. 11 ≤12 ng/mL 9% vs. 70%; p<0.001	Approached: 360 Screened: NR Eligible: 192 Enrolled: 192 (95 vs. 97) Analyzed: 191 (95 vs. 96)	12 months	18.9% (18/95) vs. 28.9% (28/97) Overall: 24.0% (46/192)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total: 800 IU/day) and 500 mg of calcium BID (total:1000 mg/day) Control: Identical placebo tablet BID
Chapuy, *et al.,* 2002[122] *Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The Decalyos II Study*	Shown in figure; vitamin D groups had significant increase in level from baseline (p=0.0001); placebo group did not have significant increase in level from baseline; in figure, means at followup are 30 and 35 for vitamin D groups and 5 for placebo	Approached: NR Screened: NR Enrolled: 639 (610 randomized) Analyzed: 583 (393 vs. 190)	24 months	28.2† vs. 36.1§ Overall: 30.8% (188/610)	NR (RCT)	Vitamin D: 800 IU of vitamin D_3 daily and 1200 mg of calcium daily Control: Identical placebo daily
Gallagher, *et al*., 2013[159] *Effects of vitamin D supplementation in older African American women*	Shown in figure; dose-response curve predicted that 97.5% of those on 800 IU of vitamin D per day reached a 25(OH)D level >20 ng/mL; vitamin D levels higher in all vitamin D groups individually vs. placebo (p<0.05)	Approached: 526 Screened: 303 Eligible: 108 (303 screened minus 195 ineligible=108, but figure reports 110) Enrolled: 110 (93 [2 to 24 per dosage] vs. 17) Analyzed: 82 (68 vs. 14) for ITT dose reponse analysis; 110 for harms	12 months (NR if mean or median; range NR)	17.2% (16/93) vs. 17.6% (3/17) Overall: 17.3% (19/110)	Primary outcome adjusted for age, BMI, calcium intake, smoking status, alcohol use, average caffeine intake, serum creatinine, and season	Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control: Identical placebo daily *All Participants:* Citracal calcium supplements administered to maintain total calcium intake of 1200 to1400 mg/day

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
Gallagher, *et al.,* 2014[158] *Vitamin D Supplementation in Young White and African American Women*	Shown in figure; dose-response curve predicted that 97.5% of white women on 400 IU of vitamin D per day reached a 25(OH)D level >20 ng/mL; between 800 and 1600 IU of vitamin D per day required in Black women (prediction limit 1200 IU daily)	Approached: 1514 Screened: 558 Eligible: 305 Enrolled: 198 (160 [37 to 42 per dosage] vs. 38) Analyzed: 198 (160 [37 to 42 per dosage] vs. 38)	12 months (NR if mean or median; range NR)	37.5% (60/160) vs. 26.3% (10/38) Overall: 35.4% (70/198)	Primary outcome adjusted for season at baseline, age, BMI category, calcium intake, smoking status, alcohol use, and serum creatinine	Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D^3 daily Control: Identical placebo daily *All Participants:* Citracal calcium supplements administered to maintain total calcium intake of 1000 to1200 mg/day
Grimnes, *et al.,* 2011[157] *Vitamin D, insulin secretion, sensitivity, and lipids. Results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique*	57 vs. 17; p<0.01	Approached: 1028 Screened: 337 Eligible: 172 Enrolled: 104 (51 vs. 53) Analyzed: 104 (51 vs. 52)	6 months	4% (2/51) vs. 15% (8/53) Overall: 10% (10/104)	NR (RCT)	Vitamin D: 20000 IU of vitamin D_3 twice/week (total: 40000 IU/week) Control: Identical placebo twice/week
Janssen, *et al.,* 2010[127] *Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation*	31 vs. 17 ; p<0.001	Approached: NR Screened: NR Eligible: 91 Enrolled: 70 (36 vs. 34) Analyzed: 59 (28 vs. 31)	6 months	22.2% (8/36) vs. 8.8% (3/34) Overall: 15.7% (11/70)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 daily and 500 mg of calcium daily Control: Identical placebo and 500 mg of calcium daily
Lips, *et al.,* 2010[154] *Once-weekly dose of 8400 IU vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency*	26 vs. 12 Mean difference: 13.0; p<0.001	Approached: NR Screened: 593 Enrolled: 226 (114 vs. 112) Analyzed: 226 for AEs, 213 for SPPB measure	16 weeks	7.9% (9/114) vs. 13.4% (15/112) Overall:10.6% (24/226)	Covariance model included terms for baseline body sway, baseline vitamin D stratum, and treatment group	Vitamin D: 2800 IU of vitamin D_3 given in 3 tablets once a week (total: 8400 IU/week) Control: 3 identical placebo tablets once a week *All participants:* Those with daily calcium intake <1000 mg were also given 500 mg calcium

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
Pfeifer, *et al.,* 2000[161] *Effects of a short-term Vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women*	26 vs. 17; p <0.001	Approached: 208 Screened: 165 Eligible: 151 Enrolled: 148 Analyzed: 145 in ITT; 137 for falls (70 vs. 67)	8 weeks treatment 1 year posttreatment followup	5.4% (4/74) vs. 9.5% (7/74) Overall: 7.4% (11/148)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total: 800 IU/day) and 600 mg of calcium BID (total : 1200 mg/day) Control: 600 mg of calcium BID (total: 1200 mg/day)
Wamberg, *et al.,* 2013[125] *The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study* Wamberg, *et al.,* 2013[132] *Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - Results from a randomized trial*	44 vs. 19; p<0.00001; >32: 96% vs. NR >20: 100% vs. 18%	Approached: NR Screened: 88 Eligible: 55 Enrolled: 52 (26 vs. 26) Analyzed for main outcomes¶: 43 (22 vs. 21)	26 weeks	15.4% (4/26) vs. 19.2% (5/26) Overall: 17.3% (9/52)	NR (RCT)	Vitamin D: 1400 IU of vitamin D_3 given 5 times a day (total: 7000 IU/day) Control: Identical placebo tablets given 5 times daily

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL						
Aloia, *et al.,* 2008[173] *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration*	Reported on figure by race and sex; goal of >30 ng/ml achieved by virtually all in active group; also increased by 8 ng/mL in placebo group due to seasonal change	Approached: NR Screened: 262 Eligible: 138 Enrolled: 138 (65 vs. 73) Analyzed: 138	6 months	Overall: 20% (27/138)	NR (RCT)	Vitamin D: Dosage of vitamin D_3 was dependent on 25(OH)D concentrations as follows: Baseline 20 to 32 ng/mL: start at 2000 IU/day Baseline <20 ng/mL: start at 4000 IU/day At followups <20 ng/mL: increase by 2000 IU/day At followups 20 to 32 ng/mL: increase by 2000 IU/day At followups 32 to 56 ng/mL: do not change At followups if >56 ng/mL: decrease by 2000 IU/day (unless current dose was ≤ 2000 IU/day, decrease dose to 800 IU) Mean dose: 3440 IU Control: Identical placebo
Arvold, *et al.,* 2009[169] *Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial*	45 vs. 22	Approached: NR Screened: 610 Eligible: 244 Enrolled: 100 (50 vs. 50) Analyzed: 90 (48 vs. 42)	8 weeks treatment/ followup	4% (2/50) vs. 16% (8/50) Overall: 10% (10/100)	NR (RCT)	Vitamin D: 50000 IU of vitamin D_3 weekly Control: Identical placebo tablet weekly
Berlin, *et al.,* 1986[177]** *Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3*	49 vs. 19; p<0.000001	Approached: NR Screened: NR Eligible: NR Enrolled: 24 (12 vs. 12) Analyzed: 24 (12 vs. 12)	NR, implied 2 months	NR	NR	Vitamin D: 18,000 IU of vitamin D_3 taken 3 times a week in March and April (total: 54000 IU weekly) Control: No intervention

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
Bischoff, *et al.,* 2003[164] *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*	Median 26 vs. 11; p<0.001	Approached: NR Screened: NR Eligible: 130 Enrolled: 124 in pretreatment period; 122 in treatment (62 vs. 60) Analyzed: 122 (62 vs. 60) for falls	6 weeks pretreatment 12 weeks treatment	31% (19/62) vs. 25% (15/60)†† Overall:27% (33/122)	Adjusted for treatment and baseline co-variates that reached significance p<0.1 (age, number of fallers in pretreatment period, being a faller in pretreatment period, baseline vitamin D level and baseline 1,25 dihydroxyvitamin D level, observation time during treatment)	Vitamin D: 400 IU of vitamin D_3 BID (total: 800 IU/day) and 600 mg of calcium BID (total:1200 mg/day) Control: 600 mg of calcium BID (total:1200 mg/day)
Gallagher, *et al.,* 2012[155] *Dose response to vitamin D supplementation in postmenopausal women: a randomized trial*	Shown in figure; dose-response curve predicted that 97.5% of those on 600 IU per day reached a D level >20 ng/mL; vitamin D levels higher in all vitamin D groups individually compared to placebo (p<0.05)	Approached: 2113 Screened: 633 Eligible: NR Enrolled: 163 (142 [20 to 21 per dosage] vs. 21) Analyzed: 163 (142 vs. 21)	Median: 12 months (range: 0.9 to 14.0 months)	12.7% (18/142) vs. 14.3% (3/21) Overall: 12.9% (21/163)	NR	Vitamin D: 400 IU, 800 IU, 1600 IU, 2400 IU, 3200 IU, 4000 IU, or 4800 IU of vitamin D_3 daily Control: Identical placebo daily *All Participants:* Citracal calcium supplements administered BID to maintain total calcium intake of 1200 to1400 mg/day
Harris, *et al.,* 1999[175‡‡] *Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D*	Younger men: 25 vs. 13 Older men: 19 vs. 15	Approached: NR Screened: NR Eligible: NR Enrolled: 20 (12 vs. 8) Analyzed: 18 (11 vs. 7)	3 weeks	11/20 55% (4/10 younger and 5/10 older)	NR	Vitamin D: 1800 IU of vitamin D_2 in liquid form taken with food daily in the morning Control: No intervention

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
Honkanen, *et al.,* 1990[128‡‡] *The necessity and safety of calcium and vitamin D in the elderly*	Home patients: 32 vs. 9 Hospital inpatients: 26 vs. 4 p<0.001 for change in intervention group	Approached: NR Screened: 203 Eligible: NR Enrolled: 126 (63 vs. 63) Analyzed: 126 (63 vs. 63)	11 weeks	8/63 (12.7%) vs. 3/60 (4.8%) Overall: 11/126 (8.7%)	NR (RCT)	Vitamin D: 1800 IU of vitamin D_3 daily and 1.558 g of calcium daily Control: No intervention
Karkkainen, *et al.,* 2010[165‡‡]*Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)* Karkkainen, *et al.,* 2010[152‡‡]*Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS)*	30 vs. 22; p<0.001	Approached: 5407 Screened: 3744 Eligible: 3432 Enrolled: 603 (290 vs. 313) in subsample with vitamin D levels Analyzed: 593 (287 vs. 306) in subsample with vitamin D levels	3 years Mean: 2.8 years	1.0% (3/290) vs. 2.2% (7/313) Overall: 1.7% (10/603)Subsample with vitamin D levels	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total:800 IU/day) and 500 mg of calcium BID (total: 1000 mg/day) Control: No intervention
Kjaergaard, *et al.,* 2012[170]*Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomized clinical trial*	59 vs. 21	Approached: NR (12984 in sixth Tromso study) Screened: 1351 Eligible: NR Randomized: 243 (122 vs. 121) Enrolled: 237 (121 vs. 116; 6 excluded at baseline for not meeting inclusion criteria) Analyzed: 230 per protocol (120 vs. 110)	6 months	1.6% (2/122) vs. 9.1% (11/121) Overall: 5.4% (13/243)	NR (RCT)	Vitamin D: 20,000 IU of vitamin D_3 weekly Control: Identical placebo weekly

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
Krieg, *et al.,* 1999[153‡‡] *Effect of supplementation with vitamin D_3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study*	27 vs. 6; p<0.01	Approached: NR Screened: NR Eligible: NR Enrolled: 248 (124 vs. 124) Analyzed: 248 (124 vs. 124)	2 years	60% (74/124) vs. 57% (71/124) Overall: 58% (145/248)	NR (RCT)	Vitamin D: 440 IU of vitamin D_3 BID (total:880 IU/day) and 500 mg of calcium BID (total: 1000 mg/day) Control: No intervention
Lehmann, *et al.,* 2013[115]*Bioavailability of vitamin D_2 and D_3 in healthy volunteers, a randomized placebo-controlled trial*	Vitamin D_2 vs. vitamin D_3 vs. control27 vs. 36 vs. 13; p<0.001	Approached: NR Screened: NR Eligible: NR Enrolled: 119 (50 vitamin D_2 vs. 49 vitamin D_3 vs. 20 control) Analyzed: 107 (47 vitamin D_2 vs. 46 vitamin D_3 vs. 19 control)	8 weeks	Vitamin D_2 vs. vitamin D_3 vs. control:8% (4/50) vs. 14% (7/49) vs. 5% (1/20) Overall: 10% (12/119)	NR (RCT)	Vitamin D: 2000 IU of either vitamin D_2 or D_3 daily Control: Identical placebo daily
Lips, *et al.,* 1996[160] *Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial* Ooms, *et al.,* 1995[120] *Prevention of bone loss by vitamin D supplementation in elderly women: A randomized double-blind trial*	Median: 25 vs. 9 (at 1 year)	Approached: NR Screened: NR Eligible: NR Enrolled: 348 (177 vs. 171) Analyzed: 270 with vitamin D levels	3 to 3.5 years, maximum 4 years	28.8% (51/177) vs. 31.0% (53/171) Overall: 28.7% (100/348) **Drop out in first year** Overall:19% (65/348) 16% (29/177) vs. 21% (36/171) 3.7% (13/348) are not in analysis at end of study	Covariates included age; sex; residence; sum of outdoor, sunshine, and walking scores; and compliance; fracture analysis was repeated excluding participants who used vitamin D or multivitamin supplements other than trial medication	Vitamin D: 400 IU of vitamin D_3 daily Control: Identical placebo daily
Martineau, *et al.*, 2007[178] *A single dose of vitamin D enhances immunity to mycobacteria*	27 vs. NR	Approached: NR Screened: 364 Eligible: NR Enrolled: 192 (96 vs. 96) Analyzed: 192 (96 vs. 96)	6 weeks	31.2% (29/96) vs. 33.3% (32/96) Overall: 31.8% (61/192)	NR (RCT)	Vitamin D: 100000 IU vitamin D_2 in a single dose Control: Identical lactose placebo in a single dose

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part 1

Author, Year, Title*	Mean 25(OH)D Level Attained Reported as: Vitamin D vs. Control (Ng/Ml)	Number Approached, Screened, Eligible, Enrolled, Analyzed Reported as: Vitamin D vs. Control	Duration	Attrition Reported as: Vitamin D vs. Control	Confounders Adjusted for in Analysis	Interventions
Pfeifer, *et al.,* 2009[162] *Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals*	Month 12: 34 vs. 23 Month 20: 19 vs. 15	Approached: 315 Screened: NR Eligible: NR Enrolled: 242 (121 vs. 121) Analyzed: 242 (122 vs. 120) for falls and fractures†††	12 month treatment and 8 month post-treatment followup Total: 20 months	6% (7/121) vs. 6% (7/121) Overall: 6% (14/242)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total: 800 IU/day) and 500 mg of calcium BID (total: 1000 mg/day) Control: 500 mg of calcium BID (total: 1000 mg/day)
Talwar, *et al.,* 2007[176] *Dose response to vitamin D supplementation among postmenopausal African American women* Aloia, *et al.,* 2005[174] *A randomized controlled trial of vitamin D_3 supplementation in African American women*	35 vs. 18 (at 27 months; 40% of active group still had levels <32)	Approached: 50,000Screened: 385Eligible: 322Enrolled: 208 (104 vs. 104)Analyzed: 208 (104 vs. 104)	36 months	28.8% (30/104) vs. 28.8% (30/104) Overall: 29.4% (60/208)	NR (RCT)	Vitamin D: 800 IU of vitamin D_3 daily for first 24 months, increased to 2000 IU daily Control: Identical placebo daily *All participants:* Supplements given to ensure total daily intake of 1200 to 1500 mg calcium
Wood, *et al.,* 2012[135] *Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT*	Vitamin D 400 IU vs. 1000 IU vs. control 26 vs. 30 vs. 13; p<0.001	Approached: NR Screened: 424 Enrolled: 305 (102 vitamin D 400 IU vs. 101 vitamin D 1000 IU vs. 102 control) Analyzed: 305 (102 vitamin D 400 IU vs. 101 vitamin D 1000 IU vs. 102 control)	13 months	Vitamin D 400 IU vs. 1000 IU vs. control: 18% (18/102) vs. 11% (11/101) vs. 11% (11/102) Overall: 13% (40/305)	NR (RCT)	Vitamin D: 400 IU or 1000 IU of vitamin D_3 daily Control: Identical placebo daily

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
≥90% of study participants had 25(OH)D level <20 ng/mL							
Brazier, *et al.*, 2005[156] *Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study*	NR	-Assessed followup levels -No assessment of pill content -Dietary vitamin D at baseline: 85 (85 vs. 84) IU/day	AEs: prespecified; recorded spontaneously reported and observed AEs Hypercalemia: measured serum calcium defined as ≥10.8 mg/dL, reported spontaneously	Mortality: 3.2% (3/95) vs. 1.0% (1/96); RR 3.03 (95% CI 0.32 to 28.63)†; all unrelated to drug	**All NS:** Total AEs: 187 vs. 170 Withdrew due to AE: 15.8% (15/95) vs. 17.7% (17/96); RR 0.89 (95% CI 0.47 to 1.68);† specifically, GI (3 vs. 6 cases), cardiovascular (3 vs. 4 cases); hypercalcemia (2 vs. 0 cases) **SAEs:** 14.7% (14/95) vs. 12.5% (12/96); RR 1.18 (95% CI 0.58 to 2.41)† Cardiovascular: 6.3% (6/95) vs. 5.2% (5/96); RR 1.21 (95% CI 0.38 to 3.84)† Osteomuscular: 5.3% (5/95) vs. 2.1% (2/96); RR 2.53 (95% CI 0.50 to 12.70)† Nervous system: 1.1% (1/95) vs. 2.1% (2/96); RR 0.51 (95% CI 0.05 to 5.48)† GI: 1.1% (1/95) vs. 2.1% (2/96); RR 0.51 (95% CI 0.05 to 5.48)† Body as a whole: 1.1% (1/95) vs. 1.1% (1/96); RR 1.01 (95% CI 0.06 to 15.92)† Other: 2.1% (2/95) vs. 3.2% (3/96); RR 2.02 (95% CI 0.19 to 21.92)† Had ≥1 AE: 72.6% (69/95) vs. 72.9% (70/96); RR 0.10 (95% CI 0.84 to 1.18)† **Non-SAEs:** Osteomuscular: 33.7% (32/95) vs. 25.0% (24/96); RR 1.34 (95% CI 0.83 to 2.11)† GI: 23.2% (22/95) vs. 21.9% (21/96); RR 1.06 (95% CI 0.63 to 1.79)† Metabolic and nutritional: 16.8% (16/95) vs. 18.8% (18/96); RR 0.90 (95% CI 0.49 to 1.65)† Hypercalcemia: 7.4% (7/95) vs. 11.5% (11/96); RR 0.64 (95% CI 0.26 to 1.59)† **Drug-related AEs:** 22.1% (21/95) vs. 24.0% (23/96); RR 0.92 (95% CI 0.55 to 1.55)† Metabolic and nutritional: 9.5 % (9/95) vs. 10.4% (10/96); RR 0.91 (95 %CI 0.38 to 2.14)†	Fair	Innothera Laboratories, Arcueil, France

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
					Hypercalcemia: 6.3% (6/95) vs. 8.3% (8/96); RR 0.76 (95% CI 0.27 to 2.10)[†] GI: 9.5% (9/95) vs. 8.3% (8/96); RR 1.14 (95% CI 0.46 to 2.82)[†]		
Chapuy, *et al.*, 2002[122] *Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The Decalyos II Study*	NR	-Followup levels increased in vitamin D group -No verification of pill content -Dietary vitamin D intake at baseline 40.8 IU/day	Fractures: women asked about fractures during investigator assessment every 3 months. For peripheral fractures, date, site, and cause of trauma were recorded on a case report form. For vertebral fractures, spine radiographs required for confirmation. AEs: every 3 months, women were asked whether they had experienced any AEs Falls: NR Mortality: NR Hypercalcemia: measured serum calcium, collected at baseline and after 6,12,18 and 24 months	Hip fracture: 6.9% (27/393) vs. 11.1% (21/190); RR 0.62 (95% CI 0.36 to 1.07)[†] Non-vertebral fractures: 17.8% (70/393) vs. 17.9% (34/190); RR 1.0 (95% CI 0.7 to 1.4)[†] Fallers: 63.9% (251/393) vs. 62.1% (118/190); RR 1.0 (95% CI 0.9 to 1.2)[†] Mortality: 18.1% (70/393) vs. 23.9% (45/190); RR 0.75 (95% CI 0.54 to 1.05)[†] (ITT analysis)[‖]	GI disturbance (nausea, diarrhea, epigastric pain): 6.1% (24/393) vs. 8.4% (16/190); RR 0.73 (95% CI 0.40 to 1.33)[†] Withdrew due to GI disturbance AEs: 3 (group NR) Hypercalcemia: 3 vs. 0; RR 3.39 (95% CI 0.18 to 65.4)[†] No kidney stones reported Hypercalciuria at 12 months (urinary calcium >350 mg/24 hours): 3.0% (5/166) vs. 1.3% (1/77); RR 2.32 (95% CI 0.28 to 19.52)[†] Hypercalciuria at 24 months (urinary calcium >350 mg/24 hours): 3.4% (3/89) vs. 2.9% (1/35); RR 1.18 (95% CI 0.13 to 10.96)[†]	Fair	Merck KGaA, Germany
Gallagher, *et al*., 2013[159] *Effects of vitamin D supplementation in older African American women*	Screened throughout the year from January 2008 to January 2010	-Assessed followup levels -Verified pill content -Mean baseline vitamin D intake NR	AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit Hypercalcemia: measured serum	Mortality: None (as per author correspondence)	Withdrew due to AEs: 1.1% (1/93; uncontrolled diabetes) vs. 5.9% (1/17; hypercalcemia); RR 0.18 (95% CI 0.01 to 2.78)† Patients with SAEs: 1.1% (1/93; cerebral hemmorhage) vs. 0/17; RR 0.57 (95% CI 0.02 to 14.0); thought unrelated to	Fair	Grant from the National Institute on Aging and the Office of Dietary Supplements

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
		-Participants instructed not to take non-study vitamin D and multivitamins without vitamin D were provided to those who wanted to take multivitamins	calcium, defined as either >10 mg/dL or >10.8 mg/dL, collected at baseline and after 3, 6, 9 and 12 months of treatment		treatment Hypercalcemia (serum calcium level ≥10 or ≥10.8 mg/dL): 8.6% (8/93) vs. 5.9% (1/17); RR 1.5 (95% CI 0.20 to 11.0) (as per author correspondence)		
Gallagher, *et al.,* 2014[158] *Vitamin D Supplementation in Young White and African American Women*	Screened throughout the year from January 2008 to January 2010	-Assessed followup levels -Verified pill content -Mean baseline vitamin D intake 100 mg/day -participants instructed not to take non-study vitamin D and multivitamins without vitamin D were provided to those who wanted to take multivitamins	AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit Hypercalcemia: measured serum calcium, defined as ≥10.6 mg/dL, collected at baseline and after 3, 6, 9 and 12 months of treatment	Mortality: None (as per author correspondence)	Patients with SAEs: 4 patients with 5 events (internal bleeding from auto accident; subarachnoid hemorrhage from hemangioma; maxillary hypoplasia surgery; and broken ankle and tibia); no events attributed to study treatment (NR by group) Hypercalcemia (serum calcium ≥10.3 mg/dL): one event in Black participant using 400 IU vitamin D daily; 0.63% (1/160) vs. 0/38; RR 0.73 (95% CI 0.03 to 17.5) Kidney stones: None	Fair	Grant from the Department of Defense
Grimnes, *et al.,* 2011[157] *Vitamin D, insulin secretion, sensitivity, and lipids. Results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique*	Recruited November to April; at baseline, 6% used sun bed	-Assessed followup levels -No assessment of pill content -At baseline 26% of participants took vitamin D supplements	Hypercalcemia: >10.2 mg/dL reported to be out of the normal range Other outcomes: unclear	Mortality: 0/51 vs. 1/53 (unknown cause); RR 0.34 (95% CI 0.01 to 8.15)	Number of AEs: 45 vs. 46 No hypercalcemia No kidney stones	Fair	Norwegian Council of Cardiovascular Disease

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Janssen, *et al.*, 2010[127] *Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation*	NR	-Followup levels increase in intervention group -No verification of pill content -Diet and supplement use NR	Unclear	Mortality: 1 (NR by group)	Withdrawals: 15.7% (11/70) overall; 22.2% (8/36) vs. 8.8% (3/34); RR 0.94 (95%CI 0.20 to 4.36)† Other withdrawals: cognitive decline (4), malignant lung tumor (1), recurrent upper urinary tract infections with malaise (2), acute emotional distress (1), hip fracture (1), peritonitis (1) No AE reported during intervention period, 3 participants reported nausea with the calcium tablets	Fair	Prevention Program of ZonMw
Lips, *et al.*, 2010[154] *Once-weekly dose of 8400 IU vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency*	October to June Told to limit UV exposure by avoiding or wearing sun block	-Followup levels increase in intervention -No verification of pill content -Subjects asked not to change diet, and to refrain from taking supplement with >100 IU of Vitamin D during period of observation	SPPB summary score: an ordered scale of 0 to 12 that includes an assessment of balance, a gait speed test (timed 4 minute walk), and timed rising from chair and sitting without the use of arms for 5 repetitions AEs: recorded at each study visit and by the voluntary reporting of patients at any time during the study Hypercalcemia: not specifically assessed, spontaneous reporting by patients	Mean SPPB summary score change from baseline at week 16: 0.355 (95% CI 0.1008 to 0.601) vs. 0.601 (95% CI 0.351 to 0.852); p= 0.162 Mortality: 0.9% (1/114) vs. 0/112: RR 2.95 (0.12 to 71.61)†	Withdrew due to AEs: 2.6% (3/114) vs. 4.5% (5/112): RR 0.59 (95% CI 0.14 to 2.41)† SAEs: 2.6% (3/114) vs. 2.7% (3/112): RR 0.98 (95% CI 0.20 to 4.76)† Had ≥ 1 AE: 21% (24/114) vs. 23.2% (26/112): RR 0.91 (95% CI 0.56 to 1.48)† Drug-related: 0.9% (1/114) vs. 3.6% (4/112): RR 0.25 (95% CI 0.03 to 2.16)† No kidney stones No serious laboratory AE No difference between groups in hypercalciuria, hypercalcemia, or elevated creatinine (data not shown)	Fair	Merck and Co, Inc.

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Pfeifer, *et al.,* 2000[161] *Effects of a short-term Vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women*	Baseline vitamin D levels in March and supplementation from March to May	-Followup levels increase in intervention group -No verification of pill content -During 8 weeks of treatment, instructed to maintain diets and avoid taking own supplemental calcium and vitamin D; not clear what instruction were given after 8 weeks	Number of falls: questionnairesFractures resulting from falls: verified by x-ray and medical reports	Number of participants who fell after 1 year of followup: 16% (11/70) vs. 28% (19/67); RR 0.55 (95% CI 0.29 to 1.08)[†] Mean number of falls after 1 year of followup: 0.24 (17 falls/70 persons) vs. 0.45 (30 falls/67 persons); p<0.05 Number of participants with fractures after 1 year of followup: 4% (3/70) vs. 9% (6/67) total; RR 0.48 (95% CI 0.12 to 1.84) **By fracture site** Radius/ulna: 2.9% (2/70) vs. 4.5% (3/67); RR 0.64 (95% CI 0.11 to 3.70) Pelvis: 0/70 vs. 1.5% (1/67); RR 0.32 (95% CI 0.01 to 7.70) Hip: 0/70 vs. 1.5% (1/67); RR 0.32 (95% CI 0.01 to 7.70) Ankle/foot: 1.4% (1/70) vs. 1.5% (1/67); RR 0.96 (95% CI 0.06 to 15.00)	NR	Fair	Strathmann AG Hamburg

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Wamberg, *et al.*, 2013[125] *The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study* Wamberg, *et al.*, 2013[132] *Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - Results from a randomized trial*	Recruited from February 2010 to May 2011	-Assessed followup levels- No assessment of pill content -At baseline, mean dietary vitamin D intake 760 IU/day (840 vs. 680); instructed to continue usual eating habits; did not report if study participants could take their own supplements during study	AEs: prespecified; patient visits at weeks 2, 10, and 18 for safety measures and adverse event registration; no other details provided Hypercalcemia: not specifically assessed, spontaneous reporting by patients	NR	**All NS:** Total AEs: 13 vs. 17; p=0.76 (nausea, constipation, tiredness, and headaches); RR 0.76 (95% CI 0.48 to 1.23)† Hypercalcemia: 0/26 vs. 0/26	Fair	NR

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL							
Aloia, *et al.,* 2008[173] *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration*	Recruited during three winters (November to March) and followed for 6 months (into summer/fall)	-Assessed followup levels -Probable verification of pill content (somewhat unclear) -Dietary vitamin D intake: 70.5 IU/day -Unclear if subjects were given any instructions about diet	AEs and hypercalcemia: prespecified clinical laboratory criteria for safety (serum calcium >10.6 mg/L, urine calcium/creatine ratio >0.16 mg/mL, and serum vitamin D level >80 ng/mL)	NR	High concentration of 25(OH)D (>80 ng/mL): 0.7% (1/138) Hypercalcemia: 0 Hypercalcuria: 0	Fair	Partially funded by Merck Corporation and the Empire Clinical Research Investigator Program
Arvold, *et al.,* 2009[169] *Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial*	Participants identified and study started in midwinter	-Followup levels increase in intervention group -Certificate of analysis that pills were within 10% of stated dose -Number NR of diet/supplement use during period of observation	Depressed mood: (FIQ scale from 0 to 100); ranking of depressed mood and interference with work or housework was on scale from 0 to 10	**Overall FIQ Score (mean and (SD)):** Before treatment: 33.6 (18.4) vs. 27.8 (17.5) After treatment: 29.9 (19.7) vs. 29.7 (15.8); p=0.03 **Depressed mood from FIQ Part III (mean and (SD)):** Before treatment: 2.9 (2.3) vs. 2.4 (2.6) After treatment: 2.8 (2.7) vs. 2.1 (2,0); p=NS for change from baseline in either group or between groups. **Interference with work or housework from FIQ Part III (mean and (SD)):** Before treatment (mean and (SD)): 3.1 (2.5) vs.	No AE reported by any participants	Fair	St. Luke's Foundation

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
				2.7 (2.5) After treatment (mean and (SD)): 2.7 (2.7) vs. 3.0 (2.4); p=0.08			
Berlin, *et al.,* 1986[177]** *Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3*	February to April At start of study, no subjects were exposed to extreme sunlight	-Assessed followup levels -No assessment of pill content	Unclear	NR	No AEs, objective or subjective, were reported	Poor	Grants from the Swedish Medical Research Council (project 03X-3141), Loo and Hans Ostermans Foundation, Stockholm, Sweden, and ACO Lakemedal AB, Solna, Sweden
Bischoff, *et al.,* 2003[164] *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*	Winter (November and March)	-Followup levels increase in intervention group -No verification of pill content -At baseline overall diet the same for all participants -NR of diet/supplement use during period of observation	Falls: recorded by nurses on inpatient unit who had training in fall protocol (i.e. date, time, circumstances, injuries); nurses completed fall protocol if they observed or received a report of a fall AEs: reported to the physician in charge for the patient and to one research physician Hypercalcemia: measured serum calcium, did not	**Pretreatment period** Total falls (n): 22 vs. 20 Number of fallers: 24% (15/62) vs. 23% (14/60); RR 1.04 (95% CI 0.55 to 1.96)† **During treatment** Total Falls (n): 25 vs. 55 Persons with no falls (n): 48 vs. 42; RR 1.1 (95% CI 0.9 to 1.4) Persons with 1 fall (n): 10 vs. 8; RR 1.2 (95% CI 0.5 to 2.9) Persons with 2 to 5 falls (n): 3 vs. 7; RR 0.4 (95% CI 0.1 to 1.5) Persons with 6 to 7 falls (n): 1 vs. 2; RR 0.5 (95% CI 0.05 to 5.2)	Constipation: 2 vs. 0; RR 4.8 (95% CI 0.2 to 98.8) Hypercalcemia: 0 Discontinuation of medications independent of AEs: 0 vs. 1; RR 0.3 (95% CI 0.01 to 7.8)	Fair	Stratham AG; International Foundation for the Promotion of Nutrition Research and Nutrition Education; Swiss Orthopedic Society; Swiss Foundation for Nutrition Research

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
			define hypercalcemia or frequency	Persons with >7 falls (n): 0 vs. 1; RR 0.3 (95% CI 0.01 to 7.8) Fallers (n): 23% (14/62) vs. 30% (18/60); RR 0.7 (95% CI 0.3 to 1.5)- Vitamin D group had 49% reduction (p=0.01) in falls after adjusting for age, falls in pretreatment period, baseline 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D, observation time during treatment-Using absolute number of falls as primary outcome, vitamin D group had 62% reduction in falls (p<0.0002) after adjustment -Mean number of excessive falls among fallers was lower in the vitamin D group (p=0.045), suggesting decrease in recurrent falls			

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Gallagher, *et al.,* 2012[155] *Dose response to vitamin D supplementation in postmenopausal women: a randomized trial*	Screened in late winter and early spring 1st phase: April to May 2007 2nd phase: January to May 2008	-Assessed followup levels -Verified pill content -Mean baseline vitamin D intake 114 IU/day -participants instructed not to take non-study vitamin D and multivitamins without vitamin D were provided to those who wanted to take multivitamins	AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit, validated by chart review Hypercalcemia: measured serum calcium, defined as either >10 mg/dL or >10.8 mg/dL, collected at baseline and after 3, 6, 9 and 12 months of treatment	White Mortality: 0/142 vs. 0/21	Withdrew due to AEs: 1.4% (3/142) vs. 0/21; RR 1.08 (95% CI 0.06 to 20.15)† Patients with any AEs: 85.2% (121/142) vs. 85.7% (18/21); RR 0.99 (95% CI 0.82 to 1.20)† Patients with SAEs: 6.3% (9/142; diverticulitis, cerebrovascular accident, knee replacement, partial thyroidectomy, tibia-fibula fracture, cholecystectomy, CHF, angina and stent, COPD exacerbation - no events attributed to treatment) vs. 9.5% (2/21; syncope and total hip replacement); RR 0.67 (95% CI 0.15 to 2.87)† Kidney stones: 0 vs. 0 Hypercalcemia (serum calcium level ≥10 mg/dL): 10.6% (16/142) vs. 4.8% (1/21); RR 2.22 (95% CI 0.31 to 15.93)† Hypercalcemia (serum calcium level ≥10.8 mg/dL) : 3.5% (5/142) vs. 0; RR 1.69 (95% CI 0.10 to 29.55)†	Good	Grant from the National Institute on Aging
Harris, *et al.,* 1999[175‡‡] *Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D*	Late winter (February); excluded those in outdoor jobs or those who travelled to southern locations in the previous month	-Assessed followup levels -No assessment of pill content	Unclear	NR	No AEs of supplementation reported	Poor	U.S. Department of Agriculture

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Honkanen, *et al.,* 1990[128‡‡] *The necessity and safety of calcium and vitamin D in the elderly*	November to December, Kuopos (63 degrees north with short winter [5 hour] and long summer [11 hour]days) Institutionalized had sun exposure to some extent in summer	-Assessed followup levels -No assessment of pill content	Hypercalcemia: measure serum calcium at baseline and after 11 weeks of treatment	NR	9 independently living subjects reported mild GI symptoms on treatment No kidney stones reported No hypercalcemia	Fair	Grant no. 7430/304/85, Academy of Finland, the Remeda Pharmaceutical Company, and the Sandoz Pharmaceutical Company

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Karkkainen, *et al.,* 2010[165‡‡] *Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)* Karkkainen, *et al.,* 2010[152‡‡] *Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS)*	Baseline vitamin D measures: February to May Followup vitamin D measures: January to May	-Followup levels increase in intervention group -Pills distributed by pharmacist but no verification of pill content -Groups asked to continue with their previous diet during study	Number of falls, number of falls requiring medical attention: recorded every 4 months via telephone interviews for subsample with vitamin D levels Mortality: NR	Number of falls: 430 vs. 524 Number of woman with falls: 62% (179/287) vs. 67% (205/306); RR 0.82 (95% CI 0.73 to 0.92); OR no fall vs. fall, 0.82 (95% CI 0.58 to 1.14); OR 0 or 1 fall vs. ≥ 2 falls, 0.70 (95% CI 0.50 to 0.97) Number of women with falls requiring medical attention: 33% (95/287) vs. 35% (106/306); OR no fall requiring medical attention vs. fall requiring medical attention, 0.93 (95% CI 0.66 to 1.31); OR 0 or 1 fall requiring medical attention vs. ≥ 2 falls requiring medical attention, 0.82 (95% CI 0.49 to 1.37) Mortality: 1% (3/290) vs. 0.3% (1/313); RR 3.24 (95% CI 0.34 to 30.95)[†]	Discontinued due to AE: 6% (17/290; GI symptoms [n=9], exacerbation of diseases [n=2], mouth irritation [n=1], skin symptoms [n=1], nausea [n=1], cough [n=1], backache [n=1] weight increase [n=1]) vs. NR	Fair	Finnish Cultural Foundation, Sigrid Juselius Foundation, Academy of Finland, Kuopia University-Hospital EVO-grant

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Kjaergaard, *et al.,* 2012[170] *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomized clinical trial*	Inclusion period from October to April of following year Study performed from October to November of following year Excluded those planning a trip to a sunny location during the trial	-Assessed followup levels -Pills distributed by pharmacist but no verification of pill content	Depressive symptoms: Beck Depression Inventory (21-item self-report depression scale, with higher score indicative of depressed mood, 2 sub-scales assess cognitive-affective and somatic-vegetative symptoms); Hospital Anxiety and Depression Scale (14-item anxiety and depression scale, with higher scores indicative of depression/anxiety); Montgomery-Asberg Depression Rating Scale (interview to evaluate change in depression before and after treatment with higher scores indicative of depressed mood) AEs: self-report via telephone interview at 3 months; serum levels measured at baseline and end of study	Median total Black Depression Inventory (scale 0 to 63) at 6 months: 3 vs. 2; p=NSMedian total Hospital Anxiety and Depression Scale (scale 0 to 42) at 6 months: 4 vs. 3; p=NS Median Montgomery-Asberg Depression Rating Scale (scale 0 to 60) at 6 months: 2 vs. 1; p=NS No significant difference between groups for change from baseline when stratifying by gender, age, BMI, serum 25(OH)D level at baseline or smoking status	No significant difference between groups for AEs Hypercalcemia: 1 participant in placebo group had serum calcium = 10.5 mg/dL, resolved 4 weeks later; 0/120 vs. 1/110; RR 0.31 (95% CI 0.01 to 7.43) **AEs by organ system** Gastrointestinal: 14 vs. 12 Respiratory: 67 vs. 61 Dermatological: 13 vs. 9 Musculoskeletal: 22 vs. 18 Urogenital: 7 vs. 4 Circulatory: 5 vs. 7 Neurological: 5 vs. 5 Endocrinological: 14 vs. 17 Other: 30 vs. 25 Total AEs: 177 vs. 158 Note: Figure 1 indicates that 6 participants in the placebo group discontinued because of side-effects, AEs, or other reasons but no further information provided	Good	Northern Norway Regional Health Authority grant

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Krieg, *et al.,* 1999[153‡‡] *Effect of supplementation with vitamin D_3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study*	NR	-Assessed followup levels -No assessment of pill content	Unclear	Mortality: 17% (21/124) vs. 21% (26/124); RR 0.81 (95% CI 0.48 to 1.36)[†] (no deaths were deemed to be related to treatment)	Withdrew due to psychiatric disturbances and severe illness: 2.4% (3/124) vs. 1.6% (2/124); RR 1.50 (95% CI 0.26 to 8.82)[†] Withdrew due to upper GI AEs: 4.8% (6/124) vs. 0; RR 13.00 (95% CI 0.74 to 228.32) Withdrew due to hypercalcemia: 0.8% (1/124) vs. 0; RR 3.00 (95% CI 0.12 to 72.94)[†] (due to hyperparathyroidism)	Fair	NR
Lehmann, *et al.,* 2013[115] *Bioavailability of vitamin D_2 and D_3 in healthy volunteers, a randomized placebo-controlled trial*	January to March (no measurable UV radiation) Excluded if vacationed in places with abundant UVB irradiation during course of study	-Assessed followup levels -Verified pill content	AEs: prespecified; participants interviewed about AEs at each monthly visit	NR	No AEs reported; No hypercalcemia detected	Fair	German Ministry of Education and Research, Grant No. 0315668A

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Lips, *et al.,* 1996[160] *Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial* Ooms, *et al.,* 1995[120] *Prevention of bone loss by vitamin D supplementation in elderly women: A randomized double-blind trial*	Enrolled from August to December	-Followup levels increase in intervention group -No verification of pill content -Spontaneous use of vitamin D supplements and vitamin D was discouraged, but the prescription practices of the general practitioners were not altered-Participants allowed to take calcium	Fractures: annual questionnaire for participants; GPs or caretakers asked to immediately report hip fracture; hip fractures were verified with a GP Mortality: GP or caretaker asked to immediately report death and verified by GP Other AEs: NR Hypercalcemia: measured serum calcium at baseline and after 1 year of treatment	Number of hip fractures: 49 vs. 36; HR 1.3 (95% CI 0.84 to 2.0) Mortality: 6.2% (11/177) vs. 12.3% (21/171); RR 0.51 (95% CI 0.25 to 1.02)†	Reported AE: 0.6% (1/177) vs. 0; RR 2.90 (95% CI 0.12 to 70.68)† Hypercalcemia: 0.6% (1/177) vs. 0; RR 2.90 (95% CI 0.12 to 70.68)†	Fair	Praeventiefonds grant

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Martineau, *et al.*, 2007[178] *A single dose of vitamin D enhances immunity to mycobacteria*	NR	-Assessed followup levels only in intervention group -No assessment of pill content	Unclear	NR	Hypercalcemia: 0 vs. 0 No other adverse events reported	Fair	Welcome Trust, the Department of Environmental Health, London Borough of Newham, Newham University Hospital NHS Trust Research Fund, and Northwick Park Hospital Tropical Research Fund

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Pfeifer, *et al.*, 2009[162] *Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals*	May (vitamin D levels start to rise) to March (vitamin D levels at their lowest)	-Followup levels increase in intervention group at month 12 (not month 20) - Diet/supplement use during period of observation: NR -No verification of pill content -Instructed to maintain usual diet and avoid taking supplemental calcium and vitamin D on own (unclear if these instructions applied to entire trial period or only for 12 months of treatment)	Falls at 20 months: Daily fall diaries; In addition, subjects contacted by telephone every 2 months and asked whether a fall had occurred Fractures due to falls: verified by x-ray and medical reports	≥1 fall: 40% (49/122) vs. 63% (75/120); RR 0.64 (95% CI 0.50 to 0.83)† Mean number of falls: 0.63 vs. 1.41; p<0.001 Total falls (per text): 76 vs. 171 Total falls (per table 3): 106 vs. 169; p<0.001 **By number of falls**‡‡‡ 1 fall: 20% (24/120) vs. 30% (37/122); RR 0.66 (95% CI 0.42 to 1.03) 2 falls: 11% (13/120) vs. 15% (18/122); RR 0.73 (95% CI 0.38 to 1.43) 3 falls: 2.5% (3/120) vs. 5.7% (7/122); RR 0.44 (95% CI 0.12 to 1.65) >3 falls: 11% (13/120) vs. 7.4% (9/122); RR 1.47 (95% CI 0.65 to 3.31) Time to first fall at month 12: 27% reduction in those using vitamin D + calcium vs. calcium; RR 0.73 (95% CI 0.54 to 0.96) Time to first fall at month 20: 39% reduction in those using vitamin D + calcium vs. calcium; RR 0.61 (95% CI 0.34 to 0.76) Participants with fractures: 5.7% (7/122) vs. 10% (12/120) (text says 13); RR 0.57 (95% CI 0.23 to 1.41)† Total fractures: 12 vs.	NR	Fair	Meda Pharma Inc.

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
				19; p=NS			

Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency, continued part II

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Adverse Events/Harms Reported as: Vitamin D vs. Control	Quality Rating	Sponsor
Talwar, *et al.,* 2007[176] *Dose response to vitamin D supplementation among postmenopausal African American women* Aloia, *et al.,* 2005[174] *A randomized controlled trial of vitamin D_3 supplementation in African American women*	NR	-Assessed followup levels -Verified pill content	Hypercalcemia: measured serum calcium, collected at baseline and after 3, 5, 12, 18, 24 , 27, 30 , and 36 months	NR	SAE: 8 vs. 7; not deemed related to treatment Total AEs: 222 **Study related AEs** Mild hypercalcemia: 6 vs. 3 (resolved on repeat fasting sample); RR 2.00 (95% CI 0.51 to 7.78)† Transient hypercalciuria: 3 vs. 1 (2/3 in vitamin D group resolved spontaneously); RR 3.00 (95% CI 0.32 to 28.37)† Persistent hypercalciuria (resolved with stopping calcium): 1 (group NR) Kidney stones: 0 vs. 0	Fair	National Institute of Aging
Wood, *et al.,* 2012[135] *Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT*	Baseline and followup during January to March Baseline UVB exposure (weekly standard erythemal dose): 0.5	-Assessed followup levels -Capsules were reported to be analyzed but results not given -Told not to take any dietary supplements containing vitamin D for duration of study	Hypercalcemia: measured serum calcium at baseline and after 4 weeks of treatment	<u>Vitamin D 400 IU vs. 1000 IU vs. control</u> Falls: 4 vs. 0 vs. 3 Type 2 diabetes: 1 vs. 0 vs. 0; RR for 400 IU vs. control 3.0 (95% CI 0.12 to 72.8)	<u>Vitamin D 400 IU vs. 1000 IU vs. control</u> Total AEs: 17 vs. 15 vs. 20; RR for 400 IU vs. control 0.85 (95% CI 0.47 to 1.53)†; RR for 1000 IU vs. control 0.76 (95% CI 0.41 to 1.39)† GI symptoms: 3 vs. 1 vs. 0; RR for 400 IU vs. control 7.00 (95% CI 0.37 to 133.83)†; RR for 1000 IU vs. control 3.0 (95% CI 0.1 to 73.5)† Hypercalcemia: 0 vs.1 vs. 0 RR for 1000 IU vs. control 3.0 (95% CI 0.12 to 73.50)† Joint pain: 1 vs.1 vs. 0; RR for 400 IU vs. control 3.00 (95% CI 0.12 to 72.79)†; RR for 1000 IU vs. control 3.03 (95% CI 0.12 to 73.50)† SAEs: 7 vs. 8 vs. 4; none were deemed to be related to treatment; RR for 400 IU vs. control 1.75 (95% CI 0.53 to 5.80)†; RR for 1000 IU vs. control 2.02 (95% CI 0.63 to 6.50)†	Fair	U.K. Department of Health

* All studies are randomized, controlled trial unless otherwise specified.
† Calculated.
‡ Characteristics are for participants included in intention-to-treat analysis (n=583).

§ Estimated from limited information.
‖ Proportion of deaths reported in results differs from that described as reason for drop outs (17.1%† vs. 22.4%)† estimated from limited data.
¶ Unclear if those who dropped out were still included for AE count.
** Cohort study.
†† Study provided proportion attrition per group, n values calculated, don't sum to 33 for overall attrition reported by study.
‡‡ Open randomized, controlled trial.
§§ 30% of participants refused to have blood drawn.
‖‖ Receive some care, but not as much as nursing home.
¶¶ Characteristics only reported for those who finished study (n=131).
*** Includes 9 people screened but not randomized.
††† 122 persons reported for falls/fractures outcomes analyses in the vitamin D + calcium group, which is one more than was enrolled for that group.
‡‡‡ The total number of participants with a fall doesn't sum to the number of participants who fell by number of falls.

Abbreviations: µmol = micromole; 25(OH)D = serum 25-hydroxyvitamin D; AB = Aktiebolag; AE = adverse event; AG = Aktiengesellschaft; BID = twice a day; BMD = bone mineral density; BMI = body mass index; BP = blood pressure; CHF = congestive heart failure; CI = confidence interval; cm = centimeter; Co = corporation; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DEQAS = Vitamin D External Quality Assurance Scheme; dL = deciliter; DBP = diastolic blood pressure; EVO = Engineering Virtual Organization; FIQ = Fibromyalgia Impact Questionnaire; g = gram; GI = gastrointestinal; GP = general practitioner; HPLC = high pressure liquid chromatography; HRT = hormone replacement therapy; HTN = hypertension; IU = international unit; Inc. = incorporated; ITT = intention-to-treat; kg = kilogram; L = liter; m = meter; mg = milligram; MI = myocardial infarction; mL = milliliter; mmHg = millimeters of mercury; mmol = milimole; n = number; ng = nanogram; NHS = National Health Service; No. = number; NR = not reported; NS = non significant; OSTPRE = Osteoporosis Risk Factor and Prevention Fracture Prevention Study; OSTPRE-FPS = Ssteoporosis Risk Factor and Prevention Fracture Prevention Study; pmol = picomole; PTH = parathyroid hormone; RCT = randomized, control trial; RR = risk ratio; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SPPB = Short Physical Performance Battery; St. = Saint; TB = Tuberculosis; U.K. = United Kingdom; U.S. = United States; UV = ultraviolet; UVB = ultraviolet B; vs. = versus.

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (Ng/Ml)	25(OH)D Level Attained (Ng/Ml)
Overall WHI Trial Fair	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 one fall, 9% with 2 falls, 4% with >3 falls	Inclusion: Postmenopausal women in the WHI hormone therapy and dietary modification trials ages 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
Jackson, *et al.,* 2006[163] *Calcium plus vitamin D supplementation and the risk of fractures*	Number of cases (annualized %) of hip fracture in vitamin D vs. control by baseline characteristics **Age group at screening (years);** HR all NS 50 to 59: 29 (0.06) vs. 13 (0.03) 60 to 69: 53 (0.09) vs. 71 (0.13) 70 to 79: 93 (0.44) vs. 115 (0.54) **Race or ethnic group;** HR all NS White: 167 (0.16) vs. 189 (0.18) Black: 3 (0.03) vs. 4 (0.04) Hispanic: 0 (0.00) vs. 3 (0.06) American Indian: 1 (0.19) vs. 1 (0.20) Asian or Pacific Islander: 4 (0.16) vs. 1 (0.04)	Cases: All adjudicated cases of hip, spine, and lower arm or wrist fracture. Controls: 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.	As above	NR	90% <31; outcomes presented in quartiles of baseline 25(OH)D level as >24, 18 to 24, 13 to 18, and <13 ng/mL	As above

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (Ng/Ml)	25(OH)D Level Attained (Ng/Ml)
	Unknown or not identified: 0 (0.000) vs. 1 (0.07)					
Wactawski-Wende, *et al.,* 2006[167] *Calcium plus vitamin D supplementation and the risk of colorectal cancer*	Number of cases (annualized %) of invasive colorectal cancer in vitamin D vs. control by baseline characteristics **Age group at screening (years);** HR all NS 50 to 59: 33 (0.07) vs. 32 (0.07) 60 to 69: 81 (0.14) vs. 78 (0.14) 70 to 79: 54 (0.25) vs. 44 (0.21) **Race or ethnic group;** HR all NS White: 145 (0.14) vs. 129 (0.12) Black: 13 (0.11) vs. 16 (0.14) Hispanic: 5 (0.09) vs. 4 (0.08) American Indian/Alaskan native: 2 (0.37) vs. 0 (0.00) Asian or Pacific Islander: 2 (0.08) vs. 3 (0.13) Unknown or not identified: 1 (0.07) vs. 2 (0.13)	Cases: Women with confirmed invasive colorectal cancer and adequate stored serum for analysis. Controls: Women 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.	As above	NR	NR; outcomes presented in quartiles of baseline 25(OH)D level as ≥23, 17 to 23,12 to 17, and <12 ng/mL	As above
Chlebowski, *et al.,* 2008[166] *Calcium plus vitamin D supplementation and the risk of breast cancer*	Number of cases (annualized %) of invasive breast cancer in vitamin D vs. control by baseline characteristics **Age group at screening (years);** HR all NS 50 to 59: 179 (0.36) vs. 196 (0.40) 60 to 69: 247 (0.43) vs. 257 (0.45) 70 to 79: 102 (0.48) vs. 93 (0.44)	Cases: Women diagnosed with invasive breast cancer. Controls: Women who were breast cancer-free; matched to cases on age, latitude of clinical center, race/ethnicity, date of blood collection.	As above	NR	NR; outcomes presented in quintiles of baseline 25(OH)D level as ≥27,22 to 27,18 to 22, 13 to 18, and <13 ng/mL	As above

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (Ng/Ml)	25(OH)D Level Attained (Ng/Ml)
de Boer, *et al.,* 2008[168] *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative*	Number of cases (annualized %) of incident diabetes in vitamin D vs. control by baseline characteristics **Age group at screening (years);** HR all NS 50 to 59: 431 (0.91) vs. 426 (0.91) 60 to 69: 535 (1.01) vs. 518 (0.98) 70 to 79: 188 (0.95) vs. 193 (0.98) **Race or ethnic group;** HR all NS White: 846 (0.84) vs. 855 (0.85) Black: 166 (1.66) vs. 163 (1.66) Hispanic: 89 (1.81) vs. 71 (1.57) American Indian: 4 (0.87) vs. 5 (1.05) Asian or Pacific Islander: 32 (1.41) vs. 24 (1.13) Unknown: 17 (1.29) vs. 19 (1.37)	Cases and controls: Women with prevalent diabetes at baseline were excluded; selected from controls used in case-control study of fracture (Jackson 2008), in which participants were free of fracture for the duration of study and were individually matched to fracture cases by age, latitude of clinical center, race or ethnic group, and date of venipuncture. Cases: Women with new physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin. Controls: Women with no physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin.	As above	NR	<32 for 89% of participants; <20 for 61% of participants; outcomes presented in quartiles of baseline 25(OH)D level as >24, 17 to 24, 13 to 17, and <13 ng/mL	As above
LaCroix, *et al.,* 2009[151] *Calcium plus vitamin D supplementation and mortality in postmenopausal women: The Women's Health Initiative calcium-vitamin D randomized controlled trial*	Number of cases (annualized %) of death in vitamin D vs. control by baseline characteristics **Race or ethnic group;** HR=NS, except where noted White: 607 (0.57) vs. 679 (0.64); HR 0.89 (95% CI 0.80 to 0.99) Black: 79 (0.68) vs. 89 (0.78) Hispanic: 23 (0.42) vs. 11 (0.22); HR 2.28 (95% CI 1.07 to 4.87) American Indian: 5 (0.93) vs. 4 (0.79)	Cases: Women who died and had baseline vitamin D levels from their involvement in previous WHI case-control studies of fracture and colorectal cancer (Jackson, 2008; Wactawski-Wende, 2006). Controls: Living participants from previous WHI case-control studies of fracture and colorectal cancer (Jackson, 2008; Wactawski-Wende, 2006.	As above	NR	NR; outcomes presented in tertiles of baseline 25(OH)D level as ≥21,14 to 21, and <14 ng/mL	As above

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (Ng/Ml)	25(OH)D Level Attained (Ng/Ml)
	Asian or Pacific Islander: 18 (0.73) vs. 12 (0.51) Unknown: 12 (0.83) vs. 12 (0.81)					

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial, continued part 1

Author, Year, Title	Number Approached, Screened, Eligible, Enrolled, Analyzed	Country and Setting	UV Exposure	Duration of Followup	Attrition
Overall WHI Trial Fair	Number approached: 68132 Number screened: 68132 Number eligible: 36282	Multicenter U.S. Population-based Institutionalized: NR	Solar irradiance of region for entire trial (Langley's) Mean 382+/-60 (controls matched to cases on this parameter)	Mean 7.0 (SD 1.4) years	Overall 7.0% (2531/36282) Vitamin D vs. control 6.8% (1240/18176) vs. 7.1% (1291/18106)
Jackson, *et al.,* 2006[163] *Calcium plus vitamin D supplementation and the risk of fractures*	Number enrolled: 1067 cases, 1067 controls, 357 pairs for hip fracture, 1491 pairs for total fracture in case-control study† Number analyzed: 357 (95%) pairs for hip fracture, 1491 (80%) pairs for total fracture in case-control study	As above	Number of cases (annualized %) of hip fracture in vitamin D3 vs. control by solar irradiance (Langley); HR all NS 300 to 325: 46 (0.12) vs. 53 (0.14) 350: 37 (0.14) vs. 49 (0.18) 375 to 380: 25 (0.18) vs. 17 (0.12) 400 to 430: 25 (0.12) vs. 37 (0.17) 475 to 500: 42 (0.16) vs. 43 (0.16)	As above	As above
Wactawski-Wende, *et al.,* 2006[167] *Calcium plus vitamin D supplementation and the risk of colorectal cancer*	Number of invasive colorectal cancer: 322 Number enrolled: 634 (317 pairs for case-control study) Number analyzed: 612 (306 [96.5%] pairs for case-control study)	As above	As above	As above	As above
Chlebowski, *et al.,* 2008[166] *Calcium plus vitamin D supplementation and the risk of breast cancer*	Number of invasive breast cancer cases eligible: 1074 Number enrolled: 1067 cases, 1067 controls Number analyzed: 895 cases, 895 controls	As above	As above	As above	As above
de Boer, *et al.,* 2008[168] *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative*	Number eligible to be cases or controls:1699 controls from previous case-control study (Jackson 2008)‡ Number analyzed: 3097	As above	Vitamin D vs. control Number of events/number at risk (annualized %) by region by solar irradiance (Langley's); HR all NS 400-500: 459/6455 (1.02) vs. 435/6431 (0.97) 350-380: 414/5475 (1.08) vs. 423/5467 (1.10) 300-325: 281/5069 (0.77) vs. 279/5054 (0.77)	As above	As above

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial, continued part 1

Author, Year, Title	Number Approached, Screened, Eligible, Enrolled, Analyzed	Country and Setting	UV Exposure	Duration of Followup	Attrition
LaCroix, *et al.,* 2009[151] *Calcium plus vitamin D supplementation and mortality in postmenopausal women: The Women's Health Initiative calcium-vitamin D randomized controlled trial*	Number eligible to be cases or controls: 3594 (2982 from fracture case-control study, 612 from colorectal case-control cancer) Number enrolled: 2285 (323 cases, 1962 controls) Number analyzed: 2285 (323 cases, 1962 controls)	As above	As above	As above	As above

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial, continued part 2

Author, Year, Title	Interventions	Calcium and Other Nutrients	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Sponsor
Overall WHI Trial Fair	Vitamin D: 200 IU of vitamin D_3 BID (total: 400 IU/day) + 500 mg of calcium carbonate BID (total: 1000 mg/day) Control: Identical placebo BID	Personal use of ≤1000 mg of calcium and ≤600 IU of vitamin D daily allowed. Vitamin D allowance increased to ≤1000 IU daily during trial. At baseline, 39% of participants had intake ≥1200 mg and 43% of participants were using ≥400 IU daily of vitamin D. At year 6 of trial, nonprotocol vitamin D use reported by 52% of participants and nonprotocol calcium intake increased by about 100 mg daily in both groups during the trial.	See individual studies below	See individual studies below	National Institutes of Health
Jackson, *et al.*, 2006[163] *Calcium plus vitamin D supplementation and the risk of fractures*	As above	As above	Fractures: Verified by review of radiologic, magnetic resonance imaging, or operative reports by blinded physician adjudicators at each clinical center. Final adjudication of hip fractures performed centrally.	**Incidence and risk of hip fracture (number of cases/controls) by baseline vitamin D level (ng/mL)** ≥24: 32/49 vs. 42/40; OR 0.61 (95% CI 0.32 to1.15) 18 to 24: 44/40 vs. 52/39; OR 0.86 (95% CI 0.48 to 1.15) 13 to 18: 43/48 vs. 48/49; OR 0.92 (95% CI 0.53 to 1.62) <13: 47/44 vs. 49/48; OR 1.06 (95% CI 0.60 to 1.86) p=0.64 for interaction **Incidence and risk of total fracture (number of cases/controls) by baseline vitamin D level (ng/mL)** ≥24: 178/185 vs. 177/201; OR 1.09 (95% CI 0.81 to 1.47) 18 to 24: 170/179 vs. 205/191; OR 0.89 (95% CI 0.66 to 1.18) 13 to 18: 179/183 vs. 204/181; OR 0.87 (95% CI 0.66 to 1.16) <13: 196/167 vs. 182/204; OR 1.32 (95% CI 0.99 to 1.76) p=0.15 for interaction	National Heart, Lung, Blood Institute; General Clinical Research Center Program of the National Center for Research Resources, Department of Health and Human Services; Several investigators supported by industry

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial, continued part 2

Author, Year, Title	Interventions	Calcium and Other Nutrients	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Sponsor
Wactawski-Wende, *et al.,* 2006[167] *Calcium plus vitamin D supplementation and the risk of colorectal cancer*	As above	As above	Invasive colorectal cancer: Reported colorectal cancers verified in a blinded fashion by local and central physician adjudicators. Tests for colorectal cancer screening were not part of the protocol and were ordered by each participants' personal physician.	**Incidence and risk of colorectal cancer (number cases/controls) by baseline vitamin D level (ng/mL)** ≥23: 33/48 vs. 27/45; OR 1.15 (95% CI 0.58 to 2.27) 17 to 23: 44/41 vs. 34/32; OR 1.12 (95% CI 0.59 to 2.12) 12 to 23: 35/32 vs. 45/41; OR 0.99 (95% CI 0.51 to 1.91) <12.4: 46/39 vs. 42/28; OR 0.75 (95% CI 0.39 to 1.48) p=0.54 for interaction	National Heart, Lung, and Blood Institute, Department of Health and Human Service; many clinical centers supported by General Clinical Research Center program of the National Center for Research Resources; Several investigators supported by industry
Chlebowski, *et al.,* 2008[166] *Calcium plus vitamin D supplementation and the risk of breast cancer*	As above	As above	Invasive breast cancer: Confirmed by both local and central medical record and pathology report review by trained adjudicators who were blinded to group allocation.	**Incidence and risk of invasive breast cancer (number of cases/controls) by baseline vitamin D level (ng/mL)** ≥27: 86/109 vs. 76/86; aOR 0.89 (95% CI 0.58 to 1.36) 22 to 27: 95/87 vs. 86/98; aOR 1.25 (95% CI 0.83 to 1.90) 18 to 22: 102/87 vs. 92/84; aOR 1.07 (0.70 to 1.62) 13 to 18: 71/84 vs. 102/87; aOR 0.69 (95% CI 0.45 to 1.06) <13: 94/94 vs. 91/82; aOR 0.91 (0.60 to 1.39) p≥0.99 for interaction aOR = 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, current hormone therapy use	National Heart, Lung, and Blood Institute; one author supported by industry

Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial, continued part 2

Author, Year, Title	Interventions	Calcium and Other Nutrients	Determination of Outcomes	Clinical Health Outcomes Reported as: Vitamin D vs. Control	Sponsor
de Boer, *et al.,* 2008[168] *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative*	As above	As above	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.	**Incidence and risk of diabetes (number events/at-risk) by baseline vitamin D level (ng/mL)** ≥24: 20/395 vs. 24/397; OR 0.62 (95% CI 0.32 to 1.20) 17 to 24: 22/366 vs. 16/402; OR 1.60 (95% CI 0.80 to 3.18) 13 to 17: 17/371 vs. 30/394; OR 0.66 (95% CI 0.36 to 1.23) <13: 30/381 vs. 33/391; OR 1.07 (95% CI 0.62 to 1.82) p=0.59 for interaction	National Heart, Lung, and Blood Institute, Department of Health and Human Service; National Institutes of Health Roadmap for Medical Research
LaCroix, *et al.,* 2009[151] *Calcium plus vitamin D supplementation and mortality in postmenopausal women: The Women's Health Initiative calcium-vitamin D randomized controlled trial*	As above	As above	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.	**Incidence and risk of death (number cases/controls) by baseline vitamin D level (ng/mL)** ≥21: 53/404 vs. 50/425; aOR, 1.04 (95% CI 0.69 to 1.59) 14 to 21: 57/301 vs. 59/296; aOR, 0.96 (95% CI 0.64 to 1.45) <14: 47/270 vs. 57/266; aOR, 0.79 (95% CI 0.51 to 1.23) p=0.65 for interaction aOR = stratified by age group, randomization to hormone therapy or diet modification, and adjusted for age, ethnicity, latitude of clinical center, season of blood draw, treatment assignment	National Heart, Lung, and Blood Institute of U.S. Department of Health and Human Services

* Population characteristics are of all WHI trial participants (n=36282), not the subgroup with serum vitamin D levels.
† Text states 357 case-control pairs included for hip fracture and 1491 pairs included for total fracture, which is less than sum of numbers noted above for eligible fractures, but unclear why these numbers do not match.
‡ Discrepancy between the number of controls enrolled as cited in this case-control study (n=1699) and the number that were eligible from previous case-control study based on that study's publication (n=1491). Unclear how number analyzed was arrived at.

Abbreviations: aOR = adjusted odds ratio; BMI = body mass index; BID = twice a day; CI = confidence interval; HR = hazard ratio; IU = international unit; kg = kilogram; m = meter; mg = milligram; mL = milliliter; ng = nanogram; NR = not reported; NS = not significant; OR = odds ratio; SD = standard deviation; UV = ultraviolet; U.S. = United States; WHI = Women's Health Initiative; vs. = versus.

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Randomization Adequate	Allocation Concealment Adequate	Groups Similar at Baseline	Eligibility Criteria Specified	Outcome Assessors Masked	Care Provider Masked	Patient Masked	Reporting of Attrition, Crossovers, Adherence, and Contamination
Aloia, *et al.,* 2008[173]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Arvold, *et al.,* 2009[169]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Berlin, *et al.,* 1986[177]	No	No	Unclear	Yes	No	No	No	No
Bischoff, *et al.,* 2003[164]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brazier, *et al.,* 2005[156]	Yes	Unclear	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double blind	Yes
Chapuy, *et al.,* 2002[122]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes
Gallagher, *et al.,* 2012[155]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Randomization Adequate	Allocation Concealment Adequate	Groups Similar at Baseline	Eligibility Criteria Specified	Outcome Assessors Masked	Care Provider Masked	Patient Masked	Reporting of Attrition, Crossovers, Adherence, and Contamination
Gallagher, *et al.,* 2013[159]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gallagher, *et al.,* 2014[158]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grimnes, *et al.,* 2011[157]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Harris, *et al.,* 1999[175]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Honkanen, *et al.,* 1990[128]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Janssen, *et al.,* 2010[127]	Unclear	Yes	Yes (small difference in age)	Yes	Yes	Yes	Yes	Yes
Kärkkäinen, *et al.,* 2010[152]; Kärkkäinen, *et al.,* 2010[165]	Unclear	Unclear	Yes	Yes	No	No	No	Yes

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Randomization Adequate	Allocation Concealment Adequate	Groups Similar at Baseline	Eligibility Criteria Specified	Outcome Assessors Masked	Care Provider Masked	Patient Masked	Reporting of Attrition, Crossovers, Adherence, and Contamination
Kjaergaard, *et al.,* 2012[170]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Krieg, *et al.,* 1999[153]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Lehmann, *et al.,* 2013[115]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lips, *et al.,* 1996[160]; Ooms, *et al.,* 1995[120]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Lips, *et al.,* 2010[154]	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear, described as double-blind	Yes
Martineau, *et al.,* 2007[178]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pfeifer, *et al.,* 2000[161]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Randomization Adequate	Allocation Concealment Adequate	Groups Similar at Baseline	Eligibility Criteria Specified	Outcome Assessors Masked	Care Provider Masked	Patient Masked	Reporting of Attrition, Crossovers, Adherence, and Contamination
Pfeifer, *et al.,* 2009[162]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes
Talwar, *et al.,* 2007[176]; Aloia, *et al.,* 2005[174]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes
Wamberg, *et al.,* 2013[125]; Wamberg, *et al.,* 2013[132]	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes
Womens' Health Initiative Jackson, et al., 2003[145]; Jackson, *et al.,* 2006[163]; Wactawski-Wende, *et al.,* 2006[167]; Chlebowski, *et al.,* 2008[166]; de Boer, *et al.,* 2008[168]; LaCroix, *et al.,* 2009[151]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes
Wood, *et al.,* 2012[135]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix C3. Quality Ratings of Included Randomized Controlled Trials, continued

Author, Year	Acceptable Attrition and Difference Between Groups	Analyze People in the Groups in Which They Were Randomized	Post-Randomization Exclusions	Outcomes Prespecified	Fidelity to Intervention	Quality Rating	External Validity 1. Setting; 2. Unusual Techniques Used to Recruit; 3. Proportion of Screened Actually Enrolled; 4. Applicability to a Screened Population
Aloia, *et al.,* 2008[173]	Yes	Yes	OK	Yes	Yes	Fair	1. University hospital 2. None 3. 53% 4. Good
Arvold, *et al.,* 2009[169]	No (differential)	Yes	OK	Yes	Yes	Fair	1. Outpatient clinic 2. None 3. 16% 4. Fair, one clinic
Berlin, *et al.,* 1986[177]	Unclear	Yes	Unclear	Yes	Yes: Levels	Poor	1. University hospital 2. Unclear 3. NR 4. Unclear, not much reported about population
Bischoff, *et al.,* 2003[164]	No (high)	Yes	OK	Yes	Yes: Levels	Fair	1. Long-stay geriatric clinic 2. None 3. NR 4. Fair, elderly (≥60 years), institutionalized
Brazier, *et al.,* 2005[156]	Yes	Yes	No	Yes	Yes: Levels Compliance >90%	Fair	1. 50 centers 2. None 3. Unclear 4. Fair, only women
Chapuy, *et al.,* 2002[122]	Yes	Yes	OK	Yes	Yes: Levels Compliance 95%	Fair	1. Homes for the elderly 2. None 3. NR 4. Fair, elderly (≥64 years), institutionalized
Gallagher, *et al.,* 2012[155]	Yes	Yes	OK	Yes	Yes: Levels Compliance >90%	Good	1. University medical center 2. None 3. 8% 4. Fair, only women

Appendix C3. Quality Ratings of Included Randomized Controlled Trials, continued

Author, Year	Acceptable Attrition and Difference Between Groups	Analyze People in the Groups in Which They Were Randomized	Post-Randomization Exclusions	Outcomes Prespecified	Fidelity to Intervention	Quality Rating	External Validity 1. Setting; 2. Unusual Techniques Used to Recruit; 3. Proportion of Screened Actually Enrolled; 4. Applicability to a Screened Population
Gallagher, *et al.,* 2013[159]	Yes	Yes	No	Yes	Yes	Fair *	1. University medical center 2. None 3.36% 4. Fair, only women
Gallagher, *et al.,* 2014[158]	No	Yes	No	Yes	Yes	Fair	1. University medical center 2. None 3.35% 4. Fair, only women
Grimnes, *et al.,* 2011[157]	Yes	Yes	Yes	Unclear	Yes: Levels	Fair	1. Community 2. None 3. 31% 4. Good
Harris, *et al.,* 1999[175]	Yes	Yes	Some post-randomization exclusions	Unclear	Yes: Levels	Poor	1. Tufts University 2. Unclear recruitment 3. NR 4. Unclear
Honkanen, *et al.,* 1990[128]	Yes	Yes	Unclear	Yes	Yes: Levels	Fair	1. City hospital 2. None 3. 62% 4. Fair, only women
Janssen, *et al.,* 2010[127]	No	Yes	OK	Yes	Yes: Levels Compliance >90%	Fair	1. Outpatient clinics 2. None 3. NR 4. Fair, elderly (>65 years), instutionalized
Kärkkäinen, *et al.,* 2010[152]; Kärkkäinen, *et al.,* 2010[165]	Yes	Yes	OK	Yes	Yes: Levels Compliance 79%	Fair	1. Population-based 2. None 3. Unclear, reports numbers for subsample, not full screened group 4. Fair, only women

Appendix C3. Quality Ratings of Included Randomized Controlled Trials, continued

Author, Year	Acceptable Attrition and Difference Between Groups	Analyze People in the Groups in Which They Were Randomized	Post-Randomization Exclusions	Outcomes Prespecified	Fidelity to Intervention	Quality Rating	External Validity 1. Setting; 2. Unusual Techniques Used to Recruit; 3. Proportion of Screened Actually Enrolled; 4. Applicability to a Screened Population
Kjaergaard, *et al.,* 2012[170]	Yes	Yes	Yes (6 subjects)	Yes	Yes	Good	1. Community 2. None 3. 18% 4. Good
Krieg, *et al.,* 1999[153]	No (high)	Yes	OK	No	Yes: Levels	Fair	1. Nursing homes 2. NR 3. NR 4. Fair, elderly (≥62 years), institutionalized
Lehmann, *et al.,* 2013[115]	Yes	Yes	OK	Unclear	Yes: Levels	Fair	1. Healthy community population 2. None 3. NR 4. Good
Lips, *et al.,* 1996[160]; Ooms, *et al.,* 1995[120]	No (high)	Yes	Some post-randomization exclusions	Yes	Yes: Levels Compliance 85%	Fair	1. Community 2. None 3. NR 4. Fair, elderly (≥70 years), institutionalized
Lips, *et al.,* 2010[154]	Yes	Yes	Unclear	Yes	Yes: Levels Compliance 100%	Fair	1. Medical centers and nursing homes 2. None 3. 38% 4. Fair, elderly (≥70 years)
Martineau, *et al.,* 2007[178]	No (high)	Yes	Yes	Unclear (for AEs)	Yes: Levels	Fair	1. TB contact clinics 2. Recruited from TB clinics 3. 53% 4. Poor, TB clinics
Pfeifer, *et al.,* 2000[161]	Yes	Yes	OK	Yes	Yes: Levels	Fair	1. Population-based 2. None 3. 90% 4. Fair, elderly (≥70 years)

Appendix C3. Quality Ratings of Included Randomized Controlled Trials, continued

Author, Year	Acceptable Attrition and Difference Between Groups	Analyze People in the Groups in Which They Were Randomized	Post-Randomization Exclusions	Outcomes Prespecified	Fidelity to Intervention	Quality Rating	External Validity 1. Setting; 2. Unusual Techniques Used to Recruit; 3. Proportion of Screened Actually Enrolled; 4. Applicability to a Screened Population
Pfeifer, *et al.,* 2009[162]	Yes	Yes	OK	Yes	Yes: Levels	Fair	1. Population-based 2. None 3. NR 4. Fair, elderly (≥70 years)
Talwar, *et al.,* 2007[176]; Aloia, *et al.,* 2005[174]	Yes	Yes	OK	Unclear (for AEs)	Yes: Levels Compliance ~87%	Fair	1. Population-based 2. None 3. 54% 4. Fair, only women
Wamberg, *et al.,* 2013[125]; Wamberg, *et al.,* 2013[132]	Yes	Yes	OK	Yes	Yes: Levels Compliance >90%	Fair	1. University hospital 2. None 3. 59% 4. Good
Womens' Health Initiative Jackson, et al., 2003[145]; Jackson, *et al.,* 2006[163]; Wactawski-Wende, *et al.,* 2006[167]; Chlebowski, *et al.,* 2008[166]; de Boer, *et al.,* 2008[168]; LaCroix, *et al.,* 2009[151]	Yes	Yes	OK	Yes	No	Fair	1. Population-based 2. None 3. Case-control studies of subsamples of WHI trial 4. Fair, only women
Wood, *et al.,* 2012[135]	Yes	Yes	OK	Unclear (for AEs)	Yes: Levels Compliance >90%	Fair	1. Community 2. None 3. 72% 4. Good

* Protocol for recruitment into trial arms was changed post hoc durring the study.

Abbreviations: AE = adverse events; NR = not reported; TB = tuberculosis.