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

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Suggested Citation

Structured Abstract

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

**Purpose:** The U.S. Preventive Services Task Force 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 August 2014) and MEDLINE® (1946 to August 2014), and manually reviewed reference lists from applicable review articles.

**Study Selection:** We included systematic reviews; randomized, controlled trials (RCTs); and 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 (i.e., not selected for signs or symptoms of vitamin D deficiency or medical conditions that increase risk for deficiency) adults (age ≥18 years) from the United States, Canada, and Europe with reported serum 25-hydroxyvitamin D [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 participants randomized to vitamin D treatment (with or without calcium) (11 studies; pooled risk ratio [RR], 0.83 [95% confidence interval (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]). Vitamin D treatment was associated with possible decreased risk for falling, including risk for at least one fall (5 studies; RR, 0.84 [95% CI, 0.69 to 1.02]) and number of falls per person (5 studies; incidence rate ratio, 0.66 [95% CI, 0.50 to 0.88]). 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 on the effect of vitamin D treatment on risk for cardiovascular 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 the effects of vitamin D treatment 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 nonwhite, nonfemale populations. There was variability in types of assays used to measure 25(OH)D, baseline 25(OH)D levels of the study population, dosages used, calcium cosupplementation, 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 noninstitutionalized 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 the 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 potentially affects many other cellular regulatory functions.7

vitamin d deficiency is determined by measuring serum 25-hydroxyvitamin d [25(oh)d] concentrations. the major circulating form of vitamin d is 25(oh)d, which is considered the best indicator of vitamin d status.6 measurement of 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, which stimulates 1,25(oh)2d production in the kidneys, even when blood levels of vitamin d are low.8 while measurement of levels of vitamin d–binding protein (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 used competitive protein–binding methodology. because of the multiple limitations of this method, it has been supplanted by immunoassay methods as well as high-performance 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 intermethod and interlaboratory variability of 10 to 20 percent, however, which could limit the ability to precisely define an individual’s vitamin d status using 25(oh)d levels.12-16 in studies comparing how different assays would classify a person’s deficiency status, 4 to 32 percent of the samples would have been considered either
deficient or not deficient depending on the assay used.\textsuperscript{17-20} The greatest risk for differential classification occurred when an individual’s measured levels were close to defined cutoffs (i.e., those with very high and low levels were unlikely to be classified differently depending on the assay used).\textsuperscript{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 its measurement. While this reference material has improved the accuracy of LC-MS/MS analyses, it has been less helpful in standardizing immunoassays.\textsuperscript{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 procedures. VDSP is an international effort conducted by the National Institutes of Health (NIH) Office of Dietary Supplements, in collaboration with the Centers for Disease Control and Prevention; National Center for Environmental Health; NIST; and the Belgian Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, Ghent. VDSP developed protocols for standardizing procedures for measuring 25(OH)D in the National Health and Nutrition Examination Survey (NHANES). 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 those of the NIST-NIH Vitamin D Metabolites Quality Assurance Program, the College of American Pathologists, and the Vitamin D External Quality Assurance Scheme (DEQAS). These schemes are similar to those used in other areas of clinical chemistry and can lead to decreased variability.\textsuperscript{21} DEQAS,\textsuperscript{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.\textsuperscript{12}

The level of 25(OH)D used to define vitamin D deficiency has varied over the previous two decades. There is no consensus on optimal 25(OH)D concentrations. To determine sufficiency cutoff levels, researchers have examined the level of 25(OH)D associated with maximal suppression of parathyroid hormone,\textsuperscript{12,22-25} maximum calcium absorption,\textsuperscript{26,27} and reduced fracture risk.\textsuperscript{28} In fact, the actual requirements for bone health likely reflect a distribution of values rather than a specific cutpoint. This is problematic for the purposes of diagnosing deficiency because clinicians require a specific cutpoint 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\textsuperscript{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.\textsuperscript{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.\textsuperscript{13,31-34} The Endocrine Society suggests that, because of variability in laboratory measurements of 25(OH)D, targeting a higher 25(OH)D level than the goal level (such as 40 ng/mL [100 nmol/L]) better ensures that all persons meet goal levels.\textsuperscript{13} The IOM concluded, however, that 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) at
levels higher than 50 ng/mL (125 nmol/L). Experts agree that optimal serum 25(OH)D concentrations for extraskeletal health have not been established. 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 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. 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. 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 data, which was not corrected for assay drift per instructions from the National Center for Health Statistics to do so. Between 2001 and 2004, 77 percent of noninstitutionalized U.S. participants had 25(OH)D levels below 30 ng/mL.

When total 25(OH)D levels are used to define deficiency, blacks have a twofold to ninefold greater risk for deficiency and Hispanics a twofold to threefold greater risk for deficiency compared with whites. Additionally, one recent study found that black Americans not only had lower total 25(OH)D levels compared with white Americans, they also had lower vitamin D–binding protein levels. This resulted in similar concentrations of estimated bioavailable 25(OH)D between blacks and whites. 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 nonwhite 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 age 85 years or older. While some studies reported that females had greater risk for deficiency, not all studies confirmed this finding.

In NHANES, mean 25(OH)D levels were lower in 2000 to 2004 than in 1988 to 1994. Most of the differences in 25(OH)D levels 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.

**Etiology and Natural History**

Vitamin D is synthesized in the skin under the influence of ultraviolet (UV) rays in sunlight 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).

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 parathyroid hormone, which results in excessive bone resorption. Severe vitamin D deficiency causes a mineralization defect in the skeleton. 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, diffuse bone and joint pain, muscle weakness, and difficulty walking.

**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. 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 that evidence was suggestive only for nonvertebral fractures and that no conclusions could be reached about other fractures. 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 nonwhites. 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, and 1,25(OH)2D influences genomic expression in many cells. Therefore, researchers have hypothesized possible links between low 25(OH)D levels and muscle function, cancer, and metabolic, immune, and cardiovascular systems.

The 2009 AHRQ review concluded that 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 persons. This association, however, has not been observed in community-dwelling elderly persons. Similarly, a 2014 umbrella analysis of systematic reviews and meta-analyses concluded that there was insufficient evidence to draw conclusions about the association between low levels and fall risk. The review concluded that evidence suggested that high 25(OH)D levels are linked to an increased rate of falls. Evidence on the association between 25(OH)D levels and decline in physical functioning is inconsistent.
Although the 2009 AHRQ review concluded that evidence describing the association between 25(OH)D status and cardiovascular disease was inconsistent, more recent data, mostly from white or primarily white populations, suggest an inverse association between risk for cardiovascular disease and 25(OH)D levels. Several studies have suggested an association up to 24 ng/mL. This inverse association, however, has not been observed in black individuals.

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

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

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. A 2014 umbrella review of 107 systematic reviews and 74 meta-analyses of observational studies, however, stated that there was not enough evidence to make conclusions about the association between vitamin D levels and mortality. Although previous studies have concluded that there may be a U-shaped association in which high and low 25(OH)D levels are associated with an increased risk for mortality, 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.

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 twofold to fivefold increased risk for vitamin D deficiency (<20 ng/mL). Little or no UV light exposure (e.g., due to winter season, high latitude, and sun avoidance) is also associated with an increased risk for vitamin D deficiency. While sunscreen reduces the skin’s ability to produce vitamin D in response to UV light in controlled research settings, this association has not been found in population-based studies. This finding in population-based studies is likely due to incomplete application and/or because subjects who use sunscreen are more likely to be exposed to the sun for extended periods.

Obesity is associated with an almost twofold increased risk for vitamin D deficiency. This finding is possibly due to sequestration of vitamin D in fat cells or lifestyle differences (e.g.,
lower physical activity levels or lower dietary vitamin D intake). Low levels of physical activity, education attainment, and health status are modestly associated with vitamin D deficiency in some studies. Differences in diet, supplement use, and UV light 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. Genetic factors, including genetic variants of vitamin D–metabolizing genes, may influence serum 25(OH)D concentrations.

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. 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 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 to up to 600 IU per day for adults ages 18 to 70 years and 800 IU per day for adults older than age 70 years. 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.

Vitamin D deficiency can be treated by increased dietary intake, vitamin treatment, and increased UV light exposure. UV light exposure is usually not recommended because of increased skin cancer risk. While few foods naturally contain vitamin D, several food products (e.g., milk, cereals) are available fortified with vitamin D. An AHRQ-commissioned evidence report (not for the USPSTF) 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 in adults.

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 treatment. The trials in the meta-analysis, however, used varying doses, treatment time periods, and assays to measure 25(OH)D₂ and 25(OH)D₃. 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. The Endocrine Society suggests using either vitamin D₂ or D₃ treatment based on several studies showing that physiological doses of vitamin D₂ are equally effective as vitamin D₃ treatment at increasing and maintaining serum 25(OH)D levels and maintaining 1,25(OH)₂D levels. The IOM does not differentiate between use of vitamin D₂ or D₃ supplements in its recommendations.

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 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).

The amount of vitamin D required to effectively treat vitamin D deficiency also likely depends on an individual’s vitamin D absorptive capacity, 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, 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 twofold or threefold. 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 in health outcomes, such as mortality and fractures, when studies were stratified according to whether calcium was or was not given with the vitamin D supplements.

**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 bone mineral density than placebo in some studies, but not all. Vitamin D treatment (1,000 to 5,700 IU per day) for 6 to 36 months did not improve bone mineral density compared with placebo in older men, postmenopausal black women, or younger mixed-sex populations.

In 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, leg strength, or balance after 11 to 24 weeks 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 compared with those given placebo, but this improvement in strength was not seen in a third trial that used smaller doses (400 to 1,000 IU) of vitamin D.

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

Although some studies reported that vitamin D treatment (800 to 4,000 IU per day) was associated with decreased systolic (but not diastolic) blood pressure compared with placebo, 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) and placebo in risk for incident hypertension over 7 years.

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 include hypercalcemia, hyperphosphatemia, suppressed parathyroid hormone, and hypercalciuria and can occur after less than 4 weeks of continuous excess ingestion. These symptoms are variable and, while often nonspecific, are mostly related to hypercalcemia and hypercalciuria. 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 >200 ng/mL [500 nmol/L]) is well above the level considered to be sufficient. Acute toxicity has not been linked to vitamin D intake of less than 10,000 IU per day. The IOM recommends a tolerable upper intake level 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). While the Endocrine Society recommends a maintenance regimen of 4,000 IU per day, it states that 10,000 IU per day may be needed to correct deficiency in persons at risk for deficiency or during treatment of deficiency.

**Current Clinical Practice**

While we identified no reliable data on screening rates for vitamin D deficiency, available data suggest that testing rates for vitamin D status are increasing in general. A 2009 email survey of readers of Clinical Laboratory News (a 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 testing for 25(OH)D in their laboratories 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.141

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 eightfold between 2007 and 2010.142 Use of over-the-counter supplemental vitamin D has also increased over the past decade. In 2003 to 2006, for example, NHANES data reported that 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 2002.143 Vitamin D supplementation was lower in men than in 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 nonwhites.143,144

Recommendations of Other Groups

In 2011, the Endocrine Society recommended screening for vitamin D deficiency in persons at risk for deficiency. These identified groups include persons with diseases that predispose them to deficiency, such as chronic renal disease and malabsorption syndromes; persons who use medications that increase the risk for deficiency, such as glucocorticosteroids and antiepileptics; and persons who belong to an at-risk population, such as obese persons, blacks, and Hispanics. The Endocrine Society did not recommend screening for vitamin D deficiency in persons 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 that “vitamin D testing is generally unnecessary.” It also stated that “over-the-counter vitamin D supplements and summer sun exposure are sufficient for most otherwise healthy people.” However, the report also stated 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.”145

From 2009 to 2011, the IOM convened an expert panel to update the Recommended Dietary Allowance for vitamin D. The panel assessed data on health outcomes associated with calcium and vitamin D to determine dietary reference intakes for vitamin D for the U.S. population. While the IOM did not make statements about vitamin D screening, it concluded that most persons have an average serum 25(OH)D level above that needed for good bone health. 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.” The IOM noted, however, that some subgroups 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 previously issued recommendations on screening for vitamin D deficiency, it has issued several recommendations on the effects of vitamin D supplementation on the prevention of adverse health outcomes (e.g., falls, fractures, cancer, and cardiovascular disease) in populations that are not necessarily vitamin D deficient (i.e., they included general populations that may or may not be deficient). In 2012, the USPSTF recommended vitamin D supplementation for community-dwelling adults age 65 years or older at increased risk for falls (i.e., history of falls and mobility problems) to prevent future falls (B recommendation). The USPSTF examined the effects of vitamin D and calcium on fracture risk and concluded that 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).

The USPSTF also recently issued a recommendation statement on multivitamin and single vitamin supplementation for the primary prevention of cardiovascular disease and cancer. The recommendation was based on a review that included studies of vitamin D as part of multivitamins, as well as vitamin D given as a single tablet to persons who were likely receiving adequate nutritional vitamin D. The USPSTF concluded that the 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 in 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 in reducing the incidence of future health outcomes and the harms associated with screening and treatment in persons with vitamin D deficiency. It is implicit in the indirect chain of evidence 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, BMI, UV light exposure, and institutionalized status)?
2. What are the harms of screening (e.g., risk from procedure, false-positive or false-negative results)?
3. Does treatment of vitamin D deficiency with 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, BMI, UV light exposure, and institutionalized status)?
4. What are the adverse effects of treatment of vitamin D deficiency with 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, BMI, UV light exposure, and 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 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.
Contextual Questions

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.

The contextual questions are:

1. What is the association between serum 25(OH)D 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, lipid levels)?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through August 2014) and Ovid MEDLINE® (through the third week of August 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 evaluated only English-language articles and excluded studies published only as abstracts. We also excluded studies of nonhuman 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 Women’s Health Initiative (WHI) Calcium-Vitamin D (CaD) trial. 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 institutional 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 (age ≥18 years) in countries generalizable to the United States. As a result, we included only 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 neither known to have vitamin D deficiency nor 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 if they were not being treated with vitamin D for a specific health condition (e.g., low bone mineral density, 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 nonspecific and may be relatively common.147,148 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 who had osteoporosis or who had fallen in the past and were not excluded as long as the study did not purposely select patients with these conditions). We did not examine studies that targeted populations with signs of vitamin D deficiency (e.g., osteoporosis, history of nontraumatic fracture, or history of falls) or with medical conditions that increase risk for deficiency (e.g., liver, kidney, or malabsorptive disease) because screening for vitamin D deficiency and its treatment would be considered medical management of 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 or less, 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 the 25(OH)D level that constitutes deficiency, we stratified studies according to whether at least 90 percent of persons had levels less than 20 ng/mL (“<20 ng/mL” in this report) or at least 90 percent had levels less than 30 ng/mL with at least 10 percent greater than 20 ng/mL (“≤30 ng/mL” in this report). 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 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 criteria\(^{149}\) 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, enrollment criteria and whether they resulted in a highly selected population, use of run-in and washout 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.\(^{149}\)

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, serious adverse events, and hypercalcemia) of treatment with vitamin D and/or calcium versus placebo, no treatment, or only calcium. We used the DerSimonian-Laird random effects model with Review Manager Version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) to conduct these analyses. Analyses for clinical outcomes used data on total study duration (including time following discontinuation of vitamin D treatment). For number of 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.\(^{150}\) For number of falls per person, one study reported an adjusted rate ratio and we conducted a sensitivity analysis to assess the effect of the adjusted rate ratio on the summary rate ratio. Rate ratio analysis using the profile likelihood model were conducted with StataIC 12.0 (StataCorp LP, College Station, TX).

We assessed statistical heterogeneity using the standard chi-squared test and \(I^2\) statistic.\(^{151}\) 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 combined with calcium), vitamin D dose (≤400 vs. >400 IU per day), study duration (≤12 vs. >12 months), and participant mean age (≤70 vs. >70 years).

Several analyses included nested case-control studies from the WHI. We performed sensitivity analyses restricted to RCTs, excluding the results of the WHI subanalyses. 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).

Response to Public Comments

This systematic review was posted for public comment from June 24 to July 21, 2014. The systematic review team reviewed and considered relevant comments. No comments identified missing studies that met inclusion criteria or errors in the evidence reviewed, resulting in no changes to the findings or the conclusion of this report.
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?

We found no study that addressed this key question.

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

Summary

Eleven studies examined the effect of vitamin D treatment on mortality,\textsuperscript{120,122,152-160} five examined fractures,\textsuperscript{122,161-164} six examined falls,\textsuperscript{122,136,162,163,165,166} one examined cancer,\textsuperscript{167,168} two examined type 2 diabetes,\textsuperscript{136,169} two examined psychosocial functioning and disability,\textsuperscript{170,171} and one examined physical functioning.\textsuperscript{155} While vitamin D treatment was associated with decreased risk for mortality compared with placebo/no treatment (pooled RR, 0.83 [95% CI, 0.70 to 0.99]; $I^2=0\%$; 11 studies), these studies were not designed to assess mortality.\textsuperscript{120,122,152-160} Additionally, the benefits of vitamin D treatment were confined to trials of elderly institutionalized participants with high mortality rates.\textsuperscript{120,122,154} The reduction was no longer significantly reduced when we examined only noninstitutionalized populations (RR, 0.93 [95% CI, 0.73 to 1.18]; $I^2=0\%$; 8 studies).\textsuperscript{152,153,155-158} 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).\textsuperscript{122,161-164} Falls data were mixed: while vitamin D treatment was not associated with decreased risk for experiencing a fall (pooled RR, 0.84 [95% CI, 0.69 to 1.02]; $I^2=70\%$; 5 trials),\textsuperscript{122,162,163,165,166} our primary fall endpoint, 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).\textsuperscript{136,162,163,165,166} We found limited data ($\leq2$ 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 Appendixes C1 and C2). Seven of these studies were conducted in populations in which at least 90 percent of participants had 25(OH)D levels of less than 20 ng/mL\textsuperscript{122,155,157-160,162} and 10 in populations in which at least 90 percent of participants had levels of 30 ng/mL or less.
(but at least 10% had levels of ≥20 ng/mL). Eleven studies examined the effect of vitamin D treatment on mortality, five examined effects on fracture, six examined effects on falls, one examined effects on cancer, two examined effects on type 2 diabetes, two examined effects on psychosocial functioning and disability, and one examined effects on physical functioning. 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/m². 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 light exposure was not well quantified in any study. Only six of 17 studies reported race. One study comprised 100 percent African Americans. 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 coadministered 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 levels in participants, four studies used competitive protein binding, eight used immunoassay methods, one used HPLC, and four used LC-MS/MS. Two trials used laboratories that were participating in an external accuracy-based testing system (DEQAS). Two trials were rated good quality and 15 were rated fair quality (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). The results of the overall 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 trial 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 Appendices 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. 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. The baseline characteristics of the cases and controls in the WHI CaD subanalyses 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...
Five studies were conducted in populations with a mean age older than 70 years, three trials specifically focused on older (age >80 years) women in nursing or elderly homes, and one trial specifically focused on younger (age ≥45 years) women. 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) compared with placebo, calcium alone, or no treatment. The estimates in some trials were extremely imprecise, however, because of very few events. In four studies that reported at least 10 events, RR estimates ranged from 0.51 to 0.90. 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 1, mortality was not the primary outcome in any study and was usually not a prespecified outcome. In addition, in the only good-quality trial, a U.S. 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 postmenopausal women with a mean age of 67 years, no deaths were observed in any group after 12 months. 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 with 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. The two trials with the RR that most suggested a possible benefit of vitamin D treatment on mortality (0.75 [95% CI, 0.54 to 1.05] and 0.51 [95% CI, 0.25 to 1.02]) examined the effects of 400 to 800 IU per day of vitamin D₃ treatment (with or without calcium) in older (mean age, 80 to 85 years) vitamin D–deficient (≤30 ng/mL) institutionalized European women who experienced high mortality rates (9% to 20%) during followup. When we analyzed trials of institutionalized and noninstitutionalized persons 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 4 to 6 percentage points. The reduction was no longer significantly reduced when we examined only noninstitutionalized populations (RR, 0.93 [95% CI, 0.73 to 1.18]; $I^2=0\%$; 8 studies; Figure 3). In sensitivity analyses, the reduction in mortality occurred only when studies with more than 12 months duration were pooled and in studies whose population had a mean age older than 70 years. Stratification by baseline 25(OH)D level (<20 vs. ≤30 ng/mL), treatment regimen (vitamin D treatment alone vs. 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 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 (with or without calcium) on risk for any type of fracture in ambulatory and institutionalized vitamin D–deficient persons (94%...
women) with mean ages of 62 to 85 years (N=3,551). A 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 1 (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. Stratifying studies by institutionalized status, baseline 25(OH)D level (<20 vs. ≤30 ng/mL), treatment regimen (vitamin D treatment alone vs. 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 pooled ORs affected findings.

In three trials and one nested case-control study that reported data separately (N=1,619), there was no significant reduction in hip fracture risk with vitamin D3 treatment versus placebo in any individual study, and the pooled estimate was close to 1 (pooled RR, 0.96 [95% CI, 0.72 to 1.29]; $I^2=46\%$; Figure 5). Considering only 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]).

**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). 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), institutionalized status, mobility problems, or multiple comorbid conditions. 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. While the overall summary RR indicated no statistically significant effect on risk for experiencing at least one fall in participants 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 that reported a statistically significant effect on risk for falls was a German trial conducted in an ambulatory population (75% women) with 25(OH)D levels of 30 ng/mL or less and a mean age of 77 years (n=242). 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 cosupplementation with vitamin D and calcium\textsuperscript{122,166} in order to separately examine the three trials of vitamin D\textsubscript{3} 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]; \textit{I}^2=0\%).\textsuperscript{162,163,165}

Five fair-quality trials examined the effect of 400 to 1,000 IU per day of vitamin D\textsubscript{3} treatment (with or without calcium) on the number of falls per individual (\textit{N}=1,399, Table 3).\textsuperscript{136,162,163,165,166} 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]; \textit{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 persons.\textsuperscript{165} 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 coadministered 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.\textsuperscript{162,163,165,166} In three of these trials, the risk estimates were similar.\textsuperscript{162,163,166} 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).\textsuperscript{165} 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. \textgeq12 months). The one trial that examined only risk for falls (not rate of falls) reported no reduced risk for falls in those given vitamin D\textsubscript{3} treatment with calcium versus placebo (RR, 1.03 [95% CI, 0.90 to 1.18]).\textsuperscript{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, 64 years) population in which falls were collected as part of adverse event reporting; few falls were recorded during followup, leading to wide CIs.\textsuperscript{136}

**Effect of Vitamin D Treatment on Cancer Risk**

Effects of 7 years of treatment with 400 IU per day of vitamin D\textsubscript{3} and calcium on risk for breast cancer (\textit{n}=909 cases) and colorectal cancer (\textit{n}=237 cases) in women with low 25(OH)D levels were examined in case-control studies nested within the WHI CaD trial.\textsuperscript{167,168} Compared with placebo, treatment with vitamin D\textsubscript{3} and calcium was not associated with a decreased risk for colorectal or breast cancer in women with 25(OH)D levels in the deficiency range (OR, 1.15 [95% CI, 0.58 to 2.27] for \textlt23 vs. \textgeq23 ng/mL for colorectal cancer and adjusted OR, 0.89 [95% CI, 0.58 to 1.36] for \textlt27 vs. \textgeq27 ng/mL for breast cancer).\textsuperscript{167,168}

**Effect of Vitamin D Treatment on Type 2 Diabetes Risk**

One fair-quality trial (\textit{n}=305)\textsuperscript{136} and one case-control study nested within the WHI CaD trial (\textit{n}=192 cases)\textsuperscript{169} examined the effects of treatment with 400 to 1,000 IU per day of vitamin D\textsubscript{3}...
(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 that vitamin D treatment was associated with reduced risk for developing type 2 diabetes, and the summary RR was close to 1 (pooled RR, 0.93 [95% CI, 0.68 to 1.27]; I²=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-Åsberg 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,¹⁷¹ there was no difference after 6 months of treatment on any scale (Table 2 and Appendix C1). There were also no significant differences between treatment groups in 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 eight weekly doses of 50,000 IU of vitamin D₃ on psychosocial functioning and disability as measured by the Fibromyalgia Impact Questionnaire.¹⁷² In vitamin D–deficient (<25 ng/mL) healthy persons (40% female) with a mean age of 59 years,¹⁷⁰ those randomized to vitamin D₃ treatment showed improvement in their overall score after 8 weeks (Table 2 and Appendix C1). Individuals in the placebo group, on the other hand, experienced worsening scores (mean difference from baseline on scale from 0 to 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 of vitamin D₃ on physical functioning in U.S. and European populations with an average age of 78 years.¹⁵⁵ Compared with placebo, vitamin D₃ treatment did not result in greater improvement on the Short Physical Performance Battery, a validated measure of lower extremity functioning.¹⁷³

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.¹²⁰,¹²²,¹⁵⁴ 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 light exposure.
Key Question 4. What Are the Adverse Effects of Treatment of Vitamin D Deficiency With Vitamin D?

Summary

Data on the adverse events of treatment of vitamin D deficiency with vitamin D (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 D<sub>3</sub> or D<sub>2</sub> (with or without calcium) resulted in more total adverse events, serious adverse events, withdrawals due to adverse events, hypercalcemia, kidney stones, or gastrointestinal symptoms compared with control intervention over 6 weeks to 4 years.

Evidence

We identified 24 trials that examined adverse events associated with vitamin D treatment (with or without calcium) in vitamin D–deficient (<20 or ≤30 ng/mL) populations (N=4,471; Table 4 and Appendix C1). The mean age of participants ranged from 31 to 85 years. Seven trials were conducted in the United States, 156,159,160,174-177 16 were conducted in Europe, 115,120,122,125,127,128,132,133,136,154,157,158,165,171,178,179 and one was conducted in both the United States and Europe. 155 These trials examined vitamin D<sub>3</sub> treatment (21 trials), 120,122,125,127,128,132,133,136,153-160,165,170,171,174,175,177,178 vitamin D<sub>2</sub> treatment (2 trials), 176,179 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. Nineteen 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 156,171 and 20 were rated fair quality. 115,120,122,125,127,128,132,133,136,153-155,157-160,165,170,174,175,177,179 We excluded two poor-quality studies from the synthesis of the results 176,178 (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 six fair-quality trials reported on total adverse events in participants being treated with 400 to 7,000 IU per day or 20,000 to 40,000 IU per week of vitamin D<sub>3</sub> or D<sub>2</sub> for 6 to 36 months (Table 4 and Appendix C1; N=1,296). 125,132,133,136,153-157,158,171,175,177 No trial reported significantly more total adverse events in the intervention group compared with the control group.

One good-quality and six fair-quality trials examined the effect of 400 to 4,800 IU per day or 8,400 IU per week of vitamin D<sub>3</sub> treatment (with or without calcium) on serious adverse events in vitamin D–deficient white U.S. or European women with mean ages of 37 to 78 years (N=1,401). 136,155-157,159,160,175,177 No trial reported a significantly increased risk for serious
adverse events. The summary RR did not indicate a significantly increased risk for serious adverse events in participants 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 adverse events in white U.S. and European women randomized to 400 to 4,800 IU per day or 8,400 IU per week of vitamin D3 treatment (with or without calcium) compared with placebo or no vitamin D treatment (N=938).\(^{154-157,160}\) Withdrawals were not significantly increased in the intervention group compared with the control group 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 between the intervention and control groups, but the estimate was very imprecise (7 vs. 0; RR, 15.00 [95% CI, 0.87 to 259.82]).\(^{154}\) 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 adverse events (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 of vitamin D\(_3\) or D\(_2\) (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.\(^{115,120,122,125,128,133,136,155-160,165,171,174,175,177,179}\) 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.\(^{156,157,160}\) One trial defined hypercalcemia as levels of 10.6 mg/dL or greater,\(^{174}\) while two trials defined it as levels greater than 10.2 mg/dL.\(^{158,159}\) The remaining trials did not report how hypercalcemia was detected or defined.\(^{115,120,122,125,128,133,136,155,165,171,174,175,177,179}\) No individual study reported a significantly higher incidence of hypercalcemia in the intervention group compared with the control group, although the number of events was small, and seven trials reported no cases.\(^{115,125,128,133,158,165,174,179}\) The nine trials with at least one participant with hypercalcemia measured calcium as part of followup.\(^{120,122,136,156,157,159,160,171,174,177}\) 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.\(^{155}\) 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).\(^{122,158,155,156,158,159,175,177}\) Five fair-quality trials found no significant differences in the risk for gastrointestinal symptoms in intervention compared with control participants (Table 4 and Appendix C1).\(^{122,136,157,165,171}\) Five trials reported no adverse events in any study participants, regardless of group allocation.\(^{115,170,176,178,179}\)

**Effect of Vitamin D Treatment on Adverse Events in Patient Subgroups**

In three trials that included nonwhite participants, adverse events were not increased in the vitamin D treatment group compared with placebo, but adverse events were not stratified by
race. Few trials enrolled both men and women. No study evaluated risk for adverse events stratified by sex. No data were available to determine risk for adverse events according to BMI or UV light 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)D levels was available, it had limitations. For example, we identified only two good-quality studies,\textsuperscript{156,171} 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 light 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 D\textsubscript{3} treatment and mortality, only a nested case-control analysis within the WHI CaD trial\textsuperscript{152} was designed to assess mortality risk associated with vitamin D\textsubscript{3} supplementation. While no individual study found that vitamin D\textsubscript{3} 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 D\textsubscript{3} treatment was associated with a slight but significant decrease in risk for mortality in persons with 25(OH)D 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,\textsuperscript{58,93} but not all,\textsuperscript{45} recent systematic reviews that included studies of persons with and without deficiency have concluded that supplementation in older persons (mainly women) seems to slightly reduce all-cause mortality.

Vitamin D treatment was associated with a nonsignificant reduction in the risk for experiencing one or more falls and a significantly reduced overall burden of falls, as measured by the number of falls per individual. Four trials examined both risk for falling and rate of falls per person.\textsuperscript{162,163,165,166} Risk estimates were similar in three of these trials.\textsuperscript{162,163,166} 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).\textsuperscript{165} This trial was conducted in an institutionalized population with a high comorbidity burden, and its results could account for the potential discrepancy between the pooled falls outcome estimates.

Vitamin D\textsubscript{3} treatment was not associated with decreased risk for fracture in vitamin D-deficient persons. Data were limited (≤2 studies) on its effect on cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning in persons with 25(OH)D 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, cancer, falls, or fracture outcomes.\textsuperscript{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 adverse event reporting was often suboptimal. Given the variability of the 25(OH)D 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, so 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 on the effects of vitamin D supplementation (with or without calcium) on mortality in noninstitutionalized populations. We excluded all of these trials from our review because they did not measure 25(OH)D levels in all participants at baseline. None of the three trials found that vitamin D supplementation (with or without calcium) was associated with decreased mortality risk. The USPSTF concluded that the evidence on the effects of vitamin D supplementation (alone or with other vitamins) on mortality risk was insufficient to make a recommendation.

A 2011 systematic review and meta-analysis by Chung and colleagues examined 16 studies of the association between vitamin D supplementation (with or without calcium) and fracture risk. Because the review did not require that 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 in institutionalized elderly persons. 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 that the evidence on the effects of higher doses was insufficient to make a recommendation.

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 persons at high risk for falls. We included three studies not in the previous review, two because they were published after that review and one because the population was institutionalized and the 2010 review examined only noninstitutionalized populations. Michael and colleagues concluded that vitamin D supplementation (with or without calcium) was associated with a reduced risk for falling. The USPSTF recommended that vitamin D supplementation be given to community-dwelling adults age 65 years or older who are at increased risk for falls, regardless of 25(OH)D status.

Two systematic reviews (in 2011 and 2013) examined whether vitamin D supplementation with or without calcium was associated with cancer risk. The four trials included in these prior systematic reviews were excluded from our review because the study populations, including that from the full WHI CaD trial, were not known to have low 25(OH)D levels. The authors of the most recent systematic review concluded that vitamin D and/or calcium supplementation showed no overall effect on cancer. The USPSTF concluded that the evidence was insufficient to make a recommendation.
Previous systematic reviews on the effects of vitamin D and calcium supplementation on fractures, falls, and cancer in general populations (not selected for deficiency) found that adverse event rates were generally low in both treatment and placebo groups. 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 of vitamin D and 1,000 mg calcium per day (participants were also allowed to take up to 1,000 IU of vitamin D and 1,000 mg calcium per day on their own). We did not include this evidence, however, because the reviews derived harms data from persons with unknown vitamin D status. Harms were not reported for the subgroup with 25(OH)D levels from the WHI case-control analyses.

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. 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 ORs 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 in populations similar to those that 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 or osteopenia (4 studies), risk factors for falls (5 studies), prediabetes (1 study), heart failure (2 studies), or tuberculosis (1 study). 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. The effects of vitamin D treatment on fall risk and functional status or physical performance were mixed. Vitamin D treatment did not reduce fall risk in persons with vitamin D deficiency who had recently suffered a hip fracture or who had one or more health problems or functional limitations at admission to a geriatric rehabilitation center; however, vitamin D treatment reduced falls in vitamin D–deficient populations with a history of falls. Although community-dwelling homebound persons experienced an improvement in functional status with vitamin D treatment, long-term inpatients and those in a rehabilitation center with health problems or functional limitations did not experience an improvement in physical...
functioning or the ability to complete activities of daily living with vitamin D treatment. In one trial, risk for diabetes was not reduced when vitamin D treatment was given to persons with prediabetes who had low 25(OH)D levels.

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 adverse events was not highly reliable because most trials were not designed to assess harms and had suboptimal adverse event 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 populations other than white females of European descent. While we attempted 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 baseline 25(OH)D levels, the dosages used, the use of calcium cosupplementation, 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 of vitamin D deficiency, the expected effect of misclassification would be to attenuate estimates of treatment benefit, as some persons who are not vitamin D deficient would be classified and treated as such. These persons would therefore be subject to unnecessary treatment and any associated harms.

For the WHI CaD trial, the largest trial, we included only the results of the nested case-control studies in which 25(OH)D levels were measured. Statistical power was limited for many of these stratified analyses. The results for the overall WHI CaD trial, however, were similar to those for the nested case-control studies; vitamin D supplementation did not significantly reduce risk for death, colorectal or breast cancer, or fractures. We were not able to include harm outcomes from the WHI CaD trial because they were not stratified by 25(OH)D status. The WHI CaD trial found 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 the question of 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, the level of bioavailable 25(OH)D was similar. However, this is only one study, and
the results require replication. This study highlights the need for ongoing research to examine the most accurate way to measure vitamin D deficiency, especially in nonwhite 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 are optimal, other expert bodies, including the Endocrine Society, National Osteoporosis Foundation, and International Osteoporosis Foundation, recommend 25(OH)D levels of greater than 30 ng/mL. Our survey of the literature on the association between 25(OH)D levels and outcomes (Appendix A1) found that data are still lacking about the levels 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 UV light 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., age >70 years) and/or institutionalized populations that were mainly female. 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 persons 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, is designed to address many of these issues. This large randomized, double-blind, placebo-controlled trial examines 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 in a multiethnic population of 20,000 U.S. men age 50 years or older and women age 55 years or older. The researchers estimate that about 16,000 participants will have baseline 25(OH)D levels measured. 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 persons 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.
REFERENCES


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172. Williams DA, Arnold LM. Measures of fibromyalgia: Fibromyalgia Impact Questionnaire (FIQ), Brief Pain Inventory (BPI), Multidimensional Fatigue Inventory


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Figure 1. Analytic Framework

Screening

1. Asymptomatic adults
   2. Adverse effects
   3. Vitamin D deficient
   4. Not vitamin D deficient

Treatment

3. Adverse effects
4. Decreased morbidity from selected conditions
   - Reduced disability
   - Improved psychosocial functioning
   - Reduced mortality
Figure 2. Meta-Analysis of Effects of Vitamin D Treatment on Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D &lt;20 ng/mL*</td>
<td>3 95</td>
<td>1 96</td>
<td>0.8%</td>
<td>3.03 (0.32 to 28.63)</td>
<td></td>
</tr>
<tr>
<td>Brazier, et al., 2005157</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapuy, et al., 2002122*</td>
<td>70 393</td>
<td>45 190</td>
<td>27.9%</td>
<td>0.75 (0.54 to 1.05)</td>
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</tr>
<tr>
<td>Gallagher, et al., 2013163</td>
<td>0 93</td>
<td>0 17</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Gallagher, et al., 2014159</td>
<td>0 160</td>
<td>0 38</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Grimnes, et al., 2011158</td>
<td>0 51</td>
<td>1 52</td>
<td>0.3%</td>
<td>0.34 (0.01 to 8.15)</td>
<td></td>
</tr>
<tr>
<td>Lips, et al., 2010155</td>
<td>1 114</td>
<td>0 112</td>
<td>0.3%</td>
<td>2.95 (0.12 to 71.60)</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>906</td>
<td>585</td>
<td>29.2%</td>
<td>0.78 (0.56 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>74</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau²=0.00; Chi²=2.40, df=3 (p=0.49); I²=0%</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z= .51 (p=0.13)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D ≤30 ng/mL†</td>
<td>0 142</td>
<td>0 21</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Gallagher, et al., 2012156</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kärkkäinen, et al, 2010153</td>
<td>3 290</td>
<td>1 313</td>
<td>0.8%</td>
<td>3.24 (0.34 to 30.95)</td>
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<tr>
<td>Krieg, et al, 1999142</td>
<td>21 124</td>
<td>26 124</td>
<td>11.5%</td>
<td>0.81 (0.48 to 1.36)</td>
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<tr>
<td>LaCroix, et al., 2005154</td>
<td>104 675</td>
<td>116 678</td>
<td>52.5%</td>
<td>0.90 (0.71 to 1.15)</td>
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<tr>
<td>Ooms, et al., 1995120</td>
<td>11 177</td>
<td>21 171</td>
<td>0.3%</td>
<td>0.51 (0.25 to 1.02)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1408</td>
<td>1397</td>
<td>70.8%</td>
<td>0.82 (0.62 to 1.10)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>139</td>
<td>164</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau²=0.02; Chi²=3.72, df=3 (p=0.29); I²=19%</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z=1.33 (p=0.18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI)          | 2314           | 1812           | 100.0% | 0.83 (0.70 to 0.99)     |                         |
| Total events              | 213            | 211            |        |                         |                         |
| Heterogeneity: Tau²=0.00; Chi²=0.30, df=7 (p=0.51); I²=0% |                         |
| Test for overall effect: Z=2.10 (p=0.04) |                         |
| Test for subgroup differences: Chi²=0.07, df=1 (p=0.80); I²=0% |                         |

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.
**Figure 3. Meta-Analysis of Effects of Vitamin D Treatment on Mortality by Institutionalized Status**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutionalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapuy, et al., 2002122</td>
<td>70</td>
<td>393</td>
<td>45</td>
<td>190</td>
<td>27.9%</td>
</tr>
<tr>
<td>Krieg, et al., 1999144</td>
<td>21</td>
<td>124</td>
<td>26</td>
<td>124</td>
<td>11.5%</td>
</tr>
<tr>
<td>Ooms, et al., 1995120</td>
<td>11</td>
<td>177</td>
<td>21</td>
<td>171</td>
<td>6.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>694</td>
<td>485</td>
<td>45.7%</td>
<td>0.72 (0.56 to 0.94)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>102</td>
<td>92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2=0.00; Chi^2=1.24, df=2 (p=0.54); P=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=2.43 (p=0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Noninstitutionalized   |                  |                |        |                     |                     |
| Brazier, et al., 2005157| 3                | 95             | 1      | 96                  | 0.6%                |
| Galagher, et al., 2012156| 0               | 142            | 0      | 21                  | Not estimable       |
| Gallagher, et al., 2013160| 0              | 93             | 0      | 17                  | Not estimable       |
| Gallagher, et al., 2014155| 0              | 160            | 0      | 38                  | Not estimable       |
| Grimnes, et al., 2011154| 0                | 51             | 1      | 52                  | 0.3%                |
| Karkkainen, et al., 2010153| 3              | 290            | 1      | 313                 | 0.6%                |
| LaCrox, et al., 2009152*| 104             | 675            | 116    | 678                 | 52.5%               |
| Lips, et al., 2010155  | 1                | 114            | 0      | 112                 | 0.3%                |
| Subtotal (95% CI)      | 1620             | 1327           | 54.3%  | 0.93 (0.73 to 1.19) |
| Total events           | 111              | 119            |        |                     |                     |
| Heterogeneity: Tau^2=0.00; Chi^2=3.20, df=4 (p=0.52), P=0% |
| Test for overall effect: Z=0.62 (p=0.53) |

| Total (95% CI)         | 2314             | 1812           | 100.0% | 0.83 (0.70 to 0.99) |
| Total events           | 213              | 211            |        |                     |
| Heterogeneity: Tau^2=0.00; Chi^2=0.30, df=7 (p=0.51), P=0% |
| Test for overall effect: Z=2.10 (p=0.04) |
| Test for subgroup differences: Chi^2=1.87, df=1 (p=0.17), P=48.6% |

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

**Abbreviation:** CI = confidence interval.
Figure 4. Meta-Analysis of Effects of Vitamin D Treatment on Any Type of Fracture Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D &lt;20 ng/mL*</td>
<td>97</td>
<td>55</td>
<td>23.7%</td>
<td>0.85 (0.64 to 1.13)</td>
<td></td>
</tr>
<tr>
<td>Chapuy, et al., 2002‡</td>
<td>3</td>
<td>6</td>
<td>1.0%</td>
<td>0.48 (0.12 to 1.84)</td>
<td></td>
</tr>
<tr>
<td>Pfeifer, et al., 2008§</td>
<td>463</td>
<td>257</td>
<td>25.4%</td>
<td>0.83 (0.63 to 1.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>100</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau²=0.00, Chi²=0.88, df=1 (p=0.41), I²=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z=1.31 (p=0.19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D ≤30 ng/mL‡</td>
<td>545</td>
<td>591</td>
<td>55.0%</td>
<td>1.00 (0.92 to 1.09)</td>
<td></td>
</tr>
<tr>
<td>Jackson, et al., 2006§</td>
<td>49</td>
<td>36</td>
<td>16.0%</td>
<td>1.31 (0.90 to 1.91)</td>
<td></td>
</tr>
<tr>
<td>Lips, et al., 1996¶</td>
<td>7</td>
<td>12</td>
<td>3.8%</td>
<td>0.57 (0.23 to 1.41)</td>
<td></td>
</tr>
<tr>
<td>Pfeifer, et al., 2009¶</td>
<td>1373</td>
<td>1458</td>
<td>74.6%</td>
<td>1.94 (0.81 to 1.34)</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>601</td>
<td>639</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau²=0.02, Chi²=3.48, df=2 (p=0.16), I²=42%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z=0.29 (p=0.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1836</td>
<td>1715</td>
<td>100.0%</td>
<td>0.98 (0.82 to 1.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>701</td>
<td>700</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau²=0.01, Chi²=5.99, df=4 (p=0.21), I²=32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z=0.28 (p=0.78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for subgroup differences:</strong> Chi²=1.33, df=1 (p=0.25), I²=25.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.
Figure 5. Meta-Analysis of Effects of Vitamin D Treatment on Hip Fracture Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D &lt;20 ng/mL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapuy, et al., 2002^{122}†</td>
<td>27</td>
<td>393</td>
<td>21</td>
<td>190</td>
<td>19.5%</td>
<td>0.62 (0.36 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Pfaaer, et al., 2000^{162}</td>
<td>0</td>
<td>70</td>
<td>1</td>
<td>67</td>
<td>0.8%</td>
<td>0.32 (0.01 to 7.70)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>463</td>
<td>257</td>
<td></td>
<td></td>
<td>20.3%</td>
<td>0.61 (0.36 to 1.04)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>27</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2=0.00; Chi^2=0.16, df=1 (p=0.69); I^2=0%
Test for overall effect: Z=1.81 (p=0.07)

25(OH)D ≤30 ng/mL‡

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson, et al., 2000^{194}†</td>
<td>134</td>
<td>260</td>
<td>149</td>
<td>285</td>
<td>49.8%</td>
<td>0.90 (0.82 to 1.13)</td>
<td></td>
</tr>
<tr>
<td>Lips, et al., 1996^{151}†</td>
<td>49</td>
<td>177</td>
<td>36</td>
<td>171</td>
<td>29.9%</td>
<td>1.31 (0.90 to 1.91)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>443</td>
<td>456</td>
<td></td>
<td></td>
<td>79.7%</td>
<td>1.07 (0.80 to 1.48)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>183</td>
<td>185</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2=0.03; Chi^2=2.30, df=1 (p=0.13); I^2=57%
Test for overall effect: Z=0.48 (p=0.63)

Total (95% CI) 906 713 100.0% 0.96 (0.72 to 1.29)

Total events 210 207

Heterogeneity: Tau^2=0.04; Chi^2=5.57, df=3 (p=0.13); I^2=46%
Test for overall effect: Z=0.26 (p=0.80)

Test for subgroup differences: Chi^2=3.29, df=1 (p=0.07), I^2=69.6%

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

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; CI = confidence interval.
* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Vitamin D Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D &lt;20 ng/mL*</td>
<td>251</td>
<td>393</td>
<td>118</td>
<td>190</td>
<td>31.0%</td>
<td>1.03 (0.90 to 1.18)</td>
<td></td>
</tr>
<tr>
<td>Chapuy, et al., 2002‡†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfeifer, et al., 2000§</td>
<td>11</td>
<td>70</td>
<td>19</td>
<td>67</td>
<td>6.9%</td>
<td>0.55 (0.29 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>463</td>
<td>267</td>
<td>37.9%</td>
<td>0.82 (0.45 to 1.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>262</td>
<td>137</td>
<td>Heterogeneity: Tau²=0.14, Chi²=3.38, df=1 (p=0.07), I²=70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=0.65 (p=0.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 25(OH)D ≤30 ng/mL† | 14 | 62 | 18 | 60 | 8.1% | 0.75 (0.41 to 1.37) | |
| Bischoff, et al., 2003 | | | | | | | |
| Karkkainen, et al., 2010 | 179 | 267 | 205 | 306 | 31.9% | 0.93 (0.63 to 1.37) | |
| Pfeifer, et al., 2009 | 49 | 122 | 75 | 120 | 22.1% | 0.64 (0.50 to 0.83) | |
| Subtotal (95% CI) | 471 | 486 | 62.1% | 0.78 (0.58 to 1.05) | |
| Total events | 242 | 296 | Heterogeneity: Tau²=0.04, Chi²=7.02, df=2 (p=0.03), I²=72% |
| Test for overall effect: Z=1.61 (p=0.11) | | | |
| Total (95% CI) | 934 | 743 | 100.0% | 0.84 (0.69 to 1.02) | |
| Total events | 504 | 435 | Heterogeneity: Tau²=0.03, Chi²=13.27, df=4 (p=0.01), I²=70% |
| Test for overall effect: Z=1.76 (p=0.08) | | | |
| Test for subgroup differences: Chi²=0.02, df=1 (p=0.89), I²=0% | | | |

0.01 0.1 1 10 100  
Favors vitamin D Favors control
**Figure 7. Meta-Analysis of Effects of Vitamin D Treatment on the Number of Falls per Person**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D (25(OH)D) &lt;20 ng/mL*</th>
<th>Control</th>
<th>Rate Ratio (95% CI)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Falls/PY</td>
<td>Events Falls/PY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfeifer, <em>et al.</em>, 2000†</td>
<td>17 0.24</td>
<td>30 0.45</td>
<td>0.54 (0.28 to 1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>25(OH)D ≤30 ng/mL†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bischoff, <em>et al.</em>, 2003‡</td>
<td>25 1.30</td>
<td>55 2.81</td>
<td>0.46 (0.28 to 0.76)</td>
<td></td>
</tr>
<tr>
<td>Kärkkäinen, <em>et al.</em>, 2010†</td>
<td>430 0.50</td>
<td>524 0.57</td>
<td>0.87 (0.77 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>Pfeiffer, <em>et al.</em>, 2000‡</td>
<td>106 0.53</td>
<td>169 0.84</td>
<td>0.63 (0.49 to 0.80)</td>
<td></td>
</tr>
<tr>
<td>Wood, <em>et al.</em>, 2012‡</td>
<td>4 0.02</td>
<td>3 0.03</td>
<td>0.67 (0.11 to 4.57)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (P= 69.9%, p=0.019)</strong></td>
<td></td>
<td></td>
<td>0.68 (0.50 to 0.93)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>565</td>
<td>751</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (P = 64.6%, p=0.024)</strong></td>
<td></td>
<td></td>
<td>0.66 (0.50 to 0.88)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>887</td>
<td>922</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval; PY = person-year.
Figure 8. Meta-Analysis of Effects of Vitamin D Treatment on Type 2 Diabetes Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D ≤30 ng/mL*</td>
<td>69</td>
<td>79</td>
<td>99.1%</td>
<td>0.93 (0.08 to 1.27)</td>
</tr>
<tr>
<td>de Boer, et al., 2008†</td>
<td>203</td>
<td>102</td>
<td>0.9%</td>
<td>1.51 (0.06 to 36.86)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1321</td>
<td>1289</td>
<td>100.0%</td>
<td>0.93 (0.68 to 1.27)</td>
</tr>
</tbody>
</table>

Total events: 70 79

Heterogeneity: Tau²=0.00; Chi²=0.09, df=1 (p=0.76); I²=0%

Test for overall effect: Z=0.45 (p=0.66)

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.
Figure 9. Meta-Analysis of Effects of Vitamin D Treatment on Serious Adverse Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D &lt;20 ng/mL*</td>
<td>14</td>
<td>95</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td>Brazier, et al., 2005</td>
<td>1</td>
<td>93</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Gallagher, et al., 2013</td>
<td>3</td>
<td>114</td>
<td>3</td>
<td>112</td>
</tr>
<tr>
<td>Lips, et al., 2010†</td>
<td>302</td>
<td>225</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>18</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=0.00; Chi²=0.22, df=2 (p=0.90); I²=0%
Test for overall effect: Z=0.32 (p=0.75)

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D ≤30 ng/mL†</td>
<td>9</td>
<td>142</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Gallagher, et al., 2012</td>
<td>8</td>
<td>104</td>
<td>7</td>
<td>104</td>
</tr>
<tr>
<td>Talwar, et al., 2007</td>
<td>15</td>
<td>203</td>
<td>4</td>
<td>102</td>
</tr>
<tr>
<td>Wood, et al., 2012</td>
<td>449</td>
<td>227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=0.00; Chi²=1.32, df=2 (p=0.52); I²=0%
Test for overall effect: Z=0.63 (p=0.53)

Total (95% CI)        | 751              | 452            | 100.0%       | 1.17 (0.74 to 1.84) |

Total events         | 50               | 28             |              |                     |

Heterogeneity: Tau²=0.00; Chi²=1.58, df=5 (p=0.90); I²=0%
Test for overall effect: Z=0.67 (p=0.50)
Test for subgroup differences: Chi²=0.05, df=1 (p=0.82); I²=0%

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.
**Figure 10. Meta-Analysis of Effects of Vitamin D Treatment on Withdrawals Due to Adverse Events**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>25(OH)D &lt;20 ng/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazier, et al., 2005[57]</td>
<td>15</td>
<td>95</td>
<td>17</td>
<td>96</td>
<td>48.0%</td>
</tr>
<tr>
<td>Gallagher, et al., 2013[58]</td>
<td>1</td>
<td>93</td>
<td>1</td>
<td>17</td>
<td>9.5%</td>
</tr>
<tr>
<td>Lips, et al., 2010[59]</td>
<td>3</td>
<td>114</td>
<td>5</td>
<td>112</td>
<td>25.2%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>302</td>
<td>226</td>
<td>82.8%</td>
<td></td>
<td>0.78 (0.44 to 1.37)</td>
</tr>
<tr>
<td>Total events</td>
<td>19</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau²=0.00, Chi²=1.41, df=2 (p=0.49); I²=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z= 0.87 (p=0.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>25(OH)D ≤30 ng/mL†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallagher, et al., 2012[58]</td>
<td>3</td>
<td>142</td>
<td>0</td>
<td>21</td>
<td>8.4%</td>
</tr>
<tr>
<td>Krieg, et al., 1999[60]</td>
<td>7</td>
<td>124</td>
<td>0</td>
<td>124</td>
<td>8.8%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>268</td>
<td>145</td>
<td>17.2%</td>
<td></td>
<td>4.10 (0.28 to 68.65)</td>
</tr>
<tr>
<td>Total events</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau²=1.60, Chi²=1.74, df=1 (p=0.19); I²= 42%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=1.03 (p=0.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>568</td>
<td>370</td>
<td>100.0%</td>
<td></td>
<td>0.90 (0.36 to 2.24)</td>
</tr>
<tr>
<td>Total events</td>
<td>29</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau²=0.35, Chi²=5.92, df=4 (p=0.20); I²= 32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=0.23 (p=0.82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi²=1.40, df=1 (p=0.24); I²= 28.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.
**Figure 11. Meta-Analysis of Effects of Vitamin D Treatment on Hypercalcemia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D &lt;20 ng/mL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazier, et al., 2005†</td>
<td>7</td>
<td>95</td>
<td>11</td>
<td>96</td>
<td>46.3%</td>
</tr>
<tr>
<td>Chapuy, et al., 2002‡</td>
<td>3</td>
<td>393</td>
<td>0</td>
<td>190</td>
<td>4.3%</td>
</tr>
<tr>
<td>Gallagher, et al., 2013</td>
<td>8</td>
<td>93</td>
<td>1</td>
<td>17</td>
<td>9.3%</td>
</tr>
<tr>
<td>Gallagher, et al., 2014</td>
<td>1</td>
<td>160</td>
<td>0</td>
<td>38</td>
<td>3.7%</td>
</tr>
<tr>
<td>Grimnes, et al., 2011</td>
<td>0</td>
<td>51</td>
<td>0</td>
<td>52</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Wamberg, et al., 2013</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>21</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>814</td>
<td>414</td>
<td>63.7%</td>
<td>0.82 (0.38 to 1.77)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>19</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2=0.00$, $Chi^2=1.52$, df=3 ($p=0.58$), $I^2=0$

Test for overall effect: $Z=0.51$ ($p=0.61$)

25(OH)D ≤30 ng/mL‡

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin D</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloa, et al., 2008</td>
<td>0</td>
<td>65</td>
<td>0</td>
<td>73</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Bischoff, et al., 2003</td>
<td>0</td>
<td>62</td>
<td>0</td>
<td>60</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Gallagher, et al., 2012</td>
<td>5</td>
<td>142</td>
<td>0</td>
<td>21</td>
<td>4.6%</td>
</tr>
<tr>
<td>Honkanen, et al., 1990</td>
<td>0</td>
<td>63</td>
<td>0</td>
<td>63</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Kjaergaard, et al., 2013</td>
<td>0</td>
<td>120</td>
<td>1</td>
<td>110</td>
<td>3.7%</td>
</tr>
<tr>
<td>Lehmann, et al., 2011</td>
<td>0</td>
<td>93</td>
<td>0</td>
<td>19</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Martineau, et al., 2007</td>
<td>0</td>
<td>96</td>
<td>0</td>
<td>96</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Ooms, et al., 1995</td>
<td>1</td>
<td>177</td>
<td>0</td>
<td>171</td>
<td>3.7%</td>
</tr>
<tr>
<td>Talwar, et al., 2007</td>
<td>6</td>
<td>104</td>
<td>3</td>
<td>102</td>
<td>3.7%</td>
</tr>
<tr>
<td>Wood, et al., 2012‡</td>
<td>1</td>
<td>203</td>
<td>0</td>
<td>102</td>
<td>3.7%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1125</td>
<td>819</td>
<td>36.3%</td>
<td>1.63 (0.59 to 4.53)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2=0.00$, $Chi^2=1.28$, df=4 ($p=0.87$), $I^2=0$

Test for overall effect: $Z=0.94$ ($p=0.35$)

Total (95% CI) 1939 1233 100.0% 1.05 (0.57 to 1.94)

Total events 32 16

Heterogeneity: $I^2=0.00$, $Chi^2=3.90$, df=8 ($p=0.87$), $I^2=0$

Test for overall effect: $Z=0.16$ ($p=0.88$)

Test for subgroup differences: $Chi^2=1.12$, df=1 ($p=0.29$), $I^2=10.4$

* ≥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 = 25-hydroxyvitamin D; CI = confidence interval.
Table 1. Summary of Current Opinions About Defining Vitamin D Deficiency and Association Between 25(OH)D Cutoff Levels and Health Outcomes

<table>
<thead>
<tr>
<th>25(OH)D Cutoff</th>
<th>Expert and Professional Body Opinions About Cutoff Levels</th>
<th>Association Between 25(OH)D Level and Health Outcomes</th>
<th>Subgroup Differences for the Association</th>
</tr>
</thead>
</table>
| <20 ng/mL       | Widely used by researchers and available guidelines as indicative of deficiency | Levels >20 ng/mL have been associated with decreased risk for fractures, cardiovascular disease, colorectal cancer, diabetes, depressed mood, cognitive decline, and mortality | • Association with fracture and cardiovascular disease not seen in blacks  
• Mortality association seen in blacks  
• Association with falls has 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  
• Levels >30 ng/mL have 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 for 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 association between vitamin D level and risk for mortality and pancreatic cancer | No data available |
| >200 ng/mL      | 25(OH)D levels above this range are 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 (1 nmol/L = 0.4 ng/mL).

Abbreviation: 25(OH)D = 25-hydroxyvitamin D.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Population Characteristics*</th>
<th>25(OH)D Level at Baseline (ng/mL)*</th>
<th>25(OH)D Level at Followup (ng/mL)*</th>
<th>Interventions</th>
<th>Duration*</th>
<th>Clinical Health Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazier et al, 2005&lt;sup&gt;67&lt;/sup&gt; Fair</td>
<td>France</td>
<td>Analyzed: 191 Age (years): 74.6 Female: 100% Comorbidities: NR History of falls: NR Institutionalized: 0%</td>
<td>7 vs. 7</td>
<td>Median: 29 vs. 11</td>
<td>Vitamin D (n=95): 800 IU vitamin D&lt;sub&gt;3&lt;/sub&gt; and 1000 mg calcium daily Control (n=97): Placebo</td>
<td>12 months</td>
<td>Mortality</td>
</tr>
<tr>
<td>Chapuy et al, 2002&lt;sup&gt;122&lt;/sup&gt; Fair</td>
<td>France</td>
<td>Analyzed: 583 Age (years): 85 Female: 100% Comorbidities: NR History of falls: 16.1% Use of walking device: 40.7% Institutionalized: 100%</td>
<td>9 vs. 9</td>
<td>~33 vs. 5 (from figure); p=0.0001 for change from baseline for vitamin D group only</td>
<td>Vitamin D (n=393): 800 IU of vitamin D&lt;sub&gt;3&lt;/sub&gt; and 1200 mg calcium daily Control (n=190): Placebo</td>
<td>24 months</td>
<td>Fractures (primary outcome)</td>
</tr>
<tr>
<td>Gallagher et al, 2013&lt;sup&gt;59&lt;/sup&gt; Fair</td>
<td>United States</td>
<td>Analyzed: 110 Age (years): 67 Female: 100% BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;): 32.7 Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>Placebo: 14 Vitamin D 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14 NR for 400, 3600, or 4000 IU groups</td>
<td>97.5% (from figure) of those using vitamin D 800 IU reached serum 25(OH)D &gt;20 ng/mL; p&lt;0.05 vs. placebo for all vitamin D groups</td>
<td>Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D&lt;sub&gt;3&lt;/sub&gt; daily Control: Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg/day</td>
<td>12 months</td>
<td>Mortality&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gallagher et al, 2014&lt;sup&gt;59&lt;/sup&gt; Fair</td>
<td>United States</td>
<td>Analyzed: 198 Age (years): 37 Female: 100% BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>Placebo: 13 Vitamin D 400 IU: 13 800 IU: 14 1600 IU: 13 2400 IU: 14</td>
<td>97.5% (from figure) of white women using vitamin D 400 IU reached serum 25(OH)D &gt;20 ng/mL; 97.5% of black women using vitamin D 800 to 1600 IU reached serum 25(OH)D &gt;20 ng/mL</td>
<td>Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D&lt;sub&gt;3&lt;/sub&gt; daily Control: Placebo All participants supplemented to maintain total calcium intake of 1000 to 1200 mg/day</td>
<td>12 months</td>
<td>Mortality&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Author, Year Quality</td>
<td>Country</td>
<td>Population Characteristics*</td>
<td>25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)</td>
<td>25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)</td>
<td>Interventions</td>
<td>Duration*</td>
<td>Clinical Health Outcomes Reported</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>--------------</td>
<td>-----------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Grimnes et al, 2011 Fair</td>
<td>Norway</td>
<td>Analyzed: 104 Age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) BMI (kg/m²): 26.5 (27.2 vs. 26.3) History of falls: NR Institutionalized: 0%</td>
<td>17 vs. 16</td>
<td>57 vs. 17</td>
<td>Vitamin D (n=51): 40,000 IU of vitamin D₃ weekly Control (n=52): Placebo</td>
<td>6 months</td>
<td>Mortality</td>
</tr>
<tr>
<td>Lips et al, 2010 Fair</td>
<td>The Netherlands, Germany, United States</td>
<td>Analyzed: 213 for SPPB; 226 for mortality Age (years): 78 Female: NR BMI (kg/m²): 27.8† Comorbidities: NR History of falls: NR Use of walking device: 15% Institutionalized: 14%</td>
<td>14 vs. 14</td>
<td>26 vs. 12; p&lt;0.001</td>
<td>Vitamin D (n=114): 8400 IU of Vitamin D₃ weekly Control (n=112): Placebo Those with daily calcium intake &lt;1000 mg were also given 500 mg calcium</td>
<td>16 weeks</td>
<td>Physical functioning Mortality</td>
</tr>
<tr>
<td>Pfeifer et al, 2000 Fair</td>
<td>Germany</td>
<td>Analyzed: 137 Age (years): 74.8† Female: 100% BMI (kg/m²): 25.5† Comorbidities: 39% cardiovascular; 12% central nervous, neurological; &lt;1% psychiatric; 22% musculoskeletal History of falls: NR Use of walking device: NR Institutionalized: 0%</td>
<td>10 vs. 10</td>
<td>26 vs. 17; p&lt;0.001</td>
<td>Vitamin D (n=70): 800 IU of vitamin D₃ and 1200 mg of calcium daily Control (n=67): 1200 mg of calcium daily</td>
<td>8 weeks treatment; 1 year followup</td>
<td>Falls Fractures</td>
</tr>
<tr>
<td>Arvold et al, 2009 Fair</td>
<td>United States</td>
<td>Analyzed: 90 Age (years): 58.8† Female: 40% BMI: NR Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 0%</td>
<td>18 vs. 18</td>
<td>45 vs. 22</td>
<td>Vitamin D (n=48): 50,000 IU of vitamin D₃ weekly Control (n=42): Placebo</td>
<td>8 weeks</td>
<td>Psychosocial functioning Disability</td>
</tr>
</tbody>
</table>

25(OH)D level ≤30 ng/mL†
### Table 2. Studies of Effectiveness of Vitamin D Treatment

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Population Characteristics*</th>
<th>25(OH)D Level at Baseline (ng/mL)† (Vitamin D vs. Control)</th>
<th>25(OH)D Level at Followup (ng/mL)† (Vitamin D vs. Control)</th>
<th>Interventions</th>
<th>Interventions</th>
<th>Clinical Health Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff et al, 2003⁶⁵</td>
<td>Switzerland</td>
<td>Analyzed: 122 Age (years): 85 Female: 100% BMI (kg/m²): 24.7 Comorbidities: 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%</td>
<td>Median, 12 vs. 12</td>
<td>Median, 26 vs. 11; p&lt;0.001</td>
<td>Vitamin D (n=62): 800 IU of vitamin D₃ and 1200 mg of calcium daily Control (n=60): 1200 mg calcium daily</td>
<td>6 weeks pre-treatment; 12 weeks treatment</td>
<td>Falls (primary outcome)</td>
</tr>
<tr>
<td>Gallagher et al, 2012¹⁵⁶</td>
<td>United States</td>
<td>Analyzed: 163 Age (years): 67 Female: 100% BMI (kg/m²): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>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</td>
<td>97.5% (from figure) of those using vitamin D 600 IU reached serum 25(OH)D &gt;20 ng/mL; p&lt;0.05 vs. placebo for all vitamin D groups</td>
<td>Vitamin D (n=142): Either 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D₃ daily Control (n=21): Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg/day</td>
<td>Median, 12 months</td>
<td>Mortality</td>
</tr>
<tr>
<td>Kärkkäinen et al, 2010¹⁵⁶</td>
<td>Finland</td>
<td>Analyzed: 593 Age (years): 67.4¹ Female: 100% BMI (kg/m²): 27.5¹ Comorbidities: NR History of falls: NR Ambulatory: 100% Institutionalized: NR</td>
<td>20 vs. 20</td>
<td>30 vs. 22</td>
<td>Vitamin D (n=290) and 287**: 800 IU of vitamin D₃ and 1000 mg of calcium daily Control (n=313) and 306**: No treatment</td>
<td>3 years</td>
<td>Falls (primary outcome)</td>
</tr>
</tbody>
</table>

Screening for Vitamin D Deficiency 57 Pacific Northwest EPC
Table 2. Studies of Effectiveness of Vitamin D Treatment

<table>
<thead>
<tr>
<th>Author, Year Quality</th>
<th>Country</th>
<th>Population Characteristics*</th>
<th>25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)</th>
<th>25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)</th>
<th>Interventions</th>
<th>Duration*</th>
<th>Clinical Health Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kjærsgaard et al, 2012 ‡1</td>
<td>Norway</td>
<td>Analyzed: 230 (per protocol) Age (years): 53.4 † Female: 56% BMI (kg/m²): 27.7 † Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>19 vs. 19</td>
<td>59 vs. 21</td>
<td>Vitamin D (n=120): 20,000 IU of vitamin D₃ weekly Control (n=110): Placebo</td>
<td>6 months</td>
<td>Psychosocial functioning (primary outcome)</td>
</tr>
<tr>
<td>Krieg et al, 1999 ‡1</td>
<td>Switzerland</td>
<td>Analyzed: 248 Age (years): 84.5 † Female: 100% BMI (kg/m²): 24.7 † History of falls: NR Institutionalized: NR</td>
<td>12 vs. 12</td>
<td>27 vs. 6</td>
<td>Vitamin D (n=124): 880 IU of vitamin D₃ and 1000 mg calcium daily Control (n=124): No supplementation</td>
<td>2 years</td>
<td>Mortality</td>
</tr>
<tr>
<td>Lips et al, 1996 ‡1 Ooms et al, 1995 ‡1</td>
<td>The Netherlands</td>
<td>Analyzed: 270 for fracture; 348 for mortality Age (years): 80.4 † Female: 100% BMI (kg/m²): 28.3 † Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 100% ††</td>
<td>Median, 11 vs. 10 (at 1 year)</td>
<td></td>
<td>Vitamin D (n=177): 400 IU of vitamin D₃ daily Control (n=171): Placebo</td>
<td>3 to 3.5 years, maximum 4 years</td>
<td>Fractures (primary outcome) Mortality</td>
</tr>
<tr>
<td>Pfeifer et al, 2009 ‡1</td>
<td>Austria and Germany</td>
<td>Analyzed: 242 Age (years): 76.5 Female: 74.5% BMI (kg/m²): 27.3 Comorbidities: NR History of falls: NR Ambulatory: 100% Institutionalized: 0%</td>
<td>22 vs. 22</td>
<td>Month 12: 34 vs. 23 Month 20: 19 vs. 15</td>
<td>Vitamin D (n=122): 800 IU of vitamin D₃ and 1000 mg calcium daily Control (n=120): 1000 mg of calcium daily</td>
<td>12 month treatment; 8 months post-treatment</td>
<td>Falls (primary outcome) Fallers Fractures</td>
</tr>
<tr>
<td>Wood et al, 2012 ‡1</td>
<td>United Kingdom</td>
<td>Analyzed: 305 Age (years): 63.8 † Female: 100% BMI (kg/m²): 26.7 † History of falls: NR Institutionalized: NR</td>
<td>Vitamin D 400 IU vs. 1000 IU vs. control: 13 vs. 13 vs. 14</td>
<td>Vitamin D 400 IU vs. 1000 IU vs. control: 26 vs. 30 vs. 13</td>
<td>Vitamin D (n=102 and 101): 400 or 1000 IU of vitamin D₃ daily Control (n=102): Placebo</td>
<td>12 months treatment; 1 month followup</td>
<td>Falls Type 2 diabetes</td>
</tr>
</tbody>
</table>
Table 2. Studies of Effectiveness of Vitamin D Treatment

<table>
<thead>
<tr>
<th>Author, Year Quality</th>
<th>Country</th>
<th>Population Characteristics*</th>
<th>25(OH)D Level at Baseline (ng/mL)*†</th>
<th>25(OH)D Level at Followup (ng/mL)*†</th>
<th>Interventions</th>
<th>Duration*</th>
<th>Clinical Health Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHI Calcium with Vitamin D Trial Fair</td>
<td>United States</td>
<td>Analyzed: 36,282 case-control studies</td>
<td>Fractures: 1491 cases/controls Colorectal cancer: 612 cases/controls Breast cancer: 895 cases/controls Diabetes: 192 cases/2905 controls Mortality: 323 cases/1962 controls</td>
<td>Entire trial: NR case-control studies Fractures: &lt;24 Colorectal cancer: &lt;23 Breast cancer: &lt;27 Diabetes: &lt;24 Mortality: &lt;21</td>
<td>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</td>
<td>7 years</td>
<td>Fractures Mortality Type 2 diabetes Cancer</td>
</tr>
<tr>
<td>Associated case-control studies with outcome reported: Jackson et al, 200664 (for fractures) Wactawski-Wende et al, 200665 (for colorectal cancer) Chlebowski et al, 200866 (for breast cancer) de Boer et al, 200867 (for breast cancer) LaCroix et al, 200968 (for mortality)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vitamin D: 400 IU of vitamin D3 + 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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reported as means, unless otherwise noted.
† Calculated.
‡ ≥90% of study participants had 25(OH)D levels <20 ng/mL.
§ 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.
‖ For mortality outcomes.
** For falls/fallers outcomes.
†† Received care, but not as much as in a nursing home.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; BMI = body mass index; NR = not reported; SPPB = Short Physical Performance Battery.
Table 3. Studies Examining the Association Between Vitamin D Treatment and Falls

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

* 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

<table>
<thead>
<tr>
<th>Author, Year Quality</th>
<th>Country</th>
<th>Population Characteristics*</th>
<th>25(OH)D Level at Baseline (ng/mL):*†</th>
<th>Vitamin D vs. Control</th>
<th>25(OH)D Level at Followup (ng/mL):*†</th>
<th>Vitamin D vs. Control</th>
<th>Interventions</th>
<th>Duration*</th>
<th>Adverse Events or Harms Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D level &lt;20 ng/mL*</td>
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<tr>
<td>Brazier et al, 2005 Fair</td>
<td>France</td>
<td>Analyzed: 191 Age (years): 74.6 (74.2 vs. 75.0) Female: 100% Comorbidities: NR History of falls: NR Institutionalized: 0%</td>
<td>7 vs. 7</td>
<td>Median, 29 vs. 11</td>
<td>Vitamin D (n=95): 800 IU vitamin D₃ and 1000 mg calcium daily Control (n=97): Placebo</td>
<td>12 months</td>
<td>Total AEs Withdrawal due to AEs Serious AEs Any AE Hypercalcemia Gastrointestinal AEs Osteomuscular AEs Nervous system AEs Metabolic/nutritional AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapuy et al, 2002 Fair</td>
<td>France</td>
<td>Analyzed: 583 Age (years): 85 Female: 100% Comorbidities: NR History of falls: 16.1% Use of walking device: 40.7% Institutionalized: 100%</td>
<td>9.2 vs. 9.2</td>
<td>~ 33 vs. 5 (from figure); p=0.0001 for change from baseline for vitamin D group only</td>
<td>Vitamin D (n=393): 800 IU of vitamin D₃ and 1200 mg calcium daily Control (n=190): Placebo</td>
<td>24 months</td>
<td>Withdrawal due to AEs (NR by group) Hypercalcemia Kidney stones Hypercalciuria Gastrointestinal AEs</td>
<td></td>
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<tr>
<td>Gallagher et al, 2013 Fair</td>
<td>United States</td>
<td>Analyzed: 110 Age (years): 67 Female: 100% BMI (kg/m²): 32.7 Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>Placebo: 14 Vitamin D³ 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14</td>
<td>97.5% (from figure) of those using vitamin D 800 IU reached serum 25(OH)D &gt;20 ng/mL; p&lt;0.05 vs. placebo for all vitamin D groups</td>
<td>Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D₃ daily Control: Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg/day</td>
<td>12 months</td>
<td>Withdrawal due to AEs* Serious AEs Hypercalcemia</td>
<td></td>
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<tr>
<td>Gallagher et al, 2014 Fair</td>
<td>United States</td>
<td>Analyzed: 198 Age (years): 37 Female: 100% BMI (kg/m²): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>Placebo: 13 Vitamin D 400 IU: 13 800 IU: 14 1600 IU: 13 2400 IU: 14</td>
<td>97.5% (from figure) of white women using vitamin D 400 IU reached serum 25(OH)D &gt;20 ng/mL; 97.5% of black women using vitamin D 800 to 1600 IU reached serum 25(OH)D &gt;20 ng/mL</td>
<td>Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D₃ daily Control: Placebo All participants supplemented to maintain total calcium intake of 1000 to 1200 mg/day</td>
<td>12 months</td>
<td>Serious AEs (NR by group) Hypercalcemia Kidney stones</td>
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<tr>
<td>Author, Year Quality</td>
<td>Country</td>
<td>Population Characteristics*</td>
<td>25(OH)D Level at Baseline (ng/mL):†</td>
<td>25(OH)D Level at Followup (ng/mL):†</td>
<td>Interventions</td>
<td>Duration*</td>
<td>Adverse Events or Harms Reported</td>
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<tr>
<td>Grimnes et al, 2011 Fair</td>
<td>Norway</td>
<td>Analyzed: 104 Age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) BMI (kg/m²): 26.5 (27.2 vs. 26.3) History of falls: NR Institutionalized: 0%</td>
<td>17 vs. 16</td>
<td>57 vs. 17</td>
<td>Vitamin D (n=51): 40,000 IU vitamin D₃ weekly Control (n=52): Placebo</td>
<td>6 months</td>
<td>Total AEs Hypercalcemia Kidney stones</td>
<td></td>
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</tr>
<tr>
<td>Janssen et al, 2010 Fair</td>
<td>The Netherlands</td>
<td>Analyzed: 70 Age (years): 80.8† Female: 100% BMI (kg/m²): 26.4† Comorbidities: 2.4† Medications used: 5.0† History of falls: NR Institutionalized: 100% ‡</td>
<td>13 vs. 14</td>
<td>31 vs. 17</td>
<td>Vitamin D (n=28): 400 IU of vitamin D₃ and 500 mg of calcium daily Control (n=31): Placebo and calcium 500 mg daily</td>
<td>6 months</td>
<td>Withdrawals Any AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knutsen et al, 2014 Fair</td>
<td>Norway</td>
<td>Analyzed: 215 Age (years): 37.3† Female: 73% BMI (kg/m²): 27.4† Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>11 vs. 11</td>
<td>19 vs. 10</td>
<td>Vitamin D (n=169): 25 or 10 µg of vitamin D₃ daily Control (n=82): Placebo</td>
<td>16 weeks</td>
<td>Total AEs</td>
<td></td>
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</tr>
<tr>
<td>Lips et al, 2010 Fair</td>
<td>The Netherlands Germany United States</td>
<td>Analyzed: 226 Age (years): 78 Female: NR BMI (kg/m²): 27.8† Comorbidities: NR History of falls: NR Use of walking device: 15% Institutionalized: 14%</td>
<td>14 vs. 14</td>
<td>26 vs. 12; p&lt;0.001</td>
<td>Vitamin D (n=114): 8400 IU of vitamin D₃ weekly Control (n=112): Placebo Those with daily calcium intake &lt;1000 mg were also given 500 mg calcium</td>
<td>16 weeks</td>
<td>Withdrawal due to AEs Serious AEs Any AE Kidney stones Hypercalcemia (data not shown)</td>
<td></td>
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<tr>
<td>Author, Year Quality</td>
<td>Country</td>
<td>Population Characteristics*</td>
<td>25(OH)D Level at Baseline (ng/mL):†</td>
<td>25(OH)D Level at Followup (ng/mL):†</td>
<td>Interventions</td>
<td>Duration*</td>
<td>Adverse Events or Harms Reported</td>
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<tr>
<td>Wamberg et al, 2013 Fair</td>
<td>Denmark</td>
<td>Analyzed: 43 Age (years): 40.5 Female: 71% BMI (kg/m²): 35.8%† Sedentary: 35%† Lightly active: 48%† Moderately active: 17%† Comorbidities: 2% (1/55) on lipid-lowering meds, 5% (3/55) on antihypertension meds History of falls: NR Institutionalized: NR</td>
<td>14 vs. 14</td>
<td>44 vs. 19</td>
<td>Vitamin D (n=22): 7000 IU of vitamin D₃ daily Control (n=21): Placebo</td>
<td>26 weeks</td>
<td>Total AEs Hypercalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloia et al, 2008 Fair</td>
<td>United States</td>
<td>Analyzed: 138 Age (years): 47.2† Female: 81% History of falls: NR Institutionalized: NR</td>
<td>19</td>
<td>&gt;30 ng/mL achieved by virtually all in active group; also increased by 8 ng/mL in placebo group because of seasonal change</td>
<td>Vitamin D (n=65): Dosage of vitamin D₃ depended on 25(OH)D concentration; mean dose, 3440 IU Control (n=73): Placebo</td>
<td>6 months</td>
<td>Hypercalcemia Hypercalcuria</td>
<td></td>
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</tr>
<tr>
<td>Arvold et al, 2009 Fair</td>
<td>United States</td>
<td>Analyzed: 100 Age (years): 58.8† Female: 40% BMI: NR Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 0%</td>
<td>18 vs. 18</td>
<td>45 vs. 22</td>
<td>Vitamin D (n=48): 50,000 IU vitamin D₃ weekly Control (n=42): Placebo</td>
<td>8 weeks</td>
<td>Any AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin et al, 1986 Poor</td>
<td>Sweden</td>
<td>Analyzed: 24 Age (years): 31 (range, 22 to 47) Female: 0% History of falls: NR Institutionalized: NR</td>
<td>15 vs. 15</td>
<td>49 vs. 19</td>
<td>Vitamin D (n=12): 54,000 IU of vitamin D₃ weekly Control (n=12): No treatment</td>
<td>NR; implies 2 months</td>
<td>Any AE</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Country</td>
<td>Population Characteristics</td>
<td>25(OH)D Level at Baseline (ng/mL): Vitamin D vs. Control</td>
<td>25(OH)D Level at Followup (ng/mL): Vitamin D vs. Control</td>
<td>Interventions</td>
<td>Duration</td>
<td>Adverse Events or Harms Reported</td>
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<tr>
<td>Bischoff et al, 2003</td>
<td>Switzerland</td>
<td>Analyzed: 122 Age (years): 85 Female: 100% BMI (kg/m²): 24.7 Comorbidities: 30.3% hypertension, 15.6% stroke, 50.0% myocardial infarction or congestive heart failure, 12.3% 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%</td>
<td>Median, 12 vs. 12</td>
<td>Median, 26 vs. 11; p&lt;0.001</td>
<td>Vitamin D (n=62): 800 IU of vitamin D₃ and 1200 mg of calcium daily Control (n=60): 1200 mg calcium daily</td>
<td>6 weeks pre-treatment 12 weeks treatment</td>
<td>Hypercalcemia Withdrawals Gastrointestinal AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallagher et al, 2012</td>
<td>United States</td>
<td>Analyzed: 163 Age (years): 67 Female: 100% BMI (kg/m²): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>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</td>
<td>97.5% (from figure) of those using vitamin D 600 IU per day had serum 25(OH)D &gt;20 ng/mL p&lt;0.05 vs. placebo for all vitamin D groups</td>
<td>Vitamin D (n=235): Either 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D₃ daily Control (n=38): Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg daily</td>
<td>Median, 12 months</td>
<td>Withdrawal due to AEs Any AE Serious AEs Kidney stones Hypercalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Quality</td>
<td>Country</td>
<td>Population Characteristics</td>
<td>25(OH)D Level at Baseline (ng/mL): Vitamin D vs. Control</td>
<td>25(OH)D Level at Followup (ng/mL): Vitamin D vs. Control</td>
<td>Interventions</td>
<td>Duration*</td>
<td>Adverse Events or Harms Reported</td>
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<tr>
<td>Harris et al, 1999</td>
<td>Poor</td>
<td>United States</td>
<td>Analyzed: 20 Younger men: Age (years): 31 (range, 22 to 47) Female: 0% Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>Younger men: 13 vs. 17 Older men: 16 vs. 16</td>
<td></td>
<td>Vitamin D (n=11): 1800 IU of vitamin D2 daily Control (n=7): No treatment</td>
<td>3 weeks</td>
<td>Any AE</td>
<td></td>
</tr>
<tr>
<td>Honkanen et al, 1990</td>
<td>Fair</td>
<td>Finland</td>
<td>Analyzed: 126 Home patients Age (years): 69.5† Female: 100% Weight (kg): 69.5† Comorbidities: NR History of falls: NR Home inpatients (52%) Age (years): 82.5† Female: 100% Weight (kg): 61.8† Comorbidities: NR History of falls: NR Hospital inpatients: 10 vs. 10</td>
<td>Home patients: 17 vs. 15 Hospital inpatients: 10 vs. 10</td>
<td></td>
<td>Vitamin D (n=63): 1800 IU of vitamin D3 and 1.558 g of calcium daily Control (n=63): No treatment</td>
<td>11 weeks</td>
<td>Hypercalcemia Kidney stones</td>
<td></td>
</tr>
<tr>
<td>Kärkkäinen et al, 2010</td>
<td>Fair</td>
<td>Finland</td>
<td>Analyzed: 603 Age (years): 67.4† (67.4 vs. 67.4) Female: 100% BMI (kg/m²): 27.4† (27.5 vs. 27.4) History of falls: NR Institutionalized: NR</td>
<td>20 vs. 20</td>
<td>30 vs. 22</td>
<td>Vitamin D (n=290): 800 IU of vitamin D3 and 1000 mg calcium daily Control (n=313): No treatment</td>
<td>3 years</td>
<td>Withdrawal due to AE</td>
<td></td>
</tr>
<tr>
<td>Kjaergaard et al, 2012</td>
<td>Good</td>
<td>Norway</td>
<td>Analyzed: 230 (per protocol) Age (years): 53.4† Female: 56% BMI (kg/m²): 27.7† Comorbidities: NR History of falls: NR Institutionalized: NR</td>
<td>19 vs. 19</td>
<td>59 vs. 21</td>
<td>Vitamin D (n=120): 20,000 IU of vitamin D₃ weekly Control (n=110): Placebo</td>
<td>6 months</td>
<td>Total AEs Gastrointestinal AEs Respiratory AEs Dermatological AEs Musculoskeletal AEs Urogenital AEs Circulatory AEs Neurological AEs Endocrinological AEs Other organ AEs Hypercalcemia</td>
<td></td>
</tr>
<tr>
<td>Author, Year Quality</td>
<td>Country</td>
<td>Population Characteristics*</td>
<td>25(OH)D Level at Baseline (ng/mL):† Vitamin D vs. Control</td>
<td>25(OH)D Level at Followup (ng/mL):† Vitamin D vs. Control</td>
<td>Interventions</td>
<td>Duration*</td>
<td>Adverse Events or Harms Reported</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Krieg et al, 1999†54</td>
<td>Switzerland</td>
<td>Analyzed: 248 Age (years): 84.5† Female: 100% BMI (kg/m²): 24.7† History of falls: NR Institutionalized: 100%</td>
<td>12 vs. 12</td>
<td>27 vs. 6</td>
<td>Vitamin D (n=124): 880 IU of vitamin D₃ and 1000 mg calcium daily Control (n=124): No treatment</td>
<td>2 years</td>
<td>Withdrawal due to AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehmann et al, 2013†15</td>
<td>Norway</td>
<td>Analyzed: 119 Age (years): 33.8† Female: 63.5% BMI (kg/m²): 23.8† History of falls: NR Institutionalized: NR</td>
<td>Overall (vitamin D₂ vs. vitamin D₃ vs. control): 16 (15 vs. 18 vs. 16)</td>
<td>Vitamin D₂ vs. vitamin D₃ vs. control: 27 vs. 36 vs. 13</td>
<td>Vitamin D (n=47, 46): 2000 IU of either vitamin D₂ or D₃ daily Control (n=19): Placebo</td>
<td>8 weeks</td>
<td>Any AE Hypercalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martineau et al, 2007†79</td>
<td>United Kingdom</td>
<td>Analyzed: 192 Median age (years): 33.7† Female: 51.2%† History of falls: NR Institutionalized: NR</td>
<td>14 vs. NR</td>
<td>27 vs. NR</td>
<td>Vitamin D (n=96): Single dose of 100,000 IU vitamin D₂ Control (n=96): Placebo</td>
<td>6 weeks</td>
<td>Any AE Hypercalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ooms et al, 1995†20</td>
<td>The Netherlands</td>
<td>Analyzed: 348 Age (years): 80.4† Female: 100% BMI (kg/m²): 28.3† Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 100%**</td>
<td>Median, 11 vs. 10</td>
<td>Median, 25 vs. 9 (at 1 year)</td>
<td>Vitamin D (n=177): 400 IU of vitamin D₃ daily Control (n=171): Placebo</td>
<td>3 to 3.5 years, maximum 4 years</td>
<td>Any AE Hypercalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talwar et al, 2007†77</td>
<td>United States</td>
<td>Analyzed: 208 Age (years): 60.5† Female: 100% BMI (kg/m²): 29 vs. 30 History of falls: NR Institutionalized: NR</td>
<td>19 vs. 17</td>
<td>35 vs. 18</td>
<td>Vitamin D (n=104): 800 IU of vitamin D₃ daily for first 24 months, increased to 2000 IU daily Control (n=104): Placebo Supplements given to maintain total daily intake of 1200 to 1500 mg calcium</td>
<td>36 months</td>
<td>Total AEs (NR by group) Serious AEs Hypercalcemia Hypercalcuria Kidney stones</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Screening for Vitamin D Deficiency 66 Pacific Northwest EPC
### Table 4. Studies of Harms of Vitamin D Treatment

<table>
<thead>
<tr>
<th>Author, Year Quality</th>
<th>Country</th>
<th>Population Characteristics*</th>
<th>25(OH)D Level at Baseline (ng/mL): t</th>
<th>25(OH)D Level at Followup (ng/mL): t</th>
<th>Interventions</th>
<th>Duration*</th>
<th>Adverse Events or Harms Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood et al, 2012 Fair</td>
<td>United Kingdom</td>
<td>Analyzed: 305 Age (years): 63.8† Female: 100% BMI (kg/m²): 26.7† History of falls: NR Institutionalized: NR</td>
<td>Vitamin D 400 IU vs. 1000 IU vs. control: 13 vs. 13 vs. 14</td>
<td>Vitamin D 400 IU vs. 1000 IU vs. control: 26 vs. 30 vs. 13</td>
<td>Vitamin D (n=102, 101) 400 or 1000 IU of vitamin D₃ daily Control (n=102): Placebo</td>
<td>12 months treatment; 1 month followup</td>
<td>Total AEs Serious AEs Hypercalcemia Gastrointestinal AEs Osteomuscular AEs</td>
</tr>
</tbody>
</table>

* Reported as mean, unless otherwise noted.
† Calculated.
‡ ≥90% of study participants had 25(OH)D levels <20 ng/mL.
§ NR for 400, 3600, or 4000 IU groups.
‖ 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.
** Received care, but not as much as in a nursing home.
†† Population characteristics only reported for those who finished study (n=131).

**Abbreviations:** 25(OH)D = 25-hydroxyvitamin D; AE = adverse event; BMI = body mass index; NR = not reported.
Table 5. Summary of Evidence

<table>
<thead>
<tr>
<th>Number and Type of Studies</th>
<th>Overall Quality</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Question 1. Is there direct evidence that screening for vitamin D deficiency results in improved health outcomes?</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>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, sex, race/ethnicity, body mass index, ultraviolet light exposure, and institutionalized status)?</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Key Question 2. What are the harms of screening?</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Key Question 3. Does treatment of vitamin D deficiency with vitamin D lead to improved health outcomes?</td>
<td>17 studies RCTs, nested case-control studies</td>
<td>Fair</td>
<td>Few studies addressed 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 cosupplementation, and length of followup</td>
<td>Moderate</td>
<td>Studies mostly conducted in older white U.S. or European women</td>
</tr>
<tr>
<td>Key Question 3a. Are there differences in efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency, such as age ≥65 years, sex, race/ethnicity, body mass index, ultraviolet light exposure, and institutionalized status)?</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Key Question 4. What are the adverse effects of treatment of vitamin D deficiency with vitamin D?</td>
<td>24 studies* RCTs, cohorts</td>
<td>Fair</td>
<td>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 cosupplementation, and length of followup</td>
<td>High</td>
<td>Only 7 studies were conducted in the U.S. and only 3 of these U.S. studies reported populations having a significant percentage of nonwhite participants</td>
</tr>
<tr>
<td>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, sex, race/ethnicity, body mass index, ultraviolet light exposure, and institutionalized status)?</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Includes two poor-quality trials.

**Abbreviations:** CI = confidence interval; NA = not applicable; RCT = randomized, controlled trial; RR = risk ratio.
Contextual Question 1. What Is the Association Between Serum 25(OH)D Levels and Health Outcomes?

The association between serum 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 predisease-state 25(OH)D levels and health outcomes, 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 AHRQ review (not for the 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 for 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 for 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 that 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 nonwhite 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 through July 2011 on the association between 25(OH)D levels and colorectal, breast, and prostate cancer.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
Appendix A1. Association Between 25(OH)D Levels and Health Outcomes

decreased risk for colorectal cancer in a meta-analysis of eight fair-quality nested case-control studies. For each 4 ng/mL increase in blood 25(OH)D concentration, there was a 6 percent (95% 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 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 that an increase of 10 to 20 ng/mL in 25(OH)D levels decreased the risk for colorectal cancer by 15 to 50 percent, respectively. 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. 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, 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.

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. Similarly, a nested case-control study, not included in these meta-analyses, did not find an association between 25(OH)D level and breast cancer in predominantly premenopausal women.

Prostate Cancer

No association was reported between 25(OH)D level and risk for prostate cancer in systematic reviews and meta-analyses of prospective studies, including the 2011 USPSTF review.

Pancreatic Cancer

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

Other Cancers

Two 2014 systematic reviews did not conclude that 25(OH)D level was associated with risk for other cancers, including esophageal and gastric, ovarian, endometrial, bladder, and kidney cancer, or non-Hodgkin lymphoma.
Appendix A1. Association Between 25(OH)D Levels and Health Outcomes

Fractures

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 the 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 that the evidence was suggestive only for nonvertebral 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 persons 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 for fracture compared with those with 25(OH)D levels greater than 27 ng/mL.20 Similarly, two smaller Scandinavian studies found increased risk for 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 for 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 for fracture in the WHI trial,26 but not in NHANES data.24 An association between 25(OH)D level and fracture may not exist in nonwhite 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 hormone28-32 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 IOM contends that 25(OH)D concentrations above 20 ng/mL are sufficient for optimal bone health.35 Other expert bodies such as the Endocrine Society, National Osteoporosis Foundation, and International Osteoporosis Foundation suggest that 25(OH)D levels should be higher, at least 30 ng/mL, particularly in older adults.36-40

Falls

A 2009 AHRQ review cited a 2007 Ottawa EPC review that found there was fair evidence of an association between lower serum 25(OH)D concentrations and an increased risk for falls in institutionalized elderly persons.19,41 One study suggested a serum 25(OH)D concentration below
Appendix A1. Association Between 25(OH)D Levels and Health Outcomes

16 ng/mL was associated with an increased risk for falls. We identified one additional study published on this association since 2007. In that study of community-dwelling persons, 25(OH)D levels less than 20 ng/mL were associated with increased falls in men, but not in women. 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. A recent 2014 umbrella analysis of systematic reviews and meta-analysis stated that the evidence was inconsistent and no conclusions 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.

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.

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 for incident cardiovascular disease. 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 for developing stroke compared with higher levels (>19 ng/mL).

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

Diabetes

A 2014 umbrella analysis of systematic reviews and meta-analyses concluded that the evidence was suggestive for an association between 25(OH)D level and diabetes risk. A 2013 meta-analysis concluded that each 4-ng/mL increment in 25(OH)D level was associated with a 4-percent decreased risk for diabetes. Individual studies generally found that risk for diabetes increased in the lowest (generally <10 to 20 ng/mL) versus highest quartile or quintile of 25(OH)D level.

Depression

Two 2014 systematic reviews concluded that the evidence was suggestive of a decreased risk for depression and mood disorders with high 25(OH)D concentrations. In two prospective studies,
optimal 25(OH)D levels were between 21 and 34 ng/mL.\textsuperscript{59,60}

**Cognitive Functioning**

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

**Functional Status**

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

**References**

Appendix A1. Association Between 25(OH)D Levels and Health Outcomes


Appendix A1. Association Between 25(OH)D Levels and Health Outcomes

Appendix A2. Risk Factors Associated With Vitamin D Deficiency

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 two- to five-fold increased risk for vitamin D deficiency (defined as a 25(OH)D level < 20 ng/mL).1-3

Vitamin D is also obtained through synthesis in the skin in response to UVB radiation. Large population-based studies confirm that low UVB exposure is associated with an increased risk for vitamin D deficiency.2,4-6 Persons who have blood drawn for a 25(OH)D level in winter have a 2 to 3 times greater risk for 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 for vitamin D deficiency.5 Higher latitude of residence has been modestly associated with vitamin D deficiency.2,4,5 Although sunscreen reduces the skin’s ability to produce vitamin D in response to UVB in controlled research settings,7 it is not associated with vitamin D deficiency in population-based studies.6,8 This discrepancy is likely due to incomplete application of sunscreen9 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 two- to nine-fold greater risk and Hispanics a two- to three-fold greater risk for vitamin D deficiency compared with whites.1-3 However, a recent study found that compared with 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 for vitamin D deficiency. In a cohort of older men (>65 years), the oldest participants (>85 years) had a two-fold increased risk for vitamin D deficiency compared with younger men.5 In cohorts with a smaller percentage of participants older than age 70 years, the results are mixed, with some showing significant associations between risk for 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 two-fold increased risk for vitamin D deficiency.1-3,13 In addition, since women have a higher percentage of body fat compared with men, they may be at greater risk than men. In two large cohort studies, women were at increased risk for vitamin D deficiency than men.1,5 However, in the most recent NHANES analysis, sex did not influence risk for deficiency.3
Appendix A2. Risk Factors Associated With Vitamin D Deficiency

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 levels of physical activity was modestly associated with vitamin D deficiency in three studies.1,2,4 In NHANES, lower education level was associated with an increased risk for 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 for deficiency in NHANES.3,6

However, these risk factors appear to account for a small percentage of the variation in 25(OH)D levels. In the WHI 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, BMI, and physical activity accounted for only 28 percent of the variation in 25(OH)D level.14

References

Appendix A2. Risk Factors Associated With Vitamin D Deficiency


Appendix A3. Effects of Vitamin D Treatment on Intermediate Outcomes

Contextual Question 3. What Is the Effect of Vitamin D (With or Without Calcium) on Intermediate Outcomes?

We examined RCTs of vitamin D (with or without calcium) versus placebo on the intermediate outcomes of lipids, glucose, blood pressure, bone mineral density, and physical functioning or 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 persons without diabetes.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 (age ≥70 years) 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 WHI trial, 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 for incident hypertension.7

Bone Mineral Density

We identified seven studies that examined the effect of vitamin D treatment on bone mineral density 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 bone mineral density;8-10 two9,10 of three studies found less decline at the femoral neck and one9 of two9,10 found less decline at the trochanter while the other did not.8 No study found that vitamin D treatment led to less decline at the distal radius compared with placebo.8,10 Postmenopausal black women randomized to 1,000 IU per day of vitamin D for 2 years did not have improved bone mineral density compared with 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 bone mineral density.1,12
Appendix A3. Effects of Vitamin D Treatment on Intermediate Outcomes

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.  

Physical Functioning/Balance

We reviewed four studies that evaluated the effect of vitamin D treatment on strength and one study that examined balance. Among elderly women, 400 to 1,800 IU per day of vitamin D did not improve hand strength, leg strength, or balance compared with placebo. In two studies of younger (mean age, 18 to 33 years) deficient (<30 ng/mL) persons, large (25,000 to >60,000 IU per week) doses of vitamin D improved several strength measures more in the vitamin D versus the placebo group. However, in a Norwegian trial using smaller dosages of vitamin D (400 to 1,000 IU per day) in deficient immigrants with mean ages of 35 to 40 years, strength measures were not improved in the intervention versus control group after 16 weeks.

References

Appendix A3. Effects of Vitamin D Treatment on Intermediate Outcomes

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

Search Strategy:

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 Calci$ or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihy$)).mp.
9 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 (((low or lower or circulat$ or blood or 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 Calci$ or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihy$))).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 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 Calci$ or Dihydroxycholecalciferol$ or Calcitriol or Dihydroxyvitamin D or Ergocalciferol$ or Dihy$))).mp.
9 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 (((low or lower or circulat$ or blood or serum or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (hypo$)).mp.
Appendix B1. Search Strategies

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 accur$ 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 accur$ or predict$) adj7 (hypovitamin$ adj d)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 4 or 5
Appendix B1. Search Strategies

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 morb$ 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$)).mp.
serum or hematolog$) 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

<table>
<thead>
<tr>
<th>Population</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQs 1, 3: Nonpregnant adults age ≥18 years who are generally healthy. Study participants are either:</td>
<td>Nonselected or low-risk, or</td>
<td>Selected populations with conditions including clinical signs of vitamin D deficiency, osteoporosis, malabsorption, granuloma-forming disorders, chronic kidney disease, hepatic failure, cancer, coronary heart disease, diabetes/glucose intolerance, immune disorders, high risk for falls, polycystic ovarian syndrome, and multiple sclerosis</td>
</tr>
<tr>
<td>• Unselected or low-risk, or</td>
<td>Selected for increased risk for vitamin D deficiency based on certain characteristics, including participants who are older, have darker skin pigmentation (blacks or Hispanics), or are obese or institutionalized</td>
<td></td>
</tr>
<tr>
<td>• Selected for increased risk for vitamin D deficiency</td>
<td>KQ 2: Nonpregnant adults age ≥18 years who are generally healthy. Study participants are either:</td>
<td></td>
</tr>
<tr>
<td>KQ 4: Nonpregnant adults age ≥18 years who are generally healthy with vitamin D deficiency. Study participants are either:</td>
<td>• Unselected or low-risk, or</td>
<td></td>
</tr>
<tr>
<td>• Unselected or low-risk, or</td>
<td>• Selected for increased risk for vitamin D deficiency</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Vitamin D&lt;sub&gt;2&lt;/sub&gt; or D&lt;sub&gt;3&lt;/sub&gt; (with or without calcium); food-based interventions if vitamin D dose is quantified and doses differ between comparison groups</td>
<td>Nonoral routes of vitamin D delivery; dietary intake (unless a food-based intervention, as described under inclusion criteria); ultraviolet light exposure; multivitamins</td>
</tr>
<tr>
<td>Comparators</td>
<td>KQs 1, 2: Screening</td>
<td>KQs 1, 2: No screening</td>
</tr>
<tr>
<td>KQs 3, 4: Placebo, no treatment, usual care</td>
<td>KQs 3, 4: Different dosages of vitamin D</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>KQs 1, 3: Health outcomes include decreased morbidity from osteoporosis/fractures, falls, diabetes mellitus, cardiovascular disease, cancer, and 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)</td>
<td>KQs 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 &lt;8 weeks after start of the intervention or the baseline assessment (if time from intervention start cannot be determined); baseline vitamin D level not reported or not deficient</td>
</tr>
<tr>
<td>KQs 2, 4: Mortality; renal outcomes (e.g., kidney stones); soft tissue calcification; adverse events (e.g., gastrointestinal symptoms)</td>
<td>KQs 2, 4: None</td>
<td></td>
</tr>
<tr>
<td>Settings</td>
<td>Studies conducted in primary care or feasible for conducting in or referral from primary care, including institutionalized settings. For an intervention to be feasible for primary care referral, it would need to be conducted as part of a health care setting or be widely available in the community at a national level. United States, Canada, United Kingdom, and other geographic settings generalizable to the United States</td>
<td>Studies performed in countries with populations not similar to the United States; studies conducted in schools or work sites, unless primary care–feasible</td>
</tr>
<tr>
<td>Timing</td>
<td>KQs 1, 3: ≥8 weeks</td>
<td>KQs 1, 3: &lt;8 weeks</td>
</tr>
<tr>
<td>KQs 2, 4: Any duration</td>
<td>KQs 2, 4: None</td>
<td></td>
</tr>
<tr>
<td>Study types and designs</td>
<td>KQs 1, 3: Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials</td>
<td>KQs 1, 3: Nonsystematic reviews, letters to the editor, cohort or case-control studies, noncomparative studies, and comparative efficacy trials; reviews not in English</td>
</tr>
<tr>
<td>KQs 2, 4: Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials, and large cohort or case-control studies; studies must have an appropriate comparison group</td>
<td>KQs 2, 4: Nonsystematic reviews, letters to the editor, noncomparative studies, and comparative efficacy trials; reviews not in English</td>
<td></td>
</tr>
</tbody>
</table>
Appendix B3. Literature Flow Diagram

Abstracts of potentially relevant articles identified through MEDLINE, Cochrane*, and other sources† (n = 3,652)

Excluded abstracts and background articles (n = 2,253)

Full-text articles reviewed for relevance to key questions (n = 1,399)

Articles excluded (n = 1,364)
Excluded because it doesn’t address a key question or meet inclusion criteria, but pulled to provide background information = 109
Excluded because it doesn’t address a key question or meet inclusion criteria, but pulled for a contextual question = 180
Wrong population = 249
Wrong intervention = 96
Wrong outcome = 170
Wrong study design = 190
Wrong publication type = 138
Foreign language = 1
Inadequate duration = 7
Included in an included systematic review, no original data = 1
Wrong comparison = 21
Systematic review not meeting requirements = 67
Baseline 25(OH)D level not reported = 66
Baseline 25(OH)D levels not deficient = 69

Final included studies‡§: 27¶

Key question 1: 0
Key question 2: 0
Key question 3: 17
Key question 4: 24

* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Identified from reference lists, hand searching, and suggestions by experts.
‡ 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; there were 27 unique studies but a total of 35 articles included.
Appendix B4. List of Excluded Studies

Key to Exclusion Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Doesn’t address a key question or meet inclusion criteria, but pulled to provide background information</td>
</tr>
<tr>
<td>3</td>
<td>Doesn’t address a key question or meet inclusion criteria, but pulled for contextual question(s)</td>
</tr>
<tr>
<td>4</td>
<td>Wrong population</td>
</tr>
<tr>
<td>5</td>
<td>Wrong intervention</td>
</tr>
<tr>
<td>6</td>
<td>Wrong outcomes</td>
</tr>
<tr>
<td>7</td>
<td>Wrong study design for key question</td>
</tr>
<tr>
<td>8</td>
<td>Wrong publication type</td>
</tr>
<tr>
<td>9</td>
<td>Foreign language</td>
</tr>
<tr>
<td>10</td>
<td>Inadequate duration</td>
</tr>
<tr>
<td>11</td>
<td>Included in an included systematic review, no original data</td>
</tr>
<tr>
<td>12</td>
<td>Wrong comparison</td>
</tr>
<tr>
<td>13</td>
<td>Systematic review not meeting our requirements</td>
</tr>
<tr>
<td>14</td>
<td>Baseline 25(OH)D level not reported</td>
</tr>
<tr>
<td>15</td>
<td>Baseline 25(OH)D levels not deficient</td>
</tr>
</tbody>
</table>


Screening for Vitamin D Deficiency
Appendix B4. List of Excluded Studies

Demetriou ET, Travison TG, Holick MF. Treatment with 50,000 IU vitamin D(2) every other week and effect on serum 25-hydroxyvitamin D(2), 25-hydroxyvitamin D(3), and total 25-hydroxyvitamin D in a clinical setting. Endocr Pract. 2012;18(3):399-402
Exclusion code: 12

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Gallagher JC, Jindal P, Lynette MS. Vitamin D does not Increase Calcium Absorption in Young Women: A Randomized Clinical Trial. J Bone Miner Res. 2013
Exclusion code: 6

Exclusion code: 7

Exclusion code: 8

Haines TP, Bennell KL, Osborne RH, Hill KD. Effectiveness of targeted falls prevention programme in subacute hospital setting: randomised controlled trial. BMJ. 2004;328(7441):676
Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 8

Izaks GJ. Fracture prevention with vitamin D supplementation: considering the inconsistent results. BMC Musculoskelet Disord. 2007;8:26
Exclusion code: 13

Exclusion code: 13


Exclusion code: 7

Exclusion code: 2

Appendix B4. List of Excluded Studies

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 5

Exclusion code: 3

Exclusion code: 7

Exclusion code: 13

Exclusion code: 7

Exclusion code: 7

Exclusion code: 4

Exclusion code: 3

Exclusion code: 4

Exclusion code: 13

Exclusion code: 3

Exclusion code: 13

Exclusion code: 7

Exclusion code: 3

Saliba W, Barnett O, Rennert HS, Rennert G. The risk of all-cause mortality is inversely related to serum 25(OH)D levels. *J Clin Endocrinol Metab.* 2012;97(8):2792-2798
Exclusion code: 3

Exclusion code: 8

Exclusion code: 13
Appendix B4. List of Excluded Studies

Exclusion code: 5

Exclusion code: 5

Exclusion code: 13

Exclusion code: 3

Exclusion code: 7

Exclusion code: 5

Exclusion code: 5

Vieth R. Enzyme kinetics hypothesis to explain the U-shaped risk curve for prostate cancer vs. 25-hydroxyvitamin D in Nordic countries [1]. Int J Cancer. 2004;111(3):468
Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Exclusion code: 7

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

Exclusion code: 8

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

Exclusion code: 6

Exclusion code: 7

Exclusion code: 6

Exclusion code: 6

Exclusion code: 6
Appendix B4. List of Excluded Studies

Exclusion code: 4

Exclusion code: 7

Exclusion code: 4

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

Exclusion code: 6

Exclusion code:Exclusion code: Exclusion code: 8

Exclusion code: 15

Exclusion code: 4

Exclusion code: 4

Exclusion code: 7

Exclusion code: 3

Exclusion code: 6

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 5

Exclusion code: 4

Allali F, El Aichaoui S, Saoud B, Maaroufi H, Abouqal R, Hajjaj-Hassouni N. The impact of
Appendix B4. List of Excluded Studies

Exclusion code: 5

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

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

Exclusion code: 2

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

Exclusion code: 6

Exclusion code: 4

Exclusion code: 5

American Society for Clinical Pathology. Choosing Wisely. Chicago, IL2012
Exclusion code: 2

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 3

Exclusion code: 2

Exclusion code: 7

Anderson JL, May HT, Horne BD, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general
Appendix B4. List of Excluded Studies

healthcare population. *Am J Cardiol.* 2010;106(7):963-968
Exclusion code: 3

Exclusion code: 5

Exclusion code: 13

Exclusion code: 7

Exclusion code: 7

Exclusion code: 13

Exclusion code: 7

Exclusion code: 5

Exclusion code: 3

Armas LAG, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab.* 2004;89(11):5387-5391
Exclusion code: 10

Exclusion code: 4

Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol.* 2014;2(1):76-89
Exclusion code: 2

Exclusion code: 13

Exclusion code: 14

Exclusion code: 14

Exclusion code: 13

Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane database of systematic reviews (Online).* 2005(3)
Exclusion code: 13

Exclusion code: 6
Appendix B4. List of Excluded Studies

Exclusion code: 14

Bao Y, Ng K, Wolpin BM, Michaud DS, Giovannucci E, Fuchs CS. Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. Br J Cancer. 2010;102(9):1422-1427
Exclusion code: 14

Exclusion code: 3

Exclusion code: 6

Exclusion code: 14

Exclusion code: 8

Bailey BA, Manning T, Peiris AN. Vitamin D testing patterns among six Veterans Medical Centers in the southeastern United States: links with medical costs. Mil Med. 2012;177(1):70-76
Exclusion code: 6

Exclusion code: 6

Exclusion code: 5

Exclusion code: 3

Exclusion code: 7

Bakhtiyarova S, Lesnyak O, Kyznesova N, Blankenstein MA, Lips P. Vitamin D status among patients with hip fracture and elderly control subjects in Yekaterinburg, Russia. Osteoporos Int. 2006;17(3):441-446
Exclusion code: 7

Appendix B4. List of Excluded Studies

Exclusion code: 4

Exclusion code: 14

Exclusion code: 7

Exclusion code: 5

Exclusion code: 6

Exclusion code: 2

Exclusion code: 4

Exclusion code: 6

Exclusion code: 7

Exclusion code: 4

Exclusion code: 3

Exclusion code: 6

Exclusion code: 6

Bertone-Johnson ER. Prospective studies of dietary vitamin D and breast cancer: More questions raised than answered. *Nutr Rev.* 2007;65(10):459-466
Exclusion code: 13

Exclusion code: 3

Exclusion code: 14

Exclusion code: 2

Exclusion code: 6

Biancuzzo RM, Young A, Bibuld D, et al. Fortification of orange juice with vitamin D(2) or vitamin D(3) is as effective as an oral supplement in maintaining vitamin D status in adults. *Am J Clin Nutr.* 2010;91(6):1621-1626
Exclusion code: 6
Appendix B4. List of Excluded Studies

Exclusion code: 8

Exclusion code: 7

Exclusion code: 4

Bischoff-Ferrari HA, Willett WC, Orav EJ, Kiel DP, Dawson-Hughes B. Re: Fall prevention with Vitamin D. Author's reply. BMJ. 2011;342
Exclusion code: 8

Bischoff-Ferrari H. Vitamin D: what is an adequate vitamin D level and how much supplementation is necessary? Best Pract Res Clin Rheumatol. 2009;23(6):789-795
Exclusion code: 7

Exclusion code: 7

Exclusion code: 8

Exclusion code: 8

Exclusion code: 4

Exclusion code: 3

Exclusion code: 5

Exclusion code: 4

Exclusion code: 13

Exclusion code: 12

Exclusion code: 13

Exclusion code: 6

Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr. 2004;80(3):752-758
Exclusion code: 7

Exclusion code: 2
Appendix B4. List of Excluded Studies

Exclusion code: 7

Exclusion code: 15

Exclusion code: 7

Exclusion code: 13

Exclusion code: 13

Exclusion code: 13

Exclusion code: 4

Exclusion code: 13

Exclusion code: 13

Bjorkman M, Sorva A, Risteli J, Tilvis R. Vitamin D supplementation has minor effects on parathyroid hormone and bone turnover markers in vitamin D-deficient bedridden older patients. *Age Ageing.* 2008;37(1):25-31
Exclusion code: 4

Exclusion code: 6

Exclusion code: 6

Exclusion code: 5

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4
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Bogh MKB, Gullstrand J, Svensson A, Ljunggren B, Dorkhan M. Narrowband ultraviolet B three times per week is more effective in treating vitamin D deficiency than 1600 IU oral vitamin D3 per day: a randomized clinical trial. *Br J Dermatol.* 2012;167(3):625-630
Exclusion code: 12

Exclusion code: 8

Exclusion code: 5

Exclusion code: 5

Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: Reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ.* 2011;342(7804)
Exclusion code: 14

Exclusion code: 14

Exclusion code: 2

Exclusion code: 10

Exclusion code: 7

Exclusion code: 14

Exclusion code: 6

Exclusion code: 4

Exclusion code: 8

Exclusion code: 7

Exclusion code: 4

Exclusion code: 2

Brändstedt J, Almquist M, Manjer J, Malm J. Vitamin D, PTH, and calcium and the risk of prostate...
Appendix B4. List of Excluded Studies

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 2

Exclusion code: 4

Exclusion code: 4

Exclusion code: 7

Brewer LC, Michos ED, Reis JP. Vitamin D in atherosclerosis, vascular disease, and endothelial function. *Curr Drug Targets.* 2011;12(1):54-60
Exclusion code: 13

Exclusion code: 3

Exclusion code: 3

Exclusion code: 15

Exclusion code: 3

Exclusion code: 3

Exclusion code: 4

Exclusion code: 7

Exclusion code: 8

Exclusion code: 14

Brunner RL, Wactawski-Wende J, Caan BJ, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health...
Appendix B4. List of Excluded Studies

Exclusion code: 14

Exclusion code: 4

Exclusion code: 7

Exclusion code: 7

Exclusion code: 5

Exclusion code: 4

Exclusion code: 13

Exclusion code: 3

Exclusion code: 4

Exclusion code: 4

Exclusion code: 15

Exclusion code: 7

Exclusion code: 14

Exclusion code: 5

Exclusion code: 4

Exclusion code: 4

Exclusion code: 13

Exclusion code: 13

Campbell AJ, Robertson MC, La Grow SJ, et al. Randomised controlled trial of prevention of falls in...
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people aged ≥75 with severe visual impairment: The VIP trial. *Br Med J.* 2005;331(7520):817-820
Exclusion code: 4

Exclusion code: 4

Exclusion code: 8

Exclusion code: 4

Exclusion code: 5

Exclusion code: 15

Exclusion code: 15

Exclusion code: 14

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 13

Exclusion code: 3

Exclusion code: 13

Exclusion code: 4

Exclusion code: 15

Exclusion code: 6

Chandra RK. Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. *Nutrition.* 2001;17(9):709-712
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Chao YS, Brunel L, Faris P, Veugelers PJ. The importance of dose, frequency and duration of
vitamin D supplementation for plasma 25-hydroxyvitamin D. *Nutrients*. 2013;5(10):4067-4078
Exclusion code: 7

Exclusion code: 2

Exclusion code: 14

Exclusion code: 14

Exclusion code: 6

Exclusion code: 4

Exclusion code: 13

Exclusion code: 3

Exclusion code: 15

Exclusion code: 8

Exclusion code: 5

Exclusion code: 6

Exclusion code: 15

Christakos S, DeLuca H. Minireview: Vitamin D: is there a role in extraskeletal health? *Endocrinology*. 2011;152(8):2930-2936
Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 7

Clemens TL, Zhou XY, Myles M. Serum vitamin D2 and vitamin D3 metabolite concentrations and absorption of vitamin D2 in elderly subjects. *J Clin Endocrinol Metab*. 1986;63(3):656-660
Exclusion code: 7
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Exclusion code: 7

Compston JE. The role of vitamin D and calcium supplementation in the prevention of osteoporotic fractures in the elderly. *Clin Endocrinol.* 1995;43(4):393-405
Exclusion code: 13

Exclusion code: 3

Exclusion code: 8

Exclusion code: 7

Exclusion code: 15

Exclusion code: 3

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 13

Exclusion code: 8

Exclusion code: 13

Exclusion code: 7

Exclusion code: 5

Exclusion code: 3

Exclusion code: 9

Exclusion code: 14
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Exclusion code: 4

Davidson MB, Duran P, Lee ML, Friedman TC. High-dose vitamin D supplementation in people with prediabetes and hypovitaminosis D. *Diabetes Care.* 2013;36(2):260-266
Exclusion code: 4

Exclusion code: 7

Exclusion code: 4

Exclusion code: 8

Exclusion code: 15

Exclusion code: 15

Exclusion code: 12

Exclusion code: 8

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Exclusion code: 6

Exclusion code: 4

Exclusion code: 6

Exclusion code: 6

Exclusion code: 3

Exclusion code: 8
Appendix B4. List of Excluded Studies

Exclusion code: 6

Exclusion code: 8

Exclusion code: 4

Exclusion code: 4

Exclusion code: 14

Exclusion code: 7

Diamond T, Wong YK, Golombick T. Effect of oral cholecalciferol 2,000 versus 5,000 IU on serum vitamin D, PTH, bone and muscle strength in patients with vitamin D deficiency. *Osteoporus Int.* 2013;24(3):1101-1105
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Exclusion code: 7

Exclusion code: 6

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Exclusion code: 6

Exclusion code: 13

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 8

Exclusion code: 15

Dukas L, Schacht E, Mazor Z, Stahelin HB. Treatment with alfacalcidol in elderly people significantly decreases the high risk of falls.
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associated with a low creatinine clearance of <65 ml/min. Osteoporos Int. 2005;16(2):198-203
Exclusion code: 14

Exclusion code: 14

Exclusion code: 6

Duplessis CA, Harris EB, Watenpaugh DE, Horn WG. Vitamin D supplementation in underway submariners. Aviat Space Environ Med. 2005;76(6):569-575
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Exclusion code: 3

Exclusion code: 5

Eaton C. Low vitamin D levels not useful as predictive risk marker for mortality. Cardiol Today. 2010
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Exclusion code: 6

Exclusion code: 8

Exclusion code: 4

Exclusion code: 6

Exclusion code: 4

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Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6
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Exclusion code: 6

Exclusion code: 7

Exclusion code: 7

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Exclusion code: 2

Exclusion code: 15

Exclusion code: 8

Exclusion code: 4

Exclusion code: 4

Exclusion code: 3

Exclusion code: 6

Exclusion code: 2

Exclusion code: 7

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Appendix B4. List of Excluded Studies

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Exclusion code: 2

Exclusion code: 8

Exclusion code: 4

Exclusion code: 8

Exclusion code: 2

Exclusion code: 4

Exclusion code: 15

Exclusion code: 15

Exclusion code: 4

Gallagher JC, Rapuri PB, Smith LM. An age-related decrease in creatinine clearance is associated with an increase in number of falls in untreated women but not in women receiving calcitriol treatment. *J Clin Endocrinol Metab.* 2007;92(1):51-58
Exclusion code: 15
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Exclusion code: 4

Exclusion code: 6

Exclusion code: 3

Gallieni M. High-dose oral vitamin D supplementation and risk of falls in older women. *JAMA.* 2010;304(8):855; author reply 856-857
Exclusion code: 8

Exclusion code: 2

Exclusion code: 4

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 7

Exclusion code: 6

Garland CF, Grant WB, Mohr SB, Gorham ED, Garland FC. What is the dose-response relationship between vitamin D and cancer risk? *Nutr Rev.* 2007;65(8 Pt 2):S91-95
Exclusion code: 8

Exclusion code: 5

Exclusion code: 4

Exclusion code: 15

Exclusion code: 3

Exclusion code: 4
Appendix B4. List of Excluded Studies

Exclusion code: 7

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Appendix B4. List of Excluded Studies

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Exclusion code: 7

Exclusion code: 7

Exclusion code: 14

Exclusion code: 3

Exclusion code: 14

Exclusion code: 5

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Exclusion code: 3
Grant WB. An estimate of the global reduction in mortality rates through doubling vitamin D levels. *Eur J Clin Nutr.* 2011;65(9):1016-1026
Exclusion code: 7
Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level: Implications for meta-analyses and setting vitamin D guidelines. *Dermatoendocrinol.* 2011;3(3):199-204
Exclusion code: 6
Exclusion code: 6
Exclusion code: 8
Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. *Nutr Cancer.* 2004;48(2):115-123
Exclusion code: 13
Exclusion code: 5
Exclusion code: 7
Exclusion code: 15
Green AK, Hankinson SE, Bertone-Johnson ER, Tamimi RM. Mammographic density, plasma vitamin D levels and risk of breast cancer in postmenopausal women. *Int J Cancer.* 2010;127(3):667-674
Exclusion code: 6

Green TJ, Skeaff CM, Rockell JE. Milk fortified with the current adequate intake for vitamin D (5 microg) increases serum 25-hydroxyvitamin D compared to control milk but is not sufficient to prevent a seasonal decline in young women. *Asia Pac J Clin Nutr.* 2010;19(2):195-199
Exclusion code: 15
Exclusion code: 7
Exclusion code: 5
Exclusion code: 4
Exclusion code: 4
Exclusion code: 5
Exclusion code: 15
Appendix B4. List of Excluded Studies

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Exclusion code: 6

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

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Exclusion code: 2

Exclusion code: 4

Exclusion code: 6
Harris S, Dawson-Hughes B. Seasonal mood changes in 250 normal women. Psychiatry Res. 1993;49(1):77-87

Exclusion code: 15

Exclusion code: 8

Exclusion code: 3

Exclusion code: 6
Harris SS, Pittas AG, Palermo NJ. A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. Diabetes Obes Metab. 2012;14(9):789-794

Exclusion code: 4
Harris SS, Soteriades E, Coolidge JA, Mudgal S, Dawson-Hughes B. Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. J Clin Endocrinol Metab. 2000;85(11):4125-4130

Exclusion code: 3

Exclusion code: 7

Exclusion code: 4
Hasling C, Nielsen HE, Melsen F, Mosekilde L. Safety of osteoporosis treatment with sodium fluoride, calcium phosphate and vitamin D. Miner Electrolyte Metab. 1987;13(2):96-103

Exclusion code: 4
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Exclusion code: 7

Exclusion code: 7

Exclusion code: 4

Exclusion code: 4

Exclusion code: 6

Heaney RP, Heikkinen AM, Tuppurainen MT, Niskanen L, Komulainen MH, Saarikoski S. Long-term vitamin D3 supplementation may have adverse effects on serum lipids during postmenopausal hormone replacement therapy. *Eur J Endocrinol.* 1997;137(5):495-502
Exclusion code: 14

Exclusion code: 4
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Exclusion code: 15

Exclusion code: 5

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Exclusion code: 10

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 2

Exclusion code: 7

Exclusion code: 4

Holick MF. Vitamin D deficiency in obesity and health consequences. *Curr Opin Endocrinol Diabetes.* 2006;13(5):412-418
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Exclusion code: 3

Exclusion code: 7

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Exclusion code: 8

Exclusion code: 8

Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab.* 2008;93(3):677-681
Exclusion code: 15

Exclusion code: 8
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Exclusion code: 8

Exclusion code: 4

Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr.* 2004;80(6 Suppl):1752S-1758S
Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 8

Exclusion code: 6

Exclusion code: 14

Exclusion code: 6

Exclusion code: 3

Exclusion code: 7

Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry.* 2008;65(5):508-512
Exclusion code: 7

Exclusion code: 6

Exclusion code: 13

Exclusion code: 3

Exclusion code: 7

Exclusion code: 3
Appendix B4. List of Excluded Studies


Inanir A, Ozoran K, Tutkak H, Mermeric B. The effects of calcitriol therapy on serum interleukin-1, interleukin-6 and tumour necrosis factor-alpha
Appendix B4. List of Excluded Studies


Institute of Medicine. 2011 Dietary reference intakes for calcium and vitamin D Washington, DC2011Exclusion code: 2


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Exclusion code: 4

Exclusion code: 6

Exclusion code: 7

Exclusion code: 3

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Exclusion code: 8

Exclusion code: 5

Exclusion code: 14

Exclusion code: 6

Exclusion code: 14

Exclusion code: 7

Exclusion code: 5

Exclusion code: 15

Exclusion code: 15

Exclusion code: 7

Exclusion code: 15

Jorde R, Svee M, Torjesen P, Figenschau Y, Hansen JB. Parameters of the thrombogram are associated with serum 25-hydroxyvitamin D levels at baseline, but not affected during supplementation with vitamin D. *Thrombosis Research.* 2010;125(5):e210-e213
Exclusion code: 6
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Jorde R, Sneve M, Torjesen PA, Figenschau Y, Hansen JB, Grimnes G. No significant effect on bone mineral density by high doses of vitamin D3 given to overweight subjects for one year. *Nutr J.* 2010;9(1) Exclusion code: 15


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Exclusion code: 5

Exclusion code: 3

Exclusion code: 4

Exclusion code: 4

Exclusion code: 6

Exclusion code: 4

Exclusion code: 3

Exclusion code: 12

Exclusion code: 2

Exclusion code: 14

Exclusion code: 6

Exclusion code: 6

Exclusion code: 5

Exclusion code: 6

Exclusion code: 6

Exclusion code: 14

Exclusion code: 14

Kota SK, Jammula S, Kota SK, Tripathy PR, Panda S, Modi KD. Effect of vitamin D supplementation in screening for Vitamin D Deficiency 125 Pacific Northwest EPC
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Exclusion code: 4


Exclusion code: 6


Exclusion code: 5


Exclusion code: 4


Exclusion code: 7


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Exclusion code: 3


Exclusion code: 6


Exclusion code: 6


Exclusion code: 15


Exclusion code: 3


Exclusion code: 6


Exclusion code: 6
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Lagunova Z, Porojnicu AC, Grant WB, Bruland O, Moan JE. Obesity and increased risk of cancer: does decrease of serum 25-hydroxyvitamin D level with increasing body mass index explain some of the association? Mol Nutr Food Res. 2010;54(8):1127-1133
Exclusion code: 7

Exclusion code: 4

Exclusion code: 7

Exclusion code: 14

Exclusion code: 7

Exclusion code: 4

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Exclusion code: 14

Exclusion code: 14

Exclusion code: 15

Exclusion code: 7

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

Exclusion code: 7

Exclusion code: 14

LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in...
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Exclusion code: 7

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Exclusion code: 3

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Exclusion code: 5

Exclusion code: 4

Exclusion code: 4

Exclusion code: 5

Exclusion code: 3

Exclusion code: 12

Exclusion code: 7

Exclusion code: 8

Exclusion code: 7

Levitan EB, Judd SE. Can vitamin D supplementation improve physical function and quality of life in older patients with heart failure? *Circ Heart Fail*. 2010;3(2):183-184
Exclusion code: 8

Exclusion code: 15

Exclusion code: 6

Exclusion code: 4

Exclusion code: 7
Appendix B4. List of Excluded Studies

Exclusion code: 6

Exclusion code: 5

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Exclusion code: 7

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Exclusion code: 8

Lips P. Vitamin D physiology. *Prog Biophys Mol Biol.* 2006;92(1):4-8
Exclusion code: 13

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Appendix B4. List of Excluded Studies

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Exclusion code: 6

Løken-Amsrud KH, T; Bakke, SJ; Beiske, AG; Bjerve, KS; Bjornarå, BT; Hovdal, H; Lilleås, F; Midgard, R; Pedersen, T; Bent, JS; Sandvik, L; Torkilden, O; Wergeland, S; Myhr, KM. Vitamin D and disease activity in multiple sclerosis before and during interferon-β treatment. *Neurology.* 2012;79(3):261-266
Exclusion code: 6

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Exclusion code: 2

Exclusion code: 2

Exclusion code: 7

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Exclusion code: 7

Exclusion code: 4

Exclusion code: 14

Appendix B4. List of Excluded Studies

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Exclusion code: 5


Exclusion code: 3


Exclusion code: 4


Exclusion code: 3


Exclusion code: 6


Exclusion code: 4

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McGrath J, Eyles DW, Pedersen CB, et al. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. *Arch Gen Psychiatry.* 2010;67(9):889-894 Exclusion code: 4


McKiernan FE, Wiley C. Vitamin D2, vitamin D3, and the tolerable upper intake level. *J Bone Miner Res.* 2008;23(12):2060-2061 Exclusion code: 8
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Exclusion code: 7

McMurdo ME, Millar AM, Daly F. A randomized controlled trial of fall prevention strategies in old peoples' homes. *Gerontology.* 2000;46(2):83-87
Exclusion code: 5

Exclusion code: 15

Exclusion code: 7

Exclusion code: 7

Exclusion code: 3

Exclusion code: 5

Exclusion code: 4

Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. *J Clin Endocrinol Metab.* 2009;94(3):940-945
Exclusion code: 4

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 15

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Exclusion code: 2
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Exclusion code: 7

Michos E. Vitamin-D deficiency linked to fatal stroke in whites but not blacks. *Risk of Fatal Stroke Associated with Vitamin-D Deficiency (25(OH)D <15 Ng/mL) in White Vs Black Participants.* 2010
Exclusion code: 8

Exclusion code: 4

Exclusion code: 5

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Exclusion code: 4

Exclusion code: 4

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Exclusion code: 8

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Exclusion code: 15

Moschos G, Manios Y. Skeletal site-dependent response of bone mineral density and quantitative ultrasound parameters following a 12-month dietary intervention using dairy products fortified with
Exclusion code: 14

Exclusion code: 4

Exclusion code: 2

Exclusion code: 2

Exclusion code: 4

Exclusion code: 15

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Exclusion code: 13

Exclusion code: 15

Exclusion code: 7

Exclusion code: 14

Exclusion code: 8

Exclusion code: 10

Exclusion code: 4

Exclusion code: 6

National Institutes of Health Office of Dietary Supplements. Dietary supplement fact sheet: Vitamin
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D. In: National Institutes of Health, ed. Bethesda, MD2011
Exclusion code: 8

Exclusion code: 2

Exclusion code: 5

Exclusion code: 15

Exclusion code: 8

Exclusion code: 4

Exclusion code: 3

Exclusion code: 5

Newmark HL, Lipkin M. Calcium, vitamin D, and colon cancer. Cancer Res. 1992;52(7 Suppl):2067s-2070s
Exclusion code: 8

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Exclusion code: 14

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Exclusion code: 4

Exclusion code: 2

Nurmi-Luthje I, Sund R, Juntunen M, Luthje P. Post-hip fracture use of prescribed calcium plus vitamin D
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or vitamin D supplements and antiosteoporotic drugs is associated with lower mortality: a nationwide study in Finland. J Bone Miner Res. 2011;26(8):1845-1853 Exclusion code: 14


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Exclusion code: 4

Exclusion code: 7

Park SY, Murphy SP, Wilkens LR, Nomura AM, Henderson BE, Kolonel LN. Calcium and vitamin D intake and risk of colorectal cancer: the Multiethnic Cohort Study. *Am J Epidemiol.* 2007;165(7):784-793
Exclusion code: 5

Exclusion code: 5

Exclusion code: 13

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Exclusion code: 15

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Exclusion code: 8

Exclusion code: 14

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Exclusion code: 6

Exclusion code: 4

Exclusion code: 6
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Exclusion code: 3

Perez-Lopez FR. Sunlight, the vitamin D endocrine system, and their relationships with gynaecologic cancer. *Maturitas.* 2008;59(2):101-113
Exclusion code: 7

Exclusion code: 8

Exclusion code: 6

Exclusion code: 7

Exclusion code: 15

Petrella RJ, Jones TJ. Do patients receive recommended treatment of osteoporosis following hip fracture in primary care? *BMC Fam Pract.* 2006;7
Exclusion code: 4

Exclusion code: 4

Exclusion code: 3

Exclusion code: 14

Exclusion code: 7

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Exclusion code: 7


Exclusion code: 3


Exclusion code: 4


Exclusion code: 15


Exclusion code: 4

Ponsonby AL, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology. 2002;181-182:71-78

Exclusion code: 5


Exclusion code: 6


Exclusion code: 7


Exclusion code: 3


Exclusion code: 4

Principi N, Bianchini S, Baggi E, Esposito S. Implications of maternal vitamin D deficiency for the
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fetus, the neonate and the young infant. Eur J Nutr. 2013;52(3):859-867
Exclusion code: 4

Exclusion code: 12

Exclusion code: 7

Exclusion code: 4

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Exclusion code: 14

Exclusion code: 4

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Appendix B4. List of Excluded Studies

Exclusion code: 14

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Exclusion code: 5

Romagnoli E, Mascia ML, Cipriani C, et al. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J Clin Endocrinol Metab*. 2008;93(8):3015-3020
Exclusion code: 7

Exclusion code: 4

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Exclusion code: 13

Exclusion code: 5

Exclusion code: 7

Exclusion code: 7

Exclusion code: 5

Exclusion code: 6

Exclusion code: 14

Exclusion code: 14

Exclusion code: 7

Exclusion code: 5
Appendix B4. List of Excluded Studies

Exclusion code: 4

Exclusion code: 3

Exclusion code: 7

Exclusion code: 6

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 6

Exclusion code: 10

Exclusion code: 15

Exclusion code: 15

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Exclusion code: 3

Exclusion code: 2

Exclusion code: 6
Appendix B4. List of Excluded Studies

Exclusion code: 4

Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. [Erratum appears in *JAMA.* 2010 Jun;303(23):2357]. *JAMA.* 2010;303(18):1815-1822
Exclusion code: 14

Exclusion code: 7

Exclusion code: 5

Exclusion code: 4

Exclusion code: 4

Exclusion code: 14

Exclusion code: 4

Exclusion code: 6

Exclusion code: 5

Exclusion code: 4

Exclusion code: 7

Exclusion code: 5

Exclusion code: 4

Exclusion code: 8

Exclusion code: 13

Exclusion code: 3
Appendix B4. List of Excluded Studies

Exclusion code: 3

Exclusion code: 4

Exclusion code: 7

Exclusion code: 7

Exclusion code: 8

Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin D: *Commission E;* 2002
Exclusion code: 8

Exclusion code: 6

Exclusion code: 8

Exclusion code: 6

Exclusion code: 7

Exclusion code: 10

Exclusion code: 6

Exclusion code: 4

Exclusion code: 4

Exclusion code: 4

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Exclusion code: 5

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Exclusion code: 3

Exclusion code: 15
Appendix B4. List of Excluded Studies

Exclusion code: 3

Exclusion code: 14

Exclusion code: 12

Exclusion code: 4

Exclusion code: 15

Snijder MB, van Schoor NM, Pluijm SMF, van Dam RM, Visser M, Lips P. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab. 2006;91(8):2980-2985
Exclusion code: 6

Exclusion code: 7

Exclusion code: 3

Exclusion code: 6

Exclusion code: 7

Exclusion code: 4

Exclusion code: 2

Exclusion code: 4

Snijder MB, van Schoor NM, Pluijm SMF, van Dam RM, Visser M, Lips P. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab. 2006;91(8):2980-2985
Exclusion code: 6

Exclusion code: 7

Exclusion code: 3

Exclusion code: 6

Exclusion code: 7

Exclusion code: 4

Exclusion code: 2

Exclusion code: 4

Snijder MB, van Schoor NM, Pluijm SMF, van Dam RM, Visser M, Lips P. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab. 2006;91(8):2980-2985
Exclusion code: 6

Exclusion code: 7

Exclusion code: 3

Exclusion code: 6
Appendix B4. List of Excluded Studies

Exclusion code: 4


Exclusion code: 4


Exclusion code: 4


Exclusion code: 6


Exclusion code: 4


Exclusion code: 6

Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. *Osteoporos Int.* 2011;22(3):859-871

Exclusion code: 3


Exclusion code: 6


Exclusion code: 6


Exclusion code: 5


Exclusion code: 5


Exclusion code: 2


Exclusion code: 4


Exclusion code: 4


Exclusion code: 6


Exclusion code: 4


Exclusion code: 4

Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF. Adolescent girls in maine are at risk for...
Appendix B4. List of Excluded Studies

Exclusion code: 14

Exclusion code: 6

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Tellioğlu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral...
Appendix B4. List of Excluded Studies

Exclusion code: 12

Exclusion code: 5

Exclusion code: 4

Exclusion code: 2

Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. *Am J Obstet Gynecol*. 1998;179(2):444-452
Exclusion code: 5

Exclusion code: 4

Exclusion code: 6

Exclusion code: 12

Exclusion code: 4

Exclusion code: 8

Exclusion code: 6

Exclusion code: 6

Exclusion code: 7

Exclusion code: 6

Exclusion code: 3

Exclusion code: 7

Exclusion code: 4

Exclusion code: 2
Appendix B4. List of Excluded Studies

Exclusion code: 14

Exclusion code: 6

Exclusion code: 2

Exclusion code: 3

Tuppurainen M, Heikkinen AM, Penttila I, Saarikoski S. Does vitamin D3 have negative effects on serum levels of lipids? A follow-up study with a sequential combination of estradiol valerate and cyproterone acetate and/or vitamin D3. *Maturitas.* 1995;22(1):55-61
Exclusion code: 14

Exclusion code: 2

Exclusion code: 2.
Appendix B4. List of Excluded Studies

Exclusion code: 5
Exclusion code: 7
Exclusion code: 3
van Oeffelen AAM, Bekkers MBM, Smit HA, et al. Serum micronutrient concentrations and childhood asthma: The PIAMA birth cohort study. Pediatric Allergy and Immunology. 2011;22(8):784-793
Exclusion code: 4
Exclusion code: 3
Exclusion code: 7
Exclusion code: 5
Exclusion code: 8
Exclusion code: 7
Exclusion code: 4
Vieth R. Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. J Steriod Biochem Mol Biol. 2004;89-90(1-5):575-579
Exclusion code: 8
Vieth R. What is the optimal vitamin D status for health? Prog Biophys Mol Biol. 2006(92):26
Exclusion code: 2
Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr. 2001;73(2):288-294
Exclusion code: 12
Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J. 2004;3:8
Exclusion code: 5
Exclusion code: 6
Exclusion code: 6
Villareal DT, Civitelli R, Chines A, Avioli LV. Subclinical vitamin D deficiency in postmenopausal women with low vertebral bone mass. J Clin Endocrinol Metab. 1991;72(3):628-634
Exclusion code: 6
Exclusion code: 7
Virtanen JK, Nurmi T, Voutilainen S, Mursu J, Tuomainen T-P. Association of serum 25-hydroxyvitamin D with the risk of death in a general
Appendix B4. List of Excluded Studies

Exclusion code: 3

Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab.* 2003;88(12):5766-5772
Exclusion code: 2

von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. *Br J Nutr.* 2010;103(4):549-555
Exclusion code: 4

von Hurst PR, Stonehouse W, Kruger MC, Coad J. Vitamin D supplementation suppresses age-induced bone turnover in older women who are vitamin D deficient. *J Steroid Biochem Mol Biol.* 2010;121(1-2):293-296
Exclusion code: 6

Exclusion code: 8

Exclusion code: 6

Exclusion code: 12

Exclusion code: 4

Exclusion code: 14

Exclusion code: 5

Exclusion code: 13

Exclusion code: 3

Exclusion code: 6

Exclusion code: 4

Exclusion code: 6

Exclusion code: 6

Exclusion code: 13

Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin
Appendix B4. List of Excluded Studies

Exclusion code: 6

Exclusion code: 13

Wei MY, Giovannucci EL. Vitamin D and multiple health outcomes in the Harvard cohorts. *Mol Nutr Food Res.* 2010;54(8):1114-1126
Exclusion code: 7

Exclusion code: 15

Exclusion code: 3

Exclusion code: 8

Exclusion code: 4

Exclusion code: 2

Exclusion code: 7

Exclusion code: 7

Williams DA, Arnold LM. Measures of fibromyalgia: Fibromyalgia Impact Questionnaire (FIQ), Brief Pain Inventory (BPI), Multidimensional Fatigue Inventory (MFI-20), Medical Outcomes Study (MOS) Sleep Scale, and Multiple Ability Self-Report Questionnaire (MASQ). *Arthritis Care Res.* 2011;63(S11):S86-S97
Exclusion code: 2

Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo MET. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail.* 2010;3(2):195-201
Exclusion code: 4

Exclusion code: 13

Wijst M, Hypponen E. Vitamin D serum levels and allergic rhinitis. *Allergy.* 2007;62(9):1085-1086
Exclusion code: 7

Exclusion code: 7

Exclusion code: 3

Appendix B4. List of Excluded Studies

Exclusion code: 8
Exclusion code: 5

Exclusion code: 13

Exclusion code: 4

Exclusion code: 6

Exclusion code: 6

Exclusion code: 7

Exclusion code: 4

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Exclusion code: 4

Yusupov EL-N, Pollack, S; Yeh, JK; Mikhail, M; Aloia, JF. Vitamin D deficiency and serum cytokines in a randomized clinical trial. *Int J Endocrinol.* 2010
Exclusion code: 15

Zabihiyeganeh M, Jahed A, Nojomi M. Treatment of hypovitaminosis D with pharmacologic doses of cholecalciferol, oral vs intramuscular; an open labeled RCT. *Clin Endocrinol.* 2013;78(2):210-216
Exclusion code: 12

Zamora SA, Rizzoli R, Belli DC, Slosman DO, Bonjour JP. Vitamin D supplementation during infancy is associated with higher bone mineral mass in prepubertal girls. *J Clin Endocrinol Metab.* 1999;84(12):4541-4544
Exclusion code: 4

Exclusion code: 4

Exclusion code: 5

Zhao G, Ford ES, Li C, Croft JB. Serum 25-hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among US adults
Appendix B4. List of Excluded Studies

Exclusion code: 4

Exclusion code: 6

Exclusion code: 13

Exclusion code: 4

Exclusion code: 3

Zhu K, Bruce D, Austin N, Devine A, Ebeling PR, Prince RL. Randomized controlled trial of the effects of calcium with or without vitamin D on bone structure and bone-related chemistry in elderly women with vitamin D insufficiency. *J Bone Miner Res*. 2008;23(8):1343-1348
Exclusion code: 4

Exclusion code: 15

Exclusion code: 6

Exclusion code: 8

Exclusion code: 4

Exclusion code: 4

Exclusion code: 5

Exclusion code: 7

Exclusion code: 3

Exclusion code: 4

Exclusion code: 8

Exclusion code: 7

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
Appendix B4. List of Excluded Studies

Exclusion code: 4

Dissemination CfRa. Optimizing vitamin D status to reduce colorectal cancer risk: an evidentiary review (Structured abstract). *DARE*. 2013(4)
Exclusion code: 13

Exclusion code: 13

Exclusion code: 13

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 7

Annweiler C, Beauchet O. Vitamin D-mentia: randomized clinical trials should be the next step. *Neuropsychi Deblopedia*. 2011;37(3-4):249-258
Exclusion code: 7

Aspray TJ, Francis RM. Vitamin D and fractures: where are we now? *Maturitas*. 2010;66(3):221-222
Exclusion code: 8

Babu US, Calvo MS. Modern India and the vitamin D dilemma: evidence for the need of a national food fortification program. *Mol Nutr Food Res*. 2010;54(8):1134-1147
Exclusion code: 7

Exclusion code: 2

Exclusion code: 7

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 7

Exclusion code: 7

Exclusion code: 7

Exclusion code: 8
Appendix B4. List of Excluded Studies

Bouillon R. Why modest but widespread improvement of the vitamin D status is the best strategy? Baillieres Best Pract Res Clin Endocrinol Metab. 2011;25(4):693-702
Exclusion code: 7

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Centre for Reviews and Dissemination. Effectiveness and implementation aspects of interventions for preventing falls in elderly people in long-term care facilities: a systematic review of RCTs (Structured abstract). DARE. 2012(4)
Exclusion code: 8

Exclusion code: 6

Exclusion code: 8

Exclusion code: 7

Exclusion code: 2

Compston JE. Vitamin D deficiency: time for action. Evidence supports routine supplementation for elderly people and others at risk. BMJ. 1998;317(7171):1466-1467
Exclusion code: 8

Exclusion code: 2

Exclusion code: 7

Exclusion code: 2

Exclusion code: 2

Francis RM. What do we currently know about nutrition and bone health in relation to United Kingdom public health policy with particular reference to calcium and vitamin D? Br J Nutr. 2008;99(1):155-159
Exclusion code: 7

Fraser WD, Milan AM. Vitamin D assays: past and present debates, difficulties, and developments. Calcif Tissue Int. 2013;92(2):118-127
Exclusion code: 2

Appendix B4. List of Excluded Studies

Exclusion code: 3
Exclusion code: 7
Exclusion code: 2
Grant WB, Schwalfenberg GK, Genuis SJ, Whiting SJ. An estimate of the economic burden and premature deaths due to vitamin D deficiency in Canada. *Mol Nutr Food Res.* 2010;54(8):1172-1181
Exclusion code: 7
Exclusion code: 8
Exclusion code: 8
Heaney RP. Vitamin D: how much do we need, and how much is too much? *Osteoporos Int.* 2000;11(7):553-555
Exclusion code: 8
Exclusion code: 2
Holick MF. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. *Osteoporos Int.* 1998;8 (Suppl 2):S24-29
Exclusion code: 8
Exclusion code: 7
Exclusion code: 2
Exclusion code: 2
Exclusion code: 2
Exclusion code: 8
Exclusion code: 8
Exclusion code: 7
Exclusion code: 7
Exclusion code: 7
Exclusion code: 2
Lambert J. Vitamin D deficiency. *Br J Gen Pract.* 2007;57(541):669; author reply 669-670
Exclusion code: 8
Exclusion code: 8
Appendix B4. List of Excluded Studies

Exclusion code: 6

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Meunier P. Prevention of hip fractures by correcting calcium and vitamin D insufficiencies in elderly people. Scand J Rheumatol Suppl. 1996;103:75-78; discussion 79-80
Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 7

Exclusion code: 7

Nowson CA. Prevention of fractures in older people with calcium and vitamin D. Nutrients. 2010;2(9):975-984
Exclusion code: 7

Exclusion code: 8

Exclusion code: 8

Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ. 2010;340:b5664
Exclusion code: 7

Exclusion code: 2

Exclusion code: 7

Pham B, Klassen TP, Lawson ML, Moher D. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. J Clin Epidemiol. 2005;58(8):769-776
Exclusion code: 2

Exclusion code: 8

Pogge E. Vitamin D and Alzheimer's disease: is there a link? Consult Pharm. 2010;25(7):440-450
Exclusion code: 7

Exclusion code: 12
Appendix B4. List of Excluded Studies

Exclusion code: 8

Reid IR, Avenell A. Evidence-based policy on dietary calcium and vitamin D. *J Bone Miner Res.* 2011;26(3):452-454
Exclusion code: 8

Exclusion code: 4

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Sahota O. Calcium and vitamin d reduces falls and fractures--confusion and controversy. *J Nurt Health Aging.* 2007;11(2):176-178
Exclusion code: 7

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Exclusion code: 2

Exclusion code: 8

Exclusion code: 4

Exclusion code: 7

Exclusion code: 2

Exclusion code: 7

Exclusion code: 12

Exclusion code: 2

Appendix B4. List of Excluded Studies

Exclusion code: 8
Exclusion code: 8
Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr.* 2006;136(4):1117-1122
Exclusion code: 8
Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75nmol/L (30ng/ml). *Baillieres Best Pract Res Clin Endocrinol Metab.* 2011;25(4):681-691
Exclusion code: 2
Exclusion code: 2
Exclusion code: 8
Exclusion code: 8
Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. *J Clin Endocrinol Metab.* 2013;98(9):3821-3828
Exclusion code: 2
Exclusion code: 8
Exclusion code: 8
Zgaga L, Theodoratou E, Farrington SM, et al. Diet, environmental factors, and lifestyle underlie the high prevalence of vitamin D deficiency in healthy adults in Scotland, and supplementation reduces the proportion that are severely deficient. *J Nutr.* 2011;141(8):1535-1542
Exclusion code: 7
Exclusion code: 8
Exclusion code: 7
Exclusion code: 3
Exclusion code: 15
Exclusion code: 7
Centre for Reviews and Dissemination. Prognostic role of vitamin D status and efficacy of vitamin D supplementation in cancer patients: a systematic review (Provisional abstract). *DARE.* 2012(4)
Exclusion code: 4
Exclusion code: 4
Exclusion code: 6
Appendix B4. List of Excluded Studies

Exclusion code: 14

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

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Appendix B4. List of Excluded Studies

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Appendix B4. List of Excluded Studies

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Exclusion code: 6

Exclusion code: 3

Exclusion code: 3

Exclusion code: 15

Peiris AN, Bailey BA, Guha BN, Copeland R, Manning T. Can a model predictive of vitamin D status be developed from common laboratory tests and demographic parameters? *South Med J.* 2011;104(9):636-639
Exclusion code: 3

Exclusion code: 6

Exclusion code: 6

Exclusion code: 7

Exclusion code: 6

Appendix B4. List of Excluded Studies

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Exclusion code: 6


Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014;348
Exclusion code: 2

Exclusion code: 3

Exclusion code: 6

Exclusion code: 6

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Appendix B4. List of Excluded Studies

*Cancer Epidemiol Biomarkers Prev.* 2010;19(1):130-134
Exclusion code: 3

Exclusion code: 6

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Exclusion code: 6
Appendix B5. Quality Rating Criteria

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.

Source: USPSTF Procedure Manual\textsuperscript{149}
Appendix B6. List of Reviewers

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

Michael F. Holick, MD, PhD, Professor of Medicine, Physiology, and Biophysics at Boston University School of Medicine

Elina Hypponen, MPH, PhD, Reader in Epidemiology and Public Health, Department of Population Health Sciences, MRC Center of Epidemiology for Child Health

JoAnn E. Manson, MD, MPH, DrPH, Professor, Department of Epidemiology, Brigham and Women’s Hospital, Boston, MA; Professor of Medicine, Harvard Medical School, Boston, MA; Chief, Division of Preventive Medicine, Department of Medicine, Brigham and Women’s Hospital

Clifford Rosen, MD, Director of Clinical and Translational Research, Main Medical Center, Scarborough, ME; Senior Scientist, Maine Medical Center Research Institute, Scarborough, ME; Adjunct Staff Scientist, The Jackson Laboratory, Bar Harbor, ME; Professor of Medicine, Tufts University School of Medicine, Boston, MA; National Institute of Arthritis and Musculoskeletal and Skin Diseases Scientific Advisory Board; Food and Drug Administration Advisory Board on Endocrinologic and Metabolic Drugs

Elizabeth Yetley, PhD, MS, Scientific Consultant, Office of Dietary Supplements at the National Institutes of Health

Federal Reviewers

Margaret Brewinski Issacs, MD, MPH, Medical Officer, National Institutes of Health, Office of Research on Women’s Health

Rosemarie Filart, MD, MPH, Medical Officer, Department of Health and Human Services, National Institutes of Health

Linda S. Kisinger, MD, MPH, Chief Consultant for Preventive Medicine, National Center for Health Promotion and Disease Prevention, Office of Patient Care Services, Veterans Health Administration

Amy C. Lossie, PhD, Health Scientist, National Institutes of Health

Harold Seifried, PhD, DABT, Chief, Nutritional Science Group, Division of Cancer Prevention, National Cancer Institute

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

Screening for Vitamin D Deficiency 169 Pacific Northwest EPC
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

<table>
<thead>
<tr>
<th>Author, Year, Title*</th>
<th>Overall Population Characteristics: Vitamin D vs. Control</th>
<th>Country and Setting</th>
<th>Eligibility Criteria</th>
<th>Assay</th>
<th>Definition of Deficiency/Insufficiency (ng/mL)</th>
<th>Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazier et al, 2005** 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</td>
<td>Mean age (years): 74.6 (74.2 vs. 75.0) Female: 100% Race: NR BMI: NR Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 736 (752 vs. 721)</td>
<td>France 50 centers Institutionalized: 0%</td>
<td>Inclusion: Community-dwelling ambulatory women age &gt;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.</td>
<td>Competitive protein-binding assay</td>
<td>Insufficiency: serum 25(OH)D ≤12</td>
<td>7 vs. 7 100% &lt;20</td>
</tr>
<tr>
<td>Chapuy et al, 2002** Combined calcium and vitamin D₃ supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk. The Decalyos II Study</td>
<td>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</td>
<td>France Homes for the elderly Institutionalized: 100%</td>
<td>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 of ≥24 months. Exclusion: Women with intestinal malabsorption, hypercalcemia, or chronic renal failure; women who had received drugs known to alter bone metabolism, such as corticosteroids, anticonvulsants, or high-dose thyroxine within the past year; women who had been treated with fluoride salts (&gt;3 months), bisphosphonates, calcitonin (&gt;1 month), calcium (&gt;500 mg/day), and vitamin D (&gt;100 IU/day) in the past 12 months.</td>
<td>Competitive protein-binding assay</td>
<td>Not specifically defined</td>
<td>9.2 vs. 9.2 100% &lt;20</td>
</tr>
</tbody>
</table>

≥90% of study participants had 25(OH)D level <20 ng/mL
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tr>
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<th>Definition of Deficiency/ Insufficiency (ng/mL)</th>
<th>Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)</th>
</tr>
</thead>
</table>
| Gallagher et al, 2013 [60]  
*Effects of vitamin D supplementation in older African American women* | Mean age (years): 67  
Female: 100%  
Race: 100% black  
Mean BMI (kg/m²): 32.7  
Comorbidities: 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 fasting blood glucose level <7.8 mmol/L in persons with type 2 diabetes; active kidney stone disease or a history of >2 kidney stones 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 or >20 ng/mL; BMI >45 kg/m²; serum calcium level >2.57 mmol/L on 2 baseline tests; 24-hour urinary calcium level >7.3 mmol/day on 2 baseline tests; BMD T-score <−3 at the spine or hip; 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. | Radio-immunoassay | 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 |
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<tbody>
<tr>
<td>Gallagher et al, 2014</td>
<td>Mean age (years): 36.7 Female: 100% Race: 60% white, 40% black Mean BMI (kg/m²): 30.2 Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 655</td>
<td>Nebraska University medical center; community recruitment Institutionalized: NR</td>
<td>Inclusion: Women ages 25 to 45 years with vitamin D insufficiency. Exclusion: Pregnant; significant comorbidities; history of cancer except skin cancer within last 10 years; uncontrolled type 1 diabetes ± significant proteinuria or fasting blood sugar &gt;140 mg in type 2 diabetes; active kidney stone disease or history of &gt;2 kidney stones; chronic renal failure; evidence of chronic liver disease; alcoholism; severe vitamin D deficiency (serum 25(OH)D level &lt;5 ng/mL); serum calcium level &gt;2.57 mmol/L on 2 baseline tests; 24-hour urinary calcium level &gt;7.3 mmol/day on 2 baseline tests; BMD T-score &lt;−3 at the spine or hip (specific to race); and use of bone-active drugs such as fluoride, PTH or derivatives, calcitonin, estrogen during past 6 months, chronic high-dose corticosteroid therapy (&gt;10 mg/d), bisphosphonates for &gt;3 months in the past, anticonvulsants, or high-dose thiazide therapy (&gt;37.5 mg/d).</td>
<td>Radio-immunoassay</td>
<td>Insufficiency: serum 25(OH)D &lt;20</td>
<td>Overall: 13.4 Placebo: 12.7 Vitamin D 400 IU: 13.1 800 IU: 13.8 1600 IU: 13.3 2400 IU: 14.1</td>
</tr>
<tr>
<td>Grimnes et al, 2011</td>
<td>Mean age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) Race: NR Mean BMI (kg/m²): 26.5 (27.2 vs. 26.3) Comorbidities: NR History of falls: NR Mean dairy servings at baseline: 16/week</td>
<td>Norway Community Institutionalized: 0%</td>
<td>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 (males) or ≥110 μmol/L (females), possible primary hyperparathyroidism (plasma PTH &gt;5.0 pmol/L combined with serum calcium &gt;2.50 mmol/L), sarcoidosis, SBP &gt;175 mm Hg or DBP &gt;105 mm HG, pregnancy, lactation, or fertile age and no contraception use.</td>
<td>Liquid chromatography double mass spectrometry</td>
<td>Low: serum 25(OH)D &lt;17</td>
<td>17 vs. 16 100% &lt;17</td>
</tr>
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<th>Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)</th>
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<tr>
<td>Janssen et al, 2010</td>
<td>Mean age (years): 80.8† (82.4 vs. 79.2) Female: 100%</td>
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<tr>
<td></td>
<td>Race: NR Mean BMI (kg/m²): 26.4† (26.2 vs. 26.7)</td>
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<tr>
<td></td>
<td>Comorbidities: 2.4† (2.7 vs. 2.1) Medications used: 5.0† (5.2 vs. 4.8)</td>
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<td></td>
<td>History of falls: NR Calcium intake: NR</td>
<td>Italy</td>
<td>Inclusion: Ambulatory women age &gt;65 years, able to follow simple instructions, and a serum 25(OH)D level of 8 to 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 &gt;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.</td>
<td>NR</td>
<td>Insufficiency: serum 25(OH)D 8 to 20</td>
<td>13 vs. 14 90% &lt;19</td>
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<tr>
<td></td>
<td>The Netherlands Outpatient clinics Institutionalized: most women lived in residential homes for the elderly, number NR</td>
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<tr>
<td>Knutsen et al, 2014</td>
<td>Overall (25 vs. 10 µg/day vs. control) Mean age (years): 37.3† (36 vs. 37 vs. 39) Female: 73% (69% vs. 72% vs. 77%) Race: NR Mean BMI (kg/m²): 27.4† (27.0 vs. 27.5 vs. 27.8) Comorbidities: NR</td>
<td>Norway 11 local immigrant activity centers Institutionalized: NR</td>
<td>Inclusion: Healthy adult immigrants, ages 18 to 50 years, living in Oslo, but with parents born in the Middle East, Africa, or South Asia. Exclusion: Regularly used vitamin D-containing supplements, receiving treatment for vitamin D deficiency, pregnant or breastfeeding, known malabsorption, used medication interfering with vitamin D metabolism, kidney disease, cancer, tuberculosis, sarcoidosis, osteoporosis or a recent fracture, or used strong painkillers.</td>
<td>High performance liquid chromatography Laboratory participates in DEQAS</td>
<td>Insufficiency: serum 25(OH)D 20</td>
<td>25 vs. 10 µg/day vs. control 11 vs. 10 vs. 11 100% &lt;20</td>
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<tr>
<td></td>
<td>Serum calcium at baseline (mmol/L): 2.36† (2.37 vs. 2.36)</td>
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<tr>
<td>Lips et al, 2010</td>
<td>Mean age (years): 78 (78.5 vs. 77.6) Female: NR</td>
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<tr>
<td></td>
<td>Race: NR Mean BMI (kg/m²): 27.8† (27.4 vs. 28.2)</td>
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<tr>
<td></td>
<td>Comorbidities: NR Use of walking device: 15%</td>
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<tr>
<td></td>
<td>History of falls: NR Calcium intake: NR</td>
<td>The Netherlands, Germany, Wisconsin, Nebraska, New Jersey, Pennsylvania Medical centers and nursing homes Institutionalized: 14%</td>
<td>Inclusion: Ambulatory men and women age ≥70 years 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 hormone within 12 months, treated with &gt;800 IU vitamin D/day or with its active metabolites within 6 months, treatment with drug that might affect vitamin D metabolism or interfere with postural stability.</td>
<td>Reverse phase high performance liquid chromatography Laboratory participates in DEQAS</td>
<td>Insufficiency: serum 25(OH)D 6 to 20</td>
<td>14 vs. 14 100% &lt;20</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Pfeifer et al, 2000†</td>
<td>Mean age (years): 74.8† (74.8 vs. 74.7) Female: 100% Race: NR Mean BMI (kg/m²): 25.5† (25.5 vs. 25.4) Comorbidities: 39% cardiovascular; 12% central nervous, neurological; &lt;1% psychiatric; 22% musculoskeletal Concomitant medication: 2.8% benzodiazepine use; 13.6% thyroidotherapy; 68% cardiovascular drugs History of falls: NR Calcium intake: NR</td>
<td>Germany Population-based Institutionalized: 0%</td>
<td>Inclusion: Healthy ambulatory women age ≥70 years with serum 25(OH)D level &lt;20 ng/mL. Exclusion: Hypercalcemia or primary hyperparathyroidism; extremity fractures from osteoporosis; therapy with bisphosphonate, calcitonin, vitamin D and its 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 &gt;20% of upper limit of reference range); history of drug or alcohol abuse; nicotine abuse (&gt;20 cigarettes daily); &gt;7 cups of coffee/day; scheduled holiday along geographic longitude during study period; diabetes mellitus and other diseases; medications possibly interfering with postural stability and balance (anticonvulsants).</td>
<td>Radio-immunoassay</td>
<td>Not specifically defined, but study only included women with serum 25(OH)D &lt;20</td>
<td>10 vs. 10 100% &lt; 20</td>
</tr>
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<th>Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)</th>
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</thead>
<tbody>
<tr>
<td>Wamberg et al, 2013</td>
<td>Mean age (years): 40.5 (39.5 vs. 41.2)</td>
<td>Denmark</td>
<td>Inclusion: Healthy males and females ages 18 to 50 years with BMI &gt;30 kg/m² and plasma 25(OH)D level &lt;20 ng/mL.</td>
<td>Isotope dilution liquid chromatography-tandem mass spectrometry</td>
<td>Low: plasma 25(OH)D &lt;20</td>
<td>14 vs. 14 100% &lt;20</td>
</tr>
<tr>
<td></td>
<td>Female: 71% (69% vs. 73%)</td>
<td></td>
<td>Exclusion: Pregnant women or women planning pregnancy; history of diabetes, fasting plasma glucose &gt;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 &gt;125 kg.</td>
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<td></td>
<td>Race: NR</td>
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<tr>
<td></td>
<td>Mean BMI (kg/m²): 35.8† (36.1 vs. 35.0)</td>
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<tr>
<td></td>
<td>Sedentary: 35%† (35% vs. 35%)</td>
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<tr>
<td></td>
<td>Lightly active: 48%† (46% vs. 50%)</td>
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<tr>
<td></td>
<td>Moderately active: 17%† (19% vs. 15%)</td>
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<tr>
<td></td>
<td>Comorbidities: NR</td>
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<td></td>
<td>Concomitant medications: 2% (1/55) lipid-lowering; 5% (3/55) antihypertensive</td>
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<td>History of falls: NR</td>
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<td></td>
<td>Mean dietary calcium intake at baseline(mg/day): 992 vs. 936</td>
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<td></td>
<td>Mean age (years): 40.5 (39.5 vs. 41.2)</td>
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<tr>
<td></td>
<td>Female: 71% (69% vs. 73%)</td>
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<tr>
<td></td>
<td>Race: NR</td>
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<td>Mean BMI (kg/m²): 35.8† (36.1 vs. 35.0)</td>
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<td>Mean age (years): 40.5 (39.5 vs. 41.2)</td>
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<td>Inclusion: Healthy males and females ages 18 to 50 years with BMI &gt;30 kg/m² and plasma 25(OH)D level &lt;20 ng/mL.</td>
<td>Isotope dilution liquid chromatography-tandem mass spectrometry</td>
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<td>Female: 71% (69% vs. 73%)</td>
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<td>Exclusion: Pregnant women or women planning pregnancy; history of diabetes, fasting plasma glucose &gt;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 &gt;125 kg.</td>
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<td>Race: NR</td>
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<td>Mean BMI (kg/m²): 35.8† (36.1 vs. 35.0)</td>
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<tr>
<td></td>
<td>Comorbidities: NR</td>
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<td>History of falls: NR</td>
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<td>Mean dietary calcium intake at baseline(mg/day): 992 vs. 936</td>
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<tr>
<td>Aloia et al, 2008</td>
<td>Mean age (years): 40.5 (39.5 vs. 41.2)</td>
<td>New York University hospital</td>
<td>Inclusion: Healthy men and women ages 18 to 65 years.</td>
<td>Radio-receptor assay Laboratory participates in DEQAS</td>
<td>Not specifically defined, but study only included participants with 25(OH)D ≤32</td>
<td>Overall: 19 90% ≤30</td>
</tr>
<tr>
<td></td>
<td>Female: 81%</td>
<td></td>
<td>Exclusion: Baseline 25(OH)D &gt;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.</td>
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<tr>
<td></td>
<td>Race: 45% black; 55% white</td>
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<tr>
<td></td>
<td>BMI: NR</td>
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<td>Comorbidities: NR</td>
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<td></td>
<td>History of falls: NR</td>
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<tr>
<td></td>
<td>Mean dietary calcium intake at baseline: 665 mg/day</td>
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</tbody>
</table>

≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL
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<th>Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)</th>
</tr>
</thead>
</table>
| Arvold et al, 2009†   | Mean age (years): 58.8† (59.7 vs. 57.8)  
Female: 40% (44% vs. 36%)  
White: 95% (96% vs. 95%)  
BMI: NR  
Comorbidities: NR  
Use of over-the-counter supplements: 31% (31% vs. 31%)  
History of falls: NR  
Weekly milk intake ≥1 quart: 48% (46% vs. 50%)  
Mean age (years): 58.8† (59.7 vs. 57.8)  
Female: 40% (44% vs. 36%)  
White: 95% (96% vs. 95%)  
BMI: NR  
Comorbidities: NR  
Use of over-the-counter supplements: 31% (31% vs. 31%)  
History of falls: NR  
Weekly milk intake ≥1 quart: 48% (46% vs. 50%)  
Mean age (years): 58.8† (59.7 vs. 57.8)  
Female: 40% (44% vs. 36%)  
White: 95% (96% vs. 95%)  
BMI: NR  
Comorbidities: NR  
Use of over-the-counter supplements: 31% (31% vs. 31%)  
History of falls: NR  
Weekly milk intake ≥1 quart: 48% (46% vs. 50%)  
Mean age (years): 58.8† (59.7 vs. 57.8)  
Female: 40% (44% vs. 36%)  
White: 95% (96% vs. 95%)  
BMI: NR  
Comorbidities: 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** | Mean age (years): 31 (range, 22 to 47)  
Female: 0%  
Race: NR  
Comorbidities: NR  
History of falls: NR  
Mean calcium intake estimated to be 800 mg/day based on outside sources (not measured)  
Mean age (years): 31 (range, 22 to 47)  
Female: 0%  
Race: NR  
Comorbidities: NR  
History of falls: NR  
Mean calcium intake estimated to be 800 mg/day based on outside sources (not measured)  
Mean age (years): 31 (range, 22 to 47)  
Female: 0%  
Race: NR  
Comorbidities: 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 |
| Bischoff et al, 2003*** | Mean age (years): 85 (85 vs. 85)  
Female: 100%  
Race: NR  
Mean BMI (kg/m²): 24.7 (24.7 vs. 24.7)  
% using walking aid: 60† (58 vs. 62)  
% with history of falls: 34† (35 vs. 33)  
% with comorbidities: 95† (98 vs. 91)  
% comorbid 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 | Switzerland Long-stay geriatric clinic  
Institutionalized: 100% | Inclusion: Women age ≥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. | Radio-immunoassay | 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 |
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<thead>
<tr>
<th>Author, Year, Title*</th>
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<tbody>
<tr>
<td>Gallagher et al, 2012</td>
<td>Mean age (years): 67 Female: 100% White: 100% Mean BMI (kg/m²): 30.2 Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 685</td>
<td>Nebraska University medical center Institutionalized: NR</td>
<td>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 &lt;7.8 mmol/L in persons with type 2 diabetes; active kidney stone disease or a history of &gt;2 kidney stones; 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 &lt;5 or &gt;20 ng/mL; BMI &gt;45 kg/m²; serum calcium level &gt;2.57 mmol/L on 2 baseline tests; 24-hour urinary calcium level &gt;7.3 mmol/day on 2 baseline tests; BMD T-score &lt;-3 at the spine or hip; current use of bisphosphonates or prior use for &gt;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.</td>
<td>Radio-immunoassay</td>
<td>Insufficiency: serum 25(OH)D ≤20</td>
<td>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</td>
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<tr>
<td>Harris et al, 1999**&lt;sup&gt;‡‡&lt;/sup&gt; Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D</td>
<td>Mean age (years): 31 (range, 22 to 47) Female: 0% Race: NR BMI: NR Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>Massachusetts Tufts University Institutionalized: NR</td>
<td>Inclusion: Men with low vitamin D intake (&lt;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 worked in an outdoor occupation; usual calcium intake of ≥600 mg/day; use of calcium supplement in the past 6 months; usual consumption of &gt;3 alcoholic beverages a day; use of medications known to affect vitamin D absorption or metabolism in past year; any history of liver, kidney, or gastrointestinal disease resulting in malabsorption syndrome; gastrointestinal surgery; kidney stone in the past 5 years; or any current medical condition likely to affect vitamin D absorption or metabolism.</td>
<td>High performance liquid chromatography</td>
<td>Low: ≤26 Younger men: 13 vs. 17 Older men: 16 vs. 16 90% ≤24</td>
<td></td>
</tr>
<tr>
<td>Honkanen et al, 1990&lt;sup&gt;‡‡&lt;/sup&gt; The necessity and safety of calcium and vitamin D in the elderly</td>
<td>Home patients Mean age (years): 69.5&lt;sup&gt;†&lt;/sup&gt; (69.4 vs. 69.6) Female: 100% Weight (kg): 69.5&lt;sup&gt;†&lt;/sup&gt; (70.7 vs. 68.4) Race: NR BMI: NR Comorbidities: NR History of falls: NR Dietary calcium intake: NR Hospital inpatients (institutionalized) Mean age (years): 82.5&lt;sup&gt;†&lt;/sup&gt; (82.2 vs. 82.8) Female: 100% Weight (kg): 61.8&lt;sup&gt;†&lt;/sup&gt; (62.1 vs. 61.5) Race: NR BMI: NR Comorbidities: NR History of falls: NR Dietary calcium intake: NR</td>
<td>Finland City hospital Institutionalized: 52%</td>
<td>Inclusion: Elderly women ages 67 and 72 years living independently at home or geriatric female inpatients age ≥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.</td>
<td>NR</td>
<td>NR Home patients: 17 vs. 15 Hospital inpatients: 10 vs. 10 90% ≤24</td>
<td></td>
</tr>
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<tr>
<td>Kärkkäinen et al, 2010‡‡</td>
<td>Mean age (years): 67.4‡ (67.4 vs. 67.4)</td>
<td>Finland Population-based Institutionalized: NR</td>
<td>Inclusion: Female members of the OSTPRE cohort born in 1932 to 1941 and age ≥65 years at the end of November 2001; living in Kuopio province 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</td>
<td>Radio-immunoassay</td>
<td>NR</td>
<td>20 vs. 20 90% ≤30</td>
</tr>
<tr>
<td>Kjaergaard et al, 2012‡‡</td>
<td>Mean age (years): 53.4‡ (53.4 vs. 53.3)</td>
<td>Norway Population-based Institutionalized: NR</td>
<td>Inclusion: Adults ages 30 to 75 years with low serum vitamin D levels from the sixth Tromsø 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, or cancer or kidney stones; pregnant or lactating women; fertile women age &lt;50 years not using adequate contraception; those using vitamin D supplements, antidepressants, or other mood stabilizing medication; those regularly using a solarium; those planning a trip to a sunny location during the trial period; those with possible primary hyperparathyroidism, elevated creatinine, elevated systolic or diastolic blood pressure, high scores on depression scales, or serious depression indicated in interview.</td>
<td>Liquid chromatography with tandem mass spectrometry</td>
<td>Low: &lt;22</td>
<td>19 vs. 19 100% &lt;22</td>
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## Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<td>Krieg et al, 1999†‡‡‡‡</td>
<td>Mean age (years): 84.5† (84 vs. 85) Female: 100% Race: NR Mean BMI (kg/m²): 24.7† (25.7 vs. 23.8; p=0.04) Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>Switzerland Nursing homes Institutionalized: 100%</td>
<td>Inclusion: Women living in 19 nursing homes in the Lausanne area. Exclusion: NR</td>
<td>Protein binding assay</td>
<td>NR</td>
<td>12.95 vs. 12.95 90% ≤21</td>
</tr>
<tr>
<td>Lehmann et al, 2013†</td>
<td>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/m²): 23.8† (23.7 vs. 24.0 vs. 23.7) Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>Norway Healthy community population Institutionalized: NR</td>
<td>Inclusion: Healthy adults. Exclusion: Use of vitamin D and calcium supplements, history of chronic illness and elevated serum creatinine (females, ≥1.1 mg/dL; 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.</td>
<td>Liquid chromatography with mass spectrometry</td>
<td>NR</td>
<td>Vitamin D2 vs. D3 vs. control 15 vs. 18 vs. 16 90% ≤25</td>
</tr>
<tr>
<td>Lips et al, 1996†‡†</td>
<td>Mean age (years): 80.4† (80.1 vs. 80.6) Female: 100% Race: NR Mean BMI (kg/m²): 28.3† (28.1 vs. 28.6) Comorbidities: NR History of falls: NR Median calcium intake at baseline (mg/day): NR (876 vs. 859)</td>
<td>The Netherlands Community Institutionalized: 100%</td>
<td>Inclusion: Elderly persons age ≥70 years; nonrandom sample of female residents of homes and apartments for the elderly who were mobile enough to visit the hospital for BMD measurements 3 times. Exclusion: History of hip fracture or total hip arthroplasty; recent history of hypercalcemia, sarcoidosis, or urolithiasis</td>
<td>Competitive protein-binding assay</td>
<td>Not specifically defined</td>
<td>Median: 11 vs. 10 90% ≤20</td>
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<td>Martineau et al, 2007&lt;sup&gt;179&lt;/sup&gt; A single dose of vitamin D enhances immunity to mycobacteria</td>
<td>Median age&lt;sup&gt;¶¶&lt;/sup&gt; (years): 33.7&lt;sup&gt;†&lt;/sup&gt; (30.1 vs. 37.5) Female&lt;sup&gt;¶¶&lt;/sup&gt;: 51.2%&lt;sup&gt;†&lt;/sup&gt; (46.3% vs. 56.2%) Black&lt;sup&gt;¶¶&lt;/sup&gt;: 12.9%&lt;sup&gt;†&lt;/sup&gt; (10.4% vs. 15.6%) South Asian&lt;sup&gt;¶¶&lt;/sup&gt;: 68%&lt;sup&gt;†&lt;/sup&gt; (70.1% vs. 67.2%) White&lt;sup&gt;¶¶&lt;/sup&gt;: 13.7%&lt;sup&gt;†&lt;/sup&gt; (13.4% vs. 14.1%) BMI: NR Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>London TB contact clinics Institutionalized: NR</td>
<td>Inclusion: Persons age &gt;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.</td>
<td>Isotope dilution liquid chromatography-tandem mass spectrometry Laboratory participates in DEQAS</td>
<td>Deficiency: &lt;8 Insufficiency: &lt;30</td>
<td>14 vs. NR Overall deficient: 42% (84/192) Overall insufficient: 94% (189/192)*** 94% &lt;30</td>
</tr>
<tr>
<td>Pfeifer et al, 2009&lt;sup&gt;183&lt;/sup&gt; Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals</td>
<td>Mean age (years): 76.5 (76 vs. 77) Female: 74.5% (74% vs. 75%) Race: NR Mean BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;): 27.3 (27.0 vs. 27.5) Comorbidities: NR History of falls: NR Mean baseline nutritional calcium intake (mg/unit time NR): 618 (608 vs. 628)</td>
<td>Austria and Germany Population-based Institutionalized: 0%</td>
<td>Inclusion: Healthy ambulatory adults age ≥70 years with 25(OH)D serum level &lt;31 ng/mL. Exclusion: Hypercalcemia or primary hyperparathyroidism; extremity fractures due to osteoporosis; therapy with thiazide, bisphosphonate, calcitonin, vitamin D and its metabolites, estrogen, or anti-estrogen in past 6 months or fluoride treatment in past 2 years; known intolerance to study medication; chronic renal failure (serum creatinine &gt;20% of the upper limit of reference range); history of drug or alcohol abuse; nicotine abuse (&gt;20 cigarettes per day), &gt;7 cups of coffee per day; scheduled holidays along geographic longitude during study period; diabetes mellitus, severe cardiovascular disease.</td>
<td>Radio-immunoassay</td>
<td>Not specifically defined, but study only included participants with 25(OH)D &lt;31</td>
<td>22 vs. 22 100% &lt;31</td>
</tr>
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### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<td>Talwar et al, 2007††</td>
<td>Mean age (years): 60.5† (59.9 vs. 61.2) Female: 100% Black: 100% Mean BMI (kg/m²): 29 vs. 30 Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>New York Population-based Institutionalized: NR</td>
<td>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 &gt;400 IU/day vitamin D in past 6 months; history of previous hip fracture; uncontrolled diabetes, anemia, or thyroid disease; history of current liver, renal, neurologic, or malignant disease; malabsorption or alcoholism; history of hypercalciuria, nephrolithiasis, or active sarcoidosis; smoking &gt;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; participation in weight training or elite athletic training.</td>
<td>Radio-immunoassay Laboratory participates in DEQAS</td>
<td>Deficiency: &lt;30 19 vs. 17 90% ≤29</td>
<td></td>
</tr>
<tr>
<td>Aloia et al, 2005175</td>
<td>A randomized controlled trial of vitamin D₃ supplementation in African American women</td>
<td>Mean age (years): 60.5† (59.9 vs. 61.2) Female: 100% Black: 100% Mean BMI (kg/m²): 29 vs. 30 Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>New York Population-based Institutionalized: NR</td>
<td>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 &gt;400 IU/day vitamin D in past 6 months; history of previous hip fracture; uncontrolled diabetes, anemia, or thyroid disease; history of current liver, renal, neurologic, or malignant disease; malabsorption or alcoholism; history of hypercalciuria, nephrolithiasis, or active sarcoidosis; smoking &gt;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; participation in weight training or elite athletic training.</td>
<td>Radio-immunoassay Laboratory participates in DEQAS</td>
<td>Deficiency: &lt;30 19 vs. 17 90% ≤29</td>
</tr>
<tr>
<td>Wood et al, 2012††</td>
<td>Overall (vitamin D 400 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/m²): 26.7† (26.6 vs. 26.8 vs. 26.6) Comorbidities: NR History of falls: NR Calcium intake: NR</td>
<td>U.K. Community Institutionalized: NR</td>
<td>Inclusion: White postmenopausal women from Aberdeen Prospective Osteoporosis Screening cohort. Exclusion: Pre-existing CVD, diabetes, asthma, malabsorption, hypertension (≥160 mm Hg systolic or ≥99 mm Hg diastolic), difficulty in swallowing tablets or capsules, taking medications or supplements known to affect any dependent variable, current smokers, or abnormal blood biochemistry at screening.</td>
<td>High performance liquid chromatography-tandem mass spectrometer</td>
<td>NR 13 vs. 13 vs. 14 90% ≤23</td>
<td></td>
</tr>
</tbody>
</table>

*Title* denotes study title.
†Mean age (years) ± standard deviation.
‡Female: 100% Black: 100% Mean BMI (kg/m²) ± standard deviation.
§Comorbidities: NR History of falls: NR Calcium intake: NR

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**Notes:**
- DEQAS: Diabetes Epidemiology and Genetics Research Study.
- HRT: Hormone Replacement Therapy.
- CVD: Cardiovascular Disease.
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<th>Adjusted Confounders in Analysis</th>
<th>Interventions</th>
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<tr>
<td>≥90% of study participants had 25(OH)D level &lt;20 ng/mL</td>
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<tr>
<td></td>
<td>Median: 29 ± 11 ≤ 12 ng/mL; 9% vs. 70%; p&lt;0.001</td>
<td>Approached: 360 Screened: NR Eligible: 192 Enrolled: 192 (95 vs. 97) Analyzed: 191 (95 vs. 96)</td>
<td>12 months</td>
<td>18.9% (18/95) vs. 28.9% (28/97) Overall: 24.0% (46/192)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 400 IU of vitamin D3, BID (total, 800 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: Identical placebo tablet, BID</td>
</tr>
<tr>
<td><em>Brazier et al, 2005</em></td>
<td>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</td>
<td>Shown in figure; vitamin D groups had significant increase from baseline (p=0.0001); placebo group did not have significant increase from baseline; mean at followup was 30 and 35 for vitamin D groups and 5 for placebo group</td>
<td>Approached: NR Screened: NR Eligible: 639 (610 randomized) Enrolled: 583 (393 vs. 190)</td>
<td>24 months</td>
<td>28.2 ± vs. 36.1 ± Overall: 30.8% (188/610)</td>
<td>NR (RCT)</td>
</tr>
<tr>
<td><em>Chapuy et al, 2002</em></td>
<td>Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk. The Decalyos II Study</td>
<td>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 &gt;20 ng/mL; vitamin D levels higher in all vitamin D groups individually vs. placebo (p&lt;0.05)</td>
<td>Approached: 526 Screened: 303 Eligible: 108 (303 screened − 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 response analysis; 110 for harms</td>
<td>12 months (NR if mean or median; range NR)</td>
<td>17.2% (16/93) vs. 17.6% (3/17) Overall: 17.3% (19/110)</td>
<td>Primary outcome adjusted for age, BMI, calcium intake, smoking status, alcohol use, average caffeine intake, serum creatinine, and season</td>
</tr>
<tr>
<td><em>Gallagher et al, 2013</em></td>
<td>Effects of vitamin D supplementation in older African American women</td>
<td>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 &gt;20 ng/mL; between 800 and 1600 IU of vitamin D per day required in black women (prediction limit, 1200 IU daily)</td>
<td>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)</td>
<td>12 months (NR if mean or median; range NR)</td>
<td>37.5% (60/160) vs. 26.3% (10/38) Overall: 35.4% (70/198)</td>
<td>Primary outcome adjusted for season at baseline, age, BMI category, calcium intake, smoking status, alcohol use, and serum creatinine</td>
</tr>
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*Note: RCT = randomized controlled trial, NR = not reported, ITT = intention-to-treat.*
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<tr>
<td>Grimnes et al, 2011[^6] Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique</td>
<td>57 vs. 17; p&lt;0.01</td>
<td>Approached: 1028 Screened: 337 Eligible: 172 Enrolled: 104 (51 vs. 53) Analyzed: 104 (51 vs. 52)</td>
<td>6 months</td>
<td>4% (2/51) vs. 15% (8/53) Overall: 10% (10/104)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 20,000 IU of vitamin D₃ twice/week (total, 40,000 IU/week) Control: Identical placebo twice/week</td>
</tr>
<tr>
<td>Janssen et al, 2010[^7] Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation</td>
<td>31 vs. 17; p&lt;0.001</td>
<td>Approached: NR Screened: NR Eligible: 91 Enrolled: 70 (36 vs. 34) Analyzed: 59 (28 vs. 31)</td>
<td>6 months</td>
<td>22.2% (8/36) vs. 8.8% (3/34) Overall: 15.7% (11/70)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 400 IU of vitamin D₃ daily and 500 mg of calcium daily Control: Identical placebo and 500 mg of calcium daily</td>
</tr>
<tr>
<td>Knutsen et al, 2014[^12] Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway</td>
<td>25 vs. 10 µg/day vs. control 21 vs. 17 vs. 10</td>
<td>Approached: NR Screened: 301 Eligible: 253 Enrolled: 251 (84 vs. 85 vs. 82) Analyzed: 215 (75 [25 µg/day] vs. 69 [10 µg/day] vs. 71 control)</td>
<td>16 weeks</td>
<td>10.7% (9/84) on 25 µg/day vs. 18.8% (16/85) on 10 µg/day vs. 13.4% (11/82) control</td>
<td>NR (RCT)</td>
<td>Vitamin D: 25 or 10 µg of vitamin D₃ daily Control: Identical placebo</td>
</tr>
<tr>
<td>Lips et al, 2010[^15] Once-weekly dose of 8400 IU vitamin D₃ compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency</td>
<td>26 vs. 12 Mean difference, 13.0; p&lt;0.001</td>
<td>Approached: NR Screened: 593 Enrolled: 226 (114 vs. 112) Analyzed: 226 for AEs, 213 for SPPB measure</td>
<td>16 weeks</td>
<td>7.9% (9/114) vs. 13.4% (15/112) Overall: 10.6% (24/226)</td>
<td>Covariance model included terms for baseline body sway, baseline vitamin D stratum, and treatment group</td>
<td>Vitamin D: 2800 IU of vitamin D₃ 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 &lt;1000 mg were also given 500 mg calcium</td>
</tr>
</tbody>
</table>
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tbody>
<tr>
<td>Pfeifer et al. 2000 106</td>
<td>26 vs. 17; p &lt;0.001</td>
<td>Approached: 208 Screened: 165 Eligible: 151 Enrolled: 148 Analyzed: 145 in ITT; 137 for falls (70 vs. 67)</td>
<td>8 weeks treatment; 1 year posttreatment followup</td>
<td>5.4% (4/74) vs. 9.5% (7/74) Overall: 7.4% (11/148)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 400 IU of vitamin D₂ 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)</td>
</tr>
<tr>
<td>Wamberg et al. 2013 133</td>
<td>44 vs. 19; p&lt;0.00001 &gt;32: 96% vs. NR 20: 100% vs. 18%</td>
<td>Approached: NR Screened: 88 Eligible: 55 Enrolled: 52 (26 vs. 26) Analyzed for main outcomes: 43 (22 vs. 21)</td>
<td>26 weeks</td>
<td>15.4% (4/26) vs. 19.2% (5/26) Overall: 17.3% (9/52)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 1400 IU of vitamin D₃ given 5 times a day (total, 7000 IU/day) Control: Identical placebo tablets given 5 times daily</td>
</tr>
</tbody>
</table>

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106 Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women

133 The effect of high-dose vitamin D supplementation on calcitropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study

133 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
# Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<th>Author, Year, Title*</th>
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<tr>
<td>Aloia et al, 2008**</td>
<td>≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL</td>
<td>Reported on figure by race and sex; goal of &gt;30 ng/mL achieved by virtually all in active group; also increased by 8 ng/mL in placebo group because of seasonal change</td>
<td>6 months</td>
<td>Overall: 20% (27/138)</td>
<td>NR (RCT)</td>
<td>Vitamin D: vitamin D₃ dose depended on 25(OH)D level, as follows: Baseline 20 to 32 ng/mL: start at 2000 IU/day Baseline &lt;20 ng/mL: start at 4000 IU/day At followup &lt;20 ng/mL: increase by 2000 IU/day At followup 20 to 32 ng/mL: increase by 2000 IU/day At followup 32 to 56 ng/mL: do not change At followup &gt;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 tablet</td>
</tr>
<tr>
<td>Arvold et al, 2009***</td>
<td>Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial</td>
<td>Approached: NR Screened: 610 Eligible: 244 Enrolled: 100 (50 vs. 50) Analyzed: 90 (48 vs. 42)</td>
<td>8 weeks treatment/ followup</td>
<td>4% (2/50) vs. 16% (8/50) Overall: 10% (10/100)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 50,000 IU of vitamin D₃ weekly Control: Identical placebo tablet weekly</td>
</tr>
<tr>
<td>Berlin et al, 1986***</td>
<td>Studies on the relationship between vitamin D₃ status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D₃</td>
<td>Approached: NR Screened: NR Eligible: NR Enrolled: 24 (12 vs. 12) Analyzed: 24 (12 vs. 12)</td>
<td>NR; implied 2 months</td>
<td>NR</td>
<td>NR</td>
<td>Vitamin D: 18,000 IU of vitamin D₃ taken 3 times a week in March and April (total, 54,000 IU weekly) Control: No intervention</td>
</tr>
</tbody>
</table>
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tr>
<td>Bischoff et al, 2003 Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial</td>
<td>Median, 26 vs. 11; p&lt;0.001</td>
<td>Approached: NR Screened: NR Eligible: 130 Enrolled: 124 in pretreatment period; 122 in treatment (62 vs. 60) Analyzed: 122 (62 vs. 60) for falls</td>
<td>6 weeks pretreatment 12 weeks treatment</td>
<td>31% (19/62) vs. 25% (15/60)‡‡ Overall: 27% (33/122)</td>
<td>Adjusted for treatment and baseline covariates that reached significance of p&lt;0.1 (age, number of fallers in pretreatment period, being a faller in pretreatment period, baseline 25(OH)D level and baseline 1,25(OH)2D level, observation time during treatment)</td>
<td>Vitamin D: 400 IU of vitamin D3 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)</td>
</tr>
<tr>
<td>Gallagher et al, 2012 Dose response to vitamin D supplementation in postmenopausal women: a randomized trial</td>
<td>Shown in figure; dose-response curve predicted that 97.5% of those on 600 IU/day reached &gt;20 ng/mL; vitamin D levels higher in all vitamin D groups individually compared with placebo (p&lt;0.05)</td>
<td>Approached: 2113 Screened: 633 Eligible: NR Enrolled: 163 (142 [20 to 21 per dosage] vs. 21) Analyzed: 163 (142 vs. 21)</td>
<td>Median, 12 months (range, 0.9 to 14.0 months)</td>
<td>12.7% (18/142) vs. 14.3% (3/21) Overall: 12.9% (21/163)</td>
<td>NR</td>
<td>Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D3 daily Control: Identical placebo daily All Participants: Citracal calcium supplements administered BID to maintain total calcium intake of 1200 to 1400 mg/day</td>
</tr>
<tr>
<td>Harris et al, 1999 Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D</td>
<td>Younger men: 25 vs. 13 Older men: 19 vs. 15</td>
<td>Approached: NR Screened: NR Eligible: NR Enrolled: 20 (12 vs. 8) Analyzed: 18 (11 vs. 7)</td>
<td>3 weeks</td>
<td>55% (11/20) (4/10 younger and 5/10 older)</td>
<td>NR</td>
<td>Vitamin D: 1800 IU of vitamin D3 in liquid form taken with food daily in the morning Control: No intervention</td>
</tr>
<tr>
<td>Honkanen et al, 1990 The necessity and safety of calcium and vitamin D in the elderly</td>
<td>Home patients: 32 vs. 9 Hospital inpatients: 26 vs. 4 p&lt;0.001 for change in intervention group</td>
<td>Approached: NR Screened: 203 Eligible: NR Enrolled: 126 (63 vs. 63) Analyzed: 126 (63 vs. 63)</td>
<td>11 weeks</td>
<td>8/63 (12.7%) vs. 3/60 (4.8%) Overall: 11/126 (8.7%)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 1800 IU of vitamin D3 daily and 1.558 g of calcium daily Control: No intervention</td>
</tr>
</tbody>
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*Author, Year, Title* refers to the original study's information.
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<td>Karkkainen et al, 2010166‡‡</td>
<td>30 vs. 22; p&lt;0.001</td>
<td>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</td>
<td>3 years Mean, 2.8 years</td>
<td>1.0% (3/290) vs. 2.2% (7/313) Overall: 1.7% (10/603) in subsample with vitamin D levels</td>
<td>NR (RCT)</td>
<td>Vitamin D: 400 IU of vitamin D3 BID (total, 800 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: No intervention</td>
</tr>
<tr>
<td>Kjaergaard et al, 2012171</td>
<td>59 vs. 21</td>
<td>Approached: NR (12,984 in sixth Tromsø 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)</td>
<td>6 months</td>
<td>1.6% (2/122) vs. 9.1% (11/121) Overall: 5.4% (13/243)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 20,000 IU of vitamin D3 weekly Control: Identical placebo weekly</td>
</tr>
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Screening for Vitamin D Deficiency

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

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<td>Krieg et al, 19991999</td>
<td>27 vs. 6; p&lt;0.01</td>
<td>Approached: NR Screened: NR Eligible: NR Enrolled: 248 (124 vs. 124) Analyzed: 248 (124 vs. 124)</td>
<td>2 years</td>
<td>60% (74/124) vs. 57% (71/124) Overall: 58% (145/248)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 440 IU of vitamin D2 BID (total, 880 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: No intervention</td>
</tr>
<tr>
<td>Lehmann et al, 2013199</td>
<td>Vitamin D2 vs. D3 vs. control</td>
<td>Approached: NR Screened: NR Eligible: NR Enrolled: 119 (50 to vitamin D2 vs. 49 to vitamin D3 vs. 20 to control) Analyzed: 107 (47 to vitamin D2 vs. 46 to vitamin D3 vs. 19 to control)</td>
<td>8 weeks</td>
<td>Vitamin D2 vs. D3 vs. control: 8% (4/50) vs. 14% (7/49) vs. 5% (1/20) Overall: 10% (12/119)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 2000 IU of either vitamin D2 or D3 daily Control: Identical placebo daily</td>
</tr>
<tr>
<td>Lips et al, 1996196</td>
<td>Median, 25 vs. 9 (at 1 year)</td>
<td>Approached: NR Screened: NR Eligible: NR Enrolled: 348 (177 vs. 171) Analyzed: 270 with vitamin D levels</td>
<td>3 to 3.5 years; maximum 4 years</td>
<td>28.8% (51/177) vs. 31.0% (53/171) Overall: 28.7% (100/348) Drop out in first year: 19% (65/348) 16% (29/177) vs. 21% (36/171) 3.7% (13/348) are not in analysis at end of study</td>
<td>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</td>
<td>Vitamin D: 400 IU of vitamin D2 daily Control: Identical placebo daily</td>
</tr>
<tr>
<td>Martineau et al, 2007197</td>
<td>27 vs. NR</td>
<td>Approached: NR Screened: 364 Eligible: NR Enrolled: 192 (96 vs. 96) Analyzed: 192 (96 vs. 96)</td>
<td>6 weeks</td>
<td>31.2% (29/96) vs. 33.3% (32/96) Overall: 31.8% (61/192)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 100,000 IU vitamin D2 in a single dose Control: Identical lactose placebo in a single dose</td>
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<td>Pfeifer et al, 2009113</td>
<td>Month 12: 34 vs. 23 Month 20: 19 vs. 15</td>
<td>Approached: 315 Screened: NR Eligible: NR Enrolled: 242 (121 vs. 121) Analyzed: 242 (122 vs. 120) for falls and fractures††</td>
<td>12 month treatment and 8 month posttreatment followup Total: 20 months</td>
<td>6% (7/121) vs. 6% (7/121)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 400 IU of vitamin D3 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)</td>
</tr>
<tr>
<td>Talwar et al, 2007177</td>
<td>35 vs. 18 (at 27 months; 40% of active group still had levels &lt;32)</td>
<td>Approached: 50,000 Screened: 385 Eligible: 322 Enrolled: 208 (104 vs. 104) Analyzed: 208 (104 vs. 104)</td>
<td>36 months</td>
<td>28.8% (30/104) vs. 28.8% (30/104)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 800 IU of vitamin D3 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</td>
</tr>
<tr>
<td>Wood et al, 2012130</td>
<td>Vitamin D 400 vs. 1000 IU vs. control 26 vs. 30 vs. 13; p&lt;0.001</td>
<td>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])</td>
<td>13 months</td>
<td>Vitamin D 400 vs. 1000 IU vs. control: 18% (18/102) vs. 11% (11/101) vs. 11% (11/102) Overall: 13% (40/305)</td>
<td>NR (RCT)</td>
<td>Vitamin D: 400 or 1000 IU of vitamin D3 daily Control: Identical placebo daily</td>
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<th>Quality Rating</th>
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<tr>
<td>Brazier et al, 2005†</td>
<td>NR</td>
<td>Assessed followup levels No assessment of pill content Dietary vitamin D at baseline: 85 (85 vs. 84) IU/day</td>
<td>AEs: prespecified; recorded spontaneously reported and observed AEs Hypercalemia: measured serum calcium defined as ≥10.8 mg/dL, reported spontaneously</td>
<td>Mortality: 3.2% (3/95) vs. 1.0% (1/96); RR, 3.03 (95% CI, 0.32 to 28.63); all unrelated to drug</td>
<td>All NS: Total AEs: 187 vs. 170 Withdrawals 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) ≥1 AE: 72.6% (69/95) vs. 72.9% (70/96); RR, 0.10 (95% CI, 0.84 to 1.18) NonSAEs: 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)</td>
<td>Fair</td>
<td>Innothera Laboratories, Arcueil, France</td>
</tr>
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<tr>
<td>Brazier et al, 2005†</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Drug-related AEs: 22.1% (21/95) vs. 24.0% (23/96); RR, 0.92 (95% CI, 0.55 to 1.55)†</td>
<td>See above</td>
<td>See above</td>
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<td>Metabolic and nutritional: 9.5% (9/95) vs. 10.4% (10/96); RR, 0.91 (95% CI, 0.38 to 2.14)†</td>
<td>Hypercalcemia: 6.3% (6/95) vs. 8.3% (8/96); RR, 0.76 (95% CI, 0.27 to 2.10)†</td>
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<td>GI: 9.5% (9/95) vs. 8.3% (8/96); RR, 1.14 (95% CI, 0.46 to 2.82)†</td>
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<tr>
<td>Chapuy et al, 200222</td>
<td>NR</td>
<td>Followup levels</td>
<td>Fractures: women asked</td>
<td>Hip fracture: 6.9% (27/393) vs. 11.1% (21/190); RR, 0.62 (95% CI, 0.36 to 1.07)†</td>
<td>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)†</td>
<td></td>
<td>Merck KGaA, Germany</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased in vitamin D group</td>
<td>(2005)</td>
<td>Nonvertebral fractures: 17.8% (70/393) vs. 17.9% (34/190); RR, 1.0 (95% CI, 0.7 to 1.4)†</td>
<td>Withdrawals due to GI AEs: 3 (group NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No verification of pill content</td>
<td>fractures during investigator assessment every 3 months.</td>
<td>Fallers: 63.9% (251/393) vs. 62.1% (118/190); RR, 1.0 (95% CI, 0.9 to 1.2)†</td>
<td>Hypercalcemia: 3 vs. 0; RR, 3.39 (95% CI, 0.18 to 65.4)†</td>
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<tr>
<td></td>
<td></td>
<td>Dietary vitamin D intake at baseline: 40.8 IU/day</td>
<td>For peripheral fractures, date, site, and cause of trauma were recorded on a case report form.</td>
<td>Mortality: 18.1% (70/393) vs. 23.9% (45/190); RR, 0.75 (95% CI, 0.54 to 1.05)† (ITT analysis)†</td>
<td>No kidney stones reported</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>For vertebral fractures, spine radiographs were required for confirmation.</td>
<td></td>
<td>Hypercalcemia at 12 months (urinary calcium &gt;350 mg/24 hours): 3.0% (5/166) vs. 1.3% (1/77); RR, 2.32 (95% CI, 0.28 to 19.52)†</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>AEs: every 3 months, women were asked whether they had experienced any AEs.</td>
<td></td>
<td>Hypercalcemia at 24 months (urinary calcium &gt;350 mg/24 hours): 3.4% (3/89) vs. 2.9% (1/35); RR, 1.18 (95% CI, 0.13 to 10.96)†</td>
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<td></td>
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<td></td>
<td>Falls: NR</td>
<td>Mortality: NR</td>
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<td></td>
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<td></td>
<td>Hypercalcemia: measured serum calcium, collected at baseline and after 6, 12, 18, and 24 months</td>
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<tr>
<td>Gallagher et al, 2013160</td>
<td>Screened throughout the year from January 2008 to January 2010</td>
<td>Assessed followup levels</td>
<td>AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit</td>
<td>Mortality: none (as per author correspondence)</td>
<td>Withdrawals 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)†</td>
<td>Fair</td>
<td>Grant from the National Institute on Aging and the Office of Dietary Supplements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verified pill content</td>
<td>Hypercalcemia: measured serum calcium, defined as either &gt;10 or &gt;10.8 mg/dL, collected at baseline and after 3, 6, 9, and 12 months of treatment</td>
<td></td>
<td>Patients with SAEs: 1.1% (1/93; cerebral hemorrhage) vs. 0/17; RR, 0.57 (95% CI, 0.02 to 14.0); thought to be unrelated to treatment</td>
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<tr>
<td></td>
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<td>Mean baseline vitamin D intake</td>
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<td></td>
<td></td>
<td>NR</td>
<td>Uncontrolled Diabetes); vs. 5.9% (1/17; hypercalcemia); RR, 0.18 (95% CI, 0.01 to 2.78)†</td>
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<td></td>
<td></td>
<td>Participants instructed not to take nonstudy vitamin D; multivitamins without vitamin D were provided to those wanting it</td>
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<tr>
<td>Gallagher et al, 2014159</td>
<td>Screened throughout the year from January 2008 to January 2010</td>
<td>Assessed followup levels Verified pill content Mean baseline vitamin D intake: 100 mg/day Participants instructed not to take nonstudy vitamin D; multivitamins without vitamin D were provided to those wanting it</td>
<td>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</td>
<td>Mortality: none (as per author correspondence)</td>
<td>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): 1 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</td>
<td>Fair</td>
<td>Grant from the Department of Defense</td>
</tr>
<tr>
<td>Grimnes et al, 2011158</td>
<td>Recruited November to April; at baseline, 6% used sun bed</td>
<td>Assessed followup levels No assessment of pill content At baseline, 26% of participants took vitamin D supplements</td>
<td>Hypercalcemia: &gt;10.2 mg/dL reported to be out of the normal range Other outcomes: unclear</td>
<td>Mortality: 0/51 vs. 1/53 (unknown cause); RR, 0.34 (95% CI, 0.01 to 8.15)</td>
<td>Number of AEs: 45 vs. 46 No hypercalcemia No kidney stones</td>
<td>Fair</td>
<td>Norwegian Council of Cardiovascular Disease</td>
</tr>
<tr>
<td>Janssen et al, 2010127</td>
<td>NR</td>
<td>Followup levels increased in intervention group No verification of pill content Diet and supplement use NR</td>
<td>Unclear</td>
<td>Mortality: 1 (NR by group)</td>
<td>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</td>
<td>Fair</td>
<td>Prevention Program of ZonMw</td>
</tr>
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### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tr>
<td>Knutsen et al, 2014</td>
<td>January to March</td>
<td>Followup levels increased in intervention group</td>
<td>Pill count at followup</td>
<td>Unclear</td>
<td>NR</td>
<td>Brief hospital admission: 2.7% (2/75) in 25 µg/day vs. 0 in 10 µg/day vs. 1.4% (1/71) in control; deemed unrelated to drug</td>
<td>Fair</td>
<td>Institute of Health and Society, University of Oslo, Norwegian Women's Public Health, Association Furst Medical Laboratory and Nycomed Pharma AS</td>
</tr>
<tr>
<td>Lips et al, 2010</td>
<td>October to June</td>
<td>Followup levels increased in intervention</td>
<td>No verification of pill content</td>
<td>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</td>
<td>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</td>
<td>Withdrawals due to AEs: 2.6% (3/114) vs. 4.5% (5/112); RR, 0.59 (95% CI, 0.14 to 2.41)†</td>
<td>Fair</td>
<td>Merck and Co, Inc.</td>
</tr>
</tbody>
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*Note: Additional information included in the table regarding outcomes and adverse events can be expanded upon as necessary.
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<tr>
<td>Pfeifer et al, 2000†</td>
<td>Baseline vitamin D levels in March and supplementation from March to May</td>
<td>Followup levels increased 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 instructions were given after 8 weeks</td>
<td>Number of falls: questionnaires Fractures resulting from falls: verified by x-ray and medical reports</td>
<td>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&lt;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)</td>
<td>NR</td>
<td>Fair</td>
<td>Strathmann AG Hamburg</td>
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<tr>
<td>Wamberg et al, 2013 125</td>
<td>Recruited from February 2010 to May 2011</td>
<td>Assessed followup levels</td>
<td>AEs: prespecified; patient visits at weeks 2, 10, and 18 for safety measures and AE registration; no other details provided</td>
<td>NR</td>
<td>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</td>
<td>Fair</td>
<td>NR</td>
</tr>
<tr>
<td>Wamberg et al, 2013 133</td>
<td>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</td>
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≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D level ≥20 ng/mL

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<tr>
<td>Aloia et al, 2008 17</td>
<td>Recruited during 3 winters (November to March) and followed for 6 months (into summer/fall)</td>
<td>Assessed followup levels</td>
<td>AEs and hypercalcemia: prespecified clinical laboratory criteria for safety (serum calcium &gt;10.6 mg/L, urine calcium/creatinine ratio &gt;0.16 mg/mL, and serum vitamin D level &gt;80 ng/mL)</td>
<td>NR</td>
<td>High concentration of 25(OH)D (&gt;80 ng/mL): 0.7% (1/138) Hypercalcemia: 0 Hypercalcuria: 0</td>
<td>Fair</td>
<td>Partially funded by Merck Co. and the Empire Clinical Research Investigator Program</td>
</tr>
</tbody>
</table>
## Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tbody>
<tr>
<td>Arvold et al, 2009 Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial</td>
<td>Participants identified and study started in midwinter</td>
<td>Followup levels increased in intervention group Certificate of analysis that pills were within 10% of stated dose Number NR of diet/supplement use during period of observation</td>
<td>Depressed mood (FIQ scale from 0 to 100); ranking of depressed mood and interference with work or housework on scale from 0 to 10</td>
<td>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: 3.1 (2.5) vs. 2.7 (2.5) After treatment: 2.7 (2.7) vs. 3.0 (2.4); p=0.08</td>
<td>No AE reported by any participants</td>
<td>Fair</td>
<td>St. Luke's Foundation</td>
</tr>
<tr>
<td>Berlin et al, 1986 Studies on the relationship between vitamin D3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D3</td>
<td>February to April At start of study, no subjects were exposed to extreme sunlight</td>
<td>Assessed followup levels No assessment of pill content</td>
<td>Unclear</td>
<td>NR</td>
<td>No AEs, objective or subjective, were reported</td>
<td>Poor</td>
<td>Grants from the Swedish Medical Research Council (project 03X-3141), Loo and Hans Ostermans Foundation, Stockholm, and ACO Lakemedal AB, Solna, Sweden</td>
</tr>
</tbody>
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### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tbody>
<tr>
<td>Bischoff et al, 2003</td>
<td>Winter (November and March)</td>
<td>Follow-up levels increased in intervention group. No verification of pill content. At baseline, overall diet the same for all participants. Diet/supplement use during period of observation NR.</td>
<td>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 of the patient and to the research physician. Hypercalcemia: measured serum calcium, did not define hypercalcemia or frequency.</td>
<td>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 2–5 falls (n): 3 vs. 7; RR, 0.4 (95% CI, 0.1 to 1.5). Persons with 6–7 falls (n): 1 vs. 2; RR, 0.5 (95% CI, 0.05 to 5.2). Persons with &gt;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).</td>
<td>Constipation: 2 vs. 0; RR, 4.8 (95% CI, 0.2 to 98.8). Hypercalcemia: 0. Discontinuation of medication independent of AEs: 0 vs. 1; RR, 0.3 (95% CI, 0.01 to 7.8).</td>
<td>Fair</td>
<td>Stratham AG; International Foundation for the Promotion of Nutrition Research and Nutrition Education; Swiss Orthopedic Society; Swiss Foundation for Nutrition Research.</td>
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<tbody>
<tr>
<td>Bischoff et al, 2003 (cont’d)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Mean number of excessive falls among fallers was lower in the vitamin D group (p=0.045), suggesting decrease in recurrent falls</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>Gallagher et al, 2012</td>
<td>Screened in late winter and early spring 1st phase: April to May 2007 2nd phase: January to May 2008</td>
<td>Assessed followup levels Verified pill content Mean baseline vitamin D intake: 114 IU/day Participants instructed not to take nonstudy vitamin D; multivitamins without vitamin D were provided to those who wanted it</td>
<td>AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit, validated by chart review Hypercalcemia: measured serum calcium, defined as either &gt;10 or &gt;10.8 mg/dL, collected at baseline and after 3, 6, 9, and 12 months of treatment</td>
<td>White Mortality: 0/142 vs. 0/21 Withdrawals 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)†</td>
<td>Good</td>
<td>Grant from the National Institute on Aging</td>
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<tr>
<td>Harris et al, 1999</td>
<td>Late winter (February); excluded those in outdoor jobs or those who traveled to southern locations in the previous month</td>
<td>Assessed followup levels No assessment of pill content</td>
<td>Unclear</td>
<td>NR</td>
<td>No AEs of supplementation reported</td>
<td>Poor</td>
<td>U.S. Department of Agriculture</td>
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</table>

**Notes:**
- UV Exposure: See above
- Intervention Fidelity: See above
- Determination of Outcomes: See above
- Clinical Health Outcomes: Vitamin D vs. Control: See above
- Adverse Events/Harms: Vitamin D vs. Control: See above
- Quality Rating: See above
- Sponsor: See above

[†] Indicates that the results are statistically significant (p < 0.05).
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<tr>
<td>Honkanen et al, 1990‡‡</td>
<td>November to December, Kuopos (63° north with short winter [5 hour] and long summer [11 hour] days) Institutionalized had sun exposure to some extent in summer</td>
<td>Assessed followup levels No assessment of pill content</td>
<td>Hypercalcemia: measure serum calcium at baseline and after 11 weeks of treatment</td>
<td>NR</td>
<td>9 independently living subjects reported mild GI symptoms with treatment No kidney stones reported No hypercalcemia</td>
<td>Fair</td>
<td>Grant from Academy of Finland, the Remeda Pharmaceutical Company, and the Sandoz Pharmaceutical Company</td>
</tr>
<tr>
<td>Karkkainen et al, 2010‡‡</td>
<td>Baseline vitamin D measures: February to May Followup vitamin D measures: January to May</td>
<td>Followup levels increased in intervention group Pills distributed by pharmacist but no verification of pill content Groups asked to continue with their previous diet during study</td>
<td>Number of falls and number of falls requiring medical attention recorded every 4 months via telephone interviews for subsample with vitamin D levels Mortality: NR</td>
<td>Number of falls: 430 vs. 524 Number of women with falls: 62% (179/287) vs. 67% (205/306); RR, 0.82 (95% CI, 0.73 to 0.92); no fall vs. fall, OR, 0.82 (95% CI, 0.58 to 1.14); 0 or 1 fall vs. ≥2 falls, OR, 0.70 (95% CI, 0.50 to 0.97) Number of women with falls requiring medical attention: 33% (95/287) vs. 35% (106/306); no fall vs. fall requiring medical attention, OR, 0.93 (95% CI, 0.66 to 1.31); 0 or 1 fall vs. ≥2 falls requiring medical attention, OR, 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)†</td>
<td>Discontinued medication 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</td>
<td>Fair</td>
<td>Finnish Cultural Foundation, Sigrid Juselius Foundation, Academy of Finland, Kuopio University-Hospital EVO-grant</td>
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<tr>
<td><strong>Kjaergaard et al, 2012</strong>&lt;sup&gt;171&lt;/sup&gt; 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</td>
<td>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</td>
<td>Assessed followup levels Pills distributed by pharmacist but no verification of pill content</td>
<td>Depressive symptoms: Beck Depression Inventory (BDI); Hospital Anxiety and Depression Scale (HADS); Montgomery-Åsberg Depression Rating Scale (MADRS) AEs: self-report via telephone interview at 3 months; serum levels measured at baseline and end of study</td>
<td>Median total BDI score at 6 months: 3 vs. 2; p=NS Median total HADS score at 6 months: 4 vs. 3; p=NS Median MADRS score at 6 months: 2 vs. 1; p=NS No significant difference between groups for change from baseline when stratifying by sex, age, BMI, serum 25(OH)D level at baseline, or smoking status</td>
<td>No significant difference between groups for AEs Hypercalcemia: 1 patient in placebo group had serum calcium of 10.5 mg/dL (resolved 4 weeks later); 0/120 vs. 1/110; RR, 0.31 (95% CI, 0.01 to 7.43)</td>
<td>Good</td>
<td>Northern Norway Regional Health Authority grant</td>
</tr>
<tr>
<td><strong>Krieg et al, 1999</strong>&lt;sup&gt;15&lt;/sup&gt; Effect of supplementation with vitamin D&lt;sub&gt;3&lt;/sub&gt; and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study</td>
<td>NR</td>
<td>Assessed followup levels No assessment of pill content</td>
<td>Unclear</td>
<td>Mortality: 17% (21/124) vs. 21% (26/124); RR, 0.81 (95% CI, 0.48 to 1.36)&lt;sup&gt;†&lt;/sup&gt; (no deaths were deemed to be related to treatment) Withdrawals 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)&lt;sup&gt;†&lt;/sup&gt; Withdrawals due to upper GI AEs: 4.8% (6/124) vs. 0; RR, 13.00 (95% CI, 0.74 to 228.32) Withdrawals due to hypercalcemia: 0.8% (1/124) vs. 0; RR, 3.00 (95% CI, 0.12 to 72.94)&lt;sup&gt;†&lt;/sup&gt; (due to hyperparathyroidism)</td>
<td></td>
<td>Fair</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Lehmann et al, 2013</strong>&lt;sup&gt;115&lt;/sup&gt; Bioavailability of vitamin D&lt;sub&gt;2&lt;/sub&gt; and D&lt;sub&gt;3&lt;/sub&gt; in healthy volunteers, a randomized placebo-controlled trial</td>
<td>Jan to March (no measurable UV radiation). Excluded if vacationed somewhere with abundant UVB irradiation during course of study</td>
<td>Assessed followup levels Verified pill content</td>
<td>AEs: prespecified; participants interviewed about AEs at each monthly visit</td>
<td>NR</td>
<td>No AEs reported; no hypercalcemia detected</td>
<td>Fair</td>
<td>German Ministry of Education and Research</td>
</tr>
</tbody>
</table>
## Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

<table>
<thead>
<tr>
<th>Author, Year, Title*</th>
<th>UV Exposure</th>
<th>Intervention Fidelity</th>
<th>Determination of Outcomes</th>
<th>Clinical Health Outcomes: Vitamin D vs. Control</th>
<th>Adverse Events/Harms: Vitamin D vs. Control</th>
<th>Quality Rating</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lips et al, 1996&lt;sup&gt;101&lt;/sup&gt; Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial</td>
<td>Enrolled from August to December</td>
<td>Followup levels increased in intervention group No verification of pill content Spontaneous use of vitamin D supplements and vitamin D was discouraged, but prescription practices of GPs were not altered Participants allowed to take calcium</td>
<td>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</td>
<td>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)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Reported AE: 0.6% (1/177) vs. 0; RR, 2.90 (95% CI, 0.12 to 70.68)&lt;sup&gt;†&lt;/sup&gt; Hypercalcemia: 0.6% (1/177) vs. 0; RR, 2.90 (95% CI, 0.12 to 70.68)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Fair</td>
<td>Praeventiefonds grant</td>
</tr>
<tr>
<td>Ooms et al, 1995&lt;sup&gt;120&lt;/sup&gt; Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial</td>
<td>NR</td>
<td>Assessed followup levels only in intervention group No assessment of pill content</td>
<td>Unclear</td>
<td>NR</td>
<td>Hypercalcemia: 0 vs. 0 No other AEs reported</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Martineau et al, 2007&lt;sup&gt;179&lt;/sup&gt; A single dose of vitamin D enhances immunity to mycobacteria</td>
<td>NR</td>
<td>Assessed followup levels only in intervention group No assessment of pill content</td>
<td>Unclear</td>
<td>NR</td>
<td>Hypercalcemia: 0 vs. 0 No other AEs reported</td>
<td>Fair</td>
<td>Welcome Trust, Department of Environmental Health, London Borough of Newham, Newham University Hospital NHS Trust Research Fund, and Northwick Park Hospital Tropical Research Fund</td>
</tr>
</tbody>
</table>

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<sup>†</sup> Significant difference.
<table>
<thead>
<tr>
<th>Author, Year, Title*</th>
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<th>Intervention Fidelity</th>
<th>Determination of Outcomes</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pfeifer et al, 2009</td>
<td>May (vitamin D levels start to rise) to March (vitamin D levels at their lowest)</td>
<td>Followup levels increased 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)</td>
<td>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</td>
<td>≥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&lt;0.001 Total falls (per text): 76 vs. 171 Total falls (per Table 3): 106 vs. 169; p&lt;0.001 By number of falls‡‡‡ 1: 20% (24/120) vs. 30% (37/122); RR, 0.66 (95% CI, 0.42 to 1.03) 2: 11% (13/120) vs. 15% (18/122); RR, 0.73 (95% CI, 0.38 to 1.43) 3: 2.5% (3/120) vs. 5.7% (7/122); RR, 0.44 (95% CI, 0.12 to 1.65) &gt;3: 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) Patients 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. 19; p=NS</td>
<td>NR</td>
<td>Fair</td>
<td>Meda Pharma Inc.</td>
</tr>
</tbody>
</table>
### Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

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<tr>
<th>Author, Year, Title*</th>
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<th>Quality Rating</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talwar et al, 2007&lt;sup&gt;177&lt;/sup&gt; Dose response to vitamin D supplementation among postmenopausal African American women</td>
<td>NR</td>
<td>Assessed followup levels Verified pill content</td>
<td>Hypercalcemia: measured serum calcium, collected at baseline and after 3, 5, 12, 18, 24, 27, 30, and 36 months</td>
<td>NR</td>
<td>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)&lt;sup&gt;†&lt;/sup&gt; Transient hypercalciuria: 3 vs. 1 (2/3 in vitamin D group resolved spontaneously); RR, 3.00 (95% CI, 0.32 to 28.37)&lt;sup&gt;†&lt;/sup&gt; Persistent hypercalciuria (resolved with stopping calcium): 1 (group NR) Kidney stones: 0 vs. 0</td>
<td>Fair</td>
<td>National Institute of Aging</td>
</tr>
<tr>
<td>Aloia et al, 2005&lt;sup&gt;175&lt;/sup&gt; A randomized controlled trial of vitamin D&lt;sub&gt;3&lt;/sub&gt; supplementation in African American women</td>
<td>NR</td>
<td>Assessed followup levels</td>
<td>Hypercalcemia: measured serum calcium, collected at baseline and after 3, 5, 12, 18, 24, 27, 30, and 36 months</td>
<td>NR</td>
<td>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)&lt;sup&gt;†&lt;/sup&gt; Transient hypercalciuria: 3 vs. 1 (2/3 in vitamin D group resolved spontaneously); RR, 3.00 (95% CI, 0.32 to 28.37)&lt;sup&gt;†&lt;/sup&gt; Persistent hypercalciuria (resolved with stopping calcium): 1 (group NR) Kidney stones: 0 vs. 0</td>
<td>Fair</td>
<td>National Institute of Aging</td>
</tr>
<tr>
<td>Wood et al, 2012&lt;sup&gt;178&lt;/sup&gt; Vitamin D&lt;sub&gt;3&lt;/sub&gt; supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT</td>
<td>Baseline and followup during January to March Baseline UVB exposure (weekly standard erythemal dose): 0.5</td>
<td>Assessed followup levels Capsules were reported to be analyzed but results NR Participants told not to take any dietary supplements containing vitamin D for duration of study</td>
<td>Hypercalcemia: measured serum calcium at baseline and after 4 weeks of treatment</td>
<td>Vitamin D 400 vs. 1000 IU vs. control 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)</td>
<td>Vitamin D 400 vs. 1000 IU vs. control Total AEs: 17 vs. 15 vs. 20; RR for 400 IU vs. control, 0.85 (95% CI, 0.47 to 1.53)&lt;sup&gt;‡&lt;/sup&gt;; RR for 1000 IU vs. control, 0.76 (95% CI, 0.41 to 1.39)&lt;sup&gt;‡&lt;/sup&gt; GI symptoms: 3 vs. 1 vs. 0; RR for 400 IU vs. control, 3.0 (95% CI, 0.1 to 73.5)&lt;sup&gt;‡&lt;/sup&gt; Hypercalcemia: 0 vs.1 vs. 0; RR for 1000 IU vs. control, 3.0 (95% CI, 0.12 to 73.50)&lt;sup&gt;‡&lt;/sup&gt; Joint pain: 1 vs.1 vs. 0; RR for 400 IU vs. control, 3.00 (95% CI, 0.12 to 72.79)&lt;sup&gt;‡&lt;/sup&gt;; RR for 1000 IU vs. control, 3.03 (95% CI, 0.12 to 73.50)&lt;sup&gt;‡&lt;/sup&gt; 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)&lt;sup&gt;‡&lt;/sup&gt;; RR for 1000 IU vs. control, 2.02 (95% CI, 0.63 to 6.50)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Fair</td>
<td>U.K. Department of Health</td>
</tr>
</tbody>
</table>

* All studies are RCTs 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%) and estimated from limited data.
Appendix C1. Evidence Table of Included Studies of Benefits and Harms of Treatment of Vitamin D Deficiency

† Unclear if those who dropped out were still included for AE count.
** Cohort study.
†† Study provided proportion attrition per group, n values calculated, do not sum to 33 for overall attrition reported by study.
‡‡ Open RCT.
§§ 30% of participants refused to have blood drawn.
¶¶ Received some care, but not as much as nursing home.
□□ Characteristics only reported for those who finished study (n=131).
*** Includes 9 persons screened but not randomized.
††† 122 persons reported for falls/fractures outcome analyses in the vitamin D + calcium group, which is 1 more than was enrolled for that group.
‡‡‡ Total number of participants with a fall does not sum to the number of participants who fell by number of falls.

Abbreviations: 25(OH)D = 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; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DEQAS = Vitamin D External Quality Assurance Scheme; DBP = diastolic blood pressure; EVO = Engineering Virtual Organization; FIQ = Fibromyalgia Impact Questionnaire; GI = gastrointestinal; GP = general practitioner; HPLC = high performance liquid chromatography; HR = hazard ratio; HRT = hormone replacement therapy; HTN = hypertension; ITT = intention-to-treat; MI = myocardial infarction; n = number; NHS = National Health Service; NR = not reported; NS = not significant; OR = odds ratio; OSTPRE = Osteoporosis Risk Factor and Prevention Study; OSTPRE-FPS = Osteoporosis Risk Factor and Prevention Fracture Prevention Study; PTH = parathyroid hormone; RCT = randomized, controlled trial; RR = risk ratio; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SPPB = Short Physical Performance Battery; TB = tuberculosis; UV = ultraviolet; UVB = ultraviolet B.
## Appendix C2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial

<table>
<thead>
<tr>
<th>Author, Year, Title</th>
<th>Population Characteristics</th>
<th>Eligibility Criteria</th>
<th>Assay</th>
<th>Definition of Deficiency/Insufficiency</th>
<th>Baseline 25(OH)D Level (ng/mL)</th>
<th>25(OH)D Level Attained (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall WHI Trial Fair</strong></td>
<td>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/m²): 29 History of fracture at any age: 35% Number of women with falls in last 12 months: 67% with no falls, 20% with 1 fall, 9% with 2 falls, 4% with &gt;3 falls</td>
<td>Inclusion: Postmenopausal women in the WHI hormone therapy and dietary modification trials ages 50 to 70 years with predicted survival of &gt;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.</td>
<td>Chemiluminescent immunoassay</td>
<td>NR</td>
<td>NR</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Jackson et al, 2006</strong> Calcium plus vitamin D supplementation and the risk of fractures</td>
<td>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) vs. 3 (0.06) American Indian: 1 (0.19) vs. 1 (0.20) Asian or Pacific Islander: 4 (0.16) vs. 1 (0.04) Unknown or not identified: 0 (0) vs. 1 (0.07)</td>
<td>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.</td>
<td>As above</td>
<td>NR</td>
<td>90% &lt;31; outcomes presented in quartiles of baseline 25(OH)D level as &gt;24, 18 to 24, 13 to 18, and &lt;13 ng/mL</td>
<td>As above</td>
</tr>
<tr>
<td>Author, Year, Title</td>
<td>Population Characteristics</td>
<td>Eligibility Criteria</td>
<td>Assay</td>
<td>Definition of Deficiency/Insufficiency</td>
<td>Baseline 25(OH)D Level (ng/mL)</td>
<td>25(OH)D Level Attained (ng/mL)</td>
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</tr>
<tr>
<td>Wactawski-Wende et al, 2006&lt;sup&gt;168&lt;/sup&gt; Calcium plus vitamin D supplementation and the risk of colorectal cancer</td>
<td>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) 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.</td>
<td>As above</td>
<td>NR</td>
<td>NR; outcomes presented in quartiles of baseline 25(OH)D level as ≥23, 17 to 23, 12 to 17, and &lt;12 ng/mL</td>
<td>As above</td>
<td></td>
</tr>
<tr>
<td>Chlebowski et al, 2008&lt;sup&gt;167&lt;/sup&gt; Calcium plus vitamin D supplementation and the risk of breast cancer</td>
<td>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.</td>
<td>As above</td>
<td>NR</td>
<td>NR; outcomes presented in quintiles of baseline 25(OH)D level as ≥27, 22 to 27, 18 to 22, 13 to 18, and &lt;13 ng/mL</td>
<td>As above</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix C.2. Evidence Table of Nested Case-Control Studies From the Women's Health Initiative Trial

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<th>Baseline 25(OH)D Level (ng/mL)</th>
<th>25(OH)D Level Attained (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Boer et al, 2008</td>
<td>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/ethnic group; HR=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)</td>
<td>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.</td>
<td>As above</td>
<td>NR</td>
<td>&lt;32 for 89% of participants; &lt;20 for 61% of participants; outcomes presented in quartiles of baseline 25(OH)D level as &gt;24, 17 to 24, 13 to 17, and &lt;13 ng/mL</td>
<td></td>
</tr>
<tr>
<td>LaCroix et al, 2009</td>
<td>Number of cases (annualized %) of death in vitamin D vs. control by baseline characteristics Race/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) Asian or Pacific Islander: 18 (0.73) vs. 12 (0.51) Unknown: 12 (0.83) vs. 12 (0.81)</td>
<td>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).</td>
<td>As above</td>
<td>NR</td>
<td>NR; outcomes presented in tertiles of baseline 25(OH)D level as ≥21, 14 to 21, and &lt;14 ng/mL</td>
<td></td>
</tr>
</tbody>
</table>

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Screening for Vitamin D Deficiency 208 Pacific Northwest EPC
### Appendix C2. Evidence Table of Nested Case-Control Studies From the Women’s Health Initiative Trial

<table>
<thead>
<tr>
<th>Author, Year, Title</th>
<th>Number Approached, Screened, Eligible, Enrolled, Analyzed</th>
<th>Country and Setting</th>
<th>UV Exposure</th>
<th>Duration of Followup</th>
<th>Attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall WHI Trial Fair</td>
<td>Approached: 68,132, Screened: 68,132 Eligible: 36,282</td>
<td>Multicenter U.S. population-based Institutionalized: NR</td>
<td>Solar irradiance of region for entire trial (Langley); Mean, 382±60 (controls matched to cases on this parameter)</td>
<td>Mean, 7.0 years (SD, 1.4)</td>
<td>Overall: 7.0% (2531/36,282) Vitamin D vs. control: 6.8% (1240/18,176) vs. 7.1% (1291/18,106)</td>
</tr>
<tr>
<td>Jackson et al, 2006 Calcium plus vitamin D supplementation and the risk of fractures</td>
<td>Enrolled: 1067 cases, 1067 controls, 357 pairs for hip fracture, 1491 pairs for total fracture in case-control study † Analyzed: 357 (95%) pairs for hip fracture, 1491 (80%) pairs for total fracture in case-control study</td>
<td>As above</td>
<td>Number of cases (annualized %) of hip fracture in vitamin D3 vs. control by solar irradiance (Langley); HR=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)</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Wactawski-Wende et al, 2006 Calcium plus vitamin D supplementation and the risk of colorectal cancer</td>
<td>Eligible: 322 Enrolled: 634 (317 pairs for case-control study) Analyzed: 612 (306 [96.5%] pairs for case-control study)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Chlebowski et al, 2008 Calcium plus vitamin D supplementation and the risk of breast cancer</td>
<td>Eligible: 1074 Enrolled: 1067 cases, 1067 controls Analyzed: 895 cases, 895 controls</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>de Boer et al, 2008 Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative</td>
<td>Eligible: 1699 controls from previous case-control study (Jackson 2008) ‡ Analyzed: 3097</td>
<td>As above</td>
<td>Vitamin D vs. control Number of events/at risk (annualized %) by solar irradiance of region (Langley); HR=NS 400 to 500: 459/6455 (1.02) vs. 435/6431 (0.97) 350 to 380: 414/5475 (1.08) vs. 423/5467 (1.10) 300 to 325: 281/5069 (0.77) vs. 279/5054 (0.77)</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>LaCroix et al, 2009 Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial</td>
<td>Eligible: 3594 (2982 from fracture case-control study, 612 from colorectal case-control study) Enrolled: 2285 (323 cases, 1962 controls) Analyzed: 2285 (323 cases, 1962 controls)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

Screening for Vitamin D Deficiency 209 Pacific Northwest EPC
<table>
<thead>
<tr>
<th>Author, Year, Title</th>
<th>Interventions</th>
<th>Calcium and Other Nutrients</th>
<th>Determination of Outcomes</th>
<th>Clinical Health Outcomes: Vitamin D vs. Control</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall WHI Trial Fair</td>
<td><strong>Vitamin D:</strong> 200 IU of vitamin D₃ BID (total, 400 IU/day) + 500 mg of calcium carbonate BID (total, 1000 mg/day)</td>
<td>Personal use of ≤1000 mg/day calcium and ≤600 IU/day vitamin D allowed. Vitamin D allowance increased to ≤1000 IU/day during trial. At baseline, 39% of participants had intake ≥1200 mg and 43% were using ≥400 IU/day vitamin D. At year 6, nonprotocol vitamin D use reported by 52% of participants and nonprotocol calcium intake increased by about 100 mg/day in both groups.</td>
<td>See individual studies below</td>
<td>See individual studies below</td>
<td>National Institutes of Health</td>
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<tr>
<td>Jackson et al, 2006¹⁶⁴ Calcium plus vitamin D supplementation and the risk of fractures</td>
<td>As above</td>
<td>As above</td>
<td>Fractures: Verified by review of radiology, magnetic resonance imaging, or operative reports by blinded physician adjudicators at each clinical center. Final adjudication of hip fractures performed centrally.</td>
<td>Incidence and risk for 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 to 1.15) 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)  &lt;13: 47/44 vs. 49/48; OR, 1.06 (95% CI, 0.60 to 1.86) p=0.64 for interaction Incidence and risk for 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)  &lt;13: 196/167 vs. 182/204; OR, 1.32 (95% CI, 0.99 to 1.76) p=0.15 for interaction</td>
<td>National Heart, Lung, and Blood Institute; General Clinical Research Center Program of the National Center for Research Resources; several investigators supported by industry</td>
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</table>
## Appendix C2. Evidence Table of Nested Case-Control Studies From the Women’s Health Initiative Trial

<table>
<thead>
<tr>
<th>Author, Year, Title</th>
<th>Interventions</th>
<th>Calcium and Other Nutrients</th>
<th>Determination of Outcomes</th>
<th>Clinical Health Outcomes: Vitamin D vs. Control</th>
<th>Sponsor</th>
</tr>
</thead>
</table>
| Wactawski-Wende et al, 2006<sup>68</sup> **Calcium plus vitamin D supplementation and the risk of colorectal cancer** | As above | As above | Invasive colorectal cancer: reported cases 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 participant's personal physician. | Incidence and risk for 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 Clinical Research Center Program of the National Center for Research Resources; several investigators supported by industry |
| Chlebowski et al, 2008<sup>67</sup> **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 for 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 (95% CI, 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 (95% CI, 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, and 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

<table>
<thead>
<tr>
<th>Author, Year, Title</th>
<th>Interventions</th>
<th>Calcium and Other Nutrients</th>
<th>Determination of Outcomes</th>
<th>Clinical Health Outcomes: Vitamin D vs. Control</th>
<th>Sponsor</th>
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<tr>
<td>de Boer et al, 2008*</td>
<td>As above</td>
<td>As above</td>
<td>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.</td>
<td>Incidence and risk for diabetes (number of 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) &lt;13: 30/381 vs. 33/391; OR, 1.07 (95% CI, 0.62 to 1.82) p=0.59 for interaction</td>
<td>National Heart, Lung, and Blood Institute; National Institutes of Health Roadmap for Medical Research</td>
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<tr>
<td>LaCroix et al, 2009†</td>
<td>As above</td>
<td>As above</td>
<td>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.</td>
<td>Incidence and risk for death (number of 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) &lt;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, and treatment assignment</td>
<td>National Heart, Lung, and Blood Institute</td>
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* Population characteristics are of all WHI trial participants (n=36,282), 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 the sum of numbers noted above for eligible fractures; 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 the number analyzed was computed.

**Abbreviations:** aOR = adjusted odds ratio; BMI = body mass index; BID = twice a day; CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not significant; OR = odds ratio; SD = standard deviation; UV = ultraviolet; WHI = Women’s Health Initiative.
## Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

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<tr>
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<td>Talwar et al, 2007</td>
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### Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

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<td>Wamberg et al, 2013</td>
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<th>Author, Year</th>
<th>Acceptable Attrition and Difference Between Groups?</th>
<th>People Analyzed in the Groups in Which They Were Randomized?</th>
<th>Post-Randomization Exclusions?</th>
<th>Outcomes Prespecified?</th>
<th>Fidelity to Intervention?</th>
<th>Quality Rating</th>
<th>External Validity*</th>
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<td>No (differential)</td>
<td>Yes</td>
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<td>Fair</td>
<td>1. Outpatient clinic 2. None 3. 16% 4. Fair, one clinic</td>
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<td>4. Unclear</td>
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<tr>
<td>Honkanen et al, 1996</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes: Levels</td>
<td>Fair</td>
<td>1. City hospital</td>
</tr>
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<td>3. 62%</td>
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<td>4. Fair, only women</td>
</tr>
<tr>
<td>Janssen et al, 2010</td>
<td>No</td>
<td>Yes</td>
<td>OK</td>
<td>Yes</td>
<td>Yes: Levels Compliance &gt;90%</td>
<td>Fair</td>
<td>1. Outpatient clinics</td>
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<td>3. NR</td>
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<td>4. Fair, elderly (age &gt;65 years), institutionalized</td>
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<tr>
<td>Kärkkäinen et al, 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>OK</td>
<td>Yes</td>
<td>Yes: Levels Compliance 79%</td>
<td>Fair</td>
<td>1. Population-based</td>
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<td>2. None</td>
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<td>3. Unclear; reports numbers for subsample, not full screened group</td>
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<td></td>
<td></td>
<td>4. Fair, only women</td>
</tr>
<tr>
<td>Kjaergaard et al, 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (6 subjects)</td>
<td>Yes</td>
<td>Good</td>
<td></td>
<td>1. Community</td>
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<td>3. 18%</td>
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<td></td>
<td>4. Good</td>
</tr>
</tbody>
</table>
### Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Acceptable Attrition and Difference Between Groups?</th>
<th>People Analyzed in the Groups in Which They Were Randomized?</th>
<th>Post-Randomization Exclusions?</th>
<th>Outcomes Prespecified?</th>
<th>Fidelity to Intervention?</th>
<th>Quality Rating</th>
<th>External Validity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krieg et al, 1999&lt;sup&gt;154&lt;/sup&gt;</td>
<td>No (high)</td>
<td>Yes</td>
<td>OK</td>
<td>No</td>
<td>Yes: Levels</td>
<td>Fair</td>
<td>1. Nursing homes 2. NR 3. NR 4. Fair, elderly (age ≥62 years), institutionalized</td>
</tr>
<tr>
<td>Knutsen et al, 2014&lt;sup&gt;132&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>OK</td>
<td>Unclear; no specification whether AEs were prespecified outcome; no clear description of how outcome was collected</td>
<td>Yes: Pill count Compliance 80% consumed ≥80%</td>
<td>Fair</td>
<td>1. Immigrants’ activity centers 2. None 3. 83% 4. Fair, immigrants in Northern Europe</td>
</tr>
<tr>
<td>Lips et al, 1996&lt;sup&gt;161&lt;/sup&gt; Ooms et al, 1995&lt;sup&gt;120&lt;/sup&gt;</td>
<td>No (high)</td>
<td>Yes</td>
<td>Some post-randomization exclusions</td>
<td>Yes</td>
<td>Yes: Levels Compliance 85%</td>
<td>Fair</td>
<td>1. Community 2. None 3. NR 4. Fair, elderly (age ≥70 years), institutionalized</td>
</tr>
<tr>
<td>Lips et al, 2010&lt;sup&gt;156&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes: Levels Compliance 100%</td>
<td>Fair</td>
<td>1. Medical centers and nursing homes 2. None 3. 38% 4. Fair, elderly (age ≥70 years)</td>
</tr>
<tr>
<td>Martineau et al, 2007&lt;sup&gt;178&lt;/sup&gt;</td>
<td>No (high)</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear (for AEs)</td>
<td>Yes: Levels</td>
<td>Fair</td>
<td>1. TB contact clinics 2. Recruited from TB clinics 3. 53% 4. Poor, TB clinics</td>
</tr>
<tr>
<td>Pfeifer et al, 2000&lt;sup&gt;162&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>OK</td>
<td>Yes</td>
<td>Yes: Levels</td>
<td>Fair</td>
<td>1. Population-based 2. None 3. 90% 4. Fair, elderly (age ≥70 years)</td>
</tr>
<tr>
<td>Pfeifer et al, 2009&lt;sup&gt;163&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>OK</td>
<td>Yes</td>
<td>Yes: Levels</td>
<td>Fair</td>
<td>1. Population-based 2. None 3. NR 4. Fair, elderly (age ≥70 years)</td>
</tr>
<tr>
<td>Talwar et al, 2007&lt;sup&gt;177&lt;/sup&gt; Aloia et al, 2005&lt;sup&gt;175&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>OK</td>
<td>Unclear (for AEs)</td>
<td>Yes: Levels Compliance ~87%</td>
<td>Fair</td>
<td>1. Population-based 2. None 3. 54% 4. Fair, only women</td>
</tr>
</tbody>
</table>
## Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Acceptable Attrition and Difference Between Groups?</th>
<th>People Analyzed in the Groups in Which They Were Randomized?</th>
<th>Post-Randomization Exclusions?</th>
<th>Outcomes Prespecified?</th>
<th>Fidelity to Intervention?</th>
<th>Quality Rating</th>
<th>External Validity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Boer et al, 2008</td>
<td>Yes</td>
<td>Yes</td>
<td>OK</td>
<td>Yes</td>
<td>Yes: Levels Compliance &gt;90%</td>
<td>Fair</td>
<td>1. Population-based 2. None 3. Case-control studies of subsamples of WHI trial 4. Fair, only women</td>
</tr>
</tbody>
</table>

* 1 = Setting; 2 = Unusual techniques used to recruit; 3 = Proportion of screened actually enrolled; 4 = Applicability to a screened population.  
** Protocol for recruitment into trial arms was changed post hoc during the study.  

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