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

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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$(OH)_2$D]. 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$(OH)_2$D, 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$(OH)_2$D 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.[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).[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.[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.[21] DEQAS,[12] for example, has acted as an early warning system to alert commercial kit manufacturers when they need to modify their products and procedures or when they need to withdraw kits.[12]

The level of 25(OH)D used to define vitamin D deficiency has varied over the previous two decades. 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,[12,22-25] maximum calcium absorption,[26,27] and reduced fracture risk.[28] In fact, the actual requirements for bone health likely reflect a distribution of values rather than a specific 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[29] (**Table 1**).

In 2011, the Institute of Medicine (IOM) concluded that 20 ng/mL was the level necessary for good bone health for practically all individuals.[30] Other groups suggest that 25(OH)D levels should be greater than 30 ng/mL (75 nmol/L), particularly in older adults. These groups include the Endocrine Society, National Osteoporosis Foundation, and International Osteoporosis Foundation.[13,31-34] The Endocrine Society suggests that, because of variability in laboratory measurements of 25(OH)D, targeting a higher 25(OH)D level than the goal level (such as 40 ng/mL [100 nmol/L]) better ensures that all persons meet goal levels.[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).[30] Experts agree that optimal serum 25(OH)D concentrations for extraskeletal health have not been established.[13,30] For this report, the term "vitamin D deficient" refers to study participants who have been diagnosed with vitamin D deficiency, regardless of the study's cutoff (as long as it was ≤30 ng/mL).

Prevalence and Burden of Disease

The prevalence of vitamin D deficiency varies based on how deficiency is defined (<20 vs. ≤30 ng/mL). According to NHANES data, 8 percent of the population were at risk for very low 25(OH)D levels (<12 ng/mL) from 2001 to 2006, and about 25 percent were at risk for deficiency, as defined by serum 25(OH)D levels of 12 to 20 ng/mL.[5] The IOM has recently developed a statistical procedure to derive group prevalence estimates of nutritional inadequacy. According to this statistical model, 19 percent of the population is at risk for vitamin D deficiency as defined by the IOM.[35] Data on the prevalence of 25(OH)D levels of less than 30 ng/mL come from a 2009 study using 2001 to 2004 NHANES 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.[36]

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.[37-39] 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.[9] 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.[37-41] While some studies reported that females had greater risk for deficiency,[37, 40] not all studies confirmed this finding.[39]

In NHANES, mean 25(OH)D levels were lower in 2000 to 2004 than in 1988 to 1994.[42] 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.[42]

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).[6]

Vitamin D has a variety of actions on calcium, phosphate, and bone metabolism. Low 25(OH)D concentrations are associated with impaired intestinal calcium and phosphate absorption, negative calcium balance, phosphaturia, and a compensatory rise in parathyroid hormone, which results in excessive bone resorption. Severe vitamin D deficiency causes a mineralization defect in the skeleton.[6] In children, vitamin D deficiency results in skeletal deformities classically called "rickets." In adults, severe vitamin D deficiency can result in osteomalacia, which is associated with decreased bone mineral density, diffuse bone and joint pain, muscle weakness, and difficulty walking.[43]

Association Between 25(OH)D Levels and Health Outcomes

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

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

The 2009 AHRQ review concluded 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.[44,55] This association, however, has not been observed in community-dwelling elderly persons.[56,57] 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.[45] Evidence on the association between 25(OH)D levels and decline in physical functioning is inconsistent.[58-63]

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

While low 25(OH)D levels have not been associated with increased risk for breast, prostate, or pancreatic cancer,[45,58,70-74] studies suggest an association between 25(OH)D levels and risk for colorectal cancer,[45] with each 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.[58,71,72,75-78]

Lower 25(OH)D levels (<12 to 20 ng/mL) have been associated with an increased risk for diabetes[45,58,79-87] and depressed mood.[45,58,88,89] 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.[45,58] Risk may increase at levels below 10 to 20 ng/mL versus levels greater than 30 ng/mL.[90,91] The association may vary by sex, with the effect being seen more in women.[91,92]

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

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

Risk Factors

Low dietary vitamin D intake and/or lack of vitamin D supplements are associated with a twofold to fivefold increased risk for vitamin D deficiency (<20 ng/mL).[37-39] 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.[37,38,40,41,105] While sunscreen reduces the skin's ability to produce vitamin D in response to UV light in controlled research settings,[106] this association has not been found in population-based studies.[105,107] This finding in population-based studies is likely due to incomplete application[108] and/or because subjects who use sunscreen are more likely to be exposed to the sun for extended periods.[78]

Obesity is associated with an almost twofold increased risk for vitamin D deficiency.[37-39,109] This finding is possibly due to sequestration of vitamin D in fat cells[30] or lifestyle differences (e.g.,

lower physical activity levels or lower dietary vitamin D intake). Low levels of physical activity,[37,38,41] education attainment,[36] and health status[39,105] 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.[41,110] Genetic factors, including genetic variants of vitamin D–metabolizing genes, may influence serum 25(OH)D concentrations.[111]

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

Rationale for Screening and Screening Strategies

Vitamin D deficiency might affect one fifth to three fourths of the population, depending on which cutoff is used.[5,35,36,39] Despite this prevalence, many of those who have low 25(OH)D levels are unaware of their status. Screening could identify persons with deficiency prior to the development of adverse health outcomes associated with this condition, assuming thresholds for deficiency can be established. If interventions to increase 25(OH)D levels successfully decrease disease risk, screening 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.[30] Other expert bodies, however, suggest that the daily intake of vitamin D may need to be higher (e.g., 1,000 to 2,000 IU per day) to avoid vitamin D deficiency, especially in high-risk individuals.[13,32-34,112,113]

Vitamin D deficiency can be treated by increased dietary intake, vitamin treatment, and increased UV 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.[44]

Primary care physicians often treat vitamin D deficiency with oral vitamin D treatment. There are two commonly available forms of vitamin D treatment: vitamin D_3 (cholecalciferol) and

vitamin D_2 (ergocalciferol). A 2012 meta-analysis of seven randomized trials concluded that vitamin D^3 treatment increased serum 25(OH)D more efficiently than vitamin D_2 treatment.[114] The trials in the meta-analysis, however, used varying doses, treatment time periods, and assays to measure $25(OH)D_2$ and $25(OH)D_3$. Interpreting these findings is challenging because between-study statistical heterogeneity was present and the observed difference was of uncertain clinical significance. A 2013 bioavailability study that was powered to examine the effects of vitamin D_2 compared with D_3 treatment concluded that vitamin D_3 treatment was more effective in raising total 25(OH)D levels.[115] The Endocrine Society suggests using either vitamin D_2 or D_3 treatment[13] based on several studies showing that physiological doses of vitamin D_2 are equally effective as vitamin D_3 treatment at increasing and maintaining serum 25(OH)D levels and maintaining $1,25(OH)_2D$ levels.[116,117] The IOM does not differentiate between use of vitamin D_2 or D_3 supplements in its recommendations.[30]

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

The amount of vitamin D required to effectively treat vitamin D deficiency also likely depends 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.[13] The efficacy of this practice, however, has not been rigorously compared with daily, weekly, or monthly dosing. While optimal monitoring strategies during vitamin D treatment are also not well studied, most experts recommend measuring 25(OH)D levels after 2 to 4 months of high-dose therapy.

Vitamin D supplements are often given with oral calcium, which may affect health outcomes and harms. Meta-analyses have suggested possible differences 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.[118,119]

Effect of Vitamin D Treatment on Intermediate Outcomes

In older white women with severe vitamin D deficiency (<12 ng/mL), vitamin D treatment (400 to 800 IU per day, with or without calcium) for 12 to 24 months was associated with less decline in hip and/or spine bone mineral density than placebo in some studies,[120,121] but not all.[122] 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.[123-126]

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,[127,128] leg strength,[127] or balance after 11 to 24 weeks[129] versus placebo. Young persons (mean age, 18 to 33 years) who were vitamin D deficient (<30 ng/mL) and given large (25,000 to >60,000 IU per week) doses of vitamin D had improvement on several strength measures compared with those given placebo,[130, 131] but this improvement in strength was not seen in a third trial that used smaller doses (400 to 1,000 IU) of vitamin D.[132]

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).[133-137]

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,[135, 138] 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.[138]

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.[30] Mild hypercalcemia can result in constipation, fatigue, and depression. More severe hypercalcemia can cause polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, arrhythmias, and mental status changes. Hypercalciuria can lead to increased risk for kidney stones. The toxicity level of vitamin D (most commonly defined as >200 ng/mL [500 nmol/L]) is well above the level considered to be sufficient.[139,140] Acute toxicity has not been linked to vitamin D intake of less than 10,000 IU per day.[30] The IOM recommends a tolerable upper intake level of vitamin D supplementation for adults of 4,000 IU per day in order to avoid 25(OH)D levels greater than 50 ng/mL, which may be associated with potential risks (e.g., increased mortality, cardiovascular disease risk, certain cancers, and falls).[30] While the Endocrine Society recommends a maintenance regimen of 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.[13]

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."[12] 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).[1] 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 D_3 and 1,000 mg of calcium (I statement). The USPSTF recommended against daily supplementation with 400 IU or less of vitamin D_3 and 1,000 mg calcium for the primary prevention of fractures in this population (D recommendation).[3]

The USPSTF also recently issued a recommendation statement on multivitamin and single vitamin supplementation for the primary prevention of cardiovascular disease and cancer.[4] The recommendation was based on a review that included studies of vitamin D as part of multivitamins, as well as vitamin D 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.[146] 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,[120,122,152-160] five examined fractures,[122,161-164] six examined falls,[122,136,162,163,165,166] one examined cancer,[167,168] two examined type 2 diabetes,[136,169] two examined psychosocial functioning and disability,[170,171] and one examined physical functioning.[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.[120,122,152-160] Additionally, the benefits of vitamin D treatment were confined to trials of elderly institutionalized participants with high mortality rates.[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).[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).[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),[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).[136,162,163,165,166] We found limited data (≤2 studies) on the effect of vitamin D treatment on cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning.

Evidence

We identified 16 trials and one nested case-control study that evaluated the effects of vitamin D treatment (with or without calcium) on health outcomes in vitamin D–deficient populations (**Table 2** and **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[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).[120,136,152-154,156,161,163-171] Eleven studies examined the effect of vitamin D treatment on mortality,[120,122,152-160] five examined effects on fracture,[122,161-164] six examined effects on falls,[122,136,162,163,165,166] one examined effects on cancer,[167,168] two examined effects on type 2 diabetes,[136,169] two examined effects on psychosocial functioning and disability,[170,171] and one examined effects on physical functioning.[155] The mean age of the participants ranged from 37 to 85 years, and 40 to 100 percent were female. Mean BMIs ranged from 24 to 36 kg/m^2. The included studies were population-based or were conducted within outpatient clinics, academic institutions, and nursing or residential homes for the elderly (considered institutionalized) in the United States or Europe. UV light exposure was not well quantified in any study. Only six[136,146,152,156, 159,160,164,167-170] of 17 studies reported race. One study comprised 100 percent African Americans.[160] In the remaining studies reporting race, 83 to 100 percent of participants were white. Studies examined vitamin D_3 at dosages ranging from 400 to 4,800 IU per day to 8,400 to 50,000 IU per week. Five studies examined vitamin D_3 treatment coadministered with calcium (1,000 to 1,200 mg per day) and 12 examined vitamin D_3 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,[120,122,154,157,161] eight used immunoassay methods,[146,153,156,159,160,162,163,165,166] one used HPLC,[155] and four used LC-MS/MS.[136,158,170,171] Two trials used laboratories that were participating in an external accuracy-based testing system (DEQAS).[155,156]

Two trials were rated good quality[156,171] and 15 were rated fair quality[120,122,127,136,146,153-155,157-167, 170] (**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).[146,152,164,167-169] 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 **Appendixes 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.[167] 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.[164] 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 D_3 treatment on mortality in vitamin D–deficient populations

(N=4,126).[120,122,154,155,157,161] Five studies were conducted in populations with a mean age older than 70 years,[120,122,154,155,157,161] three trials specifically focused on older (age >80 years) women in nursing or elderly homes,[120,122,154] and one trial specifically focused on younger (age ≥45 years) women.[159] No study had death as a primary outcome.

No individual study reported a statistically significant reduction in mortality in participants randomized to vitamin D_3 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.[153,155-160] In four studies that reported at least 10 events, RR estimates ranged from 0.51 to 0.90.[120,122,152,154] When data were combined for all studies, vitamin D_3 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 D_3 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 D_3 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.[156] 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 D_3 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.[152] 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][122] and 0.51 [95% CI, 0.25 to 1.02][120]) examined the effects of 400 to 800 IU per day of vitamin D_3 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.[120,122] 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.[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; **Figure 3**).[152,153,155-158] 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 D_3 (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).[122,161-164] No individual study reported a statistically significant reduction in fracture risk in those randomized to vitamin D_3 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.[164] 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),[122,161,162,164] there was no significant reduction in hip fracture risk with vitamin D_3 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 D_3 with calcium over 24 months and had a population whose baseline 25(OH)D level was less than 20 ng/mL (RR, 0.62 [95% CI, 0.36 to 1.07]).[122]

Effects of Vitamin D Treatment on Fall Risk

Five fair-quality trials examined the effects of 2 to 36 months of 800 IU per day of vitamin D_3 treatment (with or without calcium) compared with placebo, no treatment, or calcium alone on the risk for experiencing at least one fall (N=1,677; **Table 3**).[122,162,163,165,166] Although trials did not specifically recruit participants for being at high risk for frailty or because of prior falls, the studies included persons who may have been at risk for falls based on older age (mean age, >70 years),[122,162,163,165] institutionalized status,[122,165] mobility problems,[122,165] or multiple comorbid conditions.[122,162,165] In two studies that reported how many patients had prior falls in the past 3 to 6 months, the proportions were 16 and 34 percent.[122,165] While the overall summary RR indicated no statistically significant effect on risk for experiencing at least one fall in participants given vitamin D_3 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 D_3 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).[163] This trial reported that 12 months of 800 IU per day of vitamin D_3 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[122,166] in order to separately examine the three trials of vitamin D_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]; I^2=0%).[162,163,165]

Five fair-quality trials examined the effect of 400 to 1,000 IU per day of vitamin D_3 treatment (with or without calcium) on the number of falls per individual (N=1,399, **Table 3**).[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]; 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.[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.[162,163,165,166] In three of these trials, the risk estimates were similar.[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).[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. ≥12 months). The one trial that examined only risk for falls (not rate of falls) reported no reduced risk for falls in those given vitamin D_3 treatment with calcium versus placebo (RR, 1.03 [95% CI, 0.90 to 1.18]).[122] This trial's primary outcome was risk for fractures, and the method of recording falls was not described. The trial examining only rate of falls (not risk for falls) was conducted in a younger (mean age, 64 years) population in which falls were collected as part of adverse event reporting; few falls were recorded during followup, leading to wide CIs.[136]

Effect of Vitamin D Treatment on Cancer Risk

Effects of 7 years of treatment with 400 IU per day of vitamin D_3 and calcium on risk for breast cancer (n=909 cases) and colorectal cancer (n=237 cases) in women with low 25(OH)D levels were examined in case-control studies nested within the WHI CaD trial.[167,168] Compared with placebo, treatment with vitamin D_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 <23 vs. ≥23 ng/mL for colorectal cancer and adjusted OR, 0.89 [95% CI, 0.58 to 1.36] for <27 vs. ≥27 ng/mL for breast cancer).[167,168]

Effect of Vitamin D Treatment on Type 2 Diabetes Risk

One fair-quality trial (n=305)[136] and one case-control study nested within the WHI CaD trial (n=192 cases)[169] examined the effects of treatment with 400 to 1,000 IU per day of vitamin D_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]; I^2=0%; **Figure 8**).

Effect of Vitamin D Treatment on Psychosocial Functioning and Disability

One good-quality trial examined the effect of 20,000 IU per week of vitamin D_3 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 D_3 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 D_3 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 D_3 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 D_3 on physical functioning in U.S. and European populations with an average age of 78 years.[155] Compared with placebo, vitamin D_3 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_3 or D_2 (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,[156,159,160,170,174-177] 16 were conducted in Europe,[115,120,122,125,127,128,132,133,136,153,154,157,158,165,171,178,179] and one was conducted in both the United States and Europe.[155] These trials examined vitamin D_3 treatment (21 trials),[120,122,125,127, 128,132,133,136,153-160,165,170,171,174,175,177,178] vitamin D_2 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_3 or D_2 for 6 to 36 months (**Table 4** and **Appendix C1**; N=1,296).[125,132,133,136,157,158,171,175,177] 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_3 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 D_3 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.[115,120,122,125,128,133,136,155,165,171,175,177,179] 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.[120,122,136,156,157,159,160,171,175,177] 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**).[122,128,155,156,158,159,175,177] 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,[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_3 treatment and mortality, only a nested case-control analysis within the WHI CaD trial[152] was designed to assess mortality risk associated with vitamin D_3 supplementation. While no individual study found that vitamin D_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_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,[58,93] but not all,[45] recent systematic reviews that included studies of persons with and without deficiency have concluded that supplementation in older persons (mainly women) 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.[162,163,165,166] Risk estimates were similar in three of these trials.[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).[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_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.[45,58]

Vitamin D (D_3 or D_2) 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[180] 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[70] 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.[70] The USPSTF recommended against low-dose supplementation with vitamin D (≤400 IU) and calcium (≤1,000 mg) to reduce fracture risk in noninstitutionalized populations and concluded that the evidence on the effects of higher doses was insufficient to make a recommendation.[3]

A 2010 systematic review by Michael and colleagues[181] 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[136,166] and one[165] 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.[1]

Two systematic reviews (in 2011 and 2013) examined whether vitamin D supplementation with or without calcium was associated with cancer risk.[70,180] 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.[146,182-184] The authors of the most recent systematic review concluded that vitamin D and/or calcium supplementation showed no overall effect on cancer.[180] 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.[70,180,181] The systematic reviews noted that the WHI CaD trial found a significantly increased risk for harm: a 17-percent increased risk for kidney stones in persons randomized to supplementation with 400 IU 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.[185]

Limitations of Review Methods

We excluded non–English-language articles, which could result in language bias. Some studies, however, have found empirical evidence that restricting systematic reviews of noncomplementary medicine intervention to English-language studies has little effect on the conclusions.[186,187] We did not search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods because we identified only small numbers of studies for each key question. We included the WHI nested case-control studies in the pooled trials, as the event rates were low enough (≤11%) that the 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),[188-191] risk factors for falls (5 studies),[194-196] prediabetes (1 study),[197] heart failure (2 studies),[198,199] or tuberculosis (1 study).[200] The findings from these studies of selected populations were similar to our overall results. Vitamin D treatment did not reduce risk for experiencing a compression fracture in vitamin D–deficient persons with a history of a compression fracture.[188] The effects of vitamin D treatment on fall risk and functional status 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[191] or who had one or more health problems or functional limitations at admission to a geriatric rehabilitation center;[194] however, vitamin D treatment reduced falls in vitamin D–deficient populations with a history of falls.[192] Although community-dwelling homebound persons experienced an improvement in functional status with vitamin D treatment,[195] long-term inpatients and those in a rehabilitation center with health problems or functional limitations did not experience an improvement in physical

functioning or the ability to complete activities of daily living with vitamin D treatment.[194,196] In one trial, risk for diabetes was not reduced when vitamin D treatment was given to persons with prediabetes who had low 25(OH)D levels.[197]

Limitations in the Evidence

We identified no direct evidence on the effect of vitamin D screening on health outcomes. The evidence on clinical outcomes associated with vitamin D treatment in deficient populations was relatively limited. Data on 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.[146,152,164,167-169] 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.[115] 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[30] 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.[13,31-34] Our survey of the literature on the association between 25(OH)D levels and outcomes (**Appendix A1**) found that data are still lacking about 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.[201] This large randomized, double-blind, placebo-controlled trial examines the effects of 5 years of supplementation with 2,000 IU per day of vitamin D_3 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.

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Figure 1. Analytic Framework

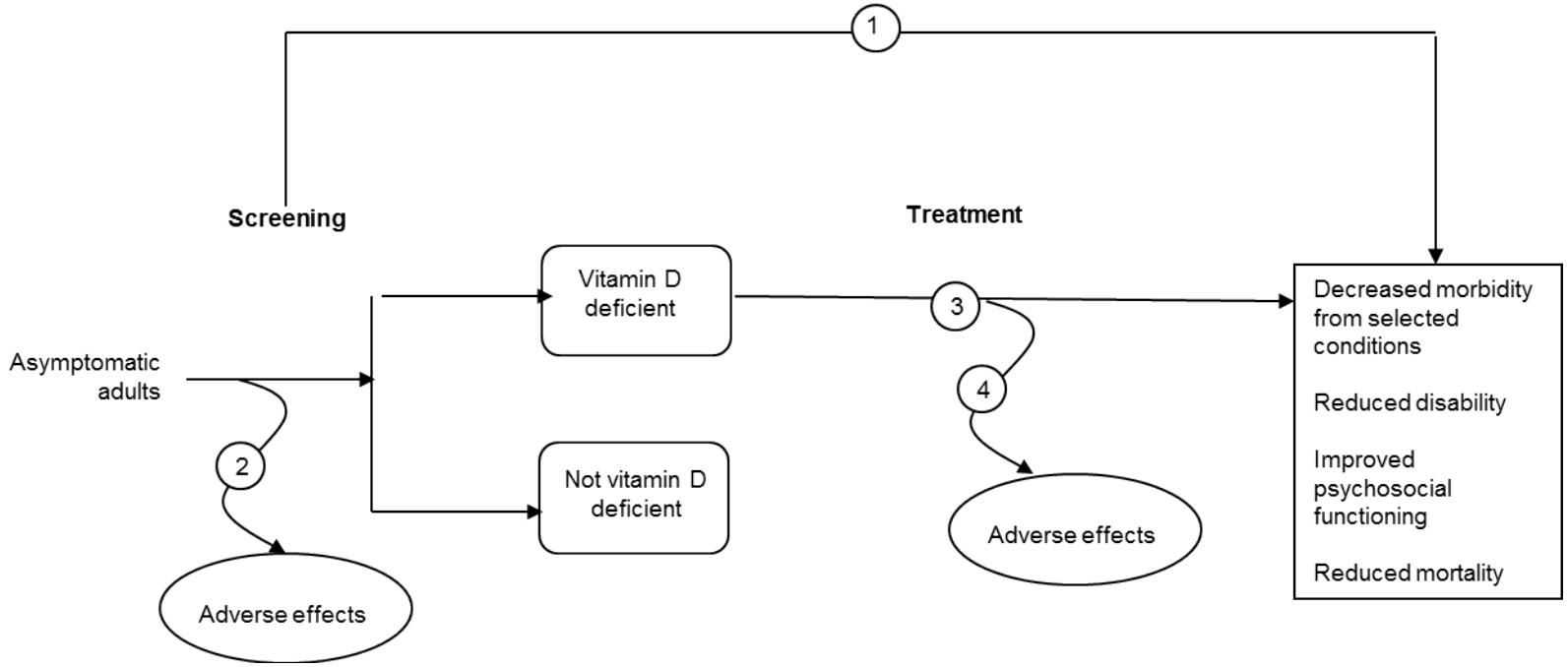
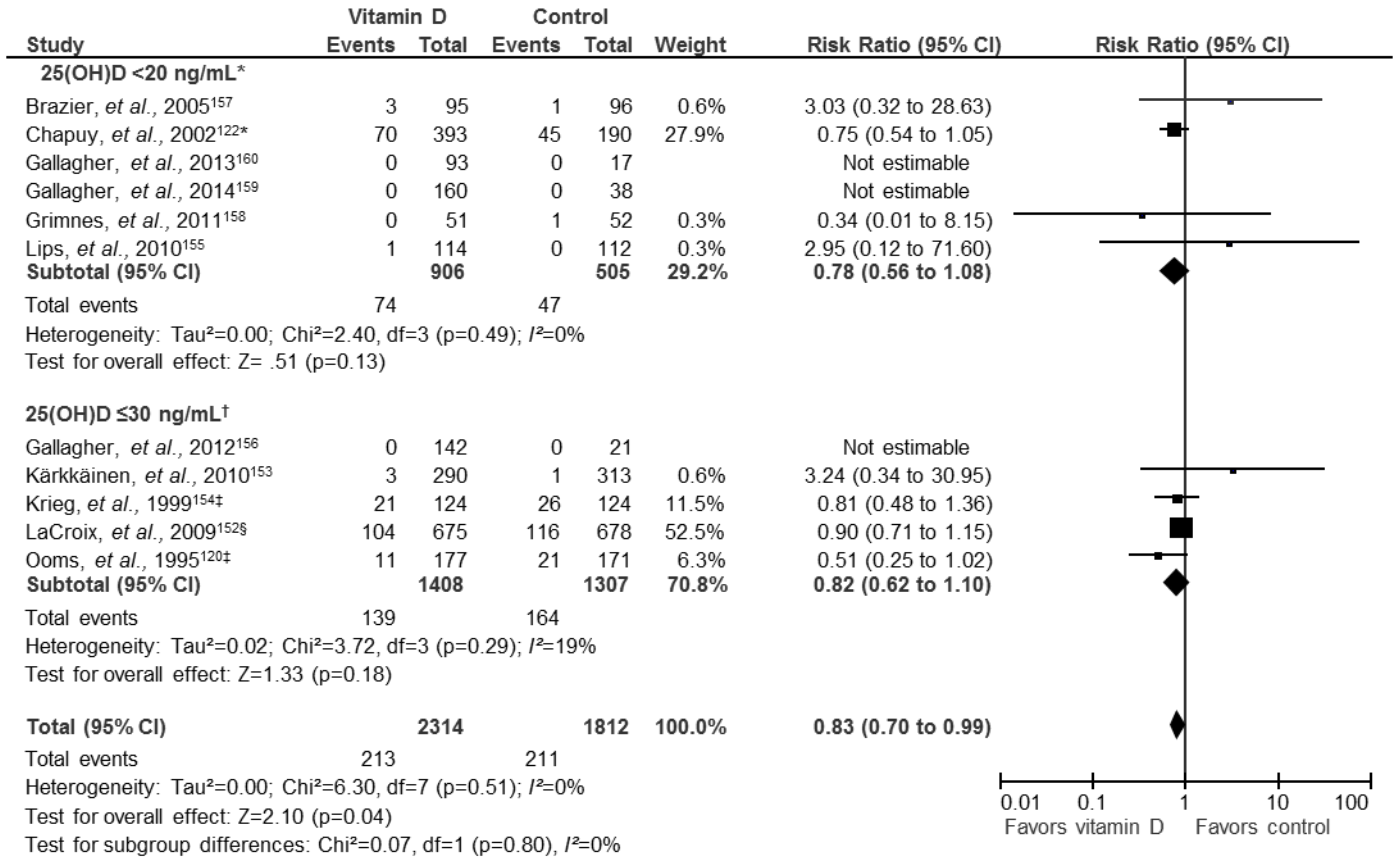


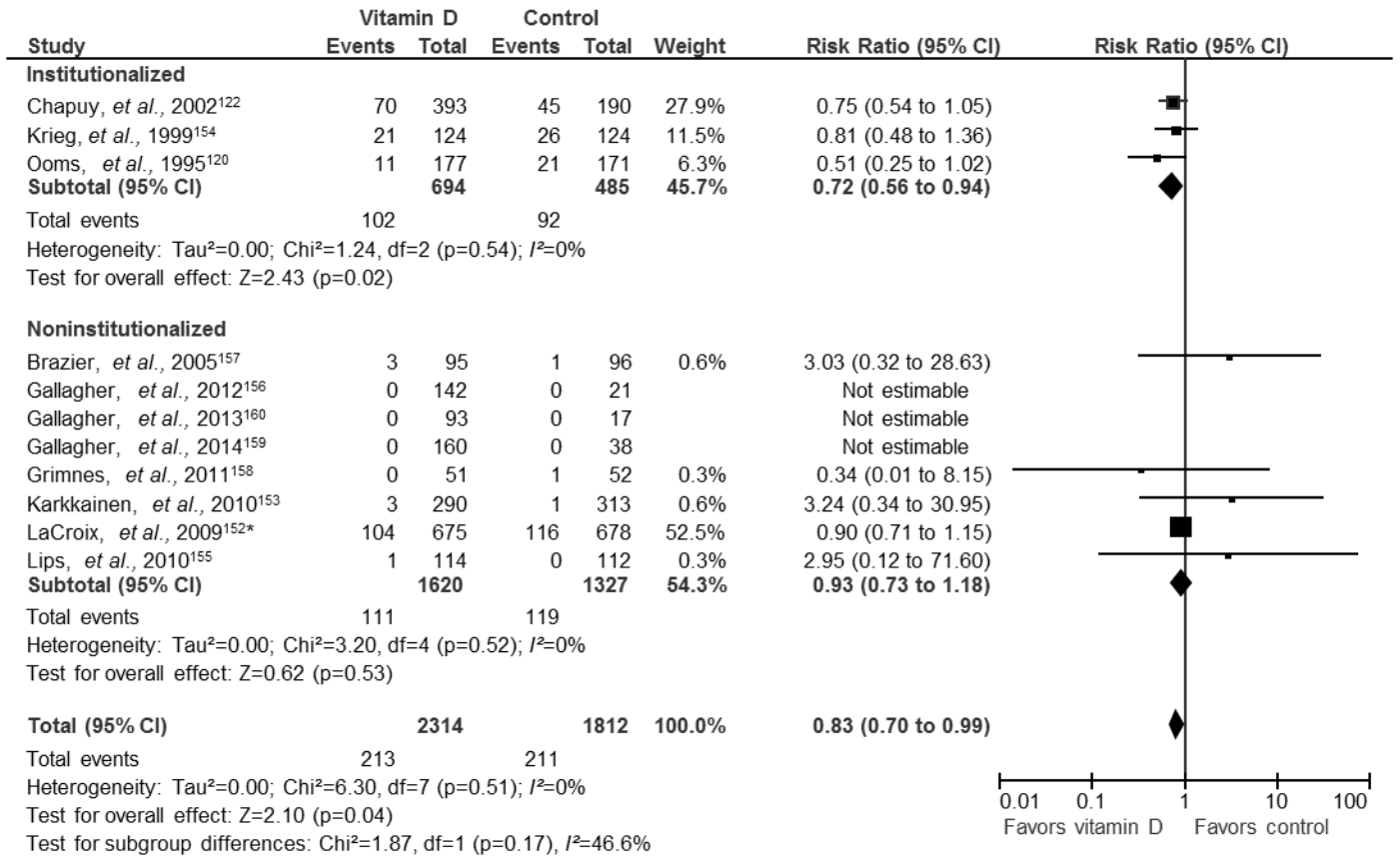
Figure 2. Meta-Analysis of Effects of Vitamin D Treatment on Mortality



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

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

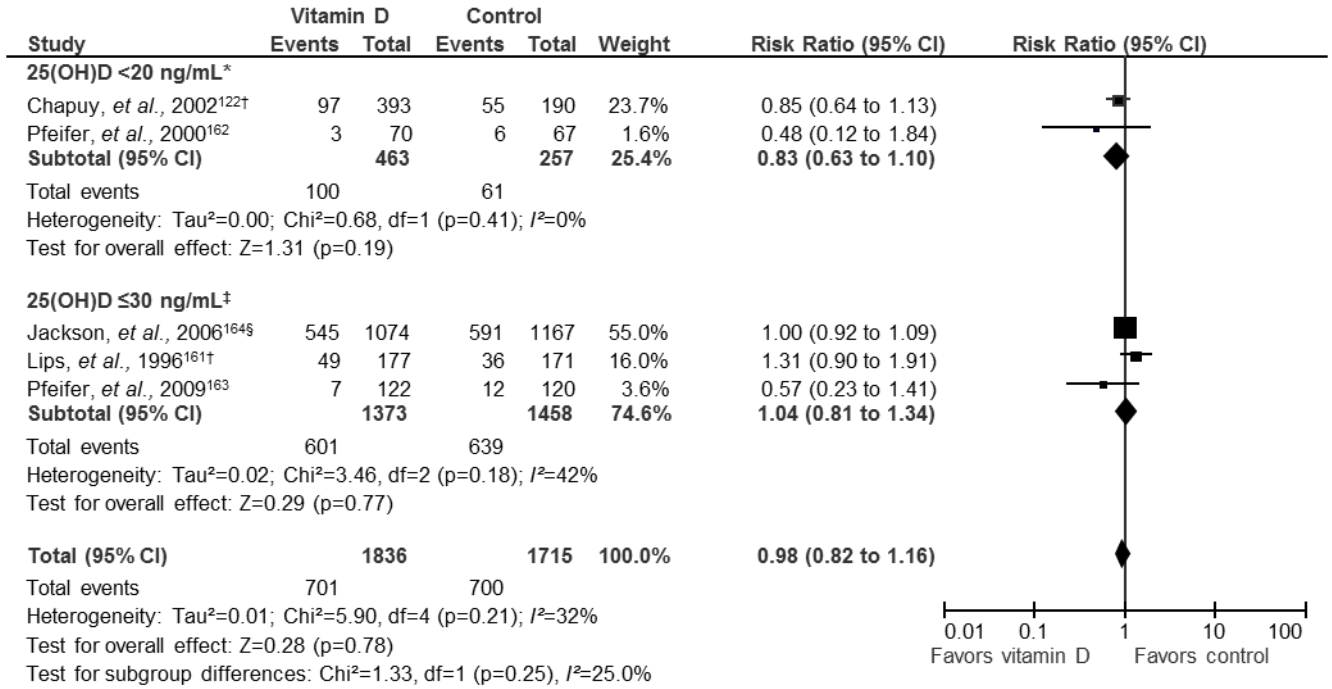
Figure 3. Meta-Analysis of Effects of Vitamin D Treatment on Mortality by Institutionalized Status



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

Abbreviation: CI = confidence interval.

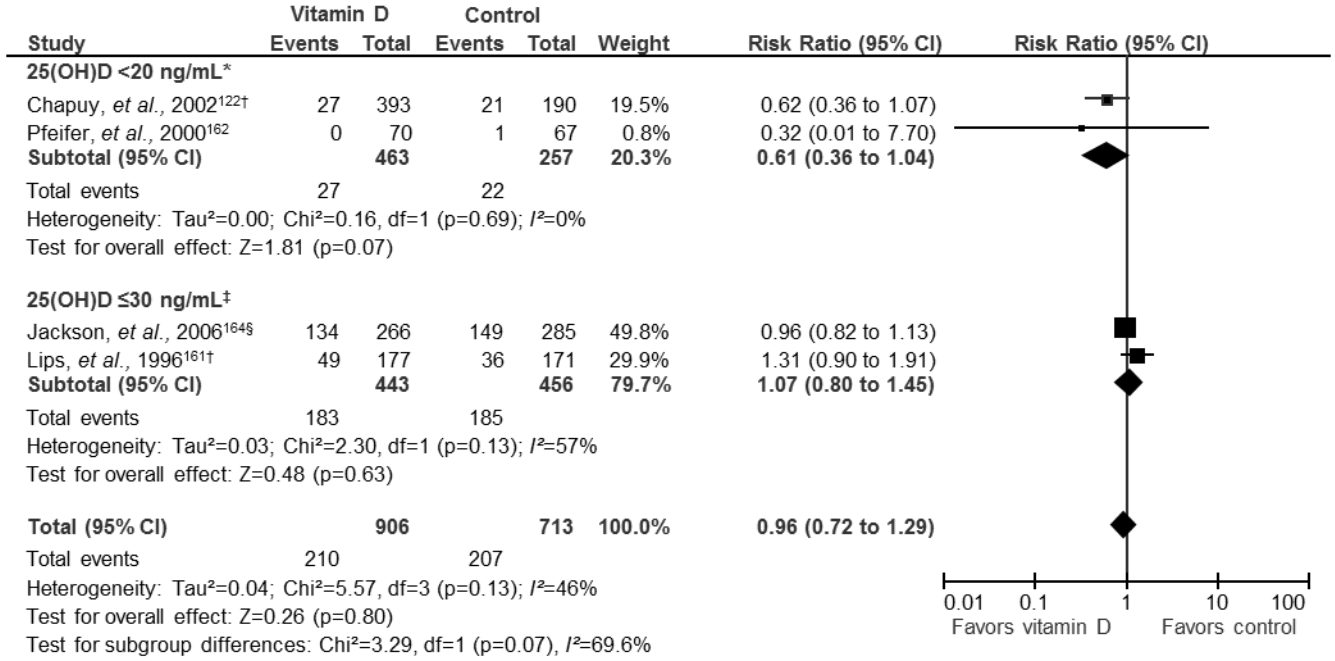
Figure 4. Meta-Analysis of Effects of Vitamin D Treatment on Any Type of Fracture Risk



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

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

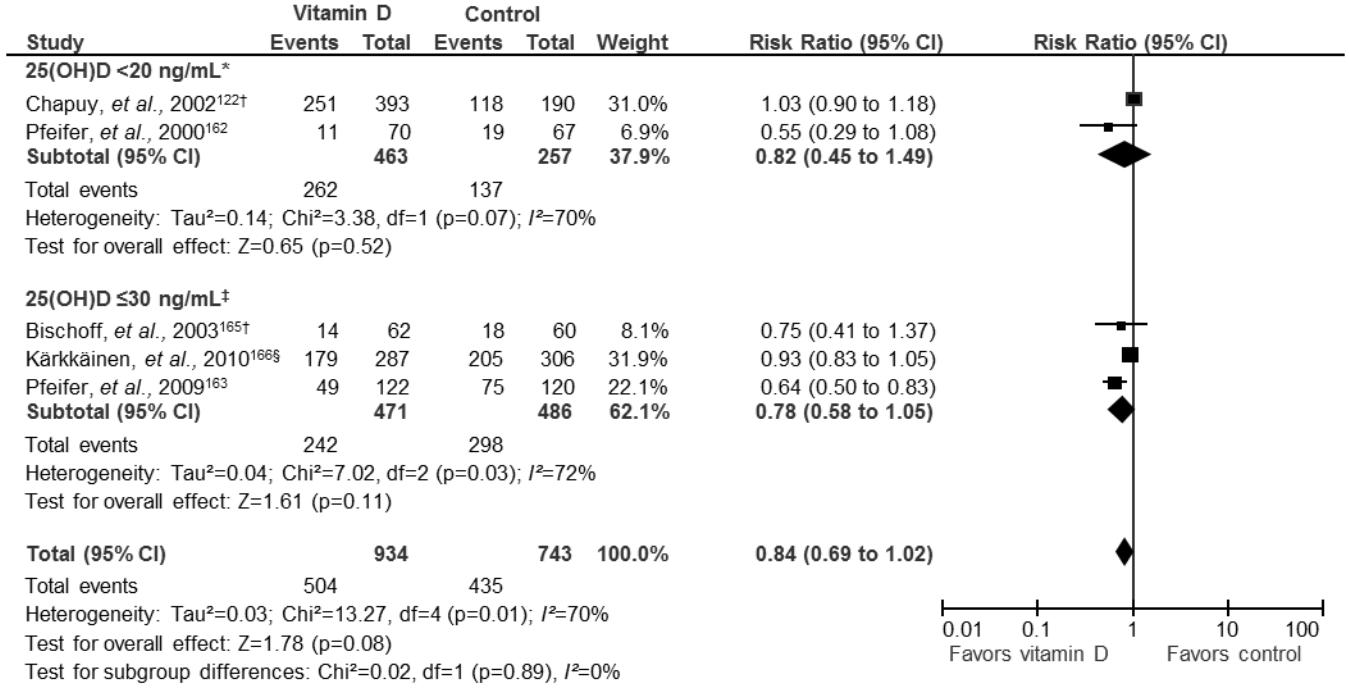
Figure 5. Meta-Analysis of Effects of Vitamin D Treatment on Hip Fracture Risk



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

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

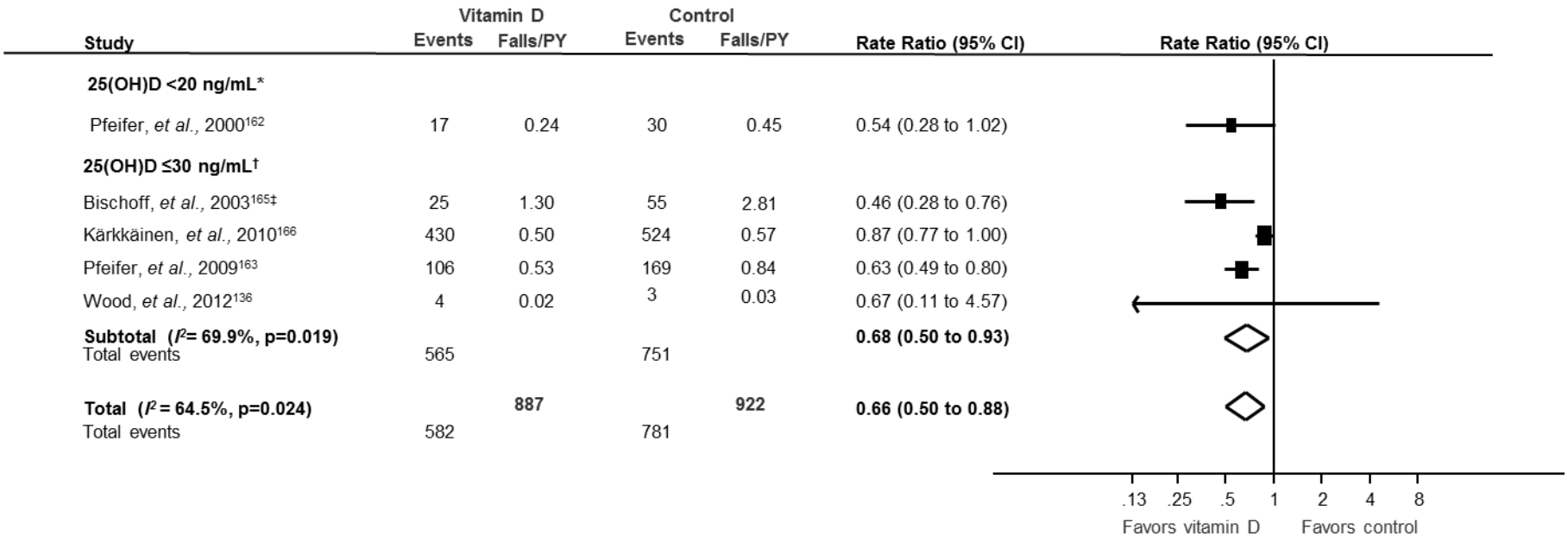
Figure 6. Meta-Analysis of Effects of Vitamin D Treatment on Falls Risk



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

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

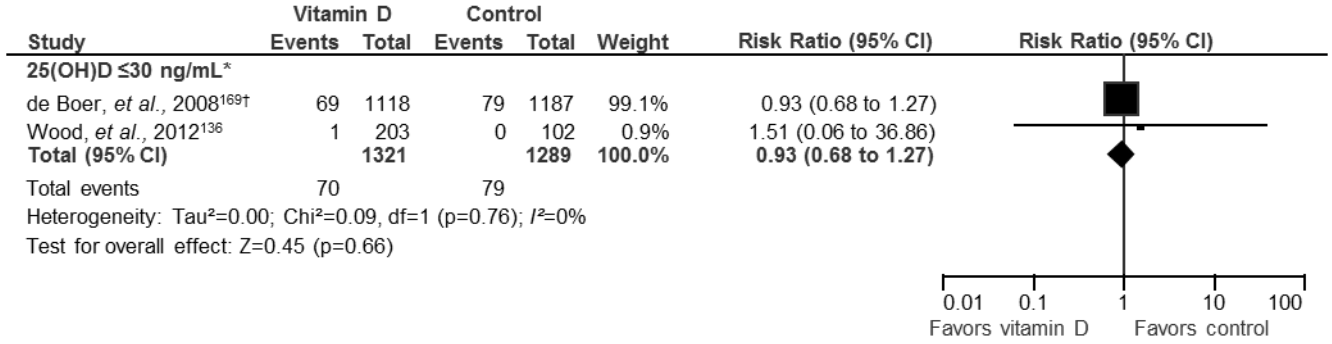
Figure 7. Meta-Analysis of Effects of Vitamin D Treatment on the Number of Falls per Person



* ≥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.

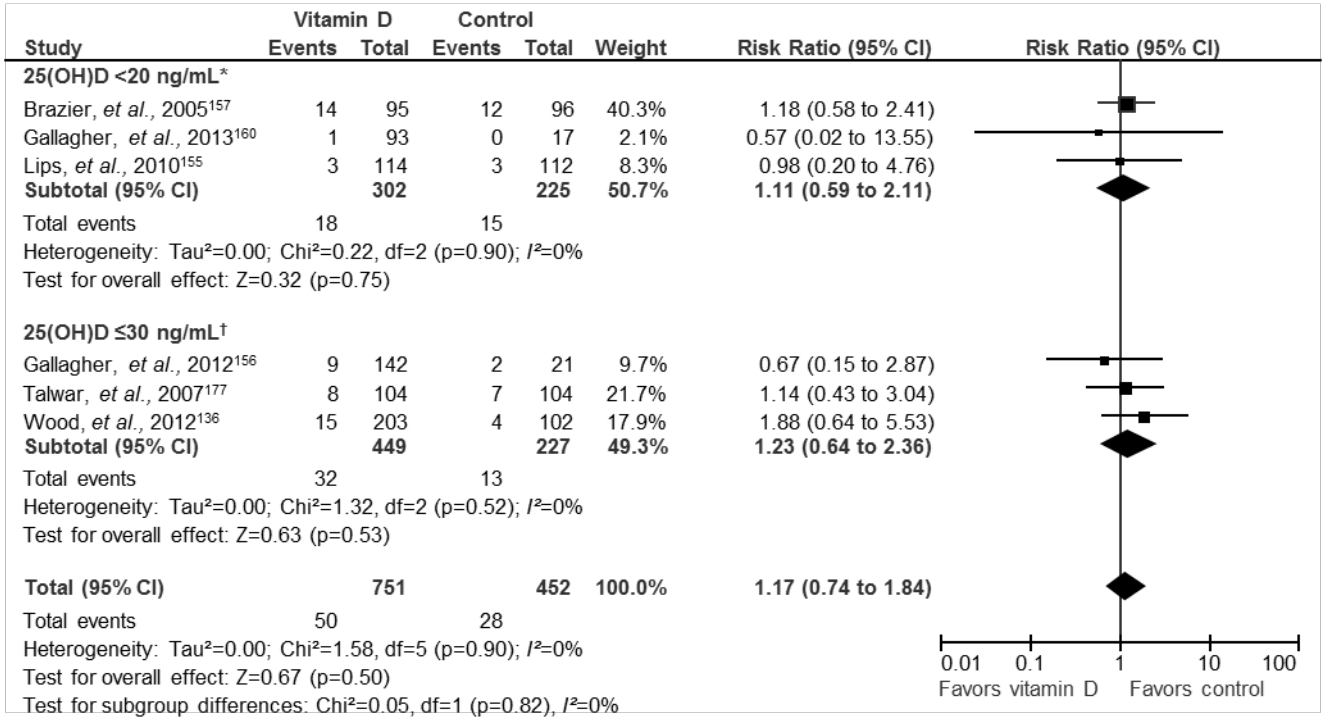
Figure 8. Meta-Analysis of Effects of Vitamin D Treatment on Type 2 Diabetes Risk



* ≥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.

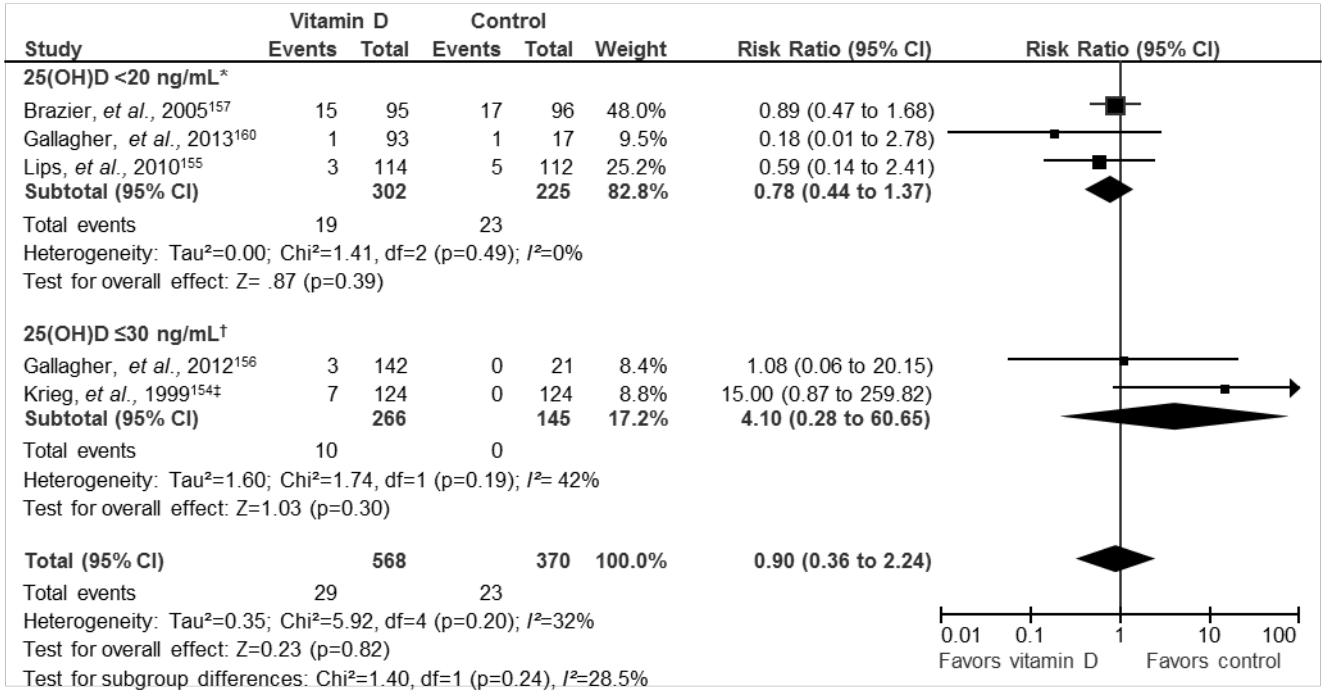
Figure 9. Meta-Analysis of Effects of Vitamin D Treatment on Serious Adverse Events



* ≥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.

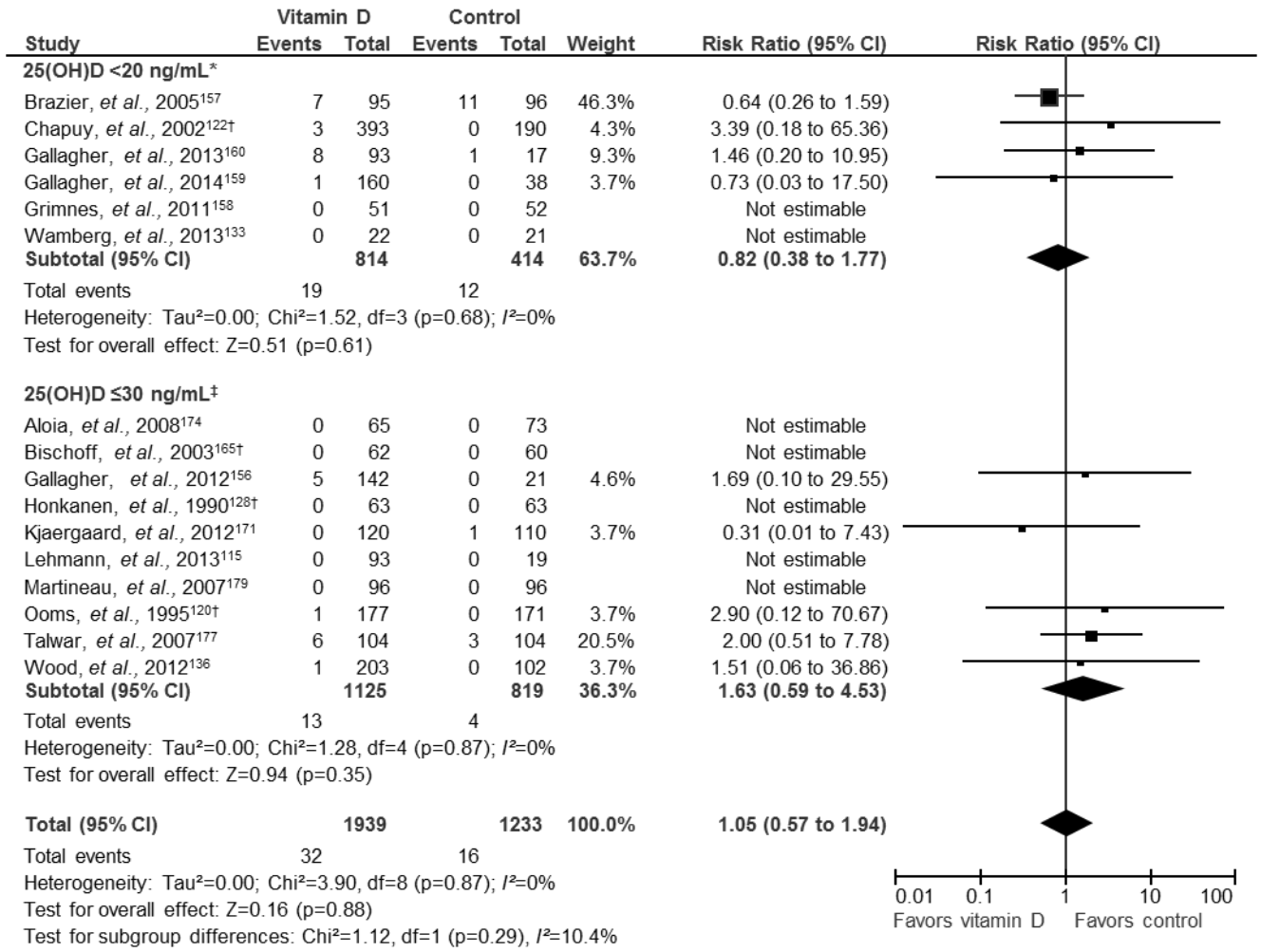
Figure 10. Meta-Analysis of Effects of Vitamin D Treatment on Withdrawals Due to Adverse Events



* ≥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



* ≥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

25(OH)D Cutoff	Expert and Professional Body Opinions About Cutoff Levels	Association Between 25(OH)D Level and Health Outcomes	Subgroup Differences for the Association
<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 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)	25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)	Interventions	Duration*	Clinical Health Outcomes Reported
25(OH)D level <20 ng/mL‡							
Brazier et al, 2005[157] Fair	France	Analyzed: 191 Age (years): 74.6 Female: 100% Comorbidities: NR History of falls: NR Institutionalized: 0%	7 vs. 7	Median: 29 vs. 11	Vitamin D (n=95): 800 IU vitamin D_3 and 1000 mg calcium daily Control (n=97): Placebo	12 months	Mortality
Chapuy et al, 2002[122] Fair	France	Analyzed: 583 Age (years): 85 Female: 100% Comorbidities: NR History of falls: 16.1% Use of walking device: 40.7% Institutionalized: 100%	9 vs. 9	~33 vs. 5 (from figure); p=0.0001 for change from baseline for vitamin D group only	Vitamin D (n=393): 800 IU of vitamin D_3 and 1200 mg calcium daily Control (n=190): Placebo	24 months	Fractures (primary outcome) Fallers Mortality
Gallagher et al, 2013[160] Fair	United States	Analyzed: 110 Age (years): 67 Female: 100% BMI (kg/m^2): 32.7 Comorbidities: NR History of falls: NR Institutionalized: NR	Placebo: 14 Vitamin D 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14 NR for 400, 3600, or 4000 IU groups	97.5% (from figure) of those using vitamin D 800 IU reached serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control: Placebo All participants supplemented to maintain total calcium intake of 1200 to1400 mg/day	12 months	Mortality§
Gallagher et al, 2014[159] Fair	United States	Analyzed: 198 Age (years): 37 Female: 100% BMI (kg/m^2): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR	Placebo: 13 Vitamin D 400 IU: 13 800 IU: 14 1600 IU: 13 2400 IU: 14	97.5% (from figure) of white women using vitamin D 400 IU reached serum 25(OH)D >20 ng/mL; 97.5% of black women using vitamin D 800 to 1600 IU reached serum 25(OH)D >20 ng/mL	Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D_3 daily Control: Placebo All participants supplemented to maintain total calcium intake of 1000 to 1200 mg/day	12 months	Mortality§

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)	25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)	Interventions	Duration*	Clinical Health Outcomes Reported
Grimnes et al, 2011[158] Fair	Norway	Analyzed: 104 Age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) BMI (kg/m^2): 26.5 (27.2 vs. 26.3) History of falls: NR Institutionalized: 0%	17 vs. 16	57 vs. 17	Vitamin D (n=51): 40,000 IU of vitamin D_3 weekly Control (n=52): Placebo	6 months	Mortality
Lips et al, 2010[155] Fair	The Netherlands, Germany, United States	Analyzed: 213 for SPPB; 226 for mortality Age (years): 78 Female: NR BMI (kg/m^2): 27.8† Comorbidities: NR History of falls: NR Use of walking device: 15% Institutionalized: 14%	14 vs. 14	26 vs. 12; p<0.001	Vitamin D (n=114): 8400 IU of Vitamin D_3 weekly Control (n=112): Placebo Those with daily calcium intake <1000 mg were also given 500 mg calcium	16 weeks	Physical functioning Mortality
Pfeifer et al, 2000[162] Fair	Germany	Analyzed: 137 Age (years): 74.8† Female: 100% BMI (kg/m^2): 25.5† Comorbidities: 39% cardiovascular; 12% central nervous, neurological; <1% psychiatric; 22% musculoskeletal History of falls: NR Use of walking device: NR Institutionalized: 0%	10 vs. 10	26 vs. 17; p<0.001	Vitamin D (n=70): 800 IU of vitamin D_3 and 1200 mg of calcium daily Control (n=67): 1200 mg of calcium daily	8 weeks treatment; 1 year followup	Falls Fallers Fractures
25(OH)D level ≤30 ng/mL‖							
Arvold et al, 2009[170] Fair	United States	Analyzed: 90 Age (years): 58.8† Female: 40% BMI: NR Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 0%	18 vs. 18	45 vs. 22	Vitamin D (n=48): 50,000 IU of vitamin D_3 weekly Control (n=42): Placebo	8 weeks	Psychosocial functioning Disability

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)	25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)	Interventions	Duration*	Clinical Health Outcomes Reported
Bischoff et al, 2003[165] Fair	Switzerland	Analyzed: 122 Age (years): 85 Female: 100% BMI (kg/m^2): 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%	Median, 12 vs. 12	Median, 26 vs. 11; p<0.001	Vitamin D (n=62): 800 IU of vitamin D_3 and 1200 mg of calcium daily Control (n=60): 1200 mg calcium daily	6 weeks pre-treatment; 12 weeks treatment	Falls (primary outcome) Fallers
Gallagher et al, 2012[156] Good	United States	Analyzed: 163 Age (years): 67 Female: 100% BMI (kg/m^2): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR	Placebo: 15 Vitamin D 400 IU: 15 800 IU: 16 1600 IU: 15 2400 IU: 15 3200 IU: 16 4000 IU: 15 4800 IU: 16	97.5% (from figure) of those using vitamin D 600 IU reached serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D (n=142): Either 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control (n=21): Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg/day	Median, 12 months	Mortality
Kärkkäinen et al, 2010[166] Kärkkäinen et al, 2010[153] Fair	Finland	Analyzed: 593 Age (years): 67.4† Female: 100% BMI (kg/m^2): 27.5† Comorbidities: NR History of falls: NR Ambulatory: 100% Institutionalized: NR	20 vs. 20	30 vs. 22	Vitamin D (n=290¶ and 287**): 800 IU of vitamin D_3 and 1000 mg of calcium daily Control (n=313¶ and 306**): No treatment	3 years	Falls (primary outcome) Fallers Mortality

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)	25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)	Interventions	Duration*	Clinical Health Outcomes Reported
Kjaergaard et al, 2012[171] Good	Norway	Analyzed: 230 (per protocol) Age (years): 53.4† Female: 56% BMI (kg/m^2): 27.7† Comorbidities: NR History of falls: NR Institutionalized: NR	19 vs. 19	59 vs. 21	Vitamin D (n=120): 20,000 IU of vitamin D_3 weekly Control (n=110): Placebo	6 months	Psychosocial functioning (primary outcome)
Krieg et al, 1999[154] Fair	Switzerland	Analyzed: 248 Age (years): 84.5† Female: 100% BMI (kg/m^2): 24.7† History of falls: NR Institutionalized: 100%	12 vs. 12	27 vs. 6	Vitamin D (n=124): 880 IU of vitamin D_3 and 1000 mg calcium daily Control (n=124): No supplementation	2 years	Mortality
Lips et al, 1996[161] Ooms et al, 1995[120] Fair	The Netherlands	Analyzed: 270 for fracture; 348 for mortality Age (years): 80.4† Female: 100% BMI (kg/m^2): 28.3† Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 100%††	Median, 11 vs. 10	Median, 25 vs. 9 (at 1 year)	Vitamin D (n=177): 400 IU of vitamin D_3 daily Control (n=171): Placebo	3 to 3.5 years, maximum 4 years	Fractures (primary outcome) Mortality
Pfeifer et al, 2009[163] Fair	Austria and Germany	Analyzed: 242 Age (years): 76.5 Female: 74.5% BMI (kg/m^2): 27.3 Comorbidities: NR History of falls: NR Ambulatory: 100% Institutionalized: 0%	22 vs. 22	Month 12: 34 vs. 23 Month 20: 19 vs. 15	Vitamin D (n=122): 800 IU of vitamin D_3 and 1000 mg of calcium daily Control (n=120): 1000 mg of calcium daily	12 month treatment; 8 months post-treatment	Falls (primary outcome) Fallers Fractures
Wood et al, 2012[136] Fair	United Kingdom	Analyzed: 305 Age (years): 63.8† Female: 100% BMI (kg/m^2): 26.7† History of falls: NR Institutionalized: NR	Vitamin D 400 IU vs. 1000 IU vs. control: 13 vs. 13 vs. 14	Vitamin D 400 IU vs. 1000 IU vs. control: 26 vs. 30 vs. 13	Vitamin D (n=102 and 101): 400 or 1000 IU of vitamin D_3 daily Control (n=102): Placebo	12 months treatment; 1 month followup	Falls Type 2 diabetes

Table 2. Studies of Effectiveness of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL)*† (Vitamin D vs. Control)	25(OH)D Level at Followup (ng/mL)*† (Vitamin D vs. Control)	Interventions	Duration*	Clinical Health Outcomes Reported
WHI Calcium with Vitamin D Trial Fair Associated case-control studies with outcome reported: Jackson et al, 2006[164] (for fractures) Wactawski-Wende et al, 2006[168] (for colorectal cancer) Chlebowski et al, 2008[167] (for breast cancer) de Boer et al, 2008[169] (for diabetes) LaCroix et al, 2009[152] (for mortality)	United States	Analyzed: 36,282 <u>Case-control studies</u> Fractures: 1491 cases/controls Colorectal cancer: 612 cases/controls Breast cancer: 895 cases/controls Diabetes: 192 cases/2905 controls Mortality: 323 cases/1962 controls <u>Entire trial characteristics</u> Age (years): 62 Female: 100% BMI (kg/m^2): 29 Race: 83.1% white; 9.1% black; 4.2% Hispanic; 0.42% American Indian or Native American; 2.0% Asian or Pacific Islander; 1.2% unknown or not identified Comorbidities: 35% with previous fracture; 67% with no falls, 20% with 1 fall, 9.0% with 2 falls, 4.0% with >3 falls in past 12 months <u>Case-control characteristics</u> NR	Entire trial: NR <u>Case-control studies</u> Fractures: <24 Colorectal cancer: <23 Breast cancer: <27 Diabetes: <24 Mortality: <21	Entire trial: After 2 years, in random sample of 1.2% of participants, vitamin D levels were 28% higher (9 ng/mL) in vitamin D vs. placebo group Case-control studies: NR	Vitamin D: 400 IU of vitamin D_3 + 1000 mg calcium daily Control: Placebo <u>Number analyzed in case-control studies per intervention (vitamin D vs. control)</u> Fractures: 266 vs. 285 Colorectal cancer: 237 vs. 222 Breast cancer: 909 vs. 722 Diabetes: 1118 vs. 1187 Mortality: 675 vs. 678	7 years	Fractures Mortality Type 2 diabetes Cancer

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

Study, Setting, Age*	Fall Risk	Intervention	IRR (95% CI) for Falls per Person	RR (95% CI) for Risk for Falling	Primary Outcome of Study
Bischoff et al, 2003[165] Institutionalized Age: 85	34% with falls 6 weeks prior; 30% of CG fell over 3 months	Vitamin D	0.46 (0.28 to 0.76)	0.75 (0.41 to 1.37)	Number of falls per person
Chapuy et al, 2002[122] Institutionalized Age: 85	16% with falls 3 months prior; 62% of CG fell over 24 months	Vitamin D + calcium	NR	1.03 (0.90 to 1.18)	Fractures
Kärkkäinen et al, 2010[166] Noninstitutionalized Age: 67	Fall history NR; 67% of CG fell over 36 months	Vitamin D + calcium	0.87 (0.77 to 1.00)	0.93 (0.83 to 1.05)	Occurrence of falls
Pfeifer et al, 2000[162] Noninstitutionalized Age: 75	Fall history NR; 28% of CG fell over 12 months	Vitamin D	0.54 (0.28 to 1.02)	0.55 (0.29 to 1.08)	Body sway; biochemical measures of bone
Pfeifer et al, 2009[163] Noninstitutionalized Age: 77	Fall history NR; 63% of CG fell over 20 months	Vitamin D	0.63 (0.49 to 0.80)	0.64 (0.50 to 0.83)	Occurrence of falls
Wood et al, 2012[136] Noninstitutionalized Age: 64	Fall history NR; 3 falls among 227 in CG	Vitamin D	0.67 (0.11 to 4.57)	NR	Reported as adverse event

* Mean age (in years) of study population.

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

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
25(OH)D level <20 ng/mL‡							
Brazier et al, 2005[157] Fair	France	Analyzed: 191 Age (years): 74.6 (74.2 vs. 75.0) Female: 100% Comorbidities: NR History of falls: NR Institutionalized: 0%	7 vs. 7	Median, 29 vs. 11	Vitamin D (n=95): 800 IU vitamin D_3 and 1000 mg calcium daily Control (n=97): Placebo	12 months	Total AEs Withdrawal due to AEs Serious AEs Any AE Hypercalcemia Gastrointestinal AEs Osteomuscular AEs Nervous system AEs Metabolic/nutritional AEs
Chapuy et al, 2002[122] Fair	France	Analyzed: 583 Age (years): 85 Female: 100% Comorbidities: NR History of falls: 16.1% Use of walking device: 40.7% Institutionalized: 100%	9.2 vs. 9.2	~ 33 vs. 5 (from figure); p=0.0001 for change from baseline for vitamin D group only	Vitamin D (n=393): 800 IU of vitamin D_3 and 1200 mg calcium daily Control (n=190): Placebo	24 months	Withdrawal due to AEs (NR by group) Hypercalcemia Kidney stones Hypercalciuria Gastrointestinal AEs
Gallagher et al, 2013[160] Fair	United States	Analyzed: 110 Age (years): 67 Female: 100% BMI (kg/m^2): 32.7 Comorbidities: NR History of falls: NR Institutionalized: NR	Placebo: 14 Vitamin D§ 800 IU: 14 1600 IU: 13 2400 IU: 14 4800 IU: 14	97.5% (from figure) of those using vitamin D 800 IU reached serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control: Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg/day	12 months	Withdrawal due to AEs‖ Serious AEs Hypercalcemia
Gallagher et al, 2014[159] Fair	United States	Analyzed: 198 Age (years): 37 Female: 100% BMI (kg/m^2): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR	Placebo: 13 Vitamin D 400 IU: 13 800 IU: 14 1600 IU: 13 2400 IU: 14	97.5% (from figure) of white women using vitamin D 400 IU reached serum 25(OH)D >20 ng/mL; 97.5% of black women using vitamin D 800 to 1600 IU reached serum 25(OH)D >20 ng/mL	Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D_3 daily Control: Placebo All participants supplemented to maintain total calcium intake of 1000 to 1200 mg/day	12 months	Serious AEs (NR by group) Hypercalcemia Kidney stones

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
Grimnes et al, 2011[158] Fair	Norway	Analyzed: 104 Age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) BMI (kg/m^2): 26.5 (27.2 vs. 26.3) History of falls: NR Institutionalized: 0%	17 vs. 16	57 vs. 17	Vitamin D (n=51): 40,000 IU vitamin D_3 weekly Control (n=52): Placebo	6 months	Total AEs Hypercalcemia Kidney stones
Janssen et al, 2010[127] Fair	The Netherlands	Analyzed: 70 Age (years): 80.8† Female: 100% BMI (kg/m^2): 26.4† Comorbidities: 2.4† Medications used: 5.0† History of falls: NR Institutionalized: 100%‡	13 vs. 14	31 vs. 17	Vitamin D (n=28): 400 IU of vitamin D_3 and 500 mg of calcium daily Control (n=31): Placebo and calcium 500 mg daily	6 months	Withdrawals Any AE
Knutsen et al, 2014[132] Fair	Norway	Analyzed: 215 Age (years): 37.3† Female: 73% BMI (kg/m^2): 27.4† Comorbidities: NR History of falls: NR Institutionalized: NR	11 vs. 11	19 vs. 10	Vitamin D (n=169): 25 or 10 μg of vitamin D_3 daily Control (n=82): Placebo	16 weeks	Total AEs
Lips et al, 2010[155] Fair	The Netherlands Germany United States	Analyzed: 226 Age (years): 78 Female: NR BMI (kg/m^2): 27.8† Comorbidities: NR History of falls: NR Use of walking device: 15% Institutionalized: 14%	14 vs. 14	26 vs. 12; p<0.001	Vitamin D (n=114): 8400 IU of vitamin D_3 weekly Control (n=112): Placebo Those with daily calcium intake <1000 mg were also given 500 mg calcium	16 weeks	Withdrawal due to AEs Serious AEs Any AE Kidney stones Hypercalcemia (data not shown)

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
Wamberg et al, 2013[125] Wamberg et al, 2013[133] Fair	Denmark	Analyzed: 43 Age (years): 40.5 Female: 71% BMI (kg/m^2): 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	14 vs. 14	44 vs. 19	Vitamin D (n=22): 7000 IU of vitamin D_3 daily Control (n=21): Placebo	26 weeks	Total AEs Hypercalcemia
25(OH)D level ≤30 ng/mL							
Aloia et al, 2008[174] Fair	United States	Analyzed: 138 Age (years): 47.2† Female: 81% History of falls: NR Institutionalized: NR	19	>30 ng/mL achieved by virtually all in active group; also increased by 8 ng/mL in placebo group because of seasonal change	Vitamin D (n=65): Dosage of vitamin D_3 depended on 25(OH)D concentration; mean dose, 3440 IU Control (n=73): Placebo	6 months	Hypercalcemia Hypercalcuria
Arvold et al, 2009[170] Fair	United States	Analyzed: 100 Age (years): 58.8† Female: 40% BMI: NR Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 0%	18 vs. 18	45 vs. 22	Vitamin D (n=48): 50,000 IU vitamin D_3 weekly Control (n=42): Placebo	8 weeks	Any AE
Berlin et al, 1986[178] Poor	Sweden	Analyzed: 24 Age (years): 31 (range, 22 to 47) Female: 0% History of falls: NR Institutionalized: NR	15 vs. 15	49 vs. 19	Vitamin D (n=12): 54,000 IU of vitamin D_3 weekly Control (n=12): No treatment	NR; implies 2 months	Any AE

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
Bischoff et al, 2003[165] Fair	Switzerland	Analyzed: 122 Age (years): 85 Female: 100% BMI (kg/m^2): 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%	Median, 12 vs. 12	Median, 26 vs. 11; p<0.001	Vitamin D (n=62): 800 IU of vitamin D_3 and 1200 mg of calcium daily Control (n=60): 1200 mg calcium daily	6 weeks pre-treatment 12 weeks treatment	Hypercalcemia Withdrawals Gastrointestinal AEs
Gallagher et al, 2012[156] Good	United States	Analyzed: 163 Age (years): 67 Female: 100% BMI (kg/m^2): 30.2 Comorbidities: NR History of falls: NR Institutionalized: NR	Placebo: 15 Vitamin D 400 IU: 15 800 IU: 16 1600 IU: 15 2400 IU: 15 3200 IU: 16 4000 IU: 15 4800 IU: 16	97.5% (from figure) of those using vitamin D 600 IU per day had serum 25(OH)D >20 ng/mL; p<0.05 vs. placebo for all vitamin D groups	Vitamin D (n=235): Either 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control (n=38): Placebo All participants supplemented to maintain total calcium intake of 1200 to 1400 mg daily	Median, 12 months	Withdrawal due to AEs Any AE Serious AEs Kidney stones Hypercalcemia

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
Harris et al, 1999[176] Poor	United States	Analyzed: 20 Age (years): 31 (range, 22 to 47) Female: 0% Comorbidities: NR History of falls: NR Institutionalized: NR	Younger men: 13 vs. 17 Older men: 16 vs. 16	Younger men: 25 vs. 13 Older men: 19 vs. 15	Vitamin D (n=11): 1800 IU of vitamin D_2 daily Control (n=7): No treatment	3 weeks	Any AE
Honkanen et al, 1990[128] Fair	Finland	Analyzed: 126 Home patients Age (years): 69.5† Female: 100% Weight (kg): 69.5† Comorbidities: NR History of falls: NR Hospital inpatients (52%) Age (years): 82.5† Female: 100% Weight (kg): 61.8† Comorbidities: NR History of falls: NR	Home patients: 17 vs. 15 Hospital inpatients: 10 vs. 10	Home patients: 32 vs. 9 Hospital inpatients: 26 vs. 4	Vitamin D (n=63): 1800 IU of vitamin D_3 and 1.558 g of calcium daily Control (n=63): No treatment	11 weeks	Hypercalcemia Kidney stones
Kärkkäinen et al, 2010[153] Fair	Finland	Analyzed: 603 Age (years): 67.4† (67.4 vs. 67.4) Female: 100% BMI (kg/m^2): 27.4† (27.5 vs. 27.4) History of falls: NR Institutionalized: NR	20 vs. 20	30 vs. 22	Vitamin D (n=290): 800 IU of vitamin D_3 and 1000 mg calcium daily Control (n=313): No treatment	3 years	Withdrawal due to AE
Kjaergaard et al, 2012[171] Good	Norway	Analyzed: 230 (per protocol) Age (years): 53.4† Female: 56% BMI (kg/m^2): 27.7† Comorbidities: NR History of falls: NR Institutionalized: NR	19 vs. 19	59 vs. 21	Vitamin D (n=120): 20,000 IU of vitamin D_3 weekly Control (n=110): Placebo	6 months	Total AEs Gastrointestinal AEs Respiratory AEs Dermatological AEs Musculoskeletal AEs Urogenital AEs Circulatory AEs Neurological AEs Endocrinological AEs Other organ AEs Hypercalcemia

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
Krieg et al, 1999[154] Fair	Switzerland	Analyzed: 248 Age (years): 84.5† Female: 100% BMI (kg/m^2): 24.7† History of falls: NR Institutionalized: 100%	12 vs. 12	27 vs. 6	Vitamin D (n=124): 880 IU of vitamin D_3 and 1000 mg calcium daily Control (n=124): No treatment	2 years	Withdrawal due to AE
Lehmann et al, 2013[115] Fair	Norway	Analyzed: 119 Age (years): 33.8† Female: 63.5% BMI (kg/m^2): 23.8† History of falls: NR Institutionalized: NR	Overall (vitamin D_2 vs. vitamin D_3 vs. control): 16 (15 vs. 18 vs. 16)	Vitamin D_2 vs. vitamin D_3 vs. control: 27 vs. 36 vs. 13	Vitamin D (n=47, 46): 2000 IU of either vitamin D_2 or D_3 daily Control(n=19): Placebo	8 weeks	Any AE Hypercalcemia
Martineau et al, 2007[179] Fair	United Kingdom	Analyzed: 192†† Median age (years): 33.7† Female: 51.2%† History of falls: NR Institutionalized: NR	14 vs. NR	27 vs. NR	Vitamin D (n=96): Single dose of 100,000 IU vitamin D_2 Control (n=96): Placebo	6 weeks	Any AE Hypercalcemia
Ooms et al, 1995[120] Fair	The Netherlands	Analyzed: 348 Age (years): 80.4† Female: 100% BMI (kg/m^2): 28.3† Comorbidities: NR History of falls: NR Use of walking device: NR Institutionalized: 100%**	Median, 11 vs. 10	Median, 25 vs. 9 (at 1 year)	Vitamin D (n=177): 400 IU of vitamin D_3 daily Control (n=171): Placebo	3 to 3.5 years, maximum 4 years	Any AE Hypercalcemia
Talwar et al, 2007[177] Aloia et al, 2005[175] Fair	United States	Analyzed: 208 Age (years): 60.5† Female: 100% BMI (kg/m^2): 29 vs. 30 History of falls: NR Institutionalized: NR	19 vs. 17	35 vs. 18	Vitamin D (n=104): 800 IU of vitamin D_3 daily for first 24 months, increased to 2000 IU daily Control (n=104): Placebo Supplements given to maintain total daily intake of 1200 to 1500 mg calcium	36 months	Total AEs (NR by group) Serious AEs Hypercalcemia Hypercalcuria Kidney stones

Table 4. Studies of Harms of Vitamin D Treatment

Author, Year Quality	Country	Population Characteristics*	25(OH)D Level at Baseline (ng/mL):*† Vitamin D vs. Control	25(OH)D Level at Followup (ng/mL):*† Vitamin D vs. Control	Interventions	Duration*	Adverse Events or Harms Reported
Wood et al, 2012[136] Fair	United Kingdom	Analyzed: 305 Age (years): 63.8† Female: 100% BMI (kg/m^2): 26.7† History of falls: NR Institutionalized: NR	Vitamin D 400 IU vs. 1000 IU vs. control: 13 vs. 13 vs. 14	Vitamin D 400 IU vs. 1000 IU vs. control: 26 vs. 30 vs. 13	Vitamin D (n=102, 101) 400 or 1000 IU of vitamin D_3 daily Control (n=102): Placebo	12 months treatment; 1 month followup	Total AEs Serious AEs Hypercalcemia Gastrointestinal AEs Osteomuscular AEs

* Reported as 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.
ǁ As per author correspondence.
¶ ≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL.
** 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

Number and Type of Studies	Overall Quality	Limitations	Consistency	Applicability	Summary of Findings
Key Question 1. Is there direct evidence that screening for vitamin D deficiency results in improved health outcomes? Key Question 1a. Are there differences in screening efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency, such as age ≥65 years, sex, race/ethnicity, body mass index, ultraviolet light exposure, and institutionalized status)?					
No studies	NA	NA	NA	NA	NA
Key Question 2. What are the harms of screening?					
No studies	NA	NA	NA	NA	NA
Key Question 3. Does treatment of vitamin D deficiency with vitamin D lead to improved health outcomes?					
17 studies RCTs, nested case-control studies	Fair	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	Moderate	Studies mostly conducted in older white U.S. or European women	• Vitamin D treatment (with or without calcium) was associated with a decreased risk for mortality (11 studies; pooled RR, 0.83 [95% CI, 0.70 to 0.99]); risk reduction limited to studies of older, institutionalized persons (3 trials; pooled RR, 0.72 [95% CI, 0.56 to 0.94]) • Vitamin D treatment was not associated with decreased risk for falling (5 studies; pooled RR, 0.84 [95% CI, 0.69 to 1.02]), but was associated with a lower rate of falls per individual (pooled rate ratio, 0.66 [95% CI, 0.50 to 0.88]) • Vitamin D treatment was not associated with a decreased fracture risk (5 studies; pooled RR, 0.98 [95% CI, 0.82 to 1.16]) • Limited (≤2 studies) data on cancer risk, type 2 diabetes risk, psychosocial functioning, disability, and physical functioning, but generally no associations with vitamin D treatment were seen
Key Question 3a. Are there differences in efficacy between patient subgroups (subgroups defined by risk factors for vitamin D deficiency, such as age ≥65 years, sex, race/ethnicity, body mass index, ultraviolet light exposure, and institutionalized status)?					
No studies	NA	NA	NA	NA	NA
Key Question 4. What are the adverse effects of treatment of vitamin D deficiency with vitamin D?					
24 studies* RCTs, cohorts	Fair	Few studies prespecified harms outcomes; studies were not designed to address harms; variability in baseline 25(OH)D levels, doses of vitamin D treatment, use of calcium cosupplementation, and length of followup	High	Only 7 studies were conducted in the U.S. and only 3 of these U.S. studies reported populations having a significant percentage of nonwhite participants	Vitamin D treatment (with or without calcium) was not associated with increased adverse events
Key Question 4a. Are there differences in adverse effects between patient subgroups (subgroups defined by risk factors for vitamin D deficiency such as age ≥65 years, sex, race/ethnicity, body mass index, ultraviolet light exposure, and institutionalized status)?					
No studies	NA	NA	NA	NA	NA

* Includes two poor-quality trials.

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized, controlled trial; RR = risk ratio.

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

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

Breast Cancer

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

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.[6,8,10,11,16]

Pancreatic Cancer

No association between 25(OH)D level and pancreatic cancer risk was noted in two meta-analyses of prospective studies.[11,16] Both meta-analyses noted that several individual studies had observed a U-shaped association between 25(OH)D 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,[6] 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.[8]

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.[6,8]

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 hormone[28-32] and maximize calcium absorption,[33,34] experts generally agree that levels lower than 20 ng/mL are suboptimal for skeletal health. However, there is not general consensus about whether goal 25(OH)D levels should be higher than 20 ng/mL to protect the skeleton. The 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

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.[42] Of note, the one study in the 2007 Ottawa EPC review that did not find an association between 25(OH)D level and fall risk was conducted among community-dwelling women.[43] A recent 2014 umbrella analysis of systematic reviews and meta-analysis stated that 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.[8]

Cardiovascular Disease

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

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

These associations may differ by race/ethnicity; in a recent study, lower 25(OH)D 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.[48] Similarly, a recent cohort study did not find that 25(OH)D levels were associated with stroke risk in blacks.[49]

Diabetes

A 2014 umbrella analysis of systematic reviews and meta-analyses concluded that the evidence was suggestive for an association between 25(OH)D level and diabetes risk.[8] 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.[50] 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. [51-58]

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.[6,8] In two prospective studies,

optimal 25(OH)D levels were between 21 and 34 ng/mL.[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.[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.[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.[62] However, the association was not seen in older American men.[63]

Functional Status

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

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

In the United States, the main dietary sources of vitamin D are fortified foods such as milk, milk products, and cereals, as well as supplements; naturally occurring foods that contain vitamin D include fatty fish, egg yolk, and mushrooms. In large (>750 persons) population-based cross-sectional studies in predominantly American populations,[1-4] low dietary vitamin D intake and/or lack of vitamin D supplements are associated with a 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 sunscreen[9] and/or subjects who use sunscreen being in the sun for extended periods.[10]

Increased skin pigmentation reduces the skin's ability to produce vitamin D in response to UVB.[10] When total 25(OH)D levels are used to define deficiency, blacks have a 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.[2] 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]

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]

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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] two[9,10] of three studies found less decline at the femoral neck and one[9] of two[9,10] found less decline at the trochanter while the other did not.[8] No study found that vitamin D treatment 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 D_3 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] In a recent

2014 meta-analysis of eight studies with populations whose mean 25(OH)D level was less than 20 ng/mL, there was little evidence of an overall benefit of vitamin D supplementation on bone density.[14]

Physical Functioning/Balance

We reviewed four studies that evaluated the effect of vitamin D treatment on strength[15-18] and one study that examined balance.[19] Among elderly women, 400 to 1,800 IU per day of vitamin D did not improve hand strength,[15,17] leg strength,[15] or balance[19] compared with placebo. In two studies of 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.[16,18] 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.[20]

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Appendix B1. Search Strategies

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

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

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

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

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

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

Appendix B1. Search Strategies

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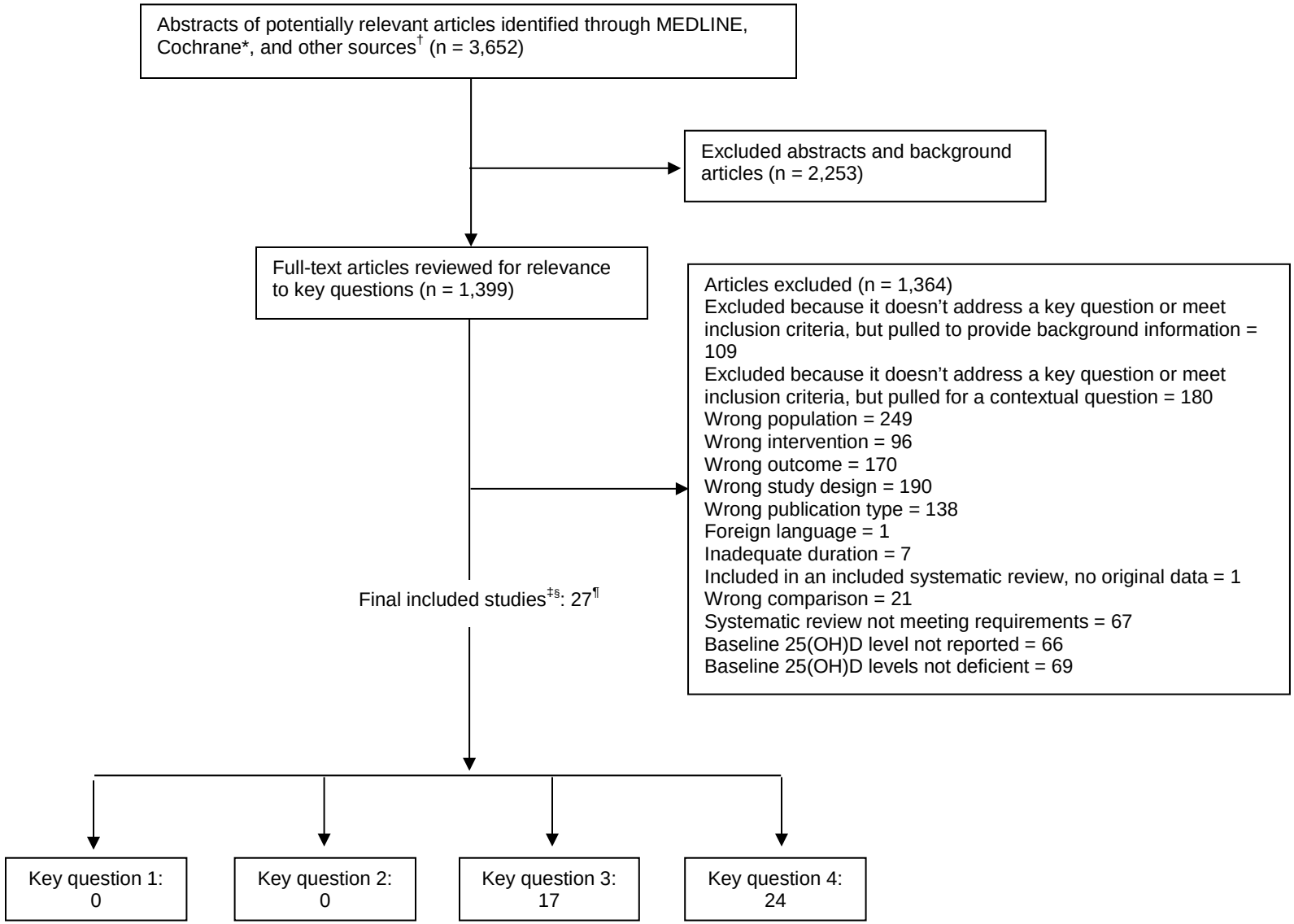
1 ((risk$ or presence or prevalence or danger$ or complicat$ or morbid$ or comorbid$ or mortal$) adj7 ((((low or lower or circulat$ or blood or hematolog$) adj3 (level$ or amount$)) or insuffic$ or defic$ or status or depriv$) adj5 (vitamin d or vitamin d3 or Cholecalciferol$ or Hydroxycholecalciferol$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

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

Appendix B2. Inclusion and Exclusion Criteria

	Include	Exclude
Population	**KQs 1, 3:** Nonpregnant adults age ≥18 years who are generally healthy. Study participants are either: • Unselected or low-risk, or • 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 **KQ 2:** Nonpregnant adults age ≥18 years who are generally healthy. Study participants are either: • Unselected or low-risk, or • Selected for increased risk for vitamin D deficiency **KQ 4:** Nonpregnant adults age ≥18 years who are generally healthy with vitamin D deficiency. Study participants are either: • Unselected or low-risk, or • Selected for increased risk for vitamin D deficiency	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
Interventions	Vitamin D_2 or D_3 (with or without calcium); food-based interventions if vitamin D dose is quantified and doses differ between comparison groups	Nonoral routes of vitamin D delivery; dietary intake (unless a food-based intervention, as described under inclusion criteria); ultraviolet light exposure; multivitamins
Comparators	**KQs 1, 2:** Screening **KQs 3, 4:** Placebo, no treatment, usual care	**KQs 1, 2:** No screening **KQs 3, 4:** Different dosages of vitamin D
Outcomes	**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) **KQs 2, 4:** Mortality; renal outcomes (e.g., kidney stones); soft tissue calcification; adverse events (e.g., gastrointestinal symptoms)	**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 <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 **KQs 2, 4:** None
Settings	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	Studies performed in countries with populations not similar to the United States; studies conducted in schools or work sites, unless primary care–feasible
Timing	**KQs 1, 3:** ≥8 weeks **KQs 2, 4:** Any duration	**KQs 1, 3:** <8 weeks **KQs 2, 4:** None
Study types and designs	**KQs 1, 3:** Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials **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	**KQs 1, 3:** Nonsystematic reviews, letters to the editor, cohort or case-control studies, noncomparative studies, and comparative efficacy trials; reviews not in English **KQs 2, 4:** Nonsystematic reviews, letters to the editor, noncomparative studies, and comparative efficacy trials; reviews not in English

Appendix B3. Literature Flow Diagram



* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Identified from reference lists, hand searching, 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

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

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

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

Arem H, Weinstein SJ, Horst RL, et al. Serum 25-hydroxyvitamin D and risk of oropharynx and larynx cancers in Finnish men. *Cancer Epidemiol Biomarkers Prev.* 2011;20(6):1178-1184
Exclusion code: 3

Bergman GJD, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: A meta-analysis. *Curr Med Res Opin.* 2010;26(5):1193-1201
Exclusion code: 13

Bjorkhem I, Holmberg I. Mass Fragmentography of 25 hydroxyvitamin D3. *Quantitative mass spectrometry in life sciences II : proceedings of the second international symposium held at the State University of Ghent, June 13-16, 1978 / editors, A. P. de Leenheer, R. R. Roncucci, C. van Peteghem.* 1978
Exclusion code: 2

Björkhem I, Holmberg I. [45] Mass fragmentographic assay of 25-hydroxyvitamin D3. In: Donald B. McCormick LDW, ed. *Methods in Enzymology.* Vol Volume 67: Academic Press; 1980:385-393
Exclusion code:Exclusion code: 2

Buttigliero C, Monagheddu C, Petroni P, et al. Prognostic role of vitamin d status and efficacy of vitamin D supplementation in cancer patients: a systematic review. *Oncologist.* 2011;16(9):1215-1227
Exclusion code: 4

Carter GD. Accuracy of 25-hydroxyvitamin D assays: confronting the issues. *Curr Drug Targets.* 2011;12(1):19-28
Exclusion code: 2

Cranney A, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *Am J Clin Nutr.* 2008;88(2):513S-519S
Exclusion code: 13

de Boer IH, Levin G, Robinson-Cohen C, et al. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study.[Summary for patients in Ann Intern Med. 2012 May 1;156(9):I36; PMID: 22547485]. *Ann Intern Med.* 2012;156(9):627-634
Exclusion code: 3

De Souto Barreto P, Lapeyre-Mestre M, Mathieu C, et al. A multicentric individually-tailored controlled trial of education and professional support to nursing home staff: Research protocol and baseline data of the IQUARE study. *J Nutr Health Aging.* 2013;17(2):173-178
Exclusion code: 5

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

Donald IP, Pitt K, Armstrong E, Shuttleworth H. Preventing falls on an elderly care rehabilitation ward. *Clin Rehabil.* 2000;14(2):178-185
Exclusion code: 5

Ensrud KE, Blackwell TL, Cauley JA, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc.* 2011;59(1):101-106
Exclusion code: 3

Fang F, Kasperzyk JL, Shui I, et al. Prediagnostic plasma vitamin D metabolites and mortality among patients with prostate cancer. *PLoS ONE [Electronic Resource]*. 2011;6(4):e18625
Exclusion code: 3

Forouhi NG, Ye Z, Rickard AP, et al. Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: Results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of Prospective studies. *Diabetologia.* 2012;55(8):2173-2182
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

Ganji V, Milone C, Cody MM, McCarty F, Wang YT. Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. *Int Arch Med.* 2010;3:29
Exclusion code: 7

Grant WB, Tuohimaa P. Geographic variation of prostate cancer mortality rates in the United States: Implications for prostate cancer risk related to vitamin D [3] (multiple letters). *Int J Cancer.* 2004;111(3):470-472
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

Healey F, Monro A, Cockram A, Adams V, Heseltine D. Using targeted risk factor reduction to prevent falls in older in-patients: a randomised controlled trial. *Age Ageing.* 2004;33(4):390-395
Exclusion code: 5

Hojskov CS, Heickendorff L, Moller HJ. High-throughput liquid-liquid extraction and LCMSMS assay for determination of circulating 25(OH) vitamin D3 and D2 in the routine clinical laboratory. *Clin Chim Acta.* 2010;411(1-2):114-116
Exclusion code: 2

Holick MF. Evidence-based D-bate on health benefits of vitamin D revisited. *Dermato-Endocrinology.* 2012;4(2):183-190
Exclusion code: 8

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

Lai JKC, Lucas RM, Clements MS, Roddam AW, Banks E. Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: A systematic review and meta-analysis of randomised controlled trials and observational studies. *BMC Public Health.* 2010;10
Exclusion code: 13

LeBlanc E, Chou R, Zakher B, Daeges M, Pappas M. Screening for Vitamin D Deficiency: Systematic Review for the U.S. Preventive Servies Task Force Recommendation [in press]. Rockville (MD)2014Exclusion code: 2

Lee DM, Tajar A, O'Neill TW, et al. Lower vitamin D levels are associated with depression among community-dwelling European men. *J Psychopharmacol.* 2011;25(10):1320-1328
Exclusion code: 7

Lensmeyer GL, Wiebe DA, Binkley N, Drezner MK. HPLC method for 25-hydroxyvitamin D measurement: comparison with contemporary assays. *Clin Chem.* 2006;52(6):1120-1126
Exclusion code: 2

Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal

cancer: A systematic review of prospective studies. *J Clin Oncol.* 2011;29(28):3775-3782
Exclusion code: 3

Maddock J, Berry DJ, Geoffroy MC, Power C, Hyppönen E. Vitamin D and common mental disorders in mid-life: Cross-sectional and prospective findings. *Clin Nutr.* 2013;32(5):758-764
Exclusion code: 3

Maunsell Z, Wright DJ, Rainbow SJ. Routine isotope-dilution liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of the 25-hydroxy metabolites of vitamins D2 and D3. *Clin Chem.* 2005;51(9):1683-1690
Exclusion code: 2

Mayo NE, Gloutney L, Levy AR. A randomized trial of identification bracelets to prevent falls among patients in a rehabilitation hospital. *Arch Phys Med Rehabil.* 1994;75(12):1302-1308
Exclusion code: 5

Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr.* 2011;65(9):1005-1015
Exclusion code: 3

Mora JR, Iwata M, Von Andrian UH. Vitamin effects on the immune system: Vitamins A and D take centre stage. *Nature Reviews Immunology.* 2008;8(9):685-698
Exclusion code: 13

Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2011;59(12):2291-2300
Exclusion code: 13

Nanri A, Mizoue T, Matsushita Y, et al. Association between serum 25-hydroxyvitamin D and depressive symptoms in Japanese: analysis by survey season. *Eur J Clin Nutr.* 2009;63(12):1444-1447
Exclusion code: 7

Norman PE, Powell JT. Vitamin D, shedding light on the development of disease in peripheral arteries. *Arterioscler Thromb Vasc Biol.* 2005;25(1):39-46
Exclusion code: 7

Parviainen MT, Savolainen KE, Korhonen PH, Alhava EM, Visakorpi JK. An improved method for routine determination of vitamin D and its hydroxylated metabolites in serum from children and adults. *Clin Chim Acta.* 1981;114(2-3):233-247
Exclusion code: 2

Pilz S, Dobnig H, Tomaschitz A, et al. Low 25-hydroxyvitamin D is associated with increased mortality in female nursing home residents. *J Clin Endocrinol Metab.* 2012;97(4):E653-E657
Exclusion code: 3

Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D status and mortality risk in CKD: A meta-analysis of prospective studies. *Am J Kidney Dis.* 2011;58(3):374-382
Exclusion code: 4

Pilz S, Tomaschitz A, März W, et al. Vitamin D, cardiovascular disease and mortality. *Clin Endocrinol.* 2011;75(5):575-584
Exclusion code: 13

Puts MTE, Visser M, Twisk JWR, Deeg DJH, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol.* 2005;63(4):403-411
Exclusion code: 3

Reid IR, Bolland MJ. Role of vitamin D deficiency in cardiovascular disease. *Heart.* 2012;98(8):609-614
Exclusion code: 13
Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. *Osteoporos Int.* 2008;19(8):1119-1123
Exclusion code: 7

Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet.* 2014;383(9912):146-155
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

Sattar N, Welsh P, Panarelli M, Forouhi NG. Increasing requests for vitamin D measurement: costly, confusing, and without credibility. *Lancet.* 2012;379(9811):95-96
Exclusion code: 8

Sawka AM, Ismaila N, Cranney A, et al. A scoping review of strategies for the prevention of hip fracture in elderly nursing home residents. *PLoS One.* 2010;5(3)
Exclusion code: 13

Appendix B4. List of Excluded Studies

Schaller F, Sidelnikov E, Theiler R, et al. Mild to moderate cognitive impairment is a major risk factor for mortality and nursing home admission in the first year after hip fracture. *Bone.* 2012;51(3):347-352
Exclusion code: 5

Schwendimann R, Milisen K, Buhler H, De Geest S. Fall prevention in a Swiss acute care hospital setting Reducing multiple falls. *J Gerontol Nurs.* 2006;32(3):13-22
Exclusion code: 5

Shao T, Klein P, Grossbarda ML. Vitamin D and breast cancer. *Oncologist.* 2012;17(1):36-45
Exclusion code: 13

Song Y, Wang L, Pittas AG, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A meta-analysis of prospective studies. *Diabetes Care.* 2013;36(5):1422-1428
Exclusion code: 3

Szulc P, Duboeuf F, Marchand F, Delmas PD. Hormonal and lifestyle determinants of appendicular skeletal muscle mass in men: the MINOS study. *Am J Clin Nutr.* 2004;80(2):496-503
Exclusion code: 7
Tideiksaar R, Feiner CF, Maby J. Falls prevention: the efficacy of a bed alarm system in an acute-care setting. *Mt Sinai J Med.* 1993;60(6):522-527
Exclusion code: 5

Vassallo M, Vignaraja R, Sharma JC, et al. The effect of changing practice on fall prevention in a rehabilitative hospital: the Hospital Injury Prevention Study. *J Am Geriatr Soc.* 2004;52(3):335-339
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

Wolpin BM, Ng K, Bao Y, et al. Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev.* 2012;21(1):82-91
Exclusion code: 3

Yao SG, Fine JB. A review of vitamin D as it relates to periodontal disease. *Compendium of continuing education in dentistry (Jamesburg, N.J. : 1995).* 2012;33(3):166-171; quiz 172, 182
Exclusion code: 8

Zhao G, Ford ES, Li C. Associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with surrogate markers of insulin resistance among U.S. adults without physician-diagnosed diabetes: NHANES, 2003-2006. *Diabetes Care.* 2010;33(2):344-347
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

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

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

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

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

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

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

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

Appendix B4. List of Excluded Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

clothing style on bone mineral density among post menopausal women in Morocco: a case-control study. *BMC Public Health.* 2006;6:135
Exclusion code: 5

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

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

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

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

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

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

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

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

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

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

American Society for Clinical Pathology. Choosing Wisely. Chicago, IL2012Exclusion code: 2

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

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

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

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

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

Anderson F, Smith H, Raphael H, al. e. Effect of annual intramuscular vitamin D3 supplementation on fracture risk in 9440 community-living older people: the Wessex fracture prevention trial. [Abstract]. *J Bone Miner Res.* 2004;19(S1):S2-S58
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

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

Anderson LN, Cotterchio M, Vieth R, Knight JA. Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women. *Am J Clin Nutr.* 2010;91(6):1699-1707
Exclusion code: 5

Anglin RES, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *Br J Psychiatry.* 2013;202:100-107
Exclusion code: 13

Annweiler C, Allali G, Allain P, et al. Vitamin D and cognitive performance in adults: a systematic review. *Eur J Neurol.* 2009;16(10):1083-1089
Exclusion code: 7

Annweiler C, Montero-Odasso M, Hachinski V, Seshadri S, Bartha R, Beauchet O. Vitamin D concentration and lateral cerebral ventricle volume in older adults. *Mol Nutr Food Res.* 2013;57(2):267-276
Exclusion code: 7

Annweiler C, Schott AM, Berrut G, Fantino B, Beauchet O. Vitamin D-related changes in physical performance: a systematic review. *J Nurt Health Aging.* 2009;13(10):893-898
Exclusion code: 13

Annweiler C, Schott AM, Montero-Odasso M, et al. Cross-sectional association between serum vitamin D concentration and walking speed measured at usual and fast pace among older women: the EPIDOS study. *J Bone Miner Res.* 2010;25(8):1858-1866
Exclusion code: 7

Arden NK, Crozier S, Smith H, et al. Knee pain, knee osteoarthritis, and the risk of fracture. *Arthritis Rheum.* 2006;55(4):610-615
Exclusion code: 5

Aregbesola A, Voutilainen S, Nurmi T, Virtanen JK, Ronkainen K, Tuomainen T-P. Serum 25-hydroxyvitamin D3 and the risk of pneumonia in an ageing general population. *J Epidemiol Community Health.* 2013;67(6):533-536
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

Arthur RS, Piraino B, Candib D, et al. Effect of low-dose calcitriol and calcium therapy on bone histomorphometry and urinary calcium excretion in osteopenic women. *Miner Electrolyte Metab.* 1990;16(6):385-390
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

Autier P, Gandini S. Vitamin D supplementation and total mortality: A meta-analysis of randomized controlled trials. *Arch Intern Med.* 2007;167(16):1730-1737
Exclusion code: 13

Avenell A, Cook JA, Maclennan GS, Macpherson GC. Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing.* 2007;36(5):574-577
Exclusion code: 14

Avenell A, Cook JA, MacLennan GS, McPherson GC, group Rt. Vitamin D supplementation and type 2 diabetes: a substudy of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing.* 2009;38(5):606-609
Exclusion code: 14

Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev.* 2009(4)
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

Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee MA. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clin Trials.* 2004;1(6):490-498
Exclusion code: 6

Appendix B4. List of Excluded Studies

Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab.* 2012;97(2):614-622
Exclusion code: 14

Avenell A, Mak CSJ, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev.* 2014(4)
Exclusion code: 13

Bacon CJ, Gamble GD, Horne AM, Scott MA, Reid IR. High-dose oral vitamin D3 supplementation in the elderly. *Osteoporos Int.* 2009;20(8):1407-1415
Exclusion code: 12

Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int.* 1998;8(3):255-260
Exclusion code: 14

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

Bailey BA, Manning T, Peiris AN. The impact of living in rural and urban areas: vitamin D and medical costs in veterans. *J Rural Health.* 2012;28(4):356-363
Exclusion code: 6

Bair TL, May HT, Horne BD, et al. Abstract 1147: Vitamin D Deficiency is Strongly Associated With Incident Death and Cardiovascular Disease in a General Healthcare Population. *American Heart Association 2009 Annual Meeting Abstract 1147 (Circulation).* 2009;120:S455
Exclusion code: 8

Baker MR, McDonnell H, Peacock M, Nordin BEC. Plasma 25-hydroxy vitamin D concentrations in patients with fractures of the femoral neck. *Br Med J.* 1979;1(6163):589
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

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

Barbour KE, Houston DK, Cummings SR, et al. Calciotropic hormones and the risk of hip and nonspine fractures in older adults: The health ABC study. *J Bone Miner Res.* 2012;27(5):1177-1185
Exclusion code: 3

Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporos Int.* 1998;8(3):222-230
Exclusion code: 12

Barnes MS, Horigan G, Cashman KD, et al. Maintenance of wintertime vitamin D status with cholecalciferol supplementation is not associated with alterations in serum cytokine concentrations among apparently healthy younger or older adults. *J Nutr.* 2011;141(3):476-481
Exclusion code: 6

Barnes MS, Robson PJ, Bonham MP, Strain JJ, Wallace JMW. Effect of vitamin D supplementation on vitamin D status and bone turnover markers in young adults. *Eur J Clin Nutr.* 2006;60(6):727-733
Exclusion code: 15

Barnett CM, Nielson CM, Shannon J, et al. Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men. *Cancer Causes and Control.* 2010;21(8):1297-1303
Exclusion code: 3

Baron JA, Beach M, Wallace K, et al. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. *Cancer Epidemiol Biomarkers Prev.* 2005;14(3):586-589
Exclusion code: 5

Barrett-Connor E, Laughlin GA, Li H, et al. The association of concurrent vitamin D and sex hormone deficiency with bone loss and fracture risk in older men: The osteoporotic fractures in men (MrOS) study. *J Bone Miner Res.* 2012;27(11):2306-2313
Exclusion code: 3

Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. *Breastfeed Med.* 2006;1(1):27-35

Appendix B4. List of Excluded Studies

Exclusion code: 4

Bates CJ, Hamer M, Mishra GD. A study of relationships between bone-related vitamins and minerals, related risk markers, and subsequent mortality in older British people: the National Diet and Nutrition Survey of People Aged 65 Years and Over. *Osteoporos Int.* 2012;23(2):457-466
Exclusion code: 14

Battault S, Whiting SJ, Peltier SL, Sadrin S, Gerber G, Maixent JM. Vitamin D metabolism, functions and needs: from science to health claims. *Eur J Nutr.* 2013;52(2):429-441
Exclusion code: 7

Becker C, Kron M, Lindemann U, et al. Effectiveness of a multifaceted intervention on falls in nursing home residents. *J Am Geriatr Soc.* 2003;51(3):306-313
Exclusion code: 5

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50(4):1088-1101
Exclusion code: 6

Beilfuss J, Berg V, Sneve M, Jorde R, Kamycheva E. Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects. *Cytokine.* 2012;60(3):870-874
Exclusion code: 15

Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics.* 2011;127(6):e1513-e1520
Exclusion code: 4

Bell NH. 25-Hydroxyvitamin D3 reverses alteration of the vitamin D-endocrine system in blacks. *Am J Med.* 1995;99(6):597-599
Exclusion code: 6

Bener A, El Ayoubi HR. The role of vitamin D deficiency and osteoporosis in breast cancer. *Int J Rheum Dis.* 2012;15(6):554-561
Exclusion code: 7

Berggren M, Stenvall M, Olofsson B, Gustafson Y. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-year follow-up. *Osteoporos Int.* 2008;19(6):801-809
Exclusion code: 4

Bergink AP, Uitterlinden AG, Van Leeuwen JPTM, et al. Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: The Rotterdam Study. *JCR.* 2009;15(5):230-237
Exclusion code: 3

Berlin T, Bjorkhem I. Lack of effects of an increased pool of 25-hydroxyvitamin D3 on urinary excretion of calcium in healthy subjects. *Contrib Nephrol.* 1987;58:143-147
Exclusion code: 6

Berry DJ, Hesketh K, Power C, Hypponen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr.* 2011;106(9):1433-1440
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

Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2005;14(8):1991-1997
Exclusion code: 3

Bertone-Johnson ER, Powers SI, Spangler L, et al. Vitamin D supplementation and depression in the women's health initiative calcium and vitamin D trial. *Am J Epidemiol.* 2012;176(1):1-13
Exclusion code: 14

Bhan A, Rao A, Rao D. Osteomalacia as a result of vitamin D deficiency. *Endocrinol Metab Clin North Am.* 2010;39(2):321
Exclusion code: 2

Biancuzzo RM, Clarke N, Reitz RE, Travison TG, Holick MF. Serum concentrations of 1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 in response to vitamin D2 and vitamin D3 supplementation. *J Clin Endocrinol Metab.* 2013;98(3):973-979
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

Biesalski HK, Aggett PJ, Anton R, et al. 26th Hohenheim Consensus Conference, September 11, 2010 Scientific substantiation of health claims: evidence-based nutrition. *Nutrition.* 2011;27(10 Suppl):S1-20
Exclusion code: 8

Bilinski K, Boyages J. Association between 25-hydroxyvitamin D concentration and breast cancer risk in an Australian population: an observational case-control study. *Breast Cancer Res Treat.* 2013;137(2):599-607
Exclusion code: 7

Binet A, Kooh SW. Persistence of vitamin D-deficiency rickets in Toronto in the 1990s. *Can J Public Health.* 1996;87(4):227-230
Exclusion code: 4

Bischoff-Ferarri 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

Bischoff-Ferrari H. Health effects of vitamin D. *Dermatol Ther.* 2010;23(1):23-30
Exclusion code: 7

Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Adv Exp Med Biol.* 2008;624:55-71
Exclusion code: 8

Bischoff-Ferrari HA. Relevance of vitamin D in muscle health. *Rev Endocr Metab Disord.* 2012;13(1):71-77
Exclusion code: 8

Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. *J Bone Miner Res.* 2004;19(2):265-269
Exclusion code: 4

Bischoff-Ferrari HA, Conzelmann M, Stahelin HB, et al. Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? *Osteoporos Int.* 2006;17(5):656-663
Exclusion code: 3

Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr.* 2007;86(6):1780-1790
Exclusion code: 5

Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Arch Intern Med.* 2010;170(9):813-820
Exclusion code: 4

Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *Br Med J (Clin Res Ed).* 2009;339
Exclusion code: 13

Bischoff-Ferrari HA, Dawson-Hughes B, Stocklin E, et al. Oral supplementation with 25(OH)D3 versus vitamin D3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. *J Bone Miner Res.* 2012;27(1):160-169
Exclusion code: 12

Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. *JAMA.* 2004;291(16):1999-2006
Exclusion code: 13

Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: A population-based study of younger and older adults. *Am J Med.* 2004;116(9):634-639
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

Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr.* 2006;84(1):18-28
Exclusion code: 2

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Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *J Bone Miner Res.* 2009;24(5):935-942
Exclusion code: 7

Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med.* 2006;166(4):424-430
Exclusion code: 15

Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. *Osteoporos Int.* 2010;21(7):1121-1132
Exclusion code: 7

Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med.* 2012;367(1):40-49
Exclusion code: 13

Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA.* 2005;293(18):2257-2264
Exclusion code: 13

Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: A meta-analysis of randomized controlled trials. *Arch Intern Med.* 2009;169(6):551-561
Exclusion code: 13

Bischoff-Ferrari HA, Zhang Y, Kiel DP, Felson DT. Positive association between serum 25-hydroxyvitamin D level and bone density in osteoarthritis. *Arthritis Rheum.* 2005;53(6):821-826
Exclusion code: 4

Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev.* 2011(8)
Exclusion code: 13

Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev.* 2014(1)
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

Bjorkman M, Sorva A, Tilvis R. Vitamin D supplementation has no major effect on pain or pain behavior in bedridden geriatric patients with advanced dementia. *Aging Clin Exp Res.* 2008;20(4):316-321
Exclusion code: 6

Bjorkman MP, Sorva AJ, Tilvis RS. C-reactive protein and fibrinogen of bedridden older patients in a six-month vitamin D supplementation trial. *J Nutr Health Aging.* 2009;13(5):435-439
Exclusion code: 6

Blicher TM, Jorgensen HL, Schwarz P, Wulf HC. Low levels of vitamin D are associated with increased mortality in patients attending a university hospital in Denmark. *Scand J Clin Lab Invest.* 2013;73(1):24-28
Exclusion code: 4

Blum M, Dolnikowski G, Seyoum E, et al. Vitamin D(3) in fat tissue. *Endocrine.* 2008;33(1):90-94
Exclusion code: 5

Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab.* 2007;92(9):3517-3522
Exclusion code: 4

Bodnar LM, Catov JM, Zmuda JM, et al. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *J Nutr.* 2010;140(5):999-1006
Exclusion code: 4

Bodnar LM, Krohn MA, Simhan HN. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J Nutr.* 2009;139(6):1157-1161
Exclusion code: 4

Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr.* 2007;137(2):447-452
Exclusion code: 4

Appendix B4. List of Excluded Studies

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

Boland R. Role of vitamin D in skeletal muscle function. *Endocr Rev.* 1986;7(4):434-448
Exclusion code: 8

Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ.* 2010;341:c3691
Exclusion code: 5

Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ.* 2008;336(7638):262-266
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

Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr.* 2011;94(4):1144-1149
Exclusion code: 14

Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol.* 2014
Exclusion code: 2

Bonjour JP, Benoit V, Pourchaire O, Rousseau B, Souberbielle JC. Nutritional approach for inhibiting bone resorption in institutionalized elderly women with vitamin D insufficiency and high prevalence of fracture. *J Nurt Health Aging.* 2011;15(5):404-409
Exclusion code: 10

Boonen S, Broos P, Verbeke G, et al. Calciotropic hormones and markers of bone remodeling in age-related (type II) femoral neck osteoporosis: alterations consistent with secondary hyperparathyroidism-induced bone resorption. *J Gerontol A Biol Sci Med Sci.* 1997;52(5):M286-293
Exclusion code: 7

Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab.* 2007;92(4):1415-1423
Exclusion code: 14

Boonen S, Mohan S, Dequeker J, et al. Down-regulation of the serum stimulatory components of the insulin-like growth factor (IGF) system (IGF-I, IGF-II, IGF binding protein [BP]-3, and IGFBP-5) in age-related (type II) femoral neck osteoporosis. *J Bone Miner Res.* 1999;14(12):2150-2158
Exclusion code: 6

Bougle D, Sabatier JP, Bureau F, et al. Relationship between bone mineralization and aluminium in the healthy infant. *Eur J Clin Nutr.* 1998;52(6):431-435
Exclusion code: 4

Bouillon R, Maes C, Verlinden L, Carmeliet G, Verstuyf A. Vitamin D and Bone In: Orwoll E, Bilezikian JP, Vanderschueren D, eds. *Osteoporosis in Men: The Effects of Gender on Skeletal Health* 2nd ed. San Diego Academic Press; 2010:243-253
Exclusion code:Exclusion code: 8

Bouillon R, Van Schoor NM, Gielen E, et al. Optimal vitamin d status: a critical analysis on the basis of evidence-based medicine. *J Clin Endocrinol Metab.* 2013;98(8):E1283-1304
Exclusion code: 7

Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. *J Am Geriatr Soc.* 2008;56(3):454-461
Exclusion code: 4

Braddy KK, Imam SN, Palla KR, Lee TA. Vitamin d deficiency/insufficiency practice patterns in a veterans health administration long-term care population: a retrospective analysis. *J Am Med Dir Assoc.* 2009;10(9):653-657
Exclusion code: 2

Brändstedt J, Almquist M, Manjer J, Malm J. Vitamin D, PTH, and calcium and the risk of prostate

cancer: A prospective nested case-control study. *Cancer Causes and Control.* 2012;23(8):1377-1385
Exclusion code: 3

Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). *Cancer Causes Control.* 1995;6(3):235-239
Exclusion code: 3

Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW. Colon cancer and serum vitamin D metabolite levels 10-17 years prior to diagnosis. *Am J Epidemiol.* 1995;142(6):608-611
Exclusion code: 3

Braverman AS. Evidence that high calcium and vitamin D intake decrease the risk of breast cancer in premenopausal women: implications for breast cancer prevention and screening. *South Med J.* 2007;100(11):1061-1062
Exclusion code: 8

Brazerol WF, McPhee AJ, Mimouni F, Specker BL, Tsang RC. Serial ultraviolet B exposure and serum 25 hydroxyvitamin D response in young adult American blacks and whites: no racial differences. *J Am Coll Nutr.* 1988;7(2):111-118
Exclusion code: 2

Brazier M, Kamel S, Lorget F, et al. Biological effects of supplementation with vitamin D and calcium in postmenopausal women with low bone mass receiving alendronate. *Clin Drug Invest.* 2002;22(12):849-857
Exclusion code: 4

Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med.* 2009;179(9):765-771
Exclusion code: 4

Breitling LP, Perna L, Muller H, Raum E, Kliegel M, Brenner H. Vitamin D and cognitive functioning in the elderly population in Germany. *Exp Gerontol.* 2012;47(1):122-127
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

Brock K, Huang WY, Fraser DR, et al. Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. *J Steriod Biochem Mol Biol.* 2010;121(1-2):462-466
Exclusion code: 3

Brodin E, Lerstad G, Grimnes G, et al. Serum levels of vitamin D are not associated with future risk of venous thromboembolism. The Tromso Study. *Thromb Haemost.* 2013;109(5):885-890
Exclusion code: 3

Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc.* 2007;55(2):234-239
Exclusion code: 15

Brondum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. *Arterioscler Thromb Vasc Biol.* 2012;32(11):2794-2802
Exclusion code: 3

Brøndum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 25-Hydroxyvitamin D and symptomatic ischemic stroke: An original study and meta-analysis. *Ann Neurol.* 2013;73(1):38-47
Exclusion code: 3

Brooke OG, Brown IR, Bone CD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *Br Med J.* 1980;280(6216):751-754
Exclusion code: 4

Brown SJ. The role of vitamin D in multiple sclerosis. *Ann Pharmacother.* 2006;40(6):1158-1161
Exclusion code: 7

Brunner EJ, Jones PJ, Friel S, Bartley M. Fish, human health and marine ecosystem health: policies in collision. *Int J Epidemiol.* 2009;38(1):93-100
Exclusion code: 8

Brunner RL, Cochrane B, Jackson RD, et al. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. *J Am Diet Assoc.* 2008;108(9):1472-1479
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

Initiative (WHI) calcium plus vitamin D randomized clinical trial. *Nutr Cancer.* 2011;63(6):827-841
Exclusion code: 14

Brunvand L, Shah SS, Bergstrom S, Haug E. Vitamin D deficiency in pregnancy is not associated with obstructed labor. A study among Pakistani women in Karachi. *Acta Obstet Gynecol Scand.* 1998;77(3):303-306
Exclusion code: 4

Bryson DJ, Nichols JS, Ford AJ, Williams SC. The incidence of vitamin D deficiency amongst patients with a femoral neck fracture: are current bone protection guidelines sufficient ? *Acta Orthop Belg.* 2013;79(4):470-473
Exclusion code: 7

Buell JS, Dawson-Hughes B, Scott TM, et al. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. *Neurology.* 2010;74(1):18-26
Exclusion code: 7

Buell JS, Scott TM, Dawson-Hughes B, et al. Vitamin D is associated with cognitive function in elders receiving home health services. *J Gerontol A Biol Sci Med Sci.* 2009;64(8):888-895
Exclusion code: 5

Bunout D, Barrera G, Leiva L, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. *Exp Gerontol.* 2006;41(8):746-752
Exclusion code: 4

Burgaz A, Orsini N, Larsson SC, Wolk A. Blood 25-hydroxyvitamin D concentration and hypertension: A meta-analysis. *Journal of Hypertension.* 2011;29(4):636-645
Exclusion code: 13

Burgi AA, Gorham ED, Garland CF, et al. High serum 25-hydroxyvitamin D is associated with a low incidence of stress fractures. *J Bone Miner Res.* 2011;26(10):2371-2377
Exclusion code: 3

Burleigh E, McColl J, Potter J. Does vitamin D stop inpatients falling? A randomised controlled trial. *Age Ageing.* 2007;36(5):507-513
Exclusion code: 4

Burris HH, Rifas-Shiman SL, Camargo CA, et al. Plasma 25-hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. *Ann Epidemiol.* 2012;22(8):581-586
Exclusion code: 4

Burton JM, Kimball S, Vieth R, et al. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology.* 2010;74(23):1852-1859
Exclusion code: 15

Byrne PM, Freaney R, McKenna MJ. Vitamin D supplementation in the elderly: review of safety and effectiveness of different regimes. *Calcif Tissue Int.* 1995;56(6):518-520
Exclusion code: 7

Caan B, Neuhouser M, Aragaki A, et al. Calcium plus vitamin D supplementation and the risk of postmenopausal weight gain. *Arch Intern Med.* 2007;167(9):893-902
Exclusion code: 14

Cadranel JL, Garabedian M, Milleron B, et al. Vitamin D metabolism by alveolar immune cells in tuberculosis: correlation with calcium metabolism and clinical manifestations. *Eur Respir J.* 1994;7(6):1103-1110
Exclusion code: 5

Camargo CA, Jr., Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr.* 2007;85(3):788-795
Exclusion code: 4

Camargo Jr CA, Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics.* 2011;127(1):e180-e187
Exclusion code: 4

Cameron ID, Gillespie LD, Robertson CM, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev.* 2012(12)
Exclusion code: 13

Cameron ID, Gillespie LD, Robertson CM, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev.* 2013(3)
Exclusion code: 13

Campbell AJ, Robertson MC, La Grow SJ, et al. Randomised controlled trial of prevention of falls in

people aged ≥75 with severe visual impairment: The VIP trial. *Br Med J.* 2005;331(7520):817-820
Exclusion code: 4

Caniggia A, Delling G, Nuti R, Lore F, Vattimo A. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D3, estradiol and placebo in post-menopausal osteoporosis. *Acta Vitaminol Enzymol.* 1984;6(2):117-128
Exclusion code: 4

Cannell JJ, Hollis BW, Zasloff M, Heaney RP. Diagnosis and treatment of vitamin D deficiency. *Expert Opin Pharmacother.* 2008;9(1):107-118
Exclusion code: 8

Carlin AM, Rao DS, Yager KM, Parikh NJ, Kapke A. Treatment of vitamin D depletion after Roux-en-Y gastric bypass: a randomized prospective clinical trial. *Surg Obes Relat Dis.* 2009;5(4):444-449
Exclusion code: 4

Carrillo AE, Flynn MG, Pinkston C, et al. Impact of vitamin D supplementation during a resistance training intervention on body composition, muscle function, and glucose tolerance in overweight and obese adults. *Clin Nutr.* 2013;32(3):375-381
Exclusion code: 5

Cashman KD, Hill TR, Lucey AJ, et al. Estimation of the dietary requirement for vitamin D in healthy adults. *Am J Clin Nutr.* 2008;88(6):1535-1542
Exclusion code: 15

Cashman KD, Wallace JM, Horigan G, et al. Estimation of the dietary requirement for vitamin D in free-living adults >=64 y of age. *Am J Clin Nutr.* 2009;89(5):1366-1374
Exclusion code: 15

Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium Plus Vitamin D Supplementation and Health Outcomes Five Years After Active Intervention Ended: The Women's Health Initiative. *J Womens Health (Larchmt).* 2013;22(11):915-929
Exclusion code: 14

Cauley JA, Danielson ME, Boudreau R, et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: the Women's Health Initiative (WHI). *J Bone Miner Res.* 2011;26(10):2378-2388
Exclusion code: 3

Cauley JA, Lacroix AZ, Wu L, et al. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. *Ann Intern Med.* 2008;149(4):242-250
Exclusion code: 2

Cauley JA, Parimi N, Ensrud KE, et al. Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. *J Bone Miner Res.* 2010;25(3):545-553
Exclusion code: 3

Cavalier E, Delanaye P, Souberbielle JC, Radermecker RP. Vitamin D and type 2 diabetes mellitus: Where do we stand? *Diabetes and Metabolism.* 2011;37(4):265-272
Exclusion code: 13

Cawthon PM, Parimi N, Barrett-Connor E, et al. Serum 25-hydroxyvitamin D, parathyroid hormone, and mortality in older men. *J Clin Endocrinol Metab.* 2010;95(10):4625-4634
Exclusion code: 3

Ceglia L. Vitamin D and skeletal muscle tissue and function. *Mol Aspects Med.* 2008;29(6):407-414
Exclusion code: 13

Ceglia L, Niramitmahapanya S, Da Silva Morais M, et al. A Randomized study on the effect of vitamin d3 supplementation on skeletal muscle morphology and vitamin d receptor concentration in older women. *J Clin Endocrinol Metab.* 2013;98(12):E1927-E1935
Exclusion code: 4

Chan R, Chan D, Woo J, et al. Not all elderly people benefit from vitamin D supplementation with respect to physical function: results from the Osteoporotic Fractures in Men Study, Hong Kong. *J Am Geriatr Soc.* 2012;60(2):290-295
Exclusion code: 4

Chandler PD, Scott JB, Drake BF, et al. Impact of vitamin D supplementation on inflammatory markers in African Americans: Results of a four-arm, randomized, placebo-controlled trial. *Cancer prevention research (Philadelphia, Pa.).* 2014;7(2):218-225
Exclusion code: 6

Chandra RK. Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. *Nutrition.* 2001;17(9):709-712
Exclusion code: 5

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

Chapuy M, Schott A, Garnero P, Hans D, Delmas P, Meunier P. Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter: E PIDOS S tudy Group. *Clin Endocrinol Metab.* 1996;81:1129-1133
Exclusion code: 2

Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Br Med J.* 1994;308(6936):1081-1082
Exclusion code: 14

Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med.* 1992;327(23):1637-1642
Exclusion code: 14

Chapuy MC, Chapuy P, Meunier PJ. Calcium and vitamin D supplements: Effects on calcium metabolism in elderly people. *Am J Clin Nutr.* 1987;46(2):324-328
Exclusion code: 6

Chen JT, Shiraki M, Hasumi K, et al. 1-alpha-Hydroxyvitamin D3 treatment decreases bone turnover and modulates calcium-regulating hormones in early postmenopausal women. *Bone.* 1997;20(6):557-562
Exclusion code: 4

Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. *Breast Cancer Res Treat.* 2010;121(2):469-477
Exclusion code: 13

Chen TC, Chimeh F, Lu Z, et al. Factors that influence the cutaneous synthesis and dietary sources of vitamin D. *Arch Biochem Biophys.* 2007;460(2):213-217
Exclusion code: 3

Cherniack EP, Florez HJ, Hollis BW, Roos BA, Troen BR, Levis S. The response of elderly veterans to daily vitamin D3 supplementation of 2,000 IU: a pilot efficacy study. *J Am Geriatr Soc.* 2011;59(2):286-290
Exclusion code: 15

Chesney RW. Vitamin D: can an upper limit be defined? *J Nutr.* 1989;119(12 Suppl):1825-1828
Exclusion code: 8

Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int.* 1994;4(5):245-252
Exclusion code: 5

Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr.* 2004;79(5):820-825
Exclusion code: 6

Chonchol M, Cigolini M, Targher G. Association between 25-hydroxyvitamin D deficiency and cardiovascular disease in type 2 diabetic patients with mild kidney dysfunction. *Nephrol Dial Transplant.* 2008;23(1):269-274
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

Chung M, Balk EM, Brendel M, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes. 2009; AHRQ Publication No. 09-E015. Rockville, MD: Agency for healthcare Research and Quality. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/vitadcal/vitadcal.pdf. Accessed January 17, 2014
Exclusion code: 2.

Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011;155(12):827-838
Exclusion code: 2

Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. *Diabetes Care.* 2006;29(3):722-724
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

Appendix B4. List of Excluded Studies

Colston KW, Lowe LC, Mansi JL, Campbell MJ. Vitamin D status and breast cancer risk. *Anticancer Res.* 2006;26(4A):2573-2580
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

Coney P, Demers LM, Dodson WC, Kunselman AR, Ladson G, Legro RS. Determination of vitamin D in relation to body mass index and race in a defined population of black and white women. *Int J Gynaecol Obstet.* 2012;119(1):21-25
Exclusion code: 3

Cooles FAH, Pratt AG, Wilson G, Isaacs JD, Ng W-F. Prevalence and diagnostic outcome relating to vitamin D deficiency in new patients presenting to an early arthritis clinic over 12 months. *Clin Rheumatol.* 2011;30(8):1137-1138
Exclusion code: 8

Cooper C, McIaren M, Wood PJ, Coulton L, Kains JA. Indices of calcium metabolism in women with hip fractures. *Bone Miner.* 1989;5(2):193-200
Exclusion code: 7

Cooper L, Clifton-Bligh PB, Nery ML, et al. Vitamin D supplementation and bone mineral density in early postmenopausal women. *Am J Clin Nutr.* 2003;77(5):1324-1329
Exclusion code: 15

Corder EH, Guess HA, Hulka BS, et al. Vitamin D and prostate cancer: a prediagnostic study with stored sera. *Cancer Epidemiol Biomarkers Prev.* 1993;2(5):467-472
Exclusion code: 3

Corless D, Dawson E, Fraser F, et al. Do vitamin D supplements improve the physical capabilities of elderly hospital patients? *Age Ageing.* 1985;14(2):76-84
Exclusion code: 4

Correia LCL, Sodre F, Garcia G, et al. Relation of severe deficiency of vitamin D to cardiovascular mortality during acute coronary syndromes. *Am J Cardiol.* 2013;111(3):324-327
Exclusion code: 4

Counts SJ, Baylink DJ, Shen FH, Sherrard DJ, Hickman RO. Vitamin D intoxication in an anephric child. *Ann Intern Med.* 1975;82(2):196-200
Exclusion code: 4

Coussement J, De Paepe L, Schwendimann R, Denhaerynck K, Dejaeger E, Milisen K. Interventions for preventing falls in acute- and chronic-care hospitals: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2008;56(1):29-36
Exclusion code: 13

Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev.* 2002;23(4):570-578
Exclusion code: 8

Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid rep/technol assess.* 2007(158):1-235
Exclusion code: 13

Crew KD, Gammon MD, Steck SE, et al. Association between plasma 25-hydroxyvitamin D and breast cancer risk. *Cancer Prev Res (Phila).* 2009;2(6):598-604
Exclusion code: 7

Cumming RG, Cummings SR, Nevitt MC, et al. Calcium intake and fracture risk: results from the study of osteoporotic fractures. *Am J Epidemiol.* 1997;145(10):926-934
Exclusion code: 5

Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. *N Engl J Med.* 1998;339(11):733-738
Exclusion code: 3

Daly RM, Nowson CA. Long-term effect of calcium-vitamin D3 fortified milk on blood pressure and serum lipid concentrations in healthy older men. *Eur J Clin Nutr.* 2009;63(8):993-1000
Exclusion code: 9

Daly RM, Petrass N, Bass S, Nowson CA. The skeletal benefits of calcium- and vitamin D3-fortified milk are sustained in older men after withdrawal of supplementation: An 18-mo follow-up study. *Am J Clin Nutr.* 2008;87(3):771-777
Exclusion code: 14

Appendix B4. List of Excluded Studies

Das G, Crocombe S, McGrath M, Berry JL, Mughal MZ. Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Arch Dis Child.* 2006;91(7):569-572
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

Davies M, Adams PH. The continuing risk of vitamin-D intoxication. *Lancet.* 1978;2(8090):621-623
Exclusion code: 7

Dawodu A, Agarwal M, Sankarankutty M, Hardy D, Kochiyil J, Badrinath P. Higher prevalence of vitamin D deficiency in mothers of rachitic than nonrachitic children. *J Pediatr.* 2005;147(1):109-111
Exclusion code: 4

Dawson-Hughes B. Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. *Am J Clin Nutr.* 2004;80(6 Suppl):1763S-1766S
Exclusion code: 8

Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med.* 1991;115(7):505-512
Exclusion code: 15

Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Eng J Med.* 1997;337(10):670-676
Exclusion code: 15

Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D. *Am J Clin Nutr.* 1995;61(5):1140-1145
Exclusion code: 12

Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int.* 2005;16(7):713-716
Exclusion code: 8

Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF Position Statement: Vitamin D Recommendations for Older Adults. *Osteoporos Int.* 2010;21(7):1151-1154
Exclusion code: 2

de Boer IH, Levin G, Robinson-Cohen C, et al. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults a cohort study. *Ann Intern Med.* 2012;156(9):627-634
Exclusion code: 3

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Exclusion code: 4

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Exclusion code: 3

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Exclusion code: 6

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Exclusion code: 4

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Exclusion code: 4

Faulkner KA, Cauley JA, Zmuda JM, et al. Higher 1,25-dihydroxyvitamin D3 concentrations associated with lower fall rates in older community-dwelling women. *Osteoporos Int.* 2006;17(9):1318-1328
Exclusion code: 3

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Exclusion code: 6

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Exclusion code: 3

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Exclusion code: 3

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Exclusion code: 8

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Exclusion code: 3

Freiberger E, de Vreede P, Schoene D, et al. Performance-based physical function in older community-dwelling persons: a systematic review of instruments. *Age Ageing.* 2012;41(6):712-721
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Exclusion code: 2

Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr.* 2008;62(1):68-77
Exclusion code: 4

Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. *J Steriod Biochem Mol Biol.* 2004;89-90(1-5):497-501
Exclusion code: 15

Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab.* 2001;86(8):3618-3628
Exclusion code: 15

Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol: A randomized controlled study. *Ann Intern Med.* 1990;113(9):649-655
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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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Gallagher JC, Yalamanchili V, Smith LM. The effect of vitamin D on calcium absorption in older women. *J Clin Endocrinol Metab.* 2012;97(10):3550-3556
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Gallagher JC, Yalamanchili V, Smith LM. The effect of vitamin D supplementation on serum 25(OH)D in thin and obese women. *J Steroid Biochem Mol Biol.* 2013;136:195-200
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

Ganji V, Zhang X, Tangpricha V. Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. *J Nutr.* 2012;142(3):498-507
Exclusion code: 2

Ganmaa D, Giovannucci E, Bloom BR, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. *Am J Clin Nutr.* 2012;96(2):391-396
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Exclusion code: 5

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Exclusion code: 8

Garland CF, Garland FC, Gorham ED. Can colon cancer incidence and death rates be reduced with calcium and vitamin D? *Am J Clin Nutr.* 1991;54(1 Suppl):193S-201S
Exclusion code: 8

Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *Am J Public Health.* 2006;96(2):252-261
Exclusion code: 8

Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: Global perspective. *Ann Epidemiol.* 2009;19(7):468-483
Exclusion code: 7

Garland CF, Gorham ED, Mohr SB, et al. Vitamin D and prevention of breast cancer: pooled analysis. *J Steriod Biochem Mol Biol.* 2007;103(3-5):708-711
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

Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med.* 1990;19(6):614-622
Exclusion code: 5

George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med.* 2012;29(8):e142-150
Exclusion code: 4

Gepner AD, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One.* 2012;7(5):e36617
Exclusion code: 15

Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. *Osteoporos Int.* 2005;16(11):1425-1431
Exclusion code: 3

Gernand AD, Simhan HN, Klebanoff MA, Bodnar LM. Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. *J Clin Endocrinol Metab.* 2013;98(1):398-404
Exclusion code: 4

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Exclusion code: 7

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Exclusion code: 4

Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1α-hydroxyvitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: A double-blind controlled study. *Bone Miner.* 1986;1(4):347-357
Exclusion code: 4

Ghose RR. Vitamin D deficiency and muscle weakness in the elderly. *N Z Med J.* 2005;118(1219):U1582
Exclusion code: 8

Gibney KB, MacGregor L, Leder K, et al. Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. *Clin Infect Dis.* 2008;46(3):443-446
Exclusion code: 7

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Exclusion code: 13

Ginde AA, Liu MC, Camargo CA, Jr. Demographic differences and trends of Vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med.* 2009;169(6):626-632
Exclusion code: 3

Ginde AA, Mansbach JM, Camargo CA, Jr. Vitamin D, respiratory infections, and asthma. *Curr Allergy Asthma Rep.* 2009;9(1):81-87
Exclusion code: 8

Ginde AA, Mansbach JM, Camargo CA, Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* 2009;169(4):384-390
Exclusion code: 7

Ginde AA, Scragg R, Schwartz RS, Camargo Jr CA. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. *J Am Geriatr Soc.* 2009;57(9):1595-1603
Exclusion code: 3

Giovannucci E. Can vitamin D reduce total mortality? *Arch Intern Med.* 2007;167(16):1709-1710
Exclusion code: 8

Giovannucci E. Strengths and limitations of current epidemiologic studies: vitamin D as a modifier of colon and prostate cancer risk. *Nutr Rev.* 2007;65(8 Pt 2):S77-79
Exclusion code: 8

Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med.* 2008;168(11):1174-1180
Exclusion code: 3

Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst.* 2006;98(7):451-459
Exclusion code: 7

Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res.* 1998;58(3):442-447
Exclusion code: 5

Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *J Bone Miner Res.* 2012;27(1):170-176
Exclusion code: 15

Glerup H, Mikkelsen K, Poulsen L, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. *Calcif Tissue Int.* 2000;66(6):419-424
Exclusion code: 2

Gloth FM, 3rd. Vitamin D. *Lancet.* 1995;345(8958):1185
Exclusion code: 8

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Exclusion code: 12

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Gloth FM, 3rd, Smith CE, Hollis BW, Tobin JD. Functional improvement with vitamin D replenishment in a cohort of frail, vitamin D-deficient older people. *J Am Geriatr Soc.* 1995;43(11):1269-1271
Exclusion code: 4

Golombick T, Diamond T. The effect of a combined oral calcium and vitamin D supplement for treating mild to moderate vitamin D deficiency in postmenopausal women. *Clin Interv Aging.* 2008;3(1):183-186
Exclusion code: 4

Gómez-Alonso C, Naves-Díaz ML, Fernández-Martín JL, Díaz-López JB, Fernández-Coto MT, Cannata-Andía JB. Vitamin D status and secondary hyperparathyroidism: The importance of 25-hydroxyvitamin D cut-off levels. *Kidney Int Suppl.* 2003;63(85):S44-S48
Exclusion code: 13

Gorai I, Chaki O, Taguchi Y, et al. Early postmenopausal bone loss is prevented by estrogen and partially by 1alpha-OH-vitamin D3: therapeutic effects of estrogen and/or 1alpha-OH-vitamin D3. *Calcif Tissue Int.* 1999;65(1):16-22
Exclusion code: 14

Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med.* 2004;158(6):531-537
Exclusion code: 4

Gordon CM, Williams AL, Feldman HA, et al. Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab.* 2008;93(7):2716-2721
Exclusion code: 4

Gordon NP, Caan BJ, Asgari MM. Variation in vitamin D supplementation among adults in a multi-race/ethnic health plan population, 2008. *Nutr J.* 2012;11:104
Exclusion code: 2

Gorham ED, Garland CF, Garland FC, et al. Vitamin D and prevention of colorectal cancer. *J Steriod Biochem Mol Biol.* 2005;97(1-2):179-194
Exclusion code: 13

Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am J Prev Med.* 2007;32(3):210-216
Exclusion code: 13

Gouni-Berthold I, Krone W, Berthold HK. Vitamin D and cardiovascular disease. *Curr Vasc Pharmacol.* 2009;7(3):414-422
Exclusion code: 7

Graafmans WC, Ooms ME, Hofstee HM, Bezemer PD, Bouter LM, Lips P. Falls in the elderly: a prospective study of risk factors and risk profiles. *Am J Epidemiol.* 1996;143(11):1129-1136
Exclusion code: 7

Grados F, Brazier M, Kamel S, et al. Effects on bone mineral density of calcium and vitamin D supplementation in elderly women with vitamin D deficiency. *Joint Bone Spine.* 2003;70(3):203-208
Exclusion code: 11

Grados F, Brazier M, Kamel S, et al. Prediction of bone mass density variation by bone remodeling markers in postmenopausal women with vitamin D insufficiency treated with calcium and vitamin D supplementation. *J Clin Endocrinol Metab.* 2003;88(11):5175-5179
Exclusion code: 3

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Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* 2005;365(9471):1621-1628
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Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer.* 2002;94(6):1867-1875
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Grant WB. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. *J Photochem Photobiol B.* 2010;101(2):130-136

Appendix B4. List of Excluded Studies

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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

Grant WB. Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyvitamin D and all-cause mortality rate. *Dermatoendocrinol.* 2012;4(2):198-202
Exclusion code: 6

Grant WB, Boucher BJ. Requirements for Vitamin D across the life span. *Biol Res Nurs.* 2011;13(2):120-133
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
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Grant WB, Giovannucci E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918-1919 influenza pandemic in the United States. *Dermatoendocrinol.* 2009;1(4):215-219
Exclusion code: 5

Grant WB, Peiris AN. Differences in vitamin D status may account for unexplained disparities in cancer survival rates between African and white Americans. *Dermatoendocrinol.* 2012;4(2):85-94
Exclusion code: 7

Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst.* 2003;95(23):1765-1771
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
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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

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Greenspan SL, Schneider DL, McClung MR, et al. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2002;136(10):742-746
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Exclusion code: 5

Grimnes G, Joakimsen R, Figenschau Y, Torjesen PA, Almas B, Jorde R. The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass--a randomized controlled 1-year trial. *Osteoporos Int.* 2012;23(1):201-211
Exclusion code: 15

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Gupta AK, Brashear MM, Johnson WD. Low vitamin D levels, prediabetes and prehypertension in healthy African American adults. *Nutr Metab Cardiovasc Dis.* 2012;22(10):877-882
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Exclusion code: 3

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Hanley DA, Cranney A, Jones G, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *CMAJ.* 2010;182(12):E610-618
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Harris S, Dawson-Hughes B. Seasonal mood changes in 250 normal women. *Psychiatry Res.* 1993;49(1):77-87
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Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr.* 1998;67(6):1232-1236
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Harris SS, Dawson-Hughes B. Plasma vitamin D and 25OHD responses of young and old men to supplementation with vitamin D3. *J Am Coll Nutr.* 2002;21(4):357-362
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
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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

Hartman TJ, Albert PS, Snyder K, et al. The association of calcium and vitamin D with risk of colorectal adenomas. *J Nutr.* 2005;135(2):252-259
Exclusion code: 7

Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ, Nottingham Neck of Femur S. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. *Age Ageing.* 2004;33(1):45-51
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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
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Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr.* 2007;85(1):6-18
Exclusion code: 7

Hatse S, Lambrechts D, Verstuyf A, et al. Vitamin D status at breast cancer diagnosis: correlation with tumor characteristics, disease outcome, and genetic determinants of vitamin D insufficiency. *Carcinogenesis.* 2012;33(7):1319-1326
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Haugen M, Brantsaeter AL, Trogstad L, et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology.* 2009;20(5):720-726
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Exclusion code: 4

He JL, Scragg RK. Vitamin D, parathyroid hormone, and blood pressure in the National Health and Nutrition Examination Surveys. *Am J Hypertens.* 2011;24(8):911-917
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Heaney R, Dowell M, Hale C, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *Am Coll Nutr.* 2003;22:142-146
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Heaney RP. Vitamin D--baseline status and effective dose. *N Engl J Med.* 2012;367(1):77-78
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Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. *J Bone Miner Res.* 2011;26(3):455-457
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Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. Vitamin D(3) is more potent than vitamin D(2) in humans. *J Clin Endocrinol Metab.* 2011;96(3):E447-452
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Heaney RP, Vieth R, Hollis BW. Vitamin D efficacy and safety. *Arch Intern Med.* 2011;171(3):266; author reply 267
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Exclusion code: 6

Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int.* 1992;51(2):105-110
Exclusion code: 5

Heikkinen A, Parviainen MT, Tuppurainen MT, Niskanen L, Komulainen MH, Saarikoski S. Effects of postmenopausal hormone replacement therapy with and without vitamin D3 on circulating levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. *Calcif Tissue Int.* 1998;62(1):26-30
Exclusion code: 6

Heikkinen AM, Tuppurainen MT, Niskanen L, Komulainen M, Penttila I, 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

Hernan MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. *Neurology.* 1999;53(8):1711-1718
Exclusion code: 5

Herndon AC, DiGuiseppi C, Johnson SL, Leiferman J, Reynolds A. Does nutritional intake differ between children with autism spectrum disorders and children with typical development? *J Autism Dev Disord.* 2009;39(2):212-222
Exclusion code: 4

Herran A, Amado JA, Garcia-Unzueta MT, Vazquez-Barquero JL, Perera L, Gonzalez-Macias J. Increased bone remodeling in first-episode major depressive disorder. *Psychosom Med.* 2000;62(6):779-782
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Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, et al. Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. *Daru.* 2012;20(1):10
Exclusion code: 15

Hiatt RA, Krieger N, Lobaugh B, Drezner MK, Vogelman JH, Orentreich N. Prediagnostic serum vitamin D and breast cancer. *J Natl Cancer Inst.* 1998;90(6):461-463
Exclusion code: 5

Hii S, Scherer S. Vitamin d deficiency and secondary hyperparathyroidism in older people with low trauma fractures. *Aust J Ageing.* 2004;23(1):45-47
Exclusion code: 7

Hill TR, Aspray TJ, Francis RM. Vitamin D and bone health outcomes in older age. *Proc Nutr Soc.* 2013;72(4):372-380
Exclusion code: 8

Hiller JE, Crowther CA, Moore VA, Willson K, Robinson JS. Calcium supplementation in pregnancy and its impact on blood pressure in children and women: follow up of a randomised controlled trial. *Aust N Z J Obstet Gynaecol.* 2007;47(2):115-121
Exclusion code: 4

Himmelstein S, Clemens TL, Rubin A, Lindsay R. Vitamin D supplementation in elderly nursing home residents increases 25(OH)D but not 1,25(OH)2D. *Am J Clin Nutr.* 1990;52(4):701-706
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Hitz MF, Jensen JE, Eskildsen PC. Bone mineral density and bone markers in patients with a recent low-energy fracture: effect of 1 y of treatment with calcium and vitamin D. *Am J Clin Nutr.* 2007;86(1):251-259
Exclusion code: 4

Hofmeyr GJ, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev.* 2006(3):CD001059
Exclusion code: 4

Hofmeyr GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of pre-eclampsia and related problems: a systematic review and commentary. *BJOG.* 2007;114(8):933-943
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Hoikka V, Alhava EM, Savolainen K, Parviainen M. Osteomalacia in fractures of the proximal femur. *Acta Orthopaedica Scandinavica.* 1982;53(2):255-260
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Holick M, Siris E, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North A merican women receiving osteoporosis therapy. *J Clin Epidemiol Metab.* 2005;90:3215-3224
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Holick MF. Vitamin D: Importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr.* 2004;79(3):362-371
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Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest.* 2006;116(8):2062-2072
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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Holick MF. Calcium plus Vitamin D and the Risk of Colorectal Cancer. *N Engl J Med.* 2006;354(21):2287-2288
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Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357(3):266-281
Exclusion code: 7

Holick MF. Vitamin D: the other steroid hormone for muscle function and strength. *Menopause.* 2009;16(6):1077-1078
Exclusion code: 8

Holick MF. Vitamin D: evolutionary, physiological and health perspectives. *Curr Drug Targets.* 2011;12(1):4-18
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

Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J Clin Endocrinol Metab.* 2012;97(4):1153-1158
Exclusion code: 8

Appendix B4. List of Excluded Studies

Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr.* 2005;135(2):317-322
Exclusion code: 8

Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res.* 2011;26(10):2341-2357
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

Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr.* 2004;79(5):717-726
Exclusion code: 4

Hollis BW, Wagner CL. Vitamin D requirements and supplementation during pregnancy. *Curr Opin Endocrinol Diabetes Obes.* 2011;18(6):371-375
Exclusion code: 4

Holmlund-Suila E, Viljakainen H, Hytinantti T, Lamberg-Allardt C, Andersson S, Mäkitie O. High-dose vitamin D intervention in infants - Effects on vitamin D status, calcium homeostasis, and bone strength. *J Clin Endocrinol Metab.* 2012;97(11):4139-4147
Exclusion code: 4

Holmoy T, Kampman MT, Smolders J. Vitamin D in multiple sclerosis: implications for assessment and treatment. *Expert Rev Neurother.* 2012;12(9):1101-1112
Exclusion code: 8

Holt PR, Arber N, Halmos B, et al. Colonic epithelial cell proliferation decreases with increasing levels of serum 25-hydroxy vitamin D. *Cancer Epidemiol Biomarkers Prev.* 2002;11(1):113-119
Exclusion code: 6

Holt PR, Bresalier RS, Ma CK, et al. Calcium plus vitamin D alters preneoplastic features of colorectal adenomas and rectal mucosa. *Cancer.* 2006;106(2):287-296
Exclusion code: 14

Holt SK, Kolb S, Fu R, Horst R, Feng Z, Stanford JL. Circulating levels of 25-hydroxyvitamin D and prostate cancer prognosis. *Cancer Epidemiology.* 2013;37(5):666-670
Exclusion code: 6

Holvik K, Ahmed LA, Forsmo S, et al. Low serum levels of 25-hydroxyvitamin D predict hip fracture in the elderly: a NOREPOS study. *J Clin Endocrinol Metab.* 2013;98(8):3341-3350
Exclusion code: 3

Hong SN, Kim JH, Choe WH, et al. Circulating vitamin D and colorectal adenoma in asymptomatic average-risk individuals who underwent first screening colonoscopy: a case-control study. *Dig Dis Sci.* 2012;57(3):753-763
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

Hopkins MH, Owen J, Ahearn T, et al. Effects of supplemental vitamin D and calcium on biomarkers of inflammation in colorectal adenoma patients: a randomized, controlled clinical trial. *Cancer Prev Res.* 2011;4(10):1645-1654
Exclusion code: 6

Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc.* 2013;88(7):720-755
Exclusion code: 13

Houston DK, Neiberg RH, Tooze JA, et al. Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: the Health ABC Study. *J Gerontol A Biol Sci Med Sci.* 2013;68(2):181-187
Exclusion code: 3

Houston DK, Tooze JA, Davis CC, et al. Serum 25-hydroxyvitamin D and physical function in older adults: the Cardiovascular Health Study All Stars. *J Am Geriatr Soc.* 2011;59(10):1793-1801
Exclusion code: 7

Houston DK, Tooze JA, Neiberg RH, et al. 25-hydroxyvitamin D status and change in physical performance and strength in older adults. *Am J Epidemiol.* 2012;176(11):1025-1034
Exclusion code: 3

Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation.* 2007;115(7):846-854
Exclusion code: 14

Hughes MR, Baylink DJ, Jones PG, Haussler MR. Radioligand receptor assay for 25-hydroxyvitamin D2/D3 and 1 alpha, 25-dihydroxyvitamin D2/D3. *J Clin Invest.* 1976;58(1):61-70
Exclusion code: 5

Huh SY, Gordon CM. Vitamin D deficiency in children and adolescents: Epidemiology, impact and treatment. *Rev Endocr metab Disord.* 2008;9(2):161-170
Exclusion code: 4

Huisman AM, White KP, Algra A, et al. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. *J Rheumatol.* 2001;28(11):2535-2539
Exclusion code: 4

Hujoel PP. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis. *Nutr Rev.* 2013;71(2):88-97
Exclusion code: 4

Hull S. Vitamin D deficiency. *Br J Gen Pract.* 2007;57(543):836-837
Exclusion code: 8

Humble MB, Gustafsson S, Bejerot S. Low serum levels of 25-hydroxyvitamin D (25-OHD) among psychiatric out-patients in Sweden: relations with season, age, ethnic origin and psychiatric diagnosis. *J Steriod Biochem Mol Biol.* 2010;121(1-2):467-470
Exclusion code: 4

Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. *Nutr Cancer.* 2009;61(1):47-69
Exclusion code: 5

Hunter D, Major P, Arden N, et al. A randomized controlled trial of vitamin D supplementation on preventing postmenopausal bone loss and modifying bone metabolism using identical twin pairs. *J Bone Miner Res.* 2000;15(11):2276-2283
Exclusion code: 4

Huntington MK, Shafer CW, Pudwill R, Boer L, Kendall J. Prevalence of vitamin D deficiency among immigrants to South Dakota. *S D Med.* 2010;63(2):51-55
Exclusion code: 6

Husemoen LLN, Skaaby T, Thuesen BH, Jorgensen T, Fenger RV, Linneberg A. Serum 25(OH)D and incident type 2 diabetes: a cohort study. *Eur J Clin Nutr.* 2012;66(12):1309-1314
Exclusion code: 3

Hutchinson MS, Grimnes G, Joakimsen RM, Figenschau Y, Jorde R. Low serum 25-hydroxyvitamin D levels are associated with increased all-cause mortality risk in a general population: the Tromso study. *Eur J Endocrinol.* 2010;162(5):935-942
Exclusion code: 7

Hypponen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes.* 2008;57(2):298-305
Exclusion code: 2

Hypponen E, Hartikainen AL, Sovio U, Jarvelin MR, Pouta A. Does vitamin D supplementation in infancy reduce the risk of pre-eclampsia? *Eur J Clin Nutr.* 2007;61(9):1136-1139
Exclusion code: 4

Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. *Lancet.* 2001;358(9292):1500-1503
Exclusion code: 4

Hypponen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr.* 2007;85(3):860-868
Exclusion code: 2

Hypponen E, Sovio U, Wjst M, et al. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann N Y Acad Sci.* 2004;1037:84-95
Exclusion code: 4

Ilahi M, Armas LAG, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Clin Nutr.* 2008;87(3):688-691
Exclusion code: 6

Inanir A, Ozoran K, Tutkak H, Mermerci B. The effects of calcitriol therapy on serum interleukin-1, interleukin-6 and tumour necrosis factor-alpha

concentrations in post-menopausal patients with osteoporosis. *J Int Med Res.* 2004;32(6):570-582
Exclusion code: 14

Inkovaara J, Gothoni G, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroid in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. *Age Ageing.* 1983;12(2):124-130
Exclusion code: 14

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

International Agency for Research on Cancer. Vitamin D and Cancer. Lyon 25 Nov 2008Exclusion code: 2

International Osteoporosis Foundation (IOF). IOF Statement of New IOM Dietary Reference Intakes for Calcium and Vitamin D. Bone Health. http://www.iofbonehealth.org/iof-statement-new-iom-dietary-reference-intakes-calcium-and-vitamin-d Accessed January 18, 2013
Exclusion code: 2

Isaia G, Giorgino R, Adami S. High prevalence of hypovitaminosis D in female type 2 diabetic population. *Diabetes Care.* 2001;24(8):1496
Exclusion code: 7

Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. *Am J Med.* 2004;117(8):549-555
Exclusion code: 4

Islam MZ, Shamim AA, Viljakainen HT, et al. Effect of vitamin D, calcium and multiple micronutrient supplementation on vitamin D and bone status in Bangladeshi premenopausal garment factory workers with hypovitaminosis D: a double-blinded, randomised, placebo-controlled 1-year intervention. *Br J Nutr.* 2010;104(2):241-247
Exclusion code: 4

Islam T, Peiris P, Copeland RJ, El Zoghby M, Peiris AN. Vitamin D: Lessons from the veterans population. *J Am Med Dir Assoc.* 2011;12(4):257-262
Exclusion code: 7

Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T, Okamura H. Prevention of preeclampsia with calcium supplementation and vitamin D3 in an antenatal protocol. *Int J Gynaecol Obstet.* 1994;47(2):115-120
Exclusion code: 4

Iuliano-Burns S, Ayton J, Hillam S, et al. Skeletal and hormonal responses to vitamin D supplementation during sunlight deprivation in Antarctic expeditioners. *Osteoporos Int.* 2012;23(10):2461-2467
Exclusion code: 12

Jablonski NG, Chaplin G. The evolution of human skin coloration. *J Hum Evol.* 2000;39(1):57-106
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Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *Qjm.* 2007;100(4):185-192
Exclusion code: 13

Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol.* 2003;13(9 Suppl):S98-106
Exclusion code: 3

Jacobs ET, Alberts DS, Benuzillo J, Hollis BW, Thompson PA, Martinez ME. Serum 25(OH)D levels, dietary intake of vitamin D, and colorectal adenoma recurrence. *J Steriod Biochem Mol Biol.* 2007;103(3-5):752-756
Exclusion code: 6

Jacobs ET, Alberts DS, Foote JA, et al. Vitamin D insufficiency in southern Arizona. *Am J Clin Nutr.* 2008;87(3):608-613
Exclusion code: 6

Jacobs ET, Giuliano AR, Martinez ME, Hollis BW, Reid ME, Marshall JR. Plasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer. *J Steriod Biochem Mol Biol.* 2004;89-90(1-5):533-537
Exclusion code: 3

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Exclusion code: 2

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Jaddou HY, Batieha AM, Khader YS, Kanaan SH, El-Khateeb MS, Ajlouni KM. Depression is associated with low levels of 25-hydroxyvitamin D among Jordanian adults: results from a national population survey. *Eur Arch Psychiatry Clin Neurosci.* 2012;262(4):321-327
Exclusion code: 4

Janet Barger-Lux M, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. *J Clin Endocrinol Metab.* 2002;87(11):4952-4956
Exclusion code: 6

Janowsky EC, Lester GE, Weinberg CR, et al. Association between low levels of 1,25-dihydroxyvitamin D and breast cancer risk. *Public Health Nutr.* 1999;2(3):283-291
Exclusion code: 7

Jassal SK, Chonchol M, Von Mhlen D, Smits G, Barrett-Connor E. Vitamin D, parathyroid hormone, and cardiovascular mortality in older adults: The rancho bernardo study. *Am J Med.* 2010;123(12):1114-1120
Exclusion code: 3

Javaid MK, Crozier SR, Harvey NC, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study.[Erratum appears in Lancet. 2006 May 6;367(9521):1486]. *Lancet.* 2006;367(9504):36-43
Exclusion code: 4

Jeans PC. Vitamin D. *J Am Med Assoc.* 1950;143(2):177-181
Exclusion code: 8

Jenab M, Ferrari P, McKay J, et al. Circulating vitamin d concentration, vitamin d receptor polymorphisms and the risk of colorectal cancer: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Eur J Cancer.* 2008;6(9):190-191
Exclusion code: 5

Jensen GF, Meinecke B, Boesen J, Transbol I. Does 1,25(OH)2D3 accelerate spinal bone loss? A controlled therapeutic trial in 70-year-old women. *Clin Orthop Relat Res.* 1985(192):215-221
Exclusion code: 14

John EM, Schwartz GG, Dreon DM, Koo J. Vitamin D and breast cancer risk: The NHANES I epidemiologic follow-up study, 1971-1975 to 1992. *Cancer Epidemiol Biomarkers Prev.* 1999;8(5):399-406
Exclusion code: 6

Johnson KR, Jobber J, Stonawski BJ. Prophylactic vitamin D in the elderly. *Age Ageing.* 1980;9(2):121-127
Exclusion code: 14

Johnson MA, Davey A, Park S, Hausman DB, Poon LW, Georgia Centenarian S. Age, race and season predict vitamin D status in African American and white octogenarians and centenarians. *J Nurt Health Aging.* 2008;12(10):690-695
Exclusion code: 7

Jorde R, Bonaa KH. Calcium from dairy products, vitamin D intake, and blood pressure: the Tromso Study. *Am J Clin Nutr.* 2000;71(6):1530-1535
Exclusion code: 5

Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. *Eur J Nutr.* 2009;48(6):349-354
Exclusion code: 15

Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med.* 2008;264(6):599-609
Exclusion code: 15

Jorde R, Sneve M, Hutchinson M, Emaus N, Figenschau Y, Grimnes G. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. *Am J Epidemiol.* 2010;171(8):903-908
Exclusion code: 7

Jorde R, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year: Original Article. *J Intern Med.* 2010;267(5):462-472
Exclusion code: 15

Jorde R, Sneve 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

Appendix B4. List of Excluded Studies

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

Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J. Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromso study. *J Neurol.* 2006;253(4):464-470
Exclusion code: 7

Judd SE, Nanes MS, Ziegler TR, Wilson PWF, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr.* 2008;87(1):136-141
Exclusion code: 7

Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. *J Am Geriatr Soc.* 2010;58(7):1299-1310
Exclusion code: 13

Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. *Autoimmun Rev.* 2006;5(2):114-117
Exclusion code: 7

Kampman MT, Steffensen LH, Mellgren SI, Jorgensen L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Mult Scler.* 2012;18(8):1144-1151
Exclusion code: 4

Kanis JA, Johnell O, Gullberg B, et al. Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. *BMJ.* 1992;305(6862):1124-1128
Exclusion code: 6

Karakas M, Thorand B, Zierer A, et al. Low levels of serum 25-hydroxyvitamin D are associated with increased risk of myocardial infarction, especially in women: Results from the MONICA/KORA Augsburg case-cohort study. *J Clin Endocrinol Metab.* 2013;98(1):272-280
Exclusion code: 3

Karhapää P, Pihlajamäki J, Pörsti I, et al. Diverse associations of 25-hydroxyvitamin D and 1,25-dihydroxy-vitamin D with dyslipidaemias. *J Intern Med.* 2010;268(6):604-610
Exclusion code: 6

Ke L, Graubard BI, Albanes D, et al. Hypertension, pulse, and other cardiovascular risk factors and vitamin D status in Finnish men. *Am J Hypertens.* 2013;26(8):951-956
Exclusion code: 3

Keane EM, Healy M, O'Moore R, Coakley D, Walsh JB. Vitamin D-fortified liquid milk: benefits for the elderly community-based population. *Calcif Tissue Int.* 1998;62(4):300-302
Exclusion code: 6

Keane EM, Rochfort A, Cox J, McGovern D, Coakley D, Walsh JB. Vitamin-D-fortified liquid milk--a highly effective method of vitamin D administration for house-bound and institutionalised elderly. *Gerontology.* 1992;38(5):280-284
Exclusion code: 6

Kearney J, Giovannucci E, Rimm EB, et al. Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am J Epidemiol.* 1996;143(9):907-917
Exclusion code: 7

Kelly JL, Friedberg JW, Calvi LM, van Wijngaarden E, Fisher SG. Vitamin D and non-Hodgkin lymphoma risk in adults: a review. *Cancer Invest.* 2009;27(9):942-951
Exclusion code: 7

Kelly JL, Friedberg JW, Calvi LM, van Wijngaarden E, Fisher SG. A case-control study of ultraviolet radiation exposure, vitamin D, and lymphoma risk in adults. *Cancer Causes Control.* 2010;21(8):1265-1275
Exclusion code: 7

Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. *J Am Geriatr Soc.* 2003;51(12):1762-1767
Exclusion code: 15

Kerse N, Butler M, Robinson E, Todd M. Fall prevention in residential care: a cluster, randomized, controlled trial. *J Am Geriatr Soc.* 2004;52(4):524-531
Exclusion code: 5

Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer.* 2005;117(1):137-144
Exclusion code: 5

Kestenbaum B, Katz R, de Boer I, et al. Vitamin D, parathyroid hormone, and cardiovascular events among older adults. *J Am Coll Cardiol.* 2011;58(14):1433-1441
Exclusion code: 3

Khadilkar AV, Sayyad MG, Sanwalka NJ, et al. Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls. *Asia Pac J Clin Nutr.* 2010;19(4):465-472
Exclusion code: 4

Khan QJ, Reddy PS, Kimler BF, et al. Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. *Breast Cancer Res Treat.* 2010;119(1):111-118
Exclusion code: 4

Khoo A-L, Koenen HJPM, Michels M, et al. High-dose vitamin D(3) supplementation is a requisite for modulation of skin-homing markers on regulatory T cells in HIV-infected patients. *AIDS Res Hum Retroviruses.* 2013;29(2):299-306
Exclusion code: 6

Kiebzak GM, Moore NL, Margolis S, Hollis B, Kevorkian CG. Vitamin D status of patients admitted to a hospital rehabilitation unit: Relationship to function and progress. *American Journal of Physical Medicine and Rehabilitation.* 2007;86(6):435-445
Exclusion code: 4

Kienreich K, Tomaschitz A, Verheyen N, et al. Vitamin d and cardiovascular disease. *Nutrients.* 2013;5(8):3005-3021
Exclusion code: 3

Kilpinen-Loisa P, Arvio M, Ilvesmaki V, Makitie O. Vitamin D status and optimal supplementation in institutionalized adults with intellectual disability. *J Intellect Disabil Res.* 2009;53(12):1014-1023
Exclusion code: 12

Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol.* 2008;102(11):1540-1544
Exclusion code: 2

Kim HW, Park CW, Shin YS, et al. Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. *Nephron Clin Pract.* 2006;102(1):c21-29
Exclusion code: 14

Kimball S, Vieth R, Dosch H-M, et al. Cholecalciferol plus calcium suppresses abnormal PBMC reactivity in patients with multiple sclerosis. *J Clin Endocrinol Metab.* 2011;96(9):2826-2834
Exclusion code: 6

Kimball SM, Ursell MR, O'Connor P, Vieth R. Safety of vitamin D3 in adults with multiple sclerosis. *Am J Clin Nutr.* 2007;86(3):645-651
Exclusion code: 15

Kinyamu HK, Gallagher JC, Balhorn KE, Petranick KM, Rafferty KA. Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes. *Am J Clin Nutr.* 1997;65(3):790-797
Exclusion code: 6

Kirii K, Mizoue T, Iso H, et al. Calcium, vitamin D and dairy intake in relation to type 2 diabetes risk in a Japanese cohort. *Diabetologia.* 2009;52(12):2542-2550
Exclusion code: 5

Kolb H, Mandrup-Poulsen T. An immune origin of type 2 diabetes? *Diabetologia.* 2005;48(6):1038-1050
Exclusion code: 6

Komulainen M, Kroger H, Tuppurainen MT, et al. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab.* 1999;84(2):546-552
Exclusion code: 14

Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas.* 1998;31(1):45-54
Exclusion code: 14

Kota SK, Jammula S, Kota SK, Tripathy PR, Panda S, Modi KD. Effect of vitamin D supplementation in

type 2 diabetes patients with pulmonary tuberculosis. *Diabetes Metab Syndr.* 2011;5(2):85-89
Exclusion code: 4

Krall EA, Dawson-Hughes B. Relation of fractional 47Ca retention to season and rates of bone loss in healthy postmenopausal women. *J Bone Miner Res.* 1991;6(12):1323-1329
Exclusion code: 6

Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet.* 1998;352(9129):709-710
Exclusion code: 5

Kreiter SR, Schwartz RP, Kirkman Jr HN, Charlton PA, Calikoglu AS, Davenport ML. Nutritional rickets in African American breast-fed infants. *J Pediatr.* 2000;137(2):153-157
Exclusion code: 4

Kristal-Boneh E, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. *Hypertension.* 1997;30(5):1289-1294
Exclusion code: 7

Kritchevsky SB, Tooze JA, Neiberg RH, et al. 25-Hydroxyvitamin D, parathyroid hormone, and mortality in black and white older adults: The health ABC study. *J Clin Endocrinol Metab.* 2012;97(11):4156-4165
Exclusion code: 3

Kruger MC, Schollum LM, Kuhn-Sherlock B, et al. The effect of a fortified milk drink on vitamin D status and bone turnover in post-menopausal women from South East Asia. *Bone.* 2010;46(3):759-767
Exclusion code: 5

Kumar A, Devi SG, Batra S, Singh C, Shukla DK. Calcium supplementation for the prevention of pre-eclampsia. *Int J Gynaecol Obstet.* 2009;104(1):32-36
Exclusion code: 4

Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. *Pediatrics.* 2009;124(3):e362-e370
Exclusion code: 4

Kumar PR, Fenton TR, Shaheen AA, Raman M. Prevalence of vitamin D deficiency and response to oral vitamin D supplementation in patients receiving home parenteral nutrition. *J Parenter Enteral Nutr.* 2012;36(4):463-469
Exclusion code: 7

Kunisaki KM, Niewoehner DE, Connett JE, Network CCR. Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study. *Am J Respir Crit Care Med.* 2012;185(3):286-290
Exclusion code: 4

Kuroda T, Shiraki M, Tanaka S, Ohta H. Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women. *Bone.* 2009;44(1):168-172
Exclusion code: 3

Kuwabara A, Tsugawa N, Tanaka K, et al. Improvement of vitamin D status in Japanese institutionalized elderly by supplementation with 800 IU of vitamin D(3). *J Nutr Sci Vitaminol.* 2009;55(6):453-458
Exclusion code: 6

Kyriakidou-Himonas M, Aloia JF, Yeh JK. Vitamin D supplementation in postmenopausal black women. *J Clin Endocrinol Metab.* 1999;84(11):3988-3990
Exclusion code: 6

Laaksi I, Ruohola JP, Mattila V, Auvinen A, Ylikomi T, Pihlajamaki H. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. *J Infect Dis.* 2010;202(5):809-814
Exclusion code: 15

Laaksi I, Ruohola J-P, Tuohimaa P, et al. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr.* 2007;86(3):714-717
Exclusion code: 3

Lagari VS, Gomez-Marin O, Levis S. Differences in vitamin D3 dosing regimens in a geriatric community-dwelling population. *Endocr Pract.* 2012;18(6):847-854
Exclusion code: 6

Lagunova Z, Porojnicu AC, Aksnes L, et al. Effect of vitamin D supplementation and ultraviolet B exposure on serum 25-hydroxyvitamin D concentrations in healthy volunteers: A randomized, crossover clinical trial. *Br J Dermatol.* 2013;169(2):434-440
Exclusion code: 6

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

Lalau JD, Jans I, el Esper N, Bouillon R, Fournier A. Calcium metabolism, plasma parathyroid hormone, and calcitriol in transient hypertension of pregnancy. *Am J Hypertens.* 1993;6(6 Pt 1):522-527
Exclusion code: 4

Landin-Wilhelmsen K, Wilhelmsen L, Bengtsson BA. Postmenopausal osteoporosis is more related to hormonal aberrations than to lifestyle factors. *Clin Endocrinol (Oxf).* 1999;51(4):387-394
Exclusion code: 7

Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl).* 1998;135(4):319-323
Exclusion code: 14

Lapid MI, Cha SS, Takahashi PY. Vitamin D and depression in geriatric primary care patients. *Clin Interv Aging.* 2013;8:509-514
Exclusion code: 7

Lappe J, Cullen D, Haynatzki G, Recker R, Ahlf R, Thompson K. Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. *J Bone Miner Res.* 2008;23(5):741-749
Exclusion code: 4

Lappe JM, Heaney RP. Why randomized controlled trials of calcium and vitamin D sometimes fail. *Dermatoendocrinol.* 2012;4(2):95-100
Exclusion code: 2

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr.* 2007;85(6):1586-1591
Exclusion code: 15

Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: A pragmatic population-based 3-year intervention study. *J Bone Miner Res.* 2004;19(3):370-378
Exclusion code: 14

Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents severe falls in elderly community-dwelling women: a pragmatic population-based 3-year intervention study. *Aging Clin.* 2005;17(2):125-132
Exclusion code: 14

Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. *Am J Hypertens.* 2012;25(11):1215-1222
Exclusion code: 15

Laslett LL, Quinn S, Burgess JR, et al. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study. *Ann Rheum Dis.* 2014;73(4):697-703
Exclusion code: 7

Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). *J Am Geriatr Soc.* 2003;51(3):291-299
Exclusion code: 4

Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. *J Am Geriatr Soc.* 2003;51(9):1219-1226
Exclusion code: 13

Lau EMC, Woo J, Swaminathan R, MacDonald D, Donnan SPB. Plasma 25-hydroxyvitamin D concentration in patients with hip fracture in Hong Kong. *Gerontology.* 1989;35(4):198-204
Exclusion code: 4

Launoy G, Milan C, Day NE, Pienkowski MP, Gignoux M, Faivre J. Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. *Int J Cancer.* 1998;76(1):7-12
Exclusion code: 7

Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing.* 2006;35(5):482-486
Exclusion code: 14

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

postmenopausal US women with acute hip fracture. *JAMA.* 1999;281(16):1505-1511
Exclusion code: 7

Lee DM, Tajar A, Ulubaev A, et al. Association between 25-hydroxyvitamin D levels and cognitive performance in middle-aged and older European men. *J Neurol Neurosurg Psychiatry.* 2009;80(7):722-729
Exclusion code: 7

Lee JE, Li H, Chan AT, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. *Cancer Prev Res.* 2011;4(5):735-743
Exclusion code: 3

Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clin Pediatr (Phila).* 2007;46(1):42-44
Exclusion code: 4

Lee L, Kang SA, Lee HO, et al. Relationships between dietary intake and cognitive function level in Korean elderly people. *Public Health.* 2001;115(2):133-138
Exclusion code: 5

Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. *Br J Nutr.* 2010;104(1):108-117
Exclusion code: 4

Lehtonen-Veromaa MK, Mottonen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. *Am J Clin Nutr.* 2002;76(6):1446-1453
Exclusion code: 4

Lemmila S, Saha H, Virtanen V, Ala-Houhala I, Pasternack A. Effect of intravenous calcitriol on cardiac systolic and diastolic function in patients on hemodialysis. *Am J Nephrol.* 1998;18(5):404-410
Exclusion code: 5

Leu M, Giovannucci E. Vitamin D: epidemiology of cardiovascular risks and events. *Best Pract Res Clin Endocrinol Metab.* 2011;25(4):633-646
Exclusion code: 3

Leventis P, Kiely PDW. The tolerability and biochemical effects of high-dose bolus vitamin D2 and D3 supplementation in patients with vitamin D insufficiency. *Scand J Rheumatol.* 2009;38(2):149-153
Exclusion code: 12

Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary intake of selected micronutrients and breast-cancer risk. *Int J Cancer.* 2001;91(2):260-263
Exclusion code: 7

Levi J, Vinter S, Richardson L, Laurent R, Segal LM. F as in Fat: How Obesity Policies Are Failing in America, 2009. Washington, DC: *Trust For America's Health*;2009
Exclusion code: 8

Levine AJ, Harper JM, Ervin CM, et al. Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk. *Nutr Cancer.* 2001;39(1):35-41
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

Lewis RM, Redzic M, Thomas DT. The effects of season-long vitamin D supplementation on collegiate swimmers and divers. *International journal of sport nutrition and exercise metabolism.* 2013;23(5):431-440
Exclusion code: 15

Li H, Stampfer MJ, Hollis JB, et al. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. *PLoS Med.* 2007;4(3):e103
Exclusion code: 6

Lieben L, Masuyama R, Torrekens S, et al. Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. *J Clin Invest.* 2012;122(5):1803-1815
Exclusion code: 4

Lim S, Kim MJ, Choi SH, et al. Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects. *Am J Clin Nutr.* 2013;97(3):524-530
Exclusion code: 7

Lim U, Freedman DM, Hollis BW, et al. A prospective investigation of serum 25-hydroxyvitamin D and risk of lymphoid cancers. *Int J Cancer.* 2009;124(4):979-986
Exclusion code: 6

Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM. Intakes of calcium and vitamin D and breast cancer risk in women. *Arch Intern Med.* 2007;167(10):1050-1059
Exclusion code: 5

Lin SW, Chen W, Fan JH, et al. Prospective study of serum 25-hydroxyvitamin d concentration and mortality in a chinese population. *Am J Epidemiol.* 2012;176(11):1043-1050
Exclusion code: 3

Lind L, Wengle B, Wide L, Ljunghall S. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status. A double-blind, placebo-controlled study. *Am J Hypertens.* 1989;2(1):20-25
Exclusion code: 14

Linday LA, Shindledecker RD, Dolitsky JN, Chen TC, Holick MF. Plasma 25-hydroxyvitamin D levels in young children undergoing placement of tympanostomy tubes. *Ann Otol Rhinol Laryngol.* 2008;117(10):740-744
Exclusion code: 4

Linden V. Vitamin D and myocardial infarction. *Br Med J.* 1974;3(5932):647-650
Exclusion code: 5

Li-Ng M, Aloia JF, Pollack S, et al. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol Infect.* 2009;137(10):1396-1404
Exclusion code: 15

Linos E, Keiser E, Kanzler M, et al. Sun protective behaviors and vitamin D levels in the US population: NHANES 2003-2006. *Cancer Causes Control.* 2012;23(1):133-140
Exclusion code: 2

Lippi G, Montagnana M, Meschi T, Borghi L. Vitamin D concentration and deficiency across different ages and genders. *Aging Clin.* 2012;24(5):548-551
Exclusion code: 6

Lippi G, Montagnana M, Targher G, Guidi GC. Relationship between serum vitamin D and inflammatory markers in the general population: comment on the article by Patel et al. *Arthritis Rheum.* 2008;58(3):913-914
Exclusion code: 7

Lips P. Vitamin D deficiency and osteoporosis: the role of vitamin D deficiency and treatment with vitamin D and analogues in the prevention of osteoporosis-related fractures. *Eur J Clin Invest.* 1996;26(6):436-442
Exclusion code: 7

Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev.* 2001;22(4):477-501
Exclusion code: 8

Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? *J Steriod Biochem Mol Biol.* 2004;89-90(1-5):611-614
Exclusion code: 8

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

Lips P, Bouillon R, van Schoor NM, et al. Reducing fracture risk with calcium and vitamin D. *Clin Endocrinol (Oxf).* 2010;73(3):277-285
Exclusion code: 7

Lips P, Duong T, Oleksik A, et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: Baseline data from the multiple outcomes of raloxifene evaluation clinical trial. *J Clin Endocrinol Metab.* 2001;86(3):1212-1221
Exclusion code: 4

Lips P, Hackeng WHL, Jongen MJM, van Ginkel FC, Netelenbos JC. Seasonal variation in serum concentrations of parathyroid hormone in elderly people. *J Clin Endocrinol Metab.* 1983;57(1):204-206
Exclusion code: 6

Lips P, Van Ginkel FC, Jongen MJM, Rubertus F, Van der Vijgh WJF, Netelenbos JC. Determinants of vitamin D status in patients with hip fracture and in elderly control subjects. *Am J Clin Nutr.* 1987;46(6):1005-1010
Exclusion code: 7

Lips P, Wiersinga A, van Ginkel FC, et al. The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. *J Clin Endocrinol Metab.* 1988;67(4):644-650
Exclusion code: 6

Lister T. Should long-term care residents be supplemented with vitamin D? *Can J Diet Pract Res.* 2008;69(1):28-31
Exclusion code: 7

Liu E, McKeown NM, Pittas AG, et al. Predicted 25-hydroxyvitamin D score and change in fasting plasma glucose in the Framingham offspring study. *Eur J Clin Nutr.* 2012;66(1):139-141
Exclusion code: 7

Liu E, Meigs JB, Pittas AG, et al. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. *Am J Clin Nutr.* 2010;91(6):1627-1633
Exclusion code: 7

Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science.* 2006;311(5768):1770-1773
Exclusion code: 4

Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care.* 2005;28(12):2926-2932
Exclusion code: 5

Llewellyn DJ, Langa KM, Lang IA. Serum 25-hydroxyvitamin D concentration and cognitive impairment. *J Geriatr Psychiatry Neurol.* 2009;22(3):188-195
Exclusion code: 7

Logan VF, Gray AR, Peddie MC, Harper MJ, Houghton LA. Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months. *Br J Nutr.* 2013;109(6):1082-1088
Exclusion code: 6

Løken-Amsrud KH, T; Bakke, SJ; Beiske, AG; Bjerve, KS; Bjørnarå, BT; Hovdal, H; Lilleås, F; Midgard, R; Pedersen, T; Benth, JS; Sandvik, L; Torkildsen, 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

Longenecker CT, Hileman CO, Carman TL, et al. Vitamin D supplementation and endothelial function in vitamin D deficient HIV-infected patients: a randomized placebo-controlled trial. *Antivir Ther.* 2012;17(4):613-621
Exclusion code: 6

Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone.* 2002;30(5):771-777
Exclusion code: 2

Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D Status: United States, 2001-2006. Hyattsville, MD2011Exclusion code: 2

Lowe LC, Guy M, Mansi JL, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. *Eur J Cancer.* 2005;41(8):1164-1169
Exclusion code: 7

Luczynska A, Kaaks R, Rohrmann S, et al. Plasma 25-hydroxyvitamin D concentration and lymphoma risk: results of the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2013;98(3):827-838
Exclusion code: 3

Lund B, Badskjaer J, Soerensen OH. Vitamin D and ischaemic heart disease. *Horm Metab Res.* 1978;10(6):553-556
Exclusion code: 7

Lund B, Sorensen OH, Christensen AB. 25-Hydroxycholecaliferol and fractures of the proximal. *Lancet.* 1975;2(7929):300-302
Exclusion code: 4

Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporos Int.* 2007;18(6):811-818
Exclusion code: 14

Maalouf J, Nabulsi M, Vieth R, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *J Clin Endocrinol Metab.* 2008;93(7):2693-2701

Exclusion code: 4

MacDonald D, Lau E, Chan ELP, et al. Serum intact parathyroid hormone levels in elderly Chinese females with hip fracture. *Calcif Tissue Int.* 1992;51(6):412-414
Exclusion code: 7

MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest.* 1985;76(4):1536-1538
Exclusion code: 4

Mai XM, Langhammer A, Camargo CA, Chen Y. Serum 25-hydroxyvitamin D levels and incident asthma in adults. *Am J Epidemiol.* 2012;176(12):1169-1176
Exclusion code: 3

Majak P, Jerzynska J, Smejda K, Stelmach I, Timler D, Stelmach W. Correlation of vitamin D with Foxp3 induction and steroid-sparing effect of immunotherapy in asthmatic children. *Ann Allergy Asthma Immunol.* 2012;109(5):329-335
Exclusion code: 4

Major GC, Alarie F, Dore J, Phouttama S, Tremblay A. Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. *Am J Clin Nutr.* 2007;85(1):54-59
Exclusion code: 14

Maki KC, Rubin MR, Wong LG, McManus JF, Jensen CD, Lawless A. Effects of vitamin D supplementation on 25-hydroxyvitamin D, high-density lipoprotein cholesterol, and other cardiovascular disease risk markers in subjects with elevated waist circumference. *Int J Food Sci Nutr.* 2011;62(4):318-327
Exclusion code: 15

Malabanan A, Veronikis I, Holick M. Redefining Vitamin D Insufficiency. *Lancet.* 1998;351(9105):805-806
Exclusion code: 2

Mallet E, Gugi B, Brunelle P, Henocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstet Gynecol.* 1986;68(3):300-304
Exclusion code: 4

Manders M, De Groot LC, Hoefnagels WH, et al. The effect of a nutrient dense drink on mental and physical function in institutionalized elderly people. *J Nurt Health Aging.* 2009;13(9):760-767
Exclusion code: 5

Manson JE, Allison MA, Carr JJ, et al. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. *Menopause.* 2010;17(4):683-691
Exclusion code: 14

Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer--ready for prime time? *N Engl J Med.* 2011;364(15):1385-1387
Exclusion code: 8

Margolis KL, Ray RM, Van Horn L, et al. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension.* 2008;52(5):847-855
Exclusion code: 3

Vitamin D deficiency rickets in northern Europe and Libya. Raven Press; 1991.
Exclusion code: 4

Marniemi J, Alanen E, Impivaara O, et al. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr Metab Cardiovasc Dis.* 2005;15(3):188-197
Exclusion code: 3

Martineau AR, Timms PM, Bothamley GH, et al. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet.* 2011;377(9761):242-250
Exclusion code: 4

Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* 2007;167(11):1159-1165
Exclusion code: 6

Marwaha RK, Tandon N, Reddy DR, et al. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr.* 2005;82(2):477-482
Exclusion code: 4

Marya RK, Rathee S, Dua V, Sangwan K. Effect of vitamin D supplementation during pregnancy on foetal growth. *Indian J Med Res.* 1988;88:488-492
Exclusion code: 4

Appendix B4. List of Excluded Studies

Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. *Gynecol Obstet Invest.* 1987;24(1):38-42
Exclusion code: 4

Mason RS, Lissner D, Grunstein HS, Posen S. A simplified assay for dihydroxylated vitamin D metabolites in human serum: application to hyper- and hypovitaminosis D. *Clin Chem.* 1980;26(3):444-450
Exclusion code: 5

Mastaglia SR, Mautalen CA, Parisi MS, Oliveri B. Vitamin D2 dose required to rapidly increase 25OHD levels in osteoporotic women. *Eur J Clin Nutr.* 2006;60(5):681-687
Exclusion code: 4

Matsuoka LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D3 synthesis. *J Clin Endocrinol Metab.* 1987;64(6):1165-1168
Exclusion code: 2

Mattila C, Knekt P, Mannisto S, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. *Diabetes Care.* 2007;30(10):2569-2570
Exclusion code: 3

Mawer EB, Hann JT, Berry JL, Davies M. Vitamin D metabolism in patients intoxicated with ergocalciferol. *Clin Sci (Lond).* 1985;68(2):135-141
Exclusion code: 7

Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *Br J Obstet Gynaecol.* 1981;88(10):987-991
Exclusion code: 4

May HT, Bair TL, Lappe DL, et al. Association of vitamin D levels with incident depression among a general cardiovascular population. *Am Heart J.* 2010;159(6):1037-1043
Exclusion code: 4

McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med.* 1996;125(5):353-359
Exclusion code: 6

McCullough ML, Bostick RM, Daniel CR, et al. Vitamin D status and impact of vitamin D3 and/or calcium supplementation in a randomized pilot study in the Southeastern United States. *J Am Coll Nutr.* 2009;28(6):678-686
Exclusion code: 15

McCullough ML, Robertson AS, Rodriguez C, et al. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control.* 2003;14(1):1-12
Exclusion code: 5

McCullough ML, Rodriguez C, Diver WR, et al. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005;14(12):2898-2904
Exclusion code: 5

McCullough ML, Stevens VL, Patel R, et al. Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. *Breast Cancer Res.* 2009;11(4):R64
Exclusion code: 3

McGill AT, Stewart JM, Lithander FE, Strik CM, Poppitt SD. Relationships of low serum vitamin D3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight and obesity. *Nutr J.* 2008;7(1)
Exclusion code: 6

McGrath J, Scragg R, Chant D, Eyles D, Burne T, Obradovic D. No association between serum 25-hydroxyvitamin D3 level and performance on psychometric tests in NHANES III. *Neuroepidemiology.* 2007;29(1-2):49-54
Exclusion code: 7

McGrath JJ, 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

McKee J. Studies find patients have low levels of Vitamin D. AAOS Now. 2012. http://www.aaos.org/news/aaosnow/mar12/clinical2.asp. Accessed January 15, 2014
Exclusion code: 2

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

Appendix B4. List of Excluded Studies

McKinney JD, Bailey BA, Garrett LH, Peiris P, Manning T, Peiris AN. Relationship between vitamin D status and ICU outcomes in veterans. *J Am Med Dir Assoc.* 2011;12(3):208-211
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

Meier C, Woitge HW, Witte K, Lemmer B, Seibel MJ. Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. *J Bone Miner Res.* 2004;19(8):1221-1230
Exclusion code: 15

Meier DE, Luckey MM, Wallenstein S, Clemens TL, Orwoll ES, Waslien CI. Calcium, vitamin D, and parathyroid hormone status in young white and black women: Association with racial differences in bone mass. *J Clin Endocrinol Metab.* 1991;72(3):703-710
Exclusion code: 7

Melamed ML, Muntner P, Michos ED, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. *Arterioscler Thromb Vasc Biol.* 2008;28(6):1179-1185
Exclusion code: 7

Melhus H, Snellman G, Gedeborg R, et al. Plasma 25-hydroxyvitamin D levels and fracture risk in a community-based cohort of elderly men in Sweden. *J Clin Endocrinol Metab.* 2010;95(6):2637-2645
Exclusion code: 3

Melin A, Wilske J, Ringertz H, Saaf M. Seasonal variations in serum levels of 25-hydroxyvitamin D and parathyroid hormone but no detectable change in femoral neck bone density in an older population with regular outdoor exposure. *J Am Geriatr Soc.* 2001;49(9):1190-1196
Exclusion code: 5

Menczel J, Foldes J, Steinberg R, et al. Alfacalcidol (alpha D3) and calcium in osteoporosis. *Clin Orthop Relat Res.* 1994(300):241-247
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

Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum.* 2004;50(1):72-77
Exclusion code: 5

Messenger W, Nielson CM, Li H, et al. Serum and dietary vitamin D and cardiovascular disease risk in elderly men: A prospective cohort study. *Nutr Metab Cardiovasc Dis.* 2012;22(10):856-863
Exclusion code: 3

Meunier PJ. Prevention of hip fractures. *Am J Med.* 1993;95(5 A):75S-78S
Exclusion code: 8

Meunier PJ, Chapuy MC, Arlot ME, Delmas PD, Duboeuf F. Can we stop bone loss and prevent hip fractures in the elderly? *Osteoporos Int.* 1994;4(SUPPL. 1):S71-S76
Exclusion code: 8

Meyer G, Warnke A, Bender R, Muhlhauser I. Effect on hip fractures of increased use of hip protectors in nursing homes: cluster randomised controlled trial. *BMJ.* 2003;326(7380):76
Exclusion code: 5

Meyer HE, Robsahm TE, Bjørge T, Brustad M, Blomhoff R. Vitamin D, season, and risk of prostate cancer: A nested case-control study within Norwegian health studies. *Am J Clin Nutr.* 2013;97(1):147-154
Exclusion code: 3

Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *J Bone Miner Res.* 2002;17(4):709-715
Exclusion code: 15

Michael YL, Smit E, Seguin R, Curb JD, Phillips LS, Manson JE. Serum 25-hydroxyvitamin D and physical performance in postmenopausal women. *J Womens Health.* 2011;20(11):1603-1608
Exclusion code: 3

Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: A systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2010;153(12):815-825
Exclusion code: 2

Michelson D, Stratakis C, Hill L, et al. Bone mineral density in women with depression. *N Engl J Med.* 1996;335(16):1176-1181
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

Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. *Curr Opin Clin Nutr Metab Care.* 2008;11(1):7-12
Exclusion code: 7

Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Hollis BW, Giovannucci E. Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk. *Prostate.* 2007;67(9):911-923
Exclusion code: 5

Miller EA, Keku TO, Satia JA, Martin CF, Galanko JA, Sandler RS. Calcium, dietary, and lifestyle factors in the prevention of colorectal adenomas. *Cancer.* 2007;109(3):510-517
Exclusion code: 7

Miller PD. Vitamin D, calcium, and cardiovascular mortality: a perspective from a plenary lecture given at the annual meeting of the American Association of Clinical Endocrinologists. *Endocr Pract.* 2011;17(5):798-806
Exclusion code: 8

Mitchell DM, Henao MP, Finkelstein JS, Burnett-Bowie S-AM. Prevalence and predictors of vitamin D deficiency in healthy adults. *Endocr Pract.* 2012;18(6):914-923
Exclusion code: 7

Mithal A, Wahl DA, Bonjour JP, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int.* 2009;20(11):1807-1820
Exclusion code: 2

Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr.* 2011;94(2):486-494
Exclusion code: 4

Mocanu V, Stitt PA, Costan AR, et al. Long-term effects of giving nursing home residents bread fortified with 125 microg (5000 IU) vitamin D(3) per daily serving. *Am J Clin Nutr.* 2009;89(4):1132-1137
Exclusion code: 6

Mølgaard C, Larnkjær A, Cashman KD, Lamberg-Allardt C, Jakobsen J, Michaelsen KF. Does vitamin D supplementation of healthy Danish Caucasian girls affect bone turnover and bone mineralization? *Bone.* 2010;46(2):432-439
Exclusion code: 4

Moncrieff MW, Chance GW. Nephrotoxic effect of vitamin D therapy in vitamin D refractory rickets. *Arch Dis Child.* 1969;44(237):571-579
Exclusion code: 4

Morales E, Romieu I, Guerra S, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. *Epidemiology.* 2012;23(1):64-71
Exclusion code: 4

Moreira-Pfrimer LDF, Pedrosa MAC, Teixeira L, Lazaretti-Castro M. Treatment of vitamin D deficiency increases lower limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial. *Ann Nutr Metab.* 2009;54(4):291-300
Exclusion code: 4

Moreno LA, Valtueña J, Pérez-López F, González-Gross M. Health effects related to low vitamin D concentrations: Beyond bone metabolism. *Ann Nutr Metab.* 2011;59(1):22-27
Exclusion code: 8

Morley R, Carlin JB, Pasco JA, Wark JD. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *J Clin Endocrinol Metab.* 2006;91(3):906-912
Exclusion code: 4

Moschonis G, Katsaroli I, Lyritis GP, Manios Y. The effects of a 30-month dietary intervention on bone mineral density: the Postmenopausal Health Study. *Br J Nutr.* 2010;104(1):100-107
Exclusion code: 15

Moschonis 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

calcium and vitamin D: the Postmenopausal Health Study. *Br J Nutr.* 2006;96(6):1140-1148
Exclusion code: 14

Mowe M, Haug E, Bohmer T. Low serum calcidiol concentration in older adults with reduced muscular function. *J Am Geriatr Soc.* 1999;47(2):220-226
Exclusion code: 4

Moyer VA. Prevention of falls in community-dwelling older adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(3):197-204
Exclusion code: 2

Moyer VA. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2013;158(9):691-696
Exclusion code: 2

Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. *J Clin Psychopharmacol.* 2013;33(3):378-385
Exclusion code: 4

Muldowney S, Lucey AJ, Hill TR, et al. Incremental cholecalciferol supplementation up to 15 mug/d throughout winter at 51-55 degrees N has no effect on biomarkers of cardiovascular risk in healthy young and older adults. *J Nutr.* 2012;142(8):1519-1525
Exclusion code: 15

Mulrow CD, Gerety MB, Kanten D, et al. A randomized trial of physical rehabilitation for very frail nursing home residents. *JAMA.* 1994;271(7):519-524
Exclusion code: 4

Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA.* 2006;296(23):2832-2838
Exclusion code: 3

Munger KL, Levin LI, Massa J, Horst R, Orban T, Ascherio A. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. *Am J Epidemiol.* 2013;177(5):411-419
Exclusion code: 3

Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology.* 2004;62(1):60-65
Exclusion code: 7

Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2011;96(10):2997-3006
Exclusion code: 13

Murdoch DR, Slow S, Chambers ST, et al. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA.* 2012;308(13):1333-1339
Exclusion code: 15

Murphy AB, Kelley B, Nyame YA, et al. Predictors of serum vitamin D levels in African American and European American men in Chicago. *Am J Mens Health.* 2012;6(5):420-426
Exclusion code: 7

Myrup B, Jensen GF, McNair P. Cardiovascular risk factors during estrogen-norethindrone and cholecalciferol treatment. *Arch Intern Med.* 1992;152(11):2265-2268
Exclusion code: 14

Nagant de Deuxchaisnes C, Devogelaer JP. Vitamin D deficiency in elderly people. *BMJ.* 1991;303(6804):718
Exclusion code: 8

Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. *Diabet Med.* 2009;26(1):19-27
Exclusion code: 10

Namgung R, Tsang RC, Lee C, Han DG, Ho ML, Sierra RI. Low total body bone mineral content and high bone resorption in Korean winter-born versus summer-born newborn infants. *J Pediatr.* 1998;132(3 Pt 1):421-425
Exclusion code: 4

Narang NK, Gupta RC, Jain MK. Role of vitamin D in pulmonary tuberculosis. *J Assoc Physicians India.* 1984;32(2):185-188
Exclusion code: 6

National Institutes of Health Office of Dietary Supplements. Dietary supplement fact sheet: Vitamin

D. In: National Institutes of Health, ed. Bethesda, MD2011
Exclusion code: 8

National Osteoporosis Foundation. Clinician Guideline. 2010. http://nof.org/files/nof/public/content/file/344/upload/159.pdf. Accessed February 12, 2014
Exclusion code: 2

Neelemaat F, Lips P, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MA. Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults. *J Am Geriatr Soc.* 2012;60(4):691-699
Exclusion code: 5

Nelson ML, Blum JM, Hollis BW, Rosen C, Sullivan SS. Supplements of 20 microg/d cholecalciferol optimized serum 25-hydroxyvitamin D concentrations in 80% of premenopausal women in winter. *J Nutr.* 2009;139(3):540-546
Exclusion code: 15

Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. *Pharmacotherapy.* 2009;29(6):691-708
Exclusion code: 8

Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr.* 2002;76(1):187-192
Exclusion code: 4

Neuhouser ML, Manson JE, Millen A, et al. The influence of health and lifestyle characteristics on the relation of serum 25-hydroxyvitamin D with risk of colorectal and breast cancer in postmenopausal women. *Am J Epidemiol.* 2012;175(7):673-684
Exclusion code: 3

Neuhouser ML, Wassertheil-Smoller S, Thomson C, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med.* 2009;169(3):294-304
Exclusion code: 5

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

Neyens JC, van Haastregt JC, Dijcks BP, et al. Effectiveness and implementation aspects of interventions for preventing falls in elderly people in long-term care facilities: a systematic review of RCTs. *J Am Med Dir Assoc.* 2011;12(6):410-425
Exclusion code: 13

Ng K, Meyerhardt JA, Wu K, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *J Clin Oncol.* 2008;26(18):2984-2991
Exclusion code: 4

Ng K, Scott JB, Drake BF, et al. Dose response to vitamin D supplementation in African Americans: results of a 4-arm, randomized, placebo-controlled trial. *Am J Clin Nutr.* 2014;99(3):587-598
Exclusion code: 4

Nieves JW, Cosman F, Grubert E, Ambrose B, Ralston SH, Lindsay R. Skeletal effects of vitamin D supplementation in postmenopausal black women. *Calcif Tissue Int.* 2012;91(5):316-324
Exclusion code: 2

Nilas L, Christiansen C. Treatment with vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. *Int J Obes (Lond).* 1984;8(5):407-411
Exclusion code: 14

Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol.* 2008;37(1):113-119
Exclusion code: 4

Nordin BE, Baker MR, Horsman A, Peacock M. A prospective trial of the effect of vitamin D supplementation on metacarpal bone loss in elderly women. *Am J Clin Nutr.* 1985;42(3):470-474
Exclusion code: 6

Norenstedt S, Pernow Y, Brismar K, et al. Primary hyperparathyroidism and metabolic risk factors, impact of parathyroidectomy and vitamin D supplementation, and results of a randomized double-blind study. *Eur J Endocrinol.* 2013;169(6):795-804
Exclusion code: 4

Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? *Br J Dermatol.* 2009;161(4):732-736
Exclusion code: 2

Nurmi-Luthje I, Sund R, Juntunen M, Luthje P. Post-hip fracture use of prescribed calcium plus vitamin D

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

Nursyam EW, Amin Z, Rumende CM. The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. *Acta Med Indones.* 2006;38(1):3-5
Exclusion code: 14

Nuti R, Bianchi G, Brandi ML, et al. Superiority of alfacalcidol compared to vitamin D plus calcium in lumbar bone mineral density in postmenopausal osteoporosis. *Rheumatol Int.* 2006;26(5):445-453
Exclusion code: 4

O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. *J Bone Miner Metab.* 2008;26(6):531-542
Exclusion code: 13

Okonofua F, Menon RK, Houlder S, et al. Parathyroid hormone and neonatal calcium homeostasis: evidence for secondary hyperparathyroidism in the Asian neonate. *Metabolisim.* 1986;35(9):803-806
Exclusion code: 4

Orimo H, Shiraki M, Hayashi Y, et al. Effects of 1 alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. *Calcif Tissue Int.* 1994;54(5):370-376
Exclusion code: 15

Orwoll E, Nielson CM, Marshall LM, et al. Vitamin D deficiency in older men. *J Clin Endocrinol Metab.* 2009;94(4):1214-1222
Exclusion code: 3

Orwoll ES, McClung MR, Oviatt SK, Recker RR, Weigel RM. Histomorphometric effects of calcium or calcium plus 25-hydroxyvitamin D3 therapy in senile osteoporosis. *J Bone Miner Res.* 1989;4(1):81-88
Exclusion code: 4

Orwoll ES, Oviatt S. Relationship of mineral metabolism and long-term calcium and cholecalciferol supplementation to blood pressure in normotensive men. *Am J Clin Nutr.* 1990;52(4):717-721
Exclusion code: 14

Orwoll ES, Oviatt SK, McClung MR, Deftos LJ, Sexton G. The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann Intern Med.* 1990;112(1):29-34
Exclusion code: 3

Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S. Plasma vitamin D and risk of colorectal cancer: the Japan Public Health Center-Based Prospective Study. *Br J Cancer.* 2007;97(3):446-451
Exclusion code: 3

Ott SM, Chesnut CH, 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis. *Ann Intern Med.* 1989;110(4):267-274
Exclusion code: 4

Pacifico L, Anania C, Osborn JF, et al. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. *Eur J Endocrinol.* 2011;165(4):603-611
Exclusion code: 4

Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. *J Affect Disord.* 2009;118(1-3):240-243
Exclusion code: 7

Panunzio MF, Pisano A, Telesforob P, Tomaiuolo P. Diet can increase 25-hydroxyvitamin-D3 plasma levels in the elderly: A dietary intervention trial. *Nutr Res.* 2003;23(9):1177-1181
Exclusion code: 6

Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev.* 2002;23(4):560-569
Exclusion code: 14

Pappa HM, Gordon CM, Saslowsky TM, et al. Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics.* 2006;118(5):1950-1961
Exclusion code: 4

Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. Vitamin D and bone health in the elderly. *Am J Clin Nutr.* 1982;36(5 Suppl):1014-1031
Exclusion code: 8

Park MJ, Namgung R, Kim DH, Tsang RC. Bone mineral content is not reduced despite low vitamin D status in breast milk-fed infants versus cow's milk based formula-fed infants. *J Pediatr.* 1998;132(4):641-645
Exclusion code: 4

Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN. Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. *Eur J Cancer.* 2010;46(5):932-936
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

Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009;169(4):391-401
Exclusion code: 5

Parker J, Hashmi O, Dutton D, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas.* 2010;65(3):225-236
Exclusion code: 13

Partonen T, Vakkuri O, Lamberg-Allardt C, Lonnqvist J. Effects of bright light on sleepiness, melatonin, and 25-hydroxyvitamin D(3) in winter seasonal affective disorder. *Biol Psychiatry.* 1996;39(10):865-872
Exclusion code: 5

Pasco JA, Henry MJ, Kotowicz MA, et al. Seasonal periodicity of serum vitamin D and parathyroid hormone, bone resorption, and fractures: the Geelong Osteoporosis Study. *J Bone Miner Res.* 2004;19(5):752-758
Exclusion code: 6

Patel P, Poretsky L, Liao E. Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in Type 2 diabetes: A pilot prospective randomized trial. *J Diabetes.* 2010;2(1):36-40
Exclusion code: 4

Patel R, Collins D, Bullock S, Swaminathan R, Blake GM, Fogelman I. The effect of season and vitamin D supplementation on bone mineral density in healthy women: a double-masked crossover study. *Osteoporos Int.* 2001;12(4):319-325
Exclusion code: 15

Pathak K, Soares MJ, Calton EK, Zhao Y, Hallett J. Vitamin D supplementation and body weight status: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev.* 2014;15(6):528-537
Exclusion code: 13

Pazdiora P, Svobodova S, Fuchsova R, et al. Vitamin D in colorectal, breast, prostate and lung cancer: a pilot study. *Anticancer Res.* 2011;31(10):3619-3621
Exclusion code: 6

Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab.* 2000;85(9):3011-3019
Exclusion code: 15

Peechakara SV, Pittas AG. Vitamin D as a potential modifier of diabetes risk. *Nat Clin Pract Endocrinol Metab.* 2008;4(4):182-183
Exclusion code: 8

Peichl P, Rintelen B, Kumpan W, Broll H. Increase of axial and appendicular trabecular and cortical bone density in established osteoporosis with intermittent nasal salmon calcitonin therapy. *Gynecol Endocrinol.* 1999;13(1):7-14
Exclusion code: 14

Peiris AN, Bailey B, Manning T, Kuriacose R, Copeland R, Garrett L. Testing for vitamin D deficiency in veterans-is there a seasonal bias? *J Am Med Dir Assoc.* 2010;11(2):128-131
Exclusion code: 6

Peiris AN, Bailey BA, Manning T. The relationship of vitamin D deficiency to health care costs in veterans. *Mil Med.* 2008;173(12):1214-1218
Exclusion code: 6

Peiris AN, Bailey BA, Manning T. Relationship of vitamin D monitoring and status to bladder cancer survival in veterans. *South Med J.* 2013;106(2):126-130
Exclusion code: 4

Peiris AN, Bailey BA, Manning T, Adebonojo L. Are 25-hydroxyvitamin D levels adequately monitored following evidence of vitamin D insufficiency in veterans? *Mil Med.* 2010;175(6):453-456
Exclusion code: 6

Appendix B4. List of Excluded Studies

Peiris AN, Bailey BA, Peiris P, Copeland RJ, Manning T. Race and vitamin D status and monitoring in male veterans. *J Natl Med Assoc.* 2011;103(6):492-497
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

Perez-Lopez FR, Brincat M, Erel CT, et al. EMAS position statement: Vitamin D and postmenopausal health. *Maturitas.* 2012;71(1):83-88
Exclusion code: 8

Peters U, Hayes RB, Chatterjee N, et al. Circulating vitamin D metabolites, polymorphism in vitamin D receptor, and colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev.* 2004;13(4):546-552
Exclusion code: 6

Peters U, McGlynn KA, Chatterjee N, et al. Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. *Cancer Epidemiol Biomarkers Prev.* 2001;10(12):1267-1274
Exclusion code: 7

Peterson A, Mattek N, Clemons A, et al. Serum vitamin D concentrations are associated with falling and cognitive function in older adults. *J Nurt Health Aging.* 2012;16(10):898-901
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

Pettifor JM, Ross FP, Moodley G, Wang J, Margo G, Skjolde C. Serum calcium, magnesium, phosphorus, alkaline phosphatase and 25-hydroxyvitamin D concentrations in children. *S Afr Med J.* 1978;53(19):751-754
Exclusion code: 4

Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab.* 2001;86(4):1633-1637
Exclusion code: 3

Pfeifer M, Dobnig H, Begerow B, Suppan K. Effects of vitamin D and calcium supplementation on falls and parameters of muscle function - a prospective, randomized, double-blind, multi-center study. *J Bone Miner Res.* 2004;19(SUPPL. 1)
Exclusion code: 14

Pietras SM, Obayan BK, Cai MH, Holick MF. Vitamin D2 treatment for vitamin D deficiency and insufficiency for up to 6 years. *Arch Intern Med.* 2009;169(19):1806-1808
Exclusion code: 7

Pike KC, Inskip HM, Robinson S, et al. Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. *Thorax.* 2012;67(11):950-956
Exclusion code: 4

Pilz S, Dobnig H, Fischer JE, et al. Low vitamin d levels predict stroke in patients referred to coronary angiography. *Stroke.* 2008;39(9):2611-2613
Exclusion code: 4

Pilz S, Dobnig H, Winklhofer-Roob B, et al. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. *Cancer Epidemiol Biomarkers Prev.* 2008;17(5):1228-1233
Exclusion code: 4

Pilz S, Marz W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab.* 2008;93(10):3927-3935
Exclusion code: 7

Pilz S, Tomaschitz A, Drechsler C, Zittermann A, Dekker JM, März W. Vitamin d supplementation: A promising approach for the prevention and treatment of strokes. *Curr Drug Targets.* 2011;12(1):88-96
Exclusion code: 13

Pilz S, Tomaschitz A, Obermayer-Pietsch B, Dobnig H, Pieber TR. Epidemiology of vitamin D insufficiency and cancer mortality. *Anticancer Res.* 2009;29(9):3699-3704
Exclusion code: 7

Pilz S, Tomaschitz A, Ritz E, Pieber TR. Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol.* 2009;6(10):621-630
Exclusion code: 7

Pimlott NJ, Evans MF. Regular vitamin D supplementation for housebound, frail elderly people. *Can Fam Physician.* 1997;43:2127-2128

Exclusion code: 7

Pittas AG, Chung M, Trikalinos T, et al. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med.* 2010;152(5):307-314
Exclusion code: 3

Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care.* 2006;29(3):650-656
Exclusion code: 7

Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care.* 2007;30(4):980-986
Exclusion code: 15

Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2007;92(6):2017-2029
Exclusion code: 3

Pittas AG, Nelson J, Mitri J, et al. Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. *Diabetes Care.* 2012;35(3):565-573
Exclusion code: 7

Pittas AG, Sun Q, Manson JE, Dawson-Hughes B, Hu FB. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. *Diabetes Care.* 2010;33(9):2021-2023
Exclusion code: 3

Platz EA, Hankinson SE, Hollis BW, et al. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and adenomatous polyps of the distal colorectum. *Cancer Epidemiol Biomarkers Prev.* 2000;9(10):1059-1065
Exclusion code: 15

Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. *Cancer Causes Control.* 2004;15(3):255-265
Exclusion code: 3

Platz EA, Rimm EB, Willett WC, Kantoff PW, Giovannucci E. Racial variation in prostate cancer incidence and in hormonal system markers among male health professionals. *J Natl Cancer Inst.* 2000;92(24):2009-2017
Exclusion code: 6

Ponda MP, Dowd K, Finkielstein D, Holt PR, Breslow JL. The short-term effects of vitamin D repletion on cholesterol: a randomized, placebo-controlled trial. *Arterioscler Thromb Vasc Biol.* 2012;32(10):2510-2515
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

Poole KE, Loveridge N, Barker PJ, et al. Reduced vitamin D in acute stroke. *Stroke.* 2006;37(1):243-245
Exclusion code: 6

Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ.* 2005;330(7498):1003
Exclusion code: 14

Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med.* 2013;369(21):1991-2000
Exclusion code: 3

Prentice RL, Anderson GL. The women's health initiative: Lessons learned. 2008;29:131-150
Exclusion code: 8

Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporos Int.* 2013;24(2):567-580
Exclusion code: 14

Priemel M, von Domarus C, Klatte TO, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *J Bone Miner Res.* 2010;25(2):305-312
Exclusion code: 6

Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med.* 2008;168(1):103-108
Exclusion code: 4

Principi N, Bianchini S, Baggi E, Esposito S. Implications of maternal vitamin D deficiency for the

fetus, the neonate and the young infant. *Eur J Nutr.* 2013;52(3):859-867
Exclusion code: 4

Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Binkley N. Rapid correction of low vitamin D status in nursing home residents. *Osteoporos Int.* 2008;19(11):1621-1628
Exclusion code: 12

Pun KK, Wong FHW, Wang C, et al. Vitamin D status among patients with fractured neck of femur in Hong Kong. *Bone.* 1990;11(5):365-368
Exclusion code: 7

Punnonen R, Salmi J, Tuimala R, Järvinen M, Pystynen P. Vitamin D deficiency in women with femoral neck fracture. *Maturitas.* 1986;8(4):291-295
Exclusion code: 4

Quint JK, Donaldson GC, Wassef N, Hurst JR, Thomas M, Wedzicha JA. 25-hydroxyvitamin D deficiency, exacerbation frequency and human rhinovirus exacerbations in chronic obstructive pulmonary disease. *BMC polm.* 2012;12:28
Exclusion code: 6

Racovan M, Walitt B, Collins CE, et al. Calcium and vitamin D supplementation and incident rheumatoid arthritis: The Women's Health Initiative Calcium plus Vitamin D trial. *Rheumatol Int.* 2012;32(12):3823-3830
Exclusion code: 14

Rajakumar K, Fernstrom JD, Janosky JE, Greenspan SL. Vitamin D insufficiency in preadolescent African-American children. *Clin Pediatr (Phila).* 2005;44(8):683-692
Exclusion code: 4

Rajakumar K, Greenspan SL, Thomas SB, Holick MF. Solar ultraviolet radiation and vitamin D: A historical perspective. *Am J Public Health.* 2007;97(10):1746-1754
Exclusion code: 8

Ranstam J, Kanis JA. Influence of age and body mass on the effects of vitamin D on hip fracture risk. *Osteoporos Int.* 1995;5(6):450-454
Exclusion code: 6

Ray JA, Meikle AW. D-light: vitamin D and good health. *MLO Med Lab Obs.* 2010;42(5):32
Exclusion code: 8

Ray WA, Taylor JA, Brown AK, et al. Prevention of fall-related injuries in long-term care: a randomized controlled trial of staff education. *Arch Intern Med.* 2005;165(19):2293-2298
Exclusion code: 5

Recker R, Lips P, Felsenberg D, et al. Alendronate with and without cholecalciferol for osteoporosis: results of a 15-week randomized controlled trial. *Curr Med Res Opin.* 2006;22(9):1745-1755
Exclusion code: 4

Reginster JY. The high prevalence of inadequate serum vitamin D levels and implications for bone health. *Curr Med Res Opin.* 2005;21(4):579-585
Exclusion code: 13

Reid IR, Ames R, Mason B, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med.* 2008;168(20):2276-2282
Exclusion code: 5

Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet.* 2013
Exclusion code: 3

Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. *J Clin Endocrinol Metab.* 2012;97(8):2670-2681
Exclusion code: 13

Remmelts HHF, van de Garde EMW, Meijvis SCA, et al. Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. *Clin Infect Dis.* 2012;55(11):1488-1494
Exclusion code: 7

Riek AE, Oh J, Sprague JE, et al. Vitamin D suppression of endoplasmic reticulum stress promotes an antiatherogenic monocyte/macrophage phenotype in type 2 diabetic patients. *J Biol Chem.* 2012;287(46):38482-38494
Exclusion code: 4

Riis B, Christiansen C, Rodbro P. The effect of different vitamin D treatments on serum vitamin D levels in early postmenopausal women. *Acta Vitaminol Enzymol.* 1984;6(2):77-82
Exclusion code: 4

Appendix B4. List of Excluded Studies

Riis BJ, Thomsen K, Christiansen C. Does 24R,25(OH)2-vitamin D3 prevent postmenopausal bone loss? *Calcif Tissue Int.* 1986;39(3):128-132
Exclusion code: 14

Ringe JD, Fardellone P, Kruse HP, Amling M, Van Der Geest SAP, Mller G. Value of a new fixed-combination pack of bisphosphonate, calcium and vitamin d in the therapy of osteoporosis: Results of two quantitative patient research studies. *Drugs Aging.* 2009;26(3):241-253
Exclusion code: 5

Rizzole R, Eisman JA, Norquist J, et al. Risk factors for vitamin D inadequacy among women with osteoporosis: An international epidemiological study. *Int J Clin Pract.* 2006;60(8):1013-1019
Exclusion code: 4

Rizzoli R, Boonen S, Brandi ML, Burlet N, Delmas P, Reginster JY. The role of calcium and vitamin D in the management of osteoporosis. *Bone.* 2008;42(2):246-249
Exclusion code: 6

Rizzoli R, Bruyere O, Cannata-Andia JB, et al. Management of osteoporosis in the elderly. *Curr Med Res Opin.* 2009;25(10):2373-2387
Exclusion code: 13

Rizzoli R, Stoermann C, Ammann P, Bonjour JP. Hypercalcemia and hyperosteolysis in vitamin D intoxication: effects of clodronate therapy. *Bone.* 1994;15(2):193-198
Exclusion code: 7

Robien K, Cutler GJ, Lazovich D. Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. *Cancer Causes Control.* 2007;18(7):775-782
Exclusion code: 5

Rohan TE, Negassa A, Chlebowski RT, et al. A randomized controlled trial of calcium plus vitamin D supplementation and risk of benign proliferative breast disease. *Breast Cancer Res Treat.* 2009;116(2):339-350
Exclusion code: 14

Rolland Y, de Souto Barreto P, Abellan Van Kan G, et al. Vitamin D supplementation in older adults: searching for specific guidelines in nursing homes. *J Nurt Health Aging.* 2013;17(4):402-412
Exclusion code: 7

Rollins G. Vitamin D Testing—What's the Right Answer? Labs Grapple with Confusing Analytics, Evidence. *Clinical Laboratory News.* 2009;35(7)
Exclusion code: 2

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

Rosen CJ, Adams JS, Bikle DD, et al. The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. *Endrocr Rev.* 2012;33(3):456-492
Exclusion code: 3

Rosen CJ, Morrison A, Zhou H, et al. Elderly women in northern New England exhibit seasonal changes in bone mineral density and calciotropic hormones. *Bone Miner.* 1994;25(2):83-92
Exclusion code: 6

Rossi M, McLaughlin JK, Lagiou P, et al. Vitamin D intake and breast cancer risk: a case-control study in Italy. *Ann Oncol.* 2009;20(2):374-378
Exclusion code: 5

Rossini M, Alberti V, Flor L, et al. Effect of oral vitamin D2 yearly bolus on hip fracture risk in elderly women: a community primary prevention study. *Aging Clin.* 2004;16(6):432-436
Exclusion code: 7

Rossini M, Bianchi G, Di Munno O, et al. Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporos Int.* 2006;17(6):914-921
Exclusion code: 6

Rossom RC, Espeland MA, Manson JE, et al. Calcium and vitamin D supplementation and cognitive impairment in the women's health initiative. *J Am Geriatr Soc.* 2012;60(12):2197-2205
Exclusion code: 14

Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333
Exclusion code: 5

Roth DE, Al Mahmud A, Raqib R, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: The AViDD trial. *Nutr J.* 2013;12(1)
Exclusion code: 4

Rouzi AA, Al-Sibiani SA, Al-Senani NS, Radaddi RM, Ardawi MSM. Independent predictors of all osteoporosis-related fractures among healthy Saudi postmenopausal women: The CEOR Study. *Bone.* 2012;50(3):713-722
Exclusion code: 3

Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology.* 2008;47(6):920-923
Exclusion code: 7

Runia TF, Hop WCJ, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology.* 2012;79(3):261-266
Exclusion code: 6

Ruohola J-P, Laaksi I, Ylikomi T, et al. Association between serum 25(OH)D concentrations and bone stress fractures in Finnish young men. *J Bone Miner Res.* 2006;21(9):1483-1488
Exclusion code: 3

Russell R, Chung M, Balk EM, et al. Issues and Challenges in Conducting Systematic Reviews to Support Development of Nutrient Reference Values: Workshop Summary: Nutrition Research Series, Vol. 2. Rockville, MD: 2009.
Exclusion code: 2

Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS ONE.* 2010;5(6):e11088
Exclusion code: 3

Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between vitamin D, parathyroid hormone, and bone health. *J Clin Endocrinol Metab.* 2011;96(3):E436-446
Exclusion code: 6

Sakalli H, Arslan D, Yucel AE. The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. *Rheumatol Int.* 2012;32(8):2279-2283
Exclusion code: 10

Salesi M, Farajzadegan Z. Efficacy of vitamin D in patients with active rheumatoid arthritis receiving methotrexate therapy. *Rheumatol Int.* 2012;32(7):2129-2133
Exclusion code: 15

Salovaara K, Tuppurainen M, Karkkainen M, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. *J Bone Miner Res.* 2010;25(7):1487-1495
Exclusion code: 15

Salzer J, Hallmans G, Nyström M, Stenlund H, Wadell G, Sundström P. VitaminDas a protective factor in multiple sclerosis. *Neurology.* 2012;79(21):2140-2145
Exclusion code: 3

Sambrook PN, Chen CJ, March L, et al. High bone turnover is an independent predictor of mortality in the frail elderly. *J Bone Miner Res.* 2006;21(4):549-555
Exclusion code: 3

Sambrook PN, Chen JS, March LM, et al. Serum parathyroid hormone predicts time to fall independent of vitamin D status in a frail elderly population. *J Clin Endocrinol Metab.* 2004;89(4):1572-1576
Exclusion code: 6

Samefors M, Ostgren CJ, Molstad S, Lannering C, Midlov P, Tengblad A. Vitamin D deficiency in elderly people in Swedish nursing homes is associated with increased mortality. *Eur J Endocrinol.* 2014;170(5):667-675
Exclusion code: 3

Samuel L, Borrell LN. The effect of body mass index on optimal vitamin D status in U.S. adults: the National Health and Nutrition Examination Survey 2001-2006. *Ann Epidemiol.* 2013;23(7):409-414
Exclusion code: 2

Sanders KM, Stuart AL, Merriman EN, et al. Trials and tribulations of recruiting 2,000 older women onto a clinical trial investigating falls and fractures: Vital D study. *BMC Med Res Methodol.* 2009;9:78
Exclusion code: 6

Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. *Br J Psychiatry.* 2011;198(5):357-364
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 16;303(23):2357]. *JAMA.* 2010;303(18):1815-1822
Exclusion code: 14

Sarkis KS, Salvador MB, Pinheiro MM, Silva RG, Zerbini CA, Martini LA. Association between osteoporosis and rheumatoid arthritis in women: a cross-sectional study. *Sao Paulo Med J.* 2009;127(4):216-222
Exclusion code: 7

Sato Y, Honda Y, Hayashida N, Iwamoto J, Kanoko T, Satoh K. Vitamin K deficiency and osteopenia in elderly women with Alzheimer's disease. *Arch Phys Med Rehabil.* 2005;86(3):576-581
Exclusion code: 5

Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis.* 2005;20(3):187-192
Exclusion code: 4

Sato Y, Iwamoto J, Kanoko T, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in hospitalized, elderly women with Alzheimer's disease: A randomized controlled trial. *J Bone Miner Res.* 2005;20(8):1327-1333
Exclusion code: 4

Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1 alpha-hydroxyvitamin D3 and calcium supplementation. *Stroke.* 1997;28(4):736-739
Exclusion code: 14

Sato Y, Metoki N, Iwamoto J, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. *Neurology.* 2003;61(3):338-342
Exclusion code: 4

Schaafsma A, Muskiet FA, Storm H, Hofstede GJ, Pakan I, Van der Veer E. Vitamin D(3) and vitamin K(1) supplementation of Dutch postmenopausal women with normal and low bone mineral densities: effects on serum 25-hydroxyvitamin D and carboxylated osteocalcin. *Eur J Clin Nutr.* 2000;54(8):626-631
Exclusion code: 6

Schaafsma A, van Doormaal JJ, Muskiet FA, Hofstede GJ, Pakan I, van der Veer E. Positive effects of a chicken eggshell powder-enriched vitamin-mineral supplement on femoral neck bone mineral density in healthy late post-menopausal Dutch women. *Br J Nutr.* 2002;87(3):267-275
Exclusion code: 5

Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr.* 2006;83(4):754-759
Exclusion code: 4

Schneider B, Weber B, Frensch A, Stein J, Fritz J. Vitamin D in schizophrenia, major depression and alcoholism. *J Neural Transm.* 2000;107(7):839-842
Exclusion code: 7

Schnelle JF, Kapur K, Alessi C, et al. Does an exercise and incontinence intervention save healthcare costs in a nursing home population? *J Am Geriatr Soc.* 2003;51(2):161-168
Exclusion code: 5

Scholl TO, Chen X. Vitamin D intake during pregnancy: association with maternal characteristics and infant birth weight. *Early Hum Dev.* 2009;85(4):231-234
Exclusion code: 4

Schott GD, Wills MR. Muscle weakness in osteomalacia. *Lancet.* 1976;1(7960):626-629
Exclusion code: 8

Schottker B, Ball D, Gellert C, Brenner H. Serum 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. *Ageing Res Rev.* 2012
Exclusion code: 13

Schottker B, Haug U, Schomburg L, et al. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. *Am J Clin Nutr.* 2013;97(4):782-793
Exclusion code: 3

Schottker B, Herder C, Rothenbacher D, Perna L, Muller H, Brenner H. Serum 25-hydroxyvitamin D levels and incident diabetes mellitus type 2: a competing risk analysis in a large population-based cohort of older adults. *Eur J Epidemiol.* 2013;28(3):267-275
Exclusion code: 3

Schroth RJ, Jeal NS, Kliewer E, Sellers EA. The relationship between vitamin D and severe early childhood caries: a pilot study. *Int J Vitam Nutr Res.* 2012;82(1):53-62
Exclusion code: 4

Schwalfenberg G. Vitamin D and diabetes: improvement of glycemic control with vitamin D3 repletion. *Can Fam Physician.* 2008;54(6):864-866
Exclusion code: 7

Schwalfenberg GK, Genuis SJ. Vitamin D supplementation in a nursing home population. *Mol Nutr Food Res.* 2010;54(8):1072-1076
Exclusion code: 7

Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Res.* 1990;10(5A):1307-1311
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

Scott D, Blizzard L, Fell J, Ding C, Winzenberg T, Jones G. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. *Clin Endocrinol.* 2010;73(5):581-587
Exclusion code: 6

Scragg KRR, Kenealy T, Bryant JL, Camargo Jr CA. Vitamin D for preventing cardiovascular disease. *Cochrane Database Syst Rev.* 2011(1)
Exclusion code: 8

Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. *Diabetes Res Clin Pract.* 1995;27(3):181-188
Exclusion code: 6

Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. *Int J Epidemiol.* 1990;19(3):559-563
Exclusion code: 7

Scragg R, Khaw KT, Murphy S. Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. *Eur J Clin Nutr.* 1995;49(9):640-646
Exclusion code: 10

Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, Ethnicity, and Blood Pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens.* 2007;20(7):713-719
Exclusion code: 6

Seely EW, Wood RJ, Brown EM, Graves SW. Lower serum ionized calcium and abnormal calciotropic hormone levels in preeclampsia. *J Clin Endocrinol Metab.* 1992;74(6):1436-1440
Exclusion code: 4

Segal E, Zinman C, Raz B, Ish-Shalom S. Low patient compliance-A major negative factor in achieving vitamin D adequacy in elderly hip fracture patients supplemented with 800 IU of vitamin D3 daily. *Archives of Gerontology and Geriatrics.* 2009;49(3):364-367
Exclusion code: 4

Semba RD, Houston DK, Ferrucci L, et al. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. *Nutr Res.* 2009;29(8):525-530
Exclusion code: 4

Shah M, Salhab N, Patterson D, Seikaly MG. Nutritional rickets still afflict children in north Texas. *Tex Med.* 2000;96(6):64-68
Exclusion code: 4

Shaikh U, Alpert PT. Nutritional rickets in Las Vegas, Nevada. *J Pediatr Endocrinol Metab.* 2006;19(3):209-212
Exclusion code: 4

Shea MK, Booth SL, Massaro JM, et al. Vitamin K and vitamin D status: associations with inflammatory markers in the Framingham Offspring Study. *Am J Epidemiol.* 2008;167(3):313-320
Exclusion code: 6

Shea MK, Houston DK, Tooze JA, et al. Correlates and prevalence of insufficient 25-hydroxyvitamin D

status in black and white older adults: the health, aging and body composition study. *J Am Geriatr Soc.* 2011;59(7):1165-1174
Exclusion code: 2

Shin M, Minden C. Evaluation of the effectiveness of cholecalciferol in long-term care elderly patients with hypovitaminosis D. *Consult Pharm.* 2011;26(2):101-107
Exclusion code: 7

Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC. Intake of dairy products, calcium, and vitamin d and risk of breast cancer. *J Natl Cancer Inst.* 2002;94(17):1301-1311
Exclusion code: 5

Shipowick CD, Moore CB, Corbett C, Bindler R. Vitamin D and depressive symptoms in women during the winter: a pilot study. *Appl Nurs Res.* 2009;22(3):221-225
Exclusion code: 7

Shiraki M, Kushida K, Yamazaki K, Nagai T, Inoue T, Orimo H. Effects of 2 years' treatment of osteoporosis with 1 alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. *Endocr J.* 1996;43(2):211-220
Exclusion code: 4

Shiraki M, Orimo H, Ito H, et al. Long-term treatment of postmenopausal osteoporosis with active vitamin D3, 1-alpha-hydroxycholecalciferol (1 alpha-OHD3) and 1, 24 Dihydroxycholecalciferol (1, 24(OH)2D3). *Endocrinol Jpn.* 1985;32(2):305-315
Exclusion code: 4

Shirazi L, Almquist M, Malm J, Wirfalt E, Manjer J. Determinants of serum levels of vitamin D: a study of life-style, menopausal status, dietary intake, serum calcium, and PTH. *BMC Womens Health.* 2013;13(1):33
Exclusion code: 3

Shui IM, Mucci LA, Kraft P, et al. Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: A prospective nested case-control study. *J Natl Cancer Inst.* 2012;104(9):690-699
Exclusion code: 3

Signorello LB, Han X, Cai Q, et al. A prospective study of serum 25-hydroxyvitamin d levels and mortality among African Americans and non-African Americans. *Am J Epidemiol.* 2013;177(2):171-179
Exclusion code: 3

Simpson M, Brady H, Yin X, et al. No association of vitamin D intake or 25-hydroxyvitamin D levels in childhood with risk of islet autoimmunity and type 1 diabetes: The Diabetes Autoimmunity Study in the Young (DAISY). *Diabetologia.* 2011;54(11):2779-2788
Exclusion code: 4

Sita-Lumsden A, Lapthorn G, Swaminathan R, Milburn HJ. Reactivation of tuberculosis and vitamin D deficiency: the contribution of diet and exposure to sunlight. *Thorax.* 2007;62(11):1003-1007
Exclusion code: 7

Skaaby T, Husemoen LLN, Pisinger C, et al. Vitamin D status and cause-specific mortality: a general population study. *PLoS ONE [Electronic Resource].* 2012;7(12):e52423
Exclusion code: 3

Skaaby T, Husemoen LLN, Pisinger C, et al. Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population. *Cardiology.* 2012;123(1):62-70
Exclusion code: 6

Skaaby T, Husemoen LLN, Pisinger C, et al. Vitamin D status and incident cardiovascular disease and all-cause mortality: a general population study. *Endocrine.* 2013;43(3):618-625
Exclusion code: 3

Skinner HG, Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006;15(9):1688-1695
Exclusion code: 5

Slinin Y, Paudel M, Taylor BC, et al. Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women. *J Gerontol A Biol Sci Med Sci.* 2012;67(10):1092-1098
Exclusion code: 3

Slinin Y, Paudel ML, Taylor BC, et al. 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. *Neurology.* 2010;74(1):33-41
Exclusion code: 3

Smedshaug GB, Pedersen JI, Meyer HE. Can vitamin D supplementation improve grip strength in elderly nursing home residents? A double-blinded controlled trial. *Scand J Food Nutr.* 2007;51(2):74-78
Exclusion code: 15

Appendix B4. List of Excluded Studies

Smit E, Crespo CJ, Michael Y, et al. The effect of vitamin D and frailty on mortality among non-institutionalized US older adults. *Eur J Clin Nutr.* 2012;66(9):1024-1028
Exclusion code: 3

Smith H, Anderson F, Raphael H, Crozier S, Cooper C. Effect of annual intramuscular vitamin D supplementation on fracture risk: Population-based, randomised, double-blind, placebo-controlled trial. *Rheumatology.* 2007;46(12):1852-1857
Exclusion code: 14

Smith SM, Gardner KK, Locke J, Zwart SR. Vitamin D supplementation during Antarctic winter. *Am J Clin Nutr.* 2009;89(4):1092-1098
Exclusion code: 12

Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. *Mult Scler.* 2008;14(9):1220-1224
Exclusion code: 4

Sneve M, Figenschau Y, Jorde R. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. *Eur J Endocrinol.* 2008;159(6):675-684
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

Sohl E, Heymans MW, de Jongh RT, et al. Prediction of vitamin D deficiency by simple patient characteristics. *Am J Clin Nutr.* 2014;99(5):1089-1095
Exclusion code: 7

Sohl E, van Schoor NM, de Jongh RT, Visser M, Deeg DJH, Lips P. Vitamin D Status Is Associated With Functional Limitations and Functional Decline in Older Individuals. *J Clin Endocrinol Metab.* 2013;98(9):E1483-E1490
Exclusion code: 3

Soilu-Hanninen M, Aivo J, Lindstrom BM, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83(5):565-571
Exclusion code: 6

Soilu-Hanninen M, Laaksonen M, Laitinen I, Eralinna JP, Lilius EM, Mononen I. A longitudinal study of serum 25-hydroxyvitamin D and intact parathyroid hormone levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2008;79(2):152-157
Exclusion code: 7

Sokol SI, Srinivas V, Crandall JP, et al. The effects of vitamin D repletion on endothelial function and inflammation in patients with coronary artery disease. *Vasc Med.* 2012;17(6):394-404
Exclusion code: 4

Sonderman JS, Munro HM, Blot WJ, Signorello LB. Reproducibility of serum 25-hydroxyvitamin d and vitamin D-binding protein levels over time in a prospective cohort study of black and white adults. *Am J Epidemiol.* 2012;176(7):615-621
Exclusion code: 2

Songpatanasilp T, Chailurkit L-O, Nichachotsalid A, Chantarasorn M. Combination of alfacalcidol with calcium can improve quadriceps muscle strength in elderly ambulatory Thai women who have hypovitaminosis D: a randomized controlled trial. *J Med Assoc Thai.* 2009;92 Suppl5:S30-41
Exclusion code: 15

Soni M, Kos K, Lang IA, Jones K, Melzer D, Llewellyn DJ. Vitamin D and cognitive function. *Scand J Clin Lab Invest.* 2012;243:79-82
Exclusion code: 8

Sørensen OH, Lund B, Saltin B, et al. Myopathy in bone loss of ageing: Improvement by treatment with 1α-hydroxycholecalciferol and calcium. *Clin Sci (Lond).* 1979;56(2):157-161
Exclusion code: 15

Sorva A, Risteli J, Risteli L, Valimaki M, Tilvis R. Effects of vitamin D and calcium on markers of bone metabolism in geriatric patients with low serum 25-hydroxyvitamin D levels. *Calcif Tissue Int.* 1991;49 Suppl:S88-89
Exclusion code: 6

Souberbielle JC, Friedlander G, Cormier C. Practical considerations in PTH testing. *Clin Chim Acta.* 2006;366(1-2):81-89
Exclusion code: 6

Specker BL, Ho ML, Oestreich A, et al. Prospective study of vitamin D supplementation and rickets in China. *J Pediatr.* 1992;120(5):733-739

Exclusion code: 4

Specker BL, Tsang RC. Cyclical serum 25-hydroxyvitamin D concentrations paralleling sunshine exposure in exclusively breast-fed infants. *J Pediatr.* 1987;110(5):744-747
Exclusion code: 4

Specker BL, Valanis B, Hertzberg V, Edwards N, Tsang RC. Sunshine exposure and serum 25-hydroxyvitamin D concentrations in exclusively breast-fed infants. *J Pediatr.* 1985;107(3):372-376
Exclusion code: 4

Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, D.C.: National Academy Press; 1999. Exclusion code: 8

Stein MS, Liu Y, Gray OM, et al. A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis. *Neurology.* 2011;77(17):1611-1618
Exclusion code: 6

Stern PH, Taylor AB, Bell NH, Epstein S. Demonstration that circulating 1 alpha, 25-dihydroxyvitamin D is loosely regulated in normal children. *J Clin Invest.* 1981;68(5):1374-1377
Exclusion code: 4

Stewart JW, Alekel DL, Ritland LM, Van Loan M, Gertz E, Genschel U. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. *Menopause.* 2009;16(6):1093-1101
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

Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):81-93
Exclusion code: 6

Stone K, Bauer DC, Black DM, Sklarin P, Ensrud KE, Cummings SR. Hormonal predictors of bone loss in elderly women: a prospective study. The Study of Osteoporotic Fractures Research Group. *J Bone Miner Res.* 1998;13(7):1167-1174
Exclusion code: 6

Storm D, Eslin R, Porter ES, et al. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: a randomized placebo-controlled trial. *J Clin Endocrinol Metab.* 1998;83(11):3817-3825
Exclusion code: 5

Strachan DP, Powell KJ, Thaker A, Millard FJ, Maxwell JD. Vegetarian diet as a risk factor for tuberculosis in immigrant south London Asians. *Thorax.* 1995;50(2):175-180
Exclusion code: 5

Stratton-Loeffler M, Lo J, Hui R, Coates A, Minkoff J, Budayr A. Treatment of Vitamin D Deficiency Within a Large Integrated Health Care Delivery System. *J Manag Care Pharm.* 2012;18(7):497-505
Exclusion code: 2

Straube S, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. *Pain.* 2009;141(1-2):10-13
Exclusion code: 4

Straube S, Derry S, Moore RA, McQuay HJ. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev.* 2010(1):CD007771
Exclusion code: 4

Streck WF, Waterhouse C, Haddad JG. Glucocorticoid effects in vitamin D intoxication. *Arch Intern Med.* 1979;139(9):974-977
Exclusion code: 6

Stubbs JR, Idiculla A, Slusser J, Menard R, Quarles LD. Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. *J Am Soc Nephrol.* 2010;21(2):353-361
Exclusion code: 4

Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. *Diabet Med.* 2008;25(3):320-325
Exclusion code: 4

Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF. Adolescent girls in maine are at risk for

vitamin D insufficiency. *J Am Diet Assoc.* 2005;105(6):971-974
Exclusion code: 4

Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke.* 2012;43(6):1470-1477
Exclusion code: 3

Suzuki T, Kwon J, Kim H, et al. Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. *J Bone Miner Res.* 2008;23(8):1309-1317
Exclusion code: 2

Swanenburg J, de Bruin ED, Stauffacher M, Mulder T, Uebelhart D. Effects of exercise and nutrition on postural balance and risk of falling in elderly people with decreased bone mineral density: randomized controlled trial pilot study. *Clin Rehabil.* 2007;21(6):523-534
Exclusion code: 5

Syroney L, Franjesevic A. Vitamin D deficiency: screening and treatment in primary care. *Adv Nurse Pract.* 2010;18(5):37-38
Exclusion code: 8

Szulc P, Claustrat B, Delmas PD. Serum concentrations of 17beta-E2 and 25-hydroxycholecalciferol (25OHD) in relation to all-cause mortality in older men--the MINOS study. *Clin Endocrinol (Oxf).* 2009;71(4):594-602
Exclusion code: 15

Szulc P, Maurice C, Marchand F, Delmas PD. Increased bone resorption is associated with higher mortality in community-dwelling men ≥50 years of age: The MINOS study. *J Bone Miner Res.* 2009;24(6):1116-1124
Exclusion code: 5

Tai K, Need AG, Horowitz M, Chapman IM. Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. *Nutrition.* 2008;24(10):950-956
Exclusion code: 10

Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet.* 2007;370(9588):657-666
Exclusion code: 13

Tang JY, Fu T, Leblanc E, et al. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. *J Clin Oncol.* 2011;29(22):3078-3084
Exclusion code: 14

Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med.* 2002;112(8):659-662
Exclusion code: 6

Tangrea J, Helzlsouer K, Pietinen P, et al. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control.* 1997;8(4):615-625
Exclusion code: 6

Tarcin O, Yavuz DG, Ozben B, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab.* 2009;94(10):4023-4030
Exclusion code: 5

Targher G, Bertolini L, Padovani R, et al. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. *Clin Endocrinol (Oxf).* 2006;65(5):593-597
Exclusion code: 5

Taussig HB. Possible injury to the cardiovascular system from vitamin D. *Ann Intern Med.* 1966;65(6):1195-1200
Exclusion code: 8

Taylor CB, Hass GM, Ho KJ, Liu LB. Risk factors in the pathogenesis of atherosclerotic heart disease and generalized atherosclerosis. *Ann Clin Lab Sci.* 1972;2(3):239-243
Exclusion code: 8

Taylor CL, Carriquiry AL, Bailey RL, Sempos CT, Yetley EA. Appropriateness of the probability approach with a nutrient status biomarker to assess population inadequacy: a study using vitamin D. *Am J Clin Nutr.* 2013;97(1):72-78
Exclusion code: 2

Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol.* 2004;15(12):3225-3232
Exclusion code: 5

Tellioglu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral

cholecalciferol in vitamin D deficient/insufficient elderly. *Maturitas.* 2012;72(4):332-338
Exclusion code: 12

Thiebaud D, Burckhardt P, Costanza M, et al. Importance of albumin, 25(OH)-vitamin D and IGFBP-3 as risk factors in elderly women and men with hip fracture. *Osteoporos Int.* 1997;7(5):457-462
Exclusion code: 5

Thomas GN, o Hartaigh B, Bosch JA, et al. Vitamin D levels predict all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. *Diabetes Care.* 2012;35(5):1158-1164
Exclusion code: 4

Thomas M, Lloyd-Jones D, Thadhani R, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med.* 1998;338(12):777-783
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

Tilyard MW, Spears GFS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med.* 1992;326(6):357-362
Exclusion code: 4

Timms PM, Mannan N, Hitman GA, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *Qjm.* 2002;95(12):787-796
Exclusion code: 6

Tjellesen L, Hummer L, Christiansen C, Rodbro P. Serum concentration of vitamin D metabolites during treatment with vitamin D2 and D3 in normal premenopausal women. *Bone Miner.* 1986;1(5):407-413
Exclusion code: 12

Tolppanen AM, Sayers A, Granell R, Fraser WD, Henderson J, Lawlor DA. Prospective association of 25-hydroxyvitamin D3 and D2 with childhood lung function, asthma, wheezing, and flexural dermatitis. *Epidemiology.* 2013;24(2):310-319
Exclusion code: 4

Toner CD, Davis CD, Milner JA. The vitamin D and cancer conundrum: aiming at a moving target. *J Am Diet Assoc.* 2010;110(10):1492-1500
Exclusion code: 8

Toriola AT, Surcel HM, Calypse A, et al. Independent and joint effects of serum 25-hydroxyvitamin D and calcium on ovarian cancer risk: a prospective nested case-control study. *Eur J Cancer.* 2010;46(15):2799-2805
Exclusion code: 6

Toss G, Andersson R, Diffey BL, Fall PA, Larko O, Larsson L. Oral vitamin D and ultraviolet radiation for the prevention of vitamin D deficiency in the elderly. *Acta Med Scand.* 1982;212(3):157-161
Exclusion code: 6

Tran B, Armstrong BK, McGeechan K, et al. Predicting vitamin D deficiency in older Australian adults. *Clin Endocrinol (Oxf).* 2013
Exclusion code: 7

Trang HM, Cole DEC, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr.* 1998;68(4):854-858
Exclusion code: 6

Travis RC, Crowe FL, Allen NE, et al. Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Epidemiol.* 2009;169(10):1223-1232
Exclusion code: 3

Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm TE. Association between serum 25(OH)D and death from prostate cancer. *Br J Cancer.* 2009;100(3):450-454
Exclusion code: 7

Tretli S, Schwartz GG, Torjesen PA, Robsahm TE. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study. *Cancer Causes Control.* 2012;23(2):363-370
Exclusion code: 4

Tripkovic L, Lambert H, Hart K, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr.* 2012;95(6):1357-1364
Exclusion code: 2

Appendix B4. List of Excluded Studies

Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *Br Med J (Clin Res Ed).* 2003;326(7387):469
Exclusion code: 14

Tsagari A, Toulis KA, Makras P, Skagias K, Galanos A, Lyritis G. Performance of the mini nutritional assessment score in the detection of vitamin D status in an elderly Greek population. *Horm Metab Res.* 2012;44(12):896-899
Exclusion code: 6

Tseng M, Giri V, Bruner DW, Giovannucci E. Prevalence and correlates of vitamin D status in African American men. *BMC Public Health.* 2009;9:191
Exclusion code: 6

Tsur A, Feldman BS, Feldhammer I, Hoshen MB, Leibowitz G, Balicer RD. Decreased serum concentrations of 25-hydroxycholecalciferol are associated with increased risk of progression to impaired fasting glucose and diabetes. *Diabetes Care.* 2013;36(5):1361-1367
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

U.S. Preventive Services Task Force. Procedure Manual. 2011; AHRQ Publication No. 08-05118-EF. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm. Accessed April 3,, 2013
Exclusion code: 2.

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Exclusion code: 2.

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Exclusion code: 6

Ward KA, Das G, Roberts SA, et al. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females. *J Clin Endocrinol Metab.* 2010;95(10):4643-4651
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Watson KE, Abrolat ML, Malone LL, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation.* 1997;96(6):1755-1760
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Wei MY, Giovannucci EL. Vitamin D and multiple health outcomes in the Harvard cohorts. *Mol Nutr Food Res.* 2010;54(8):1114-1126
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Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab.* 2007;92(6):2058-2065
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Exclusion code: 7

Wong YYE, Flicker L, Yeap BB, McCaul KA, Hankey GJ, Norman PE. Is hypovitaminosis D associated with abdominal aortic aneurysm, and is there a dose-response relationship? *Eur J Vasc Endovasc Surg.* 2013;45(6):657-664
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Wu SH, Ho SC, Zhong L. Effects of vitamin D supplementation on blood pressure. *South Med J.* 2010;103(8):729-737
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Yamshchikov AV, Desai NS, Blumberg HM, Ziegler TR, Tangpricha V. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. *Endocr Pract.* 2009;15(5):438-449
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Exclusion code: 6

Yanoff LB, Parikh SJ, Spitalnik A, et al. The prevalence of hypovitaminosis D and secondary hyperparathyroidism in obese Black Americans. *Clin Endocrinol.* 2006;64(5):523-529
Exclusion code: 6

Yaylim-Eraltan I, Arzu Ergen H, Arikan S, et al. Investigation of the VDR gene polymorphisms association with susceptibility to colorectal cancer. *Cell Biochem Funct.* 2007;25(6):731-737
Exclusion code: 7

Yesudian PD, Berry JL, Wiles S, et al. The effect of ultraviolet B-induced vitamin D levels on host resistance to Mycobacterium tuberculosis: a pilot study in immigrant Asian adults living in the United Kingdom. *Photodermatol Photoimmunol Photomed.* 2008;24(2):97-98
Exclusion code: 5

Yetley E. Assessing the vitamin D status of the US population. *Am J Clin Nutr.* 2008;88(558S)
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Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. *Aliment Pharmacol Ther.* 2009;30(2):113-125
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Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: serum vitamin D and breast cancer risk. *Eur J Cancer.* 2010;46(12):2196-2205
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Yin L, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis of longitudinal studies: Serum vitamin D and prostate cancer risk. *Cancer Epidemiol.* 2009;33(6):435-445
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Yiu YF, Yiu KH, Siu CW, et al. Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. *Atherosclerosis.* 2013;227(1):140-146
Exclusion code: 6

Yu CKH, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clin Endocrinol.* 2009;70(5):685-690
Exclusion code: 4

Yusupov EL-N, M; Pollack, S; Yeh, JK; Mikhail, M; Aloia, JF. Vitamin d and serum cytokines in a randomized clinical trial. *Int J Endocrinol.* 2010
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Exclusion code: 4

Zeghoud F, Vervel C, Guillozo H, Walrant-Debray O, Boutignon H, Garabedian M. Subclinical vitamin D deficiency in neonates: definition and response to vitamin D supplements. *Am J Clin Nutr.* 1997;65(3):771-778
Exclusion code: 4

Zermansky AG, Alldred DP, Petty DR, et al. Clinical medication review by a pharmacist of elderly people living in care homes--randomised controlled trial. *Age Ageing.* 2006;35(6):586-591
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

with hypertension: the NHANES linked mortality study. *Journal of Hypertension.* 2012;30(2):284-289
Exclusion code: 4

Zhou C, Assem M, Tay JC, et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. *J Clin Invest.* 2006;116(6):1703-1712
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Zhou G, Stoitzfus J, Swan BA. Optimizing vitamin D status to reduce colorectal cancer risk: an evidentiary review. *Clin J Oncol Nurs.* 2009;13(4):E3-E17
Exclusion code: 13

Zhou W, Heist RS, Liu G, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. *J Clin Oncol.* 2007;25(5):479-485
Exclusion code: 4

Zhu K, Austin N, Devine A, Bruce D, Prince RL. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. *J Am Geriatr Soc.* 2010;58(11):2063-2068
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

Zhu K, Devine A, Dick IM, Wilson SG, Prince RL. Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: A five-year randomized controlled trial. *J Clin Endocrinol Metab.* 2008;93(3):743-749
Exclusion code: 15

Zhu W, Cai D, Wang Y, et al. Calcium plus vitamin D3 supplementation facilitated Fat loss in overweight and obese college students with very-low calcium consumption: A randomized controlled trial. *Nutr J.* 2013:8
Exclusion code: 6

Ziambaras K, Dagogo-Jack S. Reversible muscle weakness in patients with vitamin D deficiency. *West J Med.* 1997;167(6):435-439
Exclusion code: 8

Ziegler EE, Hollis BW, Nelson SE, Jeter JM. Vitamin D deficiency in breastfed infants in Iowa. *Pediatrics.* 2006;118(2):603-610
Exclusion code: 4

Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child.* 2008;93(6):512-517
Exclusion code: 4

Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr.* 2009;89(5):1321-1327
Exclusion code: 5

Zittermann A, Gummert JF, Borgermann J. Vitamin D deficiency and mortality. *Curr Opin Clin Nutr Metab Care.* 2009;12(6):634-639
Exclusion code: 7

Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr.* 2012;95(1):91-100
Exclusion code: 3

Zittermann A, Schleithoff SS, Frisch S, et al. Circulating calcitriol concentrations and total mortality. *Clin Chem.* 2009;55(6):1163-1170
Exclusion code: 4

Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev.* 2006;11(1):25-33
Exclusion code: 8

Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol.* 2003;41(1):105-112
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

Dissemination CfRa. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis (Structured abstract). *DARE.* 2013(4)
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

Dissemination CfRa. Interventions for preventing falls in acute- and chronic-care hospitals: a systematic review and meta-analysis (Structured abstract). *DARE.* 2013(4)
Exclusion code: 13

Dissemination CfRa. 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.* 2013(4)
Exclusion code: 13

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

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

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

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

Annweiler C, Beauchet O. Vitamin D-mentia: randomized clinical trials should be the next step. *Neuroepidemiology.* 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

Bedner M, Lippa KA, Tai SS. An assessment of 25-hydroxyvitamin D measurements in comparability studies conducted by the Vitamin D Metabolites Quality Assurance Program. *Clin Chim Acta.* 2013;426:6-11
Exclusion code: 2

Bell DSH. Protean manifestations of vitamin D deficiency, part 1: the epidemic of deficiency. *South Med J.* 2011;104(5):331-334
Exclusion code: 7

Bertone-Johnson ER. Vitamin D and the occurrence of depression: causal association or circumstantial evidence? *Nutr Rev.* 2009;67(8):481-492
Exclusion code: 8

Binkley N, Krueger DC, Morgan S, Wiebe D. Current status of clinical 25-hydroxyvitamin D measurement: an assessment of between-laboratory agreement. *Clin Chim Acta.* 2010;411(23-24):1976-1982
Exclusion code: 2

Bischoff-Ferrari HA. Vitamin D and fracture prevention. *Endocrinol Metab Clin North Am.* 2010;39(2):347-353
Exclusion code: 8

Bischoff-Ferrari HA. "Vitamin D - why does it matter?" - defining vitamin D deficiency and its prevalence. *Scand J Clin Lab Invest.* 2012;243:3-6
Exclusion code: 7

Bischoff-Ferrari HA, Staehelin HB. Importance of vitamin D and calcium at older age. *Int J Vitam Nutr Res.* 2008;78(6):286-292
Exclusion code: 7

Boonen S, Bischoff-Ferrari HA, Cooper C, et al. Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. *Calcif Tissue Int.* 2006;78(5):257-270
Exclusion code: 7

Bosomworth NJ. Mitigating epidemic vitamin D deficiency: the agony of evidence. *Can Fam Physician.* 2011;57(1):16-20
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: 8

Carrozza C, Persichilli S, Canu G, et al. Measurement of 25-hydroxyvitamin vitamin D by liquid chromatography tandem-mass spectrometry with comparison to automated immunoassays. *Clin Chem Lab Med.* 2012;50(11):2033-2035
Exclusion code: 2

Carter GD, Berry JL, Gunter E, et al. Proficiency testing of 25-hydroxyvitamin D (25-OHD) assays. *J Steriod Biochem Mol Biol.* 2010;121(1-2):176-179
Exclusion code: 2

Carter GD, Jones JC. Use of a common standard improves the performance of liquid chromatography-tandem mass spectrometry methods for serum 25-hydroxyvitamin-D. *Ann Clin Biochem.* 2009;46(Pt 1):79-81
Exclusion code: 2

Cashman KD, Kiely M, Kinsella M, et al. Evaluation of Vitamin D Standardization Program protocols for standardizing serum 25-hydroxyvitamin D data: a case study of the program's potential for national nutrition and health surveys. *Am J Clin Nutr.* 2013;97(6):1235-1242
Exclusion code: 2

Cava RC, Javier AND. Vitamin D deficiency. *N Engl J Med.* 2007;357(19):1981; author reply 1981-1982
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

Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int.* 1997;7(5):439-443
Exclusion code: 6

Cherniack EP, Levis S, Troen BR. Hypovitaminosis D: a widespread epidemic. *Geriatrics.* 2008;63(4):24-30
Exclusion code: 8

Cherniack EP, Troen BR, Florez HJ, Roos BA, Levis S. Some new food for thought: the role of vitamin D in the mental health of older adults. *Curr Psychiatry Rep.* 2009;11(1):12-19
Exclusion code: 7

Christakos S, Hewison M, Gardner DG, et al. Vitamin D: beyond bone. *Ann N Y Acad Sci.* 2013;1287:45-58
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

Cornell JE, Mulrow CD, Localio R, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. *Ann Intern Med.* 2014;160(4):267-270
Exclusion code: 2

Dawson-Hughes B. Serum 25-hydroxyvitamin D and muscle atrophy in the elderly. *Proc Nutr Soc.* 2012;71(1):46-49
Exclusion code: 7

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Appendix B4. List of Excluded Studies

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Holick MF. Vitamin D: a d-lightful solution for health. *J Investig Med.* 2011;59(6):872-880
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Lips P. Worldwide status of vitamin D nutrition. *J Steriod Biochem Mol Biol.* 2010;121(1-2):297-300
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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
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Mitri J, Pittas AG. Diabetes: Shining a light: the role of vitamin D in diabetes mellitus. *Nat Rev Endocrinol.* 2010;6(9):478-480
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Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ.* 2010;340:b5664
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Straube S, Derry S, Moore AR, McQuay HJ. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev.* 2012(8)
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Vanlint SJ. Vitamin D and adult bone health in Australia and New Zealand: a position statement. *Med J Aust.* 2005;183(1):52; author reply 53-54

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Winzenberg T, van der Mei I, Mason RS, Nowson C, Jones G. Vitamin D and the musculoskeletal health of older adults. *Aust Fam Physician.* 2012;41(3):92-99
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Youssef DA, El Abbassi AM, Cutchins DC, Chhabra S, Peiris AN. Vitamin D deficiency: implications for acute care in the elderly and in patients with chronic illness. *Geriatr Gerontol Int.* 2011;11(4):395-407
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Exclusion code: 15

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Exclusion code: 7

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Exclusion code: 4

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Chlebowski RT, Pettinger M, Johnson KC, et al. Calcium plus vitamin D supplementation and joint symptoms in postmenopausal women in the women's health initiative randomized trial. *J Acad Nutr Diet.* 2013;113(10):1302-1310
Exclusion code: 14

Chowdhury R, Kunutsor S, Vitezova A, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ.* 2014;348
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Close GL, Russell J, Cobley JN, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. *J Sports Sci.* 2013;31(4):344-353
Exclusion code: 3

Dam TTL, von Muhlen D, Barrett-Connor EL. Sex-specific association of serum 25-Hydroxyvitamin D levels with physical function in older adults. *Osteoporos Int.* 2009;20(5):751-760
Exclusion code: 3

Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *Am J Clin Nutr.* 2008;88(2):537S-540S
Exclusion code: 3

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Exclusion code: 4

Ding H, Dhima K, Lockhart KC, et al. Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. *Neurology.* 2013;81(17):1531-1537
Exclusion code: 7

Fiscella K, Franks P. Vitamin D, race, and cardiovascular mortality: findings from a national US sample. *Ann Fam Med.* 2010;8(1):11-18
Exclusion code: 3

Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum Vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care.* 2005;28(5):1228-1230
Exclusion code: 7

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Exclusion code: 3

Freedman DM, Looker AC, Chang S-C, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst.* 2007;99(21):1594-1602
Exclusion code: 3

Gallicchio L, Helzlsouer KJ, Chow W-H, et al. Circulating 25-hydroxyvitamin D and the risk of rarer cancers: Design and methods of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):10-20
Exclusion code: 8

Gallicchio L, Moore LE, Stevens VL, et al. Circulating 25-hydroxyvitamin D and risk of kidney cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):47-57
Exclusion code: 6

Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. *Int J Cancer.* 2011;128(6):1414-1424
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Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJ. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 1996;5(2):121-126
Exclusion code: 6

Gilbert R, Metcalfe C, Fraser WD, et al. Associations of circulating 25-hydroxyvitamin D with prostate cancer diagnosis, stage and grade. *Int J Cancer.* 2012;131(5):1187-1196
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Gonzalez-Molero I, Rojo-Martinez G, Morcillo S, et al. Vitamin D and incidence of diabetes: a prospective cohort study. *Clin Nutr.* 2012;31(4):571-573
Exclusion code: 3

Griffin FC, Gadegbeku CA, Sowers MR. Vitamin D and subsequent systolic hypertension among women. *Am J Hypertens.* 2011;24(3):316-321

Exclusion code: 6

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Exclusion code: 8

Hosseinpanah F, Yarjanli M, Sheikholeslami F, Heibatollahi M, Eskandary PS, Azizi F. Associations between vitamin D and cardiovascular outcomes; Tehran Lipid and Glucose Study. *Atherosclerosis.* 2011;218(1):238-242
Exclusion code: 4

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Exclusion code: 6

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Exclusion code: 7

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Exclusion code: 3

Jia X, Aucott LS, McNeill G. Nutritional status and subsequent all-cause mortality in men and women aged 75 years or over living in the community. *Br J Nutr.* 2007;98(3):593-599
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Johansson H, Oden A, Kanis J, et al. Low serum vitamin D is associated with increased mortality in elderly men: MrOS Sweden. *Osteoporos Int.* 2012;23(3):991-999
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Kaloostian CL, Shil AB. Effects of vitamin D on muscle strength and mobility in older women. *J Am Geriatr Soc.* 2011;59(4):771; author reply 771-772
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Kalra P, Das V, Agarwal A, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *Br J Nutr.* 2012;108(6):1052-1058
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Kayaniyil S, Retnakaran R, Harris SB, et al. Prospective associations of vitamin D with -cell function and glycemia: the PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. *Diabetes.* 2011;60(11):2947-2953
Exclusion code: 4

Kilkkinen A, Knekt P, Aro A, et al. Vitamin D status and the risk of cardiovascular disease death. *Am J Epidemiol.* 2009;170(8):1032-1039
Exclusion code: 2

Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Saaksjarvi K, Heliovaara M. Serum vitamin D and the risk of Parkinson disease. *Arch Neurol.* 2010;67(7):808-811
Exclusion code: 3

Knekt P, Laaksonen M, Mattila C, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiology.* 2008;19(5):666-671
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Lane NE, Gore LR, Cummings SR, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum.* 1999;42(5):854-860
Exclusion code: 3

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Exclusion code: 6

Liang G, Nan H, Qureshi AA, Han J. Pre-diagnostic plasma 25-hydroxyvitamin D levels and risk of non-melanoma skin cancer in women. *PLoS ONE [Electronic Resource].* 2012;7(4):e35211
Exclusion code: 6

Llewellyn DJ, Lang IA, Langa KM, et al. Vitamin D and risk of cognitive decline in elderly persons. *Arch Intern Med.* 2010;170(13):1135-1141
Exclusion code: 3

Looker AC, Mussolino ME. Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults. *J Bone Miner Res.* 2008;23(1):143-150
Exclusion code: 3

Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared

with 2000-2004. *Am J Clin Nutr.* 2008;88(6):1519-1527
Exclusion code: 3

McCullough ML, Weinstein SJ, Freedman DM, et al. Correlates of circulating 25-hydroxyvitamin D: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):21-35
Exclusion code: 3

Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med.* 2008;168(15):1629-1637
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Menant JC, Close JCT, Delbaere K, et al. Relationships between serum vitamin D levels, neuromuscular and neuropsychological function and falls in older men and women. *Osteoporos Int.* 2012;23(3):981-989
Exclusion code: 3

Michaelsson K, Baron JA, Snellman G, et al. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. *Am J Clin Nutr.* 2010;92(4):841-848
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Michos ED, Reis JP, Post WS, et al. 25-Hydroxyvitamin D deficiency is associated with fatal stroke among whites but not blacks: The NHANES-III linked mortality files. *Nutrition.* 2012;28(4):367-371
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Milaneschi Y, Shardell M, Corsi AM, et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. *J Clin Endocrinol Metab.* 2010;95(7):3225-3233
Exclusion code: 3

Millen AE, Wactawski-Wende J, Pettinger M, et al. Predictors of serum 25-hydroxyvitamin D concentrations among postmenopausal women: the Women's Health Initiative Calcium plus Vitamin D clinical trial. *Am J Clin Nutr.* 2010;91(5):1324-1335
Exclusion code: 3

Mondul AM, Weinstein SJ, Horst RL, Purdue M, Albanes D. Serum vitamin D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial. *Cancer Epidemiol Biomarkers Prev.* 2012;21(7):1222-1225
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Mondul AM, Weinstein SJ, Mannisto S, et al. Serum vitamin D and risk of bladder cancer. *Cancer Res.* 2010;70(22):9218-9223
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Nomura AM, Stemmermann GN, Lee J, et al. Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States). *Cancer Causes Control.* 1998;9(4):425-432
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Pan WH, Wang CY, Li LA, Kao LS, Yeh SH. No significant effect of calcium and vitamin D supplementation on blood pressure and calcium metabolism in elderly Chinese. *Chin J Physiol.* 1993;36(2):85-94
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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
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Pilz S, Dobnig H, Nijpels G, et al. Vitamin D and mortality in older men and women. *Clin Endocrinol.* 2009;71(5):666-672
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Purdue MP, Freedman DM, Gapstur SM, et al. Circulating 25-hydroxyvitamin D and risk of non-hodgkin lymphoma: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):58-69
Exclusion code: 6

Rejnmark L, Tietze A, Vestergaard P, et al. Reduced prediagnostic 25-hydroxyvitamin D levels in women with breast cancer: a nested case-control study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(10):2655-2660
Exclusion code: 7

Rienstra M, Cheng S, Larson MG, et al. Vitamin D status is not related to development of atrial fibrillation in the community. *Am Heart J.* 2011;162(3):538-541
Exclusion code: 6

Robinson-Cohen C, Hoofnagle AN, Ix JH, et al. Racial differences in the association of serum 25-hydroxyvitamin d concentration with coronary heart disease eventsrace and chd events associated with vitamin drace and chd events associated with vitamin d. *JAMA.* 2013;310(2):179-188

Exclusion code: 3

Salehpour A, Shidfar F, Hosseinpanah F, et al. Vitamin D3 and the risk of CVD in overweight and obese women: a randomised controlled trial. *Br J Nutr.* 2012;108(10):1866-1873
Exclusion code: 3

Schierbeck LL, Rejnmark L, Tofteng CL, et al. Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events: a 16-year follow-up study. *Eur J Endocrinol.* 2012;167(4):553-560
Exclusion code: 3

Semba RD, Garrett E, Johnson BA, Guralnik JM, Fried LP. Vitamin D deficiency among older women with and without disability. *Am J Clin Nutr.* 2000;72(6):1529-1534
Exclusion code: 3

Semba RD, Houston DK, Bandinelli S, et al. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. *Eur J Clin Nutr.* 2010;64(2):203-209
Exclusion code: 3

Simha V, Mahmood M, Ansari M, Spellman CW, Shah P. Effect of vitamin D replacement on insulin sensitivity in subjects with vitamin D deficiency. *J Investig Med.* 2012;60(8):1214-1218
Exclusion code: 3

Sohl E, de Jongh RT, Heijboer AC, et al. Vitamin D status is associated with physical performance: the results of three independent cohorts. *Osteoporos Int.* 2013;24(1):187-196
Exclusion code: 3

Stolzenberg-Solomon RZ, Hayes RB, Horst RL, Anderson KE, Hollis BW, Silverman DT. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. *Cancer Res.* 2009;69(4):1439-1447
Exclusion code: 6

Stolzenberg-Solomon RZ, Vieth R, Azad A, et al. A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res.* 2006;66(20):10213-10219
Exclusion code: 6

Sun Q, Shi L, Rimm EB, et al. Vitamin D intake and risk of cardiovascular disease in US men and women. *Am J Clin Nutr.* 2011;94(2):534-542
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

Tuohimaa P, Tenkanen L, Ahonen M, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int J Cancer.* 2004;108(1):104-108
Exclusion code: 3

Tuohimaa P, Tenkanen L, Syvala H, et al. Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16(2):302-307
Exclusion code: 6

Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16(4):783-788
Exclusion code: 6

Visser M, Deeg DJH, Puts MTE, Seidell JC, Lips P. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. *Am J Clin Nutr.* 2006;84(3):616-622; quiz 671-612
Exclusion code: 3

Wang H, Xia N, Yang Y, Peng D-Q. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. *Lipids health dis.* 2012;11:42
Exclusion code: 3

Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation.* 2008;117(4):503-511
Exclusion code: 3

Weinstein SJ, Yu K, Horst RL, Ashby J, Virtamo J, Albanes D. Serum 25-hydroxyvitamin D and risks of colon and rectal cancer in Finnish men. *Am J Epidemiol.* 2011;173(5):499-508
Exclusion code: 6

Woolcott CG, Wilkens LR, Nomura AMY, et al. Plasma 25-hydroxyvitamin D levels and the risk of colorectal cancer: the multiethnic cohort study.

Appendix B4. List of Excluded Studies

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

Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J Natl Cancer Inst.* 2007;99(14):1120-1129
Exclusion code: 3

Zeleniuch-Jacquotte A, Gallicchio L, Hartmuller V, et al. Circulating 25-hydroxyvitamin D and risk of endometrial cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):36-46
Exclusion code: 6

Zheng W, Danforth KN, Tworoger SS, et al. Circulating 25-hydroxyvitamin D and risk of epithelial ovarian cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol.* 2010;172(1):70-80
Exclusion code: 6

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[149]

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

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

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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

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
≥90% of study participants had 25(OH)D level <20 ng/mL						
Brazier et al, 2005[157] *Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study*	Mean age (years): 74.6 (74.2 vs. 75.0) Female: 100% Race: NR BMI: NR Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 736 (752 vs. 721)	France 50 centers Institutionalized: 0%	Inclusion: Community-dwelling ambulatory women age >65 years who spontaneously consulted a practitioner and presented with vitamin D insufficiency. Exclusion: Hypercalcemia, primary hyperparathyroidism, renal insufficiency, or hepatic insufficiency; taken bisphosphonate, calcitonin, vitamin D or its metabolites, estrogen, raloxifene, fluoride, anticonvulsives, or any other treatment acting on bone metabolism in the past 6 months.	Competitive protein-binding assay	Insufficiency: serum 25(OH)D ≤12	7 vs. 7 100% <20
Chapuy et al, 2002[122] *Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk. The Decalyos II Study*	Mean age‡ (years): 85 (84.9† vs. 85.7) Female‡: 100% Race‡: NR Mean weight (kg): 59.2† (58.9† vs. 59.9) Mean height (cm): 155 (155 vs. 155) Falls in 3 months prior to randomization (%): 16.1† (16.3† vs. 15.8) Use of walking device (%): 40.7† (41.2† vs. 39.5†) Mean dietary calcium intake at baseline: 557.7 mg/day	France Homes for the elderly Institutionalized: 100%	Inclusion: Elderly women living in apartment houses for the elderly who were ambulatory (able to walk indoors with cane or walker) and had a life expectancy 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 (>3 months), bisphosphonates, calcitonin (>1 month), calcium (>500 mg/day), and vitamin D (>100 IU/day) in the past 12 months.	Competitive protein-binding assay	Not specifically defined	9.2 vs. 9.2 100% <20

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Gallagher et al, 2013[160] *Effects of vitamin D supplementation in older African American women*	Mean age (years): 67 Female: 100% Race: 100% black Mean BMI (kg/m^2): 32.7 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/m^2; 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

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Gallagher et al, 2014[159] *Vitamin D supplementation in young white and African American women*	Mean age (years): 36.7 Female: 100% Race: 60% white, 40% black Mean BMI (kg/m^2): 30.2 Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 655	Nebraska University medical center; community recruitment Institutionalized: NR	Inclusion: Women ages 25 to 45 years 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 >140 mg in type 2 diabetes; active kidney stone disease or history of >2 kidney stones; chronic renal failure; evidence of chronic liver disease; alcoholism; severe vitamin D deficiency (serum 25(OH)D level <5 ng/mL); BMI >45 kg/m^2; serum calcium level >2.57 mmol/L on 2 baseline tests; 24-hour urinary calcium level >7.3 mmol/day on 2 baseline tests; BMD T-score <−3 at the spine or hip (specific to race); and use of bone-active drugs such as fluoride, PTH or derivatives, calcitonin, estrogen during past 6 months, chronic high-dose corticosteroid therapy (>10 mg/d), bisphosphonates for >3 months in the past, anticonvulsants, or high-dose thiazide therapy (>37.5 mg/d).	Radio-immunoassay	Insufficiency: serum 25(OH)D ≤20	Overall: 13.4 Placebo: 12.7 Vitamin D 400 IU: 13.1 800 IU: 13.8 1600 IU: 13.3 2400 IU: 14.1
Grimnes et al, 2011[158] *Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique*	Mean age (years): 52.1 (51.5 vs. 52.7) Female: 49.1% (45% vs. 51%) Race: NR Mean BMI (kg/m^2): 26.5 (27.2 vs. 26.3) Comorbidities: NR History of falls: NR Mean dairy servings at baseline: 16/week	Norway Community Institutionalized: 0%	Inclusion: Ages 30 to 75 years with serum 25(OH)D between the 5th and 10th percentiles. Exclusion: Current smokers, diabetes, acute MI or stroke during the past 12 months, cancer during the past 5 years, steroid use, serum creatinine ≥130 (males) or ≥110 µmol/L (females), possible primary hyperparathyroidism (plasma PTH >5.0 pmol/L combined with serum calcium >2.50 mmol/L), sarcoidosis, SBP >175 mm Hg or DBP >105 mm HG, pregnancy, lactation, or fertile age and no contraception use.	Liquid chromatography double mass spectrometry	Low: serum 25(OH)D <17	17 vs. 16 100% <17

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Janssen et al, 2010[127] *Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation*	Mean age (years): 80.8† (82.4 vs. 79.2) Female: 100% Race: NR Mean BMI (kg/m^2): 26.4† (26.2 vs. 26.7) Comorbidities: 2.4† (2.7 vs. 2.1) Medications used: 5.0† (5.2 vs. 4.8) History of falls: NR Calcium intake: NR	The Netherlands Outpatient clinics Institutionalized: most women lived in residential homes for the elderly, number NR	Inclusion: Ambulatory women age >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 >200 µmol/L; malabsorptive bowel syndrome; primary hyperparathyroidism; uncontrolled thyroid disease; anticonvulsant drug therapy; and/or presence of any other condition that would interfere with compliance.	NR	Insufficiency: serum 25(OH)D 8 to 20	13 vs. 14 90% <19
Knutsen et al, 2014[132] *Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway*	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/m^2): 27.4† (27.0 vs. 27.5 vs. 27.8) Comorbidities: NR History of falls: NR Serum calcium at baseline (mmol/L): 2.36† (2.37 vs. 2.36 vs. 2.36)	Norway 11 local immigrant activity centers Institutionalized: NR	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.	High performance liquid chromatography Laboratory participates in DEQAS	Insufficiency: serum 25(OH)D 20	25 vs. 10 µg/day vs. control 11 vs. 10 vs. 11 100% <20
Lips et al, 2010[155] *Once-weekly dose of 8400 IU vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency*	Mean age (years): 78 (78.5 vs. 77.6) Female: NR Race: NR Mean BMI (kg/m^2): 27.8† (27.4 vs. 28.2) Comorbidities: NR Use of walking device: 15% History of falls: NR Calcium intake: NR	The Netherlands, Germany, Wisconsin, Nebraska, New Jersey, Pennsylvania Medical centers and nursing homes Institutionalized: 14%	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 >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.	Reverse phase high performance liquid chromatography Laboratory participates in DEQAS	Insufficiency: serum 25(OH)D 6 to 20	14 vs. 14 100% <20

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Pfeifer et al, 2000[162] *Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women*	Mean age (years): 74.8† (74.8 vs. 74.7) Female: 100% Race: NR Mean BMI (kg/m^2): 25.5† (25.5 vs. 25.4) Comorbidities: 39% cardiovascular; 12% central nervous, neurological; <1% psychiatric; 22% musculoskeletal Concomitant medication: 2.8% benzodiazepine use; 13.6% thyroidotherapy; 68% cardiovascular drugs History of falls: NR Calcium intake: NR	Germany Population-based Institutionalized: 0%	Inclusion: Healthy ambulatory women age ≥70 years with serum 25(OH)D level <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 >20% of upper limit of reference range); history of drug or alcohol abuse; nicotine abuse (>20 cigarettes daily); >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).	Radio-immunoassay	Not specifically defined, but study only included women with serum 25(OH)D <20	10 vs. 10 100% < 20

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Wamberg et al, 2013[125] *The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study* Wamberg et al, 2013[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*	Mean age (years): 40.5 (39.5 vs. 41.2) Female: 71% (69% vs. 73%) Race: NR Mean BMI (kg/m^2): 35.8[†] (36.1 vs. 35.0) Sedentary: 35%[†] (35% vs. 35%) Lightly active: 48%[†] (46% vs. 50%) Moderately active: 17%[†] (19% vs. 15%) Comorbidities: NR Concomitant medications: 2% (1/55) lipid-lowering; 5% (3/55) antihypertensive History of falls: NR Mean dietary calcium intake at baseline(mg/day): 992 vs. 936	Denmark University hospital Institutionalized: NR	Inclusion: Healthy males and females ages 18 to 50 years with BMI >30 kg/m^2 and plasma 25(OH)D level <20 ng/mL. Exclusion: Pregnant women or women planning pregnancy; history of diabetes, fasting plasma glucose >7.0 mmol/L, hypercalcemia, or impaired renal or hepatic function; subjects treated with vitamin D within the last 3 months; and history of sarcoidosis, osteomalacia, or alcohol or substance abuse; recent large weight change (± 3 kg); and body weight >125 kg.	Isotope dilution liquid chromatography-tandem mass spectrometry	Low: plasma 25(OH)D <20	14 vs. 14 100% <20
≥90% of study participants had 25(OH)D levels ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL						
Aloia et al, 2008[174] *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration*	Mean age (years): 47.2[†] Female: 81% Race: 45% black; 55% white BMI: NR Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline: 665 mg/day	New York University hospital Institutionalized: NR	Inclusion: Healthy men and women ages 18 to 65 years. Exclusion: Baseline 25(OH)D >32 ng/mL, morbid obesity, chronic medical conditions (history of nephrolithiasis or hypercalciuria), bone disease (osteoporosis), or taking medications known to interfere with vitamin D metabolism.	Radio-receptor assay Laboratory participates in DEQAS	Not specifically defined, but study only included participants with 25(OH)D ≤32	Overall: 19 90% ≤30

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Arvold et al, 2009[170] *Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial*	Mean age (years): 58.8† (59.7 vs. 57.8) Female: 40% (44% vs. 36%) White: 95% (96% vs. 95%) BMI: NR 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[178]** *Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3*	Mean age (years): 31 (range, 22 to 47) Female: 0% Race: NR 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[165] *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*	Mean age (years): 85 (85 vs. 85) Female: 100% Race: NR Mean BMI (kg/m^2): 24.7 (24.7 vs. 24.7) % using walking aid: 60† (58 vs. 62) % with history of falls: 34† (35 vs. 33) % with 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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Gallagher et al, 2012[156] *Dose response to vitamin D supplementation in postmenopausal women: a randomized trial*	Mean age (years): 67 Female: 100% White: 100% Mean BMI (kg/m^2): 30.2 Comorbidities: NR History of falls: NR Mean dietary calcium intake at baseline (mg/day): 685	Nebraska University medical center Institutionalized: NR	Inclusion: Healthy, postmenopausal white and African American women ages 57 to 90 years who were ≥7 years postmenopausal with vitamin D insufficiency. Exclusion: Substantial comorbid conditions; any history of nonskin cancer in last 10 years; terminal illness; previous hip fracture; hemiplegia; uncontrolled diabetes with or without significant proteinuria or a fasting blood glucose level <7.8 mmol/L in persons with type 2 diabetes; active kidney stone disease or a history of >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 <5 or >20 ng/mL; BMI >45 kg/m^2; 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: 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

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

Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Harris et al, 1999[176‡‡] *Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D*	Mean age (years): 31 (range, 22 to 47) Female: 0% Race: NR BMI: NR Comorbidities: NR History of falls: NR Calcium intake: NR	Massachusetts Tufts University Institutionalized: NR	Inclusion: Men with low vitamin D intake (<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 >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.	High performance liquid chromatography	Low: <26	Younger men: 13 vs. 17 Older men: 16 vs. 16 90% ≤24
Honkanen et al, 1990[128‡‡] *The necessity and safety of calcium and vitamin D in the elderly*	Home patients Mean age (years): 69.5† (69.4 vs. 69.6) Female: 100% Weight (kg): 69.5† (70.7 vs. 68.4) Race: NR BMI: NR Comorbidities: NR History of falls: NR Dietary calcium intake: NR Hospital inpatients (institutionalized) Mean age (years): 82.5† (82.2 vs. 82.8) Female: 100% Weight (kg): 61.8† (62.1 vs. 61.5) Race: NR BMI: NR Comorbidities: NR History of falls: NR Dietary calcium intake: NR	Finland City hospital Institutionalized (inpatients): 52%	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.	NR	NR	Home patients: 17 vs. 15 Hospital inpatients: 10 vs. 10 90% ≤26

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Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Kärkkäinen et al, 2010[166‡‡] *Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)* Kärkkäinen et al, 2010[153‡‡] *Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS)*	Mean age (years): 67.4† (67.4 vs. 67.4) Female: 100 % Race: NR Mean BMI (kg/m^2): 27.5† (27.5 vs. 27.4) Ambulatory: 100% Mean number of prescribed medications: 2.7† (2.8 vs. 2.5) History of falls: NR Baseline use of calcium supplements: 17%† (15% vs. 19%) Total calcium at baseline: 977† mg/day (988 vs. 965)	Finland Population-based Institutionalized: NR	Inclusion: Female members of the OSTPRE cohort born in 1932 to 1941 and 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	Radio-immunoassay	NR	20 vs. 20 90% ≤30
Kjaergaard et al, 2012[171] *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomized clinical trial*	Mean age (years): 53.4† (53.4 vs. 53.3) Female: 56% Race: NR Mean BMI (kg/m^2): 27.7† (27.5 vs. 28.0) Comorbidities: NR History of falls: NR Mean serum calcium at baseline (mmol/L): 2.28 (2.28 vs. 2.28)	Norway Population-based Institutionalized: NR	Inclusion: Adults ages 30 to 75 years with low serum vitamin D levels from the sixth 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 <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.	Liquid chromatography with tandem mass spectrometry	Low: <22	19 vs. 19 100% <22

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Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Krieg et al, 1999[154‡‡] *Effect of supplementation with vitamin D_3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study*	Mean age (years): 84.5[†] (84 vs. 85) Female: 100% Race: NR Mean BMI (kg/m^2): 24.7[†] (25.7 vs. 23.8; p=0.04) Comorbidities: NR History of falls: NR Calcium intake: NR	Switzerland Nursing homes Institutionalized: 100%	Inclusion: Women living in 19 nursing homes in the Lausanne area. Exclusion: NR	Protein binding assay	NR	12[§§] vs. 12[§§] 90% ≤21
Lehmann et al, 2013[115] *Bioavailability of vitamin D_2 and D_3 in healthy volunteers, a randomized placebo-controlled trial*	Overall (vitamin D_2 vs. D_3 vs. control) Mean age (years): 33.8[†] (33.2 vs. 35.6 vs. 31.6) Female: 63.5% (67.4% vs. 61.9% vs. 57.9%) Race: NR Mean BMI (kg/m^2): 23.8[†] (23.7 vs. 24.0 vs. 23.7) Comorbidities: NR History of falls: NR Calcium intake: NR	Norway Healthy community population Institutionalized: NR	Inclusion: Healthy adults. Exclusion: Use of vitamin D and calcium supplements, history of chronic illness and elevated serum creatinine (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.	Liquid chromatography with mass spectrometry	NR	Vitamin D_2 vs. D_3 vs. control) 15 vs. 18 vs. 16 90% ≤25
Lips et al, 1996[161] *Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial* Ooms et al, 1995[120] *Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial*	Mean age (years): 80.4[†] (80.1 vs. 80.6) Female: 100% Race: NR Mean BMI (kg/m^2): 28.3[†] (28.1 vs. 28.6) Comorbidities: NR History of falls: NR Median calcium intake at baseline (mg/day): NR (876 vs. 859)	The Netherlands Community Institutionalized: 100%[¶¶]	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	Competitive protein-binding assay	Not specifically defined	Median: 11 vs. 10 90% ≤20

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Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Martineau et al, 2007[179] *A single dose of vitamin D enhances immunity to mycobacteria*	Median age[¶¶] (years): 33.7[†] (30.1 vs. 37.5) Female[¶¶]: 51.2%[†] (46.3% vs. 56.2%) Black[¶¶]: 12.9%[†] (10.4% vs. 15.6%) South Asian[¶¶]: 68%[†] (70.1% vs. 67.2%) White[¶¶]: 13.7%[†] (13.4% vs. 14.1%) BMI: NR Comorbidities: NR History of falls: NR Calcium intake: NR	London TB contact clinics Institutionalized: NR	Inclusion: Persons age >17 years who had been exposed to a patient with active TB. Exclusion: Had symptoms, clinical signs, or radiographic evidence of active TB; had HIV infection, renal failure, sarcoidosis, or hyperparathyroidism; taking corticosteroids, thiazide diuretics, or supplementary vitamin D; or were breastfeeding or pregnant.	Isotope dilution liquid chromatography-tandem mass spectrometry Laboratory participates in DEQAS	Deficiency: <8 Insufficiency: <30	14 vs. NR Overall deficient: 42% (84/192) Overall insufficient: 94% (189/192)*** 94% <30
Pfeifer et al, 2009[163] *Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals*	Mean age (years): 76.5 (76 vs. 77) Female: 74.5% (74% vs. 75%) Race: NR Mean BMI (kg/m^2): 27.3 (27.0 vs. 27.5) Comorbidities: NR History of falls: NR Mean baseline nutritional calcium intake (mg/unit time NR): 618 (608 vs. 628)	Austria and Germany Population-based Institutionalized: 0%	Inclusion: Healthy ambulatory adults age ≥70 years with 25(OH)D serum level <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 >20% of the upper limit of reference range); history of drug or alcohol abuse; nicotine abuse (>20 cigarettes per day), >7 cups of coffee per day; scheduled holidays along geographic longitude during study period; diabetes mellitus, severe cardiovascular disease.	Radio-immunoassay	Not specifically defined, but study only included participants with 25(OH)D <31	22 vs. 22 100% <31

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Author, Year, Title*	Overall Population Characteristics: Vitamin D vs. Control	Country and Setting	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency (ng/mL)	Mean Baseline 25(OH)D Level: Vitamin D vs. Control (ng/mL)
Talwar et al, 2007[177] *Dose response to vitamin D supplementation among postmenopausal African American women* Aloia et al, 2005[175] *A randomized controlled trial of vitamin D_3 supplementation in African American women*	Mean age (years): 60.5† (59.9 vs. 61.2) Female: 100% Black: 100% Mean BMI (kg/m^2): 29 vs. 30 Comorbidities: NR History of falls: NR Calcium intake: NR	New York Population-based Institutionalized: NR	Inclusion: Healthy postmenopausal black women not receiving HRT. Exclusion: Previous treatment with bone-active agents and any medication or illness that affects skeletal metabolism; previous treatment with bisphosphonates or fluoride; use of estrogen, calcitonin, glucocorticoids, androgens, phosphate, anabolic steroids, or >400 IU/day vitamin D 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 hyper-calciuria, nephrolithiasis, or active sarcoidosis; smoking >10 cigarettes/day; unexplained weight loss; use of medications known to interfere with calcium or vitamin D absorption or metabolism; severe osteoarthritis or scoliosis that would interfere with bone density assessment of the spine or hip; participation in weight training or elite athletic training.	Radio-immunoassay Laboratory participates in DEQAS	Deficiency: <30	19 vs. 17 90% ≤29
Wood et al, 2012[136] *Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT*	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/m^2): 26.7† (26.6 vs. 26.8 vs. 26.6) Comorbidities: NR History of falls: NR Calcium intake: NR	U.K. Community Institutionalized: NR	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.	High performance liquid chromotography-tandem mass spectrometer	NR	Vitamin D 400 vs. 1000 IU vs. control 13 vs. 13 vs. 14 90% ≤23

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Author, Year, Title*	Mean 25(OH)D Level Attained: Vitamin D vs. Control (ng/mL)	Number Approached, Screened, Eligible, Enrolled, Analyzed: Vitamin D vs. Control	Duration	Attrition: Vitamin D vs. Control	Adjusted Confounders in Analysis	Interventions
≥90% of study participants had 25(OH)D level <20 ng/mL						
Brazier et al, 2005[157] *Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study*	Median: 29 vs. 11 ≤12 ng/mL 9% vs. 70%; p<0.001	Approached: 360 Screened: NR Eligible: 192 Enrolled: 192 (95 vs. 97) Analyzed: 191 (95 vs. 96)	12 months	18.9% (18/95) vs. 28.9% (28/97) Overall: 24.0% (46/192)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total, 800 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: Identical placebo tablet BID
Chapuy et al, 2002[122] *Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk. The Decalyos II Study*	Shown in figure; vitamin D groups had significant increase 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	Approached: NR Screened: NR Enrolled: 639 (610 randomized) Analyzed: 583 (393 vs. 190)	24 months	28.2[†] vs. 36.1[§] Overall: 30.8% (188/610)	NR (RCT)	Vitamin D: 800 IU of vitamin D_3 daily and 1200 mg of calcium daily Control: Identical placebo daily
Gallagher et al, 2013[160] *Effects of vitamin D supplementation in older African American women*	Shown in figure; dose-response curve predicted that 97.5% of those on 800 IU of vitamin D per day reached a 25(OH)D level >20 ng/mL; vitamin D levels higher in all vitamin D groups individually vs. placebo (p<0.05)	Approached: 526 Screened: 303 Eligible: 108 (303 screened − 195 ineligible=108, but figure reports 110) Enrolled: 110 (93 [2 to 24 per dosage] vs. 17) Analyzed: 82 (68 vs. 14) for ITT dose reponse analysis; 110 for harms	12 months (NR if mean or median; range NR)	17.2% (16/93) vs. 17.6% (3/17) Overall: 17.3% (19/110)	Primary outcome adjusted for age, BMI, calcium intake, smoking status, alcohol use, average caffeine intake, serum creatinine, and season	Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control: Identical placebo daily All Participants: Citracal calcium supplements administered to maintain total calcium intake of 1200 to 1400 mg/day
Gallagher et al, 2014[159] *Vitamin D supplementation in young white and African American women*	Shown in figure; dose-response curve predicted that 97.5% of white women on 400 IU of vitamin D per day reached a 25(OH)D level >20 ng/mL; between 800 and 1600 IU of vitamin D per day required in black women (prediction limit, 1200 IU daily)	Approached: 1514 Screened: 558 Eligible: 305 Enrolled: 198 (160 [37 to 42 per dosage] vs. 38) Analyzed: 198 (160 [37 to 42 per dosage] vs. 38)	12 months (NR if mean or median; range NR)	37.5% (60/160) vs. 26.3% (10/38) Overall: 35.4% (70/198)	Primary outcome adjusted for season at baseline, age, BMI category, calcium intake, smoking status, alcohol use, and serum creatinine	Vitamin D: 400, 800, 1600, or 2400 IU of vitamin D_3 daily Control: Identical placebo daily *All Participants:* Citracal calcium supplements administered to maintain total calcium intake of 1000 to 1200 mg/day

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Author, Year, Title*	Mean 25(OH)D Level Attained: Vitamin D vs. Control (ng/mL)	Number Approached, Screened, Eligible, Enrolled, Analyzed: Vitamin D vs. Control	Duration	Attrition: Vitamin D vs. Control	Adjusted Confounders in Analysis	Interventions
Grimnes et al, 2011[158] *Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique*	57 vs. 17; p<0.01	Approached: 1028 Screened: 337 Eligible: 172 Enrolled: 104 (51 vs. 53) Analyzed: 104 (51 vs. 52)	6 months	4% (2/51) vs. 15% (8/53) Overall: 10% (10/104)	NR (RCT)	Vitamin D: 20,000 IU of vitamin D_3 twice/week (total, 40,000 IU/week) Control: Identical placebo twice/week
Janssen et al, 2010[127] *Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation*	31 vs. 17 ; p<0.001	Approached: NR Screened: NR Eligible: 91 Enrolled: 70 (36 vs. 34) Analyzed: 59 (28 vs. 31)	6 months	22.2% (8/36) vs. 8.8% (3/34) Overall: 15.7% (11/70)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 daily and 500 mg of calcium daily Control: Identical placebo and 500 mg of calcium daily
Knutsen et al, 2014[132] *Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway*	25 vs. 10 µg/day vs. control 21 vs. 17 vs. 10	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)	16 weeks	10.7% (9/84) on 25 µg/day vs. 18.8% (16/85) on 10 µg/day vs. 13.4% (11/82) control	NR (RCT)	Vitamin D: 25 or 10 µg of vitamin D_3 daily Control: Identical placebo
Lips et al, 2010[155] *Once-weekly dose of 8400 IU vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency*	26 vs. 12 Mean difference, 13.0; p<0.001	Approached: NR Screened: 593 Enrolled: 226 (114 vs. 112) Analyzed: 226 for AEs, 213 for SPPB measure	16 weeks	7.9% (9/114) vs. 13.4% (15/112) Overall: 10.6% (24/226)	Covariance model included terms for baseline body sway, baseline vitamin D stratum, and treatment group	Vitamin D: 2800 IU of vitamin D_3 given in 3 tablets once a week (total, 8400 IU/week) Control: 3 identical placebo tablets once a week All participants: Those with daily calcium intake <1000 mg were also given 500 mg calcium

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Pfeifer et al, 2000[162] *Effects of a short-term vtamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women*	26 vs. 17; p <0.001	Approached: 208 Screened: 165 Eligible: 151 Enrolled: 148 Analyzed: 145 in ITT; 137 for falls (70 vs. 67)	8 weeks treatment; 1 year posttreatment followup	5.4% (4/74) vs. 9.5% (7/74) Overall: 7.4% (11/148)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total, 800 IU/day) and 600 mg of calcium BID (total, 1200 mg/day) Control: 600 mg of calcium BID (total, 1200 mg/day)
Wamberg et al, 2013[125] *The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study* Wamberg et al, 2013[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*	44 vs. 19; p<0.00001 >32: 96% vs. NR >20: 100% vs. 18%	Approached: NR Screened: 88 Eligible: 55 Enrolled: 52 (26 vs. 26) Analyzed for main outcomes[¶]: 43 (22 vs. 21)	26 weeks	15.4% (4/26) vs. 19.2% (5/26) Overall: 17.3% (9/52)	NR (RCT)	Vitamin D: 1400 IU of vitamin D_3 given 5 times a day (total, 7000 IU/day) Control: Identical placebo tablets given 5 times daily

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≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D levels ≥20 ng/mL						
Aloia et al, 2008[174] *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration*	Reported on figure by race and sex; goal of >30 ng/mL achieved by virtually all in active group; also increased by 8 ng/mL in placebo group because of seasonal change	Approached: NR Screened: 262 Eligible: 138 Enrolled: 138 (65 vs. 73) Analyzed: 138	6 months	Overall: 20% (27/138)	NR (RCT)	Vitamin D: vitamin D_3 dose depended on 25(OH)D level, as follows: Baseline 20 to 32 ng/mL: start at 2000 IU/day Baseline <20 ng/mL: start at 4000 IU/day At followup <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 >56 ng/mL: decrease by 2000 IU/day (unless current dose was ≤2000 IU/day, decrease dose to 800 IU) Mean dose: 3440 IU Control: Identical placebo
Arvold et al, 2009[170] *Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial*	45 vs. 22	Approached: NR Screened: 610 Eligible: 244 Enrolled: 100 (50 vs. 50) Analyzed: 90 (48 vs. 42)	8 weeks treatment/ followup	4% (2/50) vs. 16% (8/50) Overall: 10% (10/100)	NR (RCT)	Vitamin D: 50,000 IU of vitamin D_3 weekly Control: Identical placebo tablet weekly
Berlin et al, 1986[178]** *Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3*	49 vs. 19; p<0.000001	Approached: NR Screened: NR Eligible: NR Enrolled: 24 (12 vs. 12) Analyzed: 24 (12 vs. 12)	NR; implied 2 months	NR	NR	Vitamin D: 18,000 IU of vitamin D_3 taken 3 times a week in March and April (total, 54,000 IU weekly) Control: No intervention

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Bischoff et al, 2003[165] *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*	Median, 26 vs. 11; p<0.001	Approached: NR Screened: NR Eligible: 130 Enrolled: 124 in pretreatment period; 122 in treatment (62 vs. 60) Analyzed: 122 (62 vs. 60) for falls	6 weeks pretreatment 12 weeks treatment	31% (19/62) vs. 25% (15/60)[††] Overall: 27% (33/122)	Adjusted for treatment and baseline covariates that reached significance of p<0.1 (age, number of fallers in pre-treatment period, being a faller in pretreatment period, baseline vitamin D level and baseline 1,25$(OH)_2$D level, observation time during treatment)	Vitamin D: 400 IU of vitamin D_3 BID (total, 800 IU/day) and 600 mg of calcium BID (total, 1200 mg/day) Control: 600 mg of calcium BID (total, 1200 mg/day)
Gallagher et al, 2012[156] *Dose response to vitamin D supplementation in postmenopausal women: a randomized trial*	Shown in figure; dose-response curve predicted that 97.5% of those on 600 IU/day reached >20 ng/mL; vitamin D levels higher in all vitamin D groups individually compared with placebo (p<0.05)	Approached: 2113 Screened: 633 Eligible: NR Enrolled: 163 (142 [20 to 21 per dosage] vs. 21) Analyzed: 163 (142 vs. 21)	Median, 12 months (range, 0.9 to 14.0 months)	12.7% (18/142) vs. 14.3% (3/21) Overall: 12.9% (21/163)	NR	Vitamin D: 400, 800, 1600, 2400, 3200, 4000, or 4800 IU of vitamin D_3 daily Control: Identical placebo daily All Participants: Citracal calcium supplements administered BID to maintain total calcium intake of 1200 to 1400 mg/day
Harris et al, 1999[176‡‡] *Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D*	Younger men: 25 vs. 13 Older men: 19 vs. 15	Approached: NR Screened: NR Eligible: NR Enrolled: 20 (12 vs. 8) Analyzed: 18 (11 vs. 7)	3 weeks	55% (11/20) (4/10 younger and 5/10 older)	NR	Vitamin D: 1800 IU of vitamin D_2 in liquid form taken with food daily in the morning Control: No intervention
Honkanen et al, 1990[128‡‡] *The necessity and safety of calcium and vitamin D in the elderly*	Home patients: 32 vs. 9 Hospital inpatients: 26 vs. 4 p<0.001 for change in intervention group	Approached: NR Screened: 203 Eligible: NR Enrolled: 126 (63 vs. 63) Analyzed: 126 (63 vs. 63)	11 weeks	8/63 (12.7%) vs. 3/60 (4.8%) Overall: 11/126 (8.7%)	NR (RCT)	Vitamin D: 1800 IU of vitamin D_3 daily and 1.558 g of calcium daily Control: No intervention

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Karkkainen et al, 2010[166‡‡] *Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)* Karkkainen et al, 2010[153‡‡] *Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS)*	30 vs. 22; p<0.001	Approached: 5407 Screened: 3744 Eligible: 3432 Enrolled: 603 (290 vs. 313) in subsample with vitamin D levels Analyzed: 593 (287 vs. 306) in subsample with vitamin D levels	3 years Mean, 2.8 years	1.0% (3/290) vs. 2.2% (7/313) Overall: 1.7% (10/603) in subsample with vitamin D levels	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total, 800 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: No intervention
Kjaergaard et al, 2012[171] *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomized clinical trial*	59 vs. 21	Approached: NR (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)	6 months	1.6% (2/122) vs. 9.1% (11/121) Overall: 5.4% (13/243)	NR (RCT)	Vitamin D: 20,000 IU of vitamin D_3 weekly Control: Identical placebo weekly

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

Author, Year, Title*	Mean 25(OH)D Level Attained: Vitamin D vs. Control (ng/mL)	Number Approached, Screened, Eligible, Enrolled, Analyzed: Vitamin D vs. Control	Duration	Attrition: Vitamin D vs. Control	Adjusted Confounders in Analysis	Interventions
Krieg et al, 1999[154‡‡] *Effect of supplementation with vitamin D_3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study*	27 vs. 6; p<0.01	Approached: NR Screened: NR Eligible: NR Enrolled: 248 (124 vs. 124) Analyzed: 248 (124 vs. 124)	2 years	60% (74/124) vs. 57% (71/124) Overall: 58% (145/248)	NR (RCT)	Vitamin D: 440 IU of vitamin D_3 BID (total, 880 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: No intervention
Lehmann et al, 2013[115] *Bioavailability of vitamin D_2 and D_3 in healthy volunteers, a randomized placebo-controlled trial*	Vitamin D_2 vs. D_3 vs. control 27 vs. 36 vs. 13; p<0.001	Approached: NR Screened: NR Eligible: NR Enrolled: 119 (50 to vitamin D_2 vs. 49 to vitamin D_3 vs. 20 to control) Analyzed: 107 (47 to vitamin D_2 vs. 46 to vitamin D_3 vs. 19 to control)	8 weeks	Vitamin D_2 vs. D_3 vs. control: 8% (4/50) vs. 14% (7/49) vs. 5% (1/20) Overall: 10% (12/119)	NR (RCT)	Vitamin D: 2000 IU of either vitamin D_2 or D_3 daily Control: Identical placebo daily
Lips et al, 1996[161] *Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial* Ooms et al, 1995[120] *Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial*	Median, 25 vs. 9 (at 1 year)	Approached: NR Screened: NR Eligible: NR Enrolled: 348 (177 vs. 171) Analyzed: 270 with vitamin D levels	3 to 3.5 years; maximum 4 years	28.8% (51/177) vs. 31.0% (53/171) Overall: 28.7% (100/348) Drop out in first year: 19% (65/348) 16% (29/177) vs. 21% (36/171) 3.7% (13/348) are not in analysis at end of study	Covariates included age; sex; residence; sum of outdoor, sunshine, and walking scores; and compliance; fracture analysis was repeated excluding participants who used vitamin D or multivitamin supplements other than trial medication	Vitamin D: 400 IU of vitamin D_3 daily Control: Identical placebo daily
Martineau et al, 2007[179] *A single dose of vitamin D enhances immunity to mycobacteria*	27 vs. NR	Approached: NR Screened: 364 Eligible: NR Enrolled: 192 (96 vs. 96) Analyzed: 192 (96 vs. 96)	6 weeks	31.2% (29/96) vs. 33.3% (32/96) Overall: 31.8% (61/192)	NR (RCT)	Vitamin D: 100,000 IU vitamin D_2 in a single dose Control: Identical lactose placebo in a single dose

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

Author, Year, Title*	Mean 25(OH)D Level Attained: Vitamin D vs. Control (ng/mL)	Number Approached, Screened, Eligible, Enrolled, Analyzed: Vitamin D vs. Control	Duration	Attrition: Vitamin D vs. Control	Adjusted Confounders in Analysis	Interventions
Pfeifer et al, 2009[163] *Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals*	Month 12: 34 vs. 23 Month 20: 19 vs. 15	Approached: 315 Screened: NR Eligible: NR Enrolled: 242 (121 vs. 121) Analyzed: 242 (122 vs. 120) for falls and fractures†††	12 month treatment and 8 month posttreatment followup Total: 20 months	6% (7/121) vs. 6% (7/121) Overall: 6% (14/242)	NR (RCT)	Vitamin D: 400 IU of vitamin D_3 BID (total, 800 IU/day) and 500 mg of calcium BID (total, 1000 mg/day) Control: 500 mg of calcium BID (total, 1000 mg/day)
Talwar et al, 2007[177] *Dose response to vitamin D supplementation among postmenopausal African American women* Aloia et al, 2005[175] *A randomized controlled trial of vitamin D_3 supplementation in African American women*	35 vs. 18 (at 27 months; 40% of active group still had levels <32)	Approached: 50,000 Screened: 385 Eligible: 322 Enrolled: 208 (104 vs. 104) Analyzed: 208 (104 vs. 104)	36 months	28.8% (30/104) vs. 28.8% (30/104) Overall: 29.4% (60/208)	NR (RCT)	Vitamin D: 800 IU of vitamin D_3 daily for first 24 months, increased to 2000 IU daily Control: Identical placebo daily All participants: Supplements given to ensure total daily intake of 1200 to 1500 mg calcium
Wood et al, 2012[136] *Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT*	Vitamin D 400 vs. 1000 IU vs. control 26 vs. 30 vs. 13; p<0.001	Approached: NR Screened: 424 Enrolled: 305 (102 [vitamin D 400 IU] vs. 101 [vitamin D 1000 IU] vs. 102 [control]) Analyzed: 305 (102 [vitamin D 400 IU] vs. 101 [vitamin D 1000 IU] vs. 102 [control])	13 months	Vitamin D 400 vs. 1000 IU vs. control: 18% (18/102) vs. 11% (11/101) vs. 11% (11/102) Overall: 13% (40/305)	NR (RCT)	Vitamin D: 400 or 1000 IU of vitamin D_3 daily Control: Identical placebo daily

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
≥90% of study participants had 25(OH)D level <20 ng/mL							
Brazier et al, 2005[157] *Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study*	NR	Assessed followup levels No assessment of pill content Dietary vitamin D at baseline: 85 (85 vs. 84) IU/day	AEs: prespecified; recorded spontaneously reported and observed AEs Hypercalemia: measured serum calcium defined as ≥10.8 mg/dL, reported spontaneously	Mortality: 3.2% (3/95) vs. 1.0% (1/96); RR, 3.03 (95% CI, 0.32 to 28.63)†; all unrelated to drug	**All NS:** Total AEs: 187 vs. 170 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)†	Fair	Innothera Laboratories, Arcueil, France

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Brazier et al, 2005[157] *(Cont'd)*	See above	See above	See above	See above	**Drug-related AEs:** 22.1% (21/95) vs. 24.0% (23/96); RR, 0.92 (95% CI, 0.55 to 1.55)[†] Metabolic and nutritional: 9.5% (9/95) vs. 10.4% (10/96); RR, 0.91 (95% CI, 0.38 to 2.14)[†] Hypercalcemia: 6.3% (6/95) vs. 8.3% (8/96); RR, 0.76 (95% CI, 0.27 to 2.10)[†] GI: 9.5% (9/95) vs. 8.3% (8/96); RR, 1.14 (95% CI, 0.46 to 2.82)[†]	See above	See above
Chapuy et al, 2002[122] *Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk. The Decalyos II Study.*	NR	Followup levels increased in vitamin D group No verification of pill content Dietary vitamin D intake at baseline: 40.8 IU/day	Fractures: women asked about fractures during investigator assessment every 3 months. For peripheral fractures, date, site, and cause of trauma were recorded on a case report form. For vertebral fractures, spine radiographs were required for confirmation. AEs: every 3 months, women were asked whether they had experienced any AEs. Falls: NR Mortality: NR Hypercalcemia: measured serum calcium, collected at baseline and after 6, 12, 18, and 24 months	Hip fracture: 6.9% (27/393) vs. 11.1% (21/190); RR, 0.62 (95% CI, 0.36 to 1.07)[†] Nonvertebral fractures: 17.8% (70/393) vs. 17.9% (34/190); RR, 1.0 (95% CI, 0.7 to 1.4)[†] Fallers: 63.9% (251/393) vs. 62.1% (118/190); RR, 1.0 (95% CI, 0.9 to 1.2)[†] Mortality: 18.1% (70/393) vs. 23.9% (45/190); RR, 0.75 (95% CI, 0.54 to 1.05)[†] (ITT analysis)[‖]	GI disturbance (nausea, diarrhea, epigastric pain): 6.1% (24/393) vs. 8.4% (16/190); RR, 0.73 (95% CI, 0.40 to 1.33)[†] Withdrawals due to GI AEs: 3 (group NR) Hypercalcemia: 3 vs. 0; RR, 3.39 (95% CI, 0.18 to 65.4)[†] No kidney stones reported Hypercalciuria at 12 months (urinary calcium >350 mg/24 hours): 3.0% (5/166) vs. 1.3% (1/77); RR, 2.32 (95% CI, 0.28 to 19.52)[†] Hypercalciuria at 24 months (urinary calcium >350 mg/24 hours): 3.4% (3/89) vs. 2.9% (1/35); RR, 1.18 (95% CI, 0.13 to 10.96)[†]	Fair	Merck KGaA, Germany
Gallagher et al, 2013[160] *Effects of vitamin D supplementation in older African American women*	Screened throughout the year from January 2008 to January 2010	Assessed followup levels Verified pill content Mean baseline vitamin D intake NR Participants instructed not to take nonstudy vitamin D; multivitamins without vitamin D were provided to those wanting it	AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit Hypercalcemia: measured serum calcium, defined as either >10 or >10.8 mg/dL, collected at baseline and after 3, 6, 9, and 12 months of treatment	Mortality: none (as per author correspondence)	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)† 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 Hypercalcemia (serum calcium level ≥10 or ≥10.8 mg/dL): 8.6% (8/93) vs. 5.9% (1/17); RR, 1.5 (95% CI, 0.20 to 11.0) (as per author correspondence)	Fair	Grant from the National Institute on Aging and the Office of Dietary Supplements

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Gallagher et al, 2014[159] *Vitamin D supplementation in young white and African American women*	Screened throughout the year from January 2008 to January 2010	Assessed followup levels Verified pill content Mean baseline vitamin D intake: 100 mg/day Participants instructed not to take nonstudy vitamin D; multivitamins without vitamin D were provided to those wanting it	AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit Hypercalcemia: measured serum calcium, defined as ≥10.6 mg/dL, collected at baseline and after 3, 6, 9, and 12 months of treatment	Mortality: none (as per author correspondence)	Patients with SAEs: 4 patients with 5 events (internal bleeding from auto accident; subarachnoid hemorrhage from hemangioma; maxillary hypoplasia surgery; and broken ankle and tibia); no events attributed to study treatment (NR by group) Hypercalcemia (serum calcium ≥10.3 mg/dL): 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	Fair	Grant from the Department of Defense
Grimnes et al, 2011[158] *Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique*	Recruited November to April; at baseline, 6% used sun bed	Assessed followup levels No assessment of pill content At baseline, 26% of participants took vitamin D supplements	Hypercalcemia: >10.2 mg/dL reported to be out of the normal range Other outcomes: unclear	Mortality: 0/51 vs. 1/53 (unknown cause); RR, 0.34 (95% CI, 0.01 to 8.15)	Number of AEs: 45 vs. 46 No hypercalcemia No kidney stones	Fair	Norwegian Council of Cardiovascular Disease
Janssen et al, 2010[127] *Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation*	NR	Followup levels increased in intervention group No verification of pill content Diet and supplement use NR	Unclear	Mortality: 1 (NR by group)	Withdrawals: 15.7% (11/70) overall; 22.2% (8/36) vs. 8.8% (3/34); RR, 0.94 (95% CI, 0.20 to 4.36)[†] Other withdrawals: cognitive decline (4), malignant lung tumor (1), recurrent upper urinary tract infections with malaise (2), acute emotional distress (1), hip fracture (1), peritonitis (1) No AE reported during intervention period; 3 participants reported nausea with the calcium tablets	Fair	Prevention Program of ZonMw

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Knutsen et al, 2014[132] *Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway*	January to March	Followup levels increased in intervention group Pill count at followup	Unclear	NR	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 Few, mild, and equally reported harms between groups; otherwise no information reported	Fair	Institute of Health and Society, University of Oslo, Norwegian Women's Public Health, Association Furst Medical Laboratory and Nycomed Pharma AS
Lips et al, 2010[155] *Once-weekly dose of 8400 IU vitamin D_3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency*	October to June Told to limit UV exposure by avoiding or wearing sun block	Followup levels increased in intervention No verification of pill content Subjects asked not to change diet and to refrain from taking supplements with >100 IU of vitamin D during period of observation	SPPB summary score, an ordered scale of 0 to 12 that includes an assessment of balance, a gait speed test (timed 4-minute walk), and timed rising from chair and sitting without the use of arms for 5 repetitions AEs: recorded at each study visit and by the voluntary reporting of patients at any time during the study Hypercalcemia: not specifically assessed, spontaneous reporting by patients	Mean SPPB summary score change from baseline at week 16: 0.355 (95% CI, 0.1008 to 0.601) vs. 0.601 (95% CI, 0.351 to 0.852); p=0.162 Mortality: 0.9% (1/114) vs. 0/112; RR, 2.95 (95% CI, 0.12 to 71.61)†	Withdrawals due to AEs: 2.6% (3/114) vs. 4.5% (5/112); RR, 0.59 (95% CI, 0.14 to 2.41)† SAEs: 2.6% (3/114) vs. 2.7% (3/112); RR, 0.98 (95% CI, 0.20 to 4.76)† ≥1 AE: 21% (24/114) vs. 23.2% (26/112); RR, 0.91 (95% CI, 0.56 to 1.48)† Drug-related: 0.9% (1/114) vs. 3.6% (4/112); RR, 0.25 (95% CI, 0.03 to 2.16)† No kidney stones No serious laboratory AEs No difference between groups in hypercalciuria, hypercalcemia, or elevated creatinine (data not shown)	Fair	Merck and Co, Inc.

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Pfeifer et al, 2000[162] *Effects of a short-term Vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women*	Baseline vitamin D levels in March and supplementation from March to May	Followup levels 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	Number of falls: questionnaires Fractures resulting from falls: verified by x-ray and medical reports	Number of participants who fell after 1 year of followup: 16% (11/70) vs. 28% (19/67); RR, 0.55 (95% CI, 0.29 to 1.08)† Mean number of falls after 1 year of followup: 0.24 (17 falls/70 persons) vs. 0.45 (30 falls/67 persons); p<0.05 Number of participants with fractures after 1 year of followup: 4% (3/70) vs. 9% (6/67) total; RR, 0.48 (95% CI, 0.12 to 1.84) By fracture site Radius/ulna: 2.9% (2/70) vs. 4.5% (3/67); RR, 0.64 (95% CI, 0.11 to 3.70) Pelvis: 0/70 vs. 1.5% (1/67); RR, 0.32 (95% CI, 0.01 to 7.70) Hip: 0/70 vs. 1.5% (1/67); RR, 0.32 (95% CI, 0.01 to 7.70) Ankle/foot: 1.4% (1/70) vs. 1.5% (1/67); RR, 0.96 (95% CI, 0.06 to 15.00)	NR	Fair	Strathmann AG Hamburg

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Wamberg et al, 2013[125] *The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin D: results from a randomized controlled study* Wamberg et al, 2013[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*	Recruited from February 2010 to May 2011	Assessed followup levels No assessment of pill content At baseline, mean dietary vitamin D intake: 760 IU/day (840 vs. 680); instructed to continue usual eating habits; did not report if study participants could take their own supplements during study	AEs: prespecified; patient visits at weeks 2, 10, and 18 for safety measures and AE registration; no other details provided Hypercalcemia: not specifically assessed, spontaneous reporting by patients	NR	<u>All NS:</u> Total AEs: 13 vs. 17; p=0.76 (nausea, constipation, tiredness, and headaches); RR, 0.76 (95% CI, 0.48 to 1.23)[†] Hypercalcemia: 0/26 vs. 0/26	Fair	NR
≥90% of study participants had 25(OH)D level ≤30 ng/mL, with ≥10% with 25(OH)D level ≥20 ng/mL							
Aloia et al, 2008[174] *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration*	Recruited during 3 winters (November to March) and followed for 6 months (into summer/fall)	Assessed followup levels Probable verification of pill content (somewhat unclear) Dietary vitamin D intake: 70.5 IU/day Unclear if subjects were given any instructions about diet	AEs and hypercalcemia: prespecified clinical laboratory criteria for safety (serum calcium >10.6 mg/L, urine calcium/creatine ratio >0.16 mg/mL, and serum vitamin D level >80 ng/mL)	NR	High concentration of 25(OH)D (>80 ng/mL): 0.7% (1/138) Hypercalcemia: 0 Hypercalcuria: 0	Fair	Partially funded by Merck Co. and the Empire Clinical Research Investigator Program

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Arvold et al, 2009[170] *Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial*	Participants identified and study started in midwinter	Followup levels 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	Depressed mood (FIQ scale from 0 to 100); ranking of depressed mood and interference with work or housework on scale from 0 to 10	Overall FIQ Score, mean and (SD): Before treatment: 33.6 (18.4) vs. 27.8 (17.5) After treatment: 29.9 (19.7) vs. 29.7 (15.8); p=0.03 Depressed mood from FIQ Part III, mean and (SD): Before treatment: 2.9 (2.3) vs. 2.4 (2.6) After treatment: 2.8 (2.7) vs. 2.1 (2.0); p=NS for change from baseline in either group or between groups. Interference with work or housework from FIQ Part III, mean and (SD): Before treatment: 3.1 (2.5) vs. 2.7 (2.5) After treatment: 2.7 (2.7) vs. 3.0 (2.4); p=0.08	No AE reported by any participants	Fair	St. Luke's Foundation
Berlin et al, 1986[178]** *Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3*	February to April At start of study, no subjects were exposed to extreme sunlight	Assessed followup levels No assessment of pill content	Unclear	NR	No AEs, objective or subjective, were reported	Poor	Grants from the Swedish Medical Research Council (project 03X-3141), Loo and Hans Ostermans Foundation, Stockholm, and ACO Lakemedal AB, Solna, Sweden

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Bischoff et al, 2003[165] *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*	Winter (November and March)	Followup 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	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 1 research physician Hypercalcemia: measured serum calcium, did not define hypercalcemia or frequency	<u>Pretreatment period</u> 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)† <u>During treatment</u> 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 >7 falls (n): 0 vs. 1; RR, 0.3 (95% CI, 0.01 to 7.8) Fallers (n): 23% (14/62) vs. 30% (18/60); RR, 0.7 (95% CI, 0.3 to 1.5) Vitamin D group had 49% reduction (p=0.01) in falls after adjusting for age, falls in pretreatment period, baseline $1,25(OH)_2D$ and 25(OH)D, and observation time during treatment. Using absolute number of falls as primary outcome, vitamin D group had 62% reduction in falls (p<0.0002) after adjustment	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	Fair	Stratham AG; International Foundation for the Promotion of Nutrition Research and Nutrition Education; Swiss Orthopedic Society; Swiss Foundation for Nutrition Research

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Bischoff et al, 2003[165] *(cont'd)*	See above	See above	See above	Mean number of excessive falls among fallers was lower in the vitamin D group (p=0.045), suggesting decrease in recurrent falls	See above	See above	See above
Gallagher et al, 2012[156] *Dose response to vitamin D supplementation in postmenopausal women: a randomized trial*	Screened in late winter and early spring 1st phase: April to May 2007 2nd phase: January to May 2008	Assessed followup levels Verified pill content Mean baseline vitamin D intake: 114 IU/day Participants instructed not to take nonstudy vitamin D; multivitamins without vitamin D were provided to those who wanted it	AEs: prespecified; self-reported by patient, recorded at each regularly scheduled visit, validated by chart review Hypercalcemia: measured serum calcium, defined as either >10 or >10.8 mg/dL, collected at baseline and after 3, 6, 9, and 12 months of treatment	White Mortality: 0/142 vs. 0/21	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)†	Good	Grant from the National Institute on Aging
Harris et al, 1999[176‡‡] *Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D*	Late winter (February); excluded those in outdoor jobs or those who traveled to southern locations in the previous month	Assessed followup levels No assessment of pill content	Unclear	NR	No AEs of supplementation reported	Poor	U.S. Department of Agriculture

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Honkanen et al, 1990[128‡‡] *The necessity and safety of calcium and vitamin D in the elderly*	November to December, Kuopos (63° north with short winter [5 hour] and long summer [11 hour] days) Institutionalized had sun exposure to some extent in summer	Assessed followup levels No assessment of pill content	Hypercalcemia: measure serum calcium at baseline and after 11 weeks of treatment	NR	9 independently living subjects reported mild GI symptoms with treatment No kidney stones reported No hypercalcemia	Fair	Grant from Academy of Finland, the Remeda Pharmaceutical Company, and the Sandoz Pharmaceutical Company
Karkkainen et al, 2010[166‡‡] *Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)* Karkkainen et al, 2010[153‡‡] *Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS)*	Baseline vitamin D measures: February to May Followup vitamin D measures: January to May	Followup levels increased in intervention group Pills distributed by pharmacist but no verification of pill content Groups asked to continue with their previous diet during study	Number of falls and number of falls requiring medical attention recorded every 4 months via telephone interviews for subsample with vitamin D levels Mortality: NR	Number of falls: 430 vs. 524 Number of 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)[†]	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	Fair	Finnish Cultural Foundation, Sigrid Juselius Foundation, Academy of Finland, Kuopia University-Hospital EVO-grant

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Kjaergaard et al, 2012[171] *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomized clinical trial*	Inclusion period from October to April of following year Study performed from October to November of following year Excluded those planning a trip to a sunny location during the trial	Assessed followup levels Pills distributed by pharmacist but no verification of pill content	Depressive symptoms: Beck Depression Inventory (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	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	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) <u>AEs by organ system</u> Gastrointestinal: 14 vs. 12 Respiratory: 67 vs. 61 Dermatological: 13 vs. 9 Musculoskeletal: 22 vs. 18 Urogenital: 7 vs. 4 Circulatory: 5 vs. 7 Neurological: 5 vs. 5 Endocrinological: 14 vs. 17 Other: 30 vs. 25 Total AEs: 177 vs. 158 Note: Figure 1 indicates 6 patients in placebo group discontinued because of side effects, AEs, or other reason, but no further information provided	Good	Northern Norway Regional Health Authority grant
Krieg et al, 1999[154‡‡] *Effect of supplementation with vitamin D_3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study*	NR	Assessed followup levels No assessment of pill content	Unclear	Mortality: 17% (21/124) vs. 21% (26/124); RR, 0.81 (95% CI, 0.48 to 1.36)† (no deaths were deemed to be related to treatment)	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)† 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)† (due to hyperparathyroidism)	Fair	NR
Lehmann et al, 2013[115] *Bioavailability of vitamin D_2 and D_3 in healthy volunteers, a randomized placebo-controlled trial*	Jan to March (no measurable UV radiation). Excluded if vacationed somewhere with abundant UVB irradiation during course of study	Assessed followup levels Verified pill content	AEs: prespecified; participants interviewed about AEs at each monthly visit	NR	No AEs reported; no hypercalcemia detected	Fair	German Ministry of Education and Research

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Lips et al, 1996[161] *Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial* Ooms et al, 1995[120] *Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial*	Enrolled from August to December	Followup levels 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	Fractures: annual questionnaire for participants; GPs or caretakers asked to immediately report hip fracture; hip fractures were verified with a GP Mortality: GP or caretaker asked to immediately report death and verified by GP Other AEs: NR Hypercalcemia: measured serum calcium at baseline and after 1 year of treatment	Number of hip fractures: 49 vs. 36; HR, 1.3 (95% CI, 0.84 to 2.0) Mortality: 6.2% (11/177) vs. 12.3% (21/171); RR, 0.51 (95% CI, 0.25 to 1.02)†	Reported AE: 0.6% (1/177) vs. 0; RR, 2.90 (95% CI, 0.12 to 70.68)† Hypercalcemia: 0.6% (1/177) vs. 0; RR, 2.90 (95% CI, 0.12 to 70.68)†	Fair	Praeventiefonds grant
Martineau et al, 2007[179] *A single dose of vitamin D enhances immunity to mycobacteria*	NR	Assessed followup levels only in intervention group No assessment of pill content	Unclear	NR	Hypercalcemia: 0 vs. 0 No other AEs reported	Fair	Welcome Trust, Department of Environmental Health, London Borough of Newham, Newham University Hospital NHS Trust Research Fund, and Northwick Park Hospital Tropical Research Fund

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Pfeifer et al, 2009[163] *Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals*	May (vitamin D levels start to rise) to March (vitamin D levels at their lowest)	Followup levels 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)	Falls at 20 months: daily fall diaries; in addition, subjects contacted by telephone every 2 months and asked whether a fall had occurred Fractures due to falls: verified by x-ray and medical reports	≥1 fall: 40% (49/122) vs. 63% (75/120); RR, 0.64 (95% CI, 0.50 to 0.83)† Mean number of falls: 0.63 vs. 1.41; p<0.001 Total falls (per text): 76 vs. 171 Total falls (per Table 3): 106 vs. 169; p<0.001 By number of falls‡‡‡ 1: 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) >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	NR	Fair	Meda Pharma Inc.

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

Author, Year, Title*	UV Exposure	Intervention Fidelity	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Adverse Events/Harms: Vitamin D vs. Control	Quality Rating	Sponsor
Talwar et al, 2007[177] *Dose response to vitamin D supplementation among postmenopausal African American women* Aloia et al, 2005[175] *A randomized controlled trial of vitamin D_3 supplementation in African American women*	NR	Assessed followup levels Verified pill content	Hypercalcemia: measured serum calcium, collected at baseline and after 3, 5, 12, 18, 24, 27, 30, and 36 months	NR	SAE: 8 vs. 7; not deemed related to treatment Total AEs: 222 <u>Study-related AEs</u> Mild hypercalcemia: 6 vs. 3 (resolved on repeat fasting sample); RR, 2.00 (95% CI, 0.51 to 7.78)† Transient hypercalciuria: 3 vs. 1 (2/3 in vitamin D group resolved spontaneously); RR, 3.00 (95% CI, 0.32 to 28.37)† Persistent hypercalciuria (resolved with stopping calcium): 1 (group NR) Kidney stones: 0 vs. 0	Fair	National Institute of Aging
Wood et al, 2012[136] *Vitamin D_3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT*	Baseline and followup during January to March Baseline UVB exposure (weekly standard erythemal dose): 0.5	Assessed followup levels Capsules were reported to be analyzed but results NR Participants told not to take any dietary supplements containing vitamin D for duration of study	Hypercalcemia: measured serum calcium at baseline and after 4 weeks of treatment	<u>Vitamin D 400 vs. 1000 IU vs. control</u> Falls: 4 vs. 0 vs. 3 Type 2 diabetes: 1 vs. 0 vs. 0; RR, for 400 IU vs. control 3.0 (95% CI, 0.12 to 72.8)	<u>Vitamin D 400 vs. 1000 IU vs. control</u> Total AEs: 17 vs. 15 vs. 20; RR for 400 IU vs. control, 0.85 (95% CI, 0.47 to 1.53)†; RR for 1000 IU vs. control, 0.76 (95% CI, 0.41 to 1.39)† GI symptoms: 3 vs. 1 vs. 0; RR for 400 IU vs. control, 7.00 (95% CI, 0.37 to 133.83)†; RR for 1000 IU vs. control, 3.0 (95% CI, 0.1 to 73.5)† Hypercalcemia: 0 vs.1 vs. 0; RR for 1000 IU vs. control, 3.0 (95% CI, 0.12 to 73.50)† Joint pain: 1 vs.1 vs. 0; RR for 400 IU vs. control, 3.00 (95% CI, 0.12 to 72.79)†; RR for 1000 IU vs. control, 3.03 (95% CI, 0.12 to 73.50)† SAEs: 7 vs. 8 vs. 4; none were deemed to be related to treatment; RR for 400 IU vs. control, 1.75 (95% CI, 0.53 to 5.80)†; RR for 1000 IU vs. control, 2.02 (95% CI, 0.63 to 6.50)†	Fair	U.K. Department of Health

* All studies are 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.
ǁǁ 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

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (ng/mL)	25(OH)D Level Attained (ng/mL)
Overall WHI Trial Fair	Mean age (years): 62* Female: 100% Race: 83.1% white; 9.1% black; 4.2% Hispanic; 0.42% American Indian or Native American; 2.0% Asian or Pacific Islander; 1.2% unknown or not identified Mean BMI (kg/m^2): 29 History of fracture at any age: 35% Number of women with falls in last 12 months: 67% with no falls, 20% with 1 fall, 9% with 2 falls, 4% with >3 falls	Inclusion: Postmenopausal women in the WHI hormone therapy and dietary modification trials ages 50 to 70 years with predicted survival of >3 years and no safety, adherence, or retention risks. Exclusion: History of hypercalcemia, kidney stones; current use of corticosteroids, calcitriol, and ≥600 IU/day of vitamin D.	Chemiluminescent immunoassay	NR	NR	NR for all participants; after 2 years, in subsample (selected without regard to nonstudy supplement use or adherence to medication) of 227 women assigned to vitamin D and 221 women assigned to placebo, vitamin D levels were 28% higher (9 ng/mL) in women taking vitamin D
Jackson et al, 2006[164] *Calcium plus vitamin D supplementation and the risk of fractures*	Number of cases (annualized %) of hip fracture in vitamin D vs. control by baseline characteristics Age group at screening (years); HR all NS 50 to 59: 29 (0.06) vs. 13 (0.03) 60 to 69: 53 (0.09) vs. 71 (0.13) 70 to 79: 93 (0.44) vs. 115 (0.54) Race or ethnic group; HR all NS White: 167 (0.16) vs. 189 (0.18) Black: 3 (0.03) vs. 4 (0.04) Hispanic: 0 (0) 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)	Cases: All adjudicated cases of hip, spine, and lower arm or wrist fracture. Controls: Free of fracture for the duration of study; individually matched to cases by age, latitude of clinical center, race or ethnic group, and date of venipuncture.	As above	NR	90% <31; outcomes presented in quartiles of baseline 25(OH)D level as >24, 18 to 24, 13 to 18, and <13 ng/mL	As above

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

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (ng/mL)	25(OH)D Level Attained (ng/mL)
Wactawski-Wende et al, 2006[168] *Calcium plus vitamin D supplementation and the risk of colorectal cancer*	Number of cases (annualized %) of invasive colorectal cancer in vitamin D vs. control by baseline characteristics Age group at screening (years); HR all NS 50 to 59: 33 (0.07) vs. 32 (0.07) 60 to 69: 81 (0.14) vs. 78 (0.14) 70 to 79: 54 (0.25) vs. 44 (0.21) Race or ethnic group; HR all NS White: 145 (0.14) vs. 129 (0.12) Black: 13 (0.11) vs. 16 (0.14) Hispanic: 5 (0.09) vs. 4 (0.08) American Indian/Alaskan Native: 2 (0.37) vs. 0 (0) Asian or Pacific Islander: 2 (0.08) vs. 3 (0.13) Unknown or not identified: 1 (0.07) vs. 2 (0.13)	Cases: Women with confirmed invasive colorectal cancer and adequate stored serum for analysis. Controls: Women free of colorectal cancer for the duration of study with adequate stored serum for analysis; individually matched to cases according to age, latitude of clinical center, race or ethnic group, and date of venipuncture.	As above	NR	NR; outcomes presented in quartiles of baseline 25(OH)D level as ≥23, 17 to 23, 12 to 17, and <12 ng/mL	As above
Chlebowski et al, 2008[167] *Calcium plus vitamin D supplementation and the risk of breast cancer*	Number of cases (annualized %) of invasive breast cancer in vitamin D vs. control by baseline characteristics Age group at screening (years); HR all NS 50 to 59: 179 (0.36) vs. 196 (0.40) 60 to 69: 247 (0.43) vs. 257 (0.45) 70 to 79: 102 (0.48) vs. 93 (0.44)	Cases: Women diagnosed with invasive breast cancer. Controls: Women who were breast cancer free; matched to cases on age, latitude of clinical center, race/ethnicity, date of blood collection.	As above	NR	NR; outcomes presented in quintiles of baseline 25(OH)D level as ≥27, 22 to 27, 18 to 22, 13 to 18, and <13 ng/mL	As above

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

Author, Year, Title	Population Characteristics	Eligibility Criteria	Assay	Definition of Deficiency/ Insufficiency	Baseline 25(OH)D Level (ng/mL)	25(OH)D Level Attained (ng/mL)
de Boer et al, 2008[169] *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative*	Number of cases (annualized %) of incident diabetes in vitamin D vs. control by baseline characteristics Age group at screening (years); HR all NS 50 to 59: 431 (0.91) vs. 426 (0.91) 60 to 69: 535 (1.01) vs. 518 (0.98) 70 to 79: 188 (0.95) vs. 193 (0.98) Race/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)	Cases and controls: Women with prevalent diabetes at baseline were excluded; selected from controls used in case-control study of fracture (Jackson 2008), in which participants were free of fracture for the duration of study and were individually matched to fracture cases by age, latitude of clinical center, race or ethnic group, and date of venipuncture. Cases: Women with new physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin. Controls: Women with no physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin.	As above	NR	<32 for 89% of participants; <20 for 61% of participants; outcomes presented in quartiles of baseline 25(OH)D level as >24, 17 to 24, 13 to 17, and <13 ng/mL	As above
LaCroix et al, 2009[152] *Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial*	Number of cases (annualized %) of death in vitamin D vs. control by baseline characteristics Race/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)	Cases: Women who died and had baseline vitamin D levels from their involvement in previous WHI case-control studies of fracture and colorectal cancer (Jackson 2008; Wactawski-Wende 2006). Controls: Living participants from previous WHI case-control studies of fracture and colorectal cancer (Jackson 2008; Wactawski-Wende 2006).	As above	NR	NR; outcomes presented in tertiles of baseline 25(OH)D level as ≥21, 14 to 21, and <14 ng/mL	As above

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

Author, Year, Title	Number Approached, Screened, Eligible, Enrolled, Analyzed	Country and Setting	UV Exposure	Duration of Followup	Attrition
Overall WHI Trial Fair	Approached: 68,132 Screened: 68,132 Eligible: 36,282	Multicenter U.S. population-based Institutionalized: NR	Solar irradiance of region for entire trial (Langley): Mean, 382±60 (controls matched to cases on this parameter)	Mean, 7.0 years (SD, 1.4)	Overall: 7.0% (2531/36,282) Vitamin D vs. control: 6.8% (1240/18,176) vs. 7.1% (1291/18,106)
Jackson et al, 2006[164] *Calcium plus vitamin D supplementation and the risk of fractures*	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	As above	Number of cases (annualized %) of hip fracture in vitamin D_3 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)	As above	As above
Wactawski-Wende et al, 2006[168] *Calcium plus vitamin D supplementation and the risk of colorectal cancer*	Eligible: 322 Enrolled: 634 (317 pairs for case-control study) Analyzed: 612 (306 [96.5%] pairs for case-control study)	As above	As above	As above	As above
Chlebowski et al, 2008[167] *Calcium plus vitamin D supplementation and the risk of breast cancer*	Eligible: 1074 Enrolled: 1067 cases, 1067 controls Analyzed: 895 cases, 895 controls	As above	As above	As above	As above
de Boer et al, 2008[169] *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative*	Eligible: 1699 controls from previous case-control study (Jackson 2008)[‡] Analyzed: 3097	As above	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)	As above	As above
LaCroix et al, 2009[152] *Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial*	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)	As above	As above	As above	As above

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

Author, Year, Title	Interventions	Calcium and Other Nutrients	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Sponsor
Overall WHI Trial Fair	Vitamin D: 200 IU of vitamin D_3 BID (total, 400 IU/day) + 500 mg of calcium carbonate BID (total, 1000 mg/day) Control: Identical placebo BID	Personal use of ≤1000 mg/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.	See individual studies below	See individual studies below	National Institutes of Health
Jackson et al, 2006[164] *Calcium plus vitamin D supplementation and the risk of fractures*	As above	As above	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.	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) <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) <13: 196/167 vs. 182/204; OR, 1.32 (95% CI, 0.99 to 1.76) p=0.15 for interaction	National Heart, Lung, and Blood Institute; General Clinical Research Center Program of the National Center for Research Resources; several investigators supported by industry

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

Author, Year, Title	Interventions	Calcium and Other Nutrients	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Sponsor
Wactawski-Wende et al, 2006[168] *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 General Clinical Research Center Program of the National Center for Research Resources; several investigators supported by industry
Chlebowski et al, 2008[167] *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

Author, Year, Title	Interventions	Calcium and Other Nutrients	Determination of Outcomes	Clinical Health Outcomes: Vitamin D vs. Control	Sponsor
de Boer et al, 2008[169] *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative*	As above	As above	Diabetes: Case-identification by self-report of a doctor prescribing medication or insulin for diabetes. Study states that accuracy of self-reported treated diabetes in WHI previously assessed using medication and laboratory data.	Incidence and risk 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) <13: 30/381 vs. 33/391; OR, 1.07 (95% CI, 0.62 to 1.82) p=0.59 for interaction	National Heart, Lung, and Blood Institute; National Institutes of Health Roadmap for Medical Research
LaCroix et al, 2009[152] *Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial*	As above	As above	Mortality: For women who could not be contacted, information about vital status was sought from previously identified proxy informants, National Death Index searches, and obituary notices. Causes of death were determined based on available medical records, autopsy reports, and the death certificate in a blinded fashion by local and central physician adjudicators.	Incidence and risk 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) <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	National Heart, Lung, and Blood Institute

* 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

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Reporting of Attrition, Crossovers, Adherence, and Contamination
Aloia et al, 2008[174]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Arvold et al, 2009[170]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Berlin et al, 1986[178]	No	No	Unclear	Yes	No	No	No	No
Bischoff et al, 2003[165]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brazier et al, 2005[157]	Yes	Unclear	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double blind	Yes
Chapuy et al, 2002[122]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes
Gallagher et al, 2012[156]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gallagher et al, 2013[160]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gallagher et al, 2014[159]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grimnes et al, 2011[158]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Harris et al, 1999[176]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Honkanen et al, 1990[128]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Janssen et al, 2010[127]	Unclear	Yes	Yes (small difference in age)	Yes	Yes	Yes	Yes	Yes
Kärkkäinen et al, 2010[153] Kärkkäinen et al, 2010[166]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Kjaergaard et al, 2012[171]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Krieg et al, 1999[154]	Unclear	Unclear	Yes	Yes	No	No	No	Yes
Knutsen et al, 2014[132]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lehmann et al, 2013[115]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lips et al, 1996[161] Ooms et al, 1995[120]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Lips et al, 2010[155]	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear, described as double-blind	Yes
Martineau et al, 2007[179]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pfeifer et al, 2000[162]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes
Pfeifer et al, 2009[163]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes
Talwar et al, 2007[177] Aloia et al, 2005[175]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Reporting of Attrition, Crossovers, Adherence, and Contamination
Wamberg et al, 2013[125] Wamberg et al, 2013[133]	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes
Womens' Health Initiative Jackson et al, 2003[146] Jackson et al, 2006[164] Wactawski-Wende et al, 2006[168] Chlebowski et al, 2008[167] de Boer et al, 2008[169] LaCroix et al, 2009[152]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes
Wood et al, 2012[136]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, Year	Acceptable Attrition and Difference Between Groups?	People Analyzed in the Groups in Which They Were Randomized?	Post-Randomization Exclusions?	Outcomes Prespecified?	Fidelity to Intervention?	Quality Rating	External Validity*
Aloia et al, 2008[174]	Yes	Yes	OK	Yes	Yes	Fair	1. University hospital 2. None 3. 53% 4. Good
Arvold et al, 2009[170]	No (differential)	Yes	OK	Yes	Yes	Fair	1. Outpatient clinic 2. None 3. 16% 4. Fair, one clinic
Berlin et al, 1986[178]	Unclear	Yes	Unclear	Yes	Yes: Levels	Poor	1. University hospital 2. Unclear 3. NR 4. Unclear, not much reported about population
Bischoff et al, 2003[165]	No (high)	Yes	OK	Yes	Yes: Levels	Fair	1. Long-stay geriatric clinic 2. None 3. NR 4. Fair, elderly (age ≥60 years), institutionalized
Brazier et al, 2005[157]	Yes	Yes	OK	Yes	Yes: Levels Compliance >90%	Fair	1. 50 centers 2. None 3. Unclear 4. Fair, only women

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Acceptable Attrition and Difference Between Groups?	People Analyzed in the Groups in Which They Were Randomized?	Post-Randomization Exclusions?	Outcomes Prespecified?	Fidelity to Intervention?	Quality Rating	External Validity*
Chapuy et al, 2002[122]	Yes	Yes	OK	Yes	Yes: Levels Compliance 95%	Fair	1. Homes for the elderly 2. None 3. NR 4. Fair, elderly (age ≥64 years), institutionalized
Gallagher et al, 2012[156]	Yes	Yes	OK	Yes	Yes: Levels Compliance >90%	Good	1. University medical center 2. None 3. 8% 4. Fair, only women
Gallagher et al, 2013[160]	Yes	Yes	No	Yes	Yes	Fair**	1. University medical center 2. None 3. 36% 4. Fair, only women
Gallagher et al, 2014[159]	No	Yes	No	Yes	Yes	Fair	1. University medical center 2. None 3. 35% 4. Fair, only women
Grimnes et al, 2011[158]	Yes	Yes	Yes	Unclear	Yes: Levels	Fair	1. Community 2. None 3. 31% 4. Good
Harris et al, 1999[176]	Yes	Yes	Some post-randomization exclusions	Unclear	Yes: Levels	Poor	1. Tufts University 2. Unclear recruitment 3. NR 4. Unclear
Honkanen et al, 1990[128]	Yes	Yes	Unclear	Yes	Yes: Levels	Fair	1. City hospital 2. None 3. 62% 4. Fair, only women
Janssen et al, 2010[127]	No	Yes	OK	Yes	Yes: Levels Compliance >90%	Fair	1. Outpatient clinics 2. None 3. NR 4. Fair, elderly (age >65 years), institutionalized
Kärkkäinen et al, 2010[153] Kärkkäinen et al, 2010[166]	Yes	Yes	OK	Yes	Yes: Levels Compliance 79%	Fair	1. Population-based 2. None 3. Unclear; reports numbers for subsample, not full screened group 4. Fair, only women
Kjaergaard et al, 2012[171]	Yes	Yes	Yes (6 subjects)	Yes	Yes	Good	1. Community 2. None 3. 18% 4. Good

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Acceptable Attrition and Difference Between Groups?	People Analyzed in the Groups in Which They Were Randomized?	Post-Randomization Exclusions?	Outcomes Prespecified?	Fidelity to Intervention?	Quality Rating	External Validity*
Krieg et al, 1999[154]	No (high)	Yes	OK	No	Yes: Levels	Fair	1. Nursing homes 2. NR 3. NR 4. Fair, elderly (age ≥62 years), institutionalized
Knutsen et al, 2014[132]	Yes	Yes	OK	Unclear; no specification whether AEs were prespecified outcome; no clear description of how outcome was collected	Yes: Pill count Compliance 80% consumed ≥80%	Fair	1. Immigrants' activity centers 2. None 3. 83% 4. Fair, immigrants in Northern Europe
Lehmann et al, 2013[115]	Yes	Yes	OK	Unclear	Yes: Levels	Fair	1. Healthy community population 2. None 3. NR 4. Good
Lips et al, 1996[161] Ooms et al, 1995[120]	No (high)	Yes	Some post-randomization exclusions	Yes	Yes: Levels Compliance 85%	Fair	1. Community 2. None 3. NR 4. Fair, elderly (age ≥70 years), institutionalized
Lips et al, 2010[155]	Yes	Yes	Unclear	Yes	Yes: Levels Compliance 100%	Fair	1. Medical centers and nursing homes 2. None 3. 38% 4. Fair, elderly (age ≥70 years)
Martineau et al, 2007[179]	No (high)	Yes	Yes	Unclear (for AEs)	Yes: Levels	Fair	1. TB contact clinics 2. Recruited from TB clinics 3. 53% 4. Poor, TB clinics
Pfeifer et al, 2000[162]	Yes	Yes	OK	Yes	Yes: Levels	Fair	1. Population-based 2. None 3. 90% 4. Fair, elderly (age ≥70 years)
Pfeifer et al, 2009[163]	Yes	Yes	OK	Yes	Yes: Levels	Fair	1. Population-based 2. None 3. NR 4. Fair, elderly (age ≥70 years)
Talwar et al, 2007[177] Aloia et al, 2005[175]	Yes	Yes	OK	Unclear (for AEs)	Yes: Levels Compliance ~87%	Fair	1. Population-based 2. None 3. 54% 4. Fair, only women

Appendix C3. Quality Ratings of Included Randomized, Controlled Trials

Author, Year	Acceptable Attrition and Difference Between Groups?	People Analyzed in the Groups in Which They Were Randomized?	Post-Randomization Exclusions?	Outcomes Prespecified?	Fidelity to Intervention?	Quality Rating	External Validity*
Wamberg et al, 2013[125] Wamberg et al, 2013[133]	Yes	Yes	OK	Yes	Yes: Levels Compliance >90%	Fair	1. University hospital 2. None 3. 59% 4. Good
Womens' Health Initiative Jackson et al, 2003[146] Jackson et al, 2006[164] Wactawski-Wende et al, 2006[168] Chlebowski et al, 2008[167] de Boer et al, 2008[169] LaCroix et al, 2009[152]	Yes	Yes	OK	Yes	No	Fair	1. Population-based 2. None 3. Case-control studies of subsamples of WHI trial 4. Fair, only women
Wood et al, 2012[136]	Yes	Yes	OK	Unclear (for AEs)	Yes: Levels Compliance >90%	Fair	1. Community 2. None 3. 72% 4. Good

***** 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.