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REVIEW

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

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**Background:** Vitamin D deficiency has been associated with adverse health outcomes.

**Purpose:** To systematically review benefits and harms of vitamin D screening in asymptomatic adults.

**Data Sources:** Ovid MEDLINE (through the third week of August 2014), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews.

**Study Selection:** Randomized trials of screening for and treatment of vitamin D deficiency and case–control studies nested within the Women's Health Initiative.

**Data Extraction:** One investigator abstracted data, a second reviewed data for accuracy, and 2 investigators independently assessed study quality using predefined criteria.

**Data Synthesis:** No study examined the effects of vitamin D screening versus no screening on clinical outcomes. Vitamin D treatment was associated with decreased mortality versus placebo or no treatment (11 studies; risk ratio [RR], 0.83 [95% CI, 0.70 to 0.99]), although benefits were no longer seen after trials of institutionalized persons were excluded (8 studies; RR, 0.93 [CI, 0.73 to 1.18]). Vitamin D treatment was associated with possible decreased risk for having at least 1 fall (5 studies; RR, 0.84 [CI, 0.69 to 1.02]) and falls per person (5 studies; incidence rate ratio, 0.66 [CI, 0.50 to 0.88]) but not fractures (5 studies; RR, 0.98 [CI, 0.82 to 1.16]). Vitamin D treatment was not associated with a statistically significant increased risk for serious adverse events (RR, 1.17 [CI, 0.74 to 1.84]).

**Limitation:** Variability across studies in 25-hydroxyvitamin D assays and baseline levels, treatment doses, use of calcium, and duration of follow-up.

**Conclusion:** Treatment of vitamin D deficiency in asymptomatic persons might reduce mortality risk in institutionalized elderly persons and risk for falls but not fractures.

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For author affiliations, see end of text.
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Vitamin D is obtained through food consumption and synthesis in the skin after ultraviolet (UV) B exposure (1). Researchers have reported associations between low 25-hydroxyvitamin D [25-(OH)D] levels and risk for fractures (2–6), falls (7, 8), cardiovascular disease (9–14), colorectal cancer (13–20), diabetes (13, 14, 21–29), depressed mood (13, 14, 30, 31), cognitive decline (13, 14), and death (13, 32).

Vitamin D deficiency is determined by measuring total serum 25-(OH)D concentrations (33). Measuring 25-(OH)D levels is complicated by the presence of multiple assays (34); evidence of intermethod and interlaboratory variability in measurement (35–43); and the lack of an internationally recognized, commutable vitamin D reference standard (44). Efforts to increase standardization are in progress (34, 44).

There is no consensus on optimal 25-(OH)D concentrations. Although experts generally agree that levels lower than 50 nmol/L (20 ng/mL) are associated with bone health (36, 45), disagreement exists about whether optimal 25-(OH)D levels are higher than this threshold (Table 1). According to NHANES (National Health and Nutrition Examination Survey) data from 2001 to 2006, 33% of the U.S. population was at risk for 25-(OH)D levels below 50 nmol/L (20 ng/mL) (47) and 77% had 25-(OH)D levels below 75 nmol/L (30 ng/mL) (48). Risk factors for low vitamin D levels include darker skin pigmentation (33), low vitamin D intake (49–51), little or no UVB exposure (49, 50, 52–54), and obesity (49–51, 55). Older age (49–53), female sex (49, 51, 52), low physical activity (49, 50, 53), low education attainment (48), and low health status (51, 54) were factors also associated with vitamin D deficiency in some studies.

Vitamin D deficiency is treated by increasing dietary intake of food fortified with vitamin D or oral vitamin D treatment. Two commonly available vitamin D treatments (vitamin $D_3$ [cholecalciferol] and vitamin $D_2$ [ergocalciferol]) are available in several forms (for example, tablet and gel capsule), dosages (for example, 200 to 500 000 IU), and dosing regimens (for example, daily, weekly, monthly, or yearly) and can be given in combination with oral calcium (56, 57). Potential harms of vitamin D treatment include hypercalcemia, hyperphosphatemia, suppressed parathyroid hormone levels, and hypercalciuria (46, 58, 59). Although very high levels of vitamin D are associated with other potential harms, these events are rare with typical replacement doses (Table 1).

Screening for vitamin D deficiency can identify persons with low levels who might benefit from treatment. This report reviews the current evidence on vitamin D screening in asymptomatic adults to help the U.S. Pre-

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

| 25-(OH)D Level Cutoff | Opinions of Expert and Professional Bodies About Cutoff Levels | Summary of Previous Research on the Associations Between 25-(OH)D Levels and Risk for Health Outcomes | Subgroup Differences for the Associations |
|---|---|---|---|
| <50 nmol/L (<20 ng/mL) | Widely used by researchers and available guidelines as indicative of deficiency | Levels ≥50 nmol/L (≥20 ng/mL) have been associated with decreased risk for fractures, CVD, CRC, diabetes, depressed mood, cognitive decline, and death | Association with fractures and CVD not seen in black persons<br>Association with death seen in black persons<br>Association with falls seen in studies of institutionalized elderly populations<br>Limited data show that association with cognition may be stronger in women |
| 50–75 nmol/L (20–30 ng/mL) | Debate about whether these levels represent deficiency | Levels >60 nmol/L (>24 ng/mL) associated with decreased risk for CVD<br>Levels >75 nmol/L (>30 ng/mL) associated with decreased risk for death and CRC<br>Data conflict about whether levels >75 nmol/L (>30 ng/mL) are associated with decreased risk for fractures | Association with CVD not seen in black persons<br>Association with death seen in black persons |
| >75–125 nmol/L (>30–50 ng/mL) | General agreement that these levels do not represent deficiency; however, some recommend targeting 25-(OH)D levels to this range because results of 25-(OH)D testing vary | Levels between 87 and 100 nmol/L (35 to 40 ng/mL) may be associated with decreased for death and CRC | NA |
| >125–499 nmol/L (>50–200 ng/mL) | Debate about whether these levels are associated with adverse health outcomes | Possible U-shaped association between vitamin D levels and risk for death and pancreatic cancer | NA |
| >499 nmol/L (>200 ng/mL) | These levels are considered toxic | NA | NA |

25-(OH)D = 25-hydroxyvitamin D; CRC = colorectal cancer; CVD = cardiovascular disease; NA = not available.
* The appendix of reference 46 contains a full discussion and references.

ventive Services Task Force (USPSTF) develop a recommendation statement. Although the USPSTF has not previously issued recommendations on screening for vitamin D deficiency, it has made recommendations on vitamin D supplementation to prevent adverse health outcomes (for example, falls, fractures, cancer, and cardiovascular disease) in populations not necessarily vitamin D–deficient (that is, general populations who may or may not have been deficient) (60–63).

## METHODS

### Scope of the Review

We developed a review protocol and analytic framework (**Appendix Figure 1**, available at www.annals.org) that included the following key questions:

1. Is there direct evidence that screening for vitamin D deficiency results in improved health outcomes?

1a. Are there differences in screening efficacy between patient subgroups?

2. What are the harms of screening (for example, risk for procedure, false positives, or false negatives)?

3. Does treatment of vitamin D deficiency using vitamin D lead to improved health outcomes?

3a. Are there differences in efficacy between patient subgroups?

4. What are the adverse effects of treatment of vitamin D deficiency using vitamin D?

4a. Are there differences in adverse effects between patient subgroups?

Detailed methods and data for this review are contained in the full report, including search strategies, inclusion criteria, abstraction and quality rating tables, and contextual questions (46). We developed our protocol using a standardized process after gathering input from experts and the public. The analytic framework focuses on direct evidence that screening for vitamin D deficiency improves important health outcomes (for example, death, falls, fractures, functional status, or risk for cancer) versus not screening. Further, the framework details evidence that treatment in persons found to have vitamin D deficiency is associated with improved health outcomes, harms resulting from screening or subsequent treatment, and how effects of screening and treatment vary in subgroups defined by demographic and other factors (for example, body mass index, UV exposure, and institutionalized status). We did not review the accuracy of vitamin D testing because of the lack of an accepted reference standard and studies reporting diagnostic accuracy.

For the purposes of this report, the term "vitamin D–deficient" refers to populations in which at least 90% of persons have 25-(OH)D levels of 75 nmol/L (30 ng/mL) or less. For studies that did not restrict enrollment to persons with 25-(OH)D levels of 75 nmol/L (30 ng/mL), we used the mean 25-(OH)D level plus the SD multiplied by 1.282 to approximate the 90th percentile to determine whether this level was at or below the 75-nmol/L (30-ng/mL) threshold. Because of uncertainty

about what 25-(OH)D level constitutes deficiency, we stratified studies according to whether at least 90% of persons had levels less than 50 nmol/L ("<20 ng/mL" in this report) or at least 90% had levels less than 75 nmol/L (30 ng/mL) with at least 10% greater than 50 nmol/L (20 ng/mL) ("≤75 nmol/L [≤30 ng/mL]" in this report).

### Data Sources and Searches

A research librarian searched Ovid MEDLINE (1946 through the third week of August 2014), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (through August 2014). We supplemented our electronic searches by reviewing reference lists of retrieved articles.

### Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion eligibility. For screening studies, we included randomized, controlled trials (RCTs) of screening for vitamin D deficiency versus no screening in healthy, asymptomatic adults (aged ≥18 years). For studies of the effectiveness of vitamin D treatment, we included RCTs of vitamin D treatment with or without calcium versus placebo or no treatment in vitamin D–deficient persons that reported health outcomes after at least 8 weeks of treatment. Because the Women's Health Initiative (WHI) is the largest RCT about vitamin D (64), we included data from nested case–control studies of WHI participants with known 25-(OH)D status.

We included English-language articles only and excluded studies published only as abstracts. We included studies conducted in the United States, Canada, United Kingdom, and other geographic settings generalizable to the United States. We excluded studies that specifically targeted populations with symptoms or conditions associated with vitamin D deficiency (for example, osteoporosis, history of nontraumatic fractures, or history of falls) or with medical conditions that increase a person's risk for deficiency (such as liver, kidney, or malabsorptive disease) because screening and treatment of vitamin D deficiency could be a component of medical management in these conditions. The summary of evidence search and selection is shown in Appendix Figure 2 (available at www.annals.org).

### Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, follow-up, and results. A second investigator reviewed data for accuracy. Two investigators independently applied USPSTF criteria (65) to rate the quality of each study as good, fair, or poor. We resolved discrepancies through a consensus process. We excluded from data synthesis studies rated as poor quality. Those studies had 1 or more fatal flaws, including inadequate randomization or lack of intervention fidelity combined with postrandomization exclusions, high rates of withdrawals, and unclear randomization.

### Data Synthesis and Analysis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, or poor) using methods developed by the USPSTF on the basis of the number, quality, and size of studies; consistency of results; and directness of evidence (65).

We conducted meta-analyses to calculate risk ratios (RRs) using the DerSimonian–Laird random-effects model (Review Manager, version 5.2; Cochrane Collaboration). Analyses were based on total follow-up (including time after discontinuation of vitamin D treatment). For falls per person, we calculated incidence rate ratios and assumed equal mean length of follow-up across treatment groups if these data were not reported. For analyses with between-study heterogeneity, we conducted sensitivity analyses using profile likelihood random-effects models (66). Rate ratio analysis and analyses using the profile likelihood model were done with Stata, version 12.0 (StataCorp). We performed sensitivity analyses restricted to RCTs, excluding the WHI subanalyses, and used odds ratios rather than RRs.

We assessed statistical heterogeneity using the chi-square test and $I^2$ statistic (67). For all analyses, we stratified results by serum baseline 25-(OH)D level (<50 nmol/L [<20 ng/mL] vs. ≤75 nmol/L [≤30 ng/mL]). We performed additional analyses in which trials were stratified by institutionalized status, treatment regimen (vitamin D alone [vitamin D vs. placebo or no treatment, or vitamin D plus calcium vs. calcium alone] or vitamin D combined with calcium [vitamin D plus calcium vs. placebo or no treatment]), vitamin D dose (≤400 vs. >400 IU/d), duration of follow-up (≤12 vs. >12 months), and participant mean age (≤70 vs. >70 years).

### Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. The investigators are solely responsible for the content and the decision to submit it for publication.

## RESULTS

No study evaluated clinical outcomes or harms in persons screened versus not screened for vitamin D deficiency.

### Effectiveness of Vitamin D Treatment

Seven trials evaluated the effectiveness of vitamin D treatment (with or without calcium) in populations with at least 90% of persons with 25-(OH)D levels less than 50 nmol/L (20 ng/mL) (68–74). Nine trials and 1 nested case–control study evaluated effectiveness in

populations with at least 90% of their population with levels of 75 nmol/L (30 ng/mL) or less (75–90) (**Appendix Table**, available at www.annals.org). The mean age of the participants in these trials ranged from 37 to 85 years, and more than 70% of the studies enrolled only women. Mean body mass indices 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 elderly adults (considered institutionalized) in the United States or Europe. Ultraviolet exposure was not well-quantified in any study, and only 6 studies (64, 70, 71, 75, 82, 85) reported race. Of these, 1 study restricted enrollment to African Americans (70) and 83% to 100% of participants in the remaining 6 studies were white. Studies examined vitamin $D_3$ at dosages ranging from 400 to 4800 IU/d or 8400 to 50 000 IU/wk. Five studies examined vitamin $D_3$ treatment coadministered with calcium (1000 to 1200 mg/d), and 12 examined vitamin $D_3$ treatment alone. Study duration ranged from 2 months to 7 years, and the assays these studies used to measure 25-(OH)D varied. Methodological shortcomings among these studies included unclear randomization and allocation concealment methods or blinding. Some studies had unclear intervention fidelity (that is, they did not record postintervention 25-[OH]D levels) or reported high attrition (>20%).

### *Mortality*

One good-quality trial, 9 fair-quality trials, and 1 fair-quality nested case–control study reported effects of vitamin D treatment (dose, 400 IU/d to 40 000 IU/wk) on mortality in vitamin D–deficient populations ($n$ = 4126) (68–73, 77, 80, 82, 83, 89). Mortality was not a primary outcome in any study. No individual study reported a statistically significant reduction in mortality with vitamin D treatment versus placebo or no treatment, although the estimates were often imprecise because of very few events (68, 70–73, 77, 82). When data were pooled, vitamin D treatment with or without calcium was associated with decreased risk for mortality versus placebo or no treatment (RR, 0.83 [95% CI, 0.70 to 0.99]; $I^2$ = 0%; absolute risk difference ranged from a reduction of 6 percentage points to an increase of 2 percentage points) (**Appendix Figure 3**, available at www.annals.org).

When analyses were stratified by institutionalized status, the risk reduction was limited to studies of older, institutionalized persons (3 studies; RR, 0.72 [CI, 0.56 to 0.94]; $I^2$ = 0%; absolute risk reduction, 4 to 6 percentage points) (**Figure 1**) (69, 80, 83). The effect was not present in noninstitutionalized populations (8 studies; RR, 0.93 [CI, 0.73 to 1.18]; $I^2$ = 0%) (68, 70–73, 77, 82, 89). In additional sensitivity analyses, the reduction in mortality occurred when studies exceeding 12 months whose populations had a mean age greater than 70 years were pooled. Stratification by baseline 25-(OH)D level, calcium use, or vitamin D dosage did not affect risk estimates.

### *Fracture Risk*

Four fair-quality trials and 1 nested case–control study examined the effects of 2 months to 7 years of vitamin D treatment (with or without calcium), 400 to 800 IU/d, on the risk for any type of fracture in vitamin D–deficient persons ($n$ = 3551) (69, 74, 81, 84, 88). No individual study reported a statistically significant reduction in fracture risk with vitamin D treatment, including the largest study—a case–control analysis nested within the WHI calcium-vitamin D trial (88). The pooled estimate was close to 1 (5 trials; RR, 0.98 [CI, 0.82 to 1.16]; $I^2$ = 32%) (**Figure 2**, *top*). Sensitivity analyses resulted in similar findings of no effect and did not decrease heterogeneity. Results were similar when only hip fracture risk was examined (4 trials; RR, 0.96 [CI, 0.72 to 1.29]; $I^2$ = 46%) (**Figure 2**, *bottom*) (69, 74, 81, 88).

### *Fall Risk*

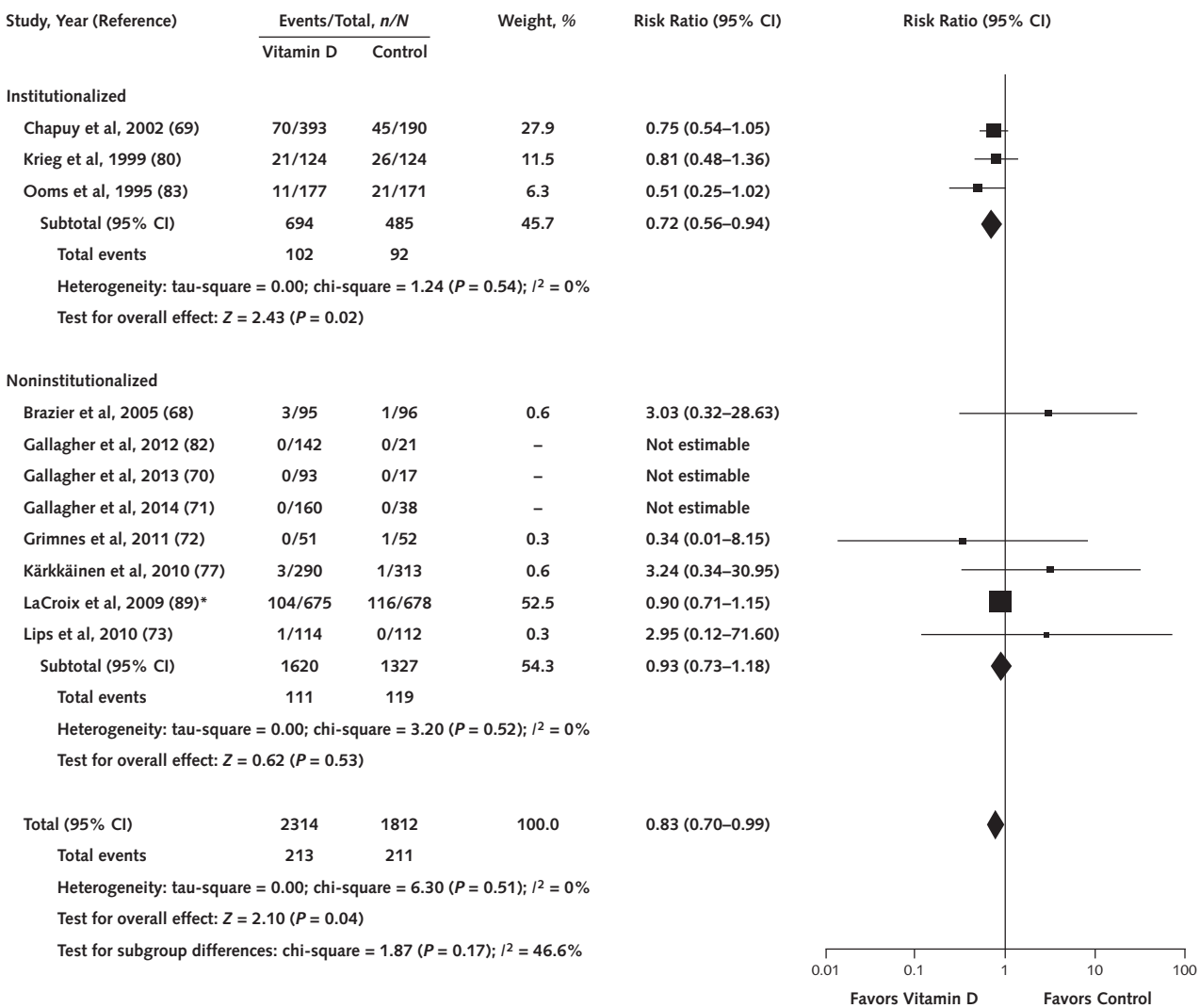
Five fair-quality trials examined the effects of 2 to 36 months of vitamin D treatment (with or without calcium), 800 IU/d, compared with control, on the risk for at least 1 fall ($n$ = 1677) (69, 74, 76, 78, 84). Although the trials did not specifically recruit participants at high risk for frailty or those who had prior falls, these studies included persons who may have been at risk for falls based on older age (mean age >70 years) (69, 74, 76, 84), institutionalized status (69, 76), mobility problems (69, 76), or multiple comorbid conditions (69, 74, 76). In 2 studies, a proportion of patients had a history of falls (69, 76). Although the overall summary RR for experiencing at least 1 fall with vitamin D treatment was consistent with reduced risk (5 trials; pooled RR, 0.84 [CI, 0.69 to 1.02]) (**Figure 3**); the result was not statistically significant, and heterogeneity was high ($I^2$ = 70%). Sensitivity analyses based on institutionalized status, baseline 25-(OH)D level, vitamin D dosage, study duration, and age did not reduce heterogeneity and resulted in similar estimates. Heterogeneity, however, was reduced to 0 when we excluded 2 trials of cotreatment with vitamin D and calcium (69, 78). Vitamin D treatment alone was associated with decreased risk for at least 1 fall (3 trials; RR, 0.65 [CI, 0.52 to 0.81]; $I^2$ = 0%) (74, 76, 84).

Five fair-quality trials examined the effect of vitamin D treatment (with or without calcium), 400 to 1000 IU/d, compared with control on the number of falls per person ($n$ = 1399) (74, 76, 78, 84, 85). Vitamin D treatment was associated with a significant reduction in the number of falls per person versus placebo or no treatment (5 trials; incidence rate ratio, 0.66 [CI, 0.50 to 0.88]; $I^2$ = 65%) (**Figure 4**). Although statistical heterogeneity was present, all estimates favored vitamin D treatment. Sensitivity analyses did not affect findings.

### *Other Health Outcomes*

One to 2 studies examined the effects of vitamin D (with or without calcium) on cancer risk (86, 90), type 2 diabetes mellitus risk (85, 87), psychosocial functioning and psychosocial disability (79, 91), and physical func-

***Figure 1.*** 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-vitamin D trial (64).

tioning (73). Findings either were mixed or showed no effect on these health outcomes.

### *Subgroup Effects*

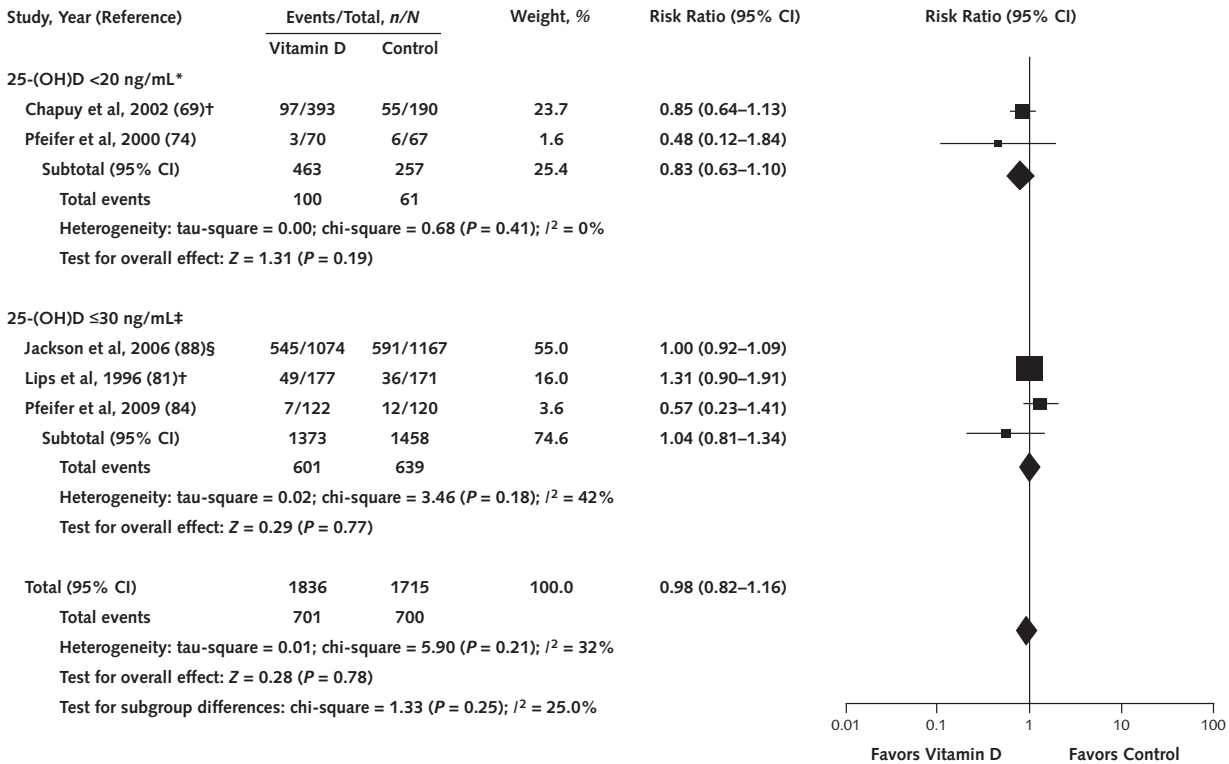
None of the included trials were designed or powered to evaluate potential subgroup effects based on factors, such as sex, race, body mass index, or UV exposure. Data suggesting benefits of vitamin D treatment on mortality and falls seemed to be primarily limited to trials of older, often institutionalized, European women (69, 80, 83).

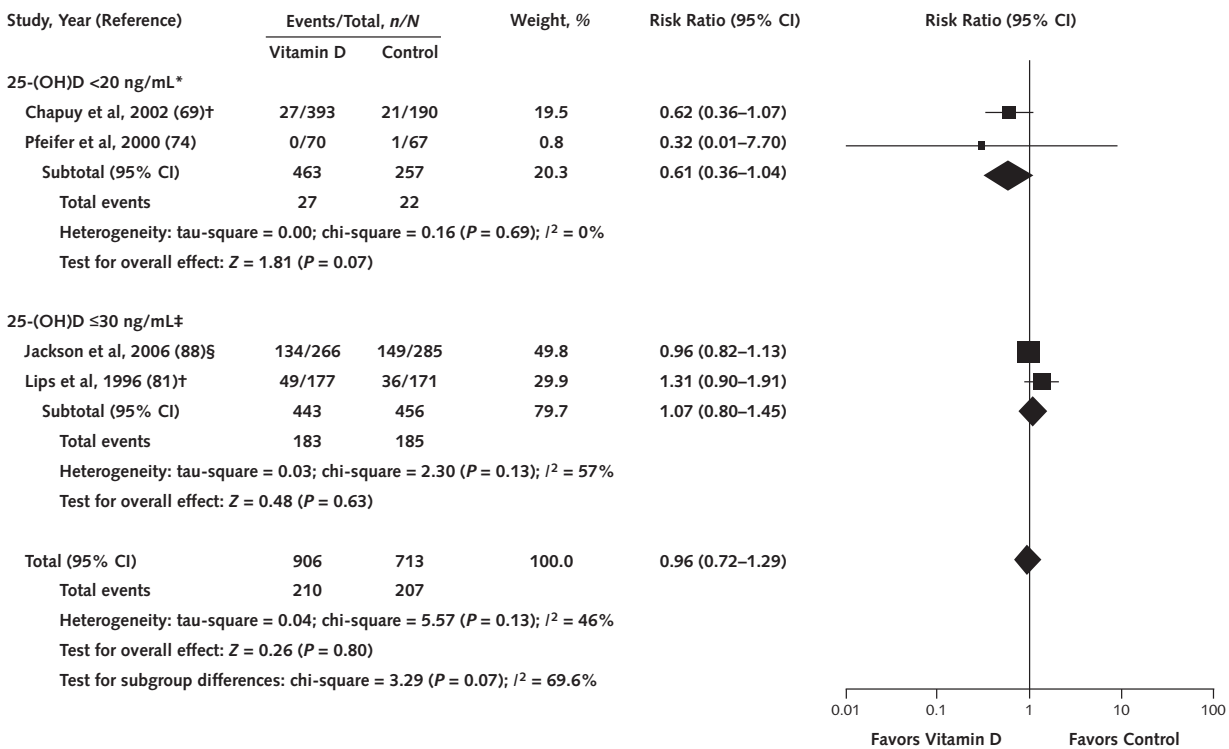
## Harms of Vitamin D Treatment

Twenty-four trials evaluated harms associated with vitamin D treatment (with or without calcium) in vitamin D–deficient populations aged 31 to 85 years ($n$ = 4722) (Appendix Table) (68–73, 75–77, 79, 80, 82, 83, 85, 92–103). Vitamin D treatment (mostly $D_3$ formulation) was given at doses of 400 to 7000 IU/d or 8400 to 54 000 IU/wk for 6 weeks to 4 years. Nineteen trials evaluated the vitamin D treatment alone, and 5 evaluated vitamin D with calcium. Methodological shortcomings included unclear randomization procedure; inadequate or unclear masking of assessors, providers, or participants; high attrition; and no clear statement that adverse events were a prespecified outcome.

We found no difference between treatment with vitamin D and placebo or no treatment in risk for any adverse event ($n$ = 1332; 7 trials), serious adverse events ($n$ = 1401; 7 trials; RR, 1.17 [CI, 0.74 to 1.84]), withdrawals due to adverse events ($n$ = 938; 5 trials; RR, 0.90 [CI, 0.36 to 2.24]), hypercalcemia ($n$ = 3172; 16 studies; RR, 1.05 [CI, 0.57 to 1.94]), kidney stones ($n$ = 1608; 7 trials, with no kidney stones reported in any trial), or gastrointestinal symptoms ($n$ = 1201; 4 trials; RR, 0.84 [CI, 0.44 to 1.58]). The studies were not de-

***Figure 2.*** Meta-analysis of effects of vitamin D treatment on risk for any fracture (*top*) or hip fracture (*bottom*).




To convert ng/mL to nmol/L, divide by 0.40. 25-(OH)D = 25-hydroxyvitamin D.
* ≥90% of study participants had 25-(OH)D levels <20 ng/mL.
† Population institutionalized.
‡ ≥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-vitamin D trial (64).

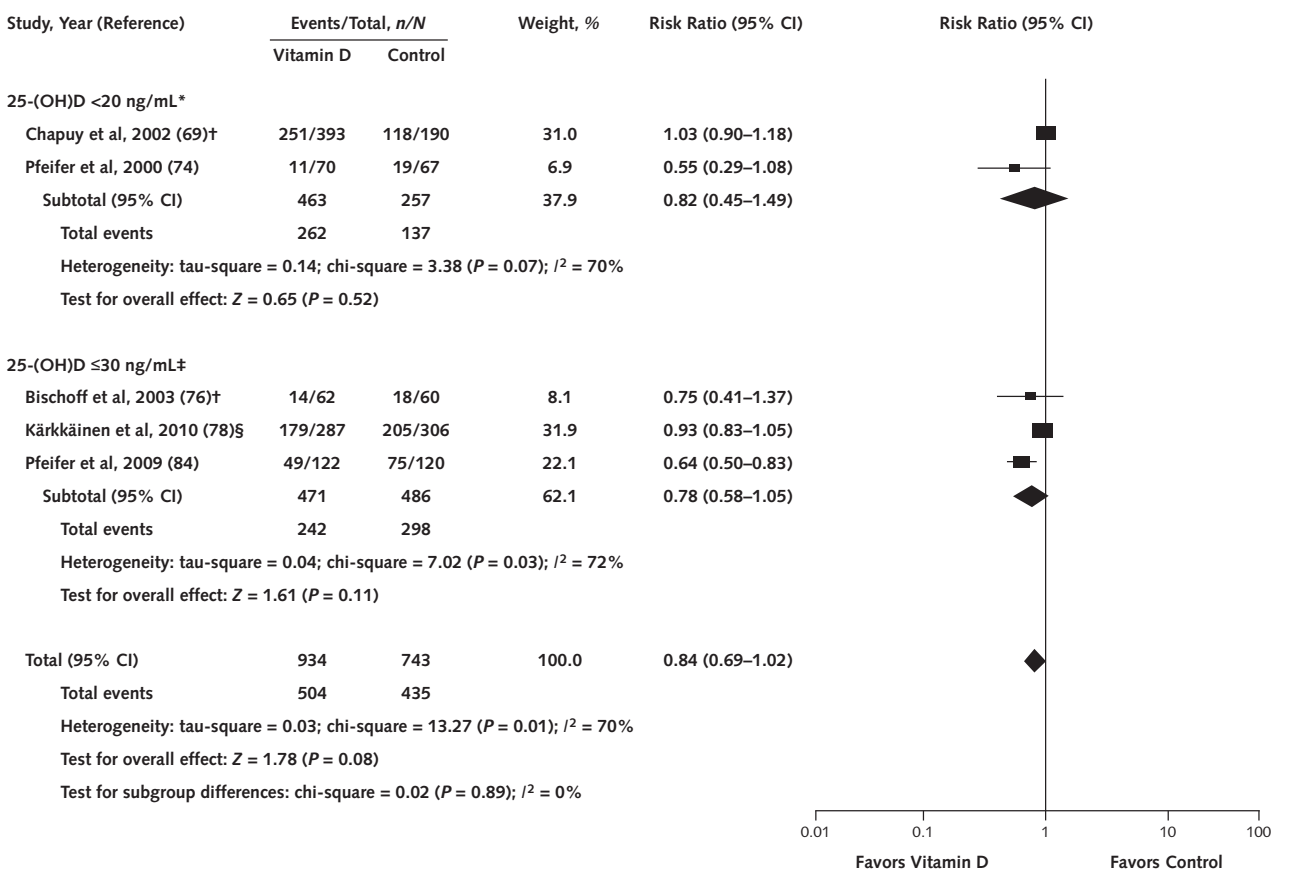
signed to evaluate whether harms differ according to demographic or other clinical characteristics.

## DISCUSSION

The evidence reviewed in this report is summarized in Table 2. We found no direct evidence on effects of screening for vitamin D deficiency versus no screening on clinical outcomes. In persons with low vitamin D levels, vitamin D treatment was associated with decreased risk for death, but effects were no longer present when 3 trials of older institutionalized women were excluded from the analysis (69, 80, 83). Vitamin D treatment was associated with a nonsignificant reduction in the risk for 1 or more falls and a significantly reduced overall burden of falls, which is measured by the number of falls per person. This potential discrepancy seems largely attributable to 1 trial that was conducted in an institutionalized population with a high comorbidity burden; the trial reported a rate ratio for falls per person as its primary outcome that was lower than the risk for at least 1 fall (0.46 [CI, 0.28 to 0.76] and 0.75 [CI, 0.41 to 1.37], respectively) (76). The risk estimates were similar in 3 other trials that reported both risk for falls and the rate of falls per person (74, 78, 84). Data were limited (≤2 studies) on the effect of vitamin D on other outcomes, such as cancer risk, type 2 diabetes mellitus risk, psychosocial functioning, disability, and physical functioning. Vitamin D treatment did not seem to be associated with increased risk for harms, although few trials were designed to specifically address harms and harms reporting was often suboptimal. Evidence to evaluate subgroup effects on the basis of such factors as race, sex, age, or risk factors for vitamin D deficiency was very limited and precludes us from drawing reliable conclusions.

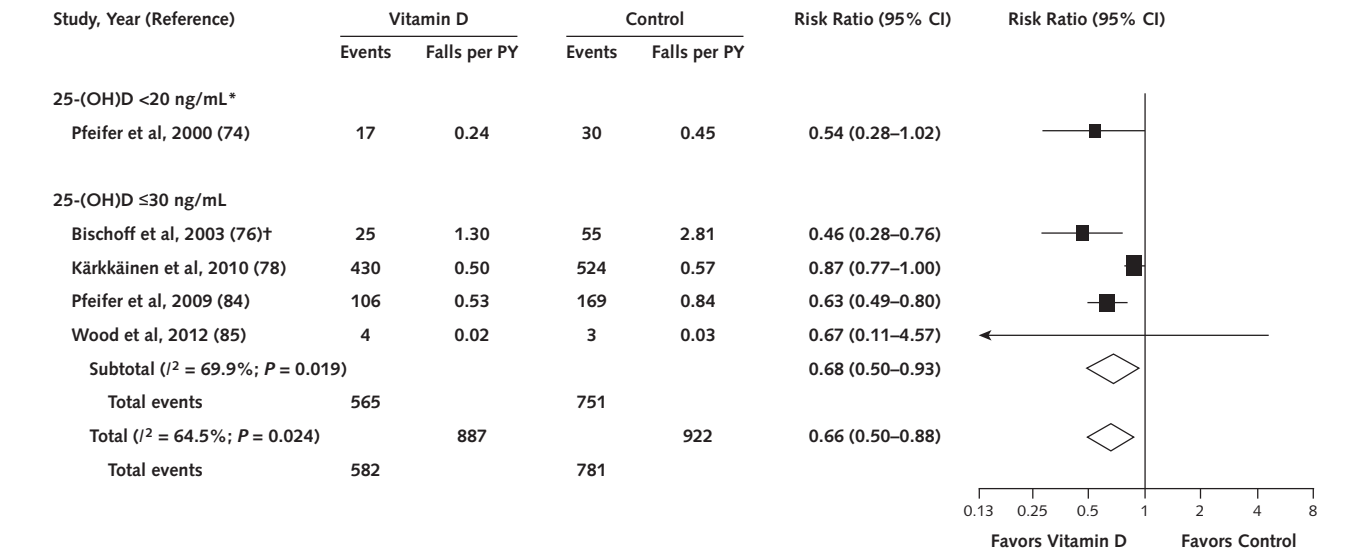
An important limitation of the evidence is that no study specifically evaluated the effect of treatment of screen-detected vitamin D deficiency, which potentially limits their applicability to screening settings. Although we excluded studies that selected patients with conditions and outcomes associated with vitamin D deficiency, symptoms were not reported, which makes it difficult to know whether patients were truly asymptomatic. In addition, baseline 25-(OH)D levels, dosages

***Figure 3.*** Meta-analysis of effects of vitamin D treatment on risk for falls.




To convert ng/mL to nmol/L, divide by 0.40. 25-(OH)D = 25-hydroxyvitamin D.
* ≥90% of study participants had 25-(OH)D levels <20 ng/mL.
† Population institutionalized.
‡ ≥90% of study participants had 25-(OH)D levels ≤30 ng/mL, and ≥10% had 25-(OH)D levels ≥20 ng/mL.
§ The calculated risk ratio is different from the one reported by the study.

***Figure 4.*** Meta-analysis of effects of vitamin D treatment on the number of falls per person.




To convert ng/mL to nmol/L, divide by 0.40. 25-(OH)D = 25-hydroxyvitamin D; PY = person-year.
* ≥90% of study participants had 25-(OH)D levels <20 ng/mL.
† Population institutionalized.

used, use of calcium cosupplementation, and duration of follow-up varied among these studies. Sensitivity and stratified analyses on these factors, however, did not affect conclusions.

The included studies also used various vitamin D assays, and we cannot precisely determine how assay variability affected findings given the lack of a reference standard to estimate diagnostic accuracy. In general, differential classification due to assay variability is likely to affect persons with levels close to the threshold used to define vitamin D deficiency. In studies of vitamin D treatment, misclassification would attenuate estimates of treatment benefit because some persons who are not vitamin D–deficient would be classified and treated as such. These patients would also be subjected to unnecessary treatment and associated harms.

For this review, we required that participants in treatment studies be vitamin D–deficient. Previous USPSTF reviews on vitamin D evaluated supplementation in persons who were or were not deficient and could be at risk for a particular condition or outcome (104–106). On the basis of these reviews, the USPSTF made recommendations about vitamin D supplementation in persons whose deficiency status is unknown or are at risk for particular conditions. The USPSTF recommended vitamin D supplementation for community-dwelling adults aged 65 years or older at increased risk for falls regardless of 25-(OH)D status (60). The USPSTF recommended against low-dose supplementation with vitamin D (≤400 IU) and calcium (≤1000 mg) to reduce fracture risk in noninstitutionalized populations and concluded that data on the effects of higher doses were insufficient (62). The USPSTF also concluded that data were insufficient about the effects of vitamin D supplementation on cardiovascular disease and cancer risk (63). Previous reviews for the USPSTF found that harms were generally low (104–106). Prior systematic reviews noted that the WHI calcium-vitamin D trial found a significantly increased risk for kidney stones (64). We did not include these results because the risk for stones was not reported for women with low 25-(OH)D levels.

Our review had limitations. We excluded non–English-language articles and studies published only as abstracts, and we could not formally assess for publication bias because of the small number of studies. Some pooled analyses were based on small numbers of studies or were characterized by the presence of statistical heterogeneity. In these cases, the DerSimonian–Laird random-effects model may result in CIs that are too narrow (107). Therefore, we performed sensitivity analyses using the profile likelihood method that resulted in similar findings. We also focused on the effects of vitamin D treatment in patients similar to those who would be identified through a screening program. As such, we excluded studies that targeted populations for which vitamin D might be considered a treatment option or with particular medical conditions associated with vitamin D deficiency, even if the participants had low 25-(OH)D levels. On the basis of these criteria, we excluded trials that required participants to have osteoporosis or osteopenia (4 studies [108–111]), risk factors for falls (5 studies [112–116]), prediabetes (1 study [117]), heart failure (2 studies [118, 119]), or tuberculosis (1 study [120]). In those trials, vitamin D treatment did not reduce fracture risk in those with a history of fractures. Treatment reduced risk for falls in persons who had a history of falls (112) but not in those with a recent hip fracture (111) or at least 1 health problem or functional limitation (114).

***Table 2.*** Summary of Evidence for Screening for Vitamin D Deficiency in Asymptomatic Adults

| Key Question | Studies, *n* | Type of Studies | Overall Quality | Limitations | Consistency | Applicability | Summary of Findings |
|---|---|---|---|---|---|---|---|
| 1. Is there direct evidence that screening for vitamin D deficiency results in improved health outcomes?<br>1a. Are there differences in screening efficacy between patient subgroups? | 0 | NA | NA | NA | NA | NA | NA |
| 2. What are the harms of screening (e.g., risk for procedure, false positives, and false negatives)? | 0 | NA | NA | NA | NA | NA | NA |
| 3. Does treatment of vitamin D deficiency using vitamin D lead to improved health outcomes? | 17 | RCTs and nested case–control studies | Fair | Few studies addressed each outcome; many studies reported few events or were underpowered; and variability in baseline 25-(OH)D levels, doses of vitamin D, use of calcium cosupplementation, and length of follow-up | Moderate | Studies mostly done in older, white, U.S. or European women | Vitamin D treatment (with or without calcium) was associated with a decreased risk for death (11 studies; pooled RR, 0.83 [95% CI, 0.70–0.99]); risk reduction limited to studies of older, institutionalized persons (3 trials; pooled RR, 0.72 [CI, 0.56–0.94]).<br>Vitamin D treatment was not associated with decreased risk for falling (5 studies; pooled RR, 0.84 [CI, 0.69–1.02]) but was associated with a lower rate of falls per person (pooled rate ratio, 0.66 [CI, 0.50–0.88]).<br>Vitamin D treatment was not associated with a decreased risk for fractures (5 studies; pooled RR, 0.98 [CI, 0.82–1.16]).<br>Limited data (≤2 studies) on risk for cancer and type 2 diabetes, psychosocial and physical functioning, and disability, but generally no associations with vitamin D treatment were seen. |
| 3a. Are there differences in efficacy between patient subgroups? | 0 | NA | NA | NA | NA | NA | NA |
| 4. What are the adverse effects of treatment of vitamin D deficiency using vitamin D? | 24* | RCTs and cohort studies | Fair | Few studies prespecified harms outcomes; studies were not designed to address harms; and variability in baseline 25-(OH)D levels, doses of vitamin D, use of calcium cosupplementation, and length of follow-up | High | Only 7 studies were done in the United States, and only 3 of these reported populations having a significant percentage of nonwhite participants | Vitamin D treatment (with or without calcium) was not associated with increased adverse events. |
| 4a. Are there differences in adverse effects between patient subgroups? | 0 | NA | NA | NA | NA | NA | NA |

25-(OH)D = 25-hydroxyvitamin D; NA = not applicable; RCT = randomized, controlled trial; RR = risk ratio.
* Includes 2 poor-quality trials.

A trial of screening for vitamin D in a diverse population would be the ideal way to evaluate benefits and harms. Greater standardization in vitamin D assays is needed for this study to be most informative. In addition, given the lack of consensus about what level of 25-(OH)D (for example, <50 vs. <75 nmol/L [<20 vs. <30 ng/mL]) defines deficiency (36, 45, 121–124), future studies of treatment should stratify results according to the baseline vitamin D level. Definitions of vitamin D deficiency may need to take into account potential racial differences in total 25-(OH)D levels relative to bioavailable levels (99).

In conclusion, no study directly examined the benefits and harms of screening for vitamin D deficiency. Based on limited evidence in persons not known to have conditions associated with vitamin D deficiency, treating this deficiency with vitamin D may be associated with decreased risk for death in institutionalized elderly adults and a reduction in the average number of falls but not fractures. Future research is needed to reduce assay variability; determine appropriate thresholds for vitamin D deficiency; and clarify effects of screening, subsequent treatment, and the subpopulations most likely to benefit.

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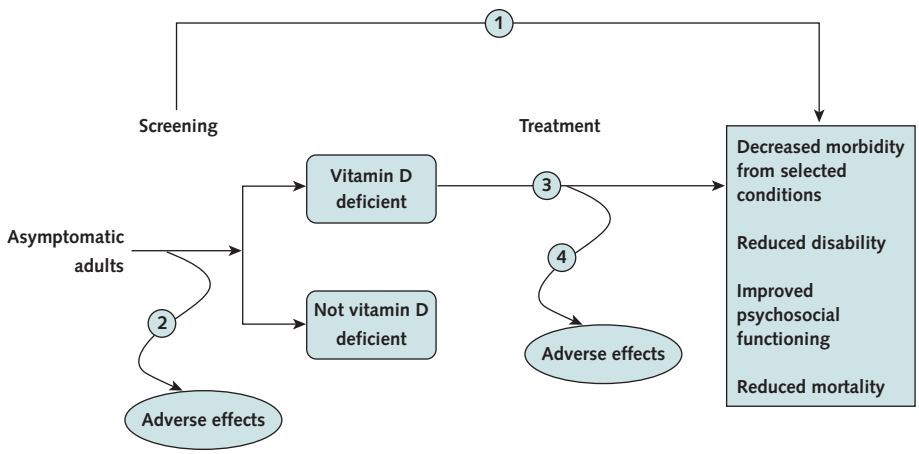
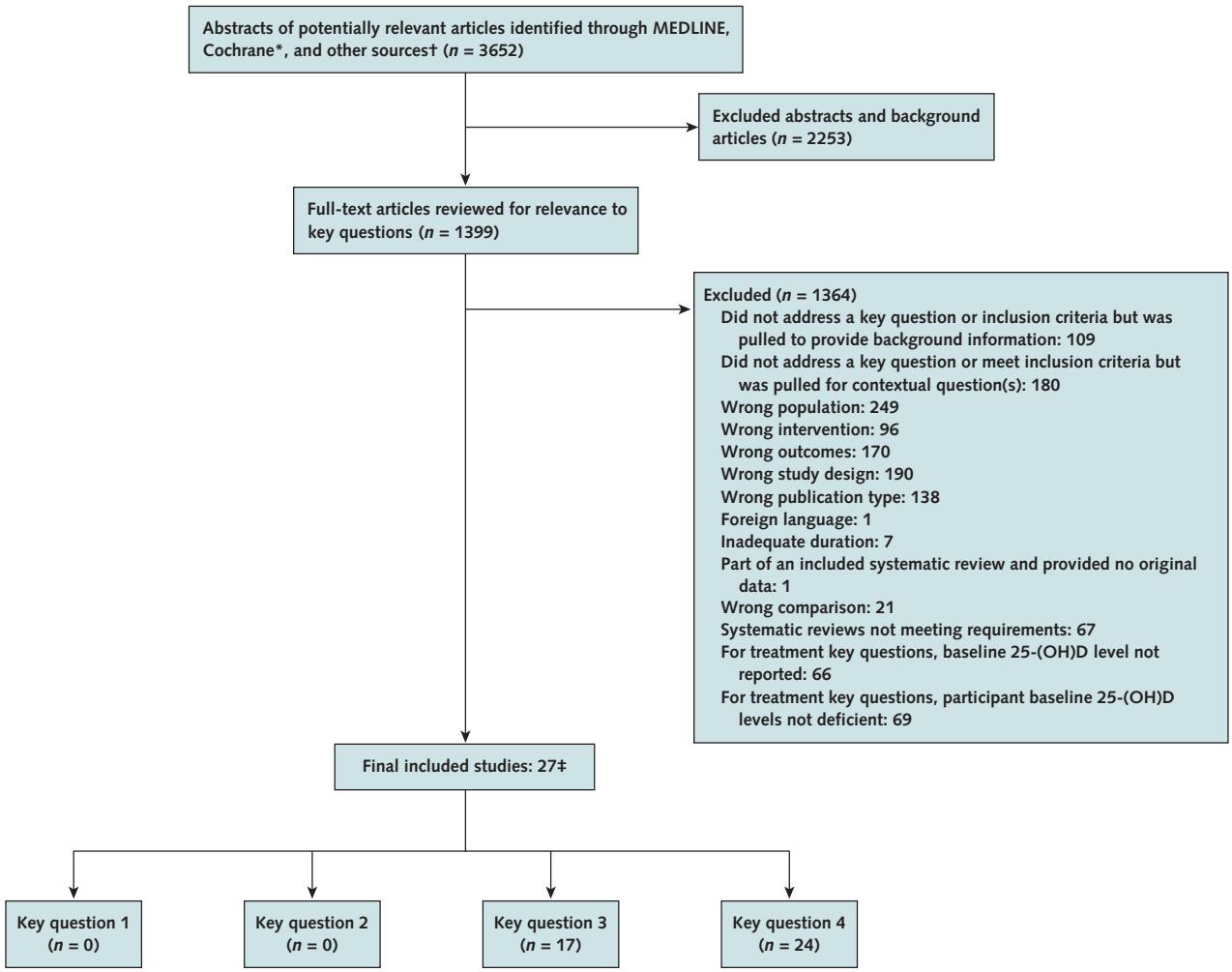
***Appendix Figure 1.*** Analytic framework.




Numbers on figures indicate key questions. For a list of key questions, see the Methods section or Table 2.

***Appendix Figure 2.*** Summary of evidence search and selection.




25-(OH)D = 25-hydroxyvitamin D.
* Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Identified from reference lists or by hand-searching or suggested by experts.
‡ Studies that provided data and contributed to the body of evidence were considered included. Studies may have provided data for more than 1 key question or published article; 27 unique studies were included, and a total of 35 articles were included.

## *Appendix Table.* Studies of Effectiveness and Harms of Vitamin D Treatment

| Study, Year (Reference) | Quality | Country | Population Characteristics* | 25-(OH)D Level at Baseline, *ng/mL**†‡ | 25-(OH)D Level at Follow-up, *ng/mL**†‡ | Intervention | Duration* | Clinical Health Outcomes Reported | AEs/Harms Reported |
|---|---|---|---|---|---|---|---|---|---|
| **25-(OH)D level <50 nmol/L§** | | | | | | | | | |
| Brazier et al, 2005 (68) | Fair | France | Analyzed: 191<br>Age: 74.6 y<br>Female: 100%<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: 0% | 7 vs. 7 | Median: 29 vs. 11 | Vitamin D group ($n$ = 95): Vitamin $D_3$, 800 IU/d, and calcium, 1000 mg/d<br>Control group ($n$ = 96): Placebo | 12 mo | Death | Total AEs; withdrawal due to AEs; serious AEs; any AE; hypercalcemia; and GI, osteomuscular, nervous system, and metabolic/nutritional AEs |
| Chapuy et al, 2002 (69) | Fair | France | Analyzed: 583<br>Age: 85 y<br>Female: 100%<br>Comorbid conditions: NR<br>History of falls: 16.1%<br>Use of walking device: 40.7%<br>Institutionalized: 100% | 9 vs. 9 | ≅33 vs. 5; $P < 0.001$ for change from baseline for vitamin D group only‖ | Vitamin D group ($n$ = 393): Vitamin $D_3$, 800 IU/d, and calcium, 1200 mg/d<br>Control group ($n$ = 190): Placebo | 24 mo | Fractures¶, persons who fell, and death | Withdrawal due to AEs (NR by group), hypercalcemia, kidney stones, hypercalciuria, and GI AEs |
| Gallagher et al, 2013 (70) | Fair | United States | Analyzed: 110<br>Age: 67 y<br>Female: 100%<br>BMI: 32.7 kg/m$^2$<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: NR | Placebo: 14<br>Vitamin D:<br>800 IU/d: 14<br>1600 IU/d: 13<br>2400 IU/d: 14<br>4800 IU/d: 14<br>400, 3600, or 4000 IU/d: NR | 97.5% of those receiving vitamin D, 800 IU/d, reached 25-(OH)D levels >20 ng/mL; $P$ <0.05 vs. placebo for all vitamin D groups‖ | Vitamin D group: Vitamin $D_3$, 400, 800, 1600, 2400, 3200, 4000, or 4800 IU/d<br>Control group: Placebo<br>All participants: Supplements to maintain total calcium intake of 1200–1400 mg/d | 12 mo | Death** | Withdrawal due to AEs**, serious AEs, and hypercalcemia |
| Gallagher et al, 2014 (71) | Fair | United States | Analyzed: 198<br>Age: 37 y<br>Female: 100%<br>BMI: 30.2 kg/m$^2$<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: NR | Placebo: 13<br>Vitamin D:<br>400 IU/d: 13<br>800 IU/d: 14<br>1600 IU/d: 13<br>2400 IU/d: 14 | 97.5% of white women receiving vitamin D, 400 IU/d, reached 25-(OH)D levels >20 ng/mL<br>97.5% of black women receiving vitamin D, 800–1600 IU/d, reached 25-(OH)D levels >20 ng/mL‖ | Vitamin D group: Vitamin $D_3$, 400, 800, 1600, or 2400 IU/d<br>Control group: Placebo<br>All participants: Supplements to maintain total calcium intake of 1000–1200 mg/d | 12 mo | Death** | Serious AEs (NR by group), hypercalcemia, and kidney stones |
| Grimnes et al, 2011 (72) | Fair | Norway | Analyzed: 104<br>Age: 52.1 y<br>Vitamin D group: 51.5 y<br>Control group: 52.7 y<br>Female: 49.1%<br>Vitamin D group: 45.0%<br>Control group: 51.0%<br>BMI: 26.5 kg/m$^2$<br>Vitamin D group: 27.2 kg/m$^2$<br>Control group: 26.3 kg/m$^2$<br>History of falls: NR<br>Institutionalized: 0% | 17 vs. 16 | 57 vs. 17 | Vitamin D group ($n$ = 51): Vitamin $D_3$, 40 000 IU/wk<br>Control group ($n$ = 53): Placebo | 6 mo | Death | Total AEs, hypercalcemia, and kidney stones |
| Janssen et al, 2010 (98) | Fair | The Netherlands | Analyzed: 59<br>Age: 80.8 y†<br>Female: 100%<br>BMI: 26.4 kg/m$^2$†<br>Comorbid conditions: 2.4†<br>Medications used: 5.0†<br>History of falls: NR<br>Institutionalized: 100%†† | 13 vs. 14 | 31 vs. 17 | Vitamin D group ($n$ = 28): Vitamin $D_3$, 400 IU/d, and calcium, 500 mg/d<br>Control group ($n$ = 31): Placebo and calcium, 500 mg/d | 6 mo | NR | Withdrawals and any AE |
| Knutsen et al, 2014 (103) | Fair | Norway | Analyzed: 215<br>Age: 37.3 y†<br>Female: 73%<br>BMI: 27.4 kg/m$^2$†<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: NR | 11 vs. 11 | 19 vs. 10 | Vitamin D group ($n$ = 144): Vitamin $D_3$, 25 or 10 mcg/d<br>Control group ($n$ = 71): Placebo | 16 wk | NR | Total AEs |
| Lips et al, 2010 (73) | Fair | The Netherlands, Germany, and United States | Analyzed for SPPB: 213<br>Analyzed for death: 226<br>Age: 78 y<br>Female: NR<br>BMI: 27.8 kg/m$^2$†<br>Comorbid conditions: NR<br>History of falls: NR<br>Use of walking device: 15%<br>Institutionalized: 14% | 14 vs. 14 | 26 vs. 12; $P < 0.001$ | Vitamin D group ($n$ = 114): Vitamin $D_3$, 8400 IU/wk<br>Control group ($n$ = 112): Placebo<br>All participants: Those with calcium intake <1000 mg/d also received calcium, 500 mg/d | 16 wk | Physical function and death | Withdrawal due to AEs, serious AEs, any AE, kidney stones, and hypercalcemia‡‡ |

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*Appendix Table*–Continued

| Study, Year (Reference) | Quality | Country | Population Characteristics* | 25-(OH)D Level at Baseline, *ng/mL**†‡ | 25-(OH)D Level at Follow-up, *ng/mL**†‡ | Intervention | Duration* | Clinical Health Outcomes Reported | AEs/Harms Reported |
|---|---|---|---|---|---|---|---|---|---|
| Pfeifer et al, 2000 (74) | Fair | Germany | Analyzed: 137<br>Age: 74.8 y†<br>Female: 100%<br>BMI: 25.5 kg/m$^2$†<br>Comorbid conditions:<br>Cardiovascular: 39%<br>CNS or neurologic: 12%<br>Psychiatric: <1%<br>Musculoskeletal: 22%<br>History of falls: NR<br>Use of walking device: NR<br>Institutionalized: 0% | 10 vs. 10 | 26 vs. 17; $P < 0.001$ | Vitamin D group ($n$ = 70): Vitamin $D_3$, 800 IU/d, and calcium, 1200 mg/d<br>Control group ($n$ = 67): Calcium, 1200 mg/d | Treatment: 8 wk<br>Follow-up: 1 y | Falls, persons who fell, and fractures | NR |
| Wamberg et al, 2013 (101, 102) | Fair | Denmark | Analyzed: 43<br>Age: 40.5 y<br>Female: 71%<br>BMI: 35.8 kg/m$^2$†<br>Sedentary: 35%†<br>Lightly active: 48%†<br>Moderately active: 17%†<br>Comorbid conditions:<br>Receiving lipid-lowering medications: 2% (1/55)<br>Receiving antihypertensive medications: 5% (3/55)<br>History of falls: NR<br>Institutionalized: NR | 14 vs. 14 | 44 vs. 19 | Vitamin D group ($n$ = 22): Vitamin $D_3$, 7000 IU/d<br>Control group ($n$ = 21): Placebo | 26 wk | NR | Total AEs and hypercalcemia |
| **25-(OH)D level ≤75 nmol/L§§** | | | | | | | | | |
| Aloia et al, 2008 (92) | Fair | United States | Analyzed: 138<br>Age: 47.2 y†<br>Female: 81%<br>History of falls: NR<br>Institutionalized: NR | 19 overall | >30 ng/mL achieved by virtually all in the active group; also increased by 8 ng/mL in the placebo group because of seasonal change | Vitamin D group ($n$ = 65): Vitamin $D_3$ dose was dependent on 25-(OH)D levels; mean dosage, 3440 IU/d<br>Control group ($n$ = 73): Placebo | 6 mo | NR | Hypercalcemia and hypercalciuria |
| Arvold et al, 2009 (75) | Fair | United States | Analyzed: 90<br>Age: 58.8 y†<br>Female: 40%<br>BMI: NR<br>Comorbid conditions: NR<br>History of falls: NR<br>Use of walking device: NR<br>Institutionalized: 0% | 18 vs. 18 | 45 vs. 22 | Vitamin D group ($n$ = 48): Vitamin $D_3$, 50 000 IU/wk<br>Control group ($n$ = 42): Placebo | 8 wk | Psychosocial function and disability | Any AE |
| Berlin et al, 1986 (96) | Poor | Sweden | Analyzed: 24<br>Age: 31 y (range, 22–47 y)<br>Female: 0%<br>History of falls: NR<br>Institutionalized: NR | 15 vs. 15 | 49 vs. 19 | Vitamin D group ($n$ = 12): Vitamin $D_3$, 54 000 IU/wk<br>Control group ($n$ = 12): No treatment | NR‖‖ | NR | Any AE |
| Bischoff et al, 2003 (76) | Fair | Switzerland | Analyzed: 122<br>Age: 85 y<br>Female: 100%<br>BMI: 24.7 kg/m$^2$<br>Comorbid conditions:<br>Hypertension: 30.3%<br>Stroke: 15.6%<br>MI or CHF: 50.0%<br>Anemia: 12.3%<br>Diabetes: 14.8%<br>COPD: 8.2%<br>Peptic ulcer disease: 16.4%<br>Depression: 24.6%<br>Malnutrition: 9.0%<br>Obesity: 4.1%<br>Dementia: 54.9%<br>Fracture at any site: 54.1%<br>History of falls: 34%<br>Use of walking device: 60%<br>Institutionalized: 100% | Median: 12 vs. 12 | Median: 26 vs. 11; $P < 0.001$ | Vitamin D group ($n$ = 62): Vitamin $D_3$, 800 IU/d, and calcium, 1200 mg/d<br>Control group ($n$ = 60): Calcium, 1200 mg/d | Pretreatment: 6 wk<br>Treatment: 12 wk | Falls¶ | Hypercalcemia, withdrawals, and GI AEs |

*Continued on following page*

*Appendix Table*–Continued

| Study, Year (Reference) | Quality | Country | Population Characteristics* | 25-(OH)D Level at Baseline, *ng/mL**†‡ | 25-(OH)D Level at Follow-up, *ng/mL**†‡ | Intervention | Duration* | Clinical Health Outcomes Reported | AEs/Harms Reported |
|---|---|---|---|---|---|---|---|---|---|
| Gallagher et al, 2012 (82) | Good | United States | Analyzed: 163<br>Age: 67 y<br>Female: 100%<br>BMI: 30.2 kg/m$^2$<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: NR | Placebo: 15<br>Vitamin D:<br>400 IU/d: 15<br>800 IU/d: 16<br>1600 IU/d: 15<br>2400 IU/d: 15<br>3200 IU/d: 16<br>4000 IU/d: 15<br>4800 IU/d: 16 | 97.5% of those receiving vitamin D, 600 IU/d, reached 25-(OH)D levels >20 ng/mL; $P < 0.05$ vs. placebo for all vitamin D groups‖ | Vitamin D group ($n$ = 142): Vitamin $D_3$, 400, 800, 1600, 2400, 3200, 4000, or 4800 IU/d<br>Control group ($n$ = 21): Placebo<br>All participants: Supplements to maintain total calcium intake of 1200–1400 mg/d | Median: 12 mo | Death | Withdrawal due to AEs, any AE, serious AEs, kidney stones, and hypercalcemia |
| Harris et al, 1999 (94) | Poor | United States | Analyzed: 18<br>Age: 31 y (range, 22–47 y)<br>Female: 0%<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: NR | Younger men: 13 vs. 17<br>Older men: 16 vs. 16 | Younger men: 25 vs. 13<br>Older men: 19 vs. 15 | Vitamin D group ($n$ = 11): Vitamin $D_2$, 1800 IU/d<br>Control group ($n$ = 7): No treatment | 3 wk | NR | Any AE |
| Honkanen et al, 1990 (97) | Fair | Finland | Analyzed: 126<br>Home patients:<br>Age: 69.5 y†<br>Female: 100%<br>Weight: 69.5 kg†<br>Comorbid conditions: NR<br>History of falls: NR<br>Hospital inpatients (52%):<br>Age: 82.5 y†<br>Female: 100%<br>Weight: 61.8 kg†<br>Comorbid conditions: NR<br>History of falls: NR | Home patients: 17 vs. 15<br>Hospital inpatients: 10 vs. 10 | Home patients: 32 vs. 9<br>Hospital inpatients: 26 vs. 4 | Vitamin D group ($n$ = 63): Vitamin $D_3$, 1800 IU/d, and calcium, 1.558 g/d<br>Control ($n$ = 63): No treatment | 11 wk | NR | Hypercalcemia and kidney stones |
| Kärkkäinen et al, 2010 (77, 78) | Fair | Finland | Analyzed: 593<br>Age: 67.4 y†<br>Female: 100%<br>BMI: 27.5 kg/m$^2$†<br>Comorbid conditions: NR<br>History of falls: NR<br>Ambulatory: 100%<br>Institutionalized: NR | 20 vs. 20 | 30 vs. 22 | Vitamin D group ($n$ = 290 for death outcomes and 287 for fall/persons who fell outcomes): Vitamin $D_3$, 800 IU/d, and calcium, 1000 mg/d<br>Control group ($n$ = 313 for death outcomes and 306 for fall/persons who fell outcomes): No treatment | 3 y | Falls¶, persons who fell, and death | Withdrawal due to AEs |
| Kjærgaard et al, 2012 (79) | Good | Norway | Analyzed: 230¶¶<br>Age: 53.4 y†<br>Female: 56%<br>BMI: 27.7 kg/m$^2$†<br>Comorbid conditions: NR<br>History of falls: NR<br>Institutionalized: NR | 19 vs. 19 | 59 vs. 21 | Vitamin D group ($n$ = 120): Vitamin $D_3$, 20 000 IU/wk<br>Control group ($n$ = 110): Placebo | 6 mo | Psychosocial function¶ | Hypercalcemia; total AEs; and GI, respiratory, dermatologic, musculoskeletal, urogenital, circulatory, neurologic, endocrine, and other organ AEs |
| Krieg et al, 1999 (80) | Fair | Switzerland | Analyzed: 248<br>Age: 84.5 y†<br>Female: 100%<br>BMI: 24.7 kg/m$^2$†<br>History of falls: NR<br>Institutionalized: 100% | 12 vs. 12 | 27 vs. 6 | Vitamin D group ($n$ = 124): Vitamin $D_3$, 880 IU/d, and calcium, 1000 mg/d<br>Control group ($n$ = 124): No supplementation | 2 y | Death | Withdrawal due to AEs |
| Lips et al, 1996 (81), and Ooms et al, 1995 (83) | Fair | The Netherlands | Analyzed for fracture: 270<br>Analyzed for death: 348<br>Age: 80.4 y†<br>Female: 100%<br>BMI: 28.3 kg/m$^2$†<br>Comorbid conditions: NR<br>History of falls: NR<br>Use of walking device: NR<br>Institutionalized: 100%†† | Median: 11 vs. 10 | Median: 25 vs. 9 (at 1 y) | Vitamin D group ($n$ = 177): Vitamin $D_3$, 400 IU/d<br>Control group ($n$ = 171): Placebo | 3.0–3.5 y; maximum 4 y | Fractures¶ and death | Any AE and hypercalcemia |

*Continued on following page*

*Appendix Table*–Continued

| Study, Year (Reference) | Quality | Country | Population Characteristics* | 25-(OH)D Level at Baseline, *ng/mL**†‡ | 25-(OH)D Level at Follow-up, *ng/mL**†‡ | Intervention | Duration* | Clinical Health Outcomes Reported | AEs/Harms Reported |
|---|---|---|---|---|---|---|---|---|---|
| Lehmann et al, 2013 (99) | Fair | Norway | Analyzed: 107<br>Age: 33.8 y†<br>Female: 63.5%<br>BMI: 23.8 kg/m$^2$†<br>History of falls: NR<br>Institutionalized: NR | Overall: 16<br>Vitamin $D_2$ vs. vitamin $D_3$ vs. control: 15 vs. 18 vs. 16 | Vitamin $D_2$ vs. vitamin $D_3$ vs. control: 27 vs. 36 vs. 13 | Vitamin D group ($n$ = 42, 46: Vitamin $D_2$ or $D_3$, 2000 IU/d<br>Control group ($n$ = 19): Placebo | 8 wk | NR | Any AE and hypercalcemia |
| Martineau et al, 2007 (100) | Fair | United Kingdom | Analyzed: 192***<br>Median age: 33.7 y†<br>Female: 51.2%†<br>History of falls: NR<br>Institutionalized: NR | 14 vs. NR | 27 vs. NR | Vitamin D group ($n$ = 96): Single dose of vitamin $D_2$, 100 000 IU<br>Control group ($n$ = 96): Placebo | 6 wk | NR | Any AE and hypercalcemia |
| Pfeifer et al, 2009 (84) | Fair | Austria and Germany | Analyzed: 242<br>Age: 76.5 y<br>Female: 74.5%<br>BMI: 27.3 kg/m$^2$<br>Comorbid conditions: NR<br>History of falls: NR<br>Ambulatory: 100%<br>Institutionalized: 0% | 22 vs. 22 | Month 12: 34 vs. 23<br>Month 20: 19 vs. 15 | Vitamin D group ($n$ = 122): Vitamin $D_3$, 800 IU/d, and calcium, 1000 mg/d<br>Control group ($n$ = 120): Calcium, 1000 mg/d | Treatment: 12 mo<br>Posttreatment: 8 mo | Falls¶, persons who fell, and fractures | NR |
| Talwar et al, 2007 (95), and Aloia et al, 2005 (93) | Fair | United States | Analyzed: 208<br>Age: 60.5 y†<br>Female: 100%<br>BMI:<br>Vitamin D group: 29 kg/m$^2$<br>Control group: 30 kg/m$^2$<br>History of falls: NR<br>Institutionalized: NR | 19 vs. 17 | 35 vs. 18 | Vitamin D group ($n$ = 104): Vitamin $D_3$, 800 IU/d, for first 24 mo increased to 2000 IU/d<br>Control group ($n$ = 104): Placebo<br>All participants: Supplements to maintain total calcium intake of 1200–1500 mg/d | 36 mo | NR | Total AEs (NR by group), serious AEs, hypercalcemia, hypercalciuria, and kidney stones |
| Wood et al, 2012 (85) | Fair | United Kingdom | Analyzed: 305<br>Age: 63.8 y†<br>Female: 100%<br>BMI: 26.7 kg/m$^2$†<br>History of falls: NR<br>Institutionalized: NR | Vitamin D, 400 IU/d, vs. vitamin D, 1000 IU/d, vs. control: 13 vs. 13 vs. 14 | Vitamin D, 400 IU/d, vs. vitamin D, 1000 IU/d, vs. control: 26 vs. 30 vs. 13 | Vitamin D group ($n$ = 102): Vitamin $D_3$, 400 IU/d<br>Vitamin D group ($n$ = 101): Vitamin $D_3$, 1000 IU/d<br>Control group ($n$ = 102): Placebo | Treatment: 12 mo<br>Follow-up: 1 mo | Falls and type 2 diabetes | Hypercalcemia, total AEs, serious AEs, and GI and osteomuscular AEs |

*Continued on following page*

*Appendix Table*–Continued

| Study, Year (Reference) | Quality | Country | Population Characteristics* | 25-(OH)D Level at Baseline, *ng/mL**†‡ | 25-(OH)D Level at Follow-up, *ng/mL**†‡ | Intervention | Duration* | Clinical Health Outcomes Reported | AEs/Harms Reported |
|---|---|---|---|---|---|---|---|---|---|
| Entire WHI calcium-vitamin D trial: Jackson et al, 2003 (64)<br>Associated case–control studies with outcome reported:<br>Fracture: Jackson et al, 2006 (88)<br>CRC: Wactawski-Wende et al, 2006 (90)<br>Breast cancer: Chlebowski et al, 2008 (86)<br>Diabetes: de Boer et al, 2008 (87)<br>Death: LaCroix et al, 2009 (89) | Fair | United States | Entire WHI calcium-vitamin D trial<br>Analyzed: 36 282<br>Age: 62 y<br>Female: 100%<br>BMI: 29 kg/m$^2$<br>Race:<br>White: 83.1%<br>Black: 9.1%<br>Hispanic: 4.2%<br>American Indian or Native American: 0.42%<br>Asian or Pacific Islander: 2.0%<br>Unknown or not identified: 1.2%<br>Comorbid conditions in past 12 mo:<br>Previous fracture: 35%<br>No falls: 67%<br>1 fall: 20%<br>2 falls: 9.0%<br>>3 falls 4.0%<br>Case–control studies:<br>Comorbid conditions:<br>Fracture: 1491 case patients/control participants<br>CRC: 612 case patients/control participants<br>Breast cancer: 895 case patients/control participants<br>Diabetes: 192 case patients/2905 control participants<br>Death: 323 case patients/1962 control participants<br>Case patient and control participant characteristics: NR | Entire WHI calcium-vitamin D trial: NR<br>Case-control studies:<br>Fracture: <24<br>CRC: <23<br>Breast cancer: <27<br>Diabetes: <24<br>Death: <21 | Entire WHI calcium-vitamin D trial: After 2 y, in a random sample of 1.2% of participants, 25-(OH)D levels were 28% higher (9 ng/mL) in the vitamin D vs. placebo group<br>Case-control studies: NR | Vitamin D group: Vitamin $D_3$, 400 IU/d, plus calcium, 1000 mg/d<br>Control group: Placebo††† | 7 y | Fractures, death, type 2 diabetes, and cancer | NR |

25-(OH)D = 25-hydroxyvitamin D; AE = adverse event; BMI = body mass index; CHF = congestive heart failure; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CRC = colorectal cancer; GI = gastrointestinal; MI = myocardial infarction; NR = not reported; SPPB = Short Physical Performance Battery; WHI = Women's Health Initiative.

* Data are means unless otherwise indicated.

† Calculated.

‡ Vitamin D vs. control group unless otherwise indicated. To convert ng/mL to nmol/L, divide by 0.40.

§ ≥90% of participants had 25-(OH)D levels <50 nmol/L.

|| Data estimated from a figure found in the study.

¶ Primary outcome.

** Gallagher JC. Personal communication.

†† Received care but not as much as in a nursing home setting.

‡‡ Data not shown.

§§ ≥90% of study participants had 25-(OH)D levels ≤75 nmol/L, with ≥10% with levels ≥50 nmol/L.

|||| Implies 2 mo.

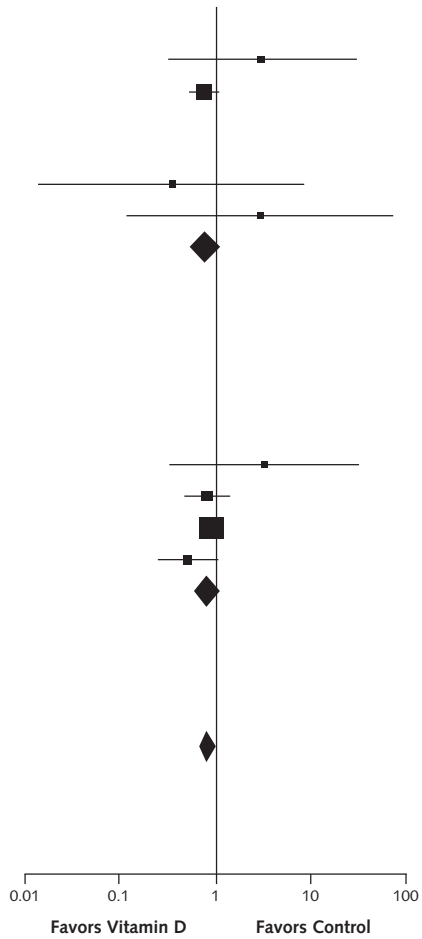
¶¶ Per protocol.

*** Population characteristics reported only for those who finished study ($n$ = 131).

††† Number analyzed in case–control studies per intervention (vitamin D vs. control): fractures: 266 vs. 285, CRC: 237 vs. 222, breast cancer: 909 vs. 722, diabetes: 1118 vs. 1187, and death: 675 vs. 678.

***Appendix Figure 3.*** Meta-analysis of effects of vitamin D treatment on mortality.

| Study, Year (Reference) | Events/Total, *n/N* | | Weight, % | Risk Ratio (95% CI) |
|---|---|---|---|---|
| | Vitamin D | Control | | |
| **25-(OH)D <20 ng/mL*** | | | | |
| Brazier et al, 2005 (68) | 3/95 | 1/96 | 0.6 | 3.03 (0.32–28.63) |
| Chapuy et al, 2002 (69)* | 70/393 | 45/190 | 27.9 | 0.75 (0.54–1.05) |
| Gallagher et al, 2013 (70) | 0/93 | 0/17 | | Not estimable |
| Gallagher et al, 2014 (71) | 0/160 | 0/38 | | Not estimable |
| Grimnes et al, 2011 (72) | 0/51 | 1/52 | 0.3 | 0.34 (0.01–8.15) |
| Lips et al, 2010 (73) | 1/114 | 0/112 | 0.3 | 2.95 (0.12–71.60) |
| Subtotal (95% CI) | 906 | 505 | 29.2 | 0.78 (0.56–1.08) |
| Total events | 74 | 47 | | |
| Heterogeneity: tau-square = 0.00; chi-square = 2.40 ($P$ = 0.49); $I^2$ = 0% | | | | |
| Test for overall effect: $Z$ = 0.51 ($P$ = 0.13) | | | | |
| **25-(OH)D ≤30 ng/mL†** | | | | |
| Gallagher et al, 2012 (82) | 0/142 | 0/21 | | Not estimable |
| Kärkkäinen et al, 2010 (78) | 3/290 | 1/313 | 0.6 | 3.24 (0.34–30.95) |
| Krieg et al, 1999 (80)‡ | 21/124 | 26/124 | 11.5 | 0.81 (0.48–1.36) |
| LaCroix et al, 2009 (89)§ | 104/675 | 116/678 | 52.5 | 0.90 (0.71–1.15) |
| Ooms et al, 1995 (83)‡ | 11/177 | 21/171 | 6.3 | 0.51 (0.25–1.02) |
| Subtotal (95% CI) | 1408 | 1307 | 70.8 | 0.82 (0.62–1.10) |
| Total events | 139 | 164 | | |
| Heterogeneity: tau-square = 0.02; chi-square = 3.72 ($P$ = 0.29); $I^2$ = 19% | | | | |
| Test for overall effect: $Z$ = 1.33 ($P$ = 0.18) | | | | |
| Total (95% CI) | 2314 | 1812 | 100.0 | 0.83 (0.70–0.99) |
| Total events | 213 | 211 | | |
| Heterogeneity: tau-square = 0.00; chi-square = 6.30 ($P$ = 0.51); $I^2$ = 0% | | | | |
| Test for overall effect: $Z$ = 2.10 ($P$ = 0.04) | | | | |
| Test for subgroup differences: chi-square = 0.07 ($P$ = 0.80); $I^2$ = 0% | | | | |




To convert ng/mL to nmol/L, divide by 0.40. 25-(OH)D = serum 25-hydroxyvitamin D.
* ≥90% of study participants had 25-(OH)D levels <20 ng/mL.
† ≥90% of study participants had 25-(OH)D levels ≤30 ng/mL, and ≥10% had 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-vitamin D trial (64).