Fracture Prevention With Vitamin D Supplementation
A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari, MD, MPH
Walter C. Willett, DrPH
John B. Wong, MD
Edward Giovannucci, ScD
Thomas Dietrich, MPH
Bess Dawson-Hughes, MD

Context The role and dose of oral vitamin D supplementation in nonvertebral fracture prevention have not been well established.

Objective To estimate the effectiveness of vitamin D supplementation in preventing hip and nonvertebral fractures in older persons.


Study Selection Only double-blind RCTs of oral vitamin D supplementation (cholecalciferol, ergocalciferol) with or without calcium supplementation vs calcium supplementation or placebo in older persons (≥60 years) that examined hip or nonvertebral fractures were included.

Data Extraction Independent extraction of articles by 2 authors using predefined data fields, including study quality indicators.

Data Synthesis All pooled analyses were based on random-effects models. Five RCTs for hip fracture (n=9294) and 7 RCTs for nonvertebral fracture risk (n=9820) met our inclusion criteria. All trials used cholecalciferol. Heterogeneity among studies for both hip and nonvertebral fracture prevention was observed, which disappeared after pooling RCTs with low-dose (400 IU/d) and higher-dose vitamin D (700-800 IU/d), separately. A vitamin D dose of 700 to 800 IU/d reduced the relative risk (RR) of hip fracture by 26% (3 RCTs with 5572 persons; pooled RR, 0.74; 95% confidence interval [CI], 0.61-0.88) and any nonvertebral fracture by 23% (5 RCTs with 6098 persons; pooled RR, 0.77; 95% CI, 0.68-0.87) vs calcium or placebo. No significant benefit was observed for RCTs with 400 IU/d vitamin D (2 RCTs with 3722 persons; pooled RR for hip fracture, 1.15; 95% CI, 0.88-1.50; and pooled RR for any nonvertebral fracture, 1.03; 95% CI, 0.86-1.24).

Conclusions Oral vitamin D supplementation between 700 to 800 IU/d appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons. An oral vitamin D dose of 400 IU/d is not sufficient for fracture prevention.

IAMA. 2005;293:2257-2264

Author Affiliations: Department of Nutrition, Harvard School of Public Health (Drs Bischoff-Ferrari, Willett, and Giovannucci); Division of Rheumatology, Immunology, and Allergy, The Robert B. Brigham Arthritis and Musculoskeletal Diseases Clinical Research Center, and Division of Aging, Brigham and Women’s Hospital (Dr Bischoff-Ferrari); Department of Epidemiology and Channing Laboratory, Brigham and Women’s Hospital (Drs Willett and Giovannucci); Department of Medicine, Tufts-New England Medical Center (Dr Wong); Department of Health Policy and Health Services Research, Boston University Goldman School of Dental Medicine (Mr Dietrich); and Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University (Dr Dawson-Hughes), Boston, Mass.

Corresponding Author: Heike A. Bischoff-Ferrari, MD, MPH, Department of Nutrition, Harvard School of Public Health, 651 Huntington Ave, Boston, MA 02115 (hbischof@hsph.harvard.edu).
We conducted a systematic review of all English and non-English articles using MEDLINE (Ovid, PubMed) and the Cochrane Controlled Trials Register from January 1960 to January 2005, and EMBASE from January 1991 to January 2005. Additional studies were identified by contacting experts and searching reference lists and abstracts presented at the American Society for Bone and Mineral Research from 1995 to 2004.

The efficacy of oral vitamin D supplementation in preventing hip and any nonvertebral fractures among older persons by performing a systematic review of the literature with a meta-analysis of RCTs.

METHODS
Search Strategy and Data Extraction
We conducted a systematic review of all English and non-English articles using MEDLINE (Ovid, PubMed) and the Cochrane Controlled Trials Register from January 1960 to January 2005, and EMBASE from January 1991 to January 2005. Additional studies were identified by contacting experts and searching reference lists and abstracts presented at the American Society for Bone and Mineral Research from 1995 to 2004.

We excluded RCTs that used active vitamin D metabolites, such as 1,25-dihydroxyvitamin D or 1-α-hydroxyvitamin D, because they require monitoring for hypercalcemia and have much higher costs, thereby limiting their public health applicability. We also excluded trials with intramuscular injections of vitamin D because it is not available over the counter, is invasive, and has resulted in small and variable increases in 25-hydroxyvitamin D levels.8

Definitions
Our primary outcome measure was the relative risk (RR) of a first hip fracture or any nonvertebral fracture in participants receiving vitamin D supplementation with or without calcium supplementation compared with those participants receiving placebo or calcium supplementation alone.

Quality Assessment
We assessed the following methodological features most relevant to the control of bias: randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals.9,10

Studies Identified for Primary Analysis
All studies were identified through our MeSH term search (Table 1).11-21 Five RCTs12,13,16-18 for hip fracture prevention and 7 RCTs12-18 for nonvertebral fracture prevention met our inclusion criteria. All trials had hip or nonvertebral fractures as the primary or secondary outcome.

Studies Identified for Sensitivity Analysis
In a sensitivity analysis, we examined the effect size when including studies meeting less stringent quality criteria for inclusion. Of 3 studies that were identified for the sensitivity analysis, 1 was retrieved through our MeSH term search19 and 2 unpublished studies were identified by searching through abstract books of the American Society of Bone and Mineral Research plus contacting experts in the field.20,21 (Table 1). Preliminary fracture...
Table 1. Characteristics of Primary Analysis of Both Included and Excluded Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Participants</th>
<th>Treatment/d</th>
<th>Dwelling</th>
<th>Age, Mean (SD), y</th>
<th>Duration, mo</th>
<th>Baseline and Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment Group</td>
</tr>
<tr>
<td>Chapuy et al, 1992 (Decalyos I)</td>
<td>3270 Women</td>
<td>800-IU cholecalciferol + 1200-mg calcium (tri-calcium phosphate powder) vs placebo</td>
<td>Ambulatory, living in nursing homes or apartments for elderly persons</td>
<td>84 (6)</td>
<td>18</td>
<td>40 (27.5) to 106 (22.5) at 18-mo follow-up</td>
</tr>
<tr>
<td>Chapuy et al, 1994 (Decalyos II)</td>
<td>601 Persons</td>
<td>800-IU cholecalciferol + 1200-mg calcium (tri-calcium phosphate powder) vs placebo</td>
<td>Ambulatory, living in nursing homes or apartments for elderly persons</td>
<td>84 (6)</td>
<td>36</td>
<td>40 (27.5) to 106 (22.5) at 18-mo follow-up</td>
</tr>
<tr>
<td>Lips et al, 1996</td>
<td>2578 Persons</td>
<td>400-IU cholecalciferol vs placebo; participants asked to consume 3 dairy products daily to reach a calcium intake of ≥800 mg/d</td>
<td>Independent, in apartments or homes for elderly persons</td>
<td>80 (8)</td>
<td>36-41</td>
<td>27 (IQR, 19-36) to 62 (IQR, 52-70) at 12-mo follow-up</td>
</tr>
<tr>
<td>Dawson-Hughes et al, 1997*</td>
<td>389 Persons</td>
<td>700-IU cholecalciferol + 500-mg calcium (calcium citrate malate) vs placebo; mean calcium intake at baseline was about 720 mg/d</td>
<td>Community-dwelling</td>
<td>71 (5)</td>
<td>36</td>
<td>76.5 (37.0) to 112 (36.8) at 36-mo follow-up</td>
</tr>
<tr>
<td>Pfeifer et al, 2000†</td>
<td>137 Women</td>
<td>800-IU cholecalciferol + 1200-mg calcium vs 1200-mg calcium</td>
<td>Community-dwelling</td>
<td>74 (1)</td>
<td>2 (with treatment plus 10 (with follow-up)</td>
<td>25.7 (13.6) to 66.1 (33.1) at 2-mo follow-up</td>
</tr>
<tr>
<td>Meyer et al, 2002</td>
<td>1144 Persons (75% women)</td>
<td>400-IU cholecalciferol in 5-mL cod liver oil vs 5-mL cod liver oil alone; mean calcium intake from milk and cheese reported to be about 450 mg/d</td>
<td>Frail nursing home residents with life expectancy of &gt;6 mo and not permanently bedridden</td>
<td>85 (7)</td>
<td>24</td>
<td>47 (28) to 64 (21) at 12-mo follow-up</td>
</tr>
<tr>
<td>Chapuy et al, 2002 (Decalyos II)</td>
<td>583 Women</td>
<td>800-IU cholecalciferol + 1200-mg calcium (tri-calcium phosphate) as fixed or separate combination vs placebo</td>
<td>Ambulatory, living in apartment houses for elderly persons</td>
<td>85 (7)</td>
<td>24</td>
<td>21.3 (13.3) to 77.5 (33.1) at 24-mo follow-up</td>
</tr>
<tr>
<td>Trivedi et al, 2003</td>
<td>2886 Persons (849 women, 2037 men)</td>
<td>100 000 IU every 4 mo (≈800 IU/d) vs placebo; mean calcium intake at 4 y was 742 mg/d as assessed by food frequency questionnaire</td>
<td>Community-dwelling</td>
<td>75 (5)</td>
<td>60</td>
<td>74.3 (20.7) at a 48-mo follow-up (no baseline)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Participants</th>
<th>Treatment/d</th>
<th>Dwelling</th>
<th>Age, Mean (SD), y</th>
<th>Duration, mo</th>
<th>Baseline and Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trials Excluded From Primary Analysis</td>
</tr>
<tr>
<td>Lassen et al, 2004†</td>
<td>7073 Persons (4256 women, 2817 men)</td>
<td>Patients offered 400-IU/d cholecalciferol + 1000-mg/d calcium vs no intervention</td>
<td>Community-dwelling</td>
<td>66-103</td>
<td>42</td>
<td>37 (19) to 47 (20) at 24-mo follow-up</td>
</tr>
<tr>
<td>Pfeifer et al, 2004†</td>
<td>242 Persons (74% women)</td>
<td>800-IU/d cholecalciferol + 1000-mg/d calcium vs 1000-mg/d calcium</td>
<td>Community-dwelling</td>
<td>77</td>
<td>20 (12 with treatment)</td>
<td>ND</td>
</tr>
<tr>
<td>Flicker et al, 2004†</td>
<td>601 Persons (53% women)</td>
<td>Ergocalciferol (initially 10,000 IU/wk, then 1000 IU/d) vs placebo + 600-mg calcium for all</td>
<td>Nursing homes and assisted-living facilities</td>
<td>“Elderly”</td>
<td>24</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; ND, not determined.
Conversion factor: To convert 25-hydroxyvitamin D to ng/mL, divide values by 2.496.
*This study only included patients with 25-hydroxyvitamin D levels of less than 50 nmol/L. All other trials did not select participants based on baseline 25-hydroxyvitamin D levels.
†None of the studies provided separate data for hip fractures.
data from 1 trial was provided by the principal investigator. None of the trials provided separate results for hip fractures, 2 trials included any osteoporotic fracture, and 1 trial provided results for any nonvertebral fracture.

**Statistical Analyses**

Outcomes were analyzed on an intention-to-treat basis with random-effects models, as these models provide a more conservative estimate than the fixed-effect model by incorporating both within- and between-study variation. In addition, we calculated the risk difference for preventing a fracture to determine the number needed-to-treat (NNT) to prevent 1 fracture.

Heterogeneity among studies was evaluated by the Cochran Q test (considered significant for P<.10). We explored heterogeneity by vitamin D dose by pooling low-dose (≤400 IU/d) and higher-dose RCTs (>400 IU/d) separately. Heterogeneity by vitamin D dose was also explored visually by plotting the achieved 25-hydroxyvitamin D levels in the treatment group of each trial against the effect size of each trial. In addition, a random-effects meta-regression analysis was performed to test whether higher achieved 25-hydroxyvitamin D level in the treatment group is a significant predictor of antifracture efficacy. This approach was chosen because the association between vitamin D dose and change in 25-hydroxyvitamin D is not linear, and both the starting 25-hydroxyvitamin D level and the vitamin D dose determine the achieved 25-hydroxyvitamin D level in the treatment group. In the presence of homogeneity, both fixed and random-effects models yielded the same results. As with all meta-analyses, our review has the potential for publication bias. Despite no evidence for publication bias in the Begg and Egger test, the funnel plot suggested a possible absence of negative studies involving small sample sizes. However, the trim and fill analysis did not confirm this suggestion. Statistical analyses were performed with STATA version 7.0 (STATA Corp, College Station, Tex).

**RESULTS**

**Primary Analyses**

Table 1 shows characteristics of the 7 RCTs that were included in the primary analysis for hip fracture or any nonvertebral fracture. These trials included 9820 individuals with an approximate mean age of 79 years, and 68% were women. All participants were in stable health states: living in the community, in apartments or housing for elderly persons, or in nursing homes. The vitamin D dose used in 2 RCTs was 400 IU/d, while the other 5 RCTs used 700 to 800 IU/d. Between 500 mg/d and 1200 mg/d of calcium supplementation was used in combination with vitamin D supplementation in 4 RCTs. Of the 3 additional trials, 1 recommended an intake of 3 dairy products per day in all participants to achieve a calcium intake of at least 800 mg/d and in the 2 remaining trials, mean calcium intake was between 450 and 742 mg/d. Only 1 trial provided calcium supplementation in the control group. Treatment duration varied between 12 and 60 months.

Two trials reported the method of randomization. 2 trials stated that treatment allocation was concealed from participants and investigators, but 1 trial specifically reported performing an intention-to-treat analysis, and all studies specifically stated masking of treatment allocation. The causes for dropout were balanced between treatment and control groups in all trials and ranged from 7% in community-dwelling participants to 67% in frail institutionalized elderly persons.

**Hip Fracture**

The pooled RR for any vitamin D dose preventing hip fractures was 0.88 (95% confidence interval [CI], 0.69-1.13) (TABLE 2). However, variation between studies was more than expected indicating heterogeneity (Q test P=.09). Once vitamin D trials with a higher and a lower dose were pooled separately, there was homogeneity (Q test P=.74 for high-dose trials and P=.68 for low-dose trials). For 3 trials, including 5572 individuals with 700 to 800 IU/d vitamin D in the treatment...
groups, the pooled RR was 0.74 (95% CI, 0.61-0.88), suggesting that 700 to 800 IU/d vitamin D reduces hip fracture risk by 26% (FIGURE 2). The pooled risk difference was 2% (95% CI, 1%-4%; \( P < .001 \)), so the NNT was 45 (95% CI, 28-114) for a treatment duration of 24 to 60 months. For 2 trials, \(^{13,16} \) which included 3722 individuals and a vitamin D dose of 400 IU/d, the pooled RR was 1.15 (95% CI, 0.88-1.50), suggesting that 400 IU/d vitamin D supplementation does not reduce hip fracture risk.

We also examined the achieved level of serum 25-hydroxyvitamin D in relation to reduction in hip fracture risk (FIGURE 3). A greater reduction in hip fractures was observed with higher achieved 25-hydroxyvitamin D levels in the treatment group (meta-regression \( P = .02 \)).

When we included the 2 trials each with only 1 hip fracture report in a sensitivity analysis, the corresponding pooled results were as follows for 7 trials with 9820 individuals and hip fracture by vitamin D supplementation between 400 to 800 IU/d (RR, 0.87; 95% CI, 0.70-0.98), hip fracture by vitamin D supplementation between 700 to 800 IU/d (RR, 0.73; 95% CI, 0.61-0.88), and hip fracture by vitamin D supplementation of 400 IU/d (RR, 1.15; 95% CI, 0.88-1.50).

### Any Nonvertebral Fracture

The pooled RR for any vitamin D dose preventing nonvertebral fractures was 0.83 (95% CI, 0.70-0.98). However, variation between studies was more than expected indicating heterogeneity (Q test \( P = .07 \)).

After stratifying trials by vitamin D dose, there was homogeneity (Q test \( P = .41 \) for high-dose trials and \( P = .36 \) for low-dose trials). For 5 trials, \(^{12,14,15,17,18} \) which included 6098 individuals and a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.77 (95% CI, 0.68-0.87), suggesting that 700 to 800 IU/d vitamin D supplementation reduces nonvertebral fracture risk by 23% (FIGURE 2). The pooled risk difference was 4% (95% CI, 2%-5%), \( P = .02 \); therefore, the NNT was 27 (95% CI, 19-49) for a treatment duration of 12 to 60 months. For 2 trials, \(^{13,16} \) which included 3722 individuals and a vitamin D dose of 400 IU/d, the pooled RR was 1.15 (95% CI, 0.88-1.50), suggesting that 400 IU/d vitamin D supplementation does not reduce hip fracture risk.

---

**Figure 2. Forest Plots Comparing the Risk of Hip and Nonvertebral Fractures Between Vitamin D (700-800 IU/d and 400 IU/d) and Control Groups**

Squares represent relative risks (RRs) and size of squares is proportional to the size of the trials. Error bars represent 95% confidence intervals (CIs). Trials are sorted by trial duration ranging from 24 to 60 months for hip fracture and 12 to 60 months for nonvertebral fracture. For 3 trials with hip fractures, \(^{12,17,18} \) which included 5572 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.74 (95% CI, 0.61-0.88; Q test \( P = .74 \)). For 5 trials with nonvertebral fractures, \(^{12,14,15,17,18} \) which included 6098 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.77 (95% CI, 0.68-0.87; Q test \( P = .41 \)). For the 2 trials, \(^{13,16} \) with a vitamin D dose of 400 IU/d, trial duration ranged from 24 months to 36 to 41 months.

©2005 American Medical Association. All rights reserved.

(Reprinted) JAMA, May 11, 2005—Vol 293, No. 18 2261

Downloaded from www.jama.com by JohnFeibel, on July 8, 2005
1.03 (95% CI, 0.86-1.24), suggesting that 400 IU/d vitamin D supplementation has no significant benefit on reducing the risk of sustaining a nonvertebral fracture.

The achieved level of serum 25-hydroxyvitamin D in relation to reduction in nonvertebral fracture risk is shown in Figure 3. A greater reduction in nonvertebral fractures was observed with the higher achieved 25-hydroxyvitamin D levels in the treatment group (meta-regression P = .03). Rather than omitting studies with different assays, we cross-calibrated to the widely used DiaSorin assay (DiaSorin, Stillwater, Minn). DiaSorin equivalent values for each of the studies were 54 nmol/L (Lips et al12); DiaSorin equivalent values not available, as reported (Meyer et al10 and Pfeifer et al15); 63 nmol/L (Dacalys II study17); 75 nmol/L (Dacalys I study15); 74 nmol/L (Trivedi et al18); and 99 nmol/L (Dawson-Hughes et al19).

Sensitivity Analysis of Trials That Did Not Meet Quality Criteria for Inclusion
Including 3 additional studies19-21 in the pooled analysis for any nonvertebral fracture doubled the total number of participants to 17,736 (Table 1). The pooled RR for any vitamin D dose preventing any nonvertebral fracture was 0.83 (95% CI, 0.73-0.94; Q test P = .13). In trials that provided 700 to 800 IU/d cholecalciferol or 1000 IU/d ergocalciferol in the treatment groups (n=6941 individuals), the pooled RR was 0.77 (95% CI, 0.67-0.87; Q test P = .40). In trials that provided 400 IU/d vitamin D (n=10,795 individuals), the pooled RR was 0.93 (95% CI, 0.76-1.12; Q test P = .12).

Subgroup Analyses
Additional Calcium Supplementation. We could not examine separately the effect of additional calcium supplementation because the 2 low-dose vitamin D trials15,16 were also the trials that did not provide calcium supplements, and the high-dose vitamin D trials did provide supplementation with 1 exception, the Trivedi trial, which gave the equivalent of 800 IU/d vitamin D without calcium.18 The other 4 high-dose vitamin D trials provided 500 to 1200 mg of calcium in the treatment group.

Sex. For hip fracture prevention, only 3 studies provided separate results by sex. The pooled RR was 0.73 (95% CI, 0.61-0.89) for 3 studies involving 3838 women,12,17,18 and the RR was 0.76 (95% CI, 0.55-1.67) for the 1 study involving 2037 men.18

For any nonvertebral fracture prevention, only 4 studies provided separate results by sex. The pooled RR was 0.80 (95% CI, 0.70-0.91) for 4 studies involving 5975 women,12,15,17,18 and the RR was 0.70 (95% CI, 0.40-1.20) for the 1 study involving 2037 men.18

Length of Follow-up. When studies were sorted by length of treatment and follow-up, we were unable to discern a clear difference in the effect of vitamin D for both hip and any nonvertebral fractures (Figure 2).

COMMENT
For both hip and nonvertebral fracture prevention by vitamin D, our pooled results indicated variation between studies that was resolved when low- and high-dose vitamin D (cholecalciferol) trials were pooled separately. For trials using 700 to 800 IU/d oral vitamin D with or without calcium supplementation, we found a significant 29% reduction in risk of sustaining a hip fracture and a significant 27% reduction in risk of sustaining any nonvertebral fracture vs calcium or placebo. The pooled risk difference indicated that 45 persons would need to be treated with 700 to 800 IU/d vitamin D to prevent 1 person from sustaining a hip fracture, and 27 persons would need to be treated to prevent 1 person from sustaining any nonvertebral fracture. In contrast, 400 IU/d vitamin D did not appreciably reduce hip or nonvertebral fractures in older persons compared with placebo or calcium.

There are 2 physiological explanations for the beneficial effect of vitamin D on fracture risk in older persons. First,
the well-described decrease in bone loss in older persons\textsuperscript{14,15}, and second, vitamin D appears to have a beneficial effect on muscle strength\textsuperscript{14} and balance\textsuperscript{15} mediated through highly specific receptors in muscle tissue.\textsuperscript{35,36} Furthermore, vitamin D has been associated with a significant 22% reduction in the risk of falling in older individuals.\textsuperscript{37} As both bone loss and falls are important risk factors for fractures in older persons,\textsuperscript{38,39} it is plausible that vitamin D supplementation in a sufficient dose reduces the risk of fracture in older persons.

The pooled results suggest that for hip and nonvertebral fracture prevention 700 to 800 IU/d of vitamin D is better than 400 IU/d. Our finding that a higher dose of vitamin D supplementation and accompanying higher serum 25-hydroxyvitamin D levels are advantageous for fracture prevention is consistent with 2 previous findings. First, in a national US survey among adults aged 50 years or older, we found that bone mineral density increased monotonically with higher serum 25-hydroxyvitamin D levels up to at least 80 nmol/L.\textsuperscript{40} Second, in our previous meta-analysis of falls, vitamin D supplementation at a dose of 800 IU/d reduced fall risk by 35%, although 400 IU/d was not effective in reducing falls.\textsuperscript{37}

This range of 700 to 800 IU/d vitamin D shown to be effective in fracture prevention is higher than the current vitamin D intake recommendation of between 400 to 600 IU/d in middle-aged and older adults. In the current uncertainty about vitamin D intake recommendations, our results support increasing the suggested dose.\textsuperscript{40-44}

Among the high-dose trials, some of the variation in achieved 25-hydroxyvitamin D levels in the treatment group may be explained by the difference in starting levels of 25-hydroxyvitamin D,\textsuperscript{45} which may relate to type of dwelling (lower levels in nursing home residents), latitude (higher levels in more southern latitudes), or food fortification with vitamin D.\textsuperscript{46-48} Optimal fracture prevention appeared to occur in trials with achieved mean 25-hydroxyvitamin D level of approximately 100 nmol/L. This level was reached in 2 high-dose trials with baseline 25-hydroxyvitamin D levels of between 40\textsuperscript{2} to 77 nmol/L,\textsuperscript{14} whereas participants in 2 other high-dose trials with baseline levels between 21\textsuperscript{17} to 26 nmol/L\textsuperscript{13} did not achieve 25-hydroxyvitamin D levels of more than 100 nmol/L. Thus, it cannot be excluded that optimal fracture prevention may require more than 700 to 800 IU/d vitamin D in populations with low baseline 25-hydroxyvitamin D levels.

Another source of variation in achieved 25-hydroxyvitamin D levels may be interlaboratory differences in assays for 25-hydroxyvitamin D.\textsuperscript{38} However, there would still be a similar trend between higher achieved 25-hydroxyvitamin D levels and fracture efficacy if the different assays were transformed into DiaSorin equivalent values.

None of the studies that were included in the primary analysis tested oral ergocalciferol as the intervention; therefore, our findings used only cholecalciferol. Previous studies, however, reported that the potency of ergocalciferol may be less than one third that of cholecalciferol in the same dose.\textsuperscript{39,50}

Because calcium was administered in combination with vitamin D in all but 1 of the higher-dose vitamin D trials, the independent effect of vitamin D could not be clearly determined. In the Trivedi trial,\textsuperscript{18} which used 100 000 IU every 4 months (equivalent to 800 IU/d) without additional calcium, the RR was similar to high-dose studies in which 500 to 1200 mg/d calcium was used in combination with vitamin D (RR, 0.67 vs pooled RR plus calcium, 0.77\textsuperscript{15,14,13,17}). Thus, additional calcium supplementation may not be critical for nonvertebral fracture prevention once 700 to 800 IU of vitamin D are provided. However, in the Trivedi trial,\textsuperscript{18} the mean total calcium intake was 742 mg/d; therefore, we cannot determine if lower dietary calcium intakes with high-dose vitamin D would prevent fractures.

Although the data in men were limited, we did not find evidence that the benefit of vitamin D differed by sex. Also, we did not find evidence that the effect of vitamin D supplementation increased with duration of trial, which may be explained by the early benefits (within 2-3 months) of vitamin D on strength and falls observed in previous studies.\textsuperscript{15,34,31} However, benefits from starting supplementation earlier in life or continuing beyond 5 years cannot be excluded. All trials were performed in primarily white populations, so our meta-analysis cannot address vitamin D effects in other racial or ethnic groups.

We performed a sensitivity analysis by including 3 RCTs that did not meet our inclusion criteria\textsuperscript{19} or were only published in abstract form.\textsuperscript{20,21} The inclusion of these RCTs would have nearly doubled the number of individuals pooled from 9820 to 17 736. Adding the 3 studies to the primary analysis for any nonvertebral fracture, the pooled RR remained 0.83 and was significant for all 10 studies; in addition, the pooled RR was 0.77 and significant for the higher-dose vitamin D supplementation trials. For the low-dose vitamin D trials, the RR was 0.93 without gaining significance. Thus, our sensitivity analysis is largely consistent with the primary analysis.

In conclusion, this meta-analysis suggests that oral vitamin D supplementation in the range of 700 to 800 IU/d should reduce the risk of hip or any nonvertebral fracture by approximately 25%. The role of additional calcium supplementation together with 700 to 800 IU/d vitamin D could not be clearly defined, but dietary calcium intakes of more than 700 mg/d may be necessary for nonvertebral fracture prevention. Given the NNT of 27 to 45 for any nonvertebral and hip fracture prevention, and the high morbidity, mortality, and cost of fractures, our results are compelling for general vitamin D supplementation in the range of 700 to 800 IU/d in elderly persons. Future research should focus on comparative vitamin D supplementation trials testing higher doses of vitamin D. Another question to be addressed in future research is whether and in what dose calcium is adding value to the fracture efficacy of vitamin D.


Trivedi DP, Roll, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women in the community: randomised double blind controlled trial. BMJ. 2003;326:469.


Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab. 2004;89:386-391.