

Fracture Prevention With Vitamin D Supplementation

A Meta-analysis of Randomized Controlled Trials

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FRACTURES CONTRIBUTE SIGNIFICANTLY to morbidity and mortality of older persons. Hip fractures increase exponentially with age so that by the ninth decade of life, an estimated 1 in every 3 women and 1 in every 6 men will have sustained a hip fracture.¹ With the aging of the population, the number of hip fractures is projected to increase worldwide.² The consequences of hip fractures are severe: 50% of older persons have permanent functional disabilities, 15% to 25% require long-term nursing home care, and 10% to 20% die within 1 year.³⁻⁶ Besides the personal burden, hip fractures account for substantial health care expenses^{3,7} with annual costs in the United States projected to increase from \$7.2 billion in 1990 to \$16 billion in 2020.⁷

Given the high prevalence, severity, and cost of osteoporotic fractures, prevention strategies that are effective, low in cost, and well-tolerated are needed. One promising prevention strategy may be oral vitamin D supplementation. Several randomized controlled trials (RCTs) have examined vitamin D supplements for fracture prevention, but the results were conflicting. The goal of our analysis was to determine

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.

Data Sources A systematic review of English and non-English articles using MEDLINE and the Cochrane Controlled Trials Register (1960-2005), and EMBASE (1991-2005). Additional studies were identified by contacting clinical experts and searching bibliographies and abstracts presented at the American Society for Bone and Mineral Research (1995-2004). Search terms included *randomized controlled trial (RCT), controlled clinical trial, random allocation, double-blind method, cholecalciferol, ergocalciferol, 25-hydroxyvitamin D, fractures, humans, elderly, falls, and bone density*.

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.

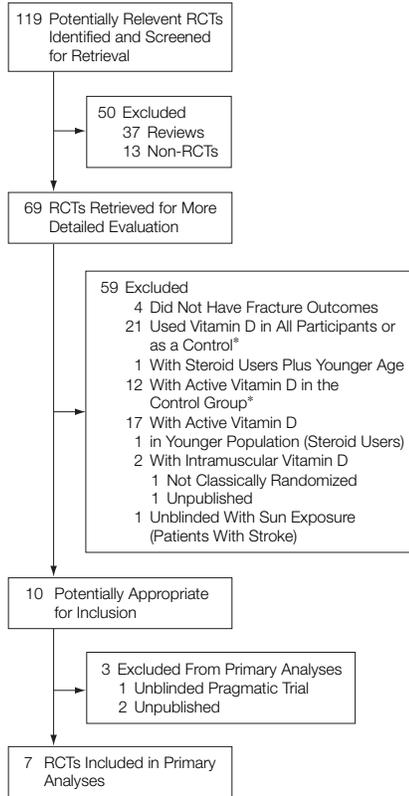
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Figure 1. QUOROM Flow Diagram

QUOROM indicates Quality of Reporting of Meta-analyses; RCTs, randomized controlled trials.

*Vitamin D or active vitamin D compared with treatments other than calcium or placebo.

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 used Medical Subject Headings (MeSH) terms, which included trials (*randomized controlled trial, controlled clinical trial, random allocation, double-blind method, single-blind method, or uncontrolled trials*), vitamin D (*cholecalciferol, ergocalciferol, or vitamin D/blood/25-hydroxyvitamin D*), fractures (*hip fractures, femoral neck fractures, femoral fractures, humeral fractures, radius fractures, or tibial fractures*), *humans, elderly, falls, and bone density*. Eligibility and exclusion criteria were prespecified. Data extraction was conducted independently by 2 authors (H.A.B.-F. and T.D.), and consensus was achieved for all data.

Eligible Studies

We included only double-blind RCTs that studied oral vitamin D supplementation (cholecalciferol or ergocalciferol) with a minimum follow-up of 1 year and required more than a total of 1 fracture in each trial. Trials that included only 1 fracture were added in a sensitivity analysis. Because the vitamin D dose may introduce heterogeneity, we also examined effect sizes separately for studies using more than 400 IU/d vitamin D and those using 400 IU/d or less. To be included in the primary analysis, we required that the authors state how fractures were ascertained and that 25-hydroxyvitamin D levels were measured during follow-up in the treatment group or a subset of the treatment group. Because our target population consisted of older community-dwelling or institutionalized persons, the mean age of study participants had to be 60 years or older to be included (FIGURE 1).

Ineligible Studies

We excluded uncontrolled trials, observational studies, and animal studies. Because health conditions that place patients at high risk for falls and fractures may confound our analysis, we excluded studies that focused on patients following organ transplantation or stroke, receiving steroid therapy or care for Parkinson disease, or unstable health states, such as after acute hospitalization.

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 RCTs^{12,13,16-18} 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

Source	No. of Participants	Treatment/d	Dwelling	Age, Mean (SD), y	Duration, mo	Baseline and Follow-up 25-Hydroxyvitamin D, Mean (SD), nmol/L	
						Treatment Group	Control Group
Trials Included in Primary Analysis							
Chapuy et al, ¹¹ 1992 (Decaloyos I)	3270 Women	800-IU cholecalciferol + 1200-mg calcium (tri-calcium phosphate powder) vs placebo	Ambulatory, living in nursing homes or apartments for elderly persons	84 (6)	18	40 (27.5) to 105 (22.5) at 18-mo follow-up	32.5 (22.5) to 27.5 (17.5) at 18-mo follow-up
Chapuy et al, ¹² 1994 (Decaloyos I)	Intention-to-treat analysis of 2303 women at 36-mo report	800-IU cholecalciferol + 1200-mg calcium (tri-calcium phosphate powder) vs placebo	Ambulatory, living in nursing homes or apartments for elderly persons	84 (6)	36	40 (27.5) to 105 (22.5) at 18-mo follow-up	32.5 (22.5) to 27.5 (17.5) at 18-mo follow-up
Lips et al, ¹³ 1996	2578 Persons (1916 women, 662 men); no separate results by sex	400-IU cholecalciferol vs placebo; participants asked to consume 3 dairy products daily to reach a calcium intake of \geq 800 mg/d	Independent, in apartments or homes for elderly persons	80 (6)	36-41	27 (IQR, 19-36) to 62 (IQR, 52-70) at 12-mo follow-up	26 (IQR, 19-37) to 23 (IQR, 17-31) at 12-mo follow-up
Dawson-Hughes et al, ¹⁴ 1997*	389 Persons (213 women, 176 men); no separate results by sex	700-IU cholecalciferol + 500-mg calcium (calcium citrate malate) vs placebo; mean calcium intake at baseline was about 720 mg/d	Community-dwelling	71 (5)	36	76.5 (37.0) to 112 (36.8) at 36-mo follow-up	72 (33.1) to 71.7 (30.5) at 36-mo follow-up
Pfeifer et al, ¹⁵ 2000*	137 Women	800-IU cholecalciferol + 1200-mg calcium vs 1200-mg calcium	Community-dwelling	74 (1)	2 (with treatment) plus 10 (with follow-up)	25.7 (13.6) to 66.1 (33.1) at 2-mo follow-up	24.6 (12.1) to 42.9 (33.1) at 2-mo follow-up (baseline was beginning of March)
Meyer et al, ¹⁶ 2002	1144 Persons (75% women)	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	Frail nursing home residents with life expectancy of $>$ 6 mo and not permanently bedridden	85 (7)	24	47 (26) to 64 (21) at 12-mo follow-up	51 (33) to 46 (20) at 12-mo follow-up
Chapuy et al, ¹⁷ 2002 (Decaloyos II)	583 Women	800-IU cholecalciferol + 1200-mg calcium (tri-calcium phosphate) as fixed or separate combination vs placebo	Ambulatory, living in apartment houses for elderly persons	85 (7)	24	21.3 (13.3) to 77.5 (ND) from bar graph at 24-mo follow-up	22.8 (17.3) to 15 (ND) from bar graph at 24-mo follow-up
Trivedi et al, ¹⁸ 2003	2686 Persons (649 women, 2037 men)	100 000 IU every 4 mo (\approx 800 IU/d) vs placebo; mean calcium intake at 4 y was 742 mg/d as assessed by food frequency questionnaire	Community-dwelling	75 (5)	60	74.3 (20.7) at a 48-mo follow-up (no baseline)	53.4 (21.1) at a 48-mo follow-up (no baseline)
Trials Excluded From Primary Analysis							
Larsen et al, ¹⁹ 2004†	7073 Persons (4256 women, 2817 men)	Patients offered 400-IU/d cholecalciferol + 1000-mg/d calcium vs no intervention	Community-dwelling	66-103	42	37 (19) to 47 (20) at 24-mo follow-up	33 (19) to 38 (18) at 24-mo follow-up
Pfeifer et al, ²⁰ 2004†	242 Persons (74% women)	800-IU/d cholecalciferol + 1000-mg/d calcium vs 1000-mg/d calcium	Community-dwelling	77	20 (12 with treatment)	ND	ND
Flicker et al, ²¹ 2004†	601 Persons (53% women)	Ergocalciferol (initially 10 000 IU/wk, then 1000 IU/d) vs placebo + 600-mg calcium for all	Nursing homes and assisted-living facilities	"Elderly"	24	ND	ND

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.

Table 2. Hip and All Nonvertebral Fractures

Citation	No./Total No. of Persons		Effect RR (95% CI)	Total No.
	Treatment	Control		
Hip Fractures				
Chapuy et al, ¹² 1994	137/1176	178/1127	0.74 (0.60-0.91)	2303
Lips et al, ¹³ 1996	58/1291	48/1287	1.21 (0.83-1.75)	2578
Dawson-Hughes et al, ¹⁴ 1997*	0/187	1/202		(389)
Pfeifer et al, ¹⁵ 2000*	0/70	1/67		(137)
Meyer et al, ¹⁶ 2002	50/569	47/575	1.08 (0.73-1.57)	1144
Chapuy et al, ¹⁷ 2002	27/393	21/190	0.62 (0.36-1.07)	583
Trivedi et al, ¹⁸ 2003	21/1345	24/1341	0.85 (0.47-1.53)†	2686
Total			0.88 (0.69-1.13)	9294
All Nonvertebral Fractures				
Chapuy et al, ¹² 1994	255/1176	308/1127	0.79 (0.69-0.92)	2303
Lips et al, ¹³ 1996	135/1291	122/1287	1.10 (0.87-1.39)	2578
Dawson-Hughes et al, ¹⁴ 1997	11/202	26/187	0.46 (0.24-0.88)	389
Pfeifer et al, ¹⁵ 2000	3/70	6/67	0.48 (0.13-1.78)	137
Meyer et al, ¹⁶ 2002	69/569	76/575	0.92 (0.68-1.24)	1144
Chapuy et al, ¹⁷ 2002	97/393	55/190	0.85 (0.64-1.13)	583
Trivedi et al, ¹⁸ 2003	43/1345	62/1341	0.67 (0.46-0.99)†	2686
Total			0.83 (0.70-0.98)	9820

Abbreviations: CI, confidence interval; RR, relative risk.

*Studies were excluded from the pooled analysis of hip fractures due to only 1 observed hip fracture in both trials.

†Age-adjusted.

data from 1 trial was provided by the principal investigator.²⁰ None of the trials provided separate results for hip fractures, 2 trials included any osteoporotic fracture,^{19,21} and 1 trial provided results for any nonvertebral fracture.²⁰

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.²² 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 $P < .10$ ^{23,24}). 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.²⁵ 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.²⁶ This approach was chosen because the association between vitamin D dose and change in 25-hydroxyvitamin D is not linear,²⁷ 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,²⁸ the funnel plot suggested a possible absence of negative studies involving small sample sizes. However, the trim and fill analysis²⁹ 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 pri-

mary analysis for hip fracture^{12,13,16-18} or any nonvertebral fracture,¹²⁻¹⁸ or both.^{12,13,16-18} 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,^{14,15,18} in apartments or housing for elderly persons,^{13,17} or in nursing homes.^{12,16}

The vitamin D dose used in 2 RCTs was 400 IU/d,^{13,16} while the other 5 RCTs used 700 to 800 IU/d. Between 500 mg/d¹⁴ and 1200 mg/d^{12,15,17} 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,¹³ and in the 2 remaining trials, mean calcium intake was between 450¹⁶ and 742 mg/d.¹⁸ Only 1 trial provided calcium supplementation in the control group.¹⁵ Treatment duration varied between 12 and 60 months.

Two trials reported the method of randomization,^{13,16} 2 trials stated that treatment allocation was concealed from participants and investigators,^{13,18} all but 1 trial¹⁵ 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%¹⁵ in community-dwelling participants to 67% in frail institutionalized elderly persons.¹⁶

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,^{12,17,18} 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, 0.70-1.09), 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).

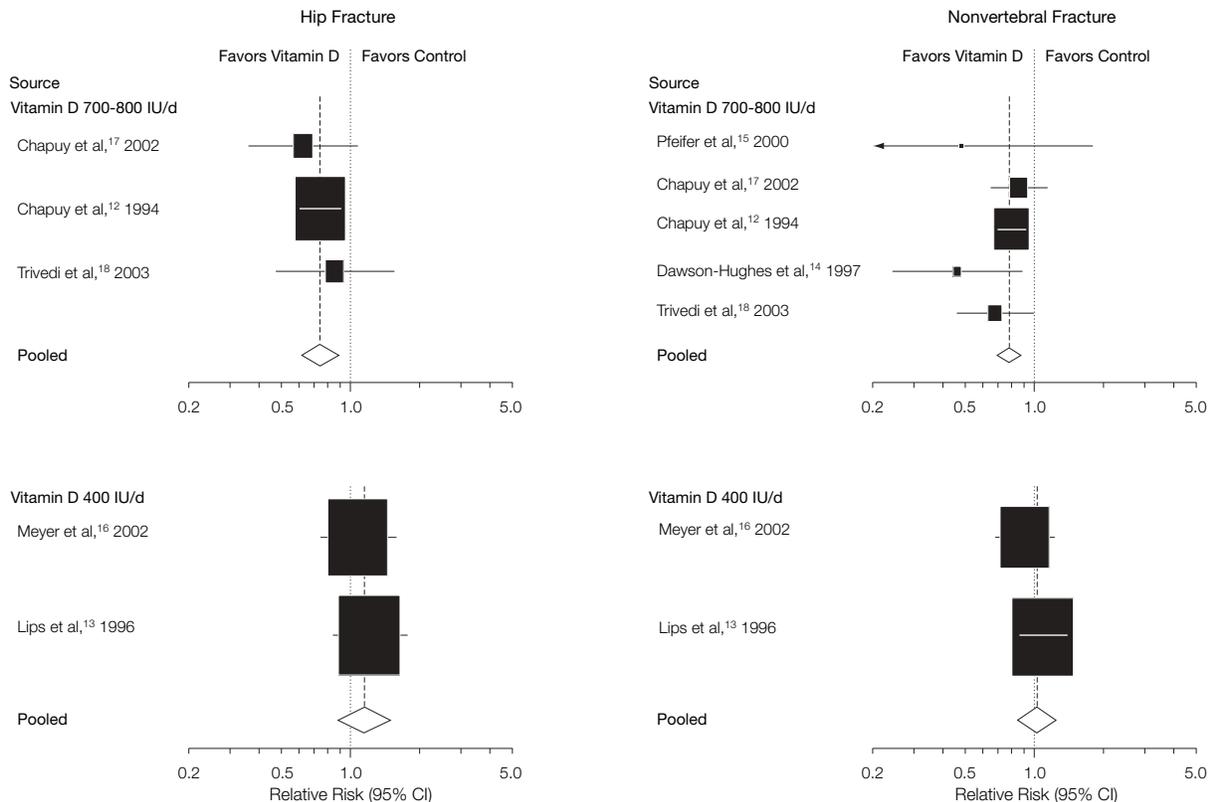
Any Nonvertebral Fracture

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 $P = .07$).

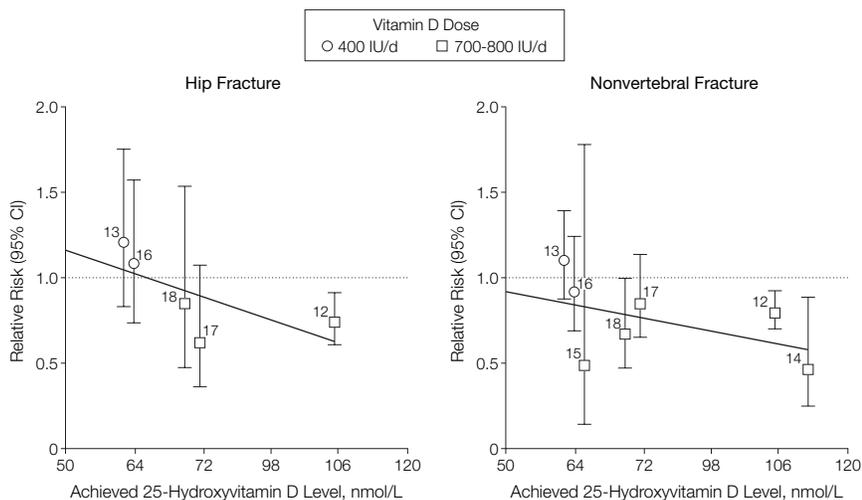
After stratifying trials by vitamin D dose, there was homogeneity (Q test $P = .41$ for high-dose trials and $P = .36$ for low-dose trials). For 5 trials,^{12,14,15,17,18} which included 6098 individuals and a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.77 (95% CI, 0.68-0.87), suggesting that 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

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.

Figure 3. Hip and Nonvertebral Fracture Efficacies by Achieved 25-Hydroxyvitamin D Levels in 400 IU/d and 700-800 IU/d Vitamin D–Treated Groups



Circles and squares represent relative risks (RRs) and error bars represent 95% confidence intervals. Trendline is based on series of effect sizes (open circles and squares). All trials identified for the primary analyses for both fractures are shown as a reference number outside each circle or square. A meta-regression, which included 9294 individuals, indicated a significant inverse relationship between higher achieved 25-hydroxyvitamin D levels in the treatment group and hip fracture risk ($\beta = -0.009$; $P = .02$; log RR of hip fracture is estimated to decrease by 0.009 per 1-nmol/L increase in 25-hydroxyvitamin D). A meta-regression, which included 9820 individuals, indicated a significant inverse relationship between higher achieved 25-hydroxyvitamin D levels in the treatment group and nonvertebral fracture risk ($\beta = -0.006$; $P = .03$; log RR of nonvertebral fracture is estimated to decrease by 0.006 per 1-nmol/L of 25-hydroxyvitamin D achieved in the treatment group). To convert 25-hydroxyvitamin D to ng/mL, divide values by 2.496.

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 3.³⁰ 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).³¹ DiaSorin equivalent values for each of the studies were 54 nmol/L (Lips et al¹³); DiaSorin equivalent values not available, as reported³² (Meyer et al¹⁶ and Pfeifer et al¹⁵); 63 nmol/L (Decalys II study¹⁷); 75 nmol/L (Decalys I study¹²); 74 nmol/L (Trivedi et al¹⁸); and 99 nmol/L (Dawson-Hughes et al¹⁴).

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 trials^{13,16} 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 5838 women,^{12,17,18} and the RR was 0.76 (95% CI, 0.35-1.67) 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 26% reduction in risk of sustaining a hip fracture and a significant 23% 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^{14,33}; and second, vitamin D appears to have a beneficial effect on muscle strength³⁴ and balance¹⁵ mediated through highly specific receptors in muscle tissue.^{35,36} Furthermore, vitamin D has been associated with a significant 22% reduction in the risk of falling in older individuals.³⁷ As both bone loss and falls are important risk factors for fractures in older persons,^{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 25-hydroxyvitamin D levels up to at least 80 nmol/L.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.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.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,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.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 40¹² to 77 nmol/L,¹⁴ whereas participants in 2 other high-dose trials with baseline levels between 21¹⁷ to 26 nmol/L¹⁵ 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.³⁰ 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.^{49,50}

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,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^{12,14,15,17}). 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,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.^{15,34,51} 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 criteria¹⁹ or were only published in abstract form.^{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.

Author Contributions: Dr Bischoff-Ferrari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bischoff-Ferrari, Willett, Giovannucci, Dawson-Hughes.

Acquisition of data: Bischoff-Ferrari, Dietrich.

Analysis and interpretation of data: Bischoff-Ferrari, Willett, Wong, Giovannucci, Dietrich, Dawson-Hughes.

Drafting of the manuscript: Bischoff-Ferrari, Dawson-Hughes.

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