

Prevention of Nonvertebral Fractures With Oral Vitamin D and Dose Dependency

A Meta-analysis of Randomized Controlled Trials

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Background: Antifracture efficacy with supplemental vitamin D has been questioned by recent trials.

Methods: We performed a meta-analysis on the efficacy of oral supplemental vitamin D in preventing nonvertebral and hip fractures among older individuals (≥ 65 years). We included 12 double-blind randomized controlled trials (RCTs) for nonvertebral fractures ($n=42\,279$) and 8 RCTs for hip fractures ($n=40\,886$) comparing oral vitamin D, with or without calcium, with calcium or placebo. To incorporate adherence to treatment, we multiplied the dose by the percentage of adherence to estimate the mean received dose (dose \times adherence) for each trial.

Results: The pooled relative risk (RR) was 0.86 (95% confidence interval [CI], 0.77-0.96) for prevention of nonvertebral fractures and 0.91 (95% CI, 0.78-1.05) for the prevention of hip fractures, but with significant heterogeneity for both end points. Including all trials, antifracture

efficacy increased significantly with a higher dose and higher achieved blood 25-hydroxyvitamin D levels for both end points. Consistently, pooling trials with a higher received dose of more than 400 IU/d resolved heterogeneity. For the higher dose, the pooled RR was 0.80 (95% CI, 0.72-0.89; $n=33\,265$ subjects from 9 trials) for nonvertebral fractures and 0.82 (95% CI, 0.69-0.97; $n=31\,872$ subjects from 5 trials) for hip fractures. The higher dose reduced nonvertebral fractures in community-dwelling individuals (-29%) and institutionalized older individuals (-15%), and its effect was independent of additional calcium supplementation.

Conclusion: Nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

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THE ANTIFRACTURE BENEFITS of vitamin D have been questioned by several recent trials,¹⁻⁴ leading to uncertainty among patients and physicians regarding recommendations for vitamin D supplementation. Two 2007 meta-analyses^{5,6} included most of these trials and concluded that vitamin D may not reduce fractures significantly or may do so only in combination with calcium and primarily among institutionalized older individuals. A third 2007 meta-analysis⁷ concluded that calcium with or without vitamin D may reduce total fracture risk by 12%, a result that was questioned by a more recent meta-analysis⁸ of high-quality trials of calcium supplementation alone in which calcium had a neutral effect on nonvertebral fractures and a possible adverse effect on hip fracture risk. Apart from the mixed data on calcium, the recent meta-analyses with vitamin D did not consider heterogeneity by received dose (incorporating adherence) or achieved level of 25-hydroxyvitamin D.

A dose-response relationship between vitamin D and fracture reduction is supported by epidemiologic data showing a significant positive trend between serum 25-hydroxyvitamin D concentrations and hip bone density⁹ and lower extremity strength.^{10,11} In addition, greater anti-fracture efficacy with higher achieved 25-hydroxyvitamin D levels was documented in an earlier meta-analysis of high-quality primary prevention trials with supplemental vitamin D.¹² Factors that may obscure a benefit of vitamin D are low adherence to treatment,² low dose of vitamin D, or the use of less potent ergocalciferol (vitamin D₂).^{13,14} Furthermore, open study design trials¹ may bias results toward the null because vitamin D supplementation is available over the counter.

Our primary goal was to determine the antifracture efficacy of oral vitamin D supplementation among individuals aged 65 years or older by performing a systematic review of the literature and meta-analysis of high-quality, double-blinded RCTs. In addition, we specifically addressed anti-

fracture efficacy by received dose, achieved 25-hydroxyvitamin D levels, and in predefined subgroups.

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 through August 2008 and EMBASE from January 1991 through August 2008. Additional studies were identified from reference lists, contacts with experts in the field, and abstracts presented at the American Society for Bone and Mineral Research from 1995 through 2007.

The medical subject headings (MeSH terms) included trials (randomized-controlled-trial or controlled-clinical-trial or random-allocation or double-blind-method or single-blind-method or uncontrolled-trials), vitamin D (cholecalciferol or hydroxycholecalciferols or calcifediol or dihydroxycholecalciferols or calcitriol or vitamin D/aa [analogs and derivatives] or ergocalciferol or vitamin D/bl [blood]), fractures (femoral fractures, femoral neck fractures, hip fractures, humerus fractures, forearm fractures, radius fractures, ankle fractures, nonvertebral fractures), accidental falls or falls, humans, elderly, bone density. Identical data were extracted independently by three of us (H.A.B.-F., A.T., and J.H.).

ELIGIBLE STUDIES

We included only RCTs that studied oral vitamin D supplementation (cholecalciferol [vitamin D₃] or ergocalciferol with a minimum follow-up of 1 year and required more than a total of 1 fracture in each trial. Because our target population consisted of older persons, the mean age of study subjects had to equal or exceed 65 years. To be included in the primary analysis, we required a double-blinded study design, a report of adherence, and a statement explaining how fractures were ascertained. We also conducted a separate pooled analysis of trials using 1- α -hydroxylated vitamin D, which included trials that used 1- α -hydroxyvitamin D₃, 1,25-hydroxyvitamin D₃, and 1 α ,25-dihydroxy-2 β (3-hydroxypropoxy) vitamin D₃ (ED-71).

INELIGIBLE STUDIES

We excluded uncontrolled trials, observational studies, and animal studies. Be-

cause health conditions that place patients at high risk for falls and fractures could have confounded our analysis, we excluded studies that focused on patients following organ transplantation or stroke and those receiving steroid therapy or care for Parkinson disease or having unstable health states.

DEFINITIONS

Our primary outcome measure was the relative risk (RR) of a first or repeated nonvertebral fracture or hip fracture in persons receiving supplemental vitamin D, with or without calcium supplementation, compared with those receiving placebo or calcium supplementation alone. To determine the effect of dose, we calculated the *received dose of supplemental vitamin D* by the cross-product of dose and percentage of adherence, which is a more comprehensive assessment of dosage, accounting for the low adherence in the latest trials. According to predefined criteria, heterogeneity by received dose of vitamin D was explored as a continuous variable plus using the same cutoff as in the 2005 meta-analysis¹² (≤ 400 IU/d compared with >400 mg/d). For the Women's Health Initiative trial,³ we also added the mean personal intake (365 IU/d) to the 400 IU/d provided in the trial to account for the significant vitamin D intake outside the study protocol. We chose achieved serum 25-hydroxyvitamin D levels, measured in at least a subgroup of the study population assessed during the trial period, because this reflects the starting 25-hydroxyvitamin D level (baseline risk for vitamin D deficiency) and the vitamin D dose received.

QUALITY ASSESSMENT AND STUDIES IDENTIFIED

To be included as trials with minimal bias, studies had to be randomized and masked to treatment allocation. Trials that met all features but had an open study design were included in sensitivity analyses. Twelve studies (listed in **Table 1**) for supplemental vitamin D were identified through our MeSH term search. Four additional studies with an open study design were identified for the sensitivity analysis^{1,24,26} (**Table 2** and **Figure 1**).

STATISTICAL ANALYSIS

Outcomes were analyzed on an intention-to-treat basis with random effects models.²⁷ We calculated the risk difference to determine the number needed to treat (NNT) to prevent 1 fracture. Heterogeneity among studies was ex-

plored by predefined covariates using the *Q*-statistic as a test (considered significant for $P < .10$).²⁸ The presence of heterogeneity suggests that the studies should not be pooled because of significant differences in results.²⁹ In such cases, we explored heterogeneity by received dose (dose \times adherence: ≤ 400 IU/d vs >400 IU/d of vitamin D)¹² and achieved 25-hydroxyvitamin D level using visual inspection, and random-effects metaregression analysis. Predefined subgroup analyses included age, type of dwelling, and additional calcium supplementation. To evaluate publication bias, we used Begg and Egger tests with all 12 trials from the primary analysis or all 16 trials from the sensitivity analysis. Although the Begg funnel plot suggested a possible absence of negative studies involving small sample sizes, the trim and fill analysis did not confirm this suggestion.³⁰ Statistical analysis was performed with Stata software (version 8.0; StataCorp LP, College Station, Texas).

RESULTS

Table 1 shows characteristics of the 12 double-blind RCTs that were included in the primary analysis for the prevention of nonvertebral fractures, 8 of which were also included in the primary analysis for hip fracture. The 12 trials included 42 279 individuals with a mean age of 78 years, and 89% were women. The received dose of vitamin D (dose \times adherence) was 400 IU/d or less in 3 trials,^{2,19,22} whereas the other 9 RCTs had mean intakes of 482 to 770 IU/d. A total of 500 to 1200 mg/d of calcium supplementation was used in combination with vitamin D supplementation in 7 RCTs. Treatment duration varied from 12 to 84 months.

NONVERTEBRAL FRACTURES

In the 12 high-quality RCTs (listed in Table 1) ($n = 42\,279$ participants), the pooled RR for any dose of vitamin D preventing nonvertebral fractures was 0.86 (95% CI, 0.77-0.96). However, heterogeneity in results was seen among studies (*Q* test: $P = .04$). After stratifying trials by received dose, heterogeneity was resolved. For the 3 high-quality trials^{2,19,22} (9014 individuals) with a *received low dose of 400 IU/d or less of vitamin D* (340-380

Table 1. Randomized Controlled Trials of Supplemental Vitamin D Included in the Primary Analyses

Source	Participants, No.	Treatment/d, % Adherence	Dwelling	Age, Mean (SD), y	Duration, mo	25-Hydroxyvitamin D Level, Mean (SD), nmol/L ^a	
						Treatment Group, No. of All Assessments (Treatment + Control)	Control Group
Lyons et al ⁴	3440 (2724 women, 716 men)	800 IU ergocalciferol (100 000 IU every 4 mo) vs placebo, 80	Residential homes, sheltered accommodation, nursing or dual registered homes (institutional care)	84 (8)	36	Only follow-up: after 5 doses (20 mo) 80.1 n=102	Only follow-up: 54
Flicker et al ¹⁵	625 (593 women, 32 men)	Initially 10 000 IU ergocalciferol weekly, then 1000 IU ergocalciferol + 600 mg calcium vs placebo + 600 mg calcium (calcium carbonate), 77	Residential care	83 (8)	24	ND	ND
Pfeifer et al ¹⁶	242 (49% women)	800 IU cholecalciferol + 1000 mg calcium vs placebo + 1000 mg calcium, 80	Healthy, ambulatory	77 (4)	12 + 8-mo follow-up	55.4 (18.4) to 84.5 (18.0) at 12-mo follow-up n=242	53.8 (18.5) to 56.6 (20) at 12-mo follow-up
Trivedi et al ¹⁷	2686 (2037 men, 649 women)	800 IU cholecalciferol (as 100 000 IU cholecalciferol every 4 mo) vs placebo, 80	Community-dwelling	75 (5)	60	Only follow-up: 74.3 (20.7) at 48-mo follow-up n=238	53.4 (21.1) at 48-mo follow-up
Chapuy et al ¹⁸	583 women	800 IU cholecalciferol + 1200 mg calcium (tricalcium-phosphate) as fixed or separate combination vs placebo, 95	Ambulatory, living in apartment houses for elderly persons	85 (7)	24	21.3 (13.3) to 77.5 (ND) from bar graph ¹⁸ at 24-mo follow-up n=583	22.8 (17.3) to 15 (ND) from bar graph at 24-mo follow-up
Meyer et al ¹⁹	1144 (858 women, 286 men)	400 IU cholecalciferol from cod liver oil vs cod liver oil with vitamin D removed, 95	Nursing home residents, including frail and mentally impaired persons	85 (7)	24	47 (26) to 64 (21) at 12-mo follow-up n=65	51 (33) to 46 (20) at 12-mo follow-up
Pfeifer et al ²⁰	137 women	800 IU cholecalciferol + 1200 mg calcium vs 1200 mg calcium, 96	Community-dwelling	74 (1)	2 (with treatment) + 10 (without treatment)	25.7 (13.6) to 66.1 (33.1) at 2-mo follow-up n=137	24.6 (12.1) to 42.9 (33.1) at 2-mo follow-up
Dawson-Hughes et al ²¹	389 (213 women, 176 men)	700 IU cholecalciferol + 500 mg calcium (calcium citrate malate) vs placebo, 93	Community-dwelling	71 (5)	36	76.5 (37.0) to 112 (36.8) at 36-mo follow-up n=313	72 (33.1) to 71.7 (30.5) at 36-mo follow-up
Lips et al ²²	2578 (1916 women, 662 men)	400 IU cholecalciferol vs placebo, 85	Ambulatory, reasonably healthy, those from GPs living independently; others received some care	80 (6)	36-41	27 (19-36) to 62 (52-79) at 12-mo follow-up n=270	26 (19-37) to 23 (17-31) at 12-mo follow-up
Chapuy et al ²³	2303 women (ITT analysis)	800 IU cholecalciferol + 1200 mg calcium (tricalcium-phosphate) vs placebo, 83	Ambulatory, living nursing homes or apartment houses for elderly persons	84 (6)	36	40 (27.5) to 106 (22.5) at 18-mo follow-up n=52	32.5 (22.5) at baseline to 27.5 (17.5) at 18-mo follow-up
Grant et al ²	5292 (4481 women, 811 men)	800 IU cholecalciferol with or without 1000 mg calcium (calcium carbonate), 47 at 24 mo	Mobile before developing a low trauma fracture	77 (6)	24 to 62, median: 45, IQR: 37-52	38 (16) to 62 (19.5) at 12-mo follow-up n=60	38 (16) to 43.6 (16) at 12-mo follow-up
Jackson et al ³	22 860 women, subgroup age >60	400 IU cholecalciferol + 1000 mg calcium (calcium carbonate) vs placebo + 365 IU vitamin D intake (mean) outside the study protocol, 63	Community-dwelling	65 of the subgroup age >60 (estimate)	Mean (SD), 84 (17)	ND	ND

Abbreviations: GP, general practitioner; IQR, interquartile range; ITT, intention-to-treat; NA, not available; ND, not determined in the trial population during the course of the trial.

Conventional unit conversion factor: To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

^aValues are given as either mean (SD) or mean (range).

IU/d; all cholecalciferol), the pooled RR was 1.02 (95% CI, 0.92-1.15; *Q* test: *P* = .64) suggesting that 380 IU/d of vitamin D or less did not reduce nonvertebral fracture risk (**Table 3**).

For 9 trials with a higher received dose of more than 400 IU/d of vitamin D (482-770 IU; 33 265 individuals; **Table 4**), the pooled RR was 0.80 (95% CI, 0.72-0.89; *Q*-test:

P = .31) suggesting that 482 to 770 IU/d of vitamin D reduced nonvertebral fracture risk by 20% (**Figure 2A**). The pooled risk difference for the higher received dose

Table 2. Supplemental Vitamin D: Open Study Design Randomized Controlled Trials Excluded From the Primary Analyses

Source	Participants, No.	Treatment/d, % Adherence	Dwelling	Age, Mean, y	Duration, mo	25-Hydroxyvitamin D Levels, mean nmol/L ^a	
						Treatment Group, No. of All Assessments (Treatment + Control)	Control Group
Porthouse et al ¹	3314 women	800 IU cholecalciferol + 1000 mg calcium (calcium carbonate) vs control group (advise on fall prevention and adequate calcium and vitamin D intake) <60	Community-dwelling	≥70	Median follow up: 25	ND	ND
Harwood et al ²⁵ (acute hip fracture)	76 women	800 IU cholecalciferol + 1000 mg calcium vs control group (no placebo) No data on adherence	Rehabilitation ward, previous community-dwelling	82 (67-92)	12	29 (6-75), to 50 at 12-mo follow-up, n=58	30 (12-64) to 27 at 12-mo follow-up
Law et al ²⁴	3717 (76% women)	1100 IU ergocalciferol (as 100 000 IU ergocalciferol every 3 mo) vs no treatment (no placebo); no data on adherence	Living in residential accommodation	85	Median=10 (IQR, 7-14)	47 (35-102), to 74 (52-110) at 3-mo follow-up, n=18 (1% of the treated population)	ND
Larsen et al ²⁶ (cluster randomization)	7073 (4256 women, 2817 men)	400 IU cholecalciferol + 1000 mg calcium (calcium carbonate) vs control group (no placebo)	Community-dwelling	75	42	37 (19), at 24-mo follow-up: 47 (20), n=85	33 (19), after 24 mo: 38 (18)

Abbreviations: IQR, interquartile range; ND, not determined in the trial population during the course of the trial. Conventional unit conversion factor: To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496. ^aValues are given as either mean or mean (range).

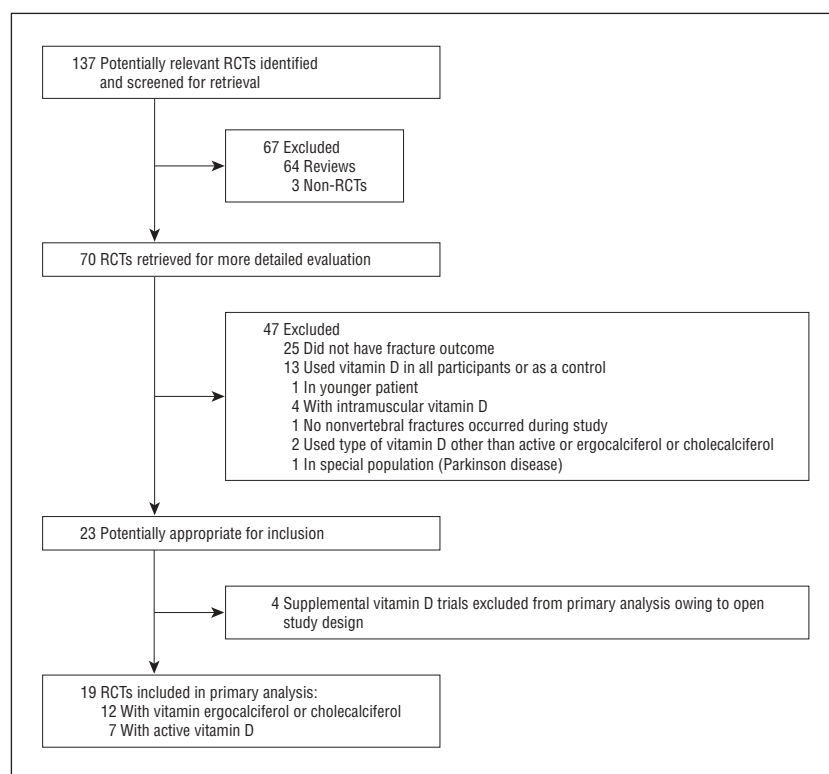


Figure 1. Flowchart of studies.

was 1.1% (95% CI, 0.6%-1.5%, $P < .001$), so the NNT was 93 [95% CI, 66-160] for 12 to 84 months.

In metaression analyses, a greater reduction in nonvertebral fractures was seen both with a higher received dose ($P = .003$; **Figure 3A**) and with higher achieved 25-

hydroxyvitamin D levels ($P = .04$; **Figure 3B**).

In subgroup analyses (Table 4), the pooled RR for nonvertebral fractures was 10% in trials that used ergocalciferol compared with 23% for trials that used cholecalciferol (for metaression, $P = .07$). The effect

of vitamin D was significant among all subgroups according to age and dwelling, with a somewhat greater effect among younger persons and those living in the community, but the differences were not significant (see Table 4 for Q -test P values). The combined effect of calcium plus vitamin D compared with placebo was tested in 4 trials (all using cholecalciferol) with a pooled RR reduction of 21%. The effect of vitamin D alone (either vitamin D vs placebo or vitamin D plus calcium compared with calcium alone) was tested in 5 trials, also with a pooled RR reduction of 21%. Thus, the addition of calcium to adequate intakes of vitamin D does not seem to enhance the effect of vitamin D in reducing nonvertebral fractures. Based on limited data for men ($n = 2037$),¹⁷ there was no significant heterogeneity by sex (Q test: $P = .93$).

SENSITIVITY ANALYSES FOR NONVERTEBRAL FRACTURES

For any received dose, after adding the 4 open study design trials^{1,24-26} to the 12 double-blinded trials, the pooled RR for vitamin D preventing any nonvertebral fracture, including 56 459 individuals, was 0.88 (95% CI, 0.80-0.97), and significant heterogeneity among studies remained (Q test:

Table 3. Primary Pooled Analysis for a Lower Received Dose of Supplemental Vitamin D (340-380 IU/d) and the Prevention of Nonvertebral Fractures (NV-FX)

Source and Type of Vitamin D Supplement	NV-FX Reduction, %	Received Dose = Treatment Dose × Adherence, IU/d	Year	No./Total Treated	No./Total Control	Effect RR (95% CI)	Total No.	P Value, Q Test
Pooled analysis of all LD DB trials								
Grant et al ² (cholecalciferol)		376	2005	349/2649	341/2643	1.021 (0.888-1.174)	5292	
Meyer et al ¹⁹ (cholecalciferol)		380	2002	69/569	76/575	0.917 (0.677-1.244)	1144	
Lips ³¹ (cholecalciferol)		340	1996	135/1291	122/1287	1.103 (0.874-1.392)	2578	
Pooled result for 3 LD DB trials	+2		Pooled	553/4509	539/4505	1.02 (0.92-1.15)	9014	.64
Sensitivity analysis: adding 1 LD OSD trial (Larsen et al ²⁶) to the pooled result of the 3 LD DB trials	-4		Pooled	871/9466	706/6621	0.96 (0.84-1.10)	16 087	.14

Abbreviations: CI, confidence interval; DB, double-blind; HD, higher dose; LD, lower dose; OSD, open study design; RR, relative risk.

Table 4. Primary Pooled Analysis for a Higher Received Dose of Supplemental Vitamin D (482-770 IU/d) and the Prevention of Nonvertebral Fractures (NV-FX)

Source and Type of Vitamin D Supplement	NV-FX Reduction, %	P Value Difference Between Subgroups ^a	Received Dose = Treatment Dose Adherence, IU/d ^a	Year	FX, No./Total Treated	FX, No./Total Control	Effect RR (95% CI)	Total No.	P Value, Q-Test Heterogeneity ^b
Pooled analysis of all HD DB trials									
Lyons et al ⁴ (ergocalciferol)			640	2007	202/1725	209/1715	0.961 (0.801-1.152)	3440	
Jackson et al ³ (cholecalciferol) (WHI trial, women ≥60 y)			482 ^c	2006	146/11 448	186/11 412	0.782 (0.631-0.970)	22 860	
Flicker et al ¹⁵ (ergocalciferol)			770	2005	25/313	35/312	0.712 (0.438-1.158)	625	
Pfeifer et al ¹⁶ (cholecalciferol)			700	2008	9/121	16/121	0.563 (0.262-1.208)	242	
Trivedi et al ¹⁷ (cholecalciferol)			640	2003	43/1345	62/1341	0.67 (0.46-0.99)	2686	
Chapuy et al ¹⁸ (cholecalciferol)			760	2002	97/393	55/190	0.853 (0.642-1.133)	583	
Pfeifer et al ²⁰ (cholecalciferol)			768	2000	3/70	6/67	0.479 (0.129-1.782)	137	
Dawson-Hughes et al ²¹ (cholecalciferol)			651	1997	11/187	26/202	0.457 (0.237-0.879)	389	
Chapuy et al ²³ (cholecalciferol)			664	1994	255/1176	308/1127	0.793 (0.687-0.916)	2303	
Pooled result for all 9 HD DB trials	-20			Pooled	791/16 778	903/16 487	0.80 (0.72-0.89)	33 265	.31
Primary subgroup analyses for HD DB trials									
Ergocalciferol ^{4,15}	-10	.07	Pooled		227/2038	244/2027	0.90 (0.71-1.15)	4065	.26
Cholecalciferol ^{3,16-18,20,21,23}	-23		Pooled		564/14 740	659/14 460	0.77 (0.70-0.85)	29 200	.57
Age 65-74 y ^{3,20,21}	-33	.34	Pooled		160/11 705	218/11 681	0.67 (0.46-0.96)	23 386	.25
Age >75 y ^{4,15-18,23}	-17		Pooled		631/5073	685/4806	0.83 (0.74-0.92)	9879	.36
Institutionalized persons ^{4,15,18,23}	-15	.09	Pooled		579/3607	607/3344	0.85 (0.76-0.94)	6951	.37
Community-dwelling persons ^{3,16,17,20,21}	-29		Pooled		212/13 171	296/13 143	0.71 (0.60-0.85) ^e	26 314	.51
With calcium ^{3,18,21,23} vs main-effect vitamin D ^{4,16,17,20}	-21	.37	Pooled		509/13 204	575/12 931	0.79 (0.71-0.88)	26 135	.40
Sensitivity analysis: add 3 HD OSD trials (Porthouse et al, ¹ Law et al, ²⁴ Harwood et al ^{25,3}) to the pooled result of the 9 HD DB trials above	-17		Pooled		916/19 900	1050/20 472	0.83 (0.74-0.95)	40 372	.07 ^b

Abbreviations: CI, confidence interval; DB, double blind; HD, higher-dose; OSD, open study design; RCT, randomized controlled trial; RR, relative risk; WHI, Women's Health Initiative.

^a P value refers to metaregression results.

^b Q test: P < .99 indicates heterogeneity.

^c Includes mean intake of vitamin D outside the study protocol.

^d Received intake could not be calculated because data for adherence were not available. Owing to 3 monthly applications, high adherence was assumed.

P = .02). We therefore again stratified studies by dose received.

For the lower received dose, after adding 1 open study design trial to the 3 double-blind trials (16 087 individuals), the pooled RR was 0.96 (95% CI, 0.84-1.10; Table 3). For the higher received dose, after adding 3 open study design trials to the 9 double-blind trials (40 372 individuals), the pooled RR was 0.83 (95% CI, 0.74-0.95; Table 4). However, variation in results was seen between open

study design (summarized in **Table 5**) and double-blind trials (Q test: P = .07), suggesting that trial quality introduces heterogeneity.

HIP FRACTURES

In the 8 high-quality trials (40 886 individuals), the pooled RR for any dose of vitamin D preventing hip fractures was 0.91 (95% CI, 0.78-1.05). However, heterogeneity in results was seen among studies (Q test: P = .08).

After stratifying trials by received dose, heterogeneity was resolved. For the 3 high-quality trials (9014 individuals) on a received low dose of less than 400 IU/d of vitamin D (340-380 IU; all using cholecalciferol), the pooled RR was 1.09 (95% CI, 0.90-1.32; Q test: P = .81) (**Table 6**).

For the 5 trials with a higher received dose of more than 400 IU/d (482-770 IU; 31 872 individuals) (**Table 7**), the pooled RR was 0.82 (95% CI, 0.69-0.97; Q test: P = .18).

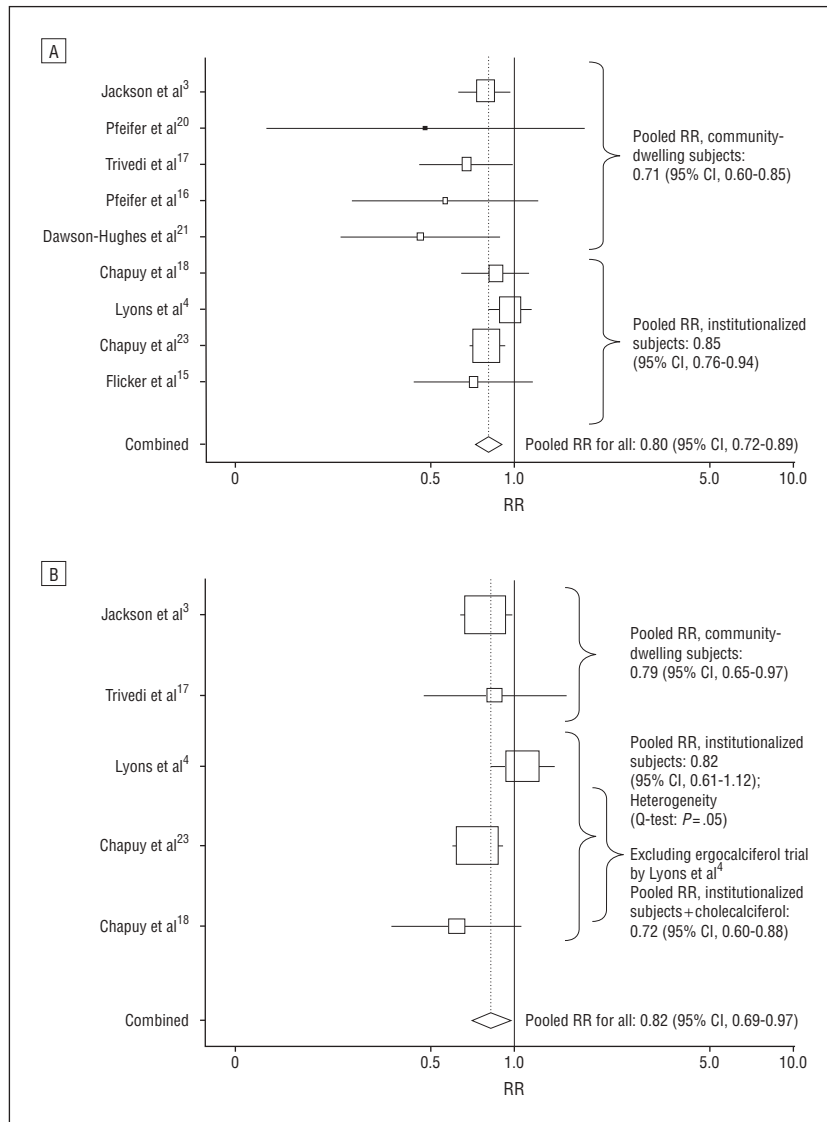


Figure 2. Nonvertebral and hip fracture reduction. Squares represent relative risks (RRs), and the size of squares is proportional to the size of the higher-dose supplemental vitamin D trials. Error bars represent 95% confidence intervals (CIs). Trials are sorted by type of dwelling. Including 9 trials, the pooled RR for any nonvertebral fractures was 0.80 (95% CI, 0.72-0.89; n=33 265 in panel A) and the pooled RR for hip fracture, including 5 trials, was 0.82 (95% CI, 0.69-0.97; n=31 872 in panel B). A, Nonvertebral fracture reduction was significant among community-dwelling (-29%) and institutionalized older individuals (-15%). B, Hip fracture reduction was significant among community-dwelling older individuals (-21%) and among institutionalized older individuals receiving cholecalciferol (-28%). To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

Thus, the higher dose of vitamin D reduced hip fracture risk by 18% (Figure 2B). The pooled risk difference for the higher received dose was 0.60% (0.23%-0.96%; $P=.02$), so the NNT was 168 (95% CI, 104-440) for 12 to 84 months.

In meta-regression analyses, a greater reduction in hip fractures was seen both with higher received dose ($P=.07$; Figure 4A) and higher achieved 25-hydroxyvitamin D levels in the treatment group ($P=.01$; Figure 4B). Owing to the smaller number of trials with a hip fracture end

point, subgroup analyses were limited because there was only 1 trial using ergocalciferol at a higher dose,⁴ 1 trial among individuals 65 to 74 years of age,³ 1 trial among men,¹⁷ and 2 trials using vitamin D alone^{4,17} (Table 7).

SENSITIVITY ANALYSES FOR HIP FRACTURE PREVENTION

For any received dose, after adding 2 open study design trials to the 8 double-blinded trials (47 917 individuals), the pooled RR was 0.92 (95% CI, 0.80-1.06), but variation among

studies remained significant (Q test: $P=.10$).

For the higher received dose, after adding 2 open study design trials to the 5 double-blinded trials (38 903 individuals), the pooled RR was 0.84 (95% CI, 0.71-0.99; Q test: $P=.17$; Table 7; higher-dose open study design trials are summarized in Table 8). For hip fractures, there were no lower-dose trials with an open study design.

1- α -HYDROXYLATED VITAMIN D AND NONVERTEBRAL FRACTURE PREVENTION

Table 9 shows characteristics of 7 RCTs that were included in the analysis for 1- α -hydroxylated vitamin D.³²⁻³⁸ None of the trials reported separate data for hip fractures. The 7 trials included 1484 individuals, all 65 to 74 years of age and 99.7% of whom were women.

The pooled RR for any type of 1- α -hydroxylated vitamin D preventing nonvertebral fractures compared with placebo or calcium was 0.58 (95% CI, 0.37-0.92), similar to the RR for a higher dose of supplemental vitamin D in the same age group (Table 4 and Table 10; the ratio of the 2 effect sizes: pooled RR of supplemental vitamin D to pooled RR of 1- α -hydroxylated vitamin D=0.67/0.58=1.16; 95% CI, 0.44-3.03).

COMMENT

In this meta-analysis of 12 double-blinded trials among individuals aged 65 years or older, the antifracture efficacy of supplemental vitamin D increased significantly with higher received dose or higher achieved 25-hydroxyvitamin D levels for any nonvertebral fractures and for hip fractures. No fracture reduction was observed for a received dose of 400 IU/d or less, whereas a higher received dose of 482 to 770 IU/d of supplemental vitamin D reduced nonvertebral fractures by 20% and hip fractures by 18%. Subgroup analyses for the prevention of nonvertebral fractures with the higher received dose suggested possibly better fracture reduction with cholecalciferol compared with ergocalciferol, whereas additional calcium did

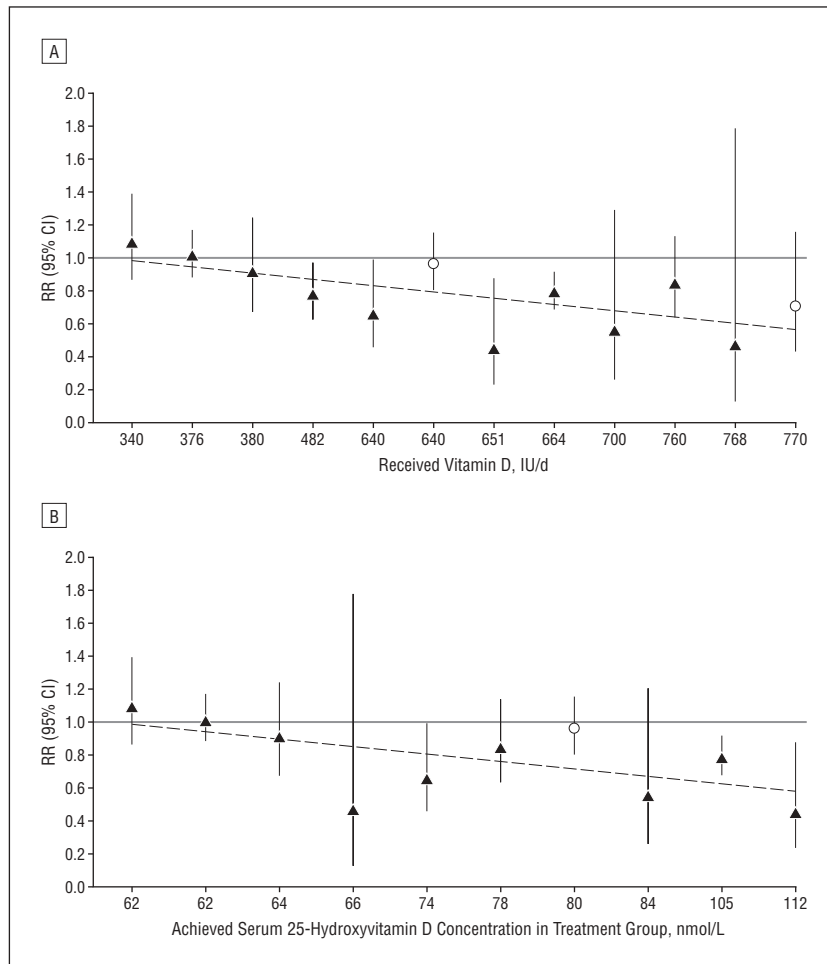


Figure 3. Nonvertebral fracture prevention by received dose and achieved 25-hydroxyvitamin D levels in treatment group. Triangles indicate trials with cholecalciferol; circles, trials with ergocalciferol. The solid curves indicate the relative risk (RR) of 1.0; the dashed curves indicate a trend line through the point estimates of all trials (RRs of individual trials). All 12 high-quality trials were included for the received dose metaregression (n=42 279 individuals). For achieved 25-hydroxyvitamin D levels 2 trials^{3,15} did not provide serum 25-hydroxyvitamin D levels measured in the study population during the trial period. For any nonvertebral fractures, antifracture efficacy increased significantly with higher received dose (metaregression: $\beta = -0.001$; $P = .003$) and higher achieved 25-hydroxyvitamin D levels (metaregression: $\beta = -0.005$; $P = .04$). A, Data points and represented trial from left to right: 340 IU, Lips et al²²; 376 IU/d, Grant et al²; 380 IU/d, Meyer et al¹⁹; 482 IU/d, Jackson et al⁹ (study medication plus personal intake); 640 IU/d (cholecalciferol), Trivedi et al¹⁷; 640 IU/d (ergocalciferol), Lyons et al⁴; 651 IU/d, Dawson-Hughes et al²¹; 664 IU/d, Chapuy et al²³; 700 IU/d, Pfeifer et al¹⁶; 760 IU/d, Chapuy et al¹⁸; 768 IU/d, Pfeifer et al²⁰; 770 IU/d (ergocalciferol), Flicker et al.¹⁵ B, Data points and represented trial from left to right: 62 nmol/L, Lips et al²²; 62 nmol/L, Grant et al²; 64 nmol/L, Meyer et al¹⁹; 66 nmol/L, Pfeifer et al²⁰; 74 nmol/L, Trivedi et al¹⁷; 78 nmol/L, Chapuy et al¹⁸; 80 nmol/L, Lyons et al⁴; 84 nmol/L, Pfeifer et al¹⁶; 105 nmol/L, Chapuy et al²³; 112 nmol/L, Dawson-Hughes et al.²¹ To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496. CI indicates confidence interval.

not further improve antifracture efficacy. Nonvertebral fracture reduction with the higher received dose was significant among all subgroups by age and dwelling, including younger individuals aged 65 to 74 years and those living in the community (see Table 4 for P values).

In August 2007, a review and meta-analysis⁵ commissioned by the US Department of Health and Human Services (DHHS) addressed the effect of vitamin D supplementation on all fractures in postmenopausal women and men aged 50 years or older. The pooled results for all fractures included 10 double-blinded and 3 open study design trials (n=58 712) and did not support a significant reduction of fractures with vitamin D (pooled odds ratio, 0.90; 95% CI, 0.81-1.02). The report⁵ suggested that the benefit of vitamin D may depend on additional calcium and may be primarily seen in institutionalized individuals, which is consistent with the meta-analysis of Boonen et al.⁶ However, in both reports,^{5,6} heterogeneity by dose may have been missed owing to the inclusion of open study design trials plus a dose evaluation that did not incorporate adherence. Biologically, the exclusion of heterogeneity by dose seems implausible even if a formal test of heterogeneity is not statistically significant.

In our meta-analysis, the dose of vitamin D and achieved 25-hydroxyvitamin D levels were identified as important sources of variation in the antifracture efficacy of supplemental vitamin D. Our findings confirm the findings of an earlier 2005 primary prevention meta-analysis¹² after including 5 additional

Table 5. Trials With Higher Received Dose for Nonvertebral Fracture Prevention With Open Study Design and Excluded From the Primary Analysis

Source and Type of Vitamin D Supplement	Received Dose = Treatment Dose × Adherence, IU/d	Year	No./Total Treated	No./Total Control	Effect RR (95% CI)	Total No.
Porthouse et al ¹ (cholecalciferol)	480	2005	58/1321	91/1993	0.962 (0.697-1.327)	3314
Law et al ²⁴ (ergocalciferol)	1100	2006	64/1762	51/1955	1.392 (0.971-1.997)	3717
Harwood et al ²⁵ (cholecalciferol)	800	2004	3/39	5/37	0.569 (0.148-2.185)	76
Pooled result for 3 HD OSD trials (these trials were included in the sensitivity analysis in Table 1 ^a)	Pooled		125/3122	147/3985	1.10 (0.78-1.55)	7107

Abbreviations: CI, confidence interval; HD, higher dose; OSD, open study design; RR, relative risk.

^aThere was a greater than 10% reduction in nonvertebral fractures, and the P value for the Q test was .20.

Table 6. Primary Pooled Analysis for a Lower Received Dose of Supplemental Vitamin D (340-380 IU/d) and the Prevention of Hip Fractures

Source and Type of Vitamin D Supplement	Received Dose = Treatment Dose × Adherence, IU/d	Year	No./Total Treated	No./Total Control	Effect RR (95% CI)	Total No.
Grant et al ² (cholecalciferol)	376	2005	93/2649	90/2643	1.031 (0.776-1.371)	5292
Meyer et al ¹⁹ (ergocalciferol)	380	2002	50/569	47/575	1.075 (0.734-1.574)	1144
Lips ³¹ (ergocalciferol)	340	1996	58/1291	48/1287	1.205 (0.829-1.751)	2578
Pooled results for 3 LD DB trials (there were no OSD trials for the LD) ^a		Pooled	201/4509	185/4505	1.09 (0.90-1.32)	9014

Abbreviations: CI, confidence interval; DB, double-blind; LD, lower-dose; OSD, open study design; RR, relative risk.

^aThere was a greater than 9% reduction in hip fractures, and the *P* value for the *Q* test was .81.

Table 7. Primary Pooled Analysis for a Higher Received Dose of Supplemental Vitamin D (482-770 IU/d) and the Prevention of Hip Fractures

Source and Type of Vitamin D Supplement	Hip FX Reduction, %	Received Dose = Treatment Dose × Adherence, IU/d ^a	Year	No./Total Treated	No./Total Control	Effect RR (95% CI)	Total No.	<i>P</i> Value, <i>Q</i> Test ^a
Pooled analyses of all HD DB trials								
Lyons et al ⁴ (ergocalciferol)		640	2007	112/1725	104/1715	1.071 (0.827-1.386)	3440	
Jackson et al ³ (cholecalciferol) (WHI trial, subgroup of women ≥60 y)		482	2006	146/11 448	186/11 412	0.782 (0.631-0.970)	22 860	
Trivedi et al ¹⁷ (cholecalciferol)		640	2003	21/1345	24/1341	0.85 (0.47-1.53)	2686	
Chapuy et al ¹⁸ (cholecalciferol)		760	2002	27/393	21/190	0.622 (0.362-1.068)	583	
Chapuy et al ²³ (cholecalciferol)		664	1994	137/1176	178/1127	0.738 (0.6-0.907)	2303	
Pooled result for all 5 HD DB trials	-18		Pooled	443/16 087	513/15 785	0.82 (0.69-0.97)	31 872	.18
Primary subgroup analyses for HD DB trials with > 1 trial per subgroup								
Cholecalciferol ^{3,17,18,23}	25		Pooled	331/14 362	409/14 070	0.75 (0.66-0.87)	28 432	.83
Age > 75 y ^{4,17,18,23}	-17		Pooled	297/4639	327/4373	0.83 (0.65-1.06)	9012	.12
Excluding ergocalciferol trial from those aged >75 y	-27		Pooled	185/2914	223/2658	0.73 (0.61-0.88)	5572	.74
Institutionalized persons ^{4,18,23}	-18		Pooled	276/3294	303/3032	0.82 (0.61-1.12)	6326	.05
Excluding ergocalciferol trial from institutionalized persons	-28		Pooled	164/1569	199/1317	0.72 (0.60-0.88)	2886	.56
Community-dwelling individuals (Jackson et al, ³ Trivedi et al ¹⁷)	-21		Pooled	167/12 793	210/12 753	0.79 (0.65-0.97)	25 546	.80
Vitamin D with calcium ^b (Jackson et al, ³ Chapuy et al ^{18,23})	-25		Pooled	310/13 017	385/12 729	0.75 (0.65-0.86)	25 746	.73
Sensitivity analysis: adding 2 HD OSD trials (Porthouse et al, ¹ Law et al ²⁴) to the pooled result of the 5 HD DB trials	-16		Pooled	475/19 170	550/19 733	0.84 (0.71-0.99)	38 903	.17

Abbreviations: DB, double-blind; FX, fracture; HD, higher-dose; OSD, open study design; RR, relative risk; WHI, Women's Health Initiative.

^a*Q* test: *P* < .99 indicates heterogeneity.

^bLimited data for vitamin D without calcium: 1 ergocalciferol trial; 1 trial not powered for hip fracture reduction.

high-quality, double-blinded trials (2005: total n=9820; 2008: total n=42 279). New to these analyses is the primary use of received dose (dose × adherence) as opposed to treatment dose. The received dose allows assessment of antifracture efficacy by a dose that accounts for the low adherence in several recent large trials.¹⁻³ The consistency of our results for both received dose and achieved 25-hydroxyvitamin D levels in the treatment group across all 12 masked trials lends support to the presence of a dose-response relationship between supplemental vitamin D and fracture reduction. Despite the well-documented inter-

laboratory and interassay variation for 25-hydroxyvitamin D,^{39,40} the consistency in the dose-response analyses for both received dose and achieved 25-hydroxyvitamin D level also lends support to our use of 25-hydroxyvitamin D levels from different trials.

Confirming our findings with some limitations, Tang et al⁷ suggested in their meta-analysis that, together with calcium supplementation, a daily intake of at least 800 IU of vitamin D increases total fracture reduction by 3% compared with daily doses of vitamin D of less than 800 IU. However, with their focus on calcium, Tang et al⁷ excluded 4

high-quality trials of vitamin D alone compared with placebo.^{4,17,19,22}

The pooled RR reduction was 21% with or without additional calcium for the higher dose of vitamin D. Previous meta-analyses may have missed this finding owing to their analyses including all doses of vitamin D. Physiologically, the calcium-sparing effect of vitamin D may explain why we did not see an additional benefit of calcium supplementation at a higher dose of vitamin D.^{39,40} Similarly, our findings suggest that, at a sufficiently high dose, vitamin D benefits are not limited to institutionalized and frail individuals, as suggested by the DHHS report.⁵

To our knowledge, the type of supplemental vitamin D was not addressed previously. With a higher received dose, the pooled effect of cho-

lecalciferol was significant with 23% fracture reduction, whereas the pooled effect with ergocalciferol was not significant with 10% fracture re-

duction. One explanation may be that ergocalciferol is less potent than cholecalciferol in maintaining 25-hydroxyvitamin D levels, as suggested by 2 direct comparison trials,^{13,41} although this was challenged by a recent trial⁴² showing similar potency of daily ergocalciferol and daily cholecalciferol. Another explanation may be dosing frequency in that 1 trial⁴ of 2 ergocalciferol trials^{4,15} dosed intermittently, which may have decreased efficiency. However, the higher-dose cholecalciferol supplement given either daily or intermittently did reduce fractures. Thus, future research efforts may wish to simply focus on higher doses of cholecalciferol.

We performed sensitivity analyses, including 4 open study design trials.^{1,24-26} This increased the number of trials to 16 and the number of individuals to 56 459 for nonvertebral fractures. The pooled RR risk from these 16 trials was 0.88 (95% CI, 0.80-0.97), suggesting that with all evidence considered, supplemental vitamin D should reduce nonvertebral fracture risk by 12% among individuals 65 years or older. However, the study variation was larger than expected for the pooled result from all 16 trials. Even within the higher received dose, adding 3 open study design trials to the 9 double-blinded trials, variation was larger than expected (pooled RR, 0.83; 95% CI, 0.74-0.95) supporting our predefined strategy of focusing on fracture efficacy from double-blinded trials.

Based on the pooled results, 1- α -hydroxylated vitamin D reduced nonvertebral fractures by 42% and among individuals of comparable age a higher dose of supplemental cholecalciferol reduced these fractures by 33%. Thus, although the number of stud-

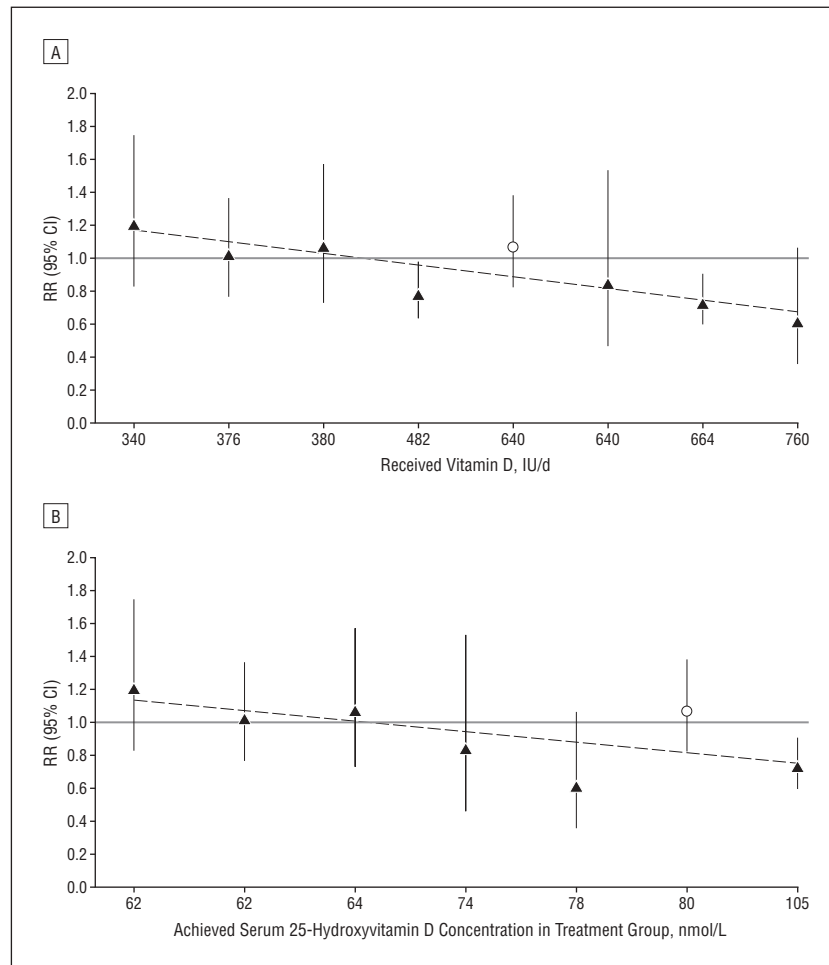


Figure 4. Hip fracture prevention by received dose and achieved 25-hydroxyvitamin D levels in the treatment groups. Triangles indicate trials with cholecalciferol; circles, trials with ergocalciferol. The solid curve indicates the relative risk (RR) of 1.0; the dashed curve, a trend line through the point estimates of all trials (RRs of individual trials). All 8 high-quality trials with a hip fracture end point were included for the received dose metaregression (n=40 886). For achieved 25-hydroxyvitamin D levels, 1 trial³ did not provide serum 25-hydroxyvitamin D levels measured in the study population during the trial period. For hip fractures, antifracture efficacy increased significantly with higher received dose (metaregression: $\beta = -0.001$; $P = .07$) and higher achieved 25-hydroxyvitamin D levels (metaregression: $\beta = -0.009$; $P = .01$). A, Data points and represented trial from left to right: 340 IU/d, Lips et al²²; 376 IU/d, Grant et al²; 380 IU/d, Meyer et al¹⁹; 482 IU/d, Jackson et al³ (study medication plus personal intake); 640 IU/d (ergocalciferol), Lyons et al⁴; 640 IU/d (cholecalciferol), Trivedi et al¹⁷; 664 IU/d, Chapuy et al²³; 760 IU/d, Chapuy et al.¹⁸ B, Data points and represented trial from left to right: 62 nmol/L, Lips et al²²; 62 nmol/L, Grant et al²; 64 nmol/L, Meyer et al¹⁹; 74 nmol/L, Trivedi et al¹⁷; 78 nmol/L, Chapuy et al¹⁸; 80 nmol/L, Lyons et al⁴; 105 nmol/L, Chapuy et al.²³ To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496. CI indicates confidence interval.

Table 8. Trials With Higher Received Dose for Hip Fracture Prevention With Open Study Design (OSD) and Excluded From the Primary Analysis

Source and Type of Vitamin D Supplement	Received Dose = Treatment Dose \times Adherence, IU/d	Year	No./Total Treated	No./Total Control	Effect RR (95% CI)	Total No.
Porthouse et al ¹ (cholecalciferol)	480	2005	8/1321	17/1993	0.710 (0.309-1.633)	3314
Law et al ²⁴ (ergocalciferol)	1100	2006	24/1762	20/1955	1.331 (0.740-2.397)	3717
Pooled result for 2 HD OSD trials these trials were included in the sensitivity analysis in Table 7 ^a		Pooled	32/3083	37/3948	1.05 (0.57-1.90)	7031

Abbreviations: CI, confidence interval; HD, higher-dose; RR, relative risk.

^aThe reduction in hip fractures was 5% reduction in hip fractures, and the *Q* test *P* value was 0.23.

Table 9. 1- α -Hydroxylated Vitamin D

Source	Participants, No.	Treatment/d	Dwelling	Age, Mean (SD), y	Duration, mo	25-Hydroxyvitamin D Levels, nmol/L ^a	
						Treatment Group	Control Group
Matsumoto et al ³²	219 (215 women, 4 men)	0.5 or 0.75 or 1 μ g of ED-71; all subjects received cholecalciferol; if 25-hydroxyvitamin D level <50, 400 IU; if >50, 200 IU vs placebo	CD (with OP)	67 (7)	12	All ED-71 groups: 42.8 (14.3) to 68 (from graph ³²) at 3-mo follow-up	43.1 (14.2) to 68 at 3-mo follow-up (from graph)
Gallagher et al ³³	246 women	0.5 μ g of calcitriol vs placebo	CD	71 (4)	36	78 (21.6), to 60.7 at 36-mo follow-up (δ change: -17.3 [19.7])	80.5 (27.4) to 63.2 at 36-mo follow-up (δ change: -17.3 [20.5])
Ishida and Kawai ³⁴	132 women (only control and 1- α -calcidiol group)	1 μ g of 1- α -calcidiol vs no treatment; OSD	CD (with OP)	70 (10)	24	ND	ND
Shikari et al ³⁵	113 women	0.75 μ g of 1- α -calcidiol + 300 mg of calcium (calcium lactate) vs placebo + 300 mg of calcium	CD (with OP)	71 (6)	24	ND	ND
Menczel et al ³⁶	66 women	0.5 μ g of 1- α -calcidiol + 1000 mg of calcium (calcium carbonate/lactogluconate) vs placebo + 1000 mg of calcium	CD (with OP)	67 (8)	36	ND	ND
Tilyard et al ³⁷	622 women	0.5 μ g of calcitriol vs 1000 mg of calcium (calcium gluconate) OSD	CD (with OP)	64 (7)	36	ND	ND
Ott and Chestnut ³⁸	86 women	0.5 μ g of calcitriol, followed by dose adjustment (to 2 μ g/d, mean intake was 0.43 μ g) + mean calcium intake 1 g (diet + supplement) vs placebo + mean calcium intake 1 g	CD (with OP)	Control: 67.1 (1.2), treatment group: 67.9 (1.0)	24	Only at baseline, 66.8 (4.8)	Only at baseline, 65.8 (6)

Abbreviations: CD, community-dwelling; ED-71, 1- α ,25-dihydroxy-2 β (3-hydroxypropoxy); ND, not determined in the trial population during the course of the trial; OP, osteoporosis; OSD, open study design.

Conventional unit conversion factor: To convert 25-hydroxyvitamin D to nanograms per milliliter, divide by 2,496.

^aValues in parentheses or brackets indicate SD of the preceding mean.

Table 10. Primary Pooled Analysis for 1- α -Hydroxylated Vitamin D and the Prevention of Nonvertebral Fractures (Ages 65-74 Years)

Source and Vitamin D Supplement	Year	No./Total Treated	No./Total Control	Effect RR (95% CI)	Total No.
Matsumoto et al ³² (ED-71 + 200-400 D ₃)	2005	4/166	1/53	1.277 (0.146-11.137)	219
Ishida and Kawai ³⁴ (1- α -hydroxyvitamin D ₃)	2004	1/66	3/66	0.333 (0.04-2.801)	132
Gallagher et al ³³ (1,25-dihydroxyvitamin D ₃)	2001	6/123	13/123	0.462 (0.186-1.145)	246
Shiraki et al ³⁵ (1- α -hydroxyvitamin D ₃)	1996	0/37	3/42	0.162 (0.009-3.03)	79
Menczel et al ³⁶ (1- α -hydroxyvitamin D ₃)	1994	2/24	5/42	0.7 (0.148-3.311)	66
Tilyard et al ³⁷ (1,25-dihydroxyvitamin D ₃)	1992	11/314	22/308	0.49 (0.246-0.978)	622
Ott and Chestnut ³⁸ (1,25-dihydroxyvitamin D ₃)	1989	5/41	2/42	2.56 (0.559-11.733)	83
Pooled result for all 7 trials with 1- α -hydroxylated vitamin D ^a		29/771	49/676	0.58 (0.37-0.92)	1447

Abbreviations: CI, confidence interval; ED-71, 1- α ,25-dihydroxy-2 β (3-hydroxypropoxy); RR, relative risk.

^aThe reduction in nonvertebral fractures was -42%, and the *P* value *Q* test score was .46.

ies for 1- α -hydroxylated vitamin D was small and differences in efficacy could not be excluded, our analyses do not support prevention of nonvertebral fractures with 1- α -hydroxylated vitamin D owing to its higher cost and higher risk profile compared with an adequate dose of supplemental vitamin D. Importantly, the efficacy of 1- α -hydrox-

ylated vitamin D adds to the evidence that improved vitamin D status will reduce fracture risk.

In conclusion, a higher received dose of supplemental vitamin D (482-770 IU/d) should reduce nonvertebral fractures by at least 20% and hip fractures by at least 18%. The greater fracture reduction with a higher received dose or higher achieved 25-

hydroxyvitamin D levels for both any nonvertebral fractures and hip fractures suggests that higher doses of vitamin D should be explored in future research to optimize antifracture efficacy. Also, it is possible that greater benefits may be achieved with earlier initiation of vitamin D supplementation and longer duration of use. Our results do not support use of low-

dose vitamin D with or without calcium in the prevention of fractures among older individuals.

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