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ORIGINAL ARTICLE

A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention

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ABSTRACT

BACKGROUND

The results of meta-analyses examining the relationship between vitamin D supplementation and fracture reduction have been inconsistent.

METHODS

We pooled participant-level data from 11 double-blind, randomized, controlled trials of oral vitamin D supplementation (daily, weekly, or every 4 months), with or without calcium, as compared with placebo or calcium alone in persons 65 years of age or older. Primary end points were the incidence of hip and any nonvertebral fractures according to Cox regression analyses, with adjustment for age group, sex, type of dwelling, and study. Our primary aim was to compare data from quartiles of actual intake of vitamin D (including each individual participant's adherence to the treatment and supplement use outside the study protocol) in the treatment groups of all trials with data from the control groups.

RESULTS

We included 31,022 persons (mean age, 76 years; 91% women) with 1111 incident hip fractures and 3770 nonvertebral fractures. Participants who were randomly assigned to receive vitamin D, as compared with those assigned to control groups, had a nonsignificant 10% reduction in the risk of hip fracture (hazard ratio, 0.90; 95% confidence interval [CI], 0.80 to 1.01) and a 7% reduction in the risk of nonvertebral fracture (hazard ratio, 0.93; 95% CI, 0.87 to 0.99). By quartiles of actual intake, reduction in the risk of fracture was shown only at the highest intake level (median, 800 IU daily; range, 792 to 2000), with a 30% reduction in the risk of hip fracture (hazard ratio, 0.70; 95% CI, 0.58 to 0.86) and a 14% reduction in the risk of any nonvertebral fracture (hazard ratio, 0.86; 95% CI, 0.76 to 0.96). Benefits at the highest level of vitamin D intake were fairly consistent across subgroups defined by age group, type of dwelling, baseline 25-hydroxyvitamin D level, and additional calcium intake.

CONCLUSIONS

High-dose vitamin D supplementation (≥800 IU daily) was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older. (Funded by the Swiss National Foundations and others.)

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Approximately 75% of fractures occur in people 65 years of age or older.[1] By 2050, the worldwide incidence of hip fractures is expected to increase by 240% among women and 310% among men.[2]

One strategy to prevent fractures in this population might be universal vitamin D supplementation. However, the results of several study level meta-analyses and one pooled participant-level analysis do not agree. Although one trial-level meta-analysis of double-blind, randomized, controlled trials suggested an 18% reduction in the incidence of hip fracture and a 20% reduction in the incidence of any nonvertebral fracture at a received dose of no less than 482 IU of vitamin D per day,[3] three study-level meta-analyses[4-6] and one pooled analysis of participant-level data[7] from open-design and blinded trials suggested that vitamin D may have no effect on total fractures[4] or may reduce hip fracture by 7 to 16%, if combined with calcium supplementation, regardless of the dose of vitamin D.[4-7] The discordant findings may be explained, in part, by differences in the criteria for including trials in the analyses, with respect to blinding, vitamin D formulation (oral vs. injectable), or accommodations for nonadherence. Our analysis was designed to estimate the effects of vitamin D supplementation according to the actual intake of each participant, rather than simply the dose to which the participant was randomly assigned.

METHODS

POOLED STUDIES

We attempted to identify all double-blind, randomized, controlled trials involving persons 65 years of age or older that evaluated oral vitamin D supplementation, alone or in combination with calcium, as compared with a control (placebo or calcium alone); that included data on low-trauma fractures; and that were published on or before August 31, 2011. We conducted searches of Medline, the Cochrane Central Register of Controlled Trials, and Embase. Of 14 qualifying trials, 2 were unavailable (lost files), both of which showed a significant reduction in fracture risk at a treatment dose that was equivalent to 800 IU of vitamin D per day.[8,9]

We included 12 studies (with a total of 33,277 participants) and received the source data for 30,011 participants 65 years of age or older from 11 trials, including type and date of fracture and dates of study entry and exit. For the 1 study of the 12 (with 3266 participants) for which events were identified by month,[10] we made the assumption that events had occurred in mid-month. One study (with 2255 participants) provided the dose once yearly[11]; in the other 11 studies (with 31,022 participants), the dose of vitamin D was given daily,[10,12-19] weekly,[20] or every 4 months.[21] The RECORD (Randomised Evaluation of Calcium or Vitamin D) trial, which had a factorial design, was split into study A (vitamin D vs. placebo) and study B (vitamin D plus calcium vs. calcium alone) trials.[16] The work was done collegially with no limitations on confidentiality, except the removal of patient identifiers. All the included studies required that participants provide written informed consent.

VARIABLES

Because adherence to the study treatment was documented differently in the published trials, we incorporated data on adherence according to a predefined protocol. For 7 trials, data on adherence were available at the participant level. For the 4 trials without participant-level reports of adherence, we applied the mean value for adherence (80%[14,19,21] or 95%[15]) of that trial to the individual participant doses. Vitamin D supplementation outside the study protocol was permitted in 5 of 11 trials,[14-17,21] 3 of which provided participant-level data that we incorporated in the assessment of actual intake in the primary analysis.[15-17] The other 2 trials either allowed up to 200 IU[14] of vitamin D per day or included persons if they had a vitamin D intake of less than 400 IU per day,[21] without providing participant-level information on additional intake. Data on sex and type of dwelling were available for all participants from all 12 studies. For 1 of the 12 studies,[10] we did not have participant-level data on age, so we applied the cohort average to each participant. Fracture events in all trials were verified by a review of medical records. We excluded vertebral fractures because they were not documented systematically in any of the trials.

PRIMARY ANALYSES

The primary end points were the risks of hip fracture and any nonvertebral fracture. The primary analyses compared the actual intake of vitamin D supplementation, in quartiles, between

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treated participants and controls (with actual intake calculated as the assigned treatment dose plus any additional supplemental dose, with adjustment for adherence). In a sensitivity analysis, we excluded any additional supplemental dose outside the study protocol from the calculation of actual intake.

To establish a bridge to earlier meta-analyses and explain the additional information gained by the comparison of actual-intake amounts, we included two additional analyses: an intention-to-treat analysis that compared participants who had been randomly assigned to receive vitamin D or a control, and an analysis according to treatment dose that maintained the assigned randomization status (vitamin D vs. control) and the assigned treatment dose (≤400 IU per day vs. >400 IU per day). All analyses were controlled for study, sex, age group, and type of dwelling.

INTERNAL VALIDATION ANALYSIS

We performed an internal validation study to compare the highest quartile of actual intake of vitamin D with the lowest quartile, regardless of the randomized study-group assignment, including controls. Furthermore, with available baseline measurements of 25-hydroxyvitamin D from a subset of 4383 participants, we performed a threshold assessment of the association between the baseline quartile of 25-hydroxyvitamin D level and the prospective risk of hip fracture or any nonvertebral fracture, independently of study group, age group, sex, type of dwelling, and study.

SENSITIVITY ANALYSES

In sensitivity analyses, we included 1 additional trial, by Sanders et al.,[11] because it used a different treatment regimen, consisting of an annual high dose (500,000 IU) of vitamin D, and we added 100 IU of vitamin D to the actual-intake amount for participants in the 2 trials in which a small dose of additional vitamin D was allowed but not documented.[14,21] To extend our participant-level data to the 2 randomized, controlled trials (by Chapuy et al.[9] and Trivedi et al.[8]) for which the source data were not available, we performed a trial-level meta-analysis that combined our pooled findings from the 11 randomized, controlled trials with the trial-level findings of these 2 trials in a random-effects meta-analysis.

SUBGROUP ANALYSES

In predefined subgroup analyses we assessed the effect of actual intake of vitamin D according to age group (younger than 75 years, 75 to 84 years, or 85 years or older), type of dwelling (community dwelling vs. institution), baseline level of 25-hydroxyvitamin D (<30 nmol per liter vs. ≥30 nmol per liter), and additional dose of a calcium supplement in the treatment group (<1000 mg per day vs. ≥1000 mg per day).

STATISTICAL ANALYSIS

After establishing homogeneity among the 11 individual trials for both fracture end points overall and at the actual-intake quartile level, we pooled the individual participant-level data and used Cox proportional-hazards regression analysis to assess the incidence of hip fracture or any nonvertebral fracture. For the primary analyses, we performed only one analysis for hip fracture and one analysis for nonvertebral fracture in which we compared all quartiles of actual intake to the control group, and it was our a priori expectation that the effect would be greatest at the highest dose. In the nonprimary analyses, because of the potential for false positive results due to multiple testing, we used a P value of 0.0125 to indicate significance. Since four subgroups were considered for each of two types of fracture outcome, an interaction term for the highest actual intake level of vitamin D and each subgroup was added to the model, and a Bonferroni-adjusted P value of less than 0.00625 was required for significance.

All analyses were adjusted for study, age group, sex, and type of dwelling; however, the analyses were not adjusted for calcium supplementation, owing to colinearity between doses of vitamin D and calcium supplementation. All reported P values are two-sided, and the proportional-hazards assumptions were satisfied for the primary analyses for both hip fracture and any nonvertebral fracture. Additional frailty analyses[22] were carried out to ensure that the results were robust with respect to the allowance specified for correlation within the study. The results of these analyses are not reported, since they remained consistent and significant. Analyses were conducted with SAS software, version 9.2 (SAS Institute).

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Table 1. Baseline Characteristics of the Study Populations in 11 Double-Blind, Randomized, Controlled Trials, According to Quartile of Actual Intake of Vitamin D among Treated Participants, as Compared with Controls.*

Variable	Control Group (N=15,495)	Treatment-Group Quartile (N=15,527)			
		0–360 IU/day (N=3935)	361–637 IU/day (N=3836)	638–791 IU/day (N=3790)	792–2000 IU/day (N=3966)
Median dose — IU/day		340	547	693	800
Age					
Mean — yr	76.4±7.5	75.2±6.4	72.5±6.1	78.0±8.8	79.8±6.2
65–74 yr — %	48.5	53.0	72.0	43.9	25.7
75–84 yr — %	38.7	38.0	22.2	29.0	65.6
≥85 yr — %	12.8	9.0	5.8	27.1	8.7
Female sex — no. (%)	14,082 (90.9)	3510 (89.2)	3696 (96.4)	3216 (84.9)	3670 (92.5)
Living in institution — no. (%)	4,760 (30.7)	573 (14.6)	380 (9.9)	1970 (52.0)	1863 (47.0)
Supplement					
Vitamin D, actual intake — IU/day	100±160	290±98	496±81	692±41	846±180
Calcium, actual intake — mg/day	84±258	396±393	697±282	403±436	830±460
25-Hydroxyvitamin D level					
No. of participants	2220	440	679	632	412
Mean value — nmol/liter	47±24	41±24	48±21	54±29	43±20
Pooled studies — no.	11	5	5	8	5

* Plus–minus values are means ±SD. In the treatment group, there were significant differences in age group, sex, and percentage of participants living in institutions across the quartiles of actual intake of vitamin D. The range of actual intake of vitamin D in the highest quartile was unchanged when the one trial with a treatment dose of 2000 IU per day[13] was excluded.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

The clinical characteristics of 31,022 participants from 11 trials are shown in Table 1. Of 4383 participants with baseline measurements of 25-hydroxyvitamin D, 24% had levels of less than 30 nmol per liter, 62% had levels of less than 50 nmol per liter, and 88% had levels of less than 75 nmol per liter. Appendix 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, shows the assigned treatment doses and actual-intake amounts in each trial.

PRIMARY ANALYSES

The intention-to-treat analysis showed a nonsignificant 10% reduction in the risk of hip fracture (hazard ratio, 0.90; 95% confidence interval [CI], 0.80 to 1.01), which did not differ according to assigned treatment dose. On the basis of our primary comparison of actual intake, however, there was a significant 30% reduction in the incidence of hip fracture at the highest actual-intake level (792 to 2000 IU per day) in treated participants, as compared with controls (Table 2), with a similar finding for the adherence-adjusted dose, which did not include supplements outside the study protocol (29% reduction). Notably, there was no reduction in the risk of hip fracture at any actual-intake level lower than 792 IU per day.

In the internal validation analysis, regardless of study assignment, the reduction in the risk of hip fracture was 30% and was significant at the highest actual-intake level (792 to 2000 IU per day), as compared with the lowest actual-intake level (0 to 360 IU per day), suggesting a dose–response relationship. Such a relationship was also suggested by the threshold assessment of hip-fracture risk according to quartile of baseline 25-hydroxyvitamin D level in the 4383 participants for whom serum measurements were available (Fig. 1A).

The intention-to-treat analysis showed a 7% overall reduction in the risk of nonvertebral frac-

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Table 2. Incidence of Fracture among 31,022 Participants, According to Vitamin D Treatment Dose and Actual Intake.*

Analysis	No. of Participants	Hip Fracture			Any Nonvertebral Fracture		
		No. of Fractures	Relative Risk (95% CI)	P Value	No. of Fractures	Relative Risk (95% CI)	P Value
Intention-to-treat analysis							
Control	15,495	586	1.00		1948	1.00	
Treatment	15,527	525	0.90 (0.80–1.01)	0.07	1822	0.93 (0.87–0.99)	0.03
Treatment-dose analysis							
Control	15,495	586	1.00		1948	1.00	
≤400 IU/day	10,111	255	0.89 (0.74–1.07)	0.20	1225	0.96 (0.89–1.05)	0.40
>400 IU/day†	5,416	270	0.91 (0.78–1.06)	0.22	597	0.89 (0.80–0.98)	0.02
Actual-intake analysis‡							
Control	15,495	586	1.00		1948	1.00	
0–360 IU/day	3,935	100	1.00 (0.79–1.26)	0.99	425	0.96 (0.86–1.07)	0.44
361–637 IU/day	3,836	110	1.03 (0.83–1.29)	0.78	520	1.01 (0.91–1.12)	0.85
638–791 IU/day	3,790	164	1.01 (0.83–1.23)	0.92	419	0.90 (0.80–1.01)	0.08
792–2000 IU/day	3,966	151	0.70 (0.58–0.86)	<0.001	458	0.86 (0.76–0.96)	0.007
Sensitivity analysis							
Control	15,495	586	1.00		1948	1.00	
0–337 IU/day	3,353	84	1.01 (0.79–1.30)	0.91	465	1.06 (0.95–1.17)	0.32
338–360 IU/day	5,652	114	0.83 (0.66–1.05)	0.11	619	0.89 (0.80–0.98)§	0.02
361–699 IU/day	2,640	180	1.14 (0.93–1.41)	0.21	326	1.05 (0.91–1.22)	0.52
700–2000 IU/day	3,882	147	0.71 (0.58–0.87)	0.001	412	0.81 (0.72–0.91)	<0.001
Internal validation							
0–360 IU/day	18,153	639	1.00		2193	1.00	
361–637 IU/day	4,976	150	1.03 (0.84–1.26)	0.80	681	1.04 (0.95–1.15)	0.37
638–791 IU/day	3,865	168	1.02 (0.84–1.24)	0.83	431	0.92 (0.82–1.03)	0.16
792–2000 IU/day	4,028	154	0.70 (0.58–0.86)	<0.001	465	0.86 (0.77–0.97)	0.01

* All analyses were adjusted for study, age group, sex, and type of dwelling. To limit false positive results and correct for multiplicity, we used a P value of 0.0125 to indicate significance.
† All trials included doses between 700 and 2000 IU per day.
‡ Among 21,241 participants from the eight trials that used vitamin D combined with any dose of calcium supplementation, a benefit was present only at the highest actual-intake level of vitamin D.
§ In the sensitivity analysis for adherence-adjusted dose without supplements outside the study protocol, 511 participants in the Women's Health Initiative trial[17] shifted from the highest actual-intake level (792 to 2000 IU per day) and 1356 shifted from the second-highest actual-intake level (638 to 791 IU per day) to the second-lowest adherence-adjusted intake level (338 to 360 IU per day). See the Supplementary Appendix for additional information.

ture (hazard ratio, 0.93; 95% CI, 0.87 to 0.99), with no risk reduction at doses of 400 IU per day or less (hazard ratio, 0.96; 95% CI, 0.89 to 1.05), and an 11% reduction at doses higher than 400 IU per day (hazard ratio, 0.89; 95% CI, 0.80 to 0.98). In the primary comparison of actual intake, the pattern was largely the same as that observed for hip fracture (Table 2). For prevention of nonvertebral fracture, a dose–response relationship was supported by the internal validation analysis (Table 2) and by the threshold assessment of baseline 25-hydroxyvitamin D level (Fig. 1B). Primary findings at the highest actual-intake level were robust when individual trials were excluded (Appendixes 2A and 2B in the Supplementary Appendix).

SENSITIVITY ANALYSES

When we included the trial-level findings for the two trials with missing source data[8,9] (treatment doses, 800 IU and 833 IU per day) at the highest

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actual-intake level, results were unchanged for hip fracture (relative risk, 0.70; 95% CI, 0.59 to 0.84) and any nonvertebral fracture (relative risk, 0.84; 95% CI, 0.74 to 0.95). The inclusion of the trial by Sanders et al.,[11] in which a high annual dose of vitamin D was administered, attenuated the findings in the intention-to-treat analysis (Appendix 3 in the Supplementary Appendix) and at the highest actual-intake level (Appendixes 2A and 2B in the Supplementary Appendix). The results of additional sensitivity analyses were robust (data not shown), and there was homogeneity among trials at the quartile level of actual intake of vitamin D (Fig. 2A and 2B).

SUBGROUP ANALYSES

There were no significant interactions, after Bonferroni adjustment, between the highest actual intake of vitamin D and subgroups defined by age, type of dwelling, baseline level of 25-hydroxyvitamin D, and additional calcium intake (Table 3). This suggests that the effect of the highest actual intake of vitamin D was relatively consistent across these subgroups. However, reduced power, especially in the subset of participants for whom baseline levels of 25-hydroxyvitamin D were available and the subset with additional calcium intake, may have masked some true differences. There was a suggestion that the highest actual-intake level of vitamin D was less beneficial for the prevention of nonvertebral fracture in participants living in community dwellings than in those living in institutions (P=0.02), with the P value indicating a significant difference on the basis of the conventional threshold for significance but not the Bonferroni-adjusted threshold.

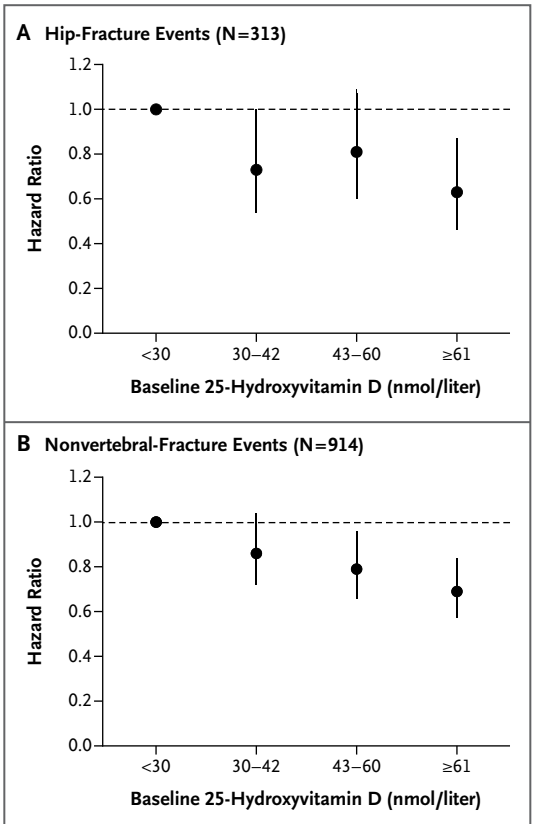


Figure 1. Threshold Assessment for the Risk of Fracture, According to Quartile of Baseline 25-Hydroxyvitamin D Level.

Panel A shows the risk of hip fracture, and Panel B the risk of any nonvertebral fracture. Among the 4383 study participants for whom data on baseline 25-hydroxyvitamin D levels were available, there were 313 hip and 914 nonvertebral fractures during follow-up. After adjustment for study, group assignment (treatment or control), age group, sex, and type of dwelling, persons 65 years of age or older with baseline serum 25-hydroxyvitamin D levels of at least 61 nmol per liter, as compared with persons with baseline levels of less than 30 nmol per liter, had a risk of hip fracture that was reduced by 37% (hazard ratio, 0.63; 95% CI, 0.46 to 0.87) and a risk of any nonvertebral fracture that was reduced by 31% (hazard ratio, 0.69; 95% CI, 0.57 to 0.84). With higher quartiles of baseline 25-hydroxyvitamin D levels, there was a significant trend toward lower risks of hip fracture (P=0.02) and any nonvertebral fracture (P<0.001). The bars indicate 95% confidence intervals.

DISCUSSION

This pooled analysis included a large participant-level data sample of double-blind, randomized, controlled trials of vitamin D supplementation that involved persons 65 years of age or older. The findings suggest that only a high intake of vitamin D leads to a significant reduction in the risk of fracture — with a 30% reduction in the risk of hip fracture and a 14% reduction in the risk of any nonvertebral fracture; this reduction is independent of the assigned treatment dose of vitamin D, age group, sex, type of dwelling, and study. Thus, it is possible that the results of typical intention-to-treat analyses of vitamin D supplementation, as replicated in this pooled analysis with a non-significant 10% reduction in the risk of hip fracture and a 7% reduction in the risk of any nonvertebral fracture, underestimate the benefit of vitamin D supplementation. Notably, the benefit at the highest actual-intake level of vitamin D was confirmed in the internal validation analysis,

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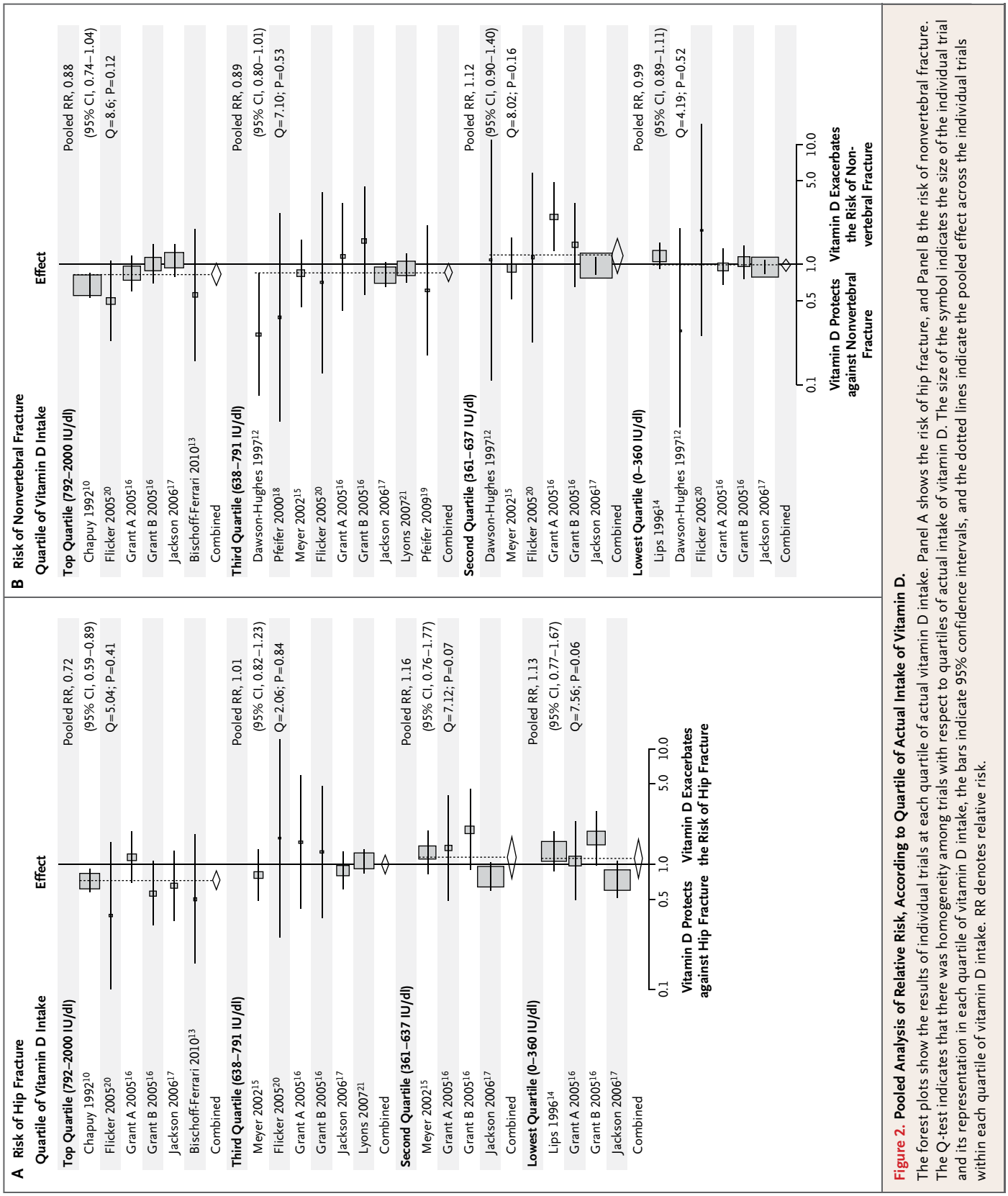


Figure 2. Pooled Analysis of Relative Risk, According to Quartile of Actual Intake of Vitamin D.

The forest plots show the results of individual trials at each quartile of actual vitamin D intake. Panel A shows the risk of hip fracture, and Panel B the risk of nonvertebral fracture. The Q-test indicates that there was homogeneity among trials with respect to quartiles of actual intake of vitamin D. The size of the symbol indicates the size of the individual trial and its representation in each quartile of vitamin D intake, the bars indicate 95% confidence intervals, and the dotted lines indicate the pooled effect across the individual trials within each quartile of vitamin D intake. RR denotes relative risk.

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Table 3. Subgroup Benefits at the Highest Actual-Intake Level of Vitamin D (792–2000 IU per Day), as Compared with Control Group.*

Subgroup	Treatment Group	Control Group	Hip Fracture				Any Nonvertebral Fracture			
			Treatment Group	Control Group	Relative Risk (95% CI)	P Value	Treatment Group	Control Group	Relative Risk (95% CI)	P Value
	no. of participants		*no. of fractures*				*no. of fractures*			
Age										
All	3966	15,495	151	586	0.70 (0.58–0.86)	<0.001	458	1948	0.86 (0.76–0.96)	0.007
65–74 yr	1018	7,521	13	128	0.72 (0.39–1.31)	0.27	122	900	1.09 (0.90–1.33)	0.39
75–84 yr	2603	5,989	130	332	0.72 (0.58–0.89)	0.003	299	791	0.76 (0.66–0.88)	<0.001
≥85 yr	345	1,985	8	126	0.54 (0.25–1.20)	0.13	37	257	0.87 (0.59–1.30)	0.50
Type of dwelling										
All	3966	15,495	151	586	0.70 (0.58–0.86)	<0.001	458	1948	0.86 (0.76–0.96)	0.007
Community dwelling	2103	10,735	42	253	0.68 (0.48–0.96)	0.03	238	1314	0.95 (0.82–1.10)	0.52
Institution	1863	4,760	109	333	0.70 (0.55–0.89)	0.004	220	634	0.74 (0.62–0.87)	<0.001
Baseline 25-hydroxyvitamin D										
All†	412	2,220	11	177	0.55 (0.29–1.05)	0.07	51	484	0.80 (0.59–1.10)	0.18
<30 nmol/liter	106	517	2	42	0.40 (0.08–1.91)	0.25	7	106	0.56 (0.24–1.34)	0.19
≥30 nmol/liter	306	1,703	9	135	0.60 (0.29–1.22)	0.17	44	378	0.87 (0.62–1.23)	0.43
Additional calcium intake										
All	2580	10,615	123	368	0.71 (0.56–0.88)	0.002	315	1414	0.87 (0.76–1.00)	0.05
<1000 mg	294	10,145	6	359	0.65 (0.25–1.68)	0.38	25	1372	0.62 (0.39–0.97)	0.04
≥1000 mg	2286	470	117	9	0.77 (0.30–1.96)	0.59	290	42	1.19 (0.82–1.74)	0.36

* All analyses were adjusted for study, age group, sex, and type of dwelling. After Bonferroni adjustment, with a P value of less than 0.00625 considered to indicate statistical significance, there were no significant interactions between the highest actual-intake level of vitamin D and the four subgroups.
† Data on baseline 25-hydroxyvitamin D levels were available for a total of 4383 participants in nine trials.

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which compared the highest actual-intake level with the lowest, regardless of study assignment (treatment or control). A dose–response relationship between vitamin D and fracture risk is further supported by our analysis of baseline levels of 25-hydroxyvitamin D and prospective fracture risk.

Our findings suggest that some previous high-quality trials of vitamin D supplementation either showed no benefit owing to lower-than-intended doses of vitamin D or showed an unexpected benefit owing to higher-than-intended doses. For example, the RECORD trial by Grant et al.[16] was designed with an intended dose of 800 IU per day, but the actual intake of vitamin D was lower, with a mean intake of 539 IU per day in the group that received vitamin D combined with calcium and 613 IU per day in the group that received vitamin D alone. Conversely, the Women's Health Initiative trial by Jackson et al.[17] was designed with an intended dose of 400 IU per day, but the actual intake of vitamin D and the proportion of participants in the highest intake range were higher, which may in part explain the reduced risk of fracture that was observed in the older participants in that trial.

Previous meta-analyses have suggested that the benefits of vitamin D may be limited to older persons who live in institutions.[4,6] Our subgroup analyses suggest that at the highest actual-intake level, the risk of hip fracture is reduced among all persons 65 years of age or older, whether they live in the community or in an institution. Our data further suggest that persons who are most vulnerable to vitamin D deficiency — those 85 years of age or older and those with very low baseline levels of 25-hydroxyvitamin D — benefit from vitamin D supplementation at least as much as others do. However, because of the reduced sample size and power, we are not able to determine whether this benefit is greater or simply equivalent.

Several previous meta-analyses suggested that the dose of vitamin D is irrelevant when vitamin D is combined with calcium.[4-7] In contrast, our pooled subgroup analyses of the eight double-blind, randomized, controlled trials that used vitamin D combined with calcium indicate that with combined supplementation, the risk of fracture is reduced only at the highest actual-intake level of vitamin D. Furthermore, our data suggest that at the highest actual-intake level of vitamin D, a smaller amount of calcium supplementation (<1000 mg per day), as compared with a larger amount (≥1000 mg per day), may be more beneficial in reducing the risk of fracture — a finding that is consonant with epidemiologic studies.[23,24]

Our sensitivity analysis suggests that the vitamin D dosing interval may be relevant for reducing the risk of fracture. When we included in our sensitivity analysis the trial by Sanders et al.,[11] in which one annual dose of vitamin was administered, the risk reduction was attenuated. Similarly, another study of annual supplementation with injectable vitamin D showed a null effect on the risk of fracture.[25] In contrast, a trial from which the source data set could not be retrieved showed that a dose of 100,000 IU of vitamin D taken orally every 4 months was associated with a 33% reduction in the risk of a first hip, wrist, or forearm fracture, suggesting that the 4-month dosing interval is satisfactory.[8] More frequent dosing (daily or weekly) in adequate amounts is supported by our analysis as a means of lowering the risk of both hip and nonvertebral fractures.

The strengths of our pooled analysis are the large sample, the assessment of fracture risk by actual intake of vitamin D, and the consistency of the primary findings and the internal validation study. The principal limitation of our analysis is the unavailability of source data for 2 of the 14 qualifying trials[8,9]; however, inclusion of the trial-level data from these studies in a random-effects meta-analysis did not alter our findings. A further limitation is that we could not assess the effect of the highest quartile of actual intake of vitamin D (792 to 1000 IU per day) without additional calcium, because all trials that gave higher doses of vitamin D (≥800 IU per day with good adherence) also gave calcium. The threshold assessment of fracture was limited because baseline levels of 25-hydroxyvitamin D were available for only a subset of participants and because the assays used to measure 25-hydroxyvitamin varied among the studies. However, after adjustment for this variation and all other covariates, the dose–response relationship remained significant.

Our findings support the most recent recommendation from the Institute of Medicine[26] that persons 65 years of age or older receive 800 IU of vitamin D per day, but suggest that a 25-hydroxyvitamin D level of more than 60 nmol per liter may be most beneficial for reducing the risk of fractures. Furthermore, although our data did not allow us to determine whether the actual-intake level of a calcium supplement influenced the effect of vitamin D at the highest actual-intake

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level, it would be important for future studies to consider the possibility that a calcium-supplement intake of 1000 mg per day or more, combined with high-dose vitamin D (≥800 IU per day) may be harmful. Calcium supplements without vitamin D have been reported to increase the risk of hip fracture.[27]

In conclusion, our data suggest that high-dose vitamin D supplementation (≥800 IU per day) may reduce the risk of hip fracture in persons 65 years of age or older, independently of type of dwelling, age, and sex. Furthermore, our data support a 25-hydroxyvitamin D level above 60 nmol per liter for the prevention of fractures.

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REFERENCES

1. Melton LJ III, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. Osteoporos Int 1999;9:29-37.
2. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int 1997;7:407-13.
3. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009; 169:551-61.
4. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess (Full Rep) 2007;August:1-235.
5. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab 2007;92:1415-23.
6. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2009;2:CD000227.
7. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 2010; 340:b5463.
8. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;326:469.
9. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002; 13:257-64.
10. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D_3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.
11. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010; 303:1815-22. [Erratum, JAMA 2010;303: 2357.]
12. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670-6.
13. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. Arch Intern Med 2010;170:813-20.
14. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124:400-6.
15. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res 2002;17:709-15.
16. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621-8.
17. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-83. [Erratum, N Engl J Med 2006;354:1102.]
18. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000;15:1113-8. [Errata, J Bone Miner Res 2001;16:1735, 1935.]
19. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int 2009;20:315-22.
20. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc 2005;53:1881-8.
21. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int 2007;18:811-8.
22. Liang K-Y, Self SG, Bandeen-Roche KJ, Zeger SL. Some recent developments for regression analysis of multivariate failure time data. Lifetime Data Anal 1995;1:403-15.
23. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 2005;294:2336-41.
24. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. J Bone Miner Res 2009;24:935-42.
25. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women — a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford) 2007;46:1852-7.
26. Ross AC, Manson JE, Abrams SA, et al. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: what dietetics practitioners need to know. J Am Diet Assoc 2011;111:524-7.
27. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 2007;86:1780-90.

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