Effect of Vitamin D on Falls
A Meta-analysis

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Context Falls among elderly individuals occur frequently, increase with age, and lead to substantial morbidity and mortality. The role of vitamin D in preventing falls among elderly people has not been well established.

Objective To assess the effectiveness of vitamin D in preventing an older person from falling.

Data Sources MEDLINE and the Cochrane Controlled Trials Register from January 1960 to February 2004, EMBASE from January 1991 to February 2004, clinical experts, bibliographies, and abstracts. Search terms included trial terms: *randomized-controlled trial* or *controlled-clinical trial* or *random-allocation* or *double-blind method*, or *single-blind method* or *uncontrolled-trials* with vitamin D terms: *cholecalciferol* or *hydroxycholecalciferols* or *calcifediol* or *dihydroxycholecalciferols* or *calcitriol* or *vitamin D/aa[analogs & derivates]* or *ergocalciferol* or *vitamin D/bl[blood];* and with *accidental falls* or *falls*, and *humans*.

Study Selection We included only double-blind randomized, controlled trials (RCTs) of vitamin D in elderly populations (mean age, 60 years) that examined falls resulting from low trauma for which the method of fall ascertainment and definition of falls were defined explicitly. Studies including patients in unstable health states were excluded. Five of 38 identified studies were included in the primary analysis and 5 other studies were included in a sensitivity analysis.

Data Extraction Independent extraction by 3 authors using predefined data fields including study quality indicators.

Data Synthesis Based on 5 RCTs involving 1237 participants, vitamin D reduced the corrected odds ratio (OR) of falling by 22% (corrected OR, 0.78; 95% confidence interval [CI], 0.64-0.92) compared with patients receiving calcium or placebo. From the pooled risk difference, the number needed to treat (NNT) was 15 (95% CI, 8-53), or equivalently 15 patients would need to be treated with vitamin D to prevent 1 person from falling. The inclusion of 5 additional studies, involving 10001 participants, in a sensitivity analysis resulted in a smaller but still significant effect size (corrected RR, 0.87; 95% CI, 0.80-0.96). Subgroup analyses suggested that the effect size was independent of calcium supplementation, type of vitamin D, duration of therapy, and sex, but reduced sample sizes made the results statistically nonsignificant for calcium supplementation, cholecalciferol, and among men.

Conclusions Vitamin D supplementation appears to reduce the risk of falls among ambulatory or institutionalized older individuals with stable health by more than 20%. Further studies examining the effect of alternative types of vitamin D and their doses, the role of calcium supplementation, and effects in men should be considered.

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FALLS REPORTEDLY OCCUR IN 30% per year of those 65 years or older and 40% to 50% of those 80 years or older.[1,2] Falls constitute the largest single cause of injury mortality in elderly individuals[3] and are an independent determinant of functional decline,[4] leading to 40% of all nursing home admissions[5] and substantial societal costs.[6] Because of the increasing proportion of older individuals, annual costs from all fall-related injuries in the United States in persons 65 years or older have been projected to increase from $20.3 billion in 1994 to $32.4 billion in 2020.[7]

Previously, the moderate protective effect of vitamin D on fracture risk has been attributed primarily to bone mineral density changes.[8] However, vitamin D may also directly improve muscle strength, thereby reducing fracture risk through fall prevention. Randomized controlled trials (RCTs)[8,9] found that vitamin D reduced fractures within 8 to 12 weeks, a finding consistent with muscle strength benefits.[10-12]

Nonetheless, the potential effect of vitamin D on falls is not well established. Several RCTs have addressed this, but results have been mixed, including several trials that reported nonsignificant results. The primary goal of this analysis was to determine the

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Table 1. Randomized Controlled Trials Included in the Primary Analysis of the Effect of Vitamin D on Preventing Falls*

Source	Study Quality	No. of Participants	Treatment per Day	Dwelling	Age, Mean (SD), y	Study Length	Change in 25-Hydroxyvitamin D Level in Intervention Group, Mean (SD), nmol/L
Graafmans et al,[19] 1996	Computer-based randomization method Double-blind throughout treatment period Fall assessment limited to a subgroup of a larger trial‡ Masking of treatment allocation using sealed envelopes Matching placebo Intention to treat unclear Drop-out not stated Study designed to study risk factors for falls Power not stated for vitamin D Fall diary	302 Women 52 Men	400 IU Cholecalciferol + estimated calcium intake from dairy products 800-1000 mg/d‡	Ambulatory in homes for older individuals	>70	7 mo	Not stated
Pfeifer et al,[11] 2000	Unclear randomization method Double-blind for first 2 months Uncontrolled follow-up Masking of treatment allocation not stated Matching placebo Intention to treat Drop-out 7% Falls were secondary outcome No fall diary, but fall questionnaire	137 Women	800 IU Cholecalciferol + 1200 mg of calcium vs 1200 mg of calcium	Ambulatory	74 (1)	2 mo + 1 y follow-up	25.7 (20.9) to 40.5 (27.0)
Gallagher et al,[17] 2001	Central computer-based randomization Double-blind throughout treatment period Masking of treatment allocation not stated Matching placebo Intention to treat Drop-out 15% Falls were secondary outcome Falls were assessed in interviews at every 3 months	246 Women	0.5 µg Calcitriol vs placebo	Community dwelling	71 (4)	3 y	74.8 (29.0) to 55.5 (24.5)†
Bischoff et al,[12] 2003	Central computer-based randomization Double-blind throughout treatment period Masking of treatment allocation in sealed envelopes Matching placebo Intention to treat Drop-out 28% Falls were primary outcome Powered for number of falls Falls were assessed by nurses on a daily basis	122 Women	800 IU Cholecalciferol + 1200 mg calcium vs 1200 mg calcium	Institutionalized	85 (6)	3 mo	41.0 (25.5) to 65.0 (23.8)
Dukas et al,[18] 2004	Central computer-based randomization Double-blind throughout treatment period Masking of treatment allocation by numbered pill containers Matching placebo Intention to treat Drop-out 13% Falls were primary outcome Power not stated Fall diary	191 Women 187 Men	1 µg 1α-Calcidiol vs placebo	Community dwelling	75 (5)	9 mo	78.0 (21.6) to 60.7 (19.7)†

*All of these trials included a fall definition and described fall ascertainment in their "Methods" sections.
†Values declined because the intervention was active D.
‡Based on data from Lips et al.[35]

overall efficacy of vitamin D in preventing falls among older individuals 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 February 2004 and EMBASE from January 1991 to February 2004. Additional studies were identified by contacting experts and searching reference lists and abstracts presented at the American Society for Bone and Mineral Research from 1995-2002.

Medical Subject Heading 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 & derivates]* or *ergocalciferol* or *vitamin D/bl[blood];* with *accidental falls* or *falls*, and *humans*. Eligibility and exclusion criteria were prespecified. Data extraction was conducted independently by 3 investigators (H.A.B.-F., M.G.B., and R.Y.Z.).

Eligible Studies

We included only double-blind RCTs that studied any type of vitamin D (TABLE 1). Because the type of vitamin D may introduce heterogeneity, we also examined effect sizes separately for studies using cholecalciferol and those using active analogs. Because our primary outcome was to assess the rate of low-trauma falls among older community-dwelling or institutionalized persons, we required that the authors state in the "Methods" section how falls were ascertained and how they were defined. Ideally falls involved "unintentionally coming to rest on the ground, floor, or other lower level,"[13] and fall diaries or questionnaires should have covered short time frames, because falls tend to be forgotten if no injuries are involved.[14] We did not include coming to rest against furniture or a wall, or high-trauma falls (eg, falling from a ladder) in this analysis.

Because our target population consisted of older community-dwelling or institutionalized persons, the mean age of study participants had to equal or exceed 60 years to be included in the primary analysis. The effects of RCTs that did not meet our eligibility criteria and of abstracts for which complete results were not available were examined in the sensitivity analysis.

Ineligible Studies

We excluded uncontrolled trials, observational studies, and animal studies. Because health conditions that place patients at high risk for falls may mask and confound results, we excluded from our primary analysis studies that focused on patients with alcoholism or unstable health states, such as those following acute hospitalization. These studies and abstracts were included in sensitivity analyses.

Definitions

Our primary outcome measure was the relative risk of having at least 1 fall among persons receiving vitamin D compared with those not receiving vitamin D.

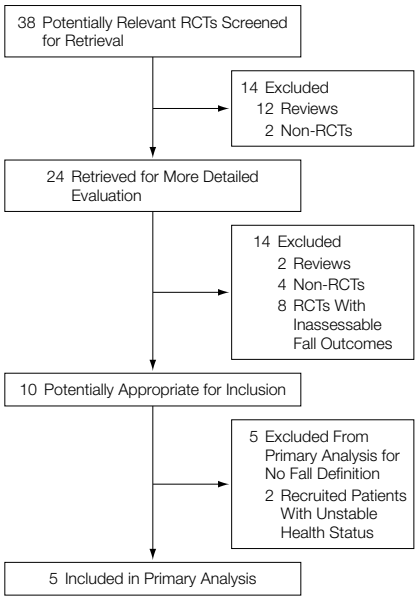
Quality Assessment

We assessed the following methodological features most relevant to the control of bias: randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals.[15,16]

Studies Identified

Primary Analysis. We identified 5 RCTs that met our inclusion criteria[11,12,17-19] (FIGURE 1). All trials assessed vitamin D treatment in the prevention of falls as a primary[12,18] or secondary outcome.[11,17,19] Three were identified as vitamin D RCTs,[11,12,18] 1 was identified through the falls search alone,[19] and the fifth by examining vitamin D RCTs with bone density or fracture as the primary outcome.[17]

Figure 1. Flow Diagram



RCT, randomized-controlled trial.

Sensitivity Analysis. The aim of the sensitivity analysis was to examine the effect size when including studies meeting less stringent inclusion criteria. We identified 5 additional trials to be included in sensitivity analysis.[20-24] None of these studies included a definition for falls. Two studies[23,24] recruited elderly patients in unstable health states following acute hospitalization or hip fracture. In 2 studies,[21,22] falls were only assessed as a tertiary outcome. Lastly, 1 study had been published only as an abstract and included falls that led to medical attention,[20] which comprise a minority of all low-trauma falls.

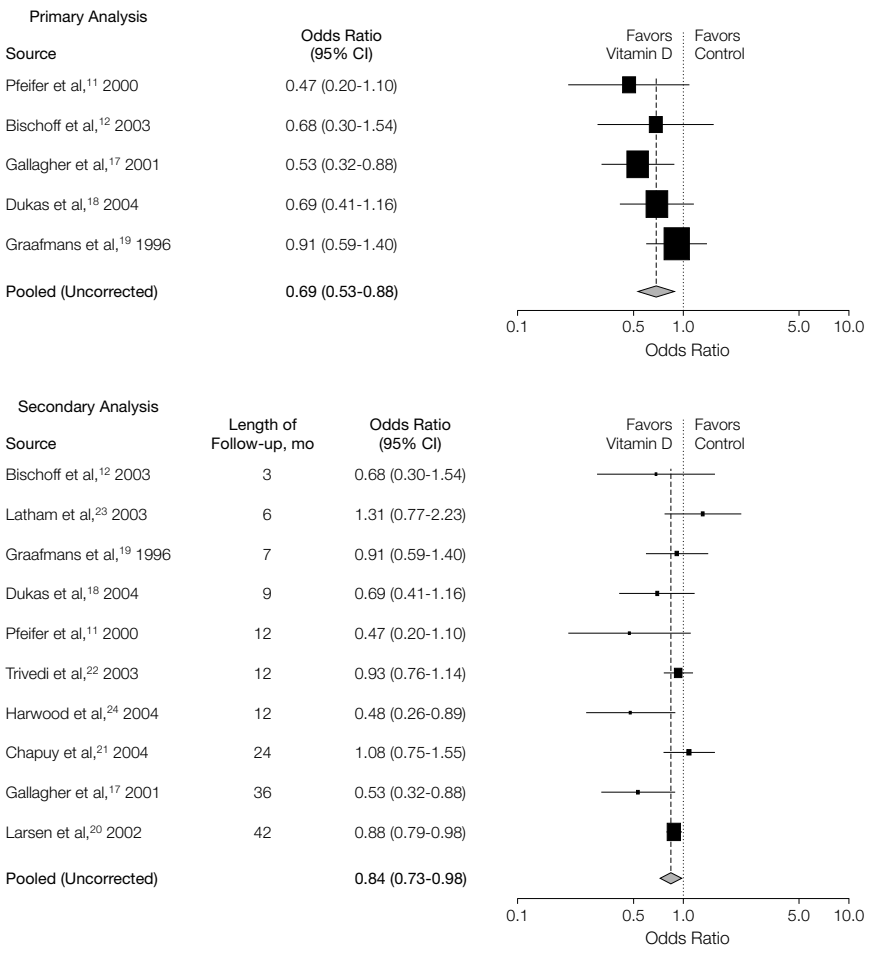
Statistical Methods. Outcomes were analyzed on an intention-to-treat basis with both fixed and random effects models. Results were similar with both models, but we present only the latter results. The random effects model provides a more conservative estimate by incorporating both within- and between-study variation.[25] We used the method of Zhang and Yu[26] to correct for the tendency of odds ratios (ORs) for common events to overestimate the relative risk (RR). Finally, we also calculated the risk difference for preventing

a fall to determine the number needed to treat (NNT) to prevent a person from falling.

Heterogeneity among studies was evaluated by the Q statistic (considered significant for P values $<.10$[27,28]) and H, R, and I statistics.[29] For all these analyses, we did not find any statistically significant evidence for heterogeneity in the primary analysis. In addition, the 95% confidence intervals (CIs) of all studies overlapped each other in the forest plots, supporting the absence of heterogeneity and suggesting that vitamin D, independent of its formulation (cholecalciferol or its active forms), may have a similar effect across trials performed in individuals living in the community or in assisted care institutions. Lastly, we further explored heterogeneity by examining effect sizes for different subgroups.

As with all meta-analyses, this review has the potential for publication bias. Using the Begg and the Egger[30] test with all 10 trials, we found no evidence for publication bias. 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[31] (results available from the authors). Statistical analyses were performed with STATA version 7.0 (STATA Corp, College Station, Tex).

Figure 2. Forest Plots Comparing the Risk of Falling Between Vitamin D–Treated Groups and Control Groups for the Primary and Sensitivity Analyses



Squares represent the odds ratios for the risk of falling among those who took vitamin D treatment (or analog) vs those in the control group. Size of the squares is proportional to the size of the trials. Error bars represent 95% confidence interval (CIs). The diamond shape represents the pooled estimates within each analysis. The corrected pooled odds ratio for the primary analysis was 0.78 (95% CI, 0.64-0.92). The primary analysis excluded randomized controlled trials for which authors did not state how falls were ascertained or how they were defined. Also, preliminary studies and studies performed in populations with an unstable health state were excluded from the primary analysis. The corrected pooled odds ratio for the sensitivity analysis was 0.87 (95% CI, 0.80-0.96). Studies for the sensitivity analysis were sorted by trial duration in months.

RESULTS

Primary Analysis

Table 1 shows characteristics of the 5 trials in the primary analysis, which included 1237 individuals, 81% women, and a mean age of 70 years.[11,12,17-19] The lowest dose of vitamin D was 400 IU/d, but reported calcium intake from dairy products was high at 800 to 1000 mg/d.[19] The other 4 trials administered either vitamin D 800 IU/d plus 1200 mg/d of calcium[11,12] or an active vitamin D analogue[17,18] and no calcium supplements. Treatment duration varied between 2 months and 3 years.

Four trials reported the method of randomization and that treatment allocation was concealed from participants and investigators, and specifically reported performing an intention-to-treat analysis.[11,12,17,18] Three studies specifically stated masking of treatment allocation.[12,18,19] The causes for drop-out were balanced between treatment and controls in all trials and ranged from 7%[11] to 28%.[12] The latter trial expected a moderately high drop-out rate (powered for 30% drop-out) because all participants were on waiting lists for nursing home placement at study entry.[12]

FIGURE 2 shows the forest plot of the primary analysis. The corrected pooled OR for vitamin D supplementation preventing a person from falling was 0.78 (95% CI, 0.64-0.92), suggesting that vitamin D supplementation reduced the risk of a person from falling by 22%. The pooled risk difference was 7% (95% CI, 2%-12%; $P=.007$), so the NNT was 15 (95% CI, 8-53).

Sensitivity Analysis

We examined the effect of including 5 additional RCTs, which expanded the

Table 2. Trials Excluded From Primary Analysis But Included in the Sensitivity Analysis

Source	Study Quality	No. of Participants	Treatment	Dwelling	Age y*	Study Length	Change in 25-Hydroxyvitamin D Level in Intervention Group, Mean (SD), nmol/L†
Larsen et al,[20] 2002	Preliminary data based on abstract Unclear randomization method No blinding of treatment allocation Intention to treat Drop-out not stated Falls that came to medical attention were primary outcome No fall definition Fall ascertainment through hospital records	5771 Women	400 IU Cholecalciferol + 1000/d mg of calcium vs other fall and fracture prevention strategies	Ambulatory	74 (Mean)	3.5 y	Not stated
Trivedi et al,[22] 2003	Unclear randomization method Double-blind throughout treatment period Masking of treatment allocation revealed by drug company at the end of the study Matching placebo Intention to treat Drop-out 35% Falls were tertiary outcome No fall definition No fall diary (any fall in the last 12 mo asked at the last study visit)	525 Women 1513 Men	100 000 IU Every 4 mo + no calcium vs placebo	Community-dwelling	65-85, (Range)	1 y§	71.3 (20.7) in a subset at follow-up
Latham et al,[23] 2003	Computer-based randomization Double-blind throughout treatment period Masking of treatment allocation not stated Matching placebo Intention to treat Drop-out 4% (death) Falls were primary outcome No fall definition Fall diary	222 (53%) Women	300 000 IU Cholecalciferol once + no calcium vs placebo (2 x 2 factorial design: other intervention was exercise: no effect)	Acute care recruitment of frail elderly	79 (7)	6 mo	42.5 (40-48) to 65 (58-76) at 3 mo follow-up‖
Chapuy et al,[21] 2004	Unclear randomization method Double-blind throughout treatment period Masking of treatment allocation not stated Matching placebo Intention to treat Drop-out 31% (mostly death) Falls were tertiary outcome No fall definition No fall diary	583 Women	800 IU Cholecalciferol + 1200 mg/d of calcium vs placebo	Ambulatory in homes for the elderly	85 (7)	2 y	21.3 (20.9) to 75‡
Harwood et al,[24] 2004	Computer-based randomization No blinding No placebo No masking of treatment allocation Unclear intention to treat Drop-out 33% Falls were secondary outcome No fall definition Falls were asked at the 3-, 6-, and 12-mo visit (no fall diary)	150 Women	300 000 IU Ergocalciferol injected once with or without 1000 mg/d calcium or 800 IU/d of cholecalciferol orally + 1000 mg/d of calcium vs placebo	Orthogeriatric ward, recruited within 7 d of surgery for a hip fracture Community-dwelling prior to hip fracture	81 (Range, 67-92)	1 y	29 (range, 6-85) to 40-50 in the different vitamin D treatment groups at 1 y follow-up

*Data are presented as mean age (SD) unless otherwise indicated.
†Data are presented as mean (SD) unless otherwise indicated.
‡Estimated from a graph.
§Falls were only assessed for the last year of the 5-year randomized controlled trial.
‖Median (95% confidence interval).

patient population to 10 001.[20-24] TABLE 2 shows the characteristics of these studies, and Figure 2 shows the forest plot with the inclusion of these studies. The corrected OR for vitamin D in preventing a person from falling was 0.87 (95% CI, 0.80-0.96), suggesting a reduction in the risk of falling by 13% with vitamin D. As expected by their clinical characteristics or their outcome measures, these additional studies decreased the effect size, but benefits still remained statistically significant.

Subgroup Analysis

We also explored potential heterogeneity by examining effect sizes in clinical subgroups by type of vitamin D (cholecalciferol or active metabolites), presence of calcium supplementation, length of treatment, and sex. For 3 studies[11,12,19] involving 613 participants treated with cholecalciferol, the corrected OR of falling was 0.83 (95% CI, 0.65-1.06). However, for the 2 trials with 259 subjects using 800 IU of cholecalciferol (excluding the trial with only 400 IU[19]), the corrected OR of falling was 0.65 (95% CI, 0.40-1.00), which approached statistical significance. For 2 studies involving 626 participants who used active vitamin D,[17,18] the corrected OR for falling was 0.71 (95% CI, 0.55-0.92).

In the primary analysis, we could not examine any effect of calcium separately because all studies that did not provide calcium supplements also used active vitamin D analogues. When separating all 10 studies by calcium supplementation, we did not find heterogeneity in the effect size. Pooled ORs ranged from 0.77 to 0.83 for studies that provided no calcium,[17,18,22,23] calcium in both treatment and control groups,[11,12,19] or calcium only in the vitamin D group but not in the control group.[20,21,24] None of these ORs reached statistical significance because of the smaller sample sizes.

When studies were sorted by length of treatment and follow-up, we were unable to discern differences in the effect of vitamin D (sensitivity analysis in Figure 2). Analyzing separately the 1700 men from the trials of Trivedi et al and Dukas et al yielded an OR of 0.79 (95% CI, 0.57-1.1; $P = .17$). Although not statistically significant, this effect size is similar to that for 7575 women with a pooled corrected OR of 0.81 (95% CI, 0.65-1.00; $P = .05$).[11,12,17,18,20-22,24]

We were unable to include the largest trials by Trivedi[22] and Larsen[20] in the primary analysis. However, adding these studies reduced the effect size from the corrected OR of 0.78 (95% CI, 0.64-0.92) in the primary analysis to 0.85 (95% CI, 0.79-0.96) including both trials and 0.87 (95% CI, 0.80-0.96) including all 10 RCTs.

TABLE 3 shows the number of individuals who fell in each study.

COMMENT

This meta-analysis included 5 RCTs with 1237 elderly individuals treated with different vitamin D analogues for 2 months up to 3 years. In all of these trials, the method of fall ascertainment and fall definitions were specified. All participants were in stable health states: living in the community,[11,17,18] in housing for elderly individuals,[19] or in long-stay geriatric care awaiting nursing home placement.[12] The pooled results found a statistically significant 22% reduction in the risk of falling with vitamin D treatment compared with calcium or placebo. The pooled risk difference indicated that 15 people would need to be treated with vitamin D to prevent 1 person from falling.

A physiologic explanation for the beneficial effect of vitamin D on the risk of falling is that 1,25-hydroxyvitamin D, the active vitamin D metabolite, binds to a highly specific nuclear receptor in muscle tissue,[32,33] leading to improved muscle function and reduced risk of falling. Specifically, vitamin D plus calcium compared with calcium alone improved body sway by 9%

Table 3. Number of Individuals Who Fell Classified by Study Group

Source	Total No. of Participants (N = 10 001)	Intervention		Control		OR Effect (95% CI)
		No. of Fallers	No. of Participants	No. of Fallers	No. of Participants	
Pfeifer et al,[11] 2000	137	11	70	19	67	0.47 (0.2-1.09)
Bischoff et al,[12] 2003	122	14	62	18	60	0.68 (0.3-1.53)
Gallagher et al,[17] 2001	246	59	123	78	123	0.53 (0.32-0.89)
Dukas et al,[18] 2004	378	40	192	46	186	0.69 (0.41-1.16)*
Graafmans et al,[19] 1996	354	62	177	66	177	0.91 (0.59-1.4)
Chapuy et al,[21] 2004	583	251	393	118	190	1.08 (0.75-1.54)
Trivedi et al,[22] 2003	2038	254	1027	261	1011	0.93 (0.76-1.14)†
Latham et al,[23] 2002	222	64	108	60	114	1.31 (0.77-2.23)
Larsen et al,[20] 2002‡	5771					0.88 (0.79-0.98)
Harwood et al,[24] 2004§	150	15	84	13	35	0.37 (0.15-0.89)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for age, sex, body mass index, creatinine clearance, number of falls in the previous 3 months, physical activity, Charlson comorbidity Index, number of medications at baseline, calcium intake at baseline, heart rate at baseline, intact parathyroid hormone, albumin at baseline, and coffee intake at baseline.
†Adjusted for age.
‡Preliminary data.
§Authors provided the exact number of fallers not for the total sample; thus, for the pooled analysis, we included the more conservative estimate published by the authors as given in Figure 2.

within 2 months in elderly ambulatory women,[11] and similarly, vitamin D plus calcium compared with calcium alone increased musculoskeletal function by 4% to 11% in institutionalized elderly women.[12] The effects of vitamin D on muscle may be mediated by de novo protein synthesis,[10,34] affecting muscle cell growth through the highly specific nuclear vitamin D receptor expressed in human muscle.[32,33] In one study, treatment with 1α-hydroxyvitamin D increased the relative number and size of type II muscle fibers of elderly women within 3 months of treatment.[10] An early vitamin D effect on muscle function may explain our inability to discern a duration of trial effect.

There were insufficient data to formally test which dose of vitamin D and which formulation would be most beneficial for individuals in specific housing situations or with specific baseline 25-hydroxyvitamin D levels. However, in a subgroup analysis, similar effect sizes for fall risk reduction were found: 35% for 800 IU of cholecalciferol and 29% for active vitamin D. The Graafmans et al trial[19] suggests that 400 IU of vitamin D may not be clinically effective in preventing falls in the elderly. Two studies also found that 400 IU of vitamin D did not significantly reduce fracture risk[35,36] while trials using 700 to 800 IU/d of vitamin D[8,9,22] did find significant reductions in observed fractures.

The role of calcium and the optimal amount necessary in combination with vitamin D could not be clearly determined. Using all studies and comparing calcium regimens (no calcium supplementation in both treatment and controls or calcium supplementation only in the treatment group), we did not detect heterogeneity in effect size, but these analyses were limited by sample size and confounded by differences in dose and form of vitamin D. In a subgroup analysis published in the Dukas et al trial,[18] only persons with total dietary calcium intake above the median (512 mg/d) appeared to have a significant reduction in falls with 1α-hydroxyvitamin D treatment. This suggests that a combination of vitamin D and calcium may be important.

Although studies used different vitamin D analogues, we did not detect heterogeneity between studies. Our subgroup analysis also showed a similar effect size for studies that used active vitamin D compared with those that used 800 IU cholecalciferol although the effect was not statistically significant for cholecalciferol. Effects of various formulations of vitamin D, (cholecalciferol or its active forms) were not significantly different and may be equivalent for individuals living in the community or in assisted living facilities. The sex-specific subgroup analyses were limited by the small number of men included in the trials; however, similar effect sizes were seen in men and women.

Our study also was limited by the absence of baseline 25-hydroxyvitamin D levels, which could be a potential determinant of treatment effect, and by the absence of physical activity levels, which may interact with treatment effect. However, our meta-analysis includes study populations in diverse living situations with likely broad variation in their baseline 25-hydroxyvitamin D levels and variable levels of physical activity.

We performed a sensitivity analysis by including RCTs that did not meet our inclusion criteria or were only published in abstract form. Their inclusion would have increased the number of individuals pooled 8-fold. All of these studies had characteristics, however, that were likely to dilute any observed treatment effect of vitamin D. The absence of a definition for falls, their assessment only as tertiary outcome, or the inclusion of only falls leading to medical attention could lead to underreporting. Populations in unstable health states such as recovering from hip fracture or acute hospitalization may be more likely to fall because of their illness, thereby obscuring any effect of vitamin D.[23,24] These prespecified inclusion criteria led to the exclusion of the 2 largest trials from the primary analysis.[20,22] The trial by Trivedi et al[22] captured falls only in the last year and had limited ascertainment of falls. The trial by Larsen et al[20] considered only falls that came to medical attention. Nevertheless, when these studies were added to the primary analysis, the corrected OR changed from 0.78 to 0.85 including both trials and to 0.87 for all 10 studies, but all of the ORs remained statistically significant. Including these studies may increase generalizability at the expense of compromising validity through potential biases introduced by less stringent outcome assessment and populations in unstable health states. However, even when including all 10 studies, the 13% reduction in a person's risk of falling was statistically significant.

In summary, this meta-analysis suggests that vitamin D should reduce an older person's risk of falling by 22% with the benefit most clearly established for women and with active vitamin D analogues. Results for men or for 800 IU/d of cholecalciferol were not significant, but the effect size appears to be similar for men and women using 800 IU of cholecalciferol or active analogues. Our results suggest that further studies in men and for cholecalciferol should be performed to definitely establish effect size in these subgroups. Moreover, the impact of calcium and its dose on fall outcomes when given in combination with vitamin D remains unknown although it did not seem to mediate the effect of vitamin D significantly in our meta-analysis. The effect and cost-effectiveness of targeted supplementation based on assessment of baseline vitamin D also remains unknown. Nevertheless, given the NNT of 15 and the high morbidity, mortality, and economic cost of falls, our results are sufficiently compelling to consider vitamin D supplementation for elderly individuals.

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Study concept and design: Bischoff-Ferrari, Wong.
Acquisition of data: Bischoff-Ferrari, Staehelin, Bazemore, Zee.
Analysis and interpretation of data: Bischoff-Ferrari, Dawson-Hughes, Willett, Bazemore, Zee, Wong.
Drafting of the manuscript: Bischoff-Ferrari, Bazemore, Zee.
Critical revision of the manuscript for important intellectual content: Bischoff-Ferrari, Dawson-Hughes, Willett, Staehelin, Zee, Wong.

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To be conscious that you are ignorant is a great step to knowledge.
—Benjamin Disraeli (1804-1881)