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The Effect of Vitamin D on Falls: A Systematic Review and Meta-Analysis

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Context: Vitamin D affects bone and muscle health and likely reduces the risk of falls in the elderly.

Objective: The aim of this systematic review is to summarize the existing evidence on vitamin D use and the risk of falls.

Data Sources: We searched electronic databases from inception through August 2010.

Study Selection: Eligible studies were randomized controlled trials in which the intervention was vitamin D and the incidence of falls was reported.

Data Extraction: Reviewers working in duplicate and independently extracted study characteristics, quality, and outcomes data.

Data Synthesis: Odds ratio and associated 95% confidence interval were estimated from each study and pooled using the random effects model.

Results: We found 26 eligible trials of moderate quality that enrolled 45,782 participants, the majority of which were elderly and female. Vitamin D use was associated with statistically significant reduction in the risk of falls (odds ratio for suffering at least one fall, 0.86; 95% confidence interval, 0.77–0.96). This effect was more prominent in patients who were vitamin D deficient at baseline and in studies in which calcium was coadministered with vitamin D. The quality of evidence was low to moderate because of heterogeneity and publication bias.

Conclusions: Vitamin D combined with calcium reduces the risk of falls. The reduction in studies without calcium coadministration did not reach statistical significance. The majority of the evidence is derived from trials enrolling elderly women. **(*J Clin Endocrinol Metab* 96: 0000–0000, 2011)**

Vitamin D exerts wide-ranging effects, including those that relate to physical function. This wide range of effects is due, in part, to the fact that most tissues in the body contain receptors for 1,25-dihydroxyvitamin D. For example, receptors in the muscle tissue may explain the association between vitamin D deficiency and myopathy, muscle weakness, and muscle pain (1). Correction of hypovitaminosis D by vitamin D administration can lead to improvement in the strength of the quadriceps muscle as measured by maximum voluntary contraction, maximal relaxation rate, and other physiological muscle testing parameters, regardless of whether patients had bone involve-

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Abbreviations: CI, Confidence interval; 25(OH) D, 25-hydroxyvitamin D; OR, odds ratio.

ment or not (2). Thus, vitamin D supplementation may improve functional outcomes, particularly falls, which are associated with significant morbidity.

The Endocrine Society assembled a task force of experts to develop clinical practice guidelines regarding use of vitamin D. To assist in formulating recommendations, we conducted a systematic review of the literature to quantitatively and qualitatively summarize the available evidence regarding the effect of vitamin D supplementation on falls.

Materials and Methods

The report of this protocol-driven systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (3) and was approved by the Vitamin D Task Force of The Endocrine Society. The quality of the collective body of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods (4).

Eligibility criteria

Eligible studies were randomized trials that enrolled adult individuals who received vitamin D supplementation and a concurrent comparison group that did not receive this intervention. We excluded studies in which the intervention was calcitriol or one of its analogs. The primary outcome of interest was falls. Studies were included regardless of their language, size, or duration of patient follow-up. Review articles, commentaries, and letters that did not contain original data and studies that only reported correlation of vitamin D levels with outcomes without providing a vitamin D-raising intervention to its participants were deemed ineligible.

Study identification

An expert reference librarian designed and conducted the electronic search strategy with input from study investigators with expertise in conducting systematic reviews. To identify eligible studies, we searched the electronic databases: MEDLINE, EMBASE, Web of Science, SCOPUS, PEDRO, Regional medical databases (KoreanMed, Scielo, LILACs, Imbiomed, Index for Australian medical literature, Eastern Mediterranean Index, IndMed, ExtraMed) through August 2010. Search was conducted using medical subject heading terms, textwords and keywords based on each database characteristics focusing on synonyms of vitamin D and multiple functional outcomes. We initially searched for other functional outcomes (quality of life, pain, independence and activities of daily living); however, minimal and heterogeneous data were found. Therefore, this report focuses on falls. A summary of search strategy is available in the Supplemental Data (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). In addition, we reviewed the reference sections of eligible studies and available reviews and requested potentially eligible studies from content experts.

Data collection

Teams of reviewers working independently and in duplicate used standardized forms and screened all abstracts and titles and, upon retrieval of candidate studies, reviewed the full text publications and determined study eligibility. Disagreements about study inclusion were resolved by consensus (*i.e.* the two reviewers discussed eligibility and reached an agreement). Reviewers extracted descriptive, methodological, and outcome data from all eligible studies.

Data collected from studies included a description of the population (*e.g.* age, sex, dwelling, comorbidities, and vitamin D status), the intervention (the type of vitamin D-raising intervention, dose, and route), study design and quality components, and data corresponding to the outcomes of interest. For dichotomous outcomes, a 2×2 table was created from each study, and if not available, the most adjusted summary measure and confidence interval (CI) values were used.

To assess the risk of fall, we considered the number of patients who suffered at least one fall as the event (outcome) of interest. We did not use the number of falls for this purpose because within-person correlation of the outcome is high (*i.e.* few patients in a cohort will likely suffer most of the falls), which may exaggerate the estimated risk. This assumption was tested in sensitivity analysis. To decrease the effect for reporting bias, we attempted to contact the authors of all included studies to determine whether any outcomes were collected but not reported, and to clarify data if needed. Pairs of blinded reviewers assessed study quality. We evaluated allocation concealment, blinding, funding, and loss to follow-up.

Statistical analysis

We used random effect meta-analysis (5) to pool odds ratios (OR) and 95% CI across included studies. OR values under 1.00 are associated with decreased risk for a particular outcome as a result of vitamin D-raising intervention. The I^2 statistic, which estimates the percentage of total variation across studies that is due to heterogeneity rather than chance, was used to assess heterogeneity (6). I^2 values of 25 or less, 50, and at least 75% represent low, moderate, and high inconsistency, respectively. Treatment effect-subgroup interactions were assessed by the ANOVA method and meta-regression analysis. Publication bias was assessed by visually inspecting the funnel plot (SE plotted *vs.* log OR) and statistically by conducting the Egger's regression test to detect asymmetry of the plot. In this regression, the size of the treatment effect is captured by the slope of the regression line, and bias is captured by the intercept. Statistical analysis was conducted using Comprehensive Meta-Analysis (version 2, 2005; Biostat Inc., Englewood, NJ).

Subgroup and sensitivity analyses

To explore the causes of inconsistency and subgroup-treatment interactions, we defined *a priori* subgroups based on patients' dwelling (community *vs.* institutionalized), vitamin D-raising intervention [oral *vs.* parenteral supplementation, calcium coadministration status, vitamin D type (D2 *vs.* D3)], and vitamin D dose (high *vs.* low; several definitions for "high" were to be tested). Two reviewers independently categorized studies as having a vitamin D-deficient population *vs.* not deficient, based on: 1) author description of the population; 2) reported baseline serum level of 25-hydroxyvitamin D [25(OH) D]; or 3) enrollment of patients with at least two vitamin D

deficiency risk factors (elderly age, dark skin, living in a nursing home, living far from the equator, winter season, sunscreen use, wearing a veil, smoking, obesity, malabsorption disease, renal or liver disease, and use of medication such as anticonvulsants, glucocorticoids, antirejection and HIV medications) (7). We also assessed whether studies that documented high adherence (>80%) or increased serum level of 25(OH) D had a significantly different treatment effect compared with studies with low adherence or undocumented increase of level, respectively. We also assessed the effect of the length of study follow-up as a continuous independent variable on the effect size. The effect of study quality on treatment effect was also evaluated. High-quality studies (in which allocation was concealed and at least patients or providers were blinded) were compared against lower quality studies.

We conducted sensitivity analysis to determine whether study conclusions are affected by choice of: 1) meta-analysis method (random effects model *vs.* fixed effect model); 2) the cutoff point that defines high dose of vitamin D (high dose was defined as >800, ≥800, or >600 IU/d); and 3) the definition of fall events (using the "number of patients who suffered at least one fall" *vs.* using the "number of falls").

Results

Study identification

We found 26 studies that fulfilled eligibility criteria. Figure 1 depicts the study selection process. Studies enrolled 45,782 participants that were randomized to a form of vitamin D or a control intervention (mean age, 76 yr; 78% females; and median study size, 604 participants). Patients had a very high baseline risk of falling (15–69%; median, 50%). The duration of vitamin D administration in these studies ranged from 3–62 months (median, 12 months). κ statistic for interreviewer agreement on study selection ranged from 0.70–0.80. We contacted the authors of 22 studies (8–29) to confirm collected data and ask for additional information/clarification if needed. Table 1 describes the included studies. Twelve additional trials that assessed other functional outcomes such as pain and quality of life were found, but these trials were markedly heterogeneous in terms of their population, setting, and outcomes; hence, they were not quantitatively pooled.

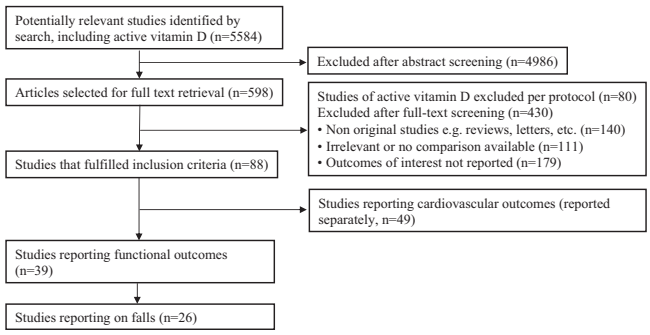

FIG. 1. The process of study selection.

The description of their characteristics and their findings are presented in Supplemental Table 1.

Study quality

Two studies used cluster randomization, and clusters were geographically defined [separate parts of residential care facilities in one study (30) and outpatient public social service centers in the second study (31)]. Allocation was concealed in 18 of 26 trials, and both patients and caregivers were blinded in 18 of 26 trials. Loss to follow-up was not reported in nine of 26 trials, and the proportion of patients lost to follow-up ranged from 0–52% with a mean of 10%. Funding included for-profit resources in 34% of studies. κ statistic for interreviewer agreement on the different elements of study quality ranged from 0.87–1.00. Table 2 describes study quality.

Meta-analysis

Vitamin D was associated with statistically significant reduction in the risk of falls (OR for the risk of suffering at least one fall, 0.86; 95% CI, 0.77–0.96; $I^2 = 66\%$; 26 studies; Fig. 2). The I^2 test indicates the presence of substantial statistical heterogeneity across studies; thus, we performed subgroup analyses to explore factors that may explain the heterogeneity.

Table 3 summarizes subgroup analyses. We found no significant subgroup-effect interactions for analyses based on patients' dwelling (community dwelling *vs.* institutionalized), vitamin D route of administration (oral *vs.* parenteral), the type of vitamin D-raising intervention (D2 *vs.* D3), study quality (high *vs.* low), adherence in intervention group (>80% *vs.* lower adherence), or whether the study documented an increase of 25(OH) D serum level in the intervention group. The effect of study duration on fall risk was assessed by meta-regression, finding no significant association ($P = 0.16$).

There was a significant interaction when subgroups were based on patients' vitamin D status (deficient *vs.* not deficient), suggesting more reduction in falls in deficient patients. Although we found no significant sex-fall risk interaction across studies, two studies reported within-study subgroup analysis demonstrating a larger effect (more reduction in the risk of falls) in women compared with men (10, 31). The inference from within-study comparison is stronger than between-study comparisons (32); therefore, a larger effect in women is plausible.

A statistically significant interaction between the risk of fall and calcium coadministration status was found ($P = 0.01$), suggesting that the reduction in the risk of fall was greater when calcium was administered to both study arms. The use of a fixed effect model instead of random effects model did not change any of the study conclusions.

TABLE 1. Study description

First author, year (Ref.)	Age (yr)	% Female	Population	Intervention
Chapuy, 1992 (47)	84	100	Healthy ambulatory women	D3 800 IU + 1200 mg calcium PO/qd
Graafmans, 1996 (48)	80	74	Ambulatory elderly	D3 400 IU/ PO/qd
Peichl, 1999 (49)	NR	100	Postmenopausal women with osteoporosis and vertebral fracture	D 400 IU + 500 mg calcium qd
Pfeifer, 2000 (17)	75	100	Healthy ambulatory elderly women	D 800 IU + calcium 1200 mg qd
Chapuy, 2002 (50)	85	100	Elderly ambulatory institutionalized women	D3 800 IU + 1200 mg of elemental calcium PO/qd
Bischoff, 2003 (9)	85	100	Elderly women, institutionalized, Vit D deficient	D3 800 IU + calcium carbonate 1200 mg PO/qd
Latham, 2003 (27)	79	53	Geriatric rehabilitation center	D 300,000 IU/PO/once
Trivedi, 2003 (25)	75	24	Elderly	D3 100,000 IU/PO/q 4 months
Dhesi, 2004 (51)	77	78	Ambulatory elderly with a history of falls and 25(OH) D $\leq$12 μ g/liter	D2 600,000 IU/im/once
Harwood, 2004 (52)	82	100	Elderly women after hip fracture, likely Vit D deficient	D2 300,000 IU/im/once or D3 800 IU + 1,000 mg calcium PO/qd
Flicker, 2005 (13)	83	95	Assisted living and nursing homes; 25(OH) D level 25–90 nmol/liter	D2 10,000 IU weekly, then 1,000 IU + 600 mg of calcium carbonate qd
Grant, 2005 (14)[c]	77	85	Mobile elderly with low-trauma fractures	D3 800 IU/PO/qd
Larsen, 2005 (31)	74	62	Community-dwelling elderly	D3 400 IU + 1,000 mg calcium qd
Porthouse, 2005 (18)	77	100	Elderly women with risk factors for hip fracture	D3 800 IU + 1,000 mg calcium carbonate qd + education on preventing fractures
Sato, 2005 (20)	74	100	Post stroke hemiplegia patients, likely Vit D deficient	D2 1,000 IU/PO/qd
Arden, 2006 (8)	79	54	Elderly	D2 300,000 IU/im/ annually
Bischoff-Ferrari, 2006 (10)	71	55	Healthy ambulatory elderly in the community	D3 700 IU + 500 mg calcium PO/ qd
Law, 2006 (30)	85	76	Nursing home residents	D2 1,100 IU/qd
Broe, 2007 (28)	89	73	Nursing home residents	D2 200, 400, 600, 800 IU/PO/qd
Burleigh, 2007 (12)	83	59	Rehabilitation wards in an acute geriatric unit, likely Vit D deficient	D 800 IU + 1,200 mg calcium carbonate PO/qd
Karkkainen, 2009 (34)	69	100	Ambulatory women	D3 800 IU + 1,000 mg calcium PO/qd
Berggren, 2008 (54)	87	74	Femoral neck fractures	D3 800 IU + 1,000 mg calcium PO/qd + fall prevention program
Pfeifer, 2009 (16)	77	75	Ambulatory community-dwelling seniors	D 800 IU + 1,000 mg calcium PO/qd
Prince, 2008 (19)	77	100	Elderly women with a fall history and low serum vitamin D	D2 1,000 IU + 1,000 mg calcium citrate qd
Sanders, 2010 (55)	76	100	Ambulatory elderly women at risk for fractures	500,000 IU PO annually for 3–5 yr
Witham, 2010 (29)	79	34	Elderly with CHF	100,000 D2 IU/PO 10 wk apart

Serum vitamin D results [25(OH) D] are presented in ng/ml; some values were converted from nmol/liter to ng/ml by dividing by 2.496. CHF, Congestive heart failure; PO, orally; qd, daily; Vit D, vitamin D; D2, ergocalciferol; D3, cholecalciferol; NR, not reported or unclear.

[a] This study excluded noncomplaint patients from analysis.

[b] Data dichotomized making patients receiving 600 and 800 IU to be the intervention group.

[c] Trial followed a factorial design. Only data of Vitamin D *vs.* placebo are presented.

[d] Post intervention value increased at 1 yr but decreased at 2 yr of follow-up.

When the number of falls (instead of the number of fallers) was used to assess the risk of fall, we also found a statistically significant decrease in the risk of falls associated with administration of vitamin D (OR, 0.79; 95% CI, 0.70–0.88; $I^2 = 90\%$). However, the reduction in risk was more pronounced, which is expected considering the within-person correlation of outcome; and it was more precise considering the larger number of events (falls). The exclusion of the two studies in which cluster randomization was used did not change the study conclusion regarding falls (OR, 0.80; 95% CI, 0.71–0.92). Changing the definition of "high dose" of vitamin D from greater than 800 IU/d to at least 800 IU/d or greater than 600 IU/d did not change the conclusion about the lack of a statistically significant

TABLE 1. Continued

Duration (months)	Control	Pre/post 25(OH) D	Documented increased level in intervention group	Adherence rate
18	Placebo	16/42	Yes, by 162%	83%
7	Placebo	NR/NR	NR	NR
12	200 IU nasal calcitonin twice a day every other month; plus, 500 mg calcium qd	NR/NR	NR	NR
2	1200 mg of calcium	24.63 (12.14)/NR	Yes, by 18.30	96%
24	Placebo	8.5 (5.3)/NR	Yes	>95%
3	1200 mg calcium qd	12.3/26.2	Yes, by >70%	>90%
NA	Placebo	17/NR	Yes, by 9	100%
60	Placebo	NR/74.3	Yes	80%
6	Placebo	10.4/17.5	Yes	NR
12	Nothing	28–30/40–50	Yes	NR
24	Placebo + 600 mg of elemental calcium qd	25–90/NR	No	86%
24 and 62	Placebo	NR/NR	NR	Unclear/ascertained by questionnaire
42	Nothing	NR/NR	NR	NR
12	Leaflet on dietary calcium intake and prevention of falls	NR/NR	NR	63%
24	Placebo	28.5/27.2	No	NR
36	Placebo	NR/NR	NR	NR
36	Placebo	28–33/41–44	Yes	82%
10	Nothing	47/74	Yes	NR
5	Placebo[b]	19.5/24–30	Yes	97.6%
1	Calcium 1,200 mg	22/NR	No	88%
36	Nothing	NR/NR	NR	NR
12	Nothing	NR/NR	NR	NR
12	1,000 mg calcium	22/33.7[d]	Yes	100%[a]
12	Placebo plus calcium 1,000 mg/d	<24/61	Yes, by 28%	86%
36–60	Placebo	21/22–29.7	Yes	NR
Twice, 10 wk apart	Placebo	8.3	Yes, 9.2	100%, supervised administration

dose-fall risk interaction. Lastly, the exclusion of one study (20) with the highest baseline risk of fall (stroke population) does not change study conclusions (OR, 0.88; 95% CI, 0.80–0.96; $I^2 = 62\%$).

Publication bias

The inspection of the funnel plot for the outcome of falls suggests the presence of publication bias; *i.e.* empty quadrant in which potentially small unpublished studies may have shown less reduction in falls (Supplemental Fig. 1). Similar inference is noted when Egger's regression test is conducted (intercept of −1.56; 95% CI, −2.41 to −0.65; $P = 0.01$, consistent with the presence of publication bias). Nevertheless, funnel plots can be misleading, particularly in the presence of substantial heterogeneity (33).

TABLE 2. Study quality

First author, year (Ref.)	Lost to F/U (%)	Blinding	Allocation concealment	Funding	F/U (months)
Chapuy, 1992 (47)	4	Caregivers, patients	Probably not	NR/NC	18
Graafmans, 1996 (48)	NR	Caregivers, data collectors, patients	Probably yes	Includes for-profit sources	7
Peichl, 1999 (49)	NR	No/NR	Probably not	NR/NC	12
Pfeifer, 2000 (17)	2	Caregivers, patients	Probably not	Includes for-profit sources	12
Chapuy, 2002 (50)	31	Caregivers, patients	Probably not	Includes for-profit sources	24
Bischoff, 2003 (9)	NR	Caregivers, outcome assessors, data collectors, patients	Probably yes	Non-for-profit	3
Latham, 2003 (27)	9	Patients	Probably yes	Non-for-profit	6
Trivedi, 2003 (25)	NR	Caregivers, data collectors, patients	Probably yes	Non-for-profit	60
Dhesi, 2004 (51)	6	Patients	Probably not	Non-for-profit	6
Harwood, 2004 (52)	16	No	Probably yes	Includes for-profit sources	12
Flicker, 2005 (13)	41	Caregivers, patients	Probably yes	Non-for-profit	24
Grant, 2005 (14)	13% at 4 months	Caregivers, patients	Probably yes	NR/NC	24 and 62
Larsen, 2005 (31)	NR	No	Probably not	Includes for-profit sources	42
Porthouse, 2005 (18)	3	Caregivers, data collectors, patients	Probably yes	Includes for-profit sources	25
Sato, 2005 (20)	11	Caregivers, data collectors, patients	Probably yes	NR/NC	24
Arden, 2006 (8)	NR	Patients	Probably not	Non-for-profit	36
Bischoff-Ferrari, 2006 (10)	NR	Caregivers, outcome assessors, data collectors, patients	Probably yes	Non-for-profit	36
Law, 2006 (30)	NR	No/NR	Probably yes	Non-for-profit	10
Broe, 2007 (28)	10	Caregivers, outcome assessors, data collectors, patients	Probably yes	Non-for-profit	5
Burleigh, 2007 (12)	2.9	Caregivers, outcome assessors, data collectors, patients	Probably yes	Includes for-profit sources	1
Karkkainen, 2009 (34)	NR	No/NR	Probably not	Non-for-profit	36
Smith, 2007 (24)	52	Caregivers, data collectors, patients	Probably yes	Non-for-profit	36
Berggren, 2008 (54)	21	Caregivers	Probably yes	Non-for-profit	12
Prince, 2008 (19)	4.3	Caregivers, outcome assessors, data collectors, patients	Probably yes	Non-for-profit	12
Pfeifer, 2009 (16)	NR	Caregiver, patients	Probably not	Includes for-profit sources	20
Sanders, 2010 (55)	10	Caregivers, patients	Yes	Non-for-profit	12
Witham, 2010 (29)	1	Caregivers, patients	Probably yes	Non-for-profit	4.7

F/U, Follow-up; RCT, randomized-controlled trial; NR/NC, not reported or not clear.

Discussion

Main findings

We conducted a systematic review and meta-analysis to evaluate the best available research evidence regarding the effect of vitamin D on falls. We found a statistically significant reduction in the risk of falls that was robust to sensitivity analyses. The reduction in risk of falls appears to be more prominent in patients who were deficient in vitamin D. This inference is strengthened by the fact that even in the cohorts that we were not able to classify as likely vitamin D deficient, a great proportion of participants were likely deficient (*e.g.* patients were elderly and lived in northern climates, but the study did not measure baseline vitamin D status). Thus, the reduction of falls noted in nondeficient cohorts could be attributed to undetected deficiency. Furthermore, within-study comparisons in two studies suggested that the risk of falls might be more pronounced in women. Falls requiring medical attention were particularly reduced by vitamin D replacement in women in one trial (OR, 0.72; 95% CI, 0.53–0.97) (34). Data on quality of life, pain, independence, and ability to perform activities of daily living were sparse. The reduction in falls in studies that did not coadminister vitamin D was not statistically significant and was most

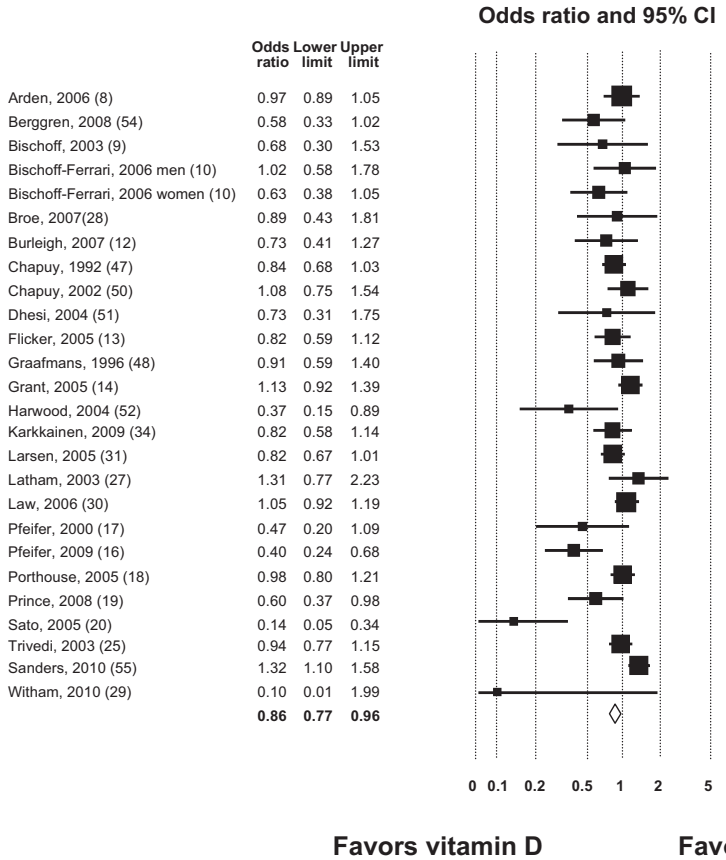

FIG. 2. Random effects meta-analysis of OR of patients suffering at least one fall. $I^2 = 66\%$; *P* value for test of heterogeneity = 0.01.

pronounced in studies that administered calcium to both study arms.

The reduction of falls associated with vitamin D is biologically plausible and can be explained by several mechanisms. Low serum 25(OH) D levels are associated with decreased muscle power and force (35). Vitamin D receptors are found in muscle tissue, and their activation leads to muscle protein synthesis (36–38). This may contribute to decreased body sway, improved muscle strength, and ultimately, decreased propensity for falls (16, 36). The secondary hyperparathyroidism that develops from vitamin D deficiency may also play a role in increasing the risk of falls. Hypophosphatemia, resulting from high PTH levels, may result in muscle weakness (35, 39). In addition, high levels of PTH itself, which has been shown to affect skeletal protein metabolism in animal models (40), has been associated with poor muscle function in some (2) but not all studies (35, 41).

Limitations and strengths

Publication bias has likely affected the results presented in this review. Although it is difficult to quantitatively assess for publication bias, statistical testing conducted in this meta-analysis suggests that it has exaggerated the estimate of risk reduction of falls. The presence of moderate heterogeneity can weaken these conclusions about publication bias and lower the overall quality of evidence. In addition, patients in this review were at high risk of falls, as indicated by high rate of falls in control cohorts; thus, generalizing results to other cohorts with lower risk will further downgrade the quality of evidence due to indirectness. The dietary sources of vitamin D represent a cointervention that could introduce noise to the signal produced by the intervention in unblinded studies and may bias the results toward the null. In this case, most patients were vitamin D deficient, indicating that the dietary sources of vitamin D were small compared with the dose given as an intervention; and the results are unlikely biased due to the cointervention. Of note, the sensitivity and subgroup analyses presented in this report are study-level aggregate analyses; thus, inference about subgroup interactions is limited by ecological bias and should be interpreted with caution. These limitations can be overcome by pooling individual patient data to examine potential modifiers of treatment effects (42).

The strengths of this review stem from the extensive literature search, protocol-driven, reproducible nature of the review, and the employment of bias protection measures such as reviewing articles and data extraction by blinded pairs of reviewers.

Comparison with other reviews

Bischoff-Ferrari *et al.* (36) conducted a meta-analysis that evaluated the effects of vitamin D supplementation on falls that was updated in 2009 (43). Our estimate of the risk of falls is similar to theirs (OR of 0.84 *vs.* 0.87), which validates both estimates. In the present report, however, more patients are included (4-fold increase in sample size) because the inclusion criteria of Bischoff-Ferrari *et al.* (36) were restricted to double-blind randomized-controlled trials with specific definitions of falls. The wider inclusion criteria allow the evaluation of heterogeneity and can only introduce bias if fall ascertainment in the included trials was incomplete or inaccurate. We found no difference in estimates between studies of higher quality and those with lower quality, validating the pooling procedure in which all studies are combined. We also attempted to investigate the effect on other functional outcomes but found minimal data.

TABLE 3. Risk of falls: subgroup analyses (random effects model)

Subgroup	OR (95% CI)	No. of studies	*P* (*I*nteraction test)[b]
Population's dwelling			0.51
Community dwelling	0.80 (0.69–0.93)	16	
Institutionalized	0.87 (0.71–1.07)	10	
Administration route			0.16
Intramuscular	0.52 (0.27–1.01)	2	
Oral	0.85 (0.76–0.95)	24	
Vitamin D deficiency status			0.00
Not deficient	0.90 (0.81–0.99)	20	
Deficient	0.53 (0.39–0.72)	6	
Documented increase in serum 25(OH) D level			0.86
Yes	0.82 (0.70–0.96)	16	
No/NR	0.84 (0.72–0.98)	10	
Vitamin D2 *vs.* D3			0.58
D2	0.79 (0.65–0.97)	8	
D3	0.85 (0.74–0.97)	18	
Adherence >80%			0.52
Yes	0.81 (0.69–0.94)	13	
No	0.87 (0.75–0.99)	13	
Vitamin D dose[a]			0.28
High dose	0.82 (0.73–0.93)	18	
Low dose	1.00 (0.72–1.37)	8	
Calcium coadministration status			0.01[b]
Vitamin D + calcium *vs.* placebo	0.83 (0.72–0.93)	10	
Vitamin D *vs.* placebo	0.97 (0.84–1.11)	10	
Vitamin D + calcium *vs.* calcium	0.63 (0.50–0.81)	6	
Study quality			0.62
High	0.82 (0.72–0.93)	19	
Low	0.87 (0.72–1.05)	7	

[a] High dose is defined as greater than 800 IU/d; changing the definition of high dose to at least 800 IU/d or at least 600 IU/d changes *P* value for interaction test to 0.85 and 0.92, respectively.

[b] Interaction test is conducted using ANOVA method.

In the meta-analysis by Bischoff-Ferrari *et al.* (36), it was concluded that the reduction in falls was only observed in studies that used high-dose vitamin D. We did not find such effect, which is consistent with the reanalysis of Bischoff-Ferrari's data performed in the Institute of Medicine report on vitamin D (44). This is also consistent with another trial (45) in which higher dose cholecalciferol treatment did not reduce falls compared with a lower dose (2000 *vs.* 800 IU/d), suggesting no dose-response effect (28% reduction; 95% CI, −4 to 68%).

Implications for practice and research

The existing body of evidence supports a reduction in the risk of falls caused by vitamin D. The overall quality (risk of bias) of this evidence is graded as moderate due to the moderate unexplained heterogeneity noted in the meta-analysis and the possibility of publication bias. The appropriate dose and duration of vitamin D treatment, as well as the target population for this intervention are yet to be fully defined. The clinical practice guidelines document from The Endocrine Society details the implications for clinicians and patients (53). Future trials should stratify participants by the baseline risk for falls and test for difference dosing regimens. The effect of supplementation on other functional outcomes should also be evaluated. Hence, we encourage all future trials of vitamin D, regardless of their purpose or outcomes, to use standardized questionnaires and measure patient-important outcomes (46) such as quality of life, other aspects of physical function, and independence.

Conclusions

Vitamin D combined with calcium reduces the risk of falls. The reduction in studies without calcium coadministration did not reach statistical significance. The majority of the evidence is derived from trials enrolling elderly women.

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