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Review

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The effect of cholecalciferol (vitamin D_3) on the risk of fall and fracture: a meta-analysis

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Summary

We evaluated the effect of supplementation with vitamin D_3 (excluding the potential effect of calcium supplementation) on the risk of fall and fracture, primarily in postmenopausal women, using a systematic literature review of MEDLINE, EMBASE, BIOSIS and the Cochrane Database of Systematic Reviews for the period January 1985 to June 2005. Studies examining the effect of vitamin D versus placebo on the risk of fall or fracture in postmenopausal females were of particular interest. Studies of vitamin D in combination with calcium were also included where the control group was treated with calcium alone. Studies of men and women where results for men and women were not presented separately were included. Nine studies met the inclusion criteria. Our primary meta-analyses examined the effect of vitamin D_3 on the risk of fall or fracture; additional analyses examined baseline and difference between baseline and final levels of several serum and urinary biochemical markers. The pooled relative risk (RR) for vitamin D_3 preventing falls was 0.88 (95%CI 0.78–1.00). For fractures, the pooled RR for vitamin D_3 preventing non-vertebral fractures was 0.96 (95%CI 0.84–1.09) and the pooled RR for vitamin D_3 preventing vertebral fractures was 1.22 (95%CI 0.64–2.31). In a subgroup analysis of postmenopausal women, the pooled RR for vitamin D_3 preventing falls was 0.92 (95%CI 0.75–1.12) and in preventing non-vertebral fractures the pooled RR was 0.81 (95%CI 0.48–1.34). There is a trend towards a reduction in the risk of fall among patients treated with vitamin D_3 alone compared with placebo, suggesting that vitamin D_3 should be an integral part of effective osteoporosis management.

Introduction

Fractures associated with falls are a significant cause of morbidity and mortality in elderly people.[1] Approximately 30% of those aged 65 years or over living in the community fall each year; this figure rises to 50% in those cared for in institutions.[2] Ninety percent of hip fractures in the elderly are associated with a fall. Each year, about 5% of the elderly population suffers a fracture caused by a fall.[3]

The prevalence of osteoporosis increases with advancing age, and is associated with increased susceptibility to fracture.[4] Osteoporosis affects both sexes, but primarily postmenopausal women, because of the substantial decline in bone mass and changes in bone architecture associated with oestrogen deficiency.[5,6] By the end of the first decade following menopause, half of all White women have osteopoenia or osteoporosis.

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Osteoporosis is both under-diagnosed and under-treated; it is estimated that <15% of American women with osteoporosis receive treatment.[5] Even the majority of high-risk patients, such as those with a fracture, are often not treated for their osteoporosis; in the Netherlands, <20% of patients admitted to hospital with non-trauma fractures received any treatment for osteoporosis during the 1-year period following their fracture;[7] a similar trend has been observed in other parts of the world.[8] As the population ages, osteoporosis is likely to become more prevalent in the future, and the costs of preventing and treating the disease are thus expected to rise.[5]

Given this high prevalence, severity and cost associated with treating osteoporotic fractures, effective methods of reducing or preventing falls and fractures in older people are needed,[9] and vitamin D supplementation is highly recommended as a standard preventative measure in osteoporosis management.[10,11] Vitamin D is essential for the maintenance of calcium homeostasis. It is synthesized in the skin after exposure to sunlight, and is also obtained through the diet.[12,13] Vitamin D inadequacy is common in elderly people, particularly in countries where it is not commonly added to food.[14]

Serum 25-hydroxyvitamin D (25(OH)D), is the accepted functional indicator of vitamin D status, and levels <50 nmol/l (20 ng/ml) have been associated with increased body sway. Values <30 nmol/l may be accompanied by decreased muscle strength,[13] while vitamin D supplementation appears to protect against falls that may lead to fracture.[15] The benefits of vitamin D plus calcium (vs. placebo) have been widely studied with regard to osteoporosis.[16–19] Furthermore, a number of published meta-analyses have combined results of studies of vitamin D given in combination with calcium, and have found that this combination is associated with a reduction in the incidence of fractures.[9,20,21]

However, the independent effect of vitamin D is less well understood for osteoporosis or for falls. Our objective was to use a meta-analysis to evaluate how supplementation with vitamin D alone affects the risk of falling, and sustaining vertebral and non-vertebral fractures, primarily in postmenopausal women.

Methods

Studies of vitamin D published in the English language were identified by systematically searching the electronic databases MEDLINE, EMBASE, BIOSIS and the Cochrane Database of Systematic Reviews for the period January 1985 to June 2005. Hand-searching of journals and conference databases was not done, nor were companies researching the therapy area contacted for additional data.

Inclusion criteria

Studies were eligible for inclusion in the analysis if they fulfilled the following criteria.

Subjects

The patient population of primary interest for this review was women of any ethnicity described as post-menopausal. Men (of any ethnicity, aged 65 years or over) were only included in the analyses where they were part of a study with women, in which results for men and women were not presented separately.

Interventions

Both studies of vitamin D versus placebo and studies of vitamin D in combination with calcium were analysed, if the comparator group was treated with calcium alone. Studies of subjects receiving concomitant non-osteoporosis medications were not excluded from the review.

Types of studies

All study types were identified as part of the review. The reference lists of relevant guidelines, systematic reviews and meta-analyses were searched for other relevant studies for inclusion. The quality of included studies was assessed using published criteria.[22]

Study selection

Identified articles were screened to ensure that the studies met the pre-determined inclusion criteria stated above. The first stage was a review of titles and/or abstracts for all identified citations, followed by a second review stage of full text publications. A positive exclusion method was used: any combination of answers to the checklist criteria that included a 'no' resulted in exclusion of the citation from the review.

Outcome measures

The primary outcomes of interest were the relative risk (RR) of any spontaneous fall (resulting in injury or not), vertebral and non-vertebral fracture. Where data permitted, pre-determined subgroup analyses of postmenopausal women with osteoporosis were done. Similarly, where sufficient data were

available, we did secondary analyses of the difference between final and baseline serum levels of the following biochemical markers: 25(OH)D, parathyroid hormone (PTH), osteocalcin, bone-specific alkaline phosphatase (BSAP) and urinary cross-linked N-telopeptides of type I collagen (NTx). Serum 25(OH)D is the accepted functional indicator of vitamin D status,[23] PTH regulates calcium homeostasis and has a major influence on bone turnover, osteocalcin is a marker of bone formation, and BSAP and NTx are markers of bone resorption.

Data analysis

Statistical analyses used the Review Manager (RevMan) 4.2.1 software package. Outcomes were analysed using fixed-effects models and heterogeneity among the studies was evaluated with a χ^2 test. The fixed-effects model was considered to be the most appropriate model to use, as the outcomes were not significant for heterogeneity. No multivariate methods were used in these analyses.

Results

The literature search resulted in a total of 2410 individual citations that were screened at the first review stage, of which 117 were considered for the second review stage. Nine studies met all of the inclusion criteria and were included in the final meta-analyses.[3,24–31]

The characteristics of included studies are summarized in Table 1, and the baseline and final levels of 25(OH)D reported in each study are presented in Table 2.

All of the included studies were high-quality randomized controlled trials, apart from one study that was a prospective study examining risk factors for falls.[25]

All the studies included cholecalciferol (vitamin D_3). Four examined vitamin D_3 in combination with calcium,[3,24,26,31] and three included postmenopausal women only.[3,26,31] Of the studies including both men and women, only results for women were used in the analyses wherever possible.[29,30] For other studies, combined results for both sexes were used.[24,25,27,28]

The mean baseline serum 25(OH)D levels for the patients included in these studies indicate that patients were vitamin-D-inadequate, as defined by a concentration of 25(OH)D <76.2 nmol/l.[32]

The studies varied in duration from 18 weeks to over 5 years. Patients were treated with daily oral doses of vitamin D_3 ranging from 300 to 800 IU, except in one study, where patients were treated with an oral capsule of 100 000 IU vitamin D_3 taken every 4 months (equivalent to 800 IU daily).[30]

Five studies reported the number of patients experiencing falls as an outcome.[3,24,25,30,31] Six reported the number of patients experiencing non-vertebral fractures,[24,26,27,29–31] and three of these also included data for vertebral fractures.[24,29,30]

Five studies included patients who were receiving concomitant medications such as corticosteroids and thyroid medications.[3,24,27,30,31]

The pooled RR for vitamin D_3 preventing falls was 0.88 (95%CI 0.78–1.00), compared with no vitamin D_3. The χ^2 test for heterogeneity was non-significant for the fall analysis ($p = 0.36$) (Figure 1). When a subgroup analysis on post-menopausal females was performed, the pooled RR for vitamin D_3 preventing falls was 0.92 (95%CI 0.75–1.12), compared with no vitamin D_3 (Figure 2). Again, the test for heterogeneity was non-significant ($p = 0.17$).

In terms of fractures, the pooled RR for vitamin D_3 preventing non-vertebral fractures was 0.96 (95%CI 0.84–1.09), compared with no vitamin D_3 (Figure 3). In post-menopausal females, the pooled RR fell to 0.81 (95%CI 0.48–1.34) (Figure 4). The pooled RR for vitamin D_3 preventing vertebral fractures was 1.22 (95%CI 0.64–2.31), compared with no vitamin D_3 (Figure 5). Data included in the analysis of vertebral fractures were only for post-menopausal women; therefore a sub-group analysis was not performed. Studies were not heterogeneous for any fracture analysis, as measured by the χ^2 test ($p = 0.40$, $p = 0.52$ and $p = 0.25$, respectively).

For the secondary evaluations, meta-analysis of the difference between final and baseline 25(OH)D levels was not possible, as only one study reported both baseline and difference between final and baseline levels.[28] Similarly, only baseline levels of NTx were analysed.

Vitamin D_3 treatment was associated with a greater decrease in PTH than no vitamin D_3 treatment in two studies;[3,31] one reported increases in PTH, the increase being greater for patients not treated with vitamin D_3.[28] Similarly, vitamin D_3 treatment was associated with a decrease in BSAP.[31] Two studies reported increases in osteocalcin with vitamin D_3 treatment,[28,31] and one reported decreased osteocalcin following vitamin D_3 treatment.[3]

Discussion

The pooled results showed a trend towards a reduction in the number of falls experienced by patients treated with vitamin D_3 (with or without calcium) compared with no vitamin D_3 (control

Table 1 Characteristics of included studies

Author	Type of study	Primary endpoint	Setting/country	Treatment groups	Study population characteristics	Dosing	Study duration
Grant *et al.*, 2005[24]	RCT	New low-energy fractures including clinical, radiologically confirmed vertebral fractures, but not those of the face or skull	21 centres in the UK	D_3 + Ca (n = 1306); D_3 (n = 1343); Ca (n = 1311); placebo (n = 1332)	Men and women aged ⩾70 years who had a low-trauma osteoporotic fracture in the previous 10 years	Daily oral dosing of 800 IU D_3	24–62 months
Trivedi *et al.*, 2003[30]	RCT	Fracture and all-cause mortality	Postal study conducted in the UK	D_3 (n = 1345; 326 women) vs. placebo (n = 1341; 323 women)	Men and women aged 65–85 years. History of fall and fracture not stated	One oral capsule (100 000 IU D_3) administered every 4 months	5 years
Lips *et al.*, 1996[27]	RCT	Fracture and all-cause mortality	Community setting in the Netherlands	D_3 (n = 1291) vs. placebo (n = 1287)	Men and women aged ⩾70 years, excluded if past hip fracture	Daily oral dosing (400 IU D_3 per day)	3.5 years
Meyer *et al.*, 2002[28]	RCT	Hip fracture, other non-vertebral fracture and death	51 nursing homes in Norway	D_3 (n = 569) vs. placebo (n = 575)	Elderly men and women (mean age 84.7 years). Some patients had previous fall and/or fracture	Daily oral dosing of cod liver oil containing 400 IU D_3	2 years
Graafmans *et al.*, 1996[25]	Prospective study of risk factors for falls	Falls	13 nursing homes or apartment houses for the elderly in the Netherlands	D_3 vs. placebo (n = 368 for both treatment groups; individual numbers not supplied)	Men and women age ⩾70, excluded if past hip fracture	Daily oral dosing (400 IU D_3 per day)	28 weeks
Peacock *et al.*, 2000[29]	RCT	Change in total hip bone mineral density from baseline to 48 months	US	D_3 (n = 124), Ca (n = 124) or placebo (n = 129)	Men and women aged ⩾60 years. Previous fracture was not an exclusion criterion	Tablets given three times per day (600 IU D_3 per day)	4 years
Komulainen *et al.*, 1998[26]	RCT	Change in bone mineral density from baseline to 5 years	Finland	HRT (n = 116), D_3 + Ca (n = 113), HRT + D_3 + Ca (n = 116), Ca alone (n = 116)	Non-ostoporotic, PM women aged 47–56 years. Some had previous fractures	D_3 group had daily dosing (300 IU D_3 per day; 100 IU in the 5th year), but no D_3 during June–August	5 years
Pfeifer *et al.*, 2000[31]	RCT	Change in PTH levels and body sway from baseline to 8 weeks	Community setting in Germany	D_3 + Ca (n = 74) vs. Ca alone (n = 74)	Women aged 70 years and above with serum 25(OH)D below 50 nmol/l. Patients with osteoporotic fractures of the extremities were excluded	Tablets given twice per day (800 IU D_3 per day)	8 weeks + 1 year follow up
Bischoff *et al.*, 2003[3]	RCT	Falls	Long-stay geriatric care units in Switzerland	D_3 + Ca (n = 62) vs. Ca alone (n = 60)	Women aged 60 years and above, excluded those with fractures in last 3 months	Tablets given twice per day (800 IU D_3 per day)	6 week pre-treatment and 12 week treatment

RCT, randomized controlled trial; 25(OH)D, 25-hydroxyvitamin D; D_3, vitamin D_3 (cholecalciferol); Ca, calcium; HRT, hormone replacement therapy; PM, postmenopausal.

Table 2 Results reported in included studies for biochemical markers

Author	Falls[a] (Y/N)	Fractures[a] (Y/N)	25(OH)D (nmol/l)		*n*
			Baseline	Final	
Lips *et al.*, 1996[27]					
Vitamin D_3	N	Y	27.00	NR	270[c]
Placebo	N	Y	26.00	NR	270[c]
Meyer *et al.*, 2002[28]					
Vitamin D_3	N	Y	47.00	64.00	34
Placebo	N	Y	51.00	46.00	31
Peacock *et al.*, 2000[29]					
Vitamin D_3	N	Y	57.50	NR	95[c]
Placebo	N	Y	60.00	NR	95[c]
Pfeifer *et al.*, 2000[31]					
Vitamin D_3	Y	Y	25.65	NR	148[c]
Calcium	Y	Y	24.63	NR	148[c]
Bischoff *et al.*, 2003[3]					
Vitamin D_3	Y	N	30.75[b]	65.50[b]	61 at baseline; 45 at follow-up
Calcium	Y	N	29.00[b]	28.50[b]	59 at baseline; 44 at follow-up

Y, measured; N, not measured; [a]RR reported in forest plots. [b]Median value (mean reported unless otherwise stated). [c]Total number of subjects in both groups.

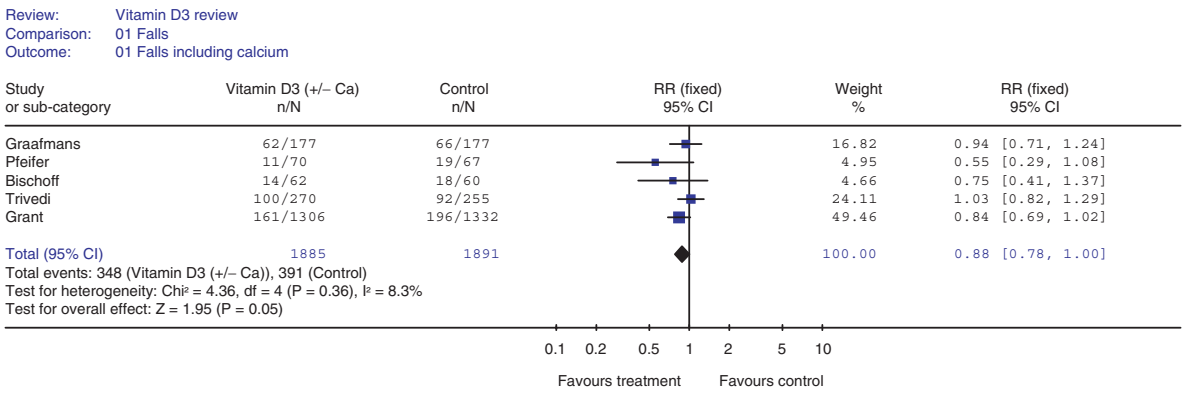

Figure 1. Results of the meta-analysis for falls.

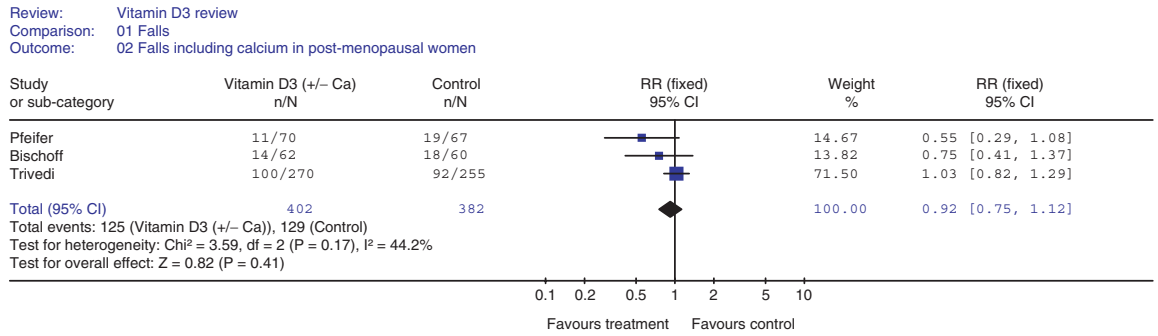

Figure 2. Results of the meta-analysis for falls in post-menopausal women only.

group: calcium or placebo). However, there was no clear evidence on the effect of vitamin D_3 on the risk of non-vertebral and vertebral fractures. Our results differ from those presented by Bischoff-Ferrari *et al.*[9] who, although not assessing the risk of falls, demonstrated a significant 26% reduction in risk of sustaining a hip fracture and a significant 23% reduction in risk of sustaining any

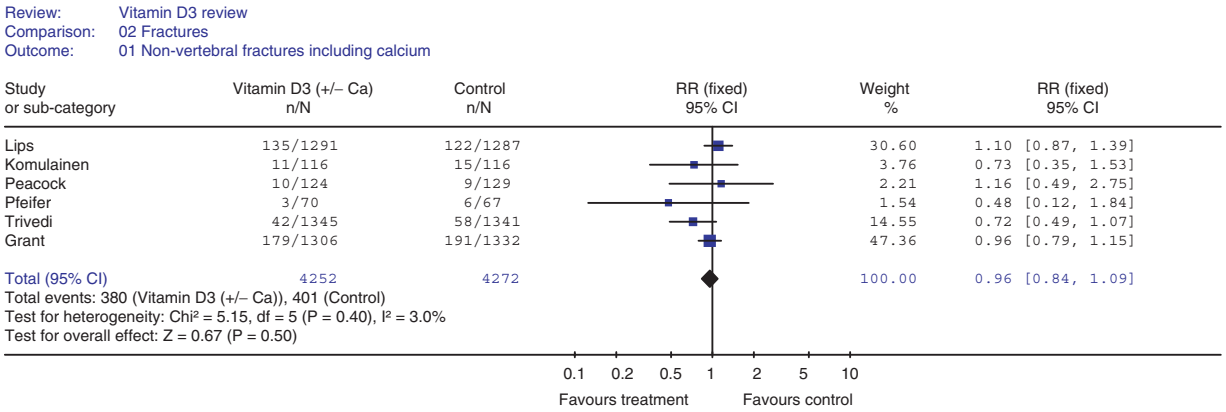

Figure 3. Results of the meta-analysis for non-vertebral fractures.

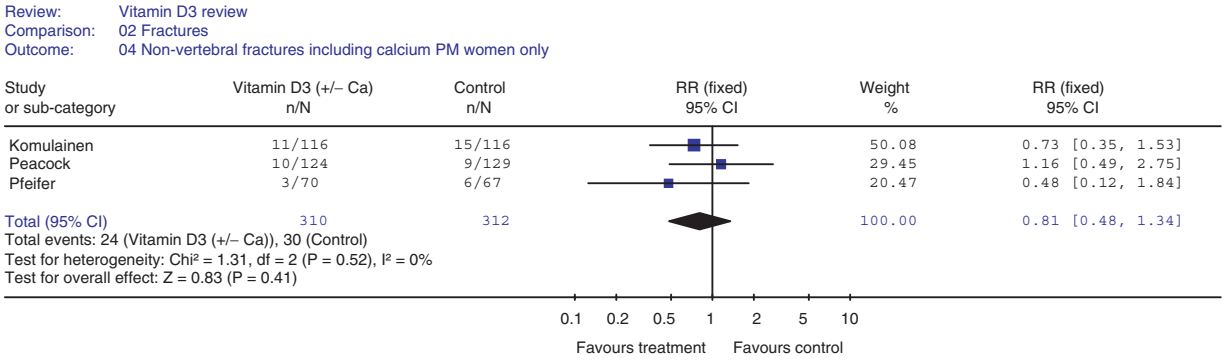

Figure 4. Results of the meta-analysis for non-vertebral fractures in post-menopausal women only.

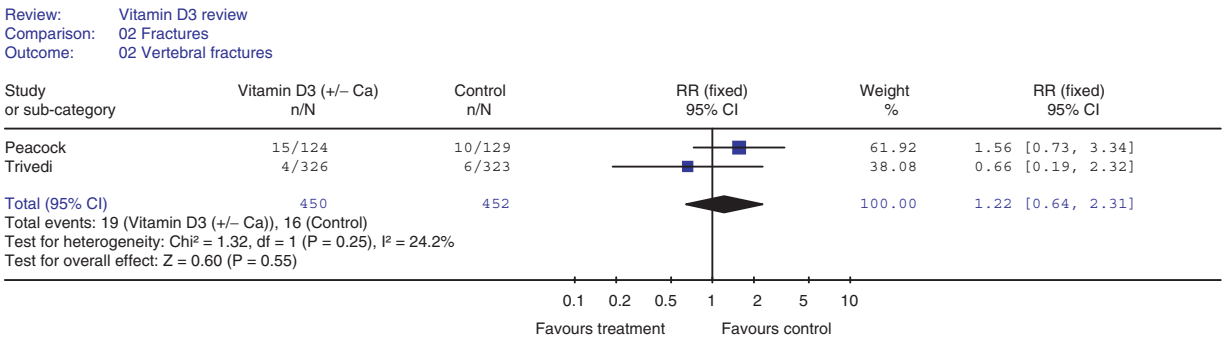

Figure 5. Results of the meta-analysis for vertebral fractures.

non-vertebral fracture for patients receiving vitamin D (700–800 IU per day). Similarly, the meta-analyses reported by Papadimitropoulos and colleagues[20] found a significant 37% decrease ($p < 0.01$) in the risk of vertebral fracture, and reported a trend towards a reduction in the incidence of non-vertebral fractures.[20] However, both of these meta-analyses[9,20] included studies comparing vitamin D with calcium vs. placebo, vitamin D vs. placebo and vitamin D with calcium vs. calcium; our meta-analysis addressed the independent effect of vitamin D, which is less well understood. Also (unlike the meta-analysis by Bishoff-Ferrari *et al.*[9]) this meta-analysis did not specifically look at the 700–800 IU dose, but instead pooled all doses.

To comply with our objective, we had to exclude three large studies comparing vitamin D with calcium vs. placebo.[16–19] In the Decalyos I study,[16,17] the number of hip fractures was reduced by 43% and the number of non-vertebral fractures was reduced by 32% (at 18 months) among women treated with vitamin D_3 and calcium compared to those receiving placebo.[16] At 36 months, there

was a decreased probability of hip fractures ($p < 0.02$) and all non-vertebral fractures ($p < 0.01$), with an odds ratio of 0.73 for hip fractures (95%CI 0.62–0.84) and 0.72 (95%CI 0.60–0.84) for all non-vertebral fractures.[17] In the Decalyos 2 study[18], the risk ratio for hip fracture among women in the placebo group compared with those in the calcium plus vitamin D_3 treatment group was 1.69 (95%CI 0.96–3.0). Finally, in the study conducted by Dawson-Hughes *et al.*,[19] including both men and women, the three-year cumulative incidence of a first osteoporotic fracture in the calcium plus vitamin D group was lower than that in the placebo group (RR = 0.4; 95%CI 0.2–0.8; $p = 0.01$).[19]

The duration of the studies varied quite widely, from 18 weeks to over 5 years.[3,26,30] It is difficult to interpret how this might affect the results of each study; shorter studies allow less time for individuals to fall or experience fractures, longer studies allow a longer period of time for the treatment to take effect.

As with all systematic reviews and meta-analyses, this study is limited by publication bias. In addition, some analyses were not possible, as relevant results were not reported in all of the references included. For example, it would have been interesting to analyse the effect of treatment with vitamin D_3 on the difference in serum 25(OH)D levels before and after treatment, and how this was related to risk of fall and fracture, but this was rarely reported in sufficient detail. Also it would have been relevant to control for 25(OH)D baseline level, since the patients who are more likely to gain from vitamin D supplementation alone are the ones with vitamin D inadequacy.

The age of patients included in the studies varied from 45 years to over 80 years and it is possible that this might have affected the findings of the meta-analysis. Elderly people are more likely to be vitamin-D-inadequate,[32] and are at higher risk of falls and fracture;[33,34] hence they are more likely to benefit from vitamin D supplementation.

It is interesting that despite differences among the studies combined, none of the analyses were associated with significant heterogeneity.

As only a maximum of two studies were included in each analysis of the difference between final and baseline levels of PTH, osteocalcin and BSAP, it is difficult to draw strong conclusions on the effect of vitamin D_3 supplementation on the level of these biochemical markers.

In conclusion, our results suggest a possible treatment effect of vitamin D_3 alone (compared with no vitamin D_3 treatment) in reducing falls. Most clinical trials of new anti-resorptive agents have included vitamin D and calcium as part of the osteoporosis management. It would be logical to adopt this approach and include vitamin D in routine clinical practice in order to have a complete protection against falls and fractures.

Conflict of interest

This study was funded by Merck & Co., Inc. Sabine Gaugris and Dr Shuvayu S. Sen, two of the authors of this manuscript, are employees of Merck & Co., Inc.

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