Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis

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Summary

Background **Findings from recent meta-analyses of vitamin D supplementation without co-administration of calcium have not shown fracture prevention, possibly because of insufficient power or inappropriate doses, or because the intervention was not targeted to deficient populations. Despite these data, almost half of older adults (older than 50 years) continue to use these supplements. Bone mineral density can be used to detect biologically significant effects in much smaller cohorts. We investigated whether vitamin D supplementation affects bone mineral density.**

Methods **We searched Web of Science, Embase, and the Cochrane Database, from inception to July 8, 2012, for trials assessing the effects of vitamin D (D3 or D2, but not vitamin D metabolites) on bone mineral density. We included all randomised trials comparing interventions that differed only in vitamin D content, and which included adults (average age >20 years) without other metabolic bone diseases. We pooled data with a random effects meta-analysis with weighted mean differences and 95% CIs reported. To assess heterogeneity in results of individual studies, we used Cochran's *Q* statistic and the I^2 statistic. The primary endpoint was the percentage change in bone mineral density from baseline.**

Findings **Of 3930 citations identified by the search strategy, 23 studies (mean duration 23·5 months, comprising 4082 participants, 92% women, average age 59 years) met the inclusion criteria. 19 studies had mainly white populations. Mean baseline serum 25-hydroxyvitamin D concentration was less than 50 nmol/L in eight studies (n=1791). In ten studies (n=2294), individuals were given vitamin D doses less than 800 IU per day. Bone mineral density was measured at one to five sites (lumbar spine, femoral neck, total hip, trochanter, total body, or forearm) in each study, so 70 tests of statistical significance were done across the studies. There were six findings of significant benefit, two of significant detriment, and the rest were non-significant. Only one study showed benefit at more than one site. Results of our meta-analysis showed a small benefit at the femoral neck (weighted mean difference 0·8%, 95% CI 0·2–1·4) with heterogeneity among trials (I^2=67%, p<0·00027). No effect at any other site was reported, including the total hip. We recorded a bias toward positive results at the femoral neck and total hip.**

Interpretation **Continuing widespread use of vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency seems to be inappropriate.**

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Introduction

Vitamin D, like calcium, has long been regarded as a fundamental part of the prevention and treatment of osteoporosis. Low vitamin D concentrations result in secondary hyperparathyroidism and accelerated bone loss, although the development of secondary hyperparathyroidism varies, even in patients with severe vitamin D deficiency.[1,2] Findings from observational studies show inconsistent associations between bone mineral density and vitamin D status,[3,4] and debate continues regarding optimum concentrations of 25-hydroxyvitamin D for the best possible skeletal health.[5,6] However, results from meta-analyses of trials of vitamin D alone (ie, not with calcium) failed to show an association between supplementation and fracture prevention.[7,8] This finding could be attributable to aspects of the study design (eg, study power, the population recruited, or the vitamin D dose used). Alternatively, vitamin D might not have a protective effect on bone, as has been postulated.[7] Therefore, surrogate endpoints such as bone mineral density, which can be used to detect biologically significant effects in small cohorts, should be examined closer.

Furthermore, some studies might have used inadequate doses of vitamin D or a baseline vitamin D status of the populations studied that was not low enough for the intervention to produce a significant effect. Thus, the study of the effect of vitamin D supplementation on bone density in terms of the dose given and baseline vitamin D status are important questions that can be addressed in the many studies assessing bone mineral density. Concerns about the cardiovascular safety of calcium plus vitamin D supplements[9] warrant the investigation of vitamin D as a monotherapy.

We aimed to address these questions by systematically reviewing all randomised, controlled trials of cholecalciferol or ergocalciferol that have included bone mineral density data, irrespective of whether this was the primary endpoint of the study, in populations without other disorders likely to affect bone and

calcium metabolism. Despite the negative findings from fracture studies, almost half of adults in the USA use vitamin D supplements.[10] Therefore, to ensure appropriate targeting of this common intervention, investigators need to establish in which groups the vitamin improves bone health.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and meta-Analyses) guidelines, and used a predetermined protocol. To qualify for inclusion,

	Trial duration (months)	N	Mean age (range; years)	Country	Sex (% female)	Mean 25OHD (SD or range; nmol/L)		Dietary calcium (mg/day)	Weight (kg)	Intervention	Co-interventions*	Comorbidities
						Baseline	On vitamin D					
Christiansen, 1980[18]	24	149	50 (inclusion criteria 45–54)	Denmark	100	..	..	..	..	Vitamin D3 2000 IU/day *vs* placebo	Calcium 500 mg/day	..
Dawson-Hughes,† 1991[19]	12	276	62	USA (white)	100	71‡	95§	390	68	Vitamin D3 400 IU/day *vs* placebo	Calcium 380 mg/day	..
Dawson-Hughes,† 1995[20]	24	261	64	USA (white)	100	66‡ ± 25	100§	450	68	Vitamin D3 100 IU/day *vs* 700 IU/day	Calcium 500 mg/day	..
Ooms,† 1995[21]	24	348	80 (inclusion criteria >70)	Holland	100	26¶ (19–37)	62§‖	About 1120¶	71	Vitamin D3 400 IU/day *vs* placebo	..	..
Tuppurainen,** 1998[22]	48	45	55 (inclusion criteria 50–59)	Finland	100	..	..	730	61	Vitamin D3 300 IU/day for 9 of 12 months per year *vs* control	Hormone treatment	..
Komulainen,†** 1999 – HRT[23]	60	231	53	Finland	100	27 (10)	..	830	70	Vitamin D3 300 IU/ day†† for 9 of 12 months per year *vs* placebo	Hormone treatment	..
Komulainen, †** 1999 – no HRT[23]	60	227	53	Finland	100	28 (11)	..	840	69	Vitamin D3: 300 IU/day†† for 9 of 12 months per year *vs* placebo	Calcium 93 mg/day	..
Hunter,† 2000[24]	24	158	59 (47–70)	UK	100	71 (29)	104§‖	1055	63	Vitamin D3 800 IU/day *vs* placebo	..	..
Patel, 2001[25] ‡‡	12	70	47 (23–70)	UK	100	72 (30–119)	+25§	570	68	Vitamin D3 800 IU/day *vs* placebo	..	..
Venkatachalam, 2003[26]	24	50	54	UK	68	..	..	..	..	Intramuscularvitamin D 300 000 IU/year *vs* placebo	..	Treated coeliac disease
Cooper,† 2003[27]	24	187	56	Australia	100	82 ± 26	81§	780	67	Vitamin D2: 10 000 IU/week *vs* placebo	Calcium 1 g/day	..
Harwood,†** 2004[28]	12	75	80 (67–92)	UK	100	29 (10–67)	40§‖§§	..	BMI 24 kg/m²	Intramuscularvitamin D2 300 000 IU *vs* no treatment	No placebo or calcium	..
Aloia,† 2005[29]	36	208	61 (50–75)	USA (100% AA)	100	46 (19; 10–100)	87‖	760	79	Vitamin D3 800 IU/day for 2 years then 2000 IU/ day *vs* placebo	Calcium, to 1·2–1·5 g/day total intake	..
Zhu,*† 2008[30]	60	79	75 (inclusion criteria 70–80) ¶¶	Australia	100	68 (26)	106§‖	990	70	Vitamin D2 1000 IU/day *vs* placebo	Calcium 1·2 g/day	..
Zhu,† 2008[31]	12	302	77	Australia	100	44 ± 13	60§	1100	73	Vitamin D2 1000 IU/day *vs* placebo	Calcium 1 g/day	..
Andersen, 2008[32]	12	173	37¶	Pakistanis in Denmark	51	16¶ (IQR 11–22)	45§‖	530¶	73¶	Vitamin D3 400 IU/day *vs* 800 IU/day *vs* placebo	..	..
Viljakainen,† 2009[33]	6	54	29 (21–49)	Finland	0	62 ± 15	82§‖	1340	79	Vitamin D3 400 IU/day *vs* 800 IU/day *vs* placebo	..	..

(Continues on next page)

	Trial duration (months)	N	Mean age (range; years)	Country	Sex (% female)	Mean 25OHD (SD or range; nmol/L)		Dietary calcium (mg/day)	Weight (kg)	Intervention	Co-interventions*	Comorbidities
						Baseline	On vitamin D					
(Continued from previous page)												
Islam, 2010[34]	12	100	22	Bangladesh	100	36 (10·7)	68§‖	..	49	Vitamin D3 400 IU/day *vs* placebo	..	..
Jorde, 2010[35]	12	421	47 (21–70)	Norway	63	58 ± 21	141§‖	..	BMI 35 kg/m²	Vitamin D3 40 000 IU/week *vs* 20 000 IU/week *vs* placebo	Calcium 500 mg/day	Overweight
Verschueren, 2011[36]	6	113	80 (inclusion criteria >70)¶¶	Belgium	100	53 (34)	146§‖	..	67	Vitamin D3 880 IU/day *vs* 1600 IU/day	Vibration, factorial design	..
Grimnes,† 2012[37]	12	297	63 (inclusion criteria 50–80) ¶¶	Norway	100	71 (23)	185§‖	820	BMI 25 kg/m²	Vitamin D3 800 IU/day *vs* 6500 IU/day	Calcium 1 g/day	..
Rastelli, 2011[38]	6	60	62	USA (13% AA)	100	56 ± 12	74§	..	BMI 32 kg/m²	Vitamin D2 50 000 IU/week *vs* per month *vs* placebo	Calcium 1 g/day, vitamin D3 400 IU/day	Anastrozole
Steffensen,† 2011[39]	22	71	40 (21–50)	Norway	71	56 (25; 18–143)	123§‖	..	BMI 26 kg/m²	Vitamin D3 20 000/week *vs* placebo	Calcium 0·5 g/day	Multiple sclerosis
Nieves,† 2012[40]	24	127	62	USA (100% AA)	100	29 (13)	55§‖	1000‖‖	82	Vitamin D3 1000 IU/day *vs* placebo	Calcium to 1 g/day total intake	..

Age and 25OHD were assessed at baseline, unless shown otherwise. Komulainen and colleagues[23] study included two cohorts, only one of which received hormone treatment, so these studies are presented separately; therefore, 24 cohorts are shown in the table. N=Number of participants randomly assigned. HRT=hormone replacement therapy. AA=African–American. 25OHD=25-hydroxyvitamin D. *Given to both groups. †Compliance reported. ‡Measured during study in group on low dose of vitamin D or placebo.§25OHD concentrations were significantly higher during the study than in the control group. ¶Median IQR. Other values for age, 25OHD, calcium intake, and weight are mean. ‖25OHD concentrations significantly increased during the study in the vitamin D group.**Unblinded study. ††100 IU/day in year 5. ‡‡12 month intervention in a crossover study, crossover study starting in late summer. This is the treatment effect derived with multivariate regression analysis. §§1 year after injection of vitamin D. ¶¶Entry criteria for study; other values are actual age ranges. ‖‖Including supplements.

Table 1: **Characteristics of randomised controlled trials assessing the effects of vitamin D on bone mineral density in adults**

studies had to be randomised controlled trials comparing interventions that differed only in vitamin D content, which were done in adults (average age >20 years). The intervention could be a preparation of vitamin D3 or D2, but not a vitamin D metabolite. If other interventions were given (eg, calcium), they had to be the same in all groups. Studies of individuals with other disorders likely to affect bone and calcium metabolism (eg, chronic kidney disease, pregnancy, glucocorticoid use, and anti-epileptic drug use) were not eligible. Data for bone mineral density (or in the case of forearm assessment, bone mineral content) had to be available, irrespective of whether this was the primary endpoint. There were no language restrictions on trial eligibility.

We searched Web of Science, Embase, and the Cochrane Database from inception to July 8, 2012, with the terms "vitamin D", or "c(h)olecalciferol", or "ergocalciferol", together with either "randomised study", "randomised trial", or "controlled clinical trial". Additionally, the reference lists of reviews of vitamin D were screened for qualifying studies.[5,11–16] Two authors (IRR, MJB) independently confirmed the eligibility of studies and collated the data from the qualifying studies. IRR extracted the data which were double checked by MJB and discrepancies resolved through discussion. Study quality was assessed as recommended in the Cochrane Handbook.[17] The complete search strategy is available in the appendix.

See **Online** for appendix

Statistical analysis

The primary endpoint was the percentage change in bone mineral density from baseline. We pooled data with a random effects meta-analysis with weighted mean differences and 95% CIs reported. To assess heterogeneity in results of individual studies, we used Cochran's Q statistic and the I^2 statistic (I^2>50% was used as a threshold indicating significant heterogeneity). Publication bias was assessed with Funnel plots and Egger's regression model. The effects of vitamin D on bone mineral density were compared between subgroups of trials defined by prespecified characteristics (eg, baseline age, vitamin D status, treatment dose, and trial duration). All tests were two-tailed and a p value of less than 0·05 was deemed statistically significant. We analysed data with Comprehensive Meta-Analysis (version 2).

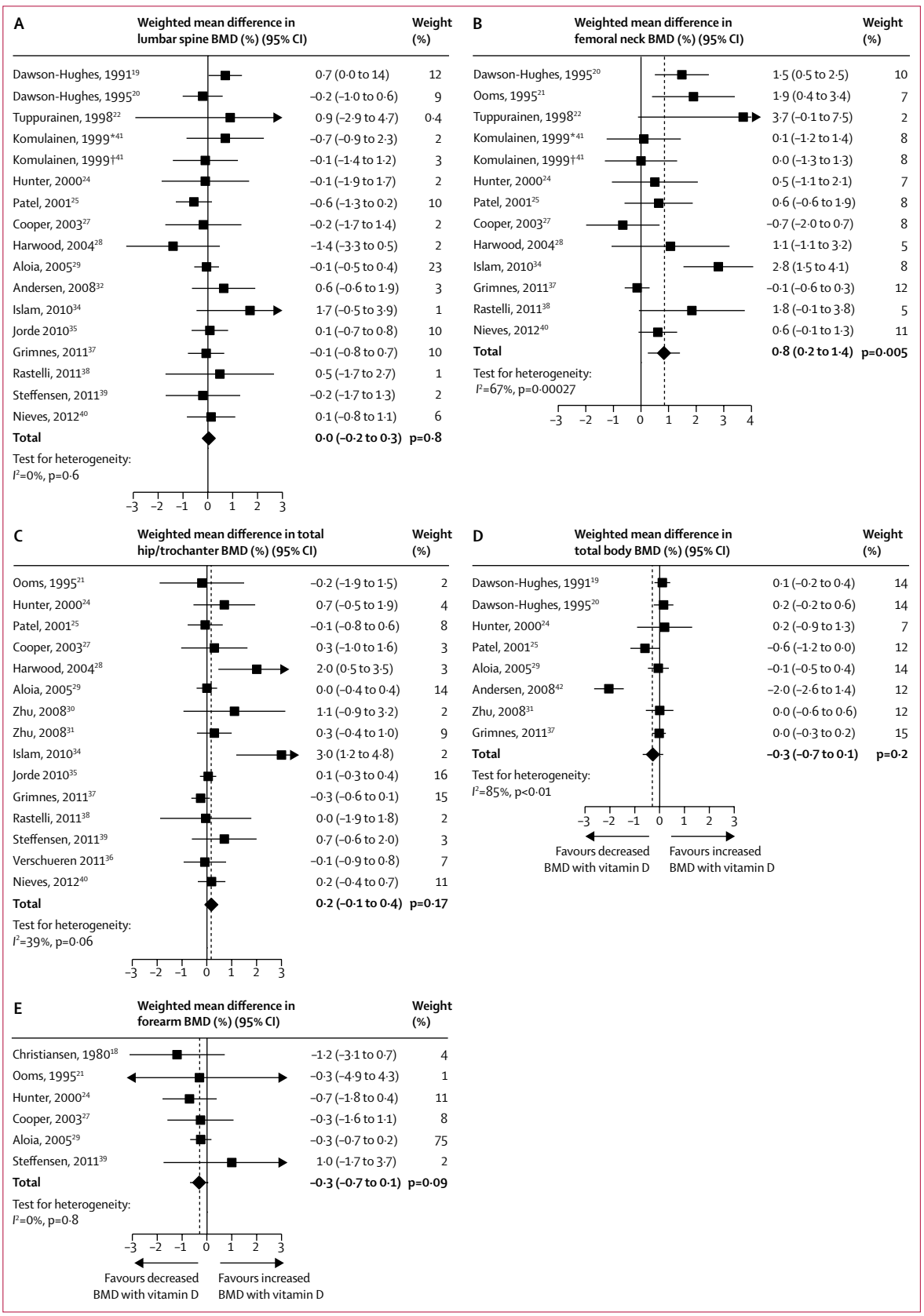

Figure 1: **Meta-analysis of the effects of vitamin D supplementation on BMD at five skeletal sites**
Weighted mean difference in (A) lumbar spine BMD, (B) femoral neck BMD, (C) total hip or trochanter BMD, (D) total body BMD, or (E) forearm BMD. BMD=bone mineral density. HRT=hormone replacement therapy. *HRT. †No HRT.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. IRR and MJB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search strategy identified 3930 unique publications, the titles and abstracts of which were screened for inclusion. The full text of 54 articles was retrieved, of which 23 met the inclusion criteria (appendix). Reasons for exclusion of the remaining articles were: intervention not vitamin D (12), patients too young (two), study not randomised (two), duplicate publication (five), no data for bone mineral density presented (six), and patients had other major pathologies (four).

Table 1 shows descriptive data for the 23 qualifying trials, and figure 1 shows the data for bone mineral density data. One study (Komulainen and colleagues) included two cohorts, one receiving and one not receiving hormone treatment, which are presented separately, so 24 cohorts are shown in the table. 18 studies were placebo-controlled, two had open control groups[22,28] (but in one of these, investigators assessing bone density assessment were masked to treatment group[22]), and three were comparisons between two different doses of vitamin D.[20,37,38] 19 studies were double-blind, and in one (presented in abstract only)[26] blinding was not described. A rigorous method of randomisation was explicitly described in 14 studies, and allocation concealment in ten studies; in the remainder, this information was absent or unclear. One study did not provide details of participants who withdrew or were lost to follow-up.[22] Participant completion rates ranged from 61% to 96%, and the weighted mean was 84%. Two studies[30,38] seemed to have more non-completers in the vitamin D group than in the control group, and one study[40] had more non-completers in the control group. Compliance was more than 80% in the 14 studies in which it was reported. Findings from two recent studies showed bone mineral density at only one site,[30] and Egger's test showed evidence of bias towards positive results at both hip sites (figure 2), but not elsewhere (data not shown), suggesting selective reporting.

The studies recruited 4082 participants, 92% women. In six studies (n=871) the average age was younger than 50 years, and the weighted mean age for the 24 cohorts was 59 years. 19 studies included mainly white populations, two were done exclusively in African–American individuals,[29,40] one took place in Bangladesh,[34] and another studied Pakistani immigrants in Denmark.[32] Two studies included mainly overweight populations.[35,38] 25-hydroxyvitamin D concentration was measured at baseline in all individuals in 19 studies, in 15% in one study,[23] and omitted in three.[18,22,26] A wide range of baseline concentrations of 25-hydroxyvitamin D were reported. The mean level was less than 30 nmol/L in five studies (n=1181), 30–50 nmol/L in three studies (n=610), 50–75 nmol/L in 11 studies (n=1860), and more than 75 nmol/L in only one study (187 healthy Australian women in early postmenopause). In 12 studies, calcium supplements were given to all trial groups. Two studies (n=243) had average total calcium intakes of less than 750 mg per day.[25,32] One study[25] used a crossover design whereas the others were all parallel group studies. Three small studies were of 6 months duration, eight for 1 year, and 12 for 2–5 years. The weighted mean trial duration was 23·5 months.

Various supplement regimens were assessed. Most trials used daily oral dosing, although in two studies, supplementation was given only for 9 months of each year. Four studies (n=739) dosed participants at weekly or monthly intervals, and two studies (n=125) gave annual intramuscular injections of 300 000 units. When doses are averaged, 500 IU per day or less was given in six studies (n=1648), 500–799 IU per day in four studies (n=646), and 800 IU per day or more in 13 studies (n=1788). Three studies had three groups (two different

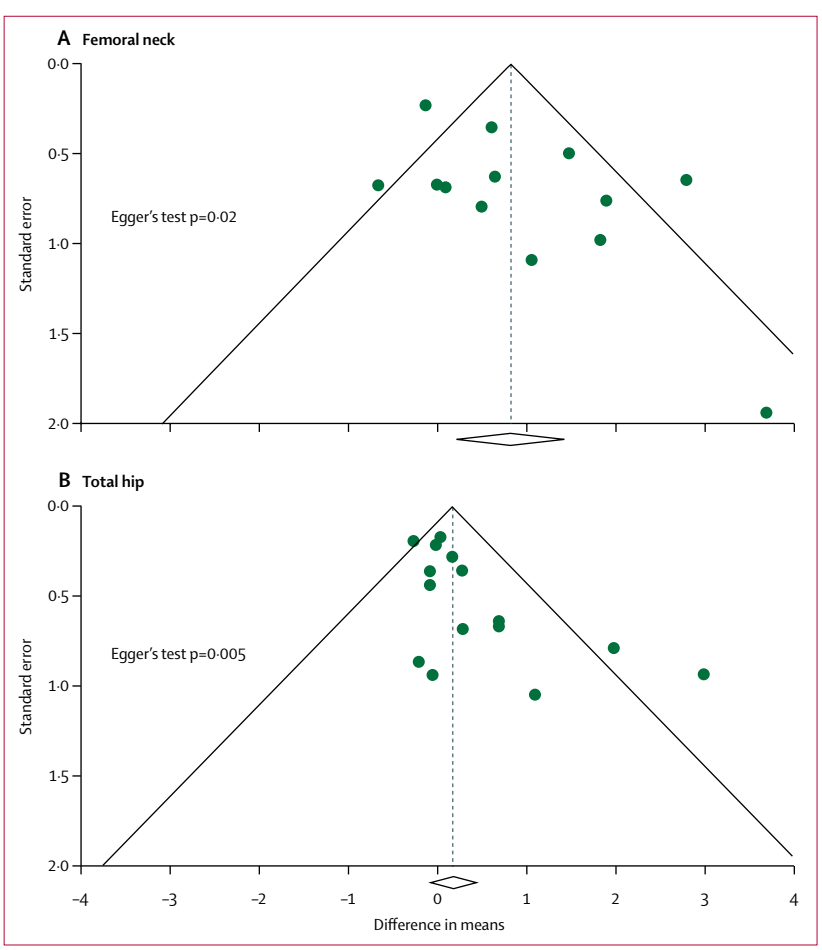

***Figure 2*: Funnel plots of femoral neck (A) and total hip (B) bone mineral density data, testing for publication bias**
Evidence of positive bias (assessed with Egger's test) was apparent for both, but not at the other bone mineral density measurement sites (data not shown).

vitamin D doses and a control group).[32,33,35] In one of these studies,[32] the results were reported separately for men and women. For this study, we pooled the results for men and women, and for all three studies, the results from the two vitamin D groups were pooled and compared with the control group.

Follow-up concentrations of 25-hydroxyvitamin D were reported in 19 studies; in all cases, concentrations were significantly increased in individuals on treatment (table 1). The unweighted mean across all studies increased from 53 nmol/L to 92 nmol/L.

Bone mineral density was measured at one to five sites (lumbar spine, femoral neck, total hip, trochanter, total body, or forearm) in each study (figure 1). The total hip site was assessed in 12 studies and the trochanter in three.[21,27,34] Because the trochanter is the major component of the total hip, we have analysed these data together. There were six findings of statistically significant beneficial effects on bone mineral density, four studies reported beneficial effects at one site only,[19–21] and one study[34] reported beneficial effects in both femoral regions (figure 1). Each of these studies assessed other sites and failed to find significant effects. Two studies reported detrimental effects at the total body ($p \leq 0 \cdot 05$).[32,43]

In three of the five studies with positive outcomes, baseline 25-hydroxyvitamin D concentrations were low (26, 29, and 36 nmol/L),[21,28,34] but in the other two, concentrations of 25-hydroxyvitamin D in the control group were 66 and 71 nmol/L.[19,20] Four studies[23,29,31,32] with baseline 25-hydroxyvitamin D concentrations of less than 50 nmol/L did not produce positive outcomes, although in one study, the vitamin D dose was only 195 IU per day and in another, 1 g calcium was given to both groups every day.[31] Three of the positive studies used vitamin D doses of 400 IU per day,[19,21,34] one compared 700 IU per day with 100 IU per day,[20] and one provided 300 000 IU per year (820 IU per day) by injection.[28] Three positive studies were of 12 months duration, and two lasted 24 months. All positive studies were in women, four in older white women[19–21,28] and one in Bangladeshi women.[34] Thus, no suggestion of ethnic differences in response was evident. Studies comparing higher vitamin D doses with 800 IU per day[36,37] showed no differences.

Figure 1 shows the results of the meta-analysis. Two studies from table 1 were not included in this analysis. In the Venkatachalam study[26] there was a 9-year age difference between the two treatment groups (49 years *vs* 58 years), suggesting that differences in bone loss might not only be related to treatment allocation. The bone mineral density changes tended to be more positive in the placebo group in this study, but this finding was not significant (data not shown). The Viljakainen study[33] was excluded because no quantitative data in the original publication were available, and we have been unable to obtain them from the authors. Investigators of the original publication reported no effects on bone mineral density.

We reported no significant effect of vitamin D on bone mineral density in either the spine or total hip. By contrast, we noted a significant increase in femoral neck bone mineral density, but evidence of heterogeneity in the data (figure 1). Meta-regression exploring the effects of age, study duration, number of participants, sex, 25-hydroxyvitamin D concentration, weight, vitamin D dose, baseline bone mineral density, and type of DXA machine on the femoral neck bone mineral density treatment effect did not show any significant interactions (data not shown). In the forearm and total body scans, both predominantly assessing cortical bone, net changes were negative, although neither was significant (figure 1). We recorded evidence of bias towards positive results at both hip sites, which might have contributed to the positive femoral neck results. However, an analysis restricted to the studies that reported both spine and femoral neck showed the change in bone mineral density to be greater at the femoral neck ($p=0 \cdot 012$; data not shown). A similar comparison in studies reporting both

	25OHD concentrations					Dose					Duration					Calcium				
	<50 nmol/L		≥50 nmol/L		p value	<800		≥800		p value	≤12 months		>12 months		p value	Calcium		No calcium		p value
	n	% difference	n	% difference		n	% difference	n	% difference		n	% difference	n	% difference		n	% difference	n	% difference	
Lumbar spine	7	0·1 (−0·3 to 0·5)	9	0·0 (−0·3 to 0·3)	0·9	7	0·4 (0·0 to 0·8)*	10	−0·1 (−0·4 to 0·2)	0·04	8	0·1 (−0·4 to 0·6)	9	0·0 (−0·4 to 0·3)	0·6	10	0·1 (−0·2 to 0·3)	7	0·1 (−0·6 to 0·7)	>0·9
Total hip	6	0·6 (−0·1 to 1·2)	9	0·0 (−0·2 to 0·2)	0·09	2	1·4 (−1·8 to 4·5)	13	0·1 (−0·1 to 0·3)	0·4	8	0·2 (−0·2 to 0·7)	7	0·2 (−0·1 to 0·5)	0·8	9	0·0 (−0·2 to 0·2)	6	0·7 (−0·1 to 1·6)	0·1
Femoral neck	6	1·0 (0·2 to 1·9)*	6	0·5 (−0·2 to 1·3)	0·2	6	1·4 (0·4 to 2·4)*	7	0·3 (−0·2 to 0·8)	0·06	5	1·2 (−0·1 to 2·4)	8	0·7 (0·0 to 1·3)*	0·5	5	0·4 (−0·5 to 1·3)	8	1·1 (0·4 to 1·9)*	0·2
Forearm	2	−0·3 (−0·7 to 0·2)	3	−0·4 (−1·2 to 0·4)	0·6	1	−0·3 (−4·9 to 4·3)	5	−0·3 (−0·7 to 0·1)	>0·9	..	..	6	−0·3 (−0·7 to 0·1)	..	4	−0·3 (−0·7 to 0·1)	2	−0·7 (−1·7 to 0·4)	0·5
Total body	3	−0·7 (−1·9 to 0·5)	5	0·0 (−0·2 to 0·2)	0·3	3	−0·6 (−1·7 to 0·6)	5	−0·1 (−0·3 to 0·1)	0·4	5	−0·5 (−1·1 to 0·2)	3	0·1 (−0·2 to 0·3)	0·12	5	0·0 (−0·1 to 0·2)	3	−0·9 (−2·1 to 0·4)	0·2

For n, several studies in subgroup. p value for heterogeneity between subgroups. 25OHD=25-hydroxyvitamin D. *Changes for which the CIs do not cross zero.

Table 2: **Meta-analysis of vitamin D effects on bone mineral density in subgroups of trials**

femoral neck and total hip or trochanter did not find those sites to be different (p=0·31; data not shown).

Table 2 summarises effects of bone mineral density in subgroups of trials categorised according to study characteristics. These data suggest that benefits are more pronounced in studies using vitamin D doses of less than 800 IU per day in the lumbar spine, and this effect was independent of the effects of baseline 25-hydroxyvitamin D (data not shown). Study duration and administration of calcium to all trial participants did not affect outcomes. The effect of mean age was analysed similarly in three categories: individuals younger than 50 years, 50–75 years, and 75 years or older. We noted no evidence of an age effect (p values 0·15–0·6 for the various sites; data not shown). Three trials had an open-label study design,[22,23,28] and two studies[30,36] reported results for only one bone mineral density site, raising the possibility of selective reporting. We did a sensitivity analysis excluding these five trials at higher risk of bias. Analyses of the remaining 16 trials produced very similar results for each bone mineral density site to the overall results (data not shown), suggesting that trial quality did not affect outcomes.

Discussion

This systematic review provides very little evidence of an overall benefit of vitamin D supplementation on bone density. Although small increases in bone density at some skeletal sites in some studies were reported, when these increases are offset against the individual findings of deleterious effects, the number of positive results is little better than what would have been expected by chance. Findings of the meta-analysis are similar; we reported a small but significant increase in bone density in the femoral neck, but not at the closely related total hip site. Such a localised effect could be artifactual, or could be a chance finding. The femoral neck has more cortical bone than does the total hip region and is usually less responsive to interventions than are trabecular-rich sites, including to the treatment of osteomalacia.[44] The other cortical-rich sites (forearm and total body) did not show a positive effect, so this is not a cortical-specific effect. Single-site effects on bone mineral density have not been associated with reduction in fractures in individuals given other interventions.

Several studies merit individual mention. Results from the investigation by Tuppurainen and colleagues[22] showed the largest end-of-study increases in femoral neck bone mineral density. This large difference between groups at 5 years is contrary to what was reported at 1 and 2 years, when the vitamin D group had smaller increases in bone mineral density than did the control group. No significant benefit was noted from the use of vitamin D during the whole study. However, exclusion of the Tuppurainen study[22] from the meta-analysis of bone mineral density of femoral neck does not change the results. The only studies to show significant increases in bone mineral density in populations not deficient in vitamin D were from the two studies by Dawson-Hughes and coworkers.[19,20] The reasons for these atypical responses are not clear, but both studies were undertaken at different times in the same cohort, so they are not independent studies. This cohort was originally selected for its low dietary calcium intake (<400 mg per day). These are very low calcium intakes for a western population, suggesting that these data should not be generalised to most western women who need prophylaxis against postmenopausal osteoporosis. Islam and colleagues' study[34] is notable because of the finding of clinically significant increases in bone density at the total hip and femoral neck. These might be chance findings, but this study was done in Bangladeshi women with mean baseline 25-hydroxyvitamin D concentrations of 36 nmol/L, who are likely to have had low dietary calcium intakes, although these data were not reported. Why findings from other studies in populations with similarly low 25-hydroxyvitamin D concentrations did not show improvements in bone density is unclear, but might be accounted for by increased calcium intakes or by the well recognised inaccuracy of many assays for 25-hydroxyvitamin D[45]—ie, the participants in Islam and coworkers' study[34] might have been more deficient in vitamin D than the measurements suggest. The more recent studies in this review (ie, done in the past 5 years) used mass spectrometry or the more reliable of the immunoassays,[43] so should have identified seriously deficient populations.

The negative findings from this systematic review of the effects of vitamin D supplementation on bone density are entirely consistent with those from meta-analyses of the efficacy of this intervention at reducing the risk of fracture.[7,8] These findings sharply conflict with those of other reviews, which show that vitamin D has a substantial beneficial effect on fracture risk.[46,47] These reviews invariably include studies in which calcium and vitamin D is the intervention assessed. Calcium supplements suppress bone turnover by about 20% and have beneficial effects on bone density,[48] so inclusion of studies in which calcium is part of the intervention and attributing the benefits to vitamin D is inappropriate. The effects of the combination of calcium and vitamin D on fracture risk are indistinguishable from those of calcium alone,[49] suggesting that vitamin D contribution is small in most studies. Findings from the study by Chapuy and coworkers[50] have most clearly shown the benefits of calcium and vitamin D. In this study, the placebo group had very low 25-hydroxyvitamin D concentrations (mean 25 nmol/L, measured in 69 women in the placebo group at 12 months) and calcium intakes of only 500 mg per day. Intervention produced a difference between groups in total hip bone mineral density of 7·3%, so the 27% reduction in hip fractures was not surprising. These benefits are consistent with the effects of vitamin D and calcium on bone mineral density in

individuals who are markedly vitamin D deficient (some possibly osteomalacic). The suggested benefit of vitamin D plus calcium on falls[51] might have contributed to the positive outcome in the study by Chapuy and colleagues. The changes in bone mineral density recorded in our meta-analysis are much smaller than those associated with fracture prevention from any intervention. Thus, the antifracture efficacy noted in the Chapuy study should not be expected to be reproduced in substantially less deficient populations, or from the use of vitamin D alone.

The negative findings of our analysis contrast with the widely held perception that vitamin D works directly on bone cells to promote mineralisation.[31,35,52] This perception is probably incorrect. Although the vitamin D receptor knockout mouse has reduced bone mass, this phenotype can be completely corrected and normal mineralisation restored by the provision of calcium and phosphate supplements.[42] Findings of studies of selective vitamin D receptor knockout show that the skeletal phenotype of the vitamin D receptor knockout mouse can be reproduced by selective knockout of the receptor in enterocytes,[53] and that the skeletal abnormalities of the receptor global knockout mouse can be corrected by selective replacement of the vitamin D receptor in enterocytes.[54,55] Thus, expression of the vitamin D receptor in enterocytes is both necessary and adequate for normal bone mineralisation. Selective loss of vitamin D receptor from bone actually increases bone mass.[53,56] This finding can be explained by the fact that vitamin D receptor in bone (in cells of the osteoblast lineage) regulates RANKL and osteoprotegerin production to stimulate osteoclastogenesis.[57] Additionally, vitamin D directly inhibits mineralisation of bone, through increasing local pyrophosphate concentrations.[53] Thus, vitamin D is not a compound mainly responsible for maintenance of bone calcium content, but rather for maintenance of circulating calcium concentrations, which are crucial for cardiac and neuronal function. Bone is merely a reservoir that can be drawn on for this purpose. Of course, in states of vitamin D deficiency, secondary hyperparathyroidism arises, which also stimulates the production of RANKL and osteoclastogenesis. Thus, the biphasic effects of vitamin D on bone mass are unsurprising, because either low or high concentrations can potentially accelerate bone resorption. Some studies of high-dose calciferol or 1α-hydroxylated vitamin D metabolites show increased bone loss[58] and fractures,[59,60] which is consistent with this finding of biphasic effects.

Although our analysis has restrictions common to individual studies (some were unblinded, were short term, used low doses of vitamin D, and most participants had adequate calcium intakes), it also has many strengths. The total number of participants is large for assessment of a bone mineral density endpoint, most individual studies were well powered, with wide ranges of baseline 25-hydroxyvitamin D concentrations, vitamin D doses, dosing regimens, and ethnic groups. Therefore, the failure of any one study and of the meta-analysed data to show consistent benefit across the skeleton is likely to be a real finding.

The clinical implication of our findings is that the widespread use of vitamin D supplements for skeletal protection in adults without specific risk factors for vitamin D deficiency is not justified. This assertion complies with findings from previous meta-analyses of studies of fracture,[7,8] and suggests that no basis exists for the notion that those studies failed to detect a clinically significant benefit as a result of deficiencies in design or execution. The small effects of vitamin D supplements on bone mineral density do not exclude a beneficial effect on fracture by prevention of falls,[51] although findings from the meta-analyses of fracture provide no evidence of this effect.[7,8] Individuals at risk of vitamin D deficiency as a result of skin pigmentation or low sunlight exposure (eg, a result of veiling or frailty) might indeed benefit, so targeting of the intervention is important if the balance of risk and benefit is to be positive.

Further studies of vitamin D supplements in these groups are needed to establish associations between baseline 25-hydroxyvitamin D concentration and responses to vitamin D supplements. Such analyses might contribute to an improved definition of vitamin D deficiency. In the past few years, some clinicians have been enthusiastic about use of vitamin D supplements in doses of more than 1000 IU per day, with a view to achieve serum 25-hydroxyvitamin D concentrations greater than 75 nmol/L. Our analysis gives no support for this target concentration of 25-hydroxyvitamin D, because the existing evidence of benefit on bone mineral density comes from doses of 400–800 IU per day. In fact, data from studies[36,37] comparing high-dose with low-dose vitamin D supplements suggest that individuals on a low dose have improved bone mineral density, although differences between the groups were not significant. Although these conclusions contrast with those of many advocates in the specialty, they align well with the 2010 report from the Institute of Medicine,[5] which concluded (partly on the basis of histological evidence) that 40 nmol/L was an adequate concentration of serum 25-hydroxyvitamin D, and that most adults in North America do not need supplementation. The increasing practice for measurement and supplementation of vitamin D is expensive.[61] Our data suggest that the targeting of low-dose vitamin D supplements only to individuals who are likely to be deficient could free up substantial resources that could be better used elsewhere in health care.

Contributors

All authors developed the concept of this study. IRR and MJB wrote the protocol. IRR and MJB collated the data for the study and MJB did the statistical analyses. The first draft of the manuscript was written by IRR and thoroughly revised by MJB and AG.

Conflicts of interest

We declare that we have no conflicts of interest.

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Vitamin D supplementation: bones of contention

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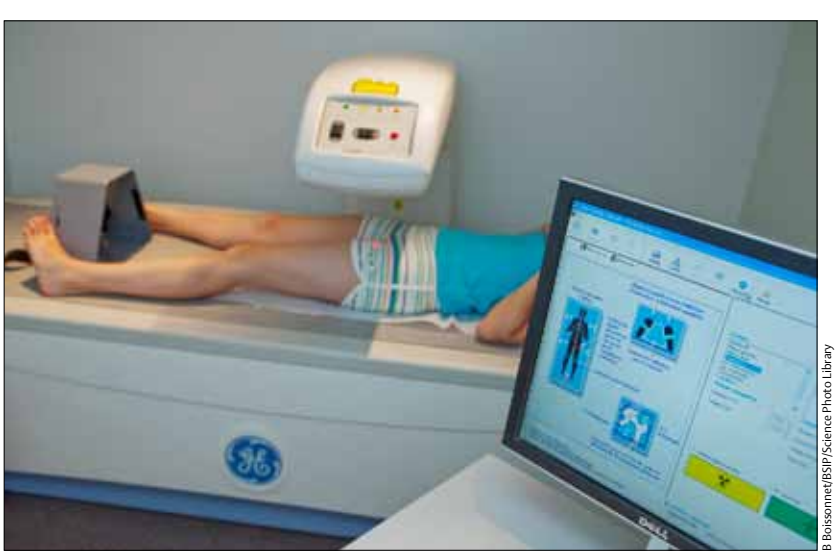
The discovery of vitamin D as an essential nutrient for skeletal development a century ago was a major public health victory. Supplementation, whether solar or dietary, prevented the devastating effects of rickets in children. Five decades later, the molecular mechanisms of the vitamin's active form (1,25-dihydroxyvitamin D) and its receptor (vitamin D receptor [VDR]), were elucidated, and subsequently clinical investigators linked vitamin D deficiency or insufficiency with osteoporosis. This finding seemed logical because osteomalacia (ie, the softening of bone in adults due to impaired mineralisation) can cause fractures and often coexists histologically with osteoporosis. Slowly, vitamin D supplementation became established for prevention of osteoporosis. But, as shown in a meta-analysis in *The Lancet*,[1] the story is more complex, both from an epidemiological and mechanistic perspective.

Ian Reid and colleagues[1] did a systematic review of the effects of vitamin D supplements on bone mineral density that included 23 randomised controlled trials encompassing more than 4000 participants, with a mean age of 59 years. The authors found that vitamin D supplementation for 2 years resulted in no change in bone mineral density at four major skeletal sites (spine, total hip, radius, and total body), with a significant increase (0·8%, 95% CI 0·2–1·4) only at the femoral neck. Surprisingly, any benefit reported in bone mineral density was independent of calcium supplementation, baseline concentration of 25-hydroxyvitamin D, duration of treatment, or age. The investigators conclude that widespread vitamin D prophylaxis in healthy community dwelling adults to prevent osteoporosis is unwarranted.

How can these surprising findings be reconciled with clinical practice and public health strategies to prevent osteoporosis? First, bone mineral density was the primary outcome in the present analysis and is widely used as a surrogate measure of fracture risk. However, changes of bone mineral density in this age group are a modest predictor of subsequent fractures.[2,3] Even with bisphosphonate treatment in high-risk elderly patients (older than 70 years), the bone mineral density increase with bisphosphonates accounts for less than 50% of the effect on fractures.[4] Thus, the absence of a positive relation between vitamin D supplementation and change in bone mineral density could be dismissed as the findings having few clinical implications. However, the results are consistent with those of two recent meta-analyses of randomised trials with vitamin D supplementation alone that recorded no efficacy in fracture prevention, nor in another meta-analysis of vitamin D with an intention-to-treat design.[5–7]

Second, it is difficult to distinguish between the effects of calcium versus those of vitamin D on skeletal integrity, because the main mechanism of action for vitamin D is promotion of calcium absorption in the gut and not direct incorporation of calcium in bone.[8] In the present meta-analysis, only half of the trials used both calcium and vitamin D supplementation.[1] In trials in which vitamin D was given simultaneously with calcium, a significant reduction of 11% in hip fractures and a very modest increase in hip bone mineral density was reported.[9,10] This finding formed the basis of the recommendation by the US Institute of Medicine that 1200 mg of calcium and 800 IU of vitamin D were optimum intakes for skeletal health in elderly people.[10] The inclusion of more studies with calcium plus vitamin D in the present report could have resulted in greater increases in bone mineral density, but confounding by calcium supplementation would not have clarified the role of vitamin D alone in supporting bone mass.

Third, mechanisms of vitamin D action on the skeleton have recently been re-examined leading to a new appreciation of the vitamin's biological role; these findings also



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lend further support to the present meta-analysis. For example, 1,25 dihydroxyvitamin D has been shown to inhibit mineralisation in bone cell cultures. To reconcile this paradoxical finding, Lieben and colleagues[11] used mice in which the VDR in intestine or bone was deleted. In mice with the intestine-specific knockout of VDR, secondary increases in 1,25-dihydroxyvitamin D concentrations stimulated bone resorption while simultaneously inhibiting mineralisation in vivo. By contrast, VDR ablation in bone cells only resulted in increased bone mass and enhanced mineralisation.[11] Lieben and coworkers surmised that, over the long run, maintenance of normocalcaemia takes precedence over skeletal integrity, hence bone is lost and mineralisation is suppressed at the expense of circulating concentrations until calcium sufficiency is restored.

If correct, these findings support the data presented by Reid and colleagues.[1] During states of adequate calcium intake and normal skeletal homoeostasis, vitamin D supplementation might have little or no role in strengthening bone mass since calcium status is adequate. However, with severe vitamin D deficiency (eg, 25-hydroxyvitamin D concentrations <40 nmol/L) or low calcium intake or both, skeletal micro-architecture (but not necessarily areal bone mineral density) is disrupted leading to micro-cracks, skeletal fragility, defects in mineralisation, and increased bone resorption from high concentrations of 1,25-dihydroxyvitamin D.[12] Replacement with vitamin D and calcium would restore skeletal homoeostasis. In Reid and coworkers' analysis,[1] the predominantly female population in middle age is almost certain to be in a state of calcium sufficiency.

Reid and colleagues' meta-analysis is consistent with our understanding of vitamin D: supplementation to prevent osteoporosis in healthy adults is not warranted. However, maintenance of vitamin D stores in the elderly combined with sufficient dietary calcium intake (800–1200 mg per day) remains an effective approach for prevention of hip fractures.

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I declare that I have no conflicts of interest.

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