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REVIEW

Vitamin D supplements with or without calcium to prevent fractures

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Vitamin D deficiency is associated with fractures. This relationship is biologically plausible. The results of 19 randomized clinical trials with vitamin D with or without calcium show varying results: a decreased fracture incidence in 7, neutral in 10 trials, whereas 2 trials with a high dose of vitamin D once per year showed an increased fracture incidence. In three out of four well-powered trials that used recommended doses of vitamin D 700–1000 IU per day, vitamin D supplementation did not significantly influence fracture risk. In one of these trials, a statistically significant fracture reduction was observed in nursing home residents having severe vitamin D deficiency, low calcium intake and good compliance. Thirteen meta-analyses were done, and 11 of these showed a significantly decreased fracture incidence in the supplemented groups. Vitamin D alone was not effective, studies combining vitamin D and calcium showed inconsistent results. Analyses for vertebral fractures were negative in all cases. In conclusion, a vitamin D supplement of 800 IU per day in combination with calcium may decrease the incidence of non-vertebral fractures, especially in persons in the older age groups having low-baseline vitamin D status and low calcium intake and showing good compliance.

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Introduction

Vitamin D deficiency is associated with fractures in several epidemiological studies.[1–3] This association could be co-incidental, as older persons get frail, and frail older persons are at high risk of fracture and vitamin D deficiency because they are less active and do not come outside in the sunshine.[1] However, in one of the studies, adjustment for physical activity levels did not change the results.[3] On the other side, a causal relationship is plausible because vitamin D deficiency (defined as a serum 25-hydroxyvitamin D (25(OH)D) level $<50\,\text{nmol}\,\text{l}^{-1}$) leads to secondary hyperparathyroidism and increased bone resorption.[1,4] In addition, the newly formed bone during high remodeling due to secondary hyperparathyroidism is less well mineralized. A randomized clinical trial with vitamin D 400 IU per day versus placebo showed a significant increase of bone mineral density in the hip, confirming a lower mineralization degree at the baseline.[5] The evidence for a causal relationship with fractures should come from randomized double-blind placebo-controlled trials. These trials have been done, but less than 50% showed a decreased incidence of fractures, whereas others did not show any effect or even a negative effect.[6] The Institute of Medicine concluded that vitamin D supplementation can have a moderate anti-fracture effect.[7] However, the US Preventive Services Task Force advised against vitamin D supplementation for the prevention of fractures.[8] This review discusses the rationale and mechanistic evidence, summarizes the data from 19 randomized clinical trials and discusses the high number of meta-analyses that have been done. It also discusses the conclusions from the Institute of Medicine and the US Preventive Services Task Force. The review ends with a conclusion and advice for further research.

Rationale

In the elderly, a negative calcium balance is common, due to low dietary calcium intake and vitamin D deficiency, resulting in lower calcium absorption from the gut. This negative calcium balance causes secondary hyperparathyroidism, an increase in bone resorption and lower mineralization of newly formed bone. When vitamin D deficiency is severe and longstanding, the newly formed bone matrix, the osteoid, will not mineralize,

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Table 1 Results of randomized clinical trials of vitamin D (and calcium) with fracture as outcome criterion (adapted from ref [6])

Reference	*Patients*	*Type*	*Vitamin D dose*	*Calcium dose mg per day*	*Baseline follow-up (FU) 25(OH)D nmol l^{-1}*	*Fracture risk reduction*
Chapuy *et al.*[16]	3270[a]	db	800 IU per day	1200	18–71[b]	Hip: −43%*, non vert: −32%*
Heikinheimo *et al.*[17]	799[a]		150 000–300 000 per year	—		Fractures −24%*
Lips *et al.*[18]	2578	db	400 IU per day	—	26–54	Hip: NS, non vert: NS
Dawson-Hughes *et al.*[19]	389	db	700 IU per day	500	71–99	Non vert: $P=0.02$
Komulainen *et al.*[20]	464		300 IU per day	—		Non vert: NS
Chapuy *et al.*[21]	583[a]	db	800 IU per day	1200	FU 80	Non vert: $P=0.07$
Meyer *et al.*[22]	569[a]	db	400 IU per day	—		Hip: NS, non vert: NS
Trivedi *et al.*[23]	2686	db	100 000 IU per 4 months	—	FU 74	Non-vert: −22%*
Larsen *et al.*[24]	9605		400 IU per day	1000	37–47	Non-vert: −16%*
Harwood *et al.*[25]	150[a]		800 IU per day or 300 000 IU*)	1000	29–50	Non-vert: NS, falls −52%*
Grant *et al.*[26]	5292	db	800 IU per day	1000	38–62	Hip: NS, non vert: NS
Porthouse *et al.*[27]	3454		800 IU per day	1000		Hip: NS, non vert: NS
Jackson *et al.*[28]	36 282	db	400 IU per day	1000		Hip: NS, total fr: NS (hip: per protocol: −29%*)
Flicker *et al.*[29]	625[a]	db	1000 IU per day	600		Non vert: NS, falls: −27%*
Lyons *et al.*[30]	3440[a]	db	100 000 IU per 4 months	—	FU 80	Non vert: NS
Smith *et al.*[31]		db	300 000 IU per year			Hip +20%
Pfeifer *et al.*[32]	242	db	800 IU per day	1000	55–84	Non vert: NS, falls: −27%*
Sanders *et al.*[33]	2256	db	500 000 IU per year	—	49–120	Fract +26%*,falls: +15%*
Salovaara *et al.*[34]	3195		800 IU per day	1000	50–75	Fract - −13% (NS)

Abbreviations: db, double blind; hip, hip fracture; non vert, non-vertebral fracture; NS, not significant.
*$=P<0.05$ * single injection, 1-year follow-up.
[a]Residential home or nursing home. [b]After cross-calibration.[35]

leading to accumulation of osteoid tissue and osteomalacia.[1] In a forensic autopsy study, osteoid volume was higher than 5% in 4.8% of the cases and higher than 10% in 1% of the cases.[9] In population-based studies, bone mineral density is positively correlated with vitamin D status.[10] In the National Health and Nutrition Examination Survey, bone mineral density increased about 5% when serum 25(OH)D increased from 20–80 nmol l^{-1}. A similar increase of bone mineral density of the hip was seen in the Longitudinal Aging Study Amsterdam (LASA) when serum 25(OH)D increased from 20–50 nmol l^{-1}.[11] Vitamin D deficiency was associated with hip fractures and other fractures in several epidemiological studies.[1–3]

Vitamin D deficiency may cause falls, as shown in epidemiological studies.[12] Probably muscle weakness and postural instability are involved. Vitamin D status was strongly associated with physical performance, measured by a walking test, five-chair stands and the tandem stand, in the LASA and B-PROOF cohorts.[13,14] However, the presence of the vitamin D receptor in muscle tissue has been debated.[15]

Clinical Trials

From 1992 onward, 19 randomized controlled clinical trials on the effect of vitamin D supplementation with or without calcium on fracture incidence have been reported.[16–34] The results of these trials are summarized in **Table 1**. Thirteen of these were randomized double-blind placebo-controlled trials and six were randomized controlled trials without placebo. The vitamin D dose varied between 300 IU once per day and 500 000 IU once per year. In 11 trials, the vitamin D supplement was combined with a calcium supplement between 500 and 1200 mg of elementary calcium per day, usually 1000 mg per day. Fracture incidence decreased significantly in five trials.[16,17,19,23,24] One trial showed a borderline-decreased incidence of fractures[21] and in another very large trial, the Women's Health Initiative, a decreased hip fracture incidence was observed in the per protocol analysis only.[28] In 10 trials, fracture incidence did not decrease, but in three of these a decreased fall incidence was seen. In two trials with one high dose vitamin D per year, orally or by injection, compared with placebo,[31,33] an increase of fracture incidence was observed. In one of these, fall incidence also increased in the vitamin D group.[33] The results of the vitamin D trials vary widely, even in the nine trials that used recommended doses of vitamin D 700–1000 IU per day in combination with calcium. This may indicate that the participants of the trials were not vitamin D-deficient or had already a high calcium intake. In addition, the fracture incidence might have been too low or the study was not adequately powered. This was not the case in the trials of Chapuy *et al.*, Grant *et al.*, Porthouse *et al.* and Salovaara *et al.*[16,26,27,34] In three of these trials, vitamin D supplementation was not significantly associated with a reduced fracture risk. The only significant effect was observed in the trial of Chapuy *et al.*, which was performed in persons living in nursing home or apartment houses for the elderly. The participants in this trial had severe vitamin D deficiency (see data in **Table 1** after cross-calibration,[35] and low calcium intake. The average baseline 25(OH)D levels in this trial were the lowest of all trials. The compliance with therapy was high as the medication was distributed daily in the nursing homes. The number needed to treat for prevention of one non-vertebral fracture in this trial can be calculated as 26. This shows what can be accomplished with adequate dosing in a well-targeted study. In community-dwelling older persons having higher average serum 25(OH)D levels, the effect of vitamin D on fracture incidence may be smaller than claimed.

Meta-analyses

From 2005 till now, 13 meta-analyses on clinical trials for fracture prevention have been published.[36–49] These meta-analyses are summarized in **Table 2**. The authors have subdivided the meta-analyses according to vitamin D dose,

Table 2 Meta-analyses of the anti-fracture efficacy of vitamin D (alone or in combination with calcium)

Reference	*Number of participants*	*Number of studies*	*Vitamin D dose*	*Calcium dose*	*Effect size on fractures*
Bischoff-Ferrari *et al.*[36]	5572	3	700–800 IU per day	750–1200 mg per day	Hip: RR 0.74 (95% CI 0.61–0.88)*
	6098	5	700–800 IU per day	750–1200 mg per day	Non-vertebral: RR 0.77 (95% 0.68–0.87)*
	3722	2	400 IU per day	450–800 mg per day	Hip: RR 1.15 (95% CI 0.88–1.50)
	3722	2	400 IU per day	450–800 mg per day	Non-vertebral: RR 1.03 (95% CI 0.86–1.24)
Boonen *et al.*[37]	9083	4	400–800 IU per day	—	Hip: RR 1.10 (95% CI 0.89–1.36)
	3361	2	700–800 IU per day	—	Hip: RR 1.04 (95% CI 0.75–1.46)
	45 509	6	400–800 IU per day	500–1200 mg per day	Non-vertebral: RR 0.88 (95% CI 0.78–0.99)* Hip: RR 0.82 (95% CI 0.71–0.94)*
	9227	5	700–800 IU per day	500–1200 mg per day	Hip: RR 0.79 (95% CI 0.64–0.97)*
Jackson *et al.*[38]	902	2	600–800 IU per day	—	Vertebral: RR 1.22 (95% CI 0.64–2.31)
	8524	6	300–800 IU per day	0–1000 mg per day	Non-vertebral: RR 0.96 (95% CI 0.84–1.09)
Tang *et al.*[39]	46 108	8	400–800 IU per day	500–1200 mg per day	Any: RR 0.87 (95% CI 0.77–0.97)*
Cranney *et al.*[40]	58 712	13	300–1100 IU per day	0–1200 mg per day	Any: OR 0.90 (95% CI 0.81–1.02)
	46 072	7	400–800 IU per day	500–1200 mg per day	Hip: OR 0.83 (95% CI 0.68–1.00)
	44 260	3	400–800 IU per day	0–1000 mg per day	Vertebral: OR 0.88 (95% CI 0.73–1.07)
	4478	3	800–1100 IU per day	1000–1200 mg per day	Any: OR 0.73 (95% CI 0.61–0.88)* in institutionalized elderly
Update: Chung *et al.*[41]		3	400–800 IU per day	0–1200 mg per day	Any: NS (no meta-analysis)
Reid *et al.*[42]	46 476	6	400–800 IU per day	500–1200 mg per day	Hip: RR 0.84 (95% CI 0.73–0.97)*
Avenell *et al.*[43]	25 016	10	⩾400 IU per day	—	Any: RR 1.01 (95% CI 0.93–1.09)
	24 749	9	⩾400 IU per day	—	Hip: RR 1.15 (95% CI 0.99–1.33)
	9138	5	⩾400 IU per day	—	Vertebral: RR 0.90 (95% CI 0.42–1.92)
	46 658	8	⩾400 IU per day	500–1200 mg per day	Hip: RR 0.84 (95% CI 0.73–0.96)*
	38 990	3	⩾400 IU per day	500–1200 mg per day	Vertebral: RR 0.91 (95% CI 0.75–1.11)
Bischoff-Ferrari *et al.*[44]	31 872	5	>400 IU per day	0–1200 mg per day	Hip: RR 0.82 (95% CI 0.69–0.97)*
	25 746	3	>400 IU per day	1000–1200 mg per day	Hip: RR 0.75 (95% CI 0.65–0.86)*
	33 265	9	>400 IU per day	0–1200 mg per day	Non-vertebral: RR 0.80 (95% 0.72–0.89)*
	26 135	4	>400 IU per day	500–1200 mg per day	Non-vertebral: RR 0.79 (95% 0.71–0.88)*
DIPART Group *et al.*[45]	68 517	7	400–800 IU per day	—	Any: HR 1.01 (95% CI 0.92–1.12) Hip: HR 1.09 (95% CI 0.92–1.29) Vertebral: 1.12 (95% CI 0.70–1.79)
			400–800 IU per day	1000 mg per day	Any: HR 0.92 (95% CI 0.86–0.99)* Hip: HR 0.84 (95% CI 0.70–1.01) Vertebral: 0.85 (95% CI 0.66–1.11)
			400 IU per day	1000 mg per day	Hip: HR 0.74 (95% CI 0.60–0.91)*
Bergman *et al.*[46]	12 658	8	800 IU per day	750–1200 mg per day	Non-vertebral: OR 0.77 (95% CI 0.60–0.93)* versus placebo Hip: OR 0.70 (95% CI 0.53–0.90)* Non-vertebral non-hip: OR 0.84 (95% CI 0.67–1.04)
			800 IU per day	750–1200 mg per day	Non-vertebral: OR 0.68 (95% CI 0.43–1.01) versus calcium alone Hip: OR 1.03 (95% CI 0.39–2.25) Non-vertebral non-hip: OR 0.64 (95% CI 0.38–0.99)*
Lai *et al.*[47]	28 324	7	400–1100 IU per day	0–1000 mg per day	Hip: RR 1.13 (95% CI 0.98–1.29)
Chung *et al.*[48]	14 583	5	400–1370 IU per day	—	Any: RR 1.03 (95% CI 0.84–1.26)
	52 915	11	300–1000 IU per day	500–1200 mg per day	Any: RR 0.88 (95% CI 0.78–0.99)* Subgroup analysis: institutionalized: RR 0.71 (95% CI 0.57–0.89)* community-dwelling: RR 0.89 (95% CI 0.76–1.04)
Bischoff-Ferrari *et al.*[49]	19 461	11	792–2000 IU per day	0–⩾1000 mg per day	Hip: RR 0.70 (95% CI 0.58–0.86)* Non-vertebral: 0.86 (95% 0.76–0.96)*
	10 439	11	792–2000 IU per day	<1000 mg per day	Hip: RR 0.65 (95% CI 0.25–1.68) Non-vertebral: 0.62 (95% 0.39–0.97)*
	2756	11	792–2000 IU per day	⩾1000 mg per day	Hip: RR 0.77 (95% CI 0.30–1.96) Non-vertebral: 1.19 (95% 0.82–1.74)

Abbreviations: CI, confidence interval; OR, odds ratio; RR, risk ratio.
*$P<0.05$.

calcium dose and fracture type. This means that actually many more analyses have been performed. The number of included studies varied between 2 and 13 according to different selection criteria. Meta-analyses or subanalyses of meta-analyses comparing the effect of vitamin D alone with placebo consistently did not show a reduction in fracture risk.[37,38,43,45,48] In contrast, the combination of vitamin D and calcium gave inconsistent results, with a 12–26% reduction in fracture risk in some (subanalyses of) meta-analyses,[36,37,39,42,44,48] but no preventive effect in other,[38,40,41,47] or different results in

subgroups of patients[40,48] or according to the dose of vitamin D and/or calcium[36,45,46,49] or the fracture site.[43,45] Analyses for vertebral fractures were negative in all cases. The meta-analyses on any fracture, non-vertebral fractures and hip fractures were positive in part with hazard ratios or risk ratios varying between 0.62 and 0.92.

Discussion

Clinical trials with a significant decrease of fracture incidence combined vitamin D and calcium with two exceptions, the Heikinheimo and Trivedi trial.[17,23] In general, a dose-response effect was visible, but even a low dose of 400 IU per day showed a decreased fracture incidence in the per protocol analysis in the Women's Health Initiative trial.[28] A great number of meta-analyses has been performed with varying results. These meta-analyses or their subanalyses consistently showed that vitamin D alone is insufficient for fracture risk reduction.[37,38,43,45,48] This is not surprising as the aforementioned negative calcium balance in elderly individuals often results from vitamin D deficiency and low calcium intake. Adding calcium supplements to vitamin D indeed resulted in a significant 12–26% reduction of fracture risk in these[37,43,45,48] and other[36,39,42,44] (subanalyses of) meta-analyses. However, despite the combination of vitamin D and calcium, other meta-analyses failed to show a consistent reduction in fracture risk.[36,38,40,41,43,45–49] Factors that may explain these inconsistent results include an inadequate dose of vitamin D, different baseline values of vitamin D and therapeutic non-compliance with the supplements.[50] First, fracture prevention requires an adequate dose of vitamin D. This was shown in the meta-analyses of Bischoff-Ferrari *et al.*,[36,44,49] in which 700–800 IU or at least a dose in excess of 400 IU of vitamin D was required to reduce fracture risk. Second, inconsistencies in the results of the meta-analyses might also be explained by different baseline values of serum 25(OH)D. Indeed, routine supplementation to the population is not effective, but should be targeted to persons with vitamin D deficiency and a low calcium intake. This can be illustrated by the RECORD trial of Grant *et al*.,[26] in which the combination of 800 IU of vitamin D and 1000 mg calcium failed to show a reduction in fracture risk. Most of the participants in this trial were mobile, healthy and community-dwelling individuals, who are less likely to have calcium or vitamin D deficiency and to benefit from substitution. On the contrary, in older (>75 years of age) or institutionalized persons and patients with osteoporosis, a low level of serum 25(OH)D ($<20\,\mathrm{ng\,ml^{-1}}$) is highly prevalent[1] and these persons will therefore benefit most from substitution therapy. This is illustrated by the first double-blind trial by Chapuy *et al.*[16] in Lyon, where 3204 severely deficient nursing home residents with low calcium intake were treated with vitamin D 800 IU per day and calcium 1200 mg per day versus double placebo. The high fracture incidence reduction in this trial can be explained by the poor vitamin D status and very low calcium intake in this frail nursing home population. Thus, supplementation will only be effective when targeted to individuals with documented or at high risk of deficiencies and those with a high fracture risk.[51] This may explain why in the meta-analyses of Cranney *et al.*[40] and Chung *et al.*[48] vitamin D supplementation reduced fracture risk in institutionalized but not in community-dwelling individuals. Most meta-analyses, however, do not provide information about baseline vitamin D status, and lack of targeting the supplements to persons with insufficiencies might explain at least some of the inconsistent results of these meta-analyses. Likewise, the inclusion of individual trials which allowed non-protocol calcium intake such as the WHI trial[28] might explain why some meta-analyses did not find an additional effect of calcium supplements besides vitamin D.[44] Finally, also differences in therapeutic compliance might explain the different results of the meta-analyses. Indeed, to prevent osteoporotic fractures, compliance and persistence with calcium and vitamin D are essential as the inhibitory effects of calcium and vitamin D on bone resorption are short-lived and cease when supplementation is discontinued. However, even in relatively healthy participants in studies like the WHI[28] and the RECORD trial,[26] compliance with supplementation was only 40–60%. The negative outcome of these trials can, at least partly, be explained by non-compliance and influences the result of meta-analyses in which these individual trials weight heavily.[40,41] Compliance in nursing homes usually is high, as medication is distributed by nurses, and this may also explain the high fracture incidence reduction in the study of Chapuy *et al.*[16] Also in the meta-analysis of the DIPART group,[45] the inconsistent fracture risk reduction with a reduction in fracture risk in the subanalysis of 400 IU of vitamin D and 1000 mg calcium but no reduction in the subanalysis of 400–800 IU of vitamin D and 1000 mg calcium might be explained by poor compliance in some of the studies with a higher dose of vitamin D. Exclusion of trials with a compliance rate of less than 80% doubled the reduction of fracture risk in the meta-analysis of Tang *et al.*[39] It is however not excluded that 'healthy adherer bias' might explain this association between better compliance with osteoporosis medication and reduction in fracture risk. The protective effect on fracture risk of a healthy lifestyle in compliers might indeed be falsely attributed to osteoporosis treatment. This was illustrated in a recent analysis of the placebo arm of the WHI trial, in which a better adherence to placebo also reduced fracture risk.[52] Cadarette *et al.*[53] however found little evidence of healthy adherer bias when examining the association between better compliance to osteoporosis medication and reduction of fracture risk, with only better compliance to osteoporosis treatment reducing fracture risk. The varying outcomes of different clinical trials and the different conclusions from the many meta-analyses can only partly be explained by baseline vitamin D status, vitamin D dose, study population and compliance with supplementation. In addition, higher, infrequent doses may be harmful.[31,33] This explains the prudent approach of the Institute of Medicine,[7] recommending vitamin D 800 IU per day or less, whereas the Endocrine Society recommended much higher doses.[54] The conclusion of the US Preventive Services Task Force even is more cautious, stating that the current evidence is insufficient to recommend vitamin D >400 IU per day and calcium >1000 mg per day, whereas lower doses are not recommended at all.[8] The discussion is ongoing and results of further trials are to be awaited.[55]

Conclusion

The overall effect of vitamin D supplementation on fracture risk depends on the combination with calcium, the dose of vitamin D and the compliance with the supplements, and

the targeted part of the population, defined by age, residence, vitamin D status and calcium intake at baseline. In general, a vitamin D supplement of 800 IU per day in combination with calcium may reduce the incidence of non-vertebral fractures by about 10–20% in an old, vitamin D-deficient population. There is a need for well-powered randomized double-blind placebo-controlled trials examining the effects of different doses of vitamin D with and without calcium on the incidence of osteoporotic fractures, eventually combined with other outcomes. Such trials should be done in different age groups including the oldest old and in populations with different vitamin D status and calcium intake at baseline.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001;**22**:477–501.
2. Holvik K, Ahmed LA, Forsmo S, Gjesdal CG, Grimnes G, Samuelsen SO *et al.* Low serum levels of 25-hydroxyvitamin D predict hip fracture in the elderly: a NOREPOS study. *J Clin Endocrinol Metab* 2013;**98**:3341–3350.
3. van Schoor NM, Visser M, Pluijm SM, Kuchuk N, Smit JH, Lips P. Vitamin D deficiency as a risk factor for osteoporotic fractures. *Bone* 2008;**42**:260–266.
4. Parfitt AM, Rao DS, Stanciu J, Villanueva AR, Kleerekoper M, Frame B. Irreversible bone loss in osteomalacia. Comparison of radial photon absorptiometry with iliac bone histomorphometry during treatment. *J Clin Invest* 1985;**76**:2403–2412.
5. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double blind trial. *J Clin Endocrinol Metab* 1995;**80**:1052–1058.
6. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. *Best Pract Res Clin Endocrinol Metab* 2011;**25**:585–591.
7. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK *et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;**96**:53–58.
8. Moyer VA, on behalf of US Preventive Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: US Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2013;158:691–696.
9. Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S *et al.* Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *J Bone Miner Res* 2010;**25**:305–312.
10. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004;**116**:634–639.
11. Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P. Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. *J Clin Endocrinol Metab* 2009;**94**:1244–1250.
12. Snijder MB, van Schoor NM, Pluijm SM, van Dam RM, Visser M, Lips P. Vitamin D status in relation to one-year risk of recurrent falling in older men and women. *J Clin Endocrinol Metab* 2006;**91**:2980–2985.
13. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J *et al.* Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007;**92**:2058–2065.
14. Sohl E, de Jongh RT, Heijboer AC, Swart KMA, Brouwer-Brolsma EM, Enneman AW *et al.* Vitamin D status is associated with physical performance: the results of three independent cohorts. *Osteoporos Int* 2013;**24**:187–196.
15. Mithal A, Bonjour JP, Boonen S, Burckhardt P, Degens H, El Hajj Fuleihan G *et al.* Impact of nutrition on muscle mass, strength and performance in older adults. *Osteoporos Int* 2013;**24**:1555–1566.
16. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S *et al.* Vitamin D3 and calcium to prevent hip fractures in the elderly women. *New Engl J Med* 1992;**327**:1637–1642.
17. Heikinheimo RJ, Inkovaara JA, Harju EJ, Haavisto MV, Kaarela RH, Kataja JM *et al.* Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992;**51**:105–110.
18. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;**124**:400–406.
19. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *New Engl J Med* 1997;**337**:670–676.
20. Komulainen MH, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R *et al.* HRT and vitamin D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas* 1998;**31**:45–54.
21. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S *et al.* Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporos Int* 2002;**13**:257–264.
22. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? a randomized controlled trial. *J Bone Miner Res* 2002;**17**:709–715.
23. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *Br Med J* 2003;**326**:469.
24. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res* 2004;**19**:370–378.
25. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. Nottingham Neck of Femur (NONOF) Study. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham Neck of Femur (NONOF) Study. *Age Ageing* 2004;**33**:45–51.
26. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC *et al.* Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005;**365**:1621–1628.
27. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T *et al.* Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *Br Med J* 2005;**330**:1003.
28. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE *et al.* Calcium plus vitamin D supplementation and the risk of fractures. *New Engl J Med* 2006;**354**:669–683.
29. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA *et al.* Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc* 2005;**53**:1881–1888.
30. Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B *et al.* Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporosis Int* 2007;**18**:811–818.
31. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women–a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology (Oxford)* 2007;**46**:1852–1857.
32. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporosis Int* 2009;**20**:315–322.
33. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D *et al.* Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *J Am Med Assoc* 2010;**303**:1815–1822.
34. Salovaara K, Tuppurainen M, Karkkainen M, Rikkonen T, Sandini L, Sirola J *et al.* Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial–the OSTPRE-FPS. *J Bone Miner Res* 2010;**25**:1487–1495.
35. Lips P, Chapuy MC, Dawson-Hughes B, Pols HAP, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. *Osteoporos Int* 1999;**9**:394–397.
36. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *J Am Med Assoc* 2005;**293**:2257–2264.
37. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab* 2007;**92**:1415–1423.
38. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *Q J Med* 2007;**100**:185–192.
39. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007;**370**:657–666.
40. Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D *et al.* Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess (Full Rep)* 2007;**158**:1–235.
41. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J *et al.* Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess (Full Rep)* 2009;**183**:1–420.
42. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. *Osteoporosis Int* 2008;**19**:1119–1123.
43. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2009;**2**:CD000227.
44. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ *et al.* Prevention of non-vertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;**169**:551–561.
45. DIPART Group. Patient level pooled analysis of 68500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010;**340**:b5463.
46. Bergman GJ, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. *Curr Medi Res Opin* 2010;**26**:1193–1201.

47. Lai JK, Lucas RM, Clements MS, Roddam AW, Banks E. Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies. *BMC Public Health* 2010;**10**:331.
48. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2011;**155**:827–838.
49. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA *et al.* A pooled analysis of vitamin D dose requirements for fracture prevention. *New Engl J Med* 2012;**367**: 40–49.
50. Heaney RP. Vitamin D – Baseline status and effective dose. *New Engl J Med* 2012;**367**:77–78.
51. Boonen S, Vanderschueren D, Haentjens P, Lips P. Calcium and vitamin D in the prevention and treatment of osteoporosis – a clinical update. *J Intern Med* 2006;**259**:539–552.
52. Curtis J, Larson J, Delzell E, Judd S, Safford MM, LaCroix A *et al.* Does the benefit of medication adherence relate more to a drug effect or the behavior itself? Quantifying the effect of adherence behavior using data from the placebo arms of the WHI. *Arthritis Rheum* 2009;**60**:613.
53. Cadarette SM, Solomon DH, Katz JN, Patrick AR, Brookhart MA. Adherence to osteoporosis drugs and fracture prevention: no evidence of healthy adherer bias in a frail cohort of seniors. *Osteoporos Int* 2011;**22**:943–954.
54. Holick MF, Binkley NC, Bisschoff-Ferrari HA, Gordon CM, Hanley CA, Heaney RP *et al.* Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;**96**:1911–1930.
55. Bouillon R, van Schoor NM, Gielen E, Boonen S, Mathieu C, Vanderschueren D *et al.* Optimal vitamin D status: a critical analysis of evidence-based medicine. *J Clin Endocrinol Metab* 2013;**98**:E1283–E1304.