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Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial

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Abstract. Reid IR, Horne AM, Mihov B, Gamble GD, Al-Abuwsi F, Singh M, Taylor L, Fenwick S, Camargo CA, Stewart AW, Scragg R (University of Auckland; Auckland District Health Board, Auckland, New Zealand; Harvard Medical School, Boston, MA, USA). Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial. *J Intern Med* 2017; **282**: 452–460.

Background. Severe vitamin D deficiency causes osteomalacia, yet trials of vitamin D supplementation in the community have not on average demonstrated benefit to bone mineral density (BMD) or fracture risk in adults.

Objective. To determine whether monthly high-dose vitamin D supplementation influences BMD in the general population and in those with low 25-hydroxyvitamin D levels.

Methods. Two-year substudy of a trial in older community-resident adults. A total of 452 participants were randomized to receive monthly doses of vitamin D3 100 000 IU, or placebo. The primary end-point was change in lumbar spine BMD. Exploratory analyses to identify thresholds of baseline 25-hydroxyvitamin D for vitamin D effects on BMD were prespecified.

Results. Intention-to-treat analyses showed no significant treatment effect in the lumbar spine (between-groups difference 0.0071 g cm^{-2}, 95% CI: −0.0012, 0.0154) or total body but BMD loss at both hip sites was significantly attenuated by ~1/2% over 2 years. There was a significant interaction between baseline 25-hydroxyvitamin D and treatment effect ($P = 0.04$). With baseline 25-hydroxyvitamin D ≤ 30 nmol L^{-1} ($n = 46$), there were between-groups BMD changes at the spine and femoral sites of ~2%, significant in the spine and femoral neck, but there was no effect on total body BMD. When baseline 25-hydroxyvitamin D was >30 nmol L^{-1}, differences were ~1/2% and significant only at the total hip.

Conclusions. This substudy finds no clinically important benefit to BMD from untargeted vitamin D supplementation of older, community-dwelling adults. Exploratory analyses suggest meaningful benefit in those with baseline 25-hydroxyvitamin D ≤ 30 nmol L^{-1}. This represents a significant step towards a trial-based definition of vitamin D deficiency for bone health in older adults.

Keywords: clinical trial, osteoporosis, vitamin D, vitamin D deficiency.

Introduction

The vitamin D endocrine system regulates the intestinal absorption of calcium and is, thereby, critical to the maintenance of normocalcaemia and the mineralization of the skeleton. Vitamin D supplements have been widely used in the prevention and treatment of osteoporosis, although recent meta-analyses have questioned their value in optimizing bone density [1] and in fracture prevention [2]. Despite the generally null findings of randomized controlled trials of vitamin D supplementation on bone end-points, it is quite clear that very low

Trial Registration: Australian New Zealand Clinical Trials Registry, Identifier ACTRN12611000402943 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336777.

levels of vitamin D result in osteomalacia, which is associated with reduced bone density as well as with musculoskeletal symptoms. Treatment of osteomalacia results in substantial increases in bone density [3]. It has not been established what the threshold is, in terms of baseline serum 25-hydroxyvitamin D, for any beneficial effects of vitamin D supplementation on bone density to occur. A further factor possibly influencing vitamin D effects on bone is the dose of supplement used. Some studies might have used doses that were inadequate to optimize vitamin D status. In the light of these considerations, we have measured BMD changes over 2 years in a subcohort of older adults taking part in a randomized controlled trial primarily assessing the effects of monthly vitamin D supplementation on cardiovascular events. We have also sought to determine whether there is a threshold of baseline 25-hydroxyvitamin D level for vitamin D supplementation to affect BMD.

Methods

The Vitamin D Assessment (*ViDA*) study is a randomized, double-blind, placebo-controlled trial designed to assess the effect of vitamin D supplementation on the incidence of cardiovascular disease. Full details of the study methods have been published [4]. In brief, the study was open to those aged 50–84 years, resident in Auckland at recruitment, and able to give informed consent. Exclusion criteria included use of vitamin D supplements in a dose >600 IU day^{-1} if aged 50–70 years or >800 IU day^{-1} if aged 71–84 years (based on Institute of Medicine recommendations [5]); history of hypercalcaemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery, or baseline serum corrected calcium >2.5 mmol L^{-1}.

Participants were recruited by mail-outs, mostly through local general practices, between April 2011 and November 2012. From 48 068 invitations, 8851 were assessed for eligibility, 5250 attended the baseline interview, and 5110 were randomized within random block sizes of 8, 10 or 12, within ethnic group and five-year age strata [6]. Treatments were allocated automatically by AWS, study biostatistician. Participants took either one vitamin D_3 softgel capsule (2.5 mg or 100 000 IU) or identical placebo (Tishcon Corporation, Westbury, NY) monthly, except for the first dose, when two capsules were taken. This dose was chosen with a view to maintaining serum 25-hydroxyvitamin D levels in the range of 80–100 nmol L^{-1}, which some observational evidence suggests to be associated with optimal health status [6]. Capsules were mailed to participants' homes, along with a reply-paid questionnaire for participants to record their adherence.

The study was approved by the New Zealand Multi-region Ethics Committee (MEC/09/08/082). The study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000402943).

Bone density substudy

From mid-2012, all subjects entering the main ViDA Study were invited to participate in the bone density substudy, with a recruitment target of 400. Subjects taking medications for treatment of osteoporosis, or those found to have a BMD T-score at any site <−2.5 were not eligible for this substudy as they were offered treatment for osteoporosis. Consenting individuals underwent BMD measurement at study entry (between 7 August 2012 and 7 December 2012) and 2 years later (mean time between scans: placebo 24.4 [SD 0.7] months, vitamin D 24.4 [SD 0.8] months), at the University of Auckland Clinical Research Centre.

Measurements

Serum was collected at baseline and at 2 years and stored at −80C until assayed for 25-hydroxyvitamin D (combining D_2 and D_3) by liquid chromatography–tandem mass spectrometry 180 (AB Sciex API 4000, Framingham, MA) in a local laboratory participating in the Vitamin D External Quality Assessment Scheme (DEQAS) programme (www.deqas.org). The interassay coefficient of variation for the assay is 12.5% at levels of 25–50 nmol L^{-1} and 8% at 100 nmol L^{-1}. Measurements of standards were, on average, within 4.1% (SD 2.9%) of target values. Samples from each participant were measured in the same assay. Bone density measurements of the lumbar spine, proximal femur and total body used a Prodigy dual-energy, X-ray absorptiometer (GE-Lunar, Madison, Wisconsin). The coefficients of variation for BMD measurements in our laboratory are as follows: lumbar spine 1.4%, total hip 1.1%, femoral neck 1.4% and total body 0.4%. Calcium intake was assessed at baseline using a food frequency questionnaire, which has been validated against four-day weighed food records [7] and by demonstration that its measures of calcium intake are inversely

related to parathyroid hormone levels in normal older men and women [8].

Statistical analysis

BMD data were analysed on an intention-to-treat basis using analysis of covariance (ANCOVA) in SAS v 9.4 (Proc Glimmix, in GLM mode, SAS Institute Inc, Cary, NC, USA) with the dependent variable being change from baseline to 2 years and covariate baseline BMD level. As change in BMD over 2 years was expected to be different in men and women, sex was included as a main and interaction effect (with treatment allocation). Ethnicity and age did not significantly influence bone loss so were omitted to produce the most parsimonious model. The prespecified primary outcome was change in lumbar spine BMD, and secondary outcomes were changes in BMD for total hips, femoral necks and total body. $P < 0.05$ was considered statistically significant (two-tailed test). For ease of interpretation and consistency with existing literature, marginal least squares adjusted means for per cent change from baseline is plotted; however, all statistical analyses were performed on change from baseline. Exploratory analyses to assess the effects of baseline 25-hydroxyvitamin D levels on BMD response to vitamin D were carried out by testing for an interaction between quintile of baseline 25-hydroxyvitamin D and treatment effect. Treatment effect was also assessed using cut-points for baseline 25-hydroxyvitamin D concentrations of 25, 30, 40 and 50 nmol L^{-1}. In secondary and exploratory analyses, no adjustment for multiplicity was performed.

Based on our observation that the standard deviation for change in spine BMD in older men is 3% over 2 years [9], it could be calculated that 100 subjects per group provided 80% power at the 5% significance level to detect between-groups differences in change in BMD of about 1%. The inclusion of both genders in this study was expected to increase the within-group variability in the change in BMD, so a larger group size of 200 was chosen. This group size was also chosen to facilitate exploratory analyses assessing the effects of baseline 25-hydroxyvitamin D levels on BMD outcomes.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study conduct and baseline data

The recruitment of participants into the study and their subsequent disposition is shown in Fig. 1. In the placebo group, 94% of randomized subjects completed the study, and in the vitamin D group, the completion rate was 91%. In the placebo group, 92% of participants took >50% of trial medication, and 76% took >90%. The respective figures for the vitamin D group were 93% and 74%. At study end, four participants were taking higher than permitted supplements of vitamin D; 50 000 IU per month in each case, three in the placebo group and one in the vitamin D group.

Baseline data are shown in Table 1. The mean age was 69 years, about two-thirds were male, and >90% were European. Calcium intakes were typical of previous results from this centre.

25-Hydroxyvitamin D

Baseline serum 25-hydroxyvitamin D levels are shown in the Figure S1. Mean (SD) levels were 56 (22) and 55 (23) nmol L^{-1} in the placebo and vitamin D groups, respectively. During the study, serum 25-hydroxyvitamin D concentrations did not change appreciably in the placebo group (+3.3 [95% confidence interval: 0.8, 6] nmol L^{-1}), but rose substantially in the vitamin D group (+73 [69, 77] nmol L^{-1}). At 2 years, mean 25-hydroxyvitamin D levels were 60 (SD 23) nmol L^{-1} and 129 (SD 28) nmol L^{-1} in placebo and vitamin D groups, respectively.

BMD

The BMD changes in the two groups are shown in Table 2 and Fig. 2, using an intention-to-treat (ITT) analysis. There was no significant treatment effect in the lumbar spine (between-groups difference ~0.6%), the primary study end-point. Both groups showed declining BMD in the proximal femur and total body. The loss in the hip sites was statistically significantly attenuated by about ½% over 2 years in the vitamin D group. Bone loss in the total body was almost identical in the two groups.

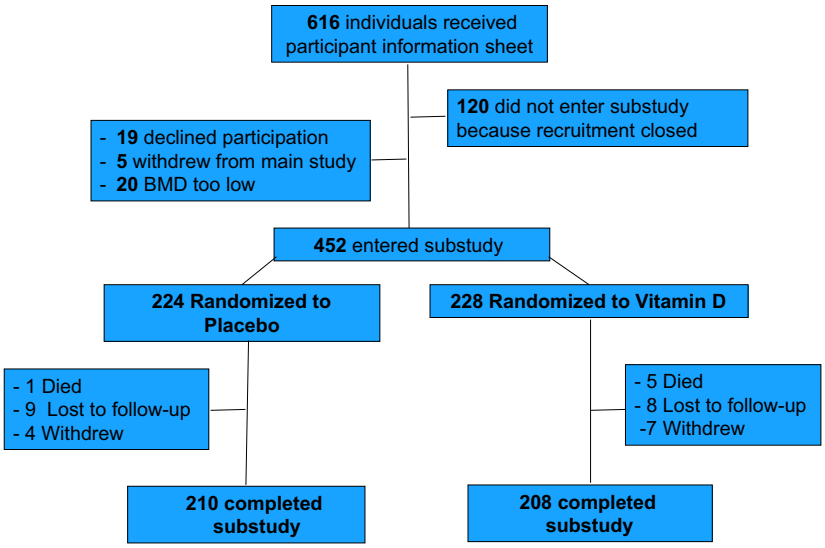

Fig. 1 *Disposition of study participants.*

During the study, two participants in the placebo group took supraphysiological doses of prednisone over periods >3 months, and two participants from the placebo group and one from the vitamin D group were started on long-term bisphosphonates. Exclusion of these individuals from the BMD analyses made no material difference to the ITT results. If the analysis was further restricted to those taking >90% of study medication ($n_{placebo}$ 168, $n_{vitamin\ D}$ 168), the size of the between-groups differences was similar to the ITT results, and the *P* values little changed.

Further analyses were carried out to determine whether the effect of vitamin D supplementation was dependent on the baseline 25-hydroxyvitamin D level. Formal tests for an interaction between baseline 25-hydroxyvitamin D quintile and treatment effect were positive at the lumbar spine ($P = 0.04$), but not at the other sites. The treatment effect was principally in the lowest quintile (25-hydroxyvitamin D 11–37 nmol L^{-1}). Prespecified exploratory analyses were then carried out to determine whether an absolute threshold for the treatment effect could be identified, dividing the cohort at baseline 25-hydroxyvitamin D concentrations of 25, 30, 40 and 50 nmol L^{-1}. This analysis was done after exclusion of the five participants taking bisphosphonates or prednisone. Only 30 participants had baseline 25-hydroxyvitamin D ≤ 25 nmol L^{-1}, and a significant treatment effect was found in the spine (mean changes in BMD: placebo −3.1% vitamin D 0.0%, $P = 0.04$), but not elsewhere. Splitting the cohort at 30 nmol L^{-1} showed between-groups BMD changes at the spine and femoral sites of ~2% in the 46 participants with baseline 25-hydroxyvitamin D ≤ 30 nmol L^{-1} (Fig. 3), statistically significant at the spine and femoral neck. There was also a statistically significant treatment effect at the total hip in those with baseline 25-hydroxyvitamin D > 30 nmol L^{-1}, but this was only ~½% in magnitude. When the cohort was divided at 40 or 50 nmol L^{-1}, the contrast in treatment effects above and below the thresholds was less marked, with between-groups differences for change in BMD being very similar at >30, >40 or >50 nmol L^{-1} (e.g. ~¼% at the spine for all). In the total body, baseline 25-hydroxyvitamin D did not influence the effect of supplementation on BMD.

The total body bone density scans also assess total body fat mass and lean mass. There was no effect of vitamin D on these measures (data not shown).

Discussion

This study has not found an effect on its primary end-point, lumbar spine BMD, but there are small but statistically significant effects on proximal femoral BMD of about ½% in the ITT analysis. There was no treatment effect on total body BMD. Whilst cumulative effects with longer term treatment are possible, it is unlikely that such small differences over a period of 2 years will be

associated with a significant difference in fracture risk, so this finding is unlikely to be clinically relevant. The absence of fracture prevention in the whole ViDA cohort is consistent with this interpretation [10]. Lumbar spine BMD was chosen as the primary end-point because it is the site that is usually most responsive to therapeutic interventions. This is the largest randomized trial of vitamin D effects on BMD reported to date, and has used one of the largest doses of vitamin D assessed. Its size and duration provide the power to detect changes in BMD that might not be clinically relevant, in terms of fracture prevention. The primary analysis of this study does not demonstrate a clinically important change to BMD from untargeted vitamin D supplementation of older community-dwelling adults, although the interaction of treatment effect with baseline 25-hydroxyvitamin D suggests that the more deficient subgroup might benefit.

Table 1 *Characteristics of study participants at baseline*

	Placebo (n = 224)	Vitamin D (n = 228)
Age	68.6 (6.7)	69.0 (6.8)
Sex – male %	146 (65%)	141 (62%)
Ethnicity		
European	205 (92%)	208 (91%)
Maori	10 (4.5%)	12 (5.3%)
Pacific Islander	7 (3.1%)	5 (2.2%)
South Asian	2 (0.9%)	3 (1.3%)
Height (m)	1.70 (0.09)	1.70 (0.09)
Weight (kg)	83.4 (15.3)	80.8 (14.6)
Dietary calcium intake (mg day^{-1})	770 (420)	850 (390)
History of fracture	109 (49%)	105 (46%)
Bone mineral density (g cm^{-2})		
Lumbar spine	1.28 (0.21)	1.27 (0.20)
Femoral neck	0.96 (0.14)	0.95 (0.13)
Total hip	1.03 (0.14)	1.02 (0.14)
Total body	1.20 (0.11)	1.21 (0.11)
Bone density T-scores		
Lumbar spine	0.62 (1.73)	0.54 (1.64)
Femoral neck	−0.73 (1.01)	−0.82 (0.95)
Total hip	−0.28 (0.97)	−0.33 (0.97)
Total body	0.22 (1.22)	0.28 (1.15)
Vigorous physical activity (h week^{-1})		
0	83 (37)	87 (38)
1–2	57 (25)	53 (23)
>2	72 (32)	76 (33)
Unknown	12 (5)	12 (5)

Data are mean (SD), or n (%).

These findings are broadly consistent with those of our recent meta-analysis [1]. That review found no benefit from vitamin D supplementation on BMD of the spine, total body, total hip or forearm, although there was a 0.8% increase in BMD of the femoral neck (P = 0.005), possibly contributed to by publication bias (suggested by Funnel plots). Thus, there was a small BMD benefit in the proximal femur, but not elsewhere, and it was concluded that this was not of a magnitude likely to result in fracture prevention. Of the studies published since that review, Macdonald showed a ½% difference in total hip BMD in Scottish postmenopausal women randomized to vitamin D 1000 IU day^{-1}, compared with vitamin D 400 IU day^{-1} or placebo over one year [11]. There was no significant effect in the spine. Wamberg reported no treatment effect of vitamin D 7000 IU day^{-1} on BMD of the hip, spine or total body, but a benefit at one forearm site, in a 6-month study of 52 obese men and women in Denmark [12]. In contrast, Iuliano-Burns found no effect of vitamin D supplements on BMD in 110 healthy adults in Antarctica [13], and Hansen reported null findings from comprehensive BMD

Table 2 *Changes in bone mineral density during the study*

	Placebo	Vitamin D	Difference	P
Lumbar spine	−0.0068 (−0.0127, −0.0008)	0.0003 (−0.0055, 0.0061)	0.0071 (−0.0012, 0.0154)	0.09
Femoral neck	−0.0112 (−0.0149, −0.0075)	−0.0056 (−0.0093, −0.0020)	0.0056 (0.0004, 0.0108)	0.04
Total hip	−0.0131 (−0.0163, −0.0100)	−0.0073 (−0.0104, −0.0042)	0.0058 (0.0014, 0.0102)	0.01
Total body	−0.0084 (−0.0110, −0.0057)	−0.0082 (−0.0108, −0.0056)	0.0002 (−0.0035, 0.0038)	0.94

Data are mean (95% confidence intervals) absolute changes in bone mineral density (g cm^{-2}) from baseline in the two groups, and the between-groups differences with the P value for this comparison. A positive value for the difference indicates a beneficial effect of vitamin D on bone mineral density.

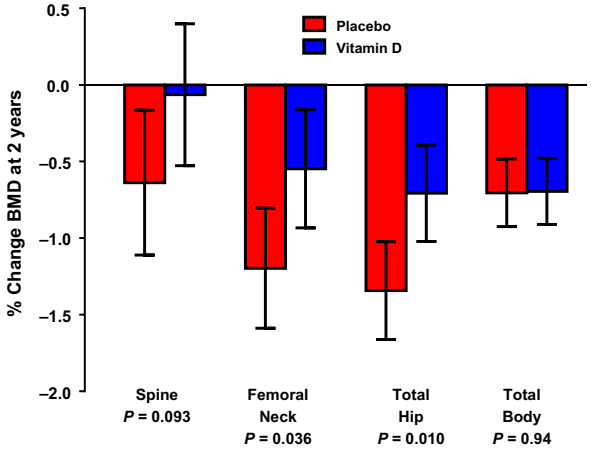

Fig. 2 *Changes in bone mineral density (BMD) from baseline to 2 years in the vitamin D and placebo groups for the substudy cohort. The analyses are intention-to-treat and data are mean ± 95% confidence intervals. Sex and baseline BMD were included as covariates in the analysis.* P *values for between-groups comparisons are shown.*

assessments in 230 postmenopausal women aged <75 years with baseline 25-hydroxyvitamin D levels of 35–68 nmol L^{-1} [14]. In the Hansen study, women were randomized to placebo, vitamin D 800 IU day^{-1} or 50 000 IU twice each month, over a period of one year. Thus, a minority of trials find small but inconsistent positive effects, but none reports changes that are likely to be clinically relevant in terms of fracture prevention.

There is an apparent contradiction between the failure of successive trials to demonstrate a meaningful benefit of vitamin D on bone density, and the acknowledged clinical problem of osteomalacia, a condition in which bone is under-mineralized as a result of vitamin D deficiency. The clinical reality of osteomalacia indicates that at some level of 25-hydroxyvitamin D, real histological, clinical and BMD abnormalities develop, which are correctable with vitamin D supplements [3]. The challenge, then, is to identify the levels of 25-hydroxyvitamin D at which osteomalacia, or its precursor, secondary hyperparathyroidism, becomes a

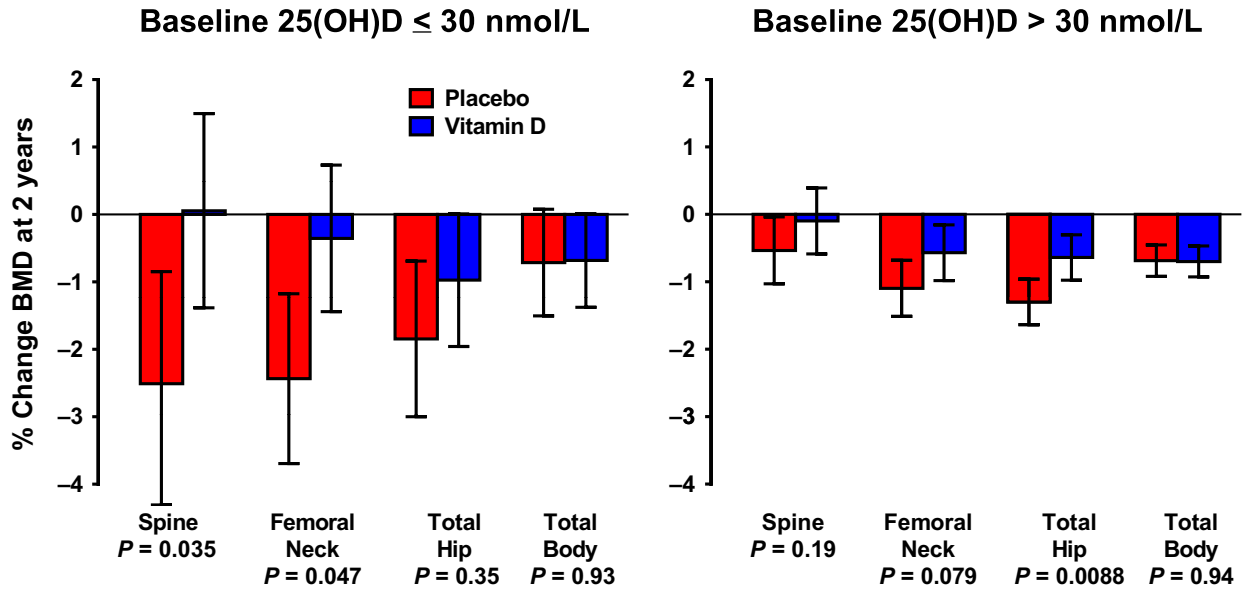

Fig. 3 *Changes in bone mineral density (BMD) from baseline to 2 years in the vitamin D and placebo groups, according to baseline serum 25-hydroxyvitamin D concentrations. Five participants taking clinically significant doses of prednisone or bisphosphonates during the study have been excluded from this analysis, so data were available for 21 participants from the placebo group and 25 from the vitamin D group with baseline 25-hydroxyvitamin D levels ≤30 nmol L^{-1}, and 185 participants from the placebo group and 179 from the vitamin D group with baseline 25-hydroxyvitamin D levels >30 nmol L^{-1}. Data are mean ± 95% confidence intervals. Sex and baseline BMD were included as covariates in the analysis.* P *values for between-groups comparisons are shown.*

significant clinical issue. This is likely to be the level at which vitamin D supplements benefit BMD. The exploratory analyses presented in Fig. 3 begin to address this question, and suggest that a larger effect of vitamin D on BMD is observed in subjects with baseline 25-hydroxyvitamin D levels ≤30 nmol L^{-1}. In this subgroup, bone loss of 1.5–2% in the spine and femur was seen in the placebo group and was eliminated by vitamin D in the spine and femoral neck. The absence of any effect in the total body scans probably reflects the predominance of metabolically unresponsive cortical bone in those scans, in contrast to the spine and hip which have a substantial trabecular content. This study has a power of 50%, 63%, 77% and 99% (5% significance level, two-tailed test) to detect a difference of 2% between spine, femoral neck, total hip and total body BMD, respectively, in the cohort with 25-hydroxyvitamin D < 30 nmol L^{-1}. As expected, there are insufficient subjects in this study with baseline 25-hydroxyvitamin D levels substantially less than 30 nmol L^{-1} to allow us to define the therapeutic threshold with any greater precision. Interestingly, there was still a statistically significant benefit of vitamin D on total hip BMD in those with baseline 25-hydroxyvitamin D > 30 nmol L^{-1}, but the absolute size of this benefit is less than half that observed in those with lower 25-hydroxyvitamin D, and probably not clinically meaningful. Multiple 25-hydroxyvitamin D thresholds were explored across several BMD sites in these analyses, so spuriously positive statistical tests are possible. Therefore, caution is needed in inferring that vitamin D supplements will be beneficial at 25-hydroxyvitamin D levels <30 nmol L^{-1}, or some lower threshold. However, these exploratory analyses do reinforce the conclusion that clinically significant benefit on BMD is most unlikely to be observed above these levels, entirely consistent with the recent negative findings of Hansen, who only recruited participants with 25-hydroxyvitamin D > 35 nmol L^{-1} [14]. An important conclusion from the present trial is that any future studies seeking benefits of vitamin D on bone should focus on individuals with baseline 25-hydroxyvitamin D levels ≤30 nmol L^{-1}.

The mechanism of the effect of vitamin D supplements on bone density will depend on the degree of vitamin D deficiency. At very low levels of 25-hydroxyvitamin D, bone will be under-mineralized as a result of reduced serum calcium levels, and vitamin D supplements will reverse this mineralization defect. With less severe degrees of vitamin D deficiency, secondary hyperparathyroidism will be present which will be reversed by vitamin D replacement. Increased bone density then follows from the reduction in parathyroid hormone levels and bone turnover. In both scenarios, the improvement in bone density will be maintained as long as normal levels of 25-hydroxyvitamin D are maintained, but the benefits will not be progressive once the underlying abnormality has been corrected. Parathyroid hormone levels have not been measured in the present study so we are not able to relate them to thresholds for bone benefit from vitamin D supplementation.

Serum 25-hydroxyvitamin D levels show a circannual variation, with peaks and troughs in late summer and late winter, respectively. Therefore, thresholds for vitamin D effects need to be considered in terms of the time of year at which they are assessed. The present trial cohort was recruited at the end of the Auckland winter, when 25-hydroxyvitamin D levels are at their nadir. It is possible to describe this circannual variation mathematically and to produce a 'deseasonalized' estimate of 25-hydroxyvitamin D, equating to the mean level across the year [15,16]. When this is done in the present cohort, who had a measured mean of 55.6 nmol L^{-1} and median of 53 nmol L^{-1} at the end of winter, the deseasonalized mean is found to be 65.4 nmol L^{-1} and the median 62.8 nmol L^{-1}. Therefore, if there is a threshold of 25-hydroxyvitamin D of ~30 nmol L^{-1} in this cohort, this equates to a deseasonalized value of ~40 nmol L^{-1}. Most studies do not consider this issue, many recruit over more than one season, and the circannual fluctuation will vary with location. These factors need to be considered when defining optimal levels of 25-hydroxyvitamin D for skeletal health.

The suggestion from the present study that beneficial effects of vitamin D supplementation on bone density occur when the baseline 25-hydroxyvitamin D level is ≤30 nmol L^{-1} accords with findings from a number of other recent studies. In the last 20 years (during which time 25-hydroxyvitamin D assays have been better standardized than previously), those studies which have found positive effects on BMD at least one site have had starting 25-hydroxyvitamin D levels of 29–36 nmol L^{-1} [11,12,17–19]. A similar threshold is suggested for vitamin D effects on other putative vitamin D targets, such as reduction in exacerbations of chronic obstructive pulmonary disease [20], reduction in mortality in the critically ill [21], and changes in bone and fat mass in the foetus [22].

These latter trials have failed to produce positive results across the whole study population, but have reported positive findings from *post hoc* analyses of those with the lowest 25-hydroxyvitamin D levels at study entry. Together, these studies suggest that serum 25-hydroxyvitamin D levels $\leq$30 nmol L^{-1} might have adverse health consequences. These studies, along with a number of others [1,23,24], also indicate a lack of benefit from vitamin supplementation on bone and other endpoints when baseline 25-hydroxyvitamin D is above this level. This suggests that untargeted vitamin D supplementation of older community-dwelling adults should not be endorsed and that any future trials of vitamin D supplementation should recruit participants with nadir 25-hydroxyvitamin D $\leq$ 30 nmol L^{-1} if they are to produce novel results likely to impact on human health.

Contributions

IRR involved in study design, data analysis, drafting of manuscript; AMH involved in study design and data collection; BM involved in data collection and management; GDG involved in study design and data analysis; FA-A, MS, LT and SF involved in data collection; CAC and AWS involved in study design; and RS involved in overall study design and management. All authors critically reviewed and approved the final manuscript. IRR is the guarantor.

Conflict of interests statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of 25-hydroxyvitamin D concentrations [25(OH)D] at baseline across the substudy cohort. Data are presented for 10 nmol L^{-1} intervals of 25-hydroxyvitamin D, the mid-point of each interval being shown on the *x*-axis.