Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial

Kay-Tee Khaw, Alistair W Stewart, Debbie Waayer, Carlene M M Lawes, Les Toop, Carlos A Camargo Jr, Robert Scragg

Summary

Background Adults with low concentrations of 25-hydroxyvitamin D (25[OH]D) in blood have an increased risk of falls and fractures, but randomised trials of vitamin D supplementation have had inconsistent results. We aimed to assess the effect of high-dose vitamin D supplementation on fractures and falls.

Methods The Vitamin D Assessment (ViDA) Study was a randomised, double-blind, placebo-controlled trial of healthy volunteers aged 50–84 years conducted at one centre in Auckland, New Zealand. Participants were randomly assigned to receive either an initial oral dose of 200 000 IU (5·0 mg) colecalciferol (vitamin D_3) followed by monthly 100 000 IU (2·5 mg) colecalciferol or equivalent placebo dosing. The prespecified primary outcome was cardiovascular disease and secondary outcomes were respiratory illness and fractures. Here, we report secondary outcome data for fractures and post-hoc outcome data for falls. Cox proportional hazards models were used to estimate hazard ratios (HRs) for time to first fracture or time to first fall in individuals allocated vitamin D compared with placebo. The analysis of fractures included all participants who gave consent and was by intention-to-treat; the analysis of falls included all individuals who returned one or more questionnaires. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000402943.

Findings Between April 5, 2011, and Nov 6, 2012, 5110 participants were recruited and randomly assigned either colecalciferol (n=2558) or placebo (n=2552). Two participants allocated placebo withdrew consent after randomisation; thus, a total of 5108 individuals were included in the analysis of fractures. The mean age of participants was 65·9 years (SD 8·3) and 2971 (58%) were men. The mean concentration of 25(OH)D in blood was 63 nmol/L (SD 24) at baseline, with 1534 (30%) having 25(OH)D concentrations lower than 50 nmol/L. Follow-up was until July 31, 2015, with a mean treatment duration of 3·4 years (SD 0·4, range 2·5–4·2). During follow-up, 2638 participants reported having a fall, 1312 (52%) of 2539 in the vitamin D group compared with 1326 (53%) of 2517 in the placebo group. The HR for falls—adjusted for age, sex, ethnic origin, history of recent fall, physical activity, and baseline 25(OH)D—was 0·99 (95% CI 0·92–1·07; p=0·82) for vitamin D compared with placebo. Non-vertebral fractures were reported in 292 individuals, 156 (6%) of 2558 in the vitamin D group and 136 (5%) of 2550 in the placebo group. The adjusted HR for fractures was 1·19 (95% CI 0·94–1·50; p=0·15) for vitamin D compared with placebo. 123 (2%) people died during the trial, 65 assigned vitamin D and 58 allocated placebo; the difference between treatment groups was not significant.

Interpretation High-dose bolus vitamin D supplementation of 100 000 IU colecalciferol monthly over 2·5–4·2 years did not prevent falls or fractures in this healthy, ambulatory, adult population. Further research is needed to ascertain the effects of daily vitamin D dosing, with or without calcium.

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Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK (Prof K-T Khaw MBBChir); **School of Population Health, University of Auckland, Auckland, New Zealand** (A W Stewart BSc, D Waayer MEd, C M M Lawes MBChB, Prof R Scragg MBBS); **Department of General Practice, University of Otago, Christchurch, New Zealand** (Prof L Toop MBChB); **and Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA** (Prof C A Camargo Jr MD)

Correspondence to:
Prof Kay-Tee Khaw, Clinical Gerontology Unit, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge CB3 0EQ, UK
kk101@medschl.cam.ac.uk

Introduction

Rickets and osteomalacia are well established consequences of vitamin D deficiency.[1] Low blood concentrations of 25-hydroxyvitamin D (25[OH]D) have also been associated with increased risk of osteoporotic fractures in some observational studies.[1–3] However, trials of vitamin D supplementation for fracture prevention have had inconsistent results. Although findings of an early trial reported a 32% reduction in non-vertebral fractures with vitamin D and calcium supplementation in elderly women,[4] later trials have variously reported null, increased, or decreased risk of fractures with vitamin D supplementation.[5,6] Similar uncertainty relates to vitamin D supplementation and risk of falls.[7–11] Inconsistencies have been attributed variously to differences in vitamin D dosage (frequency and amount), type of preparation (eg, colecalciferol [vitamin D_3] or ergocalciferol [vitamin D_2]), mode of administration (oral or intramuscular injections), baseline vitamin D status of the study population, and use of additional calcium supplementation.

The Vitamin D Assessment (ViDA) study[12] was designed to assess whether oral colecalciferol administered as a monthly dose of 100 000 IU (2·5 mg)

Research in context

Evidence before this study

When the Vitamin D Assessment (ViDA) Study was planned in 2010 with the primary and secondary outcomes of cardiovascular disease, fractures, and acute respiratory infections, extensive observational data were available linking low vitamin D status with increased risk of several important adverse health events. However, findings of the largest randomised trial to date—the Women's Health Initiative—had shown no effect of vitamin D and calcium supplementation on cardiovascular disease, and other studies were underpowered for cardiovascular events. For this report of secondary and post-hoc outcomes of falls and fractures, we initially searched PubMed between Jan 1, 1985, and Dec 31, 2010, with the terms "vitamin D", "fractures", "falls", and "randomized trials", then updated our search to Jan 31, 2016. Extensive reviews had been published, including an Institute of Medicine report and meta-analyses of randomised trials, including Cochrane reviews. Meta-analyses of randomised trials of vitamin D supplementation on risk of falls and fractures—including the Cochrane reviews—had inconsistent conclusions that were attributed variously to the formulation of vitamin D (D_2 or D_3), how vitamin D was administered (injection or orally), the frequency of administration (daily doses or large intermittent bolus doses), additional calcium supplementation, and baseline vitamin D status of the study populations. An Institute of Medicine report from 2011 highlighted the limited number of long-term clinical trials related to calcium and vitamin D intake and health outcomes. The rationale for the ViDA trial was to do a large randomised trial in a community-based population using a monthly bolus dose of 100 000 IU colecalciferol (vitamin D_3) that was designed to raise average year-round concentrations of vitamin D in blood to 80–100 nmol/L, which are levels recorded in young adults living in the tropics and associated with optimum health in observational studies up to 2010. The monthly bolus dose was designed to improve compliance and public health feasibility.

Added value of this study

Results from the ViDA trial indicate that a monthly dose of 100 000 IU colecalciferol, with good compliance in a healthy, middle-aged, older, ambulatory population, showed no reduced risk of falls or fractures over 4 years.

Implications of all the available evidence

These findings, taken in conjunction with results from other trials, suggest that large monthly bolus doses of vitamin D do not confer overall benefit either in frail elderly people or in a healthy, ambulatory, general population. Further study is needed to ascertain whether daily dosing might have different effects. Several international trials are ongoing to investigate this issue (eg, VITAL in the USA [NCT01169259]; DO-HEALTH in Europe [NCT01745263]; and FIND in Finland [NCT01463813]).

would reduce the risk of cardiovascular disease (primary outcome) or respiratory illness or fractures (secondary outcomes) in a community-based population in New Zealand. We additionally obtained data for falls (post-hoc outcome). We report here the results for fractures and falls.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled trial at the School of Population Health, University of Auckland Tāmaki Campus, Auckland, New Zealand.[12] We identified potential study participants from family practice registers and community groups and recruited them to the study by post and subsequent follow-up telephone calls. Inclusion criteria were: age 50–84 years, resident in Auckland at time of recruitment, and anticipated residence in New Zealand for the study period. Exclusion criteria were: current use of vitamin D supplements (>600 IU per day if aged 50–70 years, >800 IU per day if aged 71–84 years); having a psychiatric disorder that would limit the participant's ability to comply with the study protocol; a history of hypercalcaemia, nephrolithiasis, sarcoidosis, parathyroid disease, or gastric bypass surgery; or a serum-corrected blood calcium concentration greater than 2·5 mmol/L.

Ethics approval for the study was granted by the Multiregion Ethics Committee, Wellington (MEC/09/08/082) in October, 2010. All participants gave written informed consent.

Randomisation and masking

We randomly allocated participants by computer to either vitamin D supplementation with colecalciferol or placebo, with random block sizes of eight, ten, or 12 and stratified by ethnic origin (Māori, Pacific Islander, south Asian, European, or other) and 5-year age groups. Participants and study personnel were unaware of assigned groups. To achieve masking, the placebo capsule was identical in appearance to the colecalciferol preparation.

Procedures

We did baseline interviews at the School of Population Health.[12] We obtained information about socio-demographic status, lifestyle (eg, current tobacco smoking, alcohol consumption over the previous 12 months, and usual leisure-time physical activity over the previous 3 months), history of falls in the previous 4 weeks, intake of vitamin D or calcium supplements, and medical history of osteoporosis or fracture. We also took baseline measurements of height to the nearest 0·1 cm and bodyweight to the nearest 0·1 kg (in light clothing without shoes), and we obtained (during the

morning or afternoon) a non-fasting blood sample to screen for hypercalcaemia. We stored remaining serum samples at –80°C for later measurement of 25(OH)D.

The study drug was provided as 100 000 IU (2·5 mg) colecalciferol capsule or identical placebo. Mailing of the capsules started in June, 2011. At the start of the intervention, we sent participants two doses of the capsules, to provide an initial loading dose of 200 000 IU (5·0 mg) colecalciferol or identical placebo; thereafter, we sent one capsule of 100 000 IU (2·5 mg) colecalciferol—equivalent to a daily dose of 3290 IU (83 µg)—or identical placebo, by post every month until June, 2013. From July, 2013, to July, 2015, we posted four capsules every 4 months as a cost-control measure, and we emailed or posted monthly reminders for participants to take the capsule. We selected the monthly 100 000 IU colecalciferol dose because it was known to maintain amounts in serum of 25(OH)D above 90 nmol/L for at least a month after ingestion.[13] At the time of designing the study, observational studies suggested that a range of 80–100 nmol/L was associated with optimum health.[14]

We gathered information about falls by self-report using a one-page questionnaire and reply-paid envelope in which participants were asked to report adherence, falls, and fractures. The questionnaire was posted with the study drugs every month from June, 2011, to June, 2013, then every month with the reminder letter to November, 2013, then every 4 months with the study drugs to July, 2015. Although this questionnaire has not been validated in this population, we used the wording recommended by expert consensus to measure falls.[15] We asked participants in each monthly questionnaire, "In the past month, since you took your last capsule, have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?"; and in each 4-monthly questionnaire we asked, "In the last 4 months, have you had any falls including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?". If the participant's response was positive, we asked them to indicate the number of falls, either one or two or more for the monthly questionnaire and either one, two, three, or four or more for the 4-monthly questionnaire. If a fall caused an injury, we asked the participant to specify whether they hit their head or suffered a strain or sprain (to muscles or ligaments), whether they had a cut, bruise, bleeding, or abrasion to the skin, or whether they had a fracture of a bone or bones from the fall. We classified these falls as injury falls.

We obtained information about fractures from two sources. First, the Ministry of Health allocates all New Zealand residents a unique National Health Index number, which we used to track hospital discharges (with International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] coding) for all participants during the follow-up period. We defined fractures as hospital discharges with the primary (A code) diagnosis or the secondary (B code) diagnosis for specified ICD-10 codes. Second, we identified falls through the Accident Compensation Corporation (ACC), which is the national governmental insurance organisation that covers all New Zealand residents for any medical and hospital costs from injury. We defined fractures as claims made after randomisation with specified ICD-10 or Read version 2 codes (appendix p 1). We identified deaths using Ministry of Health mortality files.

See Online for appendix

We measured serum-corrected calcium the day after we had obtained blood samples at the baseline interview, on a 183 Siemens Advia 2400 analyser (Siemens Healthcare Diagnostics, Eschborn, Germany) in a central laboratory. We measured amounts of 25(OH)D in serum (combining vitamin D_2 and D_3) in baseline aliquots, which we had stored frozen at –80°C after the baseline interview, by high-performance liquid chromatography–tandem mass spectrometry (AB Sciex API 4000; Framingham, MA, USA) at a laboratory participating in the Vitamin D External Quality Assessment Scheme (DEQAS). To assess intervention effects on concentrations in blood of 25(OH)D we randomly selected a group of participants using a list of random numbers and asked them to return at 6, 12, 24, and 36 months to provide further blood samples for measurement of serum-corrected calcium concentration and 25(OH)D (stored with and measured at the same time as the baseline blood sample for each participant).

For more on the **DEQAS programme** see http://www.deqas.org

Outcomes

The prespecified primary outcome for the ViDA trial was incident cardiovascular disease; prespecified secondary outcomes were non-vertebral fractures and respiratory infection. In the registered protocol, data collection for falls was included as a safety outcome, and the 2011 contract with a funder (the ACC) specified detailed data for falls. Because a formal protocol amendment was not made, the falls outcome is post hoc. Results for the primary outcome (cardiovascular disease) have been reported previously,[16] and findings for the other secondary outcome (respiratory infection) will be reported elsewhere.

We assessed self-reported adverse events using the mailed questionnaire, with questions separate from those for falls. We made no attempt to grade adverse events or to judge if any adverse events were related to study treatment.

Statistical analysis

The study sample size had 80% power (estimated post hoc) to detect a 10% relative reduction in falls (1% significance level), assuming 50% of participants would have at least one fall, based on a study in primary care showing that 24% of patients reported a fall in the previous 12 months.[17] The study had an 80% chance of detecting a hazard ratio (HR) of 0·76 for non-vertebral fractures (5% significance level), based on estimated incidence in New Zealand[18] anticipating 430 people would have fractures during the trial.

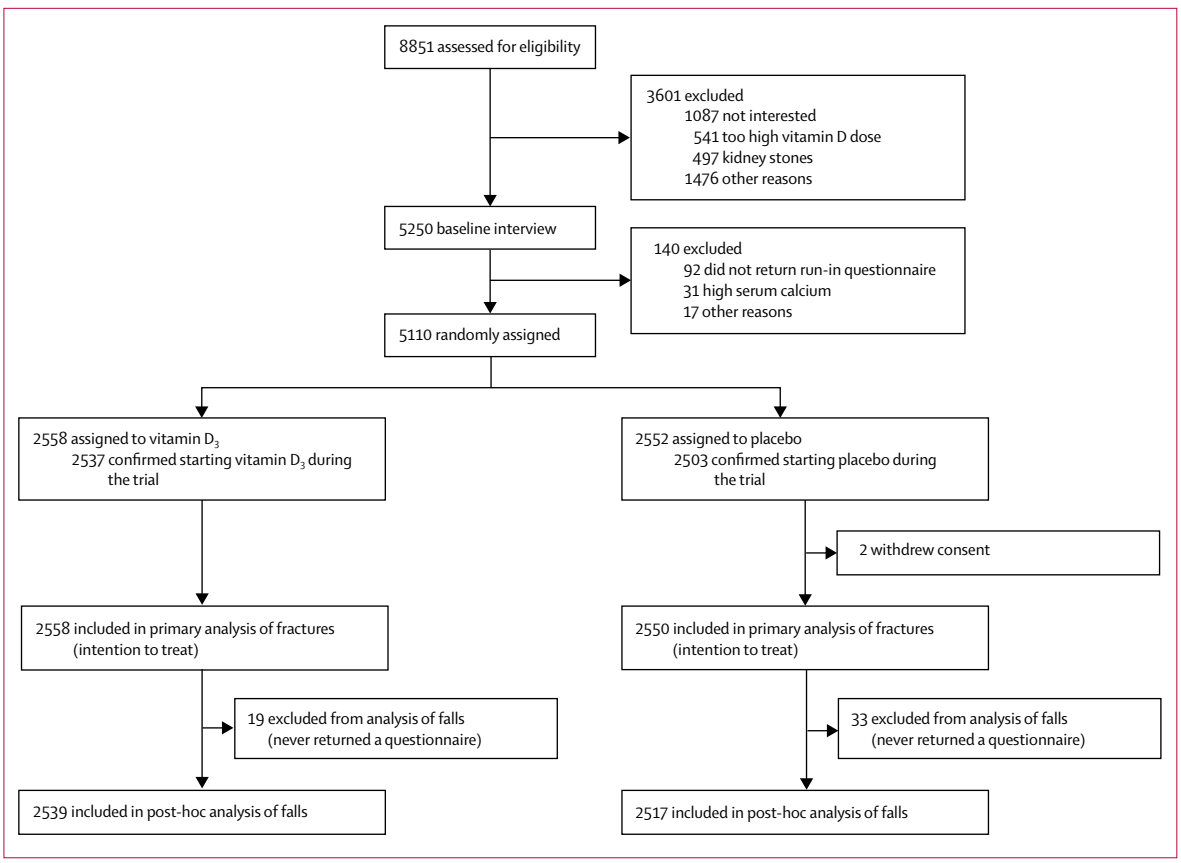

Figure 1: **Trial profile**

Analysis of the falls outcome was dependent on the number of returned questionnaires throughout the follow-up period. We included in the analysis only participants who returned one or more questionnaires. We defined the date of the fall as approximately halfway through the coverage period of the questionnaire. We assumed no fall happened during the period of the questionnaire if a questionnaire was not returned. We censored participants (ie, last date noted for estimation of follow-up time) at the last questionnaire they returned.

We analysed the fracture outcome on an intention-to-treat basis, including all participants who gave consent. We used the National Health Index number to identify admissions for fracture in Ministry of Health data and claims for fractures in ACC data, irrespective of whether participants continued to take part actively in the study by returning the home questionnaire.

For the prespecified analysis of fractures, we used the Cox proportional hazards model—with robust sandwich variance estimates and exact p values—to calculate HRs based on time to first fracture for vitamin D compared with placebo. We used a similar approach for the post-hoc analysis of falls, calculating HRs based on time to first fall. In supplemental observational analyses, to assess the validity of both outcome measures we analysed (in individuals allocated placebo) the HRs for falls and fractures associated with known risk factors. We tested the proportional hazards assumptions and none was violated. We treated individuals who died without having a documented fall or fracture up to the end of follow-up as censored observations.

Because 25(OH)D values are seasonally dependent, use of observed levels adds random variability to analyses; therefore, we calculated a deseasonalised 25(OH)D value that predicts the average level for every participant over four seasons. We calculated deseasonalised concentrations using a sinusoidal model from the baseline values for all participants.[19] We defined vitamin D sufficiency in the protocol as having a deseasonalised value for 25(OH)D greater than 50 nmol/L (adjusted baseline >50 nmol/L for at least 6 months of the year) for the a-priori prespecified subgroup analysis. For supplemental exploratory analyses for heterogeneity, we also stratified results according to baseline 25(OH)D (<25 nmol/L or ≥75 nmol/L). We adjusted testing of the treatment effect for stratification variables age, sex, ethnic origin, and deseasonalised baseline 25(OH)D. For falls, we also included history of recent fall (in the last 4 weeks) and baseline physical activity in the model. We assessed interactions between treatment group and sex, age, ethnic origin, and deseasonalised 25(OH)D.

We also did subgroup analyses for deseasonalised baseline 25(OH)D less than 50 nmol/L and—for the fall analyses—those with a history of falls and those with greater physical activity, as prespecified in the protocol.

Although not prespecified explicitly in the protocol, we did additional observational analyses of individuals assigned placebo to examine whether risk factors for fractures and falls in this population were consistent with those in existing observational published work and to indicate that the ascertainment of these endpoints was reasonable and that this population was similar to others with respect to these risk factors.

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000402943.

Data sharing

Data are not available as open access because participants did not consent to their data being shared, apart from with the research team.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. RS had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. K-TK and RS had final responsibility for the decision to submit for publication.

Results

Between April 5, 2011, and Nov 6, 2012, 47 905 people from 55 general practices in Auckland, New Zealand, were sent an invitation letter for the ViDA study, of whom 8851 replied and were assessed for eligibility (figure 1). 5250 individuals were eligible for the study and agreed to a baseline interview. 140 people were excluded after the interview, mainly those who did not return a run-in questionnaire within 4 weeks to confirm they had taken a blinded capsule. 5110 participants were randomly assigned either vitamin D supplementation with cole-calciferol (n=2558) or placebo (n=2552).

	Vitamin D (n=2558)	Placebo (n=2550)
Men	1512 (59%)	1457 (57%)
Women	1046 (41%)	1093 (43%)
Age group (years)		
50–59	571 (22%)	567 (22%)
60–69	1112 (43%)	1108 (43%)
70–79	716 (28%)	722 (28%)
80–84	159 (6%)	153 (6%)
Ethnic origin		
European or other	2127 (83%)	2126 (83%)
Māori	137 (5%)	135 (5%)
Pacific Islander	168 (7%)	166 (7%)
South Asian	126 (5%)	123 (5%)
Education (highest level)		
Primary school	53 (2%)	42 (2%)
Secondary school	1091 (43%)	1036 (41%)
Tertiary education	1412 (55%)	1470 (58%)
Refused to answer or unknown	2 (<1%)	2 (<1%)
Employment status		
Employed (full and part time)	1301 (51%)	1317 (52%)
Retired	1041 (41%)	1018 (40%)
Other	211 (8%)	212 (8%)
Refused to answer or unknown	5 (<1%)	3 (<1%)
Current tobacco smoker	164 (6%)	156 (6%)
Current alcohol drinker	2177 (85%)	2211 (87%)
Vigorous physical activity (h/week)		
0	1015 (40%)	1018 (40%)
1–2	609 (24%)	585 (23%)
>2	804 (31%)	832 (33%)
Refused to answer or unknown	130 (5%)	115 (5%)
(Table 1 continues in next column)		
(Continued from previous column)		
Past medical conditions (diagnosed by a doctor)		
Fracture	1178 (46%)	1200 (47%)
Osteoporosis	42 (2%)	29 (1%)
Fall in the last 4 weeks	147 (6%)	161 (6%)
Confident to do daily activities without falling		
Not at all	23 (1%)	25 (1%)
Quite	454 (18%)	409 (16%)
Completely	2076 (81%)	2113 (83%)
Refused to answer or unknown	5 (<1%)	3 (<1%)
Anthropometry		
Bodyweight (kg)	81·3 (16·5)	81·2 (16·0)
BMI (kg/m²)	28·4 (5·1)	28·5 (5·1)
Taking supplements		
Vitamin D*	208 (8%)	200 (8%)
Calcium	125 (5%)	127 (5%)
Serum calcium (mmol/L)	2·3 (0·1)	2·3 (0·1)
Serum 25(OH)D, observed (nmol/L)	64 (24)	63 (24)
<50, observed	746 (29%)	788 (31%)
<50, deseasonalised†	612 (24%)	658 (26%)
<25‡	46 (2%)	45 (2%)
25 to <50‡	566 (22%)	613 (24%)
50 to <75‡	1106 (43%)	1051 (41%)
≥75‡	839 (33%)	840 (33%)
Missing data	1 (<1%)	1 (<1%)

Data are number of participants (%) or mean (SD). 25(OH)D=25-hydroxyvitamin D.
*≤600 IU per day if aged 50–70 years; ≤800 IU per day if aged 71–84 years.
†Average concentration over four seasons. ‡Based on deseasonalised values.

Table 1: **Baseline characteristics**

	Vitamin D	Placebo	Hazard ratio (95% CI)	p value
All falls (n=2638)	1312/2539 (52%)	1326/2517 (53%)	0·99 (0·92–1·07)	0·82
25(OH)D <50 nmol/L*	307/602 (51%)	316/645 (49%)	1·07 (0·91–1·25)	0·45
Fall in last 4 weeks	110/145 (76%)	109/157 (69%)	1·18 (0·89–1·56)	0·25
Physically active and vigorous activity >2 h/week	405/800 (51%)	412/823 (51%)	1·01 (0·88–1·16)	0·92
Non-vertebral fracture (n=292)	156/2558 (6%)	136/2550 (5%)	1·19 (0·94–1·50)	0·15
25(OH)D <50 nmol/L*	34/612 (6%)	38/658 (6%)	0·94 (0·58–1·52)	0·80

Data are number of participants (%) reporting a fall or having a fracture during follow-up, by study group and by subgroups (defined on the basis of baseline measurements). Hazard ratios are relative to placebo and are adjusted for sex, age, ethnic origin, history of recent fall, baseline physical activity, and baseline 25(OH)D concentration. 25(OH)D=25-hydroxyvitamin D. *Deseasonalised.

Table 2: **Secondary and post-hoc outcomes**

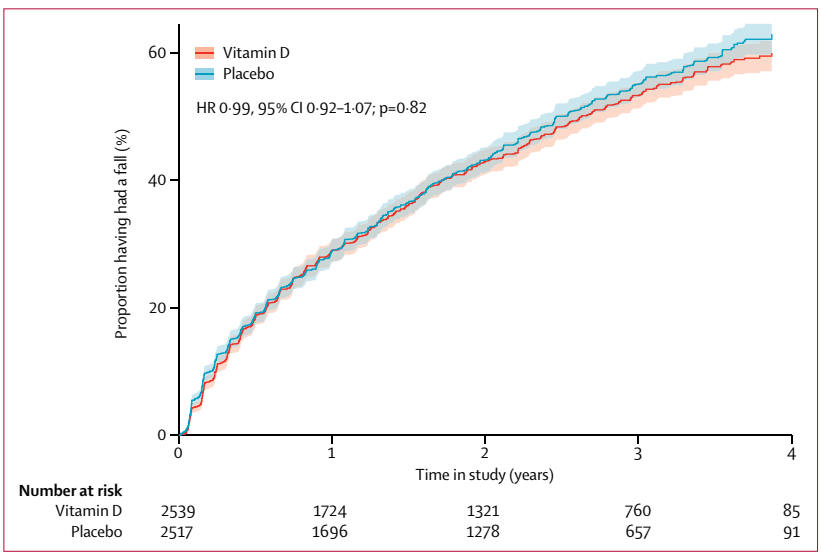

Figure 2: **Cox proportional hazards model of falls recorded during follow-up**
Lines depict the proportion of participants having a fall during follow-up, and shading represents the 95% CI. HR=hazard ratio.

Baseline characteristics of randomly assigned participants were similar between the vitamin D and placebo groups (table 1). Mean age of participants was 65·9 years (SD 8·3), with most individuals (3658 [72%] of 5110) aged 60–79 years. More men were recruited to the study than were women (2971 [58%] *vs* 2139 [42%]). Just under half of participants (2378 [47%] of 5110) reported a previous fracture. Vitamin D supplements (within the study's eligibility criteria) were taken by 408 (8%) participants.

Two participants assigned placebo withdrew their consent after randomisation; therefore, 2558 people assigned vitamin D supplementation and 2550 allocated placebo were included in the prespecified analysis of fractures and were followed up to July 31, 2015. Mean duration of study treatment was 3·4 years (SD 0·4, range 2·5–4·2). 2513 (98%) of 2558 individuals assigned vitamin D supplementation and 2491 (98%) of 2552 allocated placebo confirmed they had started the study capsules within 2 months. Only 21 (1%) participants assigned vitamin D supplementation and 49 (2%) allocated placebo never confirmed capsule ingestion at any time during the follow-up period. 122 706 questionnaires were posted, of which 107 859 (88%) were returned. 5056 people returned one or more questionnaires and were included in the post-hoc analysis of falls (figure 1). Retention of participants was good during the follow-up period, with 2177 (86%) of 2539 individuals assigned vitamin D supplementation and 2138 (85%) of 2517 people allocated placebo participating actively during the last 5 months of the follow-up period. 4032 (81%) participants returned the final July, 2015, questionnaire and a further 283 (6%) returned the penultimate March, 2015, questionnaire. 123 individuals died before an event up to the end of follow-up and were censored, 65 who were assigned vitamin D supplementation and 58 allocated placebo. We do not know whether these deaths were associated directly with a fall or fracture. Deaths did not differ between treatment groups.

Among the 5108 randomised participants, the mean baseline concentration of 25(OH)D—not corrected for season—was 63 nmol/L (SD 24), varying from a maximum monthly mean of 77 nmol/L (22) in March to a minimum monthly mean of 55 nmol/L (24) in August. The mean baseline deseasonalised value (ie, amounts averaged over four seasons) was 66 nmol/L (SD 23). Of 515 participants randomly selected to return and give blood samples for assessment of adherence, 441 accepted the invitation. Mean baseline 25(OH)D concentrations in this subpopulation (unadjusted for season) were similar to those in the whole cohort (61 nmol/L [SD 24]). The mean amount of 25(OH)D had increased substantially by 6 months among participants assigned vitamin D supplementation in this subpopulation, with mean values (unadjusted for season) 54–69 nmol/L higher than in the placebo group throughout follow-up (appendix p 2). Only a few people in the vitamin D group had a 25(OH)D concentration that remained below 50 nmol/L at any timepoint (appendix p 2). These results are consistent with the high adherence to study treatment reported by participants in the returned questionnaires (168 667 capsules [84%] were reported taken during 200 936 person-months). Vitamin D supplementation had no effect on corrected serum calcium concentrations, which were mean 2·3 mmol/L (SD 0·1) in each study group at all timepoints, apart from at 36 months when the concentration was 2·4 mmol/L (0·1) in each study group.

Falls were reported by just over half of all participants (2638 [52%] of 5056) during the follow-up period. The probability of reporting one or more falls (the falls endpoint) was similar for those assigned to vitamin D supplementation compared with placebo (1312 [52%] of 2539 *vs* 1326 [53%] of 2517; HR 0·98, 95% CI 0·92–1·06, after adjustment for sex, age, and ethnic origin; HR 0·99, 0·92–1·07, when further adjusted for history of recent fall, physical activity, and baseline 25[OH]D; table 2, figure 2). Among the participants who had a fall, the

proportion reporting one, two, or more than two falls did not differ (p=0·98) between vitamin D and placebo groups (respectively, 582 [44%] of 1312 *vs* 591 [45%] of 1326; 353 [27%] of 1312 *vs* 359 [27%] of 1326; and 377 [29%] of 1312 *vs* 376 [28%] of 1326). Furthermore, the number of injury falls did not differ between treatment groups, with 1049 (41%) reported in 2539 participants assigned vitamin D versus 1020 (41%) in 2517 individuals allocated placebo (after adjustment for sex, age, ethnic origin, 25[OH]D <50 nmol/L, falls in the last 4 weeks, and vigorous activity >2 h per week: HR 1·03, 95% CI 0·95–1·13; p=0·46).

Subgroup analyses did not show any difference in the risk of falls between participants allocated vitamin D and those assigned placebo (table 2) with respect to deseasonalised baseline 25(OH)D less than 50 nmol/L (307 [51%] of 602 *vs* 316 [49%] of 645, respectively; p=0·45), history of falls in the 4 weeks before the baseline interview (110 [76%] of 145 *vs* 109 [69%] of 157; p=0·25), or being physically active at baseline and undertaking vigorous activity for more than 2 h per week (405 [51%] of 800 *vs* 421 [51%] of 823; p=0·92). No interactions were noted between treatment and sex (p=0·13), ethnic origin (p=0·51), age (p=0·49), or deseasonalised 25(OH)D (p=0·80).

In the placebo group, reporting of falls was higher in women than in men (644 [60%] of 1082 *vs* 682 [48%] of 1435; HR 1·42, 95% CI 1·27–1·59; p<0·0001) and in those who had a fall in the 4 weeks before the study (1·73, 1·39–2·15; p<0·0001). Risk of falls increased with age, but was not associated with ethnic origin, physical activity, or baseline 25(OH)D, after adjustment for covariates (appendix p 3). The appendix (p 4) shows the number of participants reporting falls stratified by age and sex.

Non-vertebral fractures were identified in 292 (6%) of 5108 participants during follow-up (primary fracture outcome), with 156 (6%) of 2558 people allocated vitamin D supplementation and 136 (5%) of 2550 assigned placebo reporting a fracture (after adjustment for age, sex, and ethnic origin, HR 1·15, 95% CI 0·92–1·45; after further adjustment for history of recent fall, physical activity, and baseline 25[OH]D, HR 1·19, 0·94–1·50; table 2). No difference in cumulative risk of fracture was noted between participants allocated vitamin D supplementation and those assigned placebo (figure 3). Addition of 13 spinal fractures to the 292 non-vertebral fractures, to obtain the total number of fractures (305 of 5108), did not change estimates by much (age, sex, and ethnic origin adjusted HR 1·14, 95% CI 0·91–1·42). In the placebo group, fractures were more common in women than in men (80 [7%] of 1093 *vs* 56 [4%] of 1357; HR 1·77, 95% CI 1·24–2·52; p=0·002) but were not associated with age, ethnic origin, history of recent falls, physical activity, or baseline 25(OH)D, after adjustment for covariates (appendix p 5). Exploratory analyses stratifying results by baseline 25(OH)D either less than 25 nmol/L or greater than or equal to 75 nmol/L showed no heterogeneity (appendix p 6).

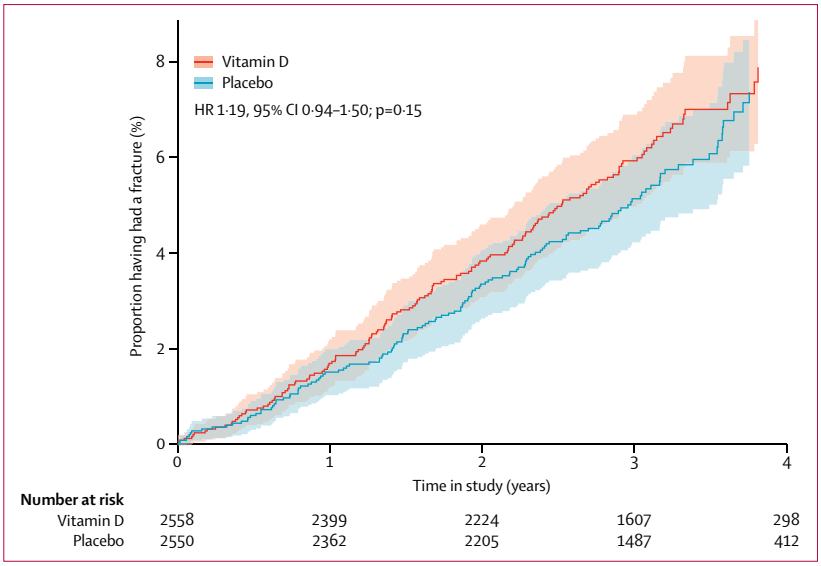

Figure 3: **Cox proportional hazards model of fractures recorded during follow-up**
Lines depict the proportion of participants having a fracture during follow-up, and shading represents the 95% CI. HR=hazard ratio.

Discussion

Monthly supplementation of 100 000 IU colecalciferol (vitamin D_3) taken for 2·5–4·2 years (mean 3·4 years) was not associated with a significant difference in risk of falls or fractures compared with placebo in this community-based randomised controlled trial in individuals predominantly without known osteoporosis. Although the statistical power of the study to detect a difference in fracture risk was low, no evidence was recorded of any reduced risk of fractures in participants assigned vitamin D supplementation.

The association between vitamin D deficiency and rickets and osteomalacia is well established, and the general consensus is that concentrations below 25 nmol/L are associated with greatly increased risk of these conditions.[1] However, the optimum vitamin D status for other health outcomes is subject to debate in terms of the optimum concentration in blood of 25(OH)D above deficiency levels[1,14,20] and the oral vitamin D dose needed to maintain particular blood concentrations of 25(OH)D when sunlight exposure is inadequate.

Most trials of vitamin D supplementation for prevention of falls or fracture have focused on groups at high risk of fracture—eg, women, older people, and institutionalised individuals (ie, those living in a nursing or long-term care home). Moreover, trials have been done in predominantly white populations. The current community-based trial included men, had a wide age range (50–84 years) of participants, and included different ethnic groups who have been documented to have a high prevalence of vitamin D deficiency.[21]

Evidence in a 2014 review did not support the hypothesis that supplementation with only vitamin D reduced the risk of falls or fractures,[22] in striking contrast

to findings of previous meta-analyses. For example, with respect to falls, the conclusion of a 2010 meta-analysis—based on ten studies meeting inclusion criteria—was that 200–1000 IU daily vitamin D reduced falls by 14% compared with calcium or placebo,[9] a conclusion supported by a review in 2012 that suggested a 17% lower risk of falling with a median oral daily dose of 800 IU vitamin D.[10] However, in trials published since those reviews, an increased falls risk with bolus vitamin D supplementation has been reported,[23,24] leading to a more cautious re-evaluation highlighting the need for evidence in various study populations and different dosage regimens. Some of the differences in conclusions from overlapping meta-analyses of vitamin D supplements and falls have been attributed to methodological variations in using data from the same trials,[25] such as inclusion criteria and data extraction.

In terms of fractures, the 43% reduction in hip fractures reported in a trial of 3270 institutionalised women (ie, those living in a nursing or long-term care home; mean age 84 years) who had very low 25(OH)D levels consistent with osteomalacia and who were given a daily 800 IU vitamin D and 1200 mg calcium supplement over 18 months[4] has not been observed consistently in subsequent trials, whether for primary or secondary prevention of fractures.[5] A meta-analysis of such trials suggested a possible weak inverse association of vitamin D and calcium supplementation with hip fractures in high-risk groups, but no overall effect of vitamin D supplementation alone on fracture risk.[26] These inconsistent findings have been attributed variously to differences in the baseline vitamin D status of the study populations and the dose, frequency, and mode of administration of vitamin D, as well as the addition or not of calcium supplementation. Questions persist about optimum vitamin D status and the dose and frequency of administration of vitamin D supplementation.

In the ViDA trial, we aimed to raise concentrations in serum of 25(OH)D to 80–100 nmol/L, which are physiological concentrations recorded in young adults in tropical latitudes and which findings of observational studies suggested were optimum for health at the time this trial was designed.[14] Findings of initial studies suggested that fairly high doses of vitamin D were needed to achieve these concentrations of 25(OH)D, and thus to be effective in fracture prevention. In a study of fracture reduction, Chapuy and colleagues[4] used 800 IU vitamin D daily; later trials in which no effects of vitamin D were reported on fractures—eg, the Women's Health Initiative—used smaller doses of 400 IU daily.[27] In the ViDA study, the monthly bolus of 100 000 IU colecalciferol was equivalent to an intake of roughly 3000 IU vitamin D a day, which is the approximate requirement to achieve these concentrations of 25(OH)D in blood when sunlight exposure is inadequate. Since 25(OH)D has a long half-life in blood, use of a bolus for supplementation had perceived advantages of improving adherence, compared with a daily dose for several years.[12] Findings of pharmacokinetic studies indicate a peak at 7 days after a 100 000 IU dose of vitamin D, with mean values declining linearly to baseline concentrations by 84 days.[13]

In an early trial using 100 000 IU oral colecalciferol every 4 months (equivalent to about 800 IU daily), a 22% reduction in fractures was reported in a community-based population of men and women older than 65 years.[28] However, later trials using large intermittent bolus doses reported no benefits;[29] indeed, in one trial of an annual autumn dose of 500 000 IU vitamin D in 2256 community-dwelling older women at high risk of fractures, a significantly increased risk of falls and fractures was reported (HR 1·15 and HR 1·26, respectively).[24] Sanders and colleagues[24] noted a temporal pattern in increased rates of falls in the 3 months immediately after the bolus and postulated that either very high levels of vitamin D metabolites or a subsequent decrease in concentration of these metabolites, or both, might be causal. In a 2016 trial, increased falls were reported with monthly 60 000 IU vitamin D_3 compared with monthly 24 000 IU vitamin D_3, which accords with this finding, with the falls risk highest in people with the highest vitamin D levels.[7] We did not have exit vitamin D levels for most participants in ViDA to enable these analyses. Findings of a review of the various trials to compare high-dose intermittent supplementation with more frequent dosing suggested that the mode of administration of vitamin D resulting in an acute increase in concentrations in blood of 25(OH)D (through large oral doses) might play a part in the physiological effects.[29]

Uncertainty surrounds what the optimum amounts of 25(OH)D might be above the suggested deficiency concentrations of less than 25–30 nmol/L in relation to various health outcomes, and these values could differ depending on the health outcome; thresholds might vary for fractures or cardiovascular disease or in different ethnic groups.[1] For bone health, no additional benefit might be gained above concentrations associated with deficiency, and possible adverse effects could arise at high concentrations (>70 nmol/L), which might be associated with increased bone turnover. In this context, the mean baseline 25(OH)D concentration of this population was higher (61 nmol/L) than the average concentrations from other trial populations. In the trial by Trivedi and colleagues[28] of 100 000 IU vitamin D every 4 months, fracture reduction was reported with increased concentrations of 25(OH)D in the vitamin D treatment group, from an average baseline of 53 nmol/L to 74 nmol/L. Although the aim of the ViDA trial was to increase concentrations to 80–100 nmol/L, the mean amounts recorded in participants allocated vitamin D supplementation were substantially higher, around 120 nmol/L on average, and more than twice that noted in individuals allocated placebo. Nevertheless, although U-shaped associations between amounts of 25(OH)D and fractures and

falls could account for the overall lack of effect on risk of falls and fractures (if supplementation resulted in some individuals having very high concentrations that might increase risk), we noted no differences in falls and fractures associated with supplementation in individuals stratified by baseline 25(OH)D status. Thus, even people with low amounts seemed to derive no fracture risk reduction from supplementation. Further stratification of results according to baseline 25(OH)D less than 25 nmol/L or at least 75 nmol/L showed no heterogeneity and provided no support for the hypothesis that supplementation might be effective in individuals with deficiency or that increasing 25(OH)D in people with high concentrations (≥75 nmol/L) might be adverse and thereby counterbalance any potential benefit in those with low amounts of 25(OH)D.

The ViDA trial was designed to test the effect of vitamin D supplementation alone, rather than in conjunction with calcium supplements. Although findings of some meta-analyses have suggested that both calcium and vitamin D are necessary for a benefit on fractures,[1,5] results are inconsistent and heterogeneity could be accounted for not only by the differing doses of vitamin D but also by the dose and type of calcium supplement.

The ViDA trial has several strengths. First, adherence was excellent. We assessed adherence in a random subset of participants and showed a substantial increase in mean blood 25(OH)D concentrations over 3 years in the group randomly allocated vitamin D supplementation compared with those assigned placebo. Second, ascertainment of fractures used two independent objective methods: hospital discharges tracked using the Ministry of Health unique National Health Index number; and the ACC system (the national governmental insurance organisation that covers all New Zealand residents for any medical and hospital costs from injury). Although we did not assess the sensitivity and specificity of the fracture data, diagnosed fractures not captured by these data will have been very few because both hospitals and family doctors have a financial incentive to claim from the ACC for any costs from treating injuries, including both inpatient and outpatient fractures. Thus, sensitivity is likely to be very high. Additionally, multiple health professionals are usually involved in the management of fractures (family doctors, radiologists, and physiotherapists at the very least). This multidisciplinary teamwork acts as a check against fraudulent ACC claims by health professionals, giving confidence that the specificity of the fracture data is also very high. Third, one of the aims of the ViDA trial was to include population subgroups in which data are sparse; the Māori and south Asian ethnic groups in New Zealand are at particular risk of vitamin D deficiency.[21] Although statistical power was limited in the various subgroups, no evidence of heterogeneity of effect was seen in any of the subgroups examined.

Our study has limitations. First, the low proportion of people invited to participate who were randomly assigned limits external validity, although this shortfall is common for trials for which the priority is to maximise internal validity. Second, later on in the study, capsules were sent to participants every 4 months. Although no checks were made as to whether four capsules were taken on one occasion rather than monthly, participants had previously been taking one capsule monthly for at least 2 years, reminder letters were sent monthly to take one capsule, and no cases of hypercalcaemia were detected in the subset returning annually for blood tests. Third, use of participant self-reports to identify falls could have resulted in a random measurement error for this outcome, attenuating any effect from vitamin D. However, we used the standard questionnaire wording recommended for this outcome[15] and obtained falls data every month, as recommended,[15] for most of the follow-up period. Although the questionnaire was not validated in this population, and we were not able to verify such a large number of falls by follow-up phone calls, the expected increased risk of falls seen for female sex, older age, and recent history of falls (appendix p 3) support the validity of our measure for this outcome. Fourth, our study had low statistical power for fracture outcome, particularly in participants with vitamin D deficiency, in age and sex subgroups, or for fracture subsites. Although falls data were gathered, the falls outcome was post hoc without a prespecified statistical analysis plan. However, the study power for the falls outcome was high, even in the 1270 participants with low vitamin D levels. Finally, we did not measure dietary vitamin D or calcium intake at baseline. However, based on findings of a national nutrition survey showing that New Zealanders of European ancestry in the study age range had a mean daily calcium intake of 862 mg for men and 771 mg for women, values that are similar to those for the European and North American population, it is unlikely that our null results are explained by inadequate intake of dietary calcium.

Results from the ViDA trial suggest that a monthly dose of 100 000 IU colecalciferol in a healthy, middle-aged, and older ambulatory population does not reduce the risk of fractures or falls over 4 years. Although the study had low power for fracture endpoints, these findings—taken in conjunction with results from other trials—suggest that use of large monthly bolus doses of vitamin D does not confer overall benefit. Further study is needed to assess the effects of daily dosing of vitamin D, with or without calcium supplementation, and international trials are ongoing (eg, VITAL in the USA [NCT01169259]; DO-HEALTH in Europe [NCT01745263]; and FIND in Finland [NCT01463813]).

Contributors

RS, AWS, CMML, LT, K-TK, and CAC Jr had the idea for the study and contributed to study design, data analysis, and data interpretation. RS, AWS, DW, and CMML contributed to data acquisition. K-TK and RS drafted the report and AWS, DW, CMML, LT, and CAC Jr contributed to critical revision for important intellectual content. AWS and RS did the statistical analysis.

Declaration of interests
We declare no competing interests.

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