Effect of Monthly High-Dose Vitamin D Supplementation on Falls and Non-Vertebral Fractures: the Vitamin D Assessment (ViDA) Study (a Randomized Double Blind Controlled Trial)

Kay-Tee Khaw[1], Alistair W. Stewart[2], Debbie Waayer[2], Carlene M.M. Lawes[2], Les Toop[3], Carlos A. Camargo Jr[4], and Robert Scragg[2]

Authors' Affiliations:

Kay-Tee Khaw, MBBChir, FRCP, Professor

[1]Department of Public Health and Primary Care, University of Cambridge, United Kingdom;

Alistair W Stewart, BSc, Senior Research Fellow

Debbie Waayer, MEd, Project Manager

Carlene MM Lawes, MBChB, PhD

Robert Scragg, MBBS, PhD, Professor

[2]School of Population Health, The University of Auckland, Auckland, New Zealand;

Les Toop, MBChB, MD, Professor

[3]Department of Public Health & General Practice, The University of Otago, Christchurch, New Zealand;

Carlos A Camargo Jr MD, DrPH, Professor

[4] Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

Short running title: **Vitamin D supplementation, falls and non-vertebral fractures**

Word count: text (excluding abstract, tables & references) 4876; abstract 347 words

Number of tables and figures: 3 Tables, 3 Figures, & 5 supplementary Tables

Key words: fall; fracture; randomized controlled trial; supplement; vitamin D;

Correspondence to:

Kay-Tee Khaw, Professor

Clinical Gerontology Unit Box 251, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, CB3 0EQ, United Kingdom

e-mail: kk101@medschl.cam.ac.uk Phone: +44 1223 336927

Abstract

Background Adults with low blood 25-hydroxyvitamin D (25(OH)D) concentrations have increased risk of falls and fractures but randomized trials of vitamin D supplementation have had inconsistent results.

Methods The Vitamin D Assessment(*ViDA*) Study, was a randomized double-blind placebo controlled trial of 5110 healthy volunteers aged 50-84 years in Auckland, New Zealand who in 2011-2012 were randomized to an initial oral dose of 200,000 IU vitamin D3 followed by 100,000 IU(2,500ug) vitamin D3 monthly(n=2558) or placebo(n=2552) till July 2015, mean 3·4 years, range 2·5-4·2 years. Two participants withdrew leaving 5108 in analyses. The prespecified primary outcome was cardiovascular disease and secondary outcomes respiratory illness and fractures. We report results for fractures, and falls assessed as a post-hoc outcome. The Cox proportional hazards model was used to estimate Hazard Ratios for time to first fracture or time to first fall in individuals on vitamin D compared to placebo.

Findings The mean age was 66 years, 58% were male, and 83% were of European/Other ethnicity, and 17% Polynesian or South Asian. Mean(SD) baseline blood 25-hydroxyvitamin D(25(OH)D) concentration was 63(24)nmol/L, with 30% having 25(OH)D concentrations <50nmol/L. In a random sample of 438 participants, vitamin D supplementation increased mean 25(OH)D to an average 135nmol/L, compared to those on placebo(mean 63nmol/L). During follow up, 2638 participants reported having a fall: 51.7% in the vitamin D group compared to 52 ·7% in the placebo group. The hazard ratio(95%CI) for falls, adjusted for age, sex and ethnicity for vitamin D compared to placebo was 0·98(0·92,1·06). Non-vertebral fracture (in 292 individuals) occurred in 6·1% of the vitamin D group and 5·3% of placebo. The adjusted hazard ratio(95%CI) for fracture was 1·15(0·92,1·45) for vitamin D compared to placebo. Results were similar in participants with baseline 25(OH)D concentrations <50 and >=50nmol/L.

Interpretation High-dose bolus vitamin D supplementation of 100,000 IU monthly over 2 to 4 years does not prevent falls or fractures in this healthy ambulatory adult population. Whether effects of daily dosing with or without calcium differ requires further study.

Funding Health Research Council of New Zealand (grant 10/400), and the Accident Compensation Corporation of New Zealand.

Trial Registration: Australian New Zealand Clinical Trials Registry, Identifier ACTRN12611000402943

Research in context

Evidence before this study

When this trial was planned in 2010 for outcomes cardiovascular disease, fractures and acute respiratory infections, there were extensive observational data linking low vitamin D status with increased risk of several important adverse health events. However, the largest randomized 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. With respect to falls and fractures, the outcomes reported in the current manuscript, a literature search using Pub Med with search terms 'vitamin D', 'fractures', 'randomized trials' yielded 238 references between 1/1/1985-31/12/2010; when updated to 31/1/2016 there were 365 references; 'vitamin D', 'falls', 'randomized trials' yielded 59 references 1/1/1985-31/12/2010 and updated to 31/12/2016 there were 128 references. However, there were already existing extensive reviews including an Institute of Medicine report and meta analyses of randomized trials including Cochrane collaboration reviews which we used (cited in text). Meta-analyses of randomized trials of vitamin D supplementation on risk of falls and fractures including the Cochrane collaboration reviews had inconsistent conclusions e.g. Avenell A, 2009, any fracture RR1.01(0.93-1.09) 10 trials,26,016 participants; IOM 2010 total fractures RR 0.90 (0.81-1.02) 13 trials, 58713 participants; Kalyani R, 2010 falls RR 0.86 (0.79-93) 10 trials; IOM 2010 falls RR 0.92 (0.85-1.00) 11 trials, 13888 participants. These inconsistencies were variously attributed to the type of formulation of vitamin D (D2 or D3), how administered (injection or orally), frequency (daily doses or large intermittent bolus doses), additional calcium supplementation, and baseline vitamin D status of the study populations. An extensive Institute of Medicine report 2011 highlighted the limited number of long term clinical trials related to calcium and vitamin D intakes and health outcomes. The rationale for the ViDA trial was to conduct a large randomized trial in a community based population, using a monthly bolus dose of 100,000 IU designed to raise average year round blood concentrations to 80-100nmol/L which are the concentrations found in young adults in the tropics and levels associated with optimal health in observational studies at that time. The monthly bolus dose was designed to improve compliance and public health feasibility.

Added value of this study

Results from this trial indicate that a monthly dose of 100,000 IU cholecalciferol with good compliance in a healthy middle aged and older ambulatory population showed no reduced risk of falls or fractures over 4 years. These findings, taken in conjunction with results from other trials, indicate that the use of large monthly bolus doses of vitamin D does not confer overall benefit either in frail elderly or in a healthy ambulatory general population. Whether the effects of daily dosing may differ requires further study; there are several ongoing trials exploring this issue internationally but not due to report for some time.

Introduction

Rickets and osteomalacia are well established consequences of vitamin D deficiency(1). Low blood 25-hydroxy-vitamin D (25(OH)D) concentrations 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. Though an early trial reported a 32% non-vertebral fracture reduction 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 variously attributed to differences in vitamin D dosage both frequency and amount, type of preparation such as cholecalciferol(vitamin D3) or ergocalciferol(vitamin D2), mode of administration of vitamin D whether oral or intramuscular injections, baseline vitamin D status of the study population as well as whether there was additional calcium supplementation.

The Vitamin D Assessment (ViDA) study was designed to assess whether oral cholecalciferol administered as a monthly dose of 100,000 IU(2·5 mg) would reduce risk of cardiovascular disease (primary outcome), respiratory illness, or fractures (secondary outcomes) in a community based population in New Zealand(12). We collected additionally data on falls. We report here the results for fractures (secondary outcome) and falls (post-hoc outcome).

Methods

Study Design

We carried out a randomized, double-blind, placebo-controlled trial in Auckland, New Zealand, with recruitment during 5 April 2011 to 6 November 2012, and follow-up to 31 July 2015(12). Ethics approval was given by the Multi-region Ethics Committee, Wellington (MEC/09/08/082) in October 2010, and the trial was registered with the Australian New Zealand Clinical Trials Registry in April 2011(ACTRN12611000402943)(12).

Primary and secondary outcomes

The pre-specified primary outcome for the trial was incident cardiovascular disease; pre-specified secondary outcomes were non-vertebral fractures and respiratory infection. In the registered protocol, data collection on falls was included as a safety outcome, and the 2011 contract with a funder, the Accident Compensation Corporation(ACC), specified detailed data on falls. Since a formal protocol amendment was not made, the falls outcome is post-hoc. Results of other outcomes (cardiovascular disease and respiratory infection) are being reported in other manuscripts.

Participants

Potential participants in the study age range were identified from family practice registers. Of 47,905 people from 55 general practices sent an invitation letter, 8688 replied, of whom 5107 were eligible and agreed to a baseline interview. Eligible participants (n=143) were identified also from community groups, giving a total of 5250 attending baseline interviews (**Figure 1**). Inclusion criteria were: age 50–84 years; resident in Auckland at recruitment; and anticipated residence in New Zealand for the study period. The 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 ability to comply with study protocol; history of hypercalcemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery; or serum corrected calcium from baseline blood sample >2·50 mmol/L.

Baseline Interview

Baseline interviews, detailed elsewhere(12) were carried out at the School of Population Health, University of Auckland Tāmaki Campus. These included information on: socio-demographic status; lifestyle (current tobacco smoking, alcohol consumption over the previous 12 months, and usual leisure-time physical activity over the previous three months; history of a fall in the previous 4 weeks; intake of vitamin D or calcium supplements; past medical history of osteoporosis and fracture; measurement of height to the nearest 0·1 cm, and weight to the nearest 0·1 kg, in light clothing without shoes; and a non-fasting blood sample to screen for hypercalcaemia collected during the morning or afternoon. Remaining serum was stored at -80°C for later measurement of 25(OH)D.

Randomization

After the baseline interview of 5250 individuals, 140 people were excluded mainly due to 92 who did not return within 4 weeks a 'run-in' questionnaire mailed to their home with a blind placebo capsule with confirmation they had taken the capsule, or who had hypercalcaemia (adjusted serum calcium >2·50 mmol/L)(**Figure 1**). The remaining 5110 people were randomized by computer automatic allocation to one of the two treatment groups within random block sizes of 8, 10 or 12, within ethnic (Maori, Pacific Islander, South Asian, European/Other) and 5-year age strata. Participants and study personnel were blind to assigned group.

Intervention

Monthly vitamin D_3 (2·5 mg or 100,000 IU, equivalent to a daily dose of 82ug(3290 IU) or placebo oral capsules, supplied by Tishcon Corporation (Westbury, New York, USA), were mailed to participants at their homes. Two capsules (i.e., 200,000 IU bolus, or placebo) were taken at the start of the intervention period, and then a monthly capsule (100,000 IU of vitamin D_3, or placebo) until follow-up stopped. The monthly 100,000 IU vitamin D dose was selected as it was known to maintain serum 25(OH)D levels 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 80-100nmol/L was associated with optimal health(14). Capsules were mailed monthly to participants until June 2013, with a 1-page questionnaire and reply-paid envelope to record self-reported adherence, falls, and fractures. From July 2013

onward, four capsules were mailed every four months as a cost control measure, and monthly reminders to take the capsule were sent by email or letter. The majority of participants confirmed starting the study capsule (vitamin D 98%, placebo 98%); and only 21 (1%) of the vitamin D group and 49 (2%) of the placebo group never confirmed capsule ingestion at any time during the follow-up period(Figure 1).

Follow-up and Outcomes

Information about falls was collected from the questionnaire mailed monthly with the capsules to participant's homes from Jun 2011 until November 2013, and then 4-monthly with four capsules from March 2014 until July 2015. Participants were asked 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: 'In the last four 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 response was 'Yes', participants were asked to indicate the number of falls ('1' or '2 or more' for the monthly questionnaire; and '1', '2', '3' or '4+' for the 4-monthly questionnaire); and if the fall caused an injury, specifically whether they hit their head or suffered a 'Strain or sprain (to muscles or ligaments)', 'Cut, bruise, bleeding or abrasion to your skin' or a 'Fracture of your bone(s)' from the fall. These were classified as injury falls. Though this questionnaire has not been validated in this population, we used the wording recommended by expert consensus to measure falls(15).

Information about fractures came from two sources. First, the Ministry of Health allocates all New Zealand residents a unique National Health Index number, which was used to track hospital discharges (with ICD-10 coding) for all participants during the follow-up period which ended on 31 July 2015. Fractures were defined as hospital discharges with the primary(A code) diagnosis or the secondary(B code) diagnosis for specified ICD-10 codes. Second, 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. Fractures were defined as claims made after randomisation with specified ICD10 or READ codes. The ICD10 and READ codes are listed in **supplementary table 1** as are fractures by site.

Deaths were identified using Ministry of Health mortality files.

Serum corrected calcium was measured the following day after collection at the baseline interview. Serum 25(OH)D(combining D_2 and D_3) was measured later in baseline aliquots, stored frozen at -80˚C, by liquid chromatography–tandem mass spectrometry(ABSciex API 4000) at a laboratory participating in the Vitamin D External Quality Assessment Scheme (DEQAS) program. A random sample of participants (438 out of 515 invited) agreed to return at 6, 12, 24 and 36 months so that further blood samples could be collected to measure corrected calcium and 25(OH)D (stored and measured in the same batch as the baseline blood sample for each participant).

Statistical Analysis

The planned completion date of the trial was 31 July 2015. The specified protocol analyses were hazard ratios for fractures for vitamin D compared to placebo group based on time to first fracture; the post hoc falls analyses used a similar approach, hazard ratios for time to first fall for an individual, using the Cox proportional hazards model. 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(16). The study had an 80% chance of detecting a hazard ratio of 0·76 for non-vertebral fractures (5% significance level), based on estimated incidence rates in New Zealand(17) anticipating 430 people would have fractures during the trial.

Analysis of the fall outcome was dependent on the number of returned questionnaires throughout the follow-up period. The analysis was conducted in the 5,056 participants who returned ≥ 1 questionnaire (52 did not return any questionnaire)(**Figure 1**). The date of the fall was defined as approximately halfway through the coverage period of the questionnaire. It was assumed there was no fall during the period of the questionnaire if a questionnaire was not returned. Participants were censored (that is, last date noted for estimation of follow up time) at the last questionnaire they returned.

Analysis of the fracture outcome was conducted on an intention-to-treat basis in 5,108 participants after excluding two who withdrew consent(**Figure 1**). This was made possible by

use of the National Health Index number to identify hospitalisations from fracture in the Ministry of Health data, and from claims for fractures in the ACC data, regardless of whether participants continued to participate actively in the study by returning the home questionnaire.

The Cox proportional hazards regression model, with robust sandwich variance estimates and exact P-values, was used to compare the time to first fall or fracture in the two treatment groups, and to calculate hazard ratios for falls according to the protocol, with a similar approach for falls. In supplemental observational analyses, hazard ratios for falls and fractures associated with known risk factors were analysed in the placebo group to assess the validity of both outcome measures. The proportional hazards assumptions were tested and none violated. We treated those who died prior to an event up to 31 July 2015 (n=123) as censored observations. As 25(OH)D values are seasonally dependent, using observed levels adds random variability to analyses so we calculated a deseasonalised 25(OH)D value that predicts the average level for each participant over four seasons. The deseasonalised concentrations were calculated using a sinusoidal model from the baseline values for all participants(18). Vitamin D sufficiency was defined in the protocol as having a deseasonalised 25(OH)D >50 nmol/L(adjusted baseline >50 nmol/L for at least 6 months of the year) for the a priori specified 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. The testing of the treatment effect was adjusted for the stratification variables, age, sex and ethnicity as well as 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. Interactions between treatment group and sex, age, ethnicity and deseasonalised 25(OH)D were assessed. Subgroup analyses were also done for deseasonalised baseline 25(OH)D<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.

Though not explicitly specified in the protocol, we conducted additional observational analyses on the placebo arm of the trial to examine whether risk factors for fractures and falls in this population were consistent with the existing observational literature, to indicate that the ascertainment of these endpoints was reasonable and that this population was similar to other with respect to these risk factors.

Results

Baseline Characteristics

The mean(SD) age of the participants was 65·9 years, with the majority in the range of 60-79 years(72%). There were more male than female participants(58% vs 42%). The ethnic distribution was Maori 5%, Pacific Islander 7%, South Asian 5% and European/Other 83%. Just over half had attended tertiary education(56%) and the majority were either employed(51%) or retired(40%). Few participants were current tobacco smokers(6%) although 43% were ex-smokers. Only 1% had been told by a doctor they had osteoporosis, although 47% reported having had a previous fracture any time in their lives and 6% reported having a fall in the 4 weeks before baseline interview. Vitamin D supplements (within the study eligibility criteria) were taken by 8% and calcium supplements by 5% and mean(SD) 25(OH)D, not corrected for season, was 63 (SD 24), varying from a maximum monthly mean of 77 in March to a minimum monthly mean of 55 in August while the deseasonalised values were 66(SD 23)nmol/L. The baseline characteristics were similar for the vitamin D and placebo groups(**Table 1**).

Follow-up 25(OH)D and Calcium

In the participants randomly selected to return and give blood samples, mean baseline 25(OH)D concentrations were similar to those in the whole cohort(61 nmol/L), and increased substantially by 6 months in the vitamin D arm with mean values 50-70 nmol/L higher than in the placebo arm throughout follow-up(Table 2). Only a small proportion(3%) in the vitamin D arm had a 25(OH)D concentration that remained below 50 nmol/L at any time-point(**Table 2**). These results are consistent with the high adherence to taking the study capsule reported in the home questionnaires (168,667 capsules (84%) reported taken during 200,936 person-months). Vitamin D supplementation had no effect on mean(SD) corrected serum calcium concentrations which were 2·3(0·1) mmol/L in each arm at all-time points, except for at 36 months when it was 2·4(0·1) mmol/L (also in in each arm).

Falls

Out of 122,706 questionnaires mailed out, 107,859(88%) were returned. There was good retention during the follow-up period, with 4032 participants(81%) returning the final July 2015 questionnaire and a further 283(6%) returning the penultimate March 2015

questionnaire, indicating that 87% were actively participating during the last five months of the follow-up period.

Falls were reported by just over half of all participants (2,638/5,056) during the follow-up period, mean 3·4 years, range 2·5-4·2 years. In the placebo group, reporting of falls was higher in women than men and in those who had had a recent fall prior to the study commencing, and increased with age, but was not associated with ethnicity, physical activity and baseline 25(OH)D, adjusting for covariates(**Supplementary Table 2**). The probability of reporting one or more falls for all participants (the falls endpoint) was similar in the vitamin D arm compared with placebo(51·7% and 52·7%, respectively, **Table 3**). The Hazard Ratio (HR)(95% CI) was 0·98(0·92,1·06) when adjusting for sex, age, ethnicity; and 0·99(0·92,1·07) when further including history of recent fall, physical activity and baseline 25(OH)D in the model(Table 3). **Supplementary Table 3** shows proportions of participants reporting falls in vitamin D and placebo group stratified by age and sex.

Subgroup analyses did not show any difference in the risk of falls between the vitamin D and placebo arms, for participants with deseasonalised baseline 25(OH)D< 50 nmol/L (vitamin D 51·0%, placebo 49·0%, p-value 0·42), those with a history of falls in the 4-weeks before baseline interview (vitamin D 75·9%, placebo 69·4%, p-value 0·25), or those who reported at baseline being physically active and undertaking vigorous activity for >2 hours per week (vitamin D 50·6%, placebo 51·2%, p-value 0·92). There were no interactions between treatment and sex (P=0·13), ethnicity (P=0·51), age P=0·49) and deseasonalised 25(OH)D (P=0·80). **Figure 2** shows there was no difference between the vitamin D and placebo arms in the proportion of participants who had a fall during follow-up. Among those who had a fall, there was no difference (P=0.98) between the proportion who reported 1,2 or more than 2 falls in the vitamin D group (44.4%, 26.9%, 28.7% respectively) and the placebo group (44.6%, 27.1%, 28.3% respectively). Neither was there a difference among all participants in the number(percent) reporting an injurious fall: vitamin D =1049(41.3%), Placebo 1020(40.5%), HR 1.03(95%CI 0.95,1.13, P=0.46) adjusted for variables in table 3.

Fractures

The pattern for non vertebral fractures (identified in 292 participants) was similar to that for falls. In the placebo group, fractures were more common in women than men, but not associated with age, ethnicity, history of recent fall, physical activity or baseline 25(OH)D, adjusting for covariates (**Supplementary Table 4**). Non vertebral fractures were identified in 6·1% of the vitamin D group compared to 5·3% in the placebo group for all participants during follow-up (primary fracture outcome); the age, sex and ethnicity adjusted HR was 1·15 (0·92,1·45) and HR 1·19 (0·94,1·59) with further adjustment including history of recent fall, physical activity and baseline 25(OH)D in the model (**Table 3**). Inclusion of 13spinfractures (identified in 305 participants) to obtain total fractures hardly changed estimates with age sex and ethnicity adjusted HR 1.14(0.91-1.42). There was no difference in cumulative risk of fracture between and the vitamin D and placebo groups (**Figure 3**). Exploratory analyses stratifying results by baseline 25(OH)D <25 nmol/L or >=75 nmol/L showed no heterogeneity (**Supplementary Table 5).**

Discussion

Monthly supplementation of 100,000 IU cholecalciferol taken for 2·5 to 4·2(mean 3·4) years was not associated with significant differences in risk of falls or fractures in this community based randomized trial in individuals predominantly without known osteoporosis. While the statistical power of the study was limited for fractures (80% power at 5% level of significance to detect a RR of 0·70 in one treatment arm), there was no evidence of any reduced risk of fractures in the vitamin D treatment arm.

The relationship between vitamin D deficiency and rickets and osteomalacia is well established and a general consensus is that concentrations below 25nmol/L are associated with greatly increased risk of these conditions(1). However, there is debate about optimal vitamin D status for other health outcomes in terms of what optimal blood concentrations of 25(OH)D above deficiency levels might be(1;14;19), as well as the oral vitamin D dose required to maintain particular blood concentrations of 25(OH)D where sunlight exposure is inadequate.

Most trials of vitamin D supplementation for falls or fracture prevention have focussed on groups at high risk of fracture such as women, older people, and institutionalised individuals; moreover, the trials have been done in predominantly white populations. The current community based trial included men, a wide age range 50-84 years and different ethnic groups documented to have a high prevalence of vitamin D deficiency(20).

A 2014 review concluded that evidence did not support the hypothesis that vitamin D only supplementation reduced the risk of falls or fractures(21), in marked contrast to previous meta analyses. For falls, a 2010 meta-analysis concluded, based on 10 studies meeting inclusion criteria, that vitamin D therapy 200-1000 IU daily reduced falls by 14% compared to calcium or placebo(22), a conclusion supported by a USPSTF review in 2012(23) indicating a 17% lower risk of falling with a median oral daily dose of 800 IU. However more recent trials reported increased falls risk with bolus vitamin D supplementation(24;25) leading to a

more cautious re-evaluation highlighting the need for evidence in different 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 differences in using data from the same trials(26) such as inclusion criteria and data extraction.

In terms of fractures, the 43% reduction in hip fractures in an early trial in 3270 institutionalised women mean age 84 years who had very low 25(OH)D levels consistent with osteomalacia with a daily 800 IU and 1200 mg calcium supplement taken over 18 months(4) has not been consistently observed in subsequent trials whether in primary or secondary prevention of fractures(5). A recent meta-analysis of such trials indicated a possible weak association of vitamin D and calcium supplement on hip fractures in high risk groups, but no overall effect of vitamin D supplement alone on fracture risk(27) . These inconsistent findings have been variously attributed 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. In particular, questions persist as to what optimal vitamin D status might be, and the dose and frequency of administration of vitamin D supplementation.

This trial aimed to raise serum 25(OH)D concentrations to 80-100 nmol/L, which are physiological concentrations observed in young adults in tropical latitudes, and which observational studies suggested were optimal for health at the time the trial was designed(14). Initial studies suggested that relatively high doses were required to achieve these concentrations to be effective in fracture prevention. The Chapuy study which reported fracture reduction used 800 IU vitamin D daily(4); later trials which reported no effects on fractures such as the Women's Health Initiative used smaller doses of 400 IU daily(28). The monthly bolus dose of 100,000 IU was equivalent to an intake of approximately 3000 IU Vitamin D a day which is the approximate requirement to achieve these blood concentrations where sunlight exposure is inadequate. Since 25(OH)D has a long half-life in the blood, the use of a bolus dose for supplementation had perceived

advantages of improving compliance compared to a daily dose for several years(12). Pharmacokinetic studies indicate a peak at 7 days following a 100,000 IU dose with mean values declining linearly to baseline concentrations by 84 days(13).

An early trial using oral cholecalciferol 100,000 IU four monthly, equivalent to about 800 IU daily, reported 22% fracture reduction in a community based population of men and women aged over 65 years(29). However, later trials using large intermittent bolus doses have reported no benefits(30) and indeed one trial of an annual autumn dose of 500,000 IU in 2256 community dwelling older women at high risk of fractures reported significantly increased risk of falls HR 1·15 and fractures HR 1·26(25). Sanders et al(25) observed a temporal pattern in increased fall rates in the 3 months immediately following the bolus and speculated that very high levels of vitamin D metabolites or subsequent decrease in levels or both might be causal. A 2016 trial reporting increased falls with monthly 60,000 IU compared to monthly 24,000 IU vitamin D3 is consistent with this, with falls risk highest in those with highest vitamin D levels(7). We did not have exit vitamin D levels for most participants to enable these analyses. A review of the various trials comparing high dose intermittent supplement with more frequent dosing suggested that the mode of administration of vitamin D resulting in acute increase in blood concentrations of 25(OH) D may well influence physiological effects(30).

In addition, there is uncertainty as to what optimal concentrations of 25(OH)D above suggested deficiency concentrations of <25 or <30 nmol/L might be, in relation to various health outcomes and these may differ depending on the health outcome; thresholds might vary for fractures or cardiovascular disease or in different ethnic groups(1). For bone health, there may be no additional benefit above concentrations associated with deficiency, and possible adverse effects at high concentrations, above 70nmol/L which may be associated with increased bone turnover. In this context, the mean baseline 25(OH)D concentration of this population was higher(61nmol/L) than the average concentrations from other trial populations. The Trivedi et al trial of 100,000 IU four monthly which reported fracture reduction increased concentrations from an average baseline of 53nmol/l

to 74 nmol/L(29). While the aim of the current trial was to increase concentrations to 80-100 nmol/L, the mean levels observed in the group allocated to supplement were substantially higher, around 120nmol/l on average, and over twice the concentrations observed in those allocated to placebo. Nevertheless, though U-shaped associations between 25OHD and fracture and falls might explain the overall lack of effect on falls and fracture risk if supplementation resulted in some individuals having very high concentrations which might increase risk, we observed no differences in falls and fractures associated with supplementation in individuals stratified by baseline 25(OH)D status, so even those with lower concentrations appeared to derive no fracture risk reduction from supplementation. Further stratification of results according to baseline 25(OH)D less than 25 nmol/L or >=75 nmol/L showed no heterogeneity and provided no support for the hypothesis that supplementation might be effective in those with deficiency nor that increasing 25(OH)D in those with high concentrations(>=75 nmol/L might be adverse and thereby counter balance any potential benefit in those with low 25(OH)D concentrations.

This trial was designed to test the effect of vitamin D supplementation alone, rather than in conjunction with calcium supplements. While some meta-analyses have suggested that both calcium and vitamin D are necessary for benefit for fractures(1;5), results are also inconsistent and heterogeneity may also be explained not just by the differing doses of vitamin D, but also of the dose and type of calcium supplement.

This trial has several strengths. Firstly, adherence was excellent. We assessed adherence in a random subset of participants and demonstrated a substantial increase in average 25(OH)D concentrations over 3 years in the group randomized to receive supplement in marked contrast to those receiving placebo. Secondly the 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. Though we did not assess the sensitivity and specificity of the fracture data, diagnosed fractures not captured by these data will have been very few as both hospitals and general practitioners have a financial incentive to claim from the ACC for any

costs from treating injuries including inpatient as well as outpatient fractures. Thus, sensitivity is likely to be very high. Additionally, multiple health professionals are usually involved in the management of fractures (GPs, radiologists and physiotherapists at the very least). This acts as a check against fraudulent ACC claims by health professionals giving confidence that the specificity of the fracture data is also very high. Thirdly, one of the aims of this trial was to include population subgroups in which there is a lack of data; the Māori and South Asian groups in New Zealand are reported to be at particular risk of vitamin D deficiency. While statistical power was limited in the various subgroups, there was no evidence of heterogeneity of effect in any of the subgroups examined.

Our study has limitations. The low proportion of people invited to participate who were eventually randomised limits external validity, although this is common for trials where the priority is to maximise internal validity. Later on in the study, capsules were sent to participants every four months. Though no checks were made as to whether four capsules were taken on one occasion rather than monthly, they had previously been taking one capsule monthly for at least two 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. The use of participant self-reports to identify falls may 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 collected falls data monthly as recommended for most of the follow-up period. Though 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(Supplementary Table 2) support the validity of our measure for this outcome. Our study had low statistical power for fracture outcome, particularly in participants with vitamin D deficiency, age and sex subgroups or for fracture subsites. Though falls data were collected, the falls outcome were post hoc without a prespecified statistical analysis plan. However, the study power for the falls outcome was high, even in the 1270 participants with lower vitamin D levels. Neither did we measure dietary vitamin D or calcium intake at baseline. However, based on a recent 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 European and North American population, it is unlikely that our null results are explained by inadequate intake of dietary calcium.

Results from this trial indicate a monthly dose of 100,000 IU cholecalciferol in a healthy middle aged and older ambulatory population showed no reduced risk of fractures or falls over 4 years. Though the study had low power for fracture endpoints, these findings, taken in conjunction with results from other trials, indicate that the use of large monthly bolus doses of vitamin D does not confer overall benefit. Whether the effects of daily dosing of vitamin D or with calcium supplementation may differ, requires further study and is being addressed in ongoing international trials.

Acknowledgements

Major funding was provided by the Health Research Council of New Zealand (grant 10/400), and the Accident Compensation Corporation of New Zealand. The sponsors had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, and preparation, review or approval of the manuscript.

Ethics and Consent

Ethics approval was given by the Multi-region Ethics Committee, Wellington (MEC/09/08/082) in October 2010, and the trial was registered with the Australian New Zealand Clinical Trials Registry in April 2011 (ACTRN12611000402943).
All participants gave signed informed consent.

Contributors

Robert Scragg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The lead author Khaw and guarantor Scragg affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
Study concept and design: Scragg, Stewart, Lawes, Toop, Khaw, Camargo
Acquisition of data: Scragg, Stewart, Waayer, Lawes
Analysis and interpretation of the data: Scragg, Stewart, Lawes, Toop, Khaw, Camargo
Drafting of the manuscript: Khaw, Scragg,
Critical revision of the manuscript for important intellectual content: Stewart, Waayer, Lawes, Toop, Camargo
Statistical analysis: Stewart, Scragg
Obtaining funding: Scragg, Stewart, Lawes, Toop, Khaw, Camargo
Administrative, technical or material support: Scragg, Stewart, Waayer, Lawes

Data sharing statement

Data are not available on open access as participants have not consented to having their data shared with anyone apart from the research team.

Conflicts of interest

None.

What is known

Low blood 25(OH)D concentrations have been associated with increased risk of falls and fractures in observational studies.

Trials of vitamin D supplementation for prevention of falls and fractures have had inconsistent results.

What this study adds

In a randomized double blind trial in community dwelling men and women aged 50-84 years in New Zealand, supplementation with monthly bolus 100,000 IU cholecalciferol over 2 to 4 years had no effect on risk of falls or fractures.

Legend for Figures

Figure 1: Flow diagram for the ViDA study.

Figure 2: Proportion of participants not having a fall during follow-up for the vitamin D and placebo groups. Cox proportional hazards model.

Table

Numbers at risk	Baseline	1 year	2 years	3 years	4 years
Vitamin D	2539	1724	1321	760	85
Placebo	2517	1696	1278	657	91

Figure 3: Proportion of participants not having a fracture during follow-up for the vitamin D and placebo groups. Cox proportional hazards model.

Table

Numbers at risk	Baseline	1 year	2 years	3 years	4 years
Vitamin D	2558	2399	2224	1607	298
Placebo	2550	2362	2205	1487	412

Table 1: Baseline comparison of vitamin D supplemented and placebo groups

Variable	**Vitamin D (n=2558)**	**Placebo (n=2550)**
	Percent (n) or Mean (SD)	Percent (n) or Mean (SD)
Sex – female %	40·9 (1046)	42·9 (1093)
Age (years) %		
50-59	22·3 (571)	22·2 (567)
60-69	43·5 (1112)	43·5 (1108)
70-79	28·0 (716)	28·3 (722)
80-84	6·2 (159)	6·0 (153)
Ethnicity %		
Maori	5·4 (137)	5·3 (135)
Pacific Islander	6·6 (168)	6·5 (166)
South Asian	4·9 (126)	4·8 (123)
European / Other	83·2 (2127)	83·4 (2126)
Education (highest level) %		
Primary school	2·1 (53)	1·7 (42)
Secondary school	42·6 (1091)	40·6 (1036)
Tertiary	55·2 (1412)	57·6 (1470)
Refused/Don't know	0.1 (2)	0.1 (2)
In paid employment or retired %		
Employed	50·9 (1301)	51·7 (1317)
Retired	40·7 (1041)	39.9 (1018)
Other	8·2 (211)	8·3 (212)
Refused/Don't know	0.2 (5)	0.1 (3)
Current tobacco smoker %	6·4 (164)	6·1 (156)
Current alcohol drinker %	85·1 (2177)	86·7 (2211)
Vigorous physical activity (hours per week) %		
None	39·7 (1015)	39·9 (1018)
1-2	23·8 (609)	22·9 (585)
>2	31·4 (804)	32·6 (832)
Refused/Don't know	5·1 (130)	4·5 (115)
Past medical conditions told by a doctor %		
Osteoporosis	1·6 (42)	1·1 (29)
Fracture	46·1 (1178)	47·1 (1200)
Fall in the last 4 weeks%	5·8 (147)	6·3 (161)
Confident to do daily activities without falling %		

Not at all	0·9 (23)	1·0 (25)
Quite	17·7 (454)	16·0 (409)
Completely	81·2 (2076)	82·9 (2113)
Refused/Don't know	0.2 (5)	0.1 (3)
Anthropometry		
Weight (kg)	81·3 (16·5)	81·2 (16·0)
Body Mass Index (kg/m^2)	28·4 (5·1)	28·5 (5·1)
Take supplements %		
Vitamin D*	8·1 (208)	7·8 (200)
Calcium	4·9 (125)	5·0 (127)
Serum calcium (mmol/L)	2·3 (0·1)	2·3 (0·1)
25-hydroxyvitamin		
Mean (nmol/L) - observed	64 (24)	63 (24)
<50 nmol/L % - observed	29·2 (746)	30·9 (788)
- Deseasonalised	23·9 (612)	25·8 (658)
25-hydroxyvitamin D category#		
< 25 nmol/L		
25-<50 nmol/L	1·8 (46)	1·8 (45)
50-<75nmol/L	22·1 (566)	24·0 (613)
>=75 nmol/L	43·2 (1106)	41·2(1051)
Missing	32·8 (839)	32.9 (840)
	0.04 (1)	0.04 (1)

* ≤600 IU per day if aged 50-70 years; ≤800 IU per day if aged 71-84 years.

based on deseasonalised values.

Table 2: Mean (SD) observed serum 25-hydroxyvitamin D (nmol/L), and percent < 50 nmol/L, at baseline, and follow-up at 6, 12, 24 and 36 months, by study group in a random subsample of participants

Months after baseline	**Placebo**				**Vitamin D**		
	N	**25(OH)D**			**N**	**25(OH)D**	
		Mean (SD)	**<50 nmol/L % (N)**			**Mean (SD)**	**<50 nmol/L N (%)**
Baseline	216	61 (24)	36% (78)		225	61 (24)	33% (74)
6	182	75 (31)	20% (36)		190	129 (42)	1% (2)
12	198	60 (28)	39% (77)		201	119 (45)	3% (6)
24	194	66 (27)	31% (60)		191	132 (39)	1% (2)
36	163	66 (29)	32% (52)		171	135 (40)	0% (0)

25(OH)D = 25-hydroxyvitamin D

Table 3: Proportion of participants reporting a fall, or having a fracture, during follow-up, by study group, and hazard ratios (placebo as reference) adjusted for sex, age, ethnicity, history of recent fall, baseline physical activity and baseline 25-hydroxyvitamin D (25(OH)D) concentration.

Outcome	**Vitamin D % with outcome (N randomized)**	**Placebo % with outcome (N randomized)**	**Hazard Ratio (95% CI)**	**P-value**
Fall (all)				
n=2638 individuals				
All participants	51·7 (2,539)	52·7 (2,517)	0·99 (0·92, 1·07)	0·82
25(OH)D < 50 nmol/L*	51·0 (602)	49·0 (645)	1·07 (0·91, 1·25)	0·45
Fall in the last 4 weeks	75·9 (145)	69·4 (157)	1·18 (0·89, 1·56)	0·25
Vigorous activity >2 hours per week	50·6 (800)	51·2 (823)	1·01 (0·88, 1·16)	0·92
Non-vertebral fracture n=292 individuals				
All participants	6·1 (2,558)	5·3 (2,550)	1·19 (0·94, 1·50)	0·15
25(OH)D < 50 nmol/L*	5·8 (612)	5·6 (658)	0·94 (0·58, 1·52)	0·80

* Deseasonalised 25(OH)D < 50 nmol/L.

Note: Numbers in the analyses for falls and fractures differ: please refer to Figure 1 for flow chart of numbers included in the analyses for

Figure 1

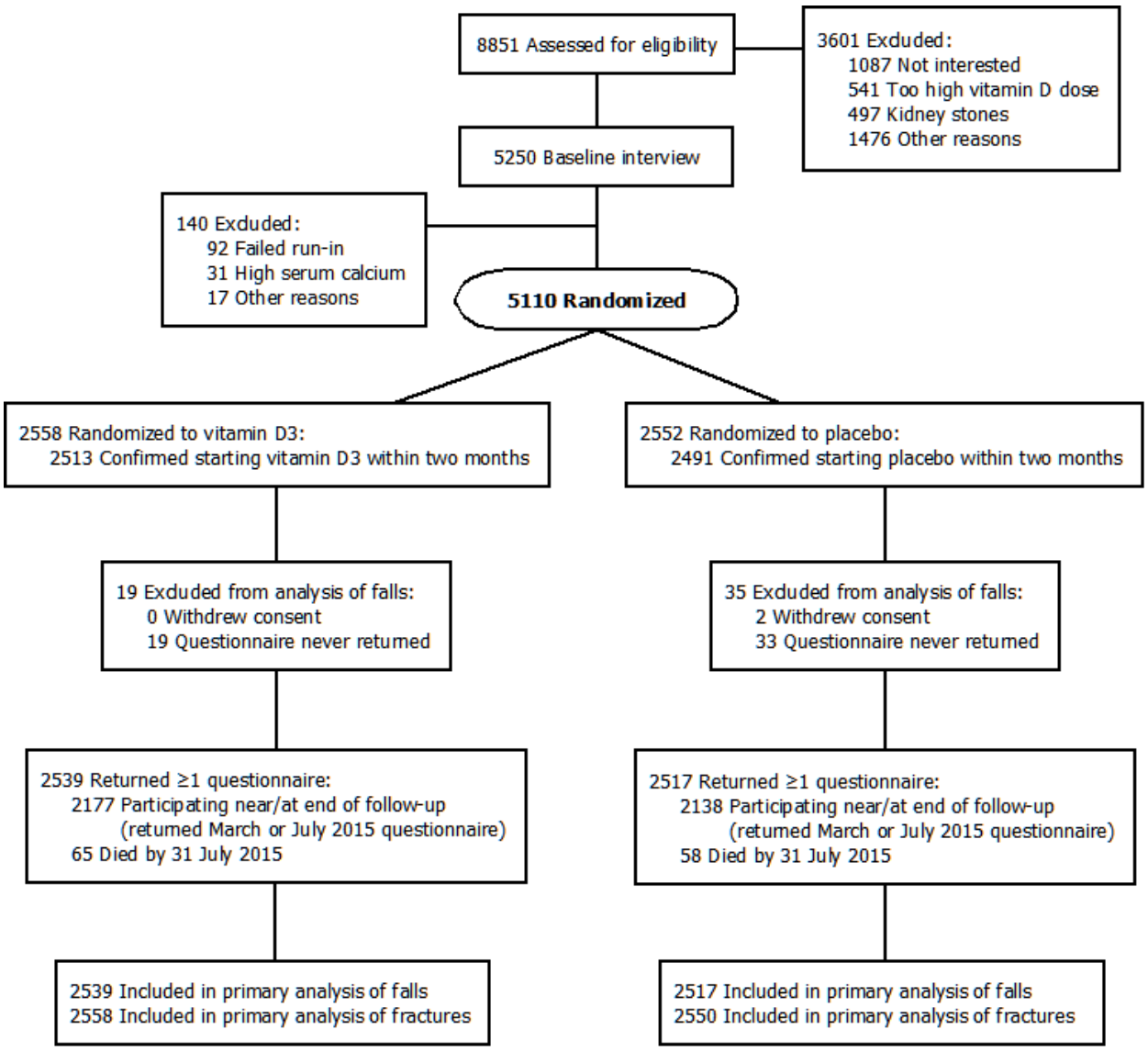
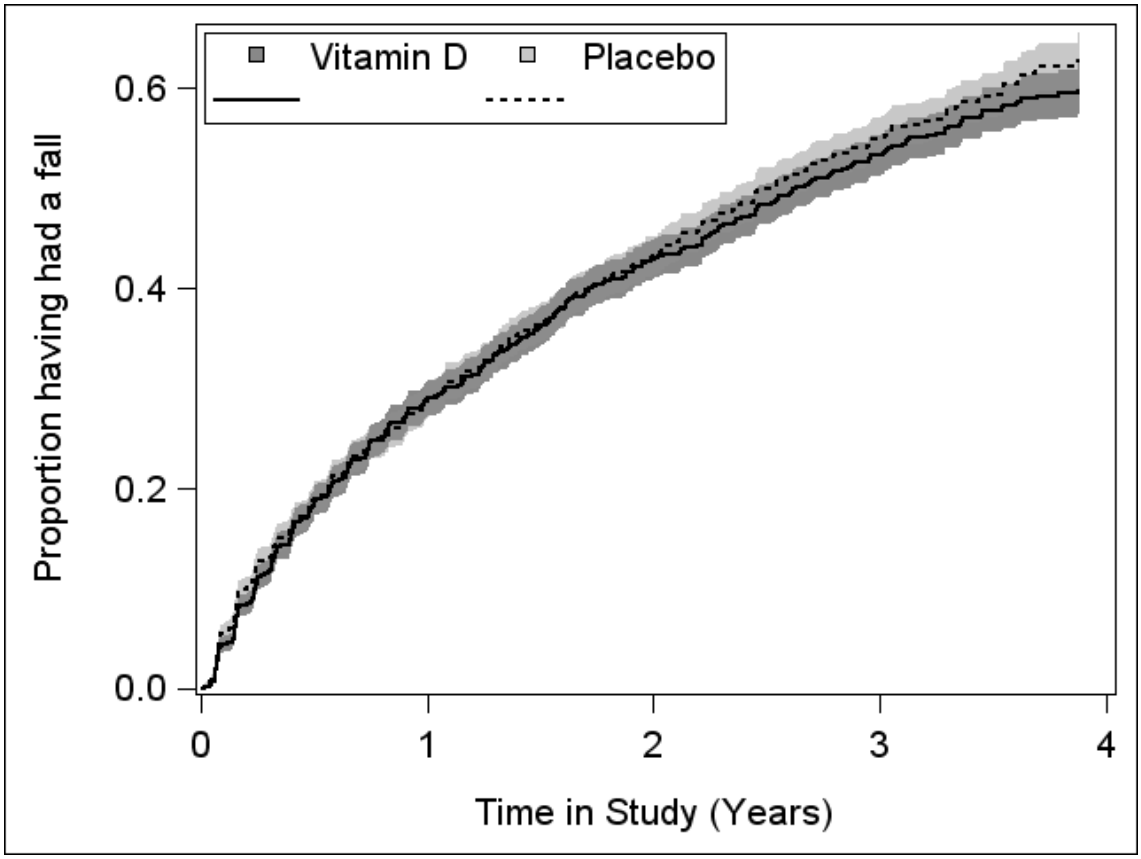
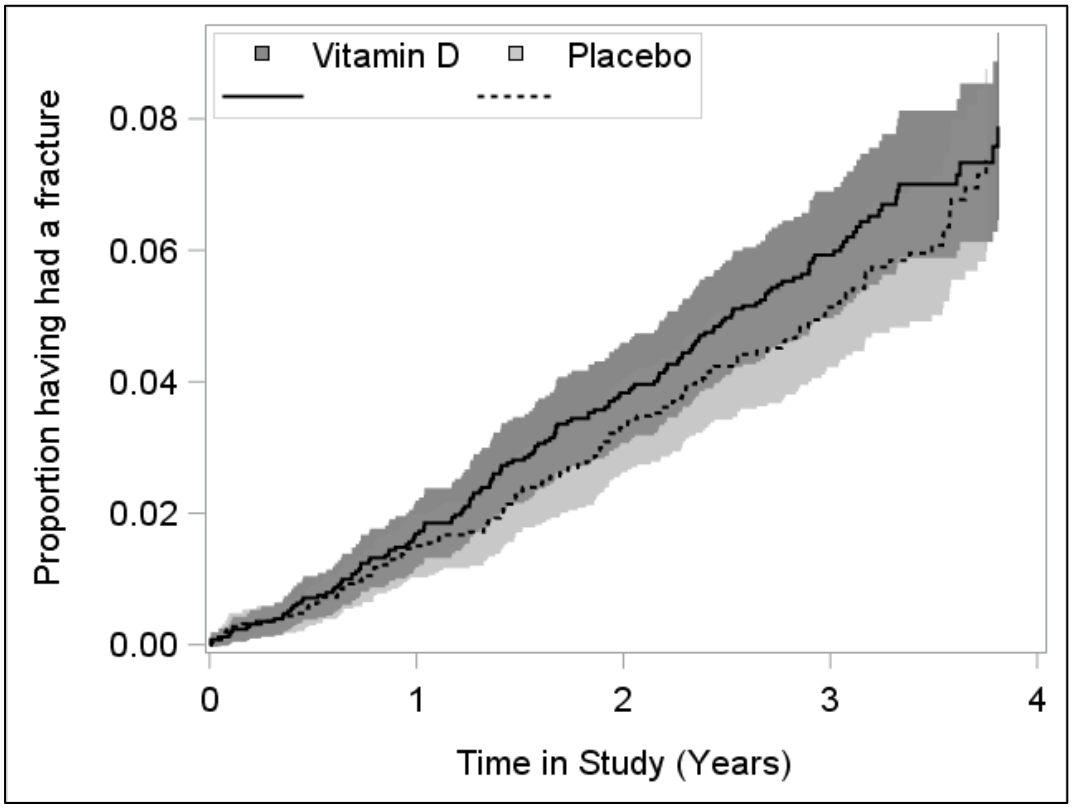

8851 Assessed for eligibility
3601 Excluded:
1087 Not interested
541 Too high vitamin D dose
497 Kidney stones
1476 Other reasons
5250 Baseline interview
140 Exduded:
92 Failed run-in
31 High serum calcium
17 Other reasons
5110 Randomized
2558 Randomized to vitamin D3:
2513 Confirmed starting vitamin D3 within two months
2552 Randomized to placebo:
2491 Confirmed starting placebo within two months
19 Exduded from analysis of falls:
0 Withdrew consent
19 Questionnaire never returned
35 Exduded from analysis of falls:
2 Withdrew consent
33 Questionnaire never returned
2539 Returned ≥1 questionnaire:
2177 Participating near/at end of follow-up
(returned March or July 2015 questionnaire)
65 Died by 31 July 2015
2517 Returned ≥1 questionnaire:
2138 Participating near/at end of follow-up
(returned March or July 2015 questionnaire)
58 Died by 31 July 2015
2539 Included in primary analysis of falls
2558 Included in primary analysis of fractures
2517 Included in primary analysis of falls
2550 Included in primary analysis of fractures

Figure 2 **Proportion (95% CI) of participants having a fall during follow-up for the vitamin D and placebo groups, Cox proportional hazards model.**



Numbers at risk	Baseline	1 year	2 years	3 years	4 years
Vitamin D	2539	1724	1321	760	85
Placebo	2517	1696	1278	657	91

Figure 3: **Proportion (95% CI) of participants having a fracture during follow-up for the vitamin D and placebo groups, Cox proportional hazards model.**



Numbers at risk	Baseline	1 year	2 years	3 years	4 years
Vitamin D	2558	2399	2224	1607	298
Placebo	2550	2362	2205	1487	412

Reference List

(1) Institute of Medicine, Eds, Ross AC, Taylor CL, Yaktine AL, del Valle H. Dietary Reference Intakes for Calcium and Vitamin D. Washington: The National Academies Press; 2011.

(2) Cauley JA, Danielson ME, Boudreau R, Barbour KE, Horwitz MJ, Bauer DC et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: the Women's Health Initiative (WHI). J Bone Miner Res 2011 October;26(10):2378-88.

(3) Khaw KT, Luben R, Wareham N. Serum 25-hydroxyvitamin D, mortality, and incident cardiovascular disease, respiratory disease, cancers, and fractures: a 13-y prospective population study. Am J Clin Nutr 2014 November;100(5):1361-70.

(4) 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. N Engl J Med 1992 December 3;327(23):1637-42.

(5) Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev 2014;4:CD000227.

(6) 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 December 20;155(12):827-38.

(7) Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA Intern Med 2016 February;176(2):175-83.

(8) Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;9:CD007146.

(9) Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. J Am Geriatr Soc 2010 July;58(7):1299-310.

(10) Moyer VA. Prevention of falls in community-dwelling older adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012 August 7;157(3):197-204.

(11) Uusi-Rasi K, Patil R, Karinkanta S, Kannus P, Tokola K, Lamberg-Allardt C et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. JAMA Intern Med 2015 May;175(5):703-11.

(12) Scragg R, Waayer D, Stewart AW, Lawes CM, Toop L, Murphy J et al. The Vitamin D Assessment (ViDA) Study: design of a randomized controlled trial of vitamin D supplementation for the prevention of cardiovascular disease, acute respiratory infection, falls and non-vertebral fractures. J Steroid Biochem Mol Biol 2015 September 10.

(13) Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. Am J Clin Nutr 2008 March;87(3):688-91.

(14) Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006 July;84(1):18-28.

(15) Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc 2005 September;53(9):1618-22.

(16) Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M et al. Falls, depression and antidepressants in later life: a large primary care appraisal. PLoS One 2008 June 18;3(6):e2423.

(17) Brown P, McNeill R, Leung W, Radwan E, Willingale J. Current and future economic burden of osteoporosis in New Zealand. Appl Health Econ Health Policy 2011 March 1;9(2):111-23.

(18) Sachs MC, Shoben A, Levin GP, Robinson-Cohen C, Hoofnagle AN, Swords-Jenny N et al. Estimating mean annual 25-hydroxyvitamin D concentrations from single measurements: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr 2013 June;97(6):1243-51.

(19) Rosen CJ, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA et al. IOM committee members respond to Endocrine Society vitamin D guideline. J Clin Endocrinol Metab 2012 April;97(4):1146-52.

(20) Rockell JE, Skeaff CM, Williams SM, Green TJ. Serum 25-hydroxyvitamin D concentrations of New Zealanders aged 15 years and older. Osteoporos Int 2006;17(9):1382-9.

(21) Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014;348:g2035.

(22) Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. J Am Geriatr Soc 2010 July;58(7):1299-310.

(23) Moyer VA. Prevention of falls in community-dwelling older adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012 August 7;157(3):197-204.

(24) Ginde AA, Blatchford P, Breese K, Zarrabi L, Linnebur SA, Wallace JI et al. High-Dose Monthly Vitamin D for Prevention of Acute Respiratory Infection in

Older Long-Term Care Residents: A Randomized Clinical Trial. J Am Geriatr Soc 2016 November 16.

(25) 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. JAMA 2010 May 12;303(18):1815-22.

(26) Bolland MJ, Grey A, Reid IR. Differences in overlapping meta-analyses of vitamin D supplements and falls. J Clin Endocrinol Metab 2014 November;99(11):4265-72.

(27) Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab 2012 February;97(2):614-22.

(28) Cauley JA, Chlebowski RT, Wactawski-Wende J, Robbins JA, Rodabough RJ, Chen Z et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health (Larchmt) 2013 November;22(11):915-29.

(29) 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. BMJ 2003 March 1;326(7387):469.

(30) Zheng YT, Cui QQ, Hong YM, Yao WG. A meta-analysis of high dose, intermittent vitamin D supplementation among older adults. PLoS One 2015;10(1):e0115850.