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Randomized Control Trials

Monthly high-dose vitamin D3 supplementation and self-reported adverse events in a 4-year randomized controlled trial

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SUMMARY

Background: The use of high-dose vitamin D supplementation has increased in recent years. However, relatively little is known about the safety of long-term high doses.
Aims: To investigate the safety of a monthly high-dose of vitamin D_3 supplementation taken for up to 4 years.
Methods: Data were collected in a randomized, double blind, placebo-controlled trial of 5108 adults aged 50–84 years old from Auckland, New Zealand. Participants were given monthly doses of 100,000 IU vitamin D_3 or placebo, for a median of 3.3 years (range 2.5–4.2 years). They answered an open-ended question in a monthly questionnaire about any adverse events they attributed to the study capsules, which were coded blindly. Incidence rates per person months were calculated for categories of adverse events. Cox regression model used to calculate hazard ratio of time to first adverse-event.
Results: In total, 419 (16.5%) participants taking vitamin D and 399 (15.8%) taking placebo reported ≥1 adverse event. Compared to placebo, the hazard ratio (HR) of reporting first adverse event in the vitamin D group was 1.03 (95% CI: 0.90, 1.18; $p = 0.63$). Despite a slightly higher incidence of recurrent adverse events in vitamin D arm, the incidence rate ratio (1.17) was not significantly higher in vitamin D (95% CI: 0.97, 1.41; $p = 0.10$). All regression results were adjusted for age, sex, and ethnicity. There was no difference between study arms in terms of participants' allocation perception ($p = 0.52$).
Conclusion: Monthly supplementation of 100,000 IU vitamin D3 for a median of 3.3 years did not affect participant-reported adverse events.
Trial registration: clinicaltrials.gov Identifier: ACTRN12611000402943; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=ACTRN12611000402943.

1. Introduction

Vitamin D_2 and D_3 supplements have been shown to be safe at ≤800 IU/day, which is the recommended dietary allowance (RDA) for adults [1]. In recent years, an increasing number of clinical trials have been conducted to investigate possible health benefits of taking larger doses of vitamin D supplementation [2–6]. However, the safety of long-term high-dose vitamin D supplementation is unclear. Concerns were raised by two trials with bolus annual dosing (≥300,000 IU), given for three or more years, that reported an increased risk of falls and fractures compared to placebo [4,7]. However, other trials with lower bolus doses have not found an increased risk of falls and fractures in vitamin D supplemented participants [8,9], while additional trials have found promising health outcomes from large and long-term doses of vitamin D supplementation in specific patient populations [10–12]. The clinical relevance of the safety of high-dose vitamin D supplementation is growing, as indicated by the large number of clinical

Abbreviations: RCT, Randomized Controlled Trial; ViDA, Vitamin D Assessment trial; RDA, Recommended Dietary Allowance; WHI, Women' Health Initiative; HR, Hazard ratio; CI, Confidence Interval; IRR, Incidence Rate Ratio; RECORD, Randomised Evaluation of Calcium Or vitamin D.

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trials registered with Clinicaltrials.gov, which in on-going trials are giving an average daily dose of 4124 IU vitamin D (Supplementary Table 1).

Yet, the safety of lower bolus doses – given more frequently than annually and for periods of more than one year – has not been properly investigated in the general population. Previous studies of frequent vitamin D bolus dosing, given one to three monthly, have either given a bolus dose for one year or less [13–18], or if for longer (up to 2 years), to patients with specific diseases such as multiple sclerosis and patients with severe lung disease requiring lung transplant [19,20]. Further, all of these studies had small samples (from 62 up to 250 participants) which would have decreased their power to detect any increased risk of adverse events from vitamin D supplementation [20–22]. Only one study with a relatively larger sample size has given frequent bolus dosing for longer period. This was a Norwegian study, which gave vitamin D 20,000 IU per week for 5 years to 511 participants with pre-diabetes, and found no difference in the number of adverse events reported in either treatment arm (vitamin D 1902, placebo 1983) [21].

Given the ongoing uncertainty about the safety of long-term high-dose vitamin D supplementation, we investigated the frequency of self-reported adverse events in a large randomized, double-blind, placebo-controlled trial where participants were given monthly bolus doses of vitamin D3 (100,000 IU), or placebo, over 3–4 years. The main aim of this analysis was to determine what the common self-reported adverse events were, and whether they were more common in participants allocated to vitamin D (versus placebo). We also investigated whether participants' perception of the treatment allocation was related to reporting of adverse events.

2. Material and methods

The main study methods have been described extensively in earlier publications [23,24]. In brief, the ViDA trial was conducted from 2011 to 2015 among adults aged 50–84 years recruited mainly from family doctor registers and also from community groups in Auckland, New Zealand. The aim of ViDA study was to investigate the impact of monthly supplementation with 100,000 IU vitamin D_3 over 3–4 years on cardiovascular disease, respiratory infections, and falls and fractures. The study was approved in October 2010 by the Multi-region Ethics Committees, Wellington (MEC/09/08/082), and registered with the Australian New Zealand Clinical Trials Registry in April 2011 (ACTRN12611000402943).

2.1. Recruitment

The flow diagram in Fig. 1 shows the total number of participants who were assessed for eligibility (n = 8851). Inclusion criteria were: age range of 50–84 years; ability to give informed consent; being resident in Auckland at recruitment; and anticipated residence in New Zealand for the 4-year study period. Exclusion criteria were: taking vitamin D supplements (>600 IU per day if aged 50–70 years; >800 IU per day if aged 71–84 years); history of hypercalcaemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery; enrolled in another study which could affect participation in the vitamin D study; having a serum corrected calcium from baseline blood sample >2.50 mmol/L; and having a psychiatric disorder that would limit ability to adhere to the study protocol.

2.2. Baseline assessment and randomisation

After exclusions, baseline assessments were carried out on 5250 participants (5107 from family doctor registers, 143 from community groups) during 2011–12. This included questions on demographic status (age, sex, self-defined ethnicity, current marital status, highest education level attended and main lifetime occupation), current prescribed medications, current intake of vitamin D supplements and lifestyle over the previous three months (e.g., use of vitamin D-supplemented milk, leisure time physical activity). Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg with participants wearing light clothing, with shoes removed. A non-fasting blood sample was collected for immediate measurement of serum corrected calcium (to confirm eligibility) and the remainder stored frozen at −80° C for later measurement of 25-hydroxyvitamin D (25(OH)D).

Participants with a baseline corrected calcium level of ≤2.50 mmol/L were sent a 'run-in' questionnaire by mail to their home, along with a placebo capsule (they were blind to the type of capsule). Participants were randomized only if they returned this questionnaire within four weeks confirming that they had taken the capsule. Randomization was performed with computer generation using blocks of 8, 10 or 12 by the study statistician. Neither study staff nor participants were aware of the treatment allocation. A total of 5110 participants were randomised, of whom two later withdrew their consent (Fig. 1) and, at their request, their data were not used in this or any other analyses.

2.3. Intervention

All participants were given two 100,000 IU vitamin D_3 (or placebo) oral soft-gel capsules (Tishcon Corporation, Westbury, New York, USA) in the first month. Then, starting one month later, they took one capsule (100,000 IU D_3 or placebo) monthly throughout the study period. Capsules were mailed to home addresses monthly up to June 2013, and, for cost reasons, 4-monthly from July 2013 with a monthly reminder (by email or letter) to take the capsule.

2.4. Questionnaires

A 1-page duplex questionnaire (with a reply-paid envelope) was enclosed with the capsule letter. Monthly mailings of questionnaires continued until November 2013, and from March 2014 were sent 4-monthly with 4 capsules. The questionnaire included questions on adverse events attributed to the study capsule. Participants were asked in the monthly questionnaire "Have you had any side effects from the study capsule you took last month?" The same question was asked in the 4-monthly questionnaire, with a slight rewording: "Over the last four months, have you had any side effects from the study capsules?", with a Yes/No response for each month. Both versions of the questionnaire had a space for writing open-ended responses describing any adverse events.

All reported adverse events were coded using a study-specific coding system. To develop this coding system, adverse events were coded from an initial sample of 375 questionnaires with reported adverse events received from 31 March 2012 until 28 September 2012, which were then grouped into study-developed symptom categories (Supplementary Table 2). Each adverse event was coded separately. So, if one person reported two adverse events at the same time, it was coded separately into their specific adverse event codes. All coding was done without any knowledge of the assigned group (vitamin D vs placebo).

In the final questionnaire mailed to home addresses in July 2015, participants were asked "Which type of study capsule do you think you received?", with response options being "Vitamin D", "Placebo" and "Not sure/don't know".

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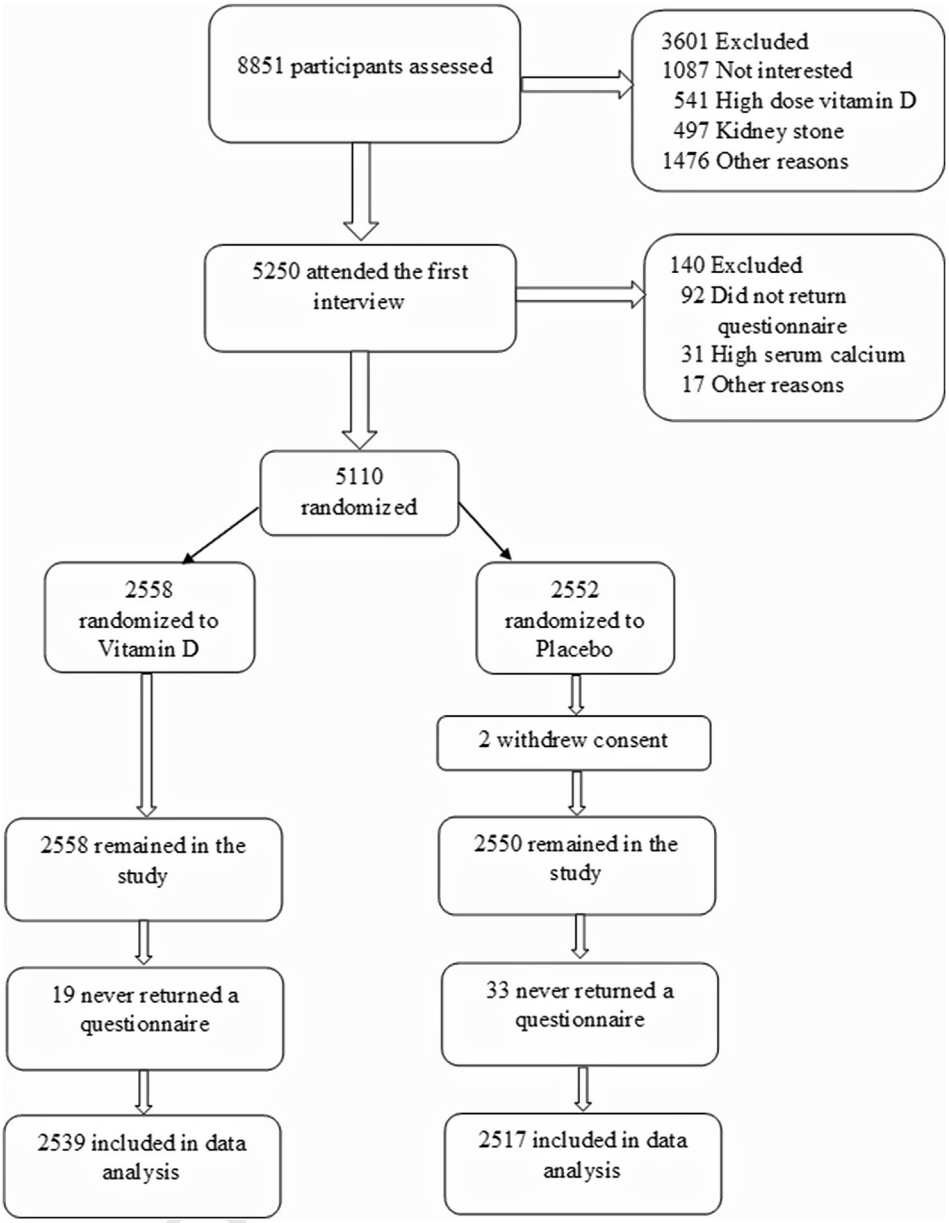

Fig. 1. Flow diagram of participants of ViDA study.

2.5. Adherence

Adherence was assessed through a question in the monthly questionnaires which asked participants if they had taken their capsule or not. This question was asked four times for each month of the 4-monthly questionnaire. In addition, objective data on serum 25(OH)D concentrations were available from blood samples collected at 6, 12, 24 and 36 months after baseline in a random sample of 441 participants.

Serum 25(OH)D concentration (combining both D_3 and D_2) was measured for all participants in the baseline aliquots stored frozen using liquid chromatography–tandem mass spectrometry (ABSciex API 4000, Illinois, USA). A deseasonalized 25(OH)D concentration was calculated for each participant from their observed concentration and date of blood sample collection using parameters derived from a sinusoidal model fitted to baseline values for all participants [25].

2.6. Statistical analyses

Analyses were conducted using SAS statistical package version 9.4 (SAS Institute, Cary, NC, USA), and were restricted to participants who returned at least one home questionnaire. The date of the adverse event was defined as halfway through the coverage period of the questionnaire. We assumed that no adverse event occurred during the period of the questionnaire if it was not returned. Participants were censored (ie, last date calculated for estimation of follow-up time) at their last returned questionnaire.

Hazard ratios (HR) comparing time to first adverse event between the vitamin D and placebo groups were calculated using the Cox proportional hazards model. Survival times were plotted using Kaplan Meier curves to compare time to the first adverse event between arms. Negative binomial regression models were used to calculate incidence rate ratios of adverse events, and also to investigate the association of allocation perception with reporting

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of adverse events. All models were adjusted for age, sex and ethnicity. Two-tailed P < 0.05 was considered statistically significant.

3. Results

Out of 5110 randomised participants, two completely withdrew from the study, and a further 52 participants did not return any questionnaire. This left 5056 in the analysed sample (vitamin D 2,539, placebo 2517) (Fig. 1). Participants' mean (SD) age was 65.9 (8.3) years, 58.5% (n = 2935) were male, and 83.6% (n = 4229) were of European or Other ethnic ancestry, with the remainder being Polynesian or South Asian. Table 1 shows baseline characteristics of the analysed participants by treatment arm.

Mean deseasonalized baseline serum 25(OH)D was 66.5 (22.5) and 65.9 (22.5) nmol/L in participants of vitamin D and placebo arm, respectively (p = 0.83). Mean 25(OH)D increased by more than 50 nmol/L in the vitamin D arm, compared with placebo, among participants in the 10% random sample who returned at 6 months, year 1, year 2 and year 3 of the study (Supplementary Figure 1), indicating that vitamin D levels were higher in the vitamin D arm.

Table 1
Baseline characteristics of participants.

Variable	Vitamin D (n = 2539)	Placebo (n = 2517)
	number (%) or mean ± SD	
Age (years)	65.9 ± 8.3	65.9 ± 8.3
Sex		
Female	1039 (40.9%)	1082 (43.0%)
Male	1500 (59.1%)	1435 (57.0%)
Ethnic Group		
European/Other	2110 (83.5%)	2119 (83.8%)
Mäori	134 (5.3%)	127 (5.0%)
Pacific Islander	161 (6.3%)	157 (6.2%)
South Asian	125 (4.9%)	123 (4.9%)
Marital Status		
Married/partnered	1860 (73.3%)	1821 (72.4%)
Separated/divorced and living alone	302 (11.9%)	329 (13.1%)
Widow/Widower	229 (9.0%)	207 (8.2%)
Never married/partnered	146 (5.7%)	157 (6.2%)
Missing	2 (0.08%)	3 (0.1%)
Education		
Primary School	51 (2.0%)	36 (1.4%)
Secondary school	1081 (42.6%)	1022 (40.6%)
Tertiary (eg. University)	1412 (55.4%)	1457 (57.9%)
Missing	2 (0.08%)	2 (0.08%)
Occupation (Current paid work)		
Yes	1293 (51.0%)	1303 (51.8%)
No	1244 (49.0%)	1211 (48.1%)
Missing	2 (0.08%)	3 (0.1%)
Currently on any medication	1981 (77.4%)	1973 (77.4%)
Take vitamin D supplements	208 (8.3%)	199 (8.0%)
Vitamin D (IU/d)	18.3 ± 79.6	16.8 ± 75.3
Take calcium supplements	125 (5.0%)	126 (5.1%)
Drink milk in tea or coffee, or add it to breakfast cereal	2334 (91.4%)	2312 (90.7%)
Drink milk with added vitamin D	240 (9.4%)	205 (8.0%)
Vigorous physical activity (hours/week)		
None	1004 (41.7%)	1005 (41.8%)
1–2	606 (25.1%)	579 (24.1%)
>2	800 (33.2%)	823 (34.2%)
Anthropometry		
Weight (kg)	81.3 ± 16.5	81.0 ± 15.6
BMI (kg/m^2)	28.3 ± 5.1	28.4 ± 4.9
25-hydroxyvitamin D (nmol/L)		
Observed	63.7 ± 23.6	63.0 ± 23.5
Deseasonalised	66.5 ± 22.5	65.9 ± 22.5
Corrected serum calcium (mmol/L)	2.27 ± 0.07	2.28 ± 0.07

During the median follow up time of 3.3 years (range: 2.5, 4.2), a total 818 participants (16.1%) reported adverse events that they attributed to the study capsule; by group, this represented 419 (16.5%) from the vitamin D group and 399 (15.8%) from the placebo group (p = 0.38). The total number of reported adverse event events was 1,957, of which descriptions were given for 1108 (56.6% of reported events); this represented 604 (54.5%) in the vitamin D group, and 504 (45.5%) in the placebo group (p = 0.01). Supplementary Table 2 summarises the adverse events that were described, by treatment group. The most common were pain (n = 300), respiratory infection symptoms (n = 171) and dizziness and/or issues with balance and vision (n = 121).

Table 2 shows the proportions of participants who reported one or more adverse events, which were similar in the vitamin D compared to the placebo group, with the HR being 1.03 (95% CI: 0.90, 1.18), adjusting for age, sex and ethnicity. The same result was seen when participants were categorised by baseline 25(OH)D concentrations and for each adverse event category described by participants (all p > 0.10). The cumulative hazard plot showed no difference between the two treatment groups in time to the first reported adverse event (Fig. 2). In total, among 818 participants who reported adverse events, there were 1066 versus 891 events reported in the vitamin D and placebo arms, respectively. The IRR for all adverse events was not significantly elevated in vitamin D compared with placebo, being 1.17 (95% CI = 0.97, 1.41; p = 0.10), nor was it different for specific adverse events (Supplementary Table 3).

Most of the specific adverse event categories also were not statistically significant, although the category of dizziness and issues with balance and vision approached statistical significance (RR = 1.66; 95% CI: 0.95, 2.92; p = 0.08).

Participants' perception of their allocation into the two treatment arms is shown in Table 3. Among 4104 participants (81.3% of analysed sample) who returned the final questionnaire and responded to the question, 63.3% did not know which arm they were allocated to. There was no difference between study treatment arms in terms of allocation perception. Moreover, the proportion of participants who reported an adverse event did not vary with allocation perception. In particular, it was not increased in participants who guessed they were in the vitamin D arm (model adjusted for age, sex and ethnicity). However, people who did not respond to the final questionnaire (missing) reported more adverse events earlier in the course of the study (IRR = 1.14; 95%CI = 1.02, 1.28; Table 4).

4. Discussion

The results from this large population-based trial show that monthly supplementation with 100,000 IU cholecalciferol for up to 4 years did not increase the proportion of people who reported adverse events compared to placebo. About one-sixth of participants – 16.5% in the vitamin D arm and 15.8% in the placebo – reported at least one adverse event during the median 3.3-year follow-up period. This is consistent with an Australian study with gave an annual vitamin D dose of 500,000 IU, in which 19.7% and 17.8% of participants in the vitamin D and placebo arms, respectively, reported at least one adverse event during a median of 2.9 years follow-up [26]. The Australian study also reported an increased risk of falls among women in the vitamin D arm compared to placebo. In our study, only a few falls were reported as adverse events (Supplementary Table 2). In addition, our extensive investigation of reported falls as a secondary outcome showed this was not increased by vitamin D supplementation, with the proportion of participants who reported at least one fall being similar in the vitamin D (45%) and placebo (44%) arms [8].

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Table 2
Proportion of participants reporting an adverse-event, and hazard ratios for time to first reported adverse-event, comparing vitamin D group with placebo (as reference), adjusted for age, sex and ethnicity.

Adverse event category	Participants reporting an adverse event n (%)		Hazard Ratio (95% CI)	P-value (Wald X^2)
	Vitamin D (n = 2539)	Placebo (n = 2517)		
Total who reported having an adverse event[a]	419 (16.5)	399 (15.8)	1.03 (0.90, 1.18)	0.57
Deseasonalised 25(OH)D: nmol/L				
<50	115 (4.5)	108 (4.3)	1.23 (0.95,1.60)	0.11
50–75	166 (6.5)	167 (6.6)	0.93 (0.75,1.15)	0.50
>75	138 (5.5)	124 (4.9)	1.08 (0.85,1.38)	0.50
Participants who described their adverse event				
Pain	80 (3.1)	85 (3.4)	0.93 (0.68, 1.26)	0.62
Respiratory infection	59 (2.3)	42 (1.7)	1.39 (0.94, 2.06)	0.10
Gastrointestinal symptoms	35 (1.4)	34 (1.3)	1.01 (0.63, 1.62)	0.94
General tiredness/weakness	22 (0.4)	19 (0.4)	1.14 (0.62, 2.11)	0.67
Dizziness/issues with balance/vision	43 (1.7)	36 (1.4)	1.18 (0.76, 1.83)	0.47
Skin	25 (1.0)	26 (1.0)	0.94 (0.54, 1.62)	0.94
Symptoms related to other conditions	83 (3.3)	72 (2.9)	1.15 (0.84, 1.57)	0.39
Unknown	50 (2.0)	49 (1.9)	1.01 (0.68, 1.50)	0.95
Total who described their adverse event[b]	288 (11.3)	277 (11.0)	1.01 (0.86, 1.19)	0.84

[a] Includes participants who indicated they had an adverse event but did not describe it in the free text box.
[b] Total who described an adverse event is less than the sum who reported the individual adverse-event categories as more than one adverse-event could be reported in the free-text box of a questionnaire. 25(OH)D = 25-hydroxyvitamin D.

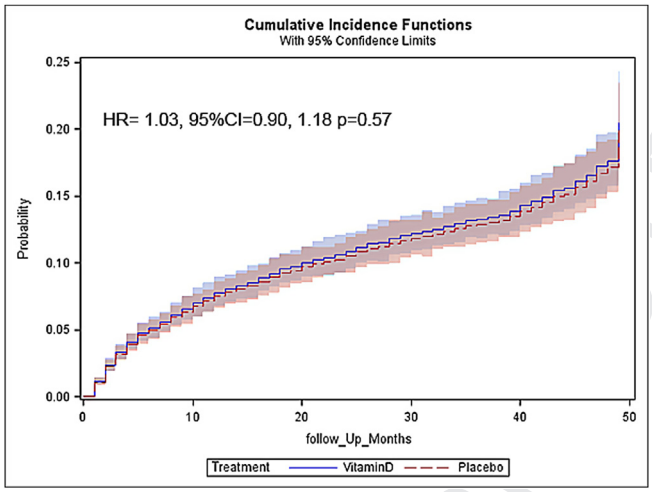

Fig. 2. Cox-regression hazards model for the first adverse event throughout the study follow up by treatment arm. (Colour print). (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

The most commonly described adverse events were pain, reported by 3.1% of participants in the vitamin D arm and 3.4% in the placebo arm, followed by respiratory infections which were attributed to the capsules by 2.3% and 1.7% of participants, respectively. Only 1.4% in the vitamin D arm and 1.3% allocated placebo in our study had at least one report of gastrointestinal symptoms throughout the median follow-up of 3.3 years (Table 2). These proportions are similar to a study which gave 50,000 IU D3/month to knee osteoarthritis patients, and found that 3.3% and 2.4% or participants in the vitamin D and placebo arms, respectively, reported gastrointestinal disorders over two years [27]. These percentages are much lower than those reported in the Women's Health Initiative (WHI), which gave a combination of calcium (1200 mg/d) and vitamin D (400 IU/d) supplementation to women in the same age range as the ViDA study, and reported over 7-years follow-up that 10.3% and 8.9% of participants had constipation, and 20.4% and 19.5% had bloating, in the calcium + vitamin D and placebo arms, respectively [28]. Our results suggest that the higher frequency of gastrointestinal symptoms in the WHI study is most likely due to the calcium supplement, not vitamin D. This conclusion is consistent with results from the RECORD (Randomised Evaluation of Calcium Or vitamin D) study, which gave 800 IU/d vitamin D and/or calcium (1000 mg/d) for 7 years in a factorial design, and found that significantly more patients withdrew in the calcium arm than in the non-calcium arms [29]. The RECORD study found that gastrointestinal symptoms were an important reason for poor compliance with the assigned study medications.

Our study results are in agreement with a recent systematic review and meta-analysis [30], which included 19,389 participants and found that the number of participants with any adverse event was not different between vitamin D and placebo arms (RR = 0.97; 95% CI: 0.92, 1.02). The studies in this meta-analysis gave vitamin D supplementation for a minimum six months, with a mean dose of 2167 IU/d for D_3 and 11,055 IU/d D_2. Gastrointestinal and skin disorders were reported in 27 and 8 studies respectively, with no increase in the risk ratio for either disorder in the vitamin D versus placebo arm [30], consistent with our results (Table 2) which provide further evidence about the safety of long-term monthly dosing of vitamin D_3, including in participants with high 25(OH)D concentrations above 75 nmol/L (Table 2).

Although the number of participants who reported at least one adverse event was not significantly different between arms, there was a trend for more recurrent events in the vitamin D, as compared to the placebo, arm, as shown by the increased IRRs of the vitamin D group. Whether this difference would have become statistically significant with longer duration of exposure is unknown. However, it is possible that adverse events in those who reported an event in vitamin D arm could be due to increased sensitivity to vitamin D in a subset of people.

The trend for an increased incidence of recurrent events in the vitamin D arm was mainly due to recurrent events categorised as dizziness or other issues with balance and vision (p = 0.08). This

Table 3
Perception of participants on the arm of the study they were allocated to, by study arm.

Participants' guess	Allocated Treatment			Chi-sqr	P
	Vitamin D	Placebo	Total		
Do not know	1324 (64.0)	1275 (62.6)	2599	1.28	0.52
Placebo	427 (20.6)	422 (20.7)	849		
Vitamin D	318 (15.4)	338 (16.6)	656		
Total	2069	2035	4104		

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Table 4
Proportion of participants reporting adverse event, and risk ratios, according to their allocation perception.

Capsule guess	Reported adverse-event		Total	Incidence rate ratio (95% CI)[a]	P-value
	Yes (%)	No			
Don't know	378 (14.5)	2221	2599	1.00	0.04
Vitamin D	123 (18.8)	533	656	1.08 (0.94, 1.23)	
Placebo	113 (13.3)	736	849	0.87 (0.76, 1.01)	
Missing	204 (21.4)	748	952	1.14 (1.02, 1.28)	
Total	818	4238	5056		

[a] Adjusted for age, sex, ethnicity and treatment allocation.

has not been found in previous RCTs with detailed reports of adverse events [15,16,31]. It is possible that dizziness could be an explanation for the increased risk of falls in older women in the 2010 Sanders' study [4], though we did not observe any difference in actual falls in our trial [32]. Lastly, we recognize that these dizziness results could be a chance finding. In sum, we encourage further evaluation of this possibility in other large vitamin D trials.

This study was unique in that it has provided a comprehensive assessment of self-reported adverse events from long-term monthly high-dose vitamin D supplementation, which to the best of our knowledge has not been done before. However, it has some potential limitations. The adverse events were based on subjective reports and were not clinically confirmed. The reports by participants were based on their own understanding of an adverse event, and it is unknown whether they considered the time lapse between taking a capsule and the experienced adverse event. However, these limitations applied equally to both the vitamin D and placebo groups who had similar characteristics at baseline. Furthermore, other studies have also asked participants to record adverse events and compare them between arms [33,34]. A strength of the study is the large sample size which provided increased statistical power for analyses of the more commonly reported adverse events. Further, allocation perception was evenly distributed between the two treatment arms which confirms the blinding achieved by the randomization method in this study. This perception was unrelated to the reporting of adverse events by participants.

5. Conclusion

Supplementation with 100,000 IU vitamin D3 per month did not significantly increase the proportion of participants who reported adverse events compared to the placebo arm. Nevertheless, among those who have reported an event, there was a tendency to report more dizziness events in the vitamin D arm. Further results, from other large randomized controlled trials similar to that of ViDA study, are required to confirm this finding. Indeed, large trials with similar bolus doses are underway or have recently finished [20,35,36]. Publication of their safety results in the next few years should shed further light on the safety of monthly (and even less frequent) bolus dosing of vitamin D supplements.

Disclaimer

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Statement of authorship

Z.M, ZW and YH analysed data. ZM and RS drafted the manuscript. CL coded adverse events. All other authors commented and contributed to the manuscript.

Conflicts of interest

The funders had no role in the research design, conduct and data collection, data analyses, drafting of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.034

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