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*(Article begins on next page)*

## RESEARCH

## CHRISTMAS 2014: GOING TO EXTREMES

# Effect of monthly vitamin D<sub>3</sub> supplementation in healthy adults on adverse effects of earthquakes: randomised controlled trial

 OPEN ACCESS

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## Abstract

**Objective** To determine whether supplementation with vitamin D improves resilience to the adverse effects of earthquakes.

**Design** Opportunistic addition to an established randomised double blind placebo controlled trial.

**Setting** Christchurch, New Zealand, where a prolonged series of catastrophic earthquakes beginning on 4 September 2010 occurred, which caused widespread destruction, fatalities, and extensive psychological damage.

**Participants** 322 healthy adults (241 women; 81 men) aged 18-67 who were already participating in the vitamin D and acute respiratory infections study (VIDARIS) between February 2010 and November 2011.

**Intervention** Participants were randomised to receive an oral dose of either 200 000 IU vitamin D<sub>3</sub> monthly for two months then 100 000 IU monthly (n=161) or placebo (n=161) for a total of 18 months.

**Main outcome measure** This is a post hoc analysis from the previously published VIDARIS trial. The primary endpoint in the current analysis was the self reported effects and overall adverse impact of the Christchurch earthquakes as assessed by questionnaire four months after the most destructive earthquake on 22 February 2011, which was used as the index event. The secondary end point was the number of "psychological" adverse events that participants reported at their usual monthly appointments as part of the original VIDARIS trial.

**Results** 308 participants completed the earthquake impact questionnaire (n=152 in the vitamin D group and 156 in the placebo group). There was no significant difference in the number of self reported adverse effects between those receiving vitamin D supplementation and those receiving placebo. There was also no difference in the overall adverse impact score between treatment groups ( $\chi^2$  P=0.44). The exception was that those in the vitamin D group experienced more adverse effects on family relationships (22% v 13%;  $\chi^2$  P=0.03). The number of psychological adverse events—such as fatigue, stress, anxiety, and insomnia—that participants reported at their usual monthly appointments was significantly higher after the earthquake ( $\chi^2$  P=0.007) but did not differ between treatment groups.

**Conclusion** In this trial, vitamin D supplementation did not reduce the adverse impact of earthquakes in healthy adults.

**Trial registration** Australian New Zealand Clinical Trials Registry (anzctr.org.au) ACTRN12609000486224

## Introduction

Vitamin D is viewed in some circles as something of a panacea, and, currently, no other vitamin receives more attention in the scientific literature.<sup>1,2</sup> One topic of interest is the potential relation between vitamin D status and mental health. Epidemiological studies suggest an association between vitamin

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Extra material supplied by the author (see <http://www.bmj.com/content/349/bmj.g7260?tab=related#datasupp>)

**Appendix:** Earthquake supplementary questions [posted as supplied by author]

D status and mental wellbeing, particularly depression and anxiety.<sup>3-6</sup> This is plausible because the requisite hydroxylases and vitamin D receptors for the local production and use of the biologically active 1,25-dihydroxyvitamin D have been found in important behavioural and emotional regions of the brain.<sup>4,7</sup> Evidence also suggests that vitamin D is involved in the biosynthesis of neurotransmitters and could have neuroprotective and psychotropic effects.<sup>8-10</sup>

Experiencing a natural disaster such as a destructive earthquake adversely affects mental health. Several studies have reported heightened anxiety, depression, and an increased incidence of post-traumatic stress disorder<sup>11-13</sup> in earthquake survivors, and these effects can last for several years.<sup>11-15</sup>

A randomised controlled trial in healthy adults that investigated the effect of monthly high dose vitamin D supplementation on upper respiratory tract infections (VIDARIS<sup>16</sup>) was undertaken in Christchurch, New Zealand from February 2010 to November 2011. During this time, the region experienced a series of catastrophic earthquakes. These began on 4 September 2010 at 4 35 am, when a magnitude 7.1 earthquake struck. A series of aftershocks followed, with the most devastating being a 6.3 magnitude earthquake on 22 February 2011 at 12 51 pm, resulting in 185 deaths, the loss of more than 60% of the central business district, and severe damage to housing and infrastructure.<sup>17</sup>

This chance occurrence provided a novel opportunity to assess in the VIDARIS participants whether vitamin D<sub>3</sub> supplementation had any effect on the adverse impact experienced during a prolonged series of devastating earthquakes.

## Methods

### Study design, participants, and randomisation

The VIDARIS trial was conducted in healthy adults in Christchurch, New Zealand, between February 2010 and November 2011 and has been described in detail elsewhere.<sup>16</sup> Briefly, participants were staff or students aged  $\geq 18$  from the Canterbury District Health Board or the University of Otago, Christchurch. Volunteers were screened for eligibility and enrolled during February through April 2010.

Interviewers administered questionnaire to determine the baseline characteristics. Both participants and study personnel conducting the trial were blinded to treatment allocation. Participants randomised to vitamin D<sub>3</sub> received orally supplementation of 200 000 IU at study initiation, another 200 000 IU one month later, and then 100 000 IU monthly thereafter for 18 months. Those randomised to placebo received matching inactive tablets given in an identical dosing regimen. The vitamin D<sub>3</sub> and placebo tablets were obtained from Tishcon (Westbury, NY).

### The earthquakes

The magnitude 7.1 earthquake on 4 September was centred 38 km west of Christchurch City at a depth of 11 km. Although this initial earthquake was strong, shallow, and close to a city, there were no fatalities and little injury. There was, however, large scale damage to buildings and infrastructure (water, sewerage, electricity, and roads) throughout the city. Over the following 15 months (September 2010 to November 2011) the region experienced 10 741 aftershocks within a 100 km radius of the city of Christchurch. Of these, over 3400 were magnitude  $\geq 3$  and  $< 20$  km deep and were readily felt by most people ([www.canterburyquakelive.co.nz](http://www.canterburyquakelive.co.nz) (C Crowe) and [www.geonet.co.nz](http://www.geonet.co.nz); fig 1).<sup>18</sup>

[www.canterburyquakelive.co.nz](http://www.canterburyquakelive.co.nz) (C Crowe) and [www.geonet.co.nz](http://www.geonet.co.nz); fig 1).

## Procedures

Dedicated research staff met participants in person each month over the 18 months to administer the dose of study treatment and to conduct a brief interview. For each participant, as part of the usual monthly questionnaire, researchers recorded any unplanned visits to a doctor/after hours clinic/hospital or any new health problem or change in the frequency/severity of an existing health problem as a new adverse event.

Separately, participants were asked a specific questionnaire about the impact of the earthquakes at their first appointment four months after the 22 February 2011 aftershock, which was used as the index event because it was the most destructive. The questionnaire included 14 questions, which covered damage to homes, the death of a family member/close friend, and personal impact. In addition, participants conveyed the overall adverse impact by answering the question: “on a scale of 1-7, with 1 being no impact at all and 7 being high impact; overall what adverse impact has the earthquake on the 22 February had on you? (circle one)” (see appendix).

## Analysis

We performed Pearson’s  $\chi^2$  tests on an intention to treat basis to determine any difference between the treatment arms in the number of self reported adverse effects and overall adverse impact score as assessed through the earthquake questionnaire and the number of adverse events reported at monthly appointments. All statistical tests were two sided and considered significant at  $P < 0.05$ . The software used was SPSS, version 22 (IBM).

## Results

In total, 322 participants (241 women) were randomised to study treatment. Table 1 shows their baseline characteristics. The earthquake questionnaire was completed by 308 participants at their usual monthly appointment four months after the index event of the 22 February 2011, including 15 (5%) participants who had previously withdrawn from treatment (fig 2). The groups were balanced in terms of reported levels of personal loss, injury, and damage to property as a result of the earthquakes. Mental wellbeing outcomes, such as disturbed sleep, increased anxiety/stress, and diminished concentration, were not significantly different between the groups (table 2). The only exception was that those receiving vitamin D reported a higher level of experiencing an adverse effect on family relationships (22% v 13%;  $\chi^2 P = 0.03$ ). There was also no relation between study arm and the distribution of the overall impact score.

Figure 3 shows the total number of adverse events reported each month during the trial (n=1282). The reported number of “psychological” adverse events, such as stress, anxiety, fatigue, or depression, did not differ between treatment arms but were significantly higher after the 22 February 2011 earthquake (n=64) compared with the number reported before the earthquake (n=37;  $\chi^2 P = 0.007$ ).

## Discussion

Our earthquake questionnaire provided a snapshot of the self reported adverse effects and broad impact of the Canterbury earthquakes in a cohort of healthy adults who were coincidentally taking part in a randomised controlled trial of

vitamin D<sub>3</sub> supplementation (VIDARIS).<sup>16</sup> We found no significant association between the receipt of monthly vitamin D supplements and the overall adverse impact score or most specific effects of earthquakes. Those receiving vitamin D reported a higher level of experiencing an adverse effect on family relationships. Although this finding was significant at  $P < 0.05$ , in the context of a lack of effect of vitamin D on the other stress related outcomes, which might be expected to underpin family relationship stress, it would not be appropriate to conclude that vitamin D increases the likelihood of adverse effects on family relationships.

## Strengths and limitations

The strengths of our study include the randomised supplementation and the high retention and response rate to the earthquake questionnaire. An important limitation was that we did not assess mental wellbeing using a validated questionnaire, such as the depression, anxiety, and stress scale. As such we cannot be sure we have captured the true extent of the psychological impact of the earthquakes. It was clear from our monthly contact with participants, however, that a large number were experiencing increased anxiety/stress, and, while we wanted to capture the impact of the earthquakes, we did not want to overburden participants with a lengthy questionnaire. A survey of the disaster literature allowed us to generate a short questionnaire that would provide an indication of the physical and mental impact of the earthquakes.

The questionnaire was not completed until four months after the index event. While participants could have “forgotten” or potentially minimised the impact of the major earthquake, there were continual aftershocks throughout this period, including a 6.3 magnitude tremor just before the start of the survey. A further limitation is that while this study was appropriately powered for the VIDARIS outcomes, for some categories of the overall adverse impact score the numbers are small.

## Possible explanatory links

The adverse psychological impact of earthquakes is well documented,<sup>12-14</sup> including several studies investigating the effect of the Canterbury earthquakes.<sup>11-21</sup> Given that there are epidemiological data supporting a possible role for vitamin D in the improvement of mental wellbeing,<sup>3-6</sup> it was plausible that vitamin D supplementation could potentially reduce anxiety or stress or the overall adverse impact of the earthquakes. Of the few randomised controlled trials that have investigated the effect of vitamin D supplementation on mental wellbeing, however, the findings have been mixed.<sup>22-26</sup> No improvement in mental wellbeing was observed when older women were given an annual high dose of vitamin D<sup>26</sup> nor was there any effect on depressive scores in participants with low vitamin D concentrations who received vitamin D supplements.<sup>25</sup> In contrast, a study with obese participants found an improvement in depressive scores after supplementation.<sup>24</sup> No other data have been reported from randomised controlled trials regarding the role of vitamin D in reducing the adverse effects of earthquakes.

One of the most remarkable aspects was the overall resilience and dedication of the participants and research team to see the study through, regardless of the personal losses, damage to property, and constant general chaos. Only two participants cited the earthquakes as the direct reason for their withdrawal, and 294 (91%) completed the study on treatment. We also learnt some lessons that could be applicable to future studies because a natural disaster can strike at any time. For example, having a back-up supply of a small amount of study treatment at an

alternative site is important if access to the study site is suddenly compromised. Similarly, ensuring that data are entered into electronic databases in real time and having offsite access to the data and all study forms/questionnaires allows the study to continue or restart quickly.

In conclusion, despite the fashion for vitamin D supplementation, this study suggests that it does not reduce the adverse impact of earthquakes.

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Contributors: DRM, STC, LCJ, AWS, PCP, CMF, CAC, JHL, and RS provided the concept and design of the study. DRM, CMF, STC, LCJ, SS, and JHL acquired the data. SS conducted the statistical analysis and drafted the manuscript. All authors critically revised the manuscript and provided important intellectual content. SS is guarantor. All authors had full access to the data and take responsibility for the integrity and accuracy of the data.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The original study was approved by the Upper South B regional ethics committee (URB/09/10/050). Additional approval from the committee was sought and given to enable the collection of the earthquake data. All participants provided written informed consent.

Data sharing: No additional data available

Transparency: The lead author (the manuscript's guarantor) affirms 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 (and, if relevant, registered) have been explained.

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**What is already known on this topic**

Though vitamin D supplementation is said to improve mental wellbeing, randomised controlled trials show mixed results as to its efficacy  
There are no data regarding the effect of vitamin D supplementation for reducing the adverse impact of real life highly stressful events, such as earthquakes

**What this study adds**

Monthly, high dose vitamin D supplementation did not reduce the self reported adverse impact of earthquakes in healthy adults

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## Tables

**Table 1 | Characteristics of participants affected by earthquakes in New Zealand in by treatment arm**

Characteristic	Vitamin D (n=161)	Placebo (n=161)
Mean (SD) age (years)	47 (10)	48 (10)
Mean (SD) BMI	27 (5)	28 (5)
No (%) of women	121 (75)	120 (75)
No (%) with Māori/Pacific ethnicity*	7 (4)	8 (5)
Mean (SD) baseline serum 25-OHD (nmol/L)	73 (22)	71 (22)

BMI=body mass index; 25OHD=25-hydroxyvitamin D<sub>3</sub> (calcidiol).

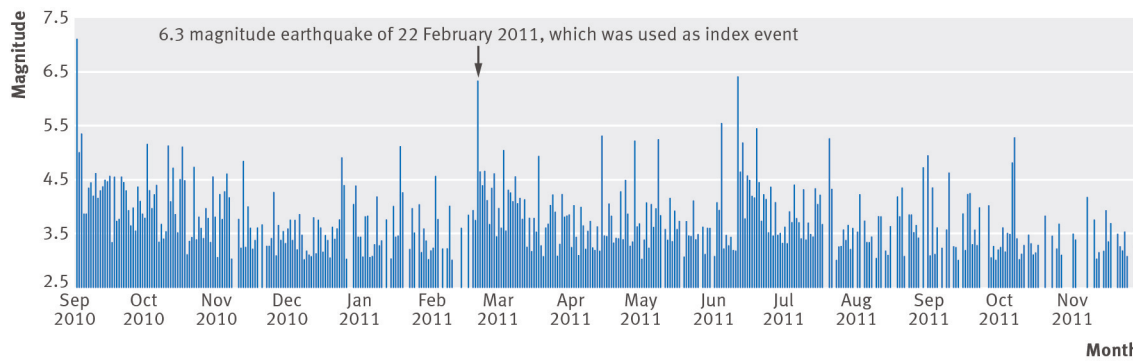
\*Self identified as Māori/Pacific ethnicity, which includes Samoan, Cook Islands, Māori, Tongan, Niuean, Fijian, Tokelauan, Tuvaluan.



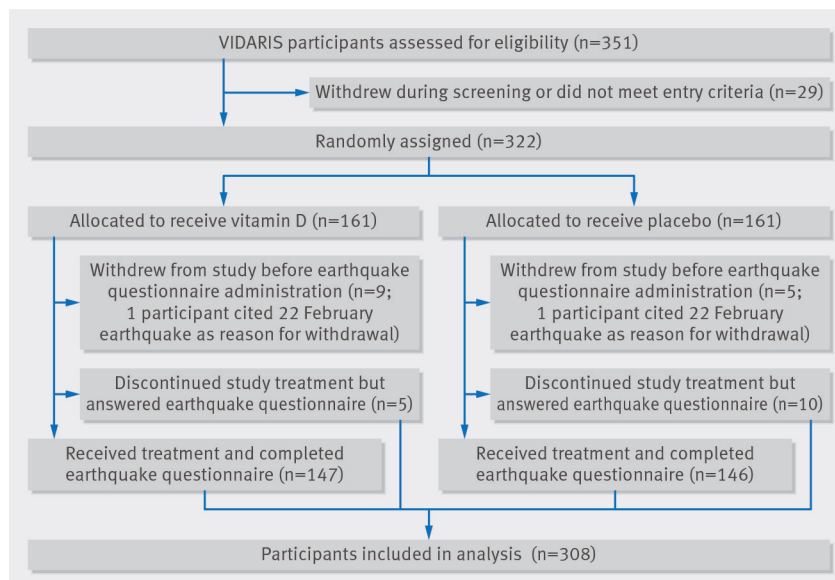
**Table 2| Self reported impact of earthquakes by treatment arm (n=308). Figures are numbers (percentage) of participants**

	Vitamin D (n=152)	Placebo (n=156)	$\chi^2$ (P value)
Felt earthquake 22 February 2011	140 (92)	151 (97)	3.25 (0.07)
Physical injury:			
Close family member or friend died	14 (9)	24 (15)	2.71 (0.10)
Personal injury	5 (3)	10 (6)	1.62 (0.20)
Close family member or friend injured	11 (7)	10 (6)	0.08 (0.77)
Property damage:			
House	108 (71)	101 (65)	1.41 (0.24)
Electricity supply	108 (71)	101 (65)	1.41 (0.24)
Water supply	99 (65)	96 (62)	0.43 (0.51)
Sewerage/waste water	83 (55)	70 (45)	2.92 (0.09)
Disruption to employment/business	90 (59)	90 (58)	0.07 (0.79)
Adverse changes to financial situation	28 (18)	21 (14)	1.42 (0.23)
Psychological impact:			
Disrupted sleeping patterns	120 (79)	109 (70)	3.33 (0.07)
Increased anxiety/stress (tense, hypervigilant, easily startled, irritable)	118 (78)	121 (78)	<0.001 (0.99)
Diminished ability to concentrate on tasks	97 (64)	93 (60)	0.58 (0.45)
Diminished interest in participating in activities	73 (48)	72 (46)	0.11 (0.74)
Adverse effect on family relationships	34 (22)	20 (13)	4.85 (0.03)
Overall adverse impact score:			
1 (low)	6 (4)	4 (3)	5.88 (0.44)
2	20 (13)	27 (17)	
3	34 (22)	38 (24)	
4	24 (16)	34 (22)	
5	46 (30)	32 (21)	
6	17 (11)	16 (10)	
7 (high)	5 (3)	5 (3)	

## Figures

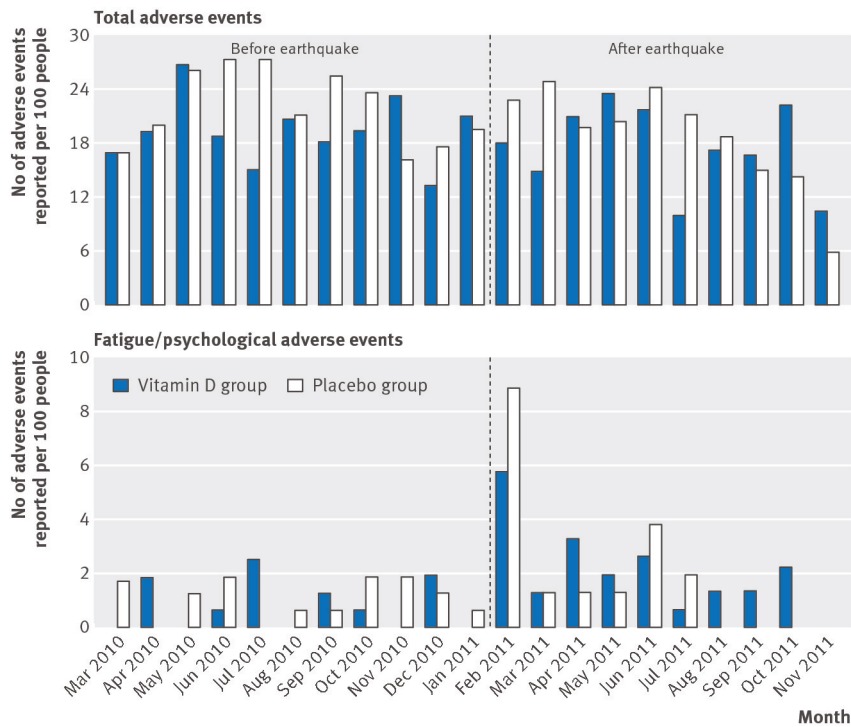


**Fig 1** Earthquakes and aftershocks during course of trial. Magnitude on Richter scale is base 10 logarithmic scale, therefore 6 on scale is 10 times magnitude of 5



**Fig 2** Flow of participants in study on effect of vitamin D<sub>3</sub> supplementation on adverse effects of earthquakes





**Fig 3** Number of adverse events reported at monthly appointments per 100 people by treatment arm. Fatigue and “psychological” adverse events included anxiety, stress, and depression