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ORIGINAL ARTICLE

Skeletal and hormonal responses to vitamin D supplementation during sunlight deprivation in Antarctic expeditioners

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Abstract
Summary Sunlight deprivation results in vitamin D deficiency but serum vitamin D levels can be maintained above 50nmol/L when supplemented with 50,000IU at least every alternate month.
Introduction Antarctic expeditioners are exposed to prolonged sunlight deprivation resulting in vitamin D deficiency. We hypothesised that monthly dosing of 50,000 IU vitamin D (~1,600 IU daily) will increase serum 25-hydroxyvitamin D (25(OH)D), suppress parathyroid hormone (PTH) and improve bone mineral density (BMD), 50,000 IU alternate months (~800 IU daily) will maintain these measures, while a single 50,000 IU dose pre-departure (~1,00 IU daily) will not be protective.
Methods This was a randomised double-blind study involving 110 healthy adults: 91 males, mean age 41 years (range 24–65 years) working in Antarctica for up to 12 months, who we administered 50,000 IU vitamin D3 monthly, alternate months or a single dose pre-departure. Serum 25(OH)D, PTH, osteocalcin, CTx and calcium were assessed at baseline, mid- and end of expedition. Proximal femur and lumbar spine BMD were assessed pre- and post-expedition.
Results Baseline 25(OH)D was 59±14 nmol/L. By mid-expedition, 25(OH)D increased by 7 nmol/L in those supplemented monthly ($p<0.05$) and remained unchanged in those supplemented in alternate months. In those given a single dose pre-departure, 25(OH)D decreased by 8 nmol/L ($p<0.05$) and PTH increased by 27% ($p<0.09$). Serum osteocalcin increased by ~22% in all groups but BMD remained unchanged. If serum 25(OH)D was >50 nmol/L at baseline, 25(OH)D was maintained above this level with all regimens. If 25(OH)D was <50 nmol/L at baseline, monthly or alternate month regimens were needed to achieve levels >50 nmol/L, the single pre-departure dose was ineffective.
Conclusion During sunlight deprivation of up to 12 months, serum 25(OH)D levels can be maintained above 50 nmol/L when expeditioners are provided with 50,000 I U at least every alternate month.

Keywords Antarctica · Sunlight deprivation · Vitamin D supplementation

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Introduction

Vitamin D deficiency is associated with accelerated bone loss and increased fracture risk [1]. Without supplementation, sunlight exposure is critical for the maintenance of vitamin D levels above 50 nmol/L; vitamin D deficiency emerges after 4 months of sunlight deprivation unless initial serum 25(OH)D is greater than 100 nmol/L [2]. Seasonal variation in serum 25(OH)D and accompanying bone loss have been observed, especially in those living in high and low latitudes where ultra violet (UV) exposure is limited during winter [3, 4]. Food fortification with vitamin D is routine in many such countries to minimise wintertime

vitamin D deficiency and bone loss [5]. Supplementation with various doses of vitamin D has been efficacious in maintaining serum 25(OH)D and preventing bone loss during winter in some, but not all, studies [3, 6, 7].

Antarctic expeditioners experience prolonged periods of sunlight deprivation as UV exposure is negligible from March to September, marginal on the shouldering months, while freezing temperatures necessitate protective clothing that further limits sunlight exposure [8]. We previously reported that by 6 months, 85% of expeditioners had serum 25(OH)D<50 nmol/L, and by 12 months, expeditioners had suffered bone loss at the proximal femur [2]. Given that the majority of expeditioners undertook prior expeditions, if this bone loss is not reversed, increased fracture risk may result.

A 5-month study using three different doses of vitamin D in healthy adults who spent winter in Antarctica has been reported but high dietary vitamin D intakes and poor compliance make it difficult to assess the dose required to achieve vitamin D levels above 50 nmol/L [9]. Dietary sources of vitamin D for healthy Australian expeditioners are negligible, so combined with their limited opportunity for cutaneous vitamin D synthesis, studying these adults provides a model of near complete vitamin D deprivation [2, 10]. We investigated the skeletal response to vitamin D supplementation during sunlight deprivation to test the following hypotheses: (i) monthly doses of 50,000 IU (~1,600 IU daily) vitamin D will increase serum 25(OH)D, suppress parathyroid hormone (PTH) and improve BMD; (ii) 50,000 IU alternate months (~800 IU daily) will maintain 25(OH)D, PTH and BMD; and (iii) a single dose of 50,000 IU vitamin D prior to departure (~100 IU daily) will not be protective; 25(OH)D will decline, PTH will increase and bone loss will occur.

Methods

This was a double-blind randomised study comparing three doses of vitamin D supplementation in 110 healthy adults (91 males) who spent winter at Australian Antarctic (Casey, Mawson, Davis; latitudes 66–68° S) or sub-Antarctic (Macquarie Island; latitude 54° S) stations during the 2007/08 (n=55) and 2008/2009 (n=55) seasons. Expeditioners departed for Antarctica from October to March depending on station destination with the majority departing during summer (December to February) and returning approximately 12 months later. Australian Antarctic expeditioners have limited opportunities to contribute to serum 25(OH)D levels as food sources are minimal, UV exposure is negligible from March to September (autumn, winter and the beginning of spring in the southern hemisphere), and marginal on the shouldering months, and extreme conditions limit the opportunity for skin exposure when vitamin D synthesis may be possible [8]. Approval for this study was obtained from the Australia Antarctic Division and the Austin Hospital Human Research Ethics committees.

Participants

One hundred and forty-four expeditioners (17 females and 127 males) free of disease or use of medication known to affect bone were eligible to participate, of which 123 (85%) consented. The exclusion criteria were severe vitamin D deficiency (<12.5 nmol/L) or serum 25(OH)D>100 nmol/L which were determined from fasting pre-departure blood samples taken at the Australian Antarctic Division [2, 11]. Two participants were vitamin D-deficient and -treated, and eight had serum 25(OH)D>100 nmol/L so they were excluded. Baseline blood samples were not available in three expeditioners due to changes in departure times, so the remaining 110 expeditioners were stratified based on station, sex and baseline serum 25(OH)D and then randomly assigned to one of the three regimens: 50,000 IU monthly, alternate months or a single dose of 50,000 IU vitamin D prior to departure. A control group was unethical as decreases in serum 25(OH)D and bone loss have been reported in expeditioners [2]. Three expeditioners reported consuming multivitamin supplements but with negligible vitamin D content. Seventeen percent of participants were female with a mean age of 34.4±5.7 years. All were premenopausal; three were taking the oral contraceptive pill.

Measurements

At baseline, participants completed a standard health and medical questionnaire and had height (±0.1 cm) measured on a stadiometer (Medizintechnic, Germany) and weight (±0.1 kg) measured on a beam scale (Wedderburn, UK). While in Antarctica, fasting serum samples were taken mid-season (the majority during winter) and at the completion of the expedition. Samples were stored at −80°C and transported to Australia at the end of the expedition. Dietary intake was assessed mid-expedition using 3-day weighed food records and analysed for macronutrient, calcium and vitamin D content using Foodworks (Professional edition 6.0.22562, Xyris Software, Qld, Australia).

BMD at the total proximal femur and lumbar spine (L1–4) was assessed at the Menzies Research Institute (Hobart, Australia) before and after the expedition using DXA (Hologic Delphi W Version 11.1, Hologic, Waltham, MA, USA; CV=1%). Baseline BMD was measured in 92 expeditioners; however, only 46 were available for follow-up assessments due to summer closure of the Institute and a medical evacuation resulting in deployment of return voyages to alternative ports.

Baseline, mid- and end of expedition serum data were available from 102 of the 110 expeditioners (three departed

early, four expeditioners spent only summer in Antarctica, and one needed medical evacuation).

Supplement

The supplement used was a 50,000 IU vitamin D3 tablet or an identical placebo (Cal-D-Forte, API Consumer Brand, Auckland, New Zealand). Participants were allocated three tablet containers; a baseline bottle containing one active tablet for all participants, and "A" and "B" bottles. For the single dose group, both the A and B bottles contained placebos, for those supplemented alternate months, the alternate bottles contained placebo and active tablets, and for the monthly group, both bottles contained active treatment. The tablets were maintained at the station medical centres and administered during monthly medical examinations by medical officers at each base with the date of administration documented. Compliance with supplementation was >99%.

Analyses

Serum samples were analysed for 25(OH)D, N-Mid Osteocalcin (OC) and c-terminal telopeptide (CTx) using an electrochemiluminescence immunoassay (Elecsys 2010 Analytics, Roche Diagnostics, Germany, CV=7–13%), for calcium using indirect potentiometry (SYNCHRON LX, Beckman Coulter, Inc., USA, CV=3%), for PTH using a chemiluminescnet immunoassay (DPC Immulite 2000, Los Angeles, USA, CV=7.2%), and for albumin using a bichromatic digital endpoint (SYNCHRON DxC-800, Beckman Coulter, Inc., USA, CV=2%). Serum 25(OH)D, PTH and calcium were analysed at Austin Pathology (Austin Hospital, Heidelberg, Australia), and bone markers were batched and assessed in-house so consecutive samples were included in a single batch. CTx analysis was only performed on participants from the first expedition (n=55). The intra- and inter-assay CV's for serum measures were 7–13% [12].

Power calculations and statistical analysis

Based on the observed 36% reduction in serum 25(OH)D with sunlight deprivation, a sample size of 16 per group was required to detect a halving of this loss with a single 50,000 IU dose with 80% power using a two-tailed test at $p<0.05$, and based on the 1% bone loss observed in non-supplemented expeditioners, 28 participants per group were required to detect a 1% improvement in BMD [2]. ANOVA was used to determine group differences at baseline. Comparisons between time points (baseline, mid- and post-expedition) were made using repeated measures analysis of variance. Delta time = age at time B minus age at time A. Percentage change was calculated as (delta value/(value A+value B)/2) × 100 to account for regression to the mean [13]. Linear and curve linear regressions were used to plot the time course of changes in serum 25(OH)D in response to supplementation. Data were presented as mean±SD unless stated otherwise. A p-value less than 0.05 is considered statistically significant, but values of $p<0.1$ are reported. Bonferroni adjustments were made.

Results

Group characteristics are presented in Table 1. Serum 25(OH)D was below 50 nmol/L at baseline in 19% of expeditioners. No differences in baseline or change data were observed between stations so data was pooled. A group effect was observed for changes in 25(OH)D. By mid-expedition, serum 25(OH)D increased by 7 nmol/L (20%/year) in those supplemented monthly, remained unchanged in those supplemented alternate months and decreased by 8 nmol/L (18%/year) in the single dose group. By expedition end, relative to baseline, serum 25(OH)D remained higher in the monthly group, remained unchanged in those supplemented alternate months and was lower in the single dose group (Table 2).

No group differences were observed for changes in PTH (Table 2). However, relative to baseline, by mid-expedition, a non-significant 10% decrease in PTH was observed in the monthly group, levels remained unchanged in the alternate month group and a 27% increase was observed in the single dose group ($p<0.09$). The difference between the monthly and single dose groups was significant after adjusting for dietary calcium intake ($p<0.02$). Serum osteocalcin increased in all groups and remained elevated until the end of the expedition; however, 99% of values remained within the reference ranges (Table 2). No changes were detected in serum calcium, CTx or BMD in any group (Table 2).

In a sub-group analysis, for those with serum 25(OH)D> 50 nmol/L, serum 25(OH)D was maintained above these levels with monthly supplementation, but based on linear regression analysis, 25(OH)D levels would be predicted to fall below 50 nmol/L at about 2.5 years with the alternate month treatment and by 1.2 years when 50,000 IU was administered prior to departure (Fig. 1, left panels). For those with serum 25(OH)D<50 nmol/L, levels above 50 nmol/L were achieved in ~5 months with monthly supplementation, in ~5.5 months when supplemented alternate months but was not achieved in those who received a single dose prior to departure (Fig. 1, right panels). Using curve linear analysis, similar outcomes were achieved except for those with serum 25(OH)D levels below 50 nmol/L who received the single dose prior to departure, where levels >50 nmol/L were predicted to be achieved after 1.5 years

Table 1 Baseline characteristics of Antarctic expeditioners randomly assigned to a 50,000-IU vitamin D monthly, every alternate month or a single dose of 50,000 IU vitamin D prior to departure (mean±SD)

	Monthly $n=37$	Bi-monthly $n=38$	Single dose $n=35$
Age (years)	41.5±11.2	39.7±10.7	42.6±11.8
Male (%)	84	81	90
Height (cm)	174.0±8.4	176.4±8.9	177.1±8.1
Weight (kg)	82.8±12.1	84.6±3.2	87.6±11.6
Caucasian (%)	94	100	100
Smoker (%) (current/past/never)	6/29/65	14/19/67	4/38/58
Alcohol (%) (current/past/never)	86/7/7	94/3/3	92/4/4
Organised sport (%) (yes/no)	41/59	40/60	33/67
Prior expeditions (%)	56	53	61
25(OH)D (nmol/L)	55±14	60±15	63±12
PTH (pmol/L)	3.8±1.5	4.2±2.0	3.8±2.0
Osteocalcin (ng/mL)	21.9±6.5	21.6±7.4	18.2±7.0
CTx (ng/mL)[b]	0.21±0.11	0.17±0.08	0.19±0.13
Calcium (mmol/L)	2.35±0.08	2.36±0.08	2.34±0.11
Bone mineral density			
BMD proximal femur (g/cm^2)	1.04±0.14	1.02±0.10	1.08±0.16
Lumbar spine (1–4) (g/cm^2)	1.02±0.15	1.03±0.11	1.10±0.03
Dietary intake (mean daily intake)[a]			
Calcium (mg)	872±574*	740±309	683±368
Vitamin D (IU)	121±51	135±40	99±45
Protein (g)	105±38	96±31	103±25
Carbohydrates (g)	231±77	229±83	207±59
Fat (g)	83±34	85±40	85±28
Energy (kJ)	8,998±2,731	8,987±2,765	8,899±2,410

[a]Data collected mid-expedition ($n=98$)

[b]CTx analysed from the 2007–2008 expedition with sample sizes: monthly=19, bi-monthly=19, and single dose=17

*$p<0.09$ (statistical significance; dietary calcium tended to be higher in the monthly than single dose group)

(data not shown). No cases of vitamin D toxicity or hypercalcemia were observed.

Discussion

We report the skeletal response to three different doses of vitamin D supplementation in Antarctic expeditioners. By mid-expedition, a monthly dose of 50,000 IU (~1,600 IU daily) increased serum 25(OH)D with a non-significant reduction in PTH observed, supplementation alternate months (~800 IU daily) maintained 25(OH)D and PTH levels, while a single dose prior to departure (~100 IU daily) resulted in a decrease in 25(OH)D with a tendency for serum PTH to rise. Osteocalcin modestly rose in all groups, but BMD, CTx and serum calcium remained unaltered. For those with serum 25(OH)D<50 nmol/L, levels above 50 nmol/L were achieved by ~5 months in those supplemented monthly or alternate months but was not achieved in those who received a single dose prior to departure in whom 25(OH)D declined. In those with serum 25(OH)D>50 nmol/L, levels were maintained and no bone loss was detected with any of the three regimens.

While changes to 25(OH)D were observed in response to vitamin D supplementation, larger changes have been observed with daily administration [6, 7, 14-18]. We used monthly administration to assist compliance, as poor compliance with daily administration is well-documented and the safety of annual mega-doses of vitamin D is in question [9, 19-21]. Monthly administration ensured excellent compliance (>99%) and so may have application to other groups with limited sunlight exposure such as house-bound elderly and those in aged care.

Based on regression analysis, serum 25(OH)D could be maintained above 50 nmol/L indefinitely using the monthly administration of 50,000 IU of vitamin D, but levels would fall below 50 nmol/L at ~2.5 years when 50,000 IU was administered in alternate months. Using mathematical modelling, Cashman et al. (2008) concluded that 1,120 IU of vitamin D daily was required to maintain serum 25(OH)D>50 nmol/L in healthy adults. Our findings support this conclusion. However, others have suggested that 700–800 IU/day is adequate to maintain stable bone turnover in healthy adult males [14, 17]. For expeditioners to Antarctica, given that the usual length of stay is 12 months, in those with serum 25(OH)D levels above 50 nmol/L at baseline, the single

Table 2 Skeletal and hormonal changes over time in Antarctic expeditioners supplemented with 50,000-IU vitamin D monthly, every alternate month or provided with a single dose of 50,000 IU prior to departure (mean±SD)

	Monthly n=36	Alternate month n=35	Single dose n=31
25(OH)D (nmol/L)			
Baseline	56±14,[a,c]	60±15	63±12[g,h]
Mid	62±16[b,a,c]	59±20	55±14[h]
End	70±19[a,b]	62±21	54±13[g]
Difference: BL–mid (%/year)	20.0±56.1[**]	−2.2±64.2	−18.4±47.9[**]
Difference: mid–end (%/year)	21.0±36.4	6.6±52.8	−6.5±33.1
PTH (pmol/L)			
Baseline	3.9±1.5	4.1±2.0	3.5±1.2[i]
Mid	3.7±1.6	4.4±1.9	4.0±1.0[i]
End	3.8±0.9	4.4±1.5	3.9±1.3
Difference: BL–mid (%/year)	−9.8±71.8[***]	9.4±75.0	27.4±6.1[***]
Difference: mid–end (%/year)	7.3±136.4	4.1±101.2	−10.1±76.2
Osteocalcin (ng/mL)			
Baseline	22.3±6.7[c,d]	21.0±7.6[e,f]	19.5±6.8[j,k]
Mid	25.5±8.7[c]	24.6±6.2[f]	24.0±6.8[k]
End	25.6±8.4[d]	25.6±7.7[e]	24.3±6.1[j]
Difference: BL–mid (%/year)	20.7±47.2	23.9±52.9	26.8±52.9
Difference: mid–end (%/year)	1.3±12.1	1.3±9.2	1.1±6.3
CTx (ng/mL)			
Baseline	0.22±0.11	0.17±0.08	0.22±0.15
Mid	0.26±0.15	0.22±0.15	0.21±0.09
End	0.25±0.17	0.19±0.11	0.18±0.08
Difference: BL–mid (%/year)	20.7±101.9	16.9±90.6	−3.7±110.8
Difference: mid–end (%/year)	29.0±174.4	−11.3±61.8	−61.3±121.0
Calcium (mmol/L)			
Baseline	2.35±0.07	2.36±0.08	2.34±0.10
Mid	2.32±0.09	2.32±0.09	2.37±0.09
End	2.32±0.14	2.32±0.09	2.34±0.11
Difference: BL–mid (%/yr)	−2.1±8.9	−2.3±8.0	3.1±8.8
Difference: mid–end (%/yr)	0.2±20.0	0.3±10.5	−2.7±9.9
Total prox. femur (g/cm^2)			
Baseline	1.02±0.13	1.01±0.08	1.08±0.16
End	0.85±0.13	1.01±0.08	1.08±0.15
Difference (%/year)	−1.0±3.3	0.7±2.3	−0.1±2.8
Femoral neck (g/cm^2)			
Baseline	0.86±0.14	0.82±0.10	0.90±0.13
End	0.85±0.13	0.82±0.10	0.91±0.13
Difference (%/year)	−1.0±3.3	0.3±4.6	0.4±3.7
Lumbar spine (g/cm^2)			
Baseline	1.00±0.17	1.00±0.10	1.08±0.17
End	0.98±0.16	1.00±0.09	1.07±0.18
Difference (%/year)	−1.6±4.3	0.1±3.1	−1.4±3.6

The same letter indicates a difference between time points for (i) monthly group: [a]$p<0.01$, [b]$p<0.01$, [c]$p<0.05$, [d]$p<0.05$; (ii) bi-monthly group: [e]$p<0.001$, [f]$p<0.01$; and (iii) single dose group: [g]$p<0.001$, [h]$p<0.001$, [i]$p<0.09$, [j]$p<0.01$, [k]$p<0.01$

The same symbol indicates group differences: [*]$p<0.01$, [**]$p<0.05$, [***]$p<0.06$ (significant after adjusting for dietary calcium intake, $p<0.02$)

Sample sizes for BMD data are: monthly, n=16; bi-monthly, n=15; and single dose, n=15

Sample sizes for CTx are: n=19, bi-monthly; and n=19, single dose; n=17 (2007/08 season only)

Reference ranges for: PTH (1.3–7.2 pmol/L), serum calcium (1.80–2.65 mmol/L), OC for healthy males 30–50 years (14–42 ng/mL) and premenopausal women >20 years (11–43 ng/mL); 25(OH)D; severe/moderate deficiency (<25 nmol/L), mild deficiency (25–50 nmol/L), sufficiency (>50 nmol/L) based on Australian standards [11]

Conversion of serum 25(OH)D to ng/mL=nmol/L divided by 2.5

50,000 IU dose prior to departure may be sufficient to maintain levels above 50 nmol/L.

No effect of vitamin D supplementation on PTH was observed, but PTH tended to rise by mid-expedition in the group given a single dose of 50,000 IU prior to departure, in whom vitamin D decreased. No threshold level of serum 25 (OH)D is established at which the rise in PTH plateaus with levels purported up to 78 nmol/L [22-24]. Only 19% of participants had serum 25(OH)D below 50 nmol/L and only 5% had elevated serum PTH at baseline which limited the

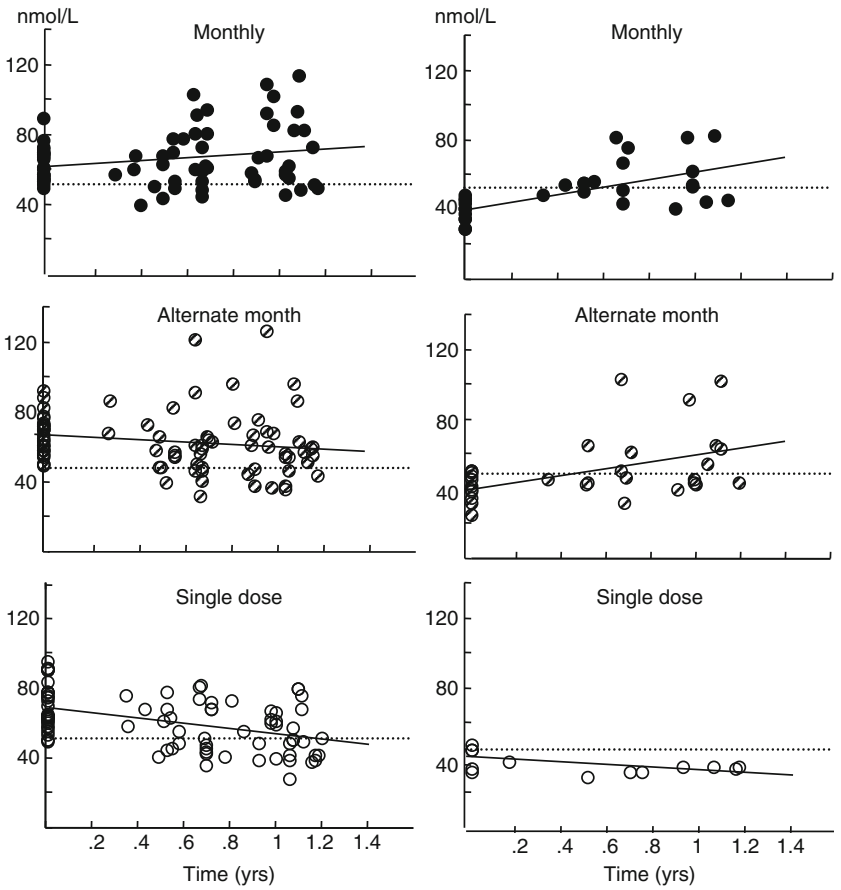

Fig. 1 Time course of changes to 25(OH)D in expeditioners with serum 25(OH)D levels above (*left panels*) or below (*right panels*) 50 nmol/L at baseline, and then treated with 50,000 IU monthly, alternate months, or provided with a single dose of 50,000 IU vitamin D prior to departure

ability to detect a decline in PTH with supplementation. Suppression of PTH with vitamin D is evident in those with overt vitamin D deficiency [6, 7, 9, 15]. As reported previously, no changes in serum calcium were observed [6, 16].

Modest increases in serum osteocalcin were observed in all groups. Others have reported no detectable effect of vitamin D supplementation on serum osteocalcin [7, 15, 25]. This observation remains unexplained. A potential influence of dietary protein intake would be unlikely as mean protein intakes were <1.3 g per kg body weight and expeditioners did not undertake physical activities or manual labour beyond what they are accustomed to prior to departure. Vitamin D supplementation is effective in preventing wintertime bone loss in community dwellers [3, 14, 26]. Bone loss has been observed in prior expeditioners when not supplemented with vitamin D; however, mean serum 25(OH)D levels were lower than for the current cohort (54 versus 61 nmol/L, $p<0.01$). Given the high proportion of expeditioners with 25(OH)D>50 nmol/L, and those with vitamin D deficiency were excluded, supplementation may have been sufficient to prevent the bone loss, or due to the limited number of post–assessments, we were underpowered to detect changes in BMD with supplementation [2].

Dietary sources of vitamin D are limited in Australian expeditioners so we were able to study the time course of serum 25(OH)D changes in response to three different vitamin D doses, without the confounder of dietary sources. Compliance was >99% and administration stringently recorded so the dose received can be accurately quantified. Limitations of the study were: (i) the absence of a control group; (ii) few expeditioners were vitamin D deficient; (iii) variability in serum assays may have influenced the ability to detect differences between doses; (iv) the power to detect changes in BMD was limited due to the reduced number of participants with post-expedition BMD assessments and (v) the participants were healthy adults, so whether similar responses would be observed in older adults in whom bone loss is occurring or in children where growth is dominating remains to be determined.

The study of Antarctic expeditioners provides a model for the study of the time course of changes to 25(OH)D with prolonged sunlight deprivation. Monthly or alternate month doses of 50,000 IU vitamin D were well-tolerated and appear to be a satisfactory approach to preventing vitamin D deficiency whether individuals are vitamin D-insufficient or -replete. Further studies are needed to establish efficacy and safety in individuals at high risk for vitamin D deficiency such as the elderly or house-bound individuals.

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Conflicts of interest None.

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