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Vitamin D status and supplementation in Antarctica: a systematic review and meta-analysis

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ABSTRACT

Living at high latitudes is associated with vitamin D (VD) deficiency. An ideal setting to study this is the Antarctic continent, which has temporary inhabitants, but the magnitude of the effect of living in Antarctica and the effects of VD supplementation on this population remain unclear. We performed a systematic review and meta-analysis to assess the effect of temporary residence in Antarctica and impact of VD supplementation on VD status of this population. Random-effects meta-analyses were performed to assess serum 25-hydroxyvitamin D (25(OH)D) concentration changes after Antarctic residence (13 studies, 294 subjects) and after VD supplementation (5 studies, 213 subjects). Serum 25(OH)D mean difference after temporary residence in Antarctica was -15.0 nmol/L (95%CI: -25.9, -4.2; $I^2=92%$). Subgroup meta-analyses of studies evaluating Antarctic summer and winter stays showed 25(OH)D only decreases when overwintering (winter 25(OH)D change -17.0 nmol/L [95%CI: -24.1, -9.8; $I^2=83%$] vs. summer 25(OH)D change 1.3 nmol/L [95%CI: -14.6, 17.1; $I^2=86%$]). The meta-analysis of VD supplementation studies in Antarctica showed a mean 25(OH)D increase after supplementation of 10.8 nmol/L (95%CI: 3.3, 18.3; $I^2=88%$). In conclusion, VD status significantly worsens after inhabiting Antarctica, particularly when over-wintering. VD supplementation can prevent worsening of VD status and should be considered in this population.

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Introduction

Vitamin D (VD) deficiency is a health condition that affects an important proportion of the worldwide population [1]. VD deficiency can lead to bone mineralisation defects such as rickets in children and osteomalacia in adults [2]. Also, studies in the general population have shown an association of VD deficiency with increased fracture risk and other health problems, including cancer, cardiovascular problems, autoimmune diseases, respiratory infections, and allergies [3–8]. VD status can be easily evaluated by measuring serum or plasma 25-hydroxyvitamin D (25(OH)D) by different methods, although these are not always comparable [9]. Establishing cut-off values of what constitutes normal VD status and VD deficiency has been difficult and controversial among experts and scientific societies, and it is possible that these thresholds differ at different ages and populations [10]. Although variable definitions have been suggested, the Endocrine Society has

proposed a serum 25(OH)D concentration below 50 nmol/L (20 ng/mL) to define VD deficiency [11], cut-off value that will be used in this work.

VD is a liposoluble pleiotropic hormone that in humans is mainly synthesised in the skin from cholesterol precursors upon exposure to solar UVB radiation (wavelength 290 to 315 nm), and in a smaller proportion acquired from dietary sources such as oily fish [3]. Low sun exposure is associated with VD deficiency, with progressively more severe deficiency at higher latitudes. These high latitudes significantly affect VD skin synthesis in the winter months in locations above 40° in both hemispheres. At extreme circumpolar latitudes, sunlight may be insufficient for VD synthesis year-round [12,13]. In Antarctica, despite the stratospheric ozone layer hole every austral spring, solar UV radiation reaching the surface is shallow at high latitudes and low solar elevation angles [14,15]. Frequent clouds accentuate this phenomenon of low UV radiation in some

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Antarctic regions, such as in the South Shetland Islands, where many Antarctic bases and a large portion of the population are located [15].

Antarctica has unique extreme environmental conditions that pose an existential challenge to humans who live and work there, particularly over long periods. In addition to high latitudes, several biological and environmental factors of life on Antarctica are associated with a higher risk of vitamin D deficiency. Reduced sun exposure due to long winter season with little daytime, harsh cold temperatures, severe winds requiring full cover clothing, and sunscreen use in spring and summer seasons also increase the risk of VD deficiency [16]. Moreover, the cold temperatures and extreme polar climate oblige its residents to spend most of their time indoors. The seasonality and duration of stays in Antarctica are highly variable, but can probably be classified well into two groups: those staying year-long or overwintering, as they inhabit Antarctica from one spring or summer to the next, and on the other hand, those with shorter stays that usually include only some spring and summer weeks or months.

Further affecting VD status is the change in dietary habits and foods that people receive during their Antarctic stay [17]. Food in Antarctica is entirely brought from other continents and none is grown naturally or cultivated due to low temperatures and Antarctic regulations. The reliance on preserved foods, and the limited connections with other continents to obtain natural foods, especially in the winter season, can generate a high negative impact on the dietary intake of VD, especially for people staying long-term [17]. All of these factors produce extreme living conditions in Antarctica that might affect VD status and its inhabitants' health.

Due to the high rates of VD deficiency in the population of countries located at high latitudes, VD supplementation has been recommended to treat this deficiency and, in the medium and long term, to prevent associated diseases [18]. However, few studies have evaluated VD supplementation's impact on people during their stay in Antarctic bases and expeditions. Besides, it is not clear if VD supplementation at usual dosing recommended by clinical guidelines is enough to avoid low VD levels during residence in Antarctica [19–21]. To understand how residence in Antarctica affects VD status and the impact of VD supplementation in this particular population, we performed a systematic review and meta-analysis of studies that measured VD concentrations in healthy humans during their residence in different Antarctic bases. We believe that these data will provide fundamental insights into

VD status at the high latitudes and extreme climatic conditions of Antarctica, which can contribute to policy development on preventing VD deficiency at very high latitudes, including the Antarctic continent.

Methods

Identification of studies and study eligibility criteria

We performed a systematic review and meta-analysis according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [22], on studies that evaluated vitamin D status and studies about VD supplementation in residents of the Antarctic continent. We searched in PubMed/Medline, Web of Science, and Scopus databases. The algorithm keywords included: "vitamin D" "cholecalciferol", and "ergocalciferol" combined with "Antarctic" or "Antarctica", from start to 1 December 2020 (last update). We limited the search to humans.

We also manually reviewed references of studies found through search algorithms to avoid missing any relevant research on the topic. Then, two authors (CC and AB) independently reviewed the selected abstracts to define inclusion. The eligibility criterion was that the study included serum levels of 25(OH)D measured before and after a residency in any Antarctic bases. The only exclusion criteria were the unavailability of numerical data of serum 25(OH)D concentrations of the groups of subjects reported in each study.

Data extraction

All data required for the systematic review and meta-analysis were extracted independently by two authors (CC and AB) from studies considered according to the eligibility criteria as follows: first author, publication year, country and Antarctic base/research station of study performance, intervention, enrolment year, demographic characteristics of the study population (n, age, sex, body weight, height, and body mass index), length of follow-up, methods used for measurement of serum 25(OH)D level, and outcomes about change in serum 25(OH)D level. In some cases, body mass index was calculated by the researchers of this review using the formula $\text{weight}/\text{height}^2$. In studies that evaluated the effect of VD supplementation, we extracted data on VD dosing and duration of supplementation. Follow-up duration was extracted as days, months, and years, but the data were

transformed into approximate days. Mean \pm range date age was transformed into a mean \pm standard deviation (SD). Data of 25(OH)D concentrations were obtained as nmol/L or ng/ml. To include them in this systematic review and subsequent meta-analysis, all data were converted to nmol/L ($1 \text{ ng/ml} * 2.496 = \text{nmol/L}$). If statistics were presented with Standard Error of the Mean (SEM), to include them in this review these data were converted to SD.

Data analysis

We extracted numerical data of the mean 25(OH)D blood concentrations in groups of subjects at each specific timepoint that was measured. The first analysis was performed, including the 25(OH)D at baseline and after an entire stay. Then, subgroup analysis was also performed, dividing the 25(OH)D change data according to Antarctic stays in summer months (January to February) and the stay in Antarctic winter (any months between March and September). Finally, a VD supplementation meta-analysis was done comparing the VD level before and after vitamin D supplementation. The statistical analysis was carried out using the Review Manager 5.3 software (the Cochrane Collaboration, 2014, Nordic Cochrane Center, Copenhagen, Denmark). The 25(OH)D level was used as the summary measurement for the meta-analysis, and the results are presented as forest plots. Heterogeneity and inconsistency of the measures were identified through Cochran's Q statistical test and I^2 test, respectively. The random-effects model was applied with inverse variance according to the results of the individual studies. The inconsistency test ($I^2 > 75\%$) was used as an indicator for high heterogeneity. The publication bias was assessed through a funnel plot. In all analyses, a confidence interval of 95% was used, and $P < 0.05$ was considered statistically significant.

Results

Study selection process

Using the search algorithm, we identified 23 abstracts published in the last 41 years (1979 – December 2020). After filtering for human studies, in total, 21 articles were reviewed by our prespecified inclusion and exclusion criteria. After this process, eight articles were excluded. One study was excluded because it did not include VD levels measured after Antarctic residence [23]. The next article was excluded because the aim was a nutritional and toxicological comparison among Antarctic krill oil and dietary supplements [24]. The

third article was excluded because the research did not include the evaluation of VD blood concentrations in the Antarctic population but only quantified dietary vitamin D intake of the study population [17]. Two articles were excluded because they incorporated data previously published in another study [25,26]. The last three articles that were excluded did not provide numerical data of serum or plasma 25(OH)D concentrations, and these could not be obtained by contacting the authors [27–29]. Finally, thirteen studies were included in this systematic review and meta-analysis. The study selection process is summarised in Figure 1.

Characteristics of the selected studies

The thirteen included studies were performed in heterogeneous populations from different countries, including England [30], Australia [19,31,32], Spain [20], Argentina [21,33], India [34], USA [35,36], Germany [37], Uruguay [38], and Japan [39]. These studies were also done in several different geographical areas of the Antarctic continent according to the location of the respective nations' bases. Antarctic bases involved in the eligible studies are shown in Figure 2. The total number of subjects that participated in the selected studies were $n = 265$ subjects for meta-analysis regarding the seasonal variation of 25(OH)D level and $n = 213$ subjects for meta-analysis about the impact of VD supplementation in the Antarctic population.

The summary of study characteristics is shown in Tables 1 and 2. These include Antarctic bases, latitude, enrolment years, study type, follow-up length, doses of VD supplementation, number of study subjects, the method used to measure 25(OH)D, and main findings. The quality and risk of bias assessment for the included studies is presented in Figure 3.

Meta-analysis of Vitamin D status during the entire Antarctic stay

The results from the meta-analysis of VD status throughout the entire Antarctic stay of subjects can be seen in Figure 4. In ten studies, the last 25(OH)D serum sample was obtained before departure from Antarctica, and results were compared to the baseline 25(OH)D serum concentration at or before arrival to the continent. The length of stay in Antarctica for these studies had a median of 365 days (range 22–456). This analysis did not include the changes in 25(OH)D serum levels in VD-supplemented subjects. The random-effects model was used to calculate the summary measurement. The result of the inconsistency test showed that there was high heterogeneity among the studies analysed ($\text{Chi}^2 = 106.9$, $\text{df} = 9$, $P < 0.00001$; $I^2 = 92\%$).

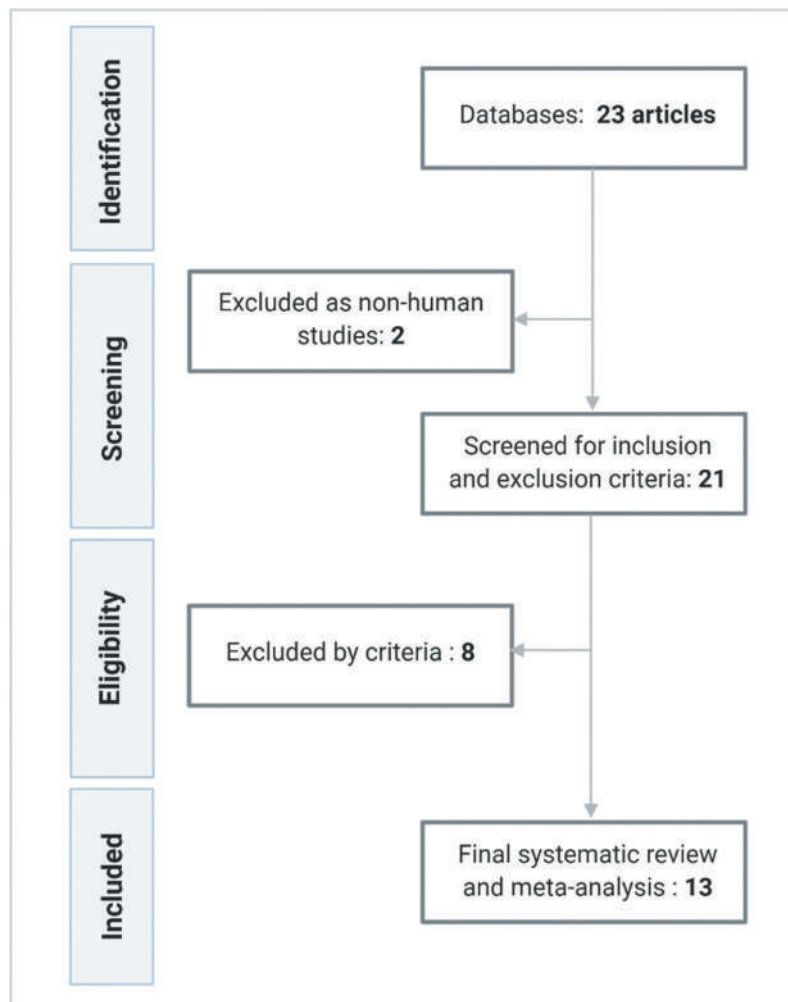


Figure 1. Flow diagram of the study selection process.

The mean baseline 25(OH)D level was 64.9 ± 19.1 nmol/L and the global effect of a full stay in Antarctica was a change of the mean 25(OH)D of -15.0 nmol/L (95% CI: $-25.9, -4.2$; $P = 0.007$), demonstrating that Antarctic residence significantly worsens VD status. No publication bias was identified according to the funnel plot (Figure 4B).

Meta-analysis of vitamin D status in summer and winter residence

We performed subgroup meta-analyses to evaluate the impact of full clarity days in summer and higher solar UVB radiation versus full darkness days in winter with minimal or null solar UVB radiation on VD status. We analysed five studies that included 25(OH)D measurements pre- and post- Antarctic residence during January and February months, and thus, assessed variations in 25(OH)D serum concentration during summertime in Antarctica. This meta-analysis only included non-supplemented groups or periods. The mean

baseline 25(OH)D level was 75.3 ± 22.9 nmol/L and the global effect of a summer stay in Antarctica had a non-significant decrease in the value of the mean 25(OH)D of 1.26 nmol/L (95% CI: $-14.6, 17.1$; $P = 0.9$). The result from the inconsistency test showed that there was high heterogeneity between the studies analysed ($\text{Chi}^2 = 28.5$, $\text{df} = 4$, $P < 0.00001$; $I^2 = 86$) (Figure 5A). Publication bias was identified according to the funnel plot (Figure 5B), although this could also be associated with heterogeneity among study design and effect measures.

On the other hand, eight studies included Antarctic residence during winter (i.e. overwintering in Antarctica). Despite the random-effects model, the analysis showed a high heterogeneity ($\text{Chi}^2 = 42.2$, $\text{df} = 7$, $P < 0.00001$; $I^2 = 83\%$). The mean baseline 25(OH)D level of studies evaluating the effect of overwintering was 59.7 ± 22.8 nmol/L and the global effect of a winter residence in Antarctica has a significant change of the mean 25(OH)D of -17.0 nmol/L (95% CI: $-24.1, -9.8$;



Figure 2. Antarctic bases of eligible studies. Referential map about locations of Antarctic bases and stations involved in studies included in the systematic review and meta-analysis.

$P < 0.0001$) (Figure 6A). The funnel plot did not identify bias (Figure 6B).

Meta-analysis of the effect of VD supplementation on VD status

To explore the effect of VD supplementation on 25(OH)D levels during the subjects' full stay in Antarctica, we analysed data from five experimental studies that included 11 different supplementation groups with varying dosing regimens. Daily VD doses were used in 4 studies, weekly dosing in one arm of one study, and monthly or bi-monthly supplementation in another study (Table 2). Groups were supplemented with different doses of oral VD treatment with a median daily dose of 1000 IU (range 100–2000 IU) and a median duration of supplementation of 180 days (range 22 – up to 365). Four studies included daily VD doses including 100, 125, 400, 1000, and 2000 IU. Also, one study had a VD dose of 10,000 IU weekly and one study supplemented their groups with 50,000 IU of VD monthly, every two months, or a single-dose pre-departure. Before supplementation, the VD level was 49.0 ± 8.7 nmol/L. Thus, VD supplementation increased 25(OH)D level with a significant increase of the mean 25(OH)D of 10.83 nmol/L (95% CI: 3.3, 18.3; $P < 0.0001$). The result from the inconsistency test showed that

there was high heterogeneity between the studies analysed ($\text{Chi}^2 = 84.0$, $\text{df} = 10$, $P < 0.0001$; $I^2 = 88\%$) (Figure 7A). The Funnel plot shape suggests that the meta-analysis did not have any publication bias (Figure 7B).

Discussion

We conducted a systematic review and meta-analysis to evaluate all available research evidence regarding the impact of residence in Antarctica on VD status and the effect of oral VD supplementation on this population. Our results demonstrate Antarctic residence's adverse effect on VD status, particularly among groups of subjects with an extended and overwintering residence. Nevertheless, serum 25(OH)D analyses also showed that change in 25(OH)D during Antarctic summers produced a mild non-significant reduction in VD levels, which is probably not clinically significant. Finally, VD supplementation improved VD status and is a likely effective intervention to prevent VD deficiency and worsening of VD status in people travelling to or residing in Antarctica.

Multiple factors affect the cutaneous synthesis of vitamin D, of which the most prominent is bare skin exposure to sunlight. The amount of sun exposure

Table 1. Summary of findings. Characteristics of studies included in the systematic review and meta-analysis involved in 25(OH)D status.

First author	Publication year	Antarctic base	Latitude (S)	Enrolment year	Country	Study type	Age (mean±SD or range) (years)	Follow-up length (estimated days)	25(OH)D measurement techniques	Number of study subjects	Sex (no. male/female)	BW or BMI (mean ± SD or/and range)	Main conclusions
Fairney, A.	1979	Halley Bay	75° 31'	Data not reported	UK	Prospective	21–39	Up to 456	Competitive binding protein assay	10	10/0	Data not reported	↓ 25(OH)D after an extended stay in Antarctica.
Lisbona, A.	1992	Juan Carlos I	62° 39'	1988–1989	Spain	Controlled trial	28–45	22	Competitive protein binding assay	11	11/0	Data not reported	↓ 25(OH)D after a very short residence in Antarctica.
Wilske, J.	1993	Aurora expedition to Filchner Ice Shelf	75° 00'	1991–1992	Uruguay	Prospective	Data not reported	90	Data not reported	4	Data not reported	Data not reported	Data not reported
↑ 25(OH)D after summer													
Oliveri, MB.	1994	Belgrano II San Martin	77° 52' 68° 07'	1990–1991	Argentina	Prospective	32 ± 4	365	Competitive protein binding assay	9	9/0	Data not reported	↓ 25(OH)D and did not increase even at the onset of summer.
Pitson, G.	1996	Davis	68° 34'	1991	Australia	Prospective	33 ± 6	273	Competitive protein binding assay	19	19/0	81 (66–97) Kg	↓ 25(OH)D for each of the latter three sampling periods.
Yonei, T.	1999	Syowa	69° 00'	1995	Japan	Prospective	35 ± 7	365	Competitive protein binding assay	31	31/0	66.0 ± 6.3 (57–80) Kg	↓ 25(OH)D after an extended stay in Antarctica.
Oliveri, MB.	1999	Belgrano II	77° 52'	1992	Argentina	Prospective	30 ± 5*	365–425	Competitive protein binding assay	10	10/0	24.6 ± 2.3 (kg/m ²)	↓ 25(OH)D in autumn and winter and recovered the initial level by the end of the campaign.
Luliano-Burns, S.	2009	Casey Mawson Davis Macquarie Island (sub-antarctic station)	66° 16' 67° 35' 68° 57' 54° 30'	2004–2006	Australia	Prospective	40 ± 11	365	Chemiluminescent immunoassay	120	101/19	27 (kg/m ²)	Staying in the white continent produces vitamin D insufficiency for volunteers with vitamin D sufficiency at baseline (>50 nmol/L), unless baseline values were >100 nmol/L.

(Continued)

Table 1. (Continued).

First author	Publication year	Antarctic base	Latitude (S)	Enrolment year	Country	Study type	Age (mean±SD or range) (years)	Follow-up length (estimated days)	25(OH)D measurement techniques	Number of study subjects	Sex (no. male/female)	BW or BMI (mean ± SD or/and range)	Main conclusions
Premkumar, M.	2013	Maitri base	70° 45'	2010–2011	India	Prospective	39 ± 10	365	Radioimmunoassay	20	20/0	Data not reported	↓ 25(OH)D after an extended stay in Antarctica. Low dietary intake reduces serum 25(OH)D levels.
Steinach, M.	2015	Neumayer II and III	70° 65'	2007–2012	Germany	Prospective	37 ± 91	395	ELISA	17	11/6	24.8 ± 3.3 (kg/m ²)	↓ 25(OH)D unaffected by age, gender, baseline fat mass, and station residence

*Mean of 17 volunteers, but 25(OH)D was assessed only in 10 volunteers. SD = standard deviation; BW = Body Weight; BMI = Body mass index.



Table 2. Summary of findings of studies evaluating the effect of VD supplementation on VD status.

First author	Publication year	Antarctic base	Latitude (S)	Intervention dates	Age (mean±SD or range)	Country	Study type	Intervention	Number of study subjects	Sex (no. male/female)	BW or BMI (mean ± SD or/and range)	Follow-up length (estimated days)	25(OH)D measurement	Main conclusions
Lisbona, A.	1992	Juan Carlos I	62° 39'	1988–1989	28–49	Spain	Controlled oral VD3 supplement entation	1,000 IU daily vs no intervention	7–11 per study arm	11/0	Data not reported	22	Competitive protein binding assay	VD3 oral supplementation did not increase serum 25(OH)D level significantly. After a decrease in 25(OH)D serum level during a 5-month residency in Antarctica, oral supplementation with VD during at least six months allows a recovery to the baseline level of 25(OH)D. Five months after supplementation started, 25(OH)D increased in all supplemented groups.
Oliveri, MB.	1999	Belgrano II	77° 52'	May 1992 to January 1993	30 ± 5*	Argentina	Open-label oral VD supplementation	(1) average 100 IU daily during May and approximately 125 IU daily from July to January	10	10/0	24.6 ± 2.3 (kg/m ²)	210	Competitive protein binding assay	Doses administered increased vitamin D level, and efficacy was influenced by baseline vitamin D status and BMI. 25(OH)D level can be maintained at sufficiency status with an oral dose of 50,000 IU at least every alternate month during residence in Antarctica.
Smith, S.	2009	McMurdo	77° 51'	March to August 2007	(1) 42 ± 12 (2) 44 ± 12 (3) 43 ± 12	USA	Randomised double-blind oral VD3 supplementation	(1) 2,000 IU daily (2) 1,000 IU daily (3) 400 IU daily	(1) 18 (2) 19 (3) 18	41/14	(1) 28 ± 6 (2) 31 ± 7 (3) 29 ± 6 (kg/m ²)	150	Radioimmunoassay	
Zwart, S.	2011	McMurdo	77° 51'	February to September 2009	(1) 37 ± 10 (2) 45 ± 10	USA	Controlled oral VD3 supplementation	2,000 IU daily or 10,000 IU weekly	(1) 15 (2) 14	(1) 9/6 (2) 12/2	(1) 28 ± 4 (2) 29 ± 4 (kg/m ²)	180	Radioimmunoassay	
Iuliano-Burns, S.	2012	Casey, Mawson, Davis, Macquarie Island	66° 16' 67° 35' 68° 57' 54° 30'	Summer 2007 to Summer 2008 or Summer 2008 to 2009	(1) 42 ± 11 (2) 40 ± 11 (3) 43 ± 12		Randomised double-blind oral VD3 supplementation	(1) 50,000 IU monthly, (2) 50,000 IU every two months and placebo on alternate months, (3) 50,000 IU single dose pre-departure and monthly placebo thereafter	(1) 37 (2) 38 (3) 35	(1) 31/6 (2) 27/9 (3) 31/7 (3) 32/3	(1) 23.7 (2) 27.2 (3) 27.9 (kg/m ²)	Up to 365	Electrochemiluminescence immunoassay	

*Mean of 17 volunteers, but 25(OH)D was assessed only in 10 volunteers; IU = international units; SD = standard deviation; VD3 = vitamin D3; BMI = Body mass index; BW = Body Weight

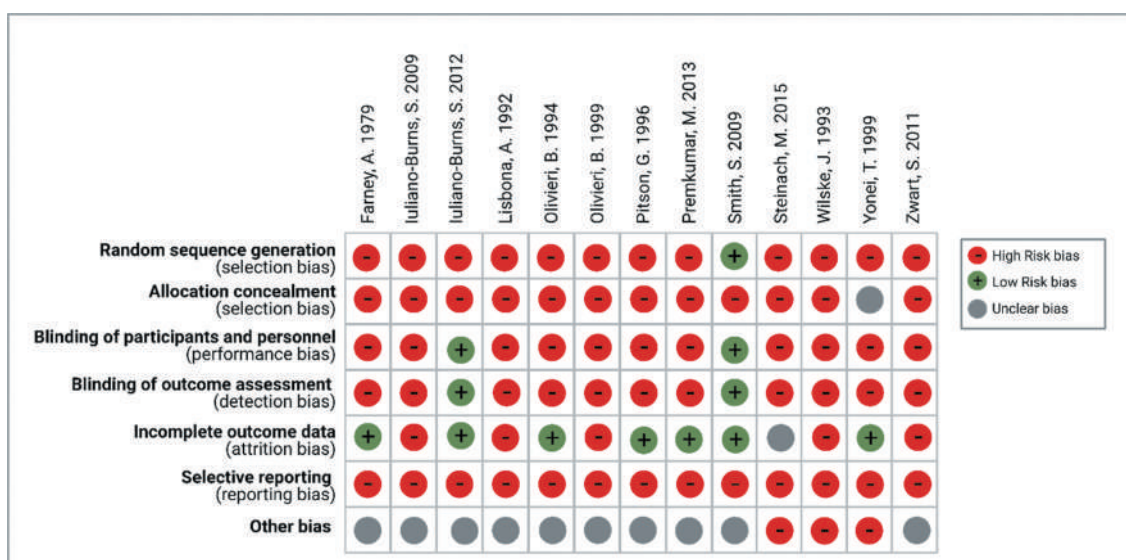


Figure 3. Assessment of risk of bias in included studies.

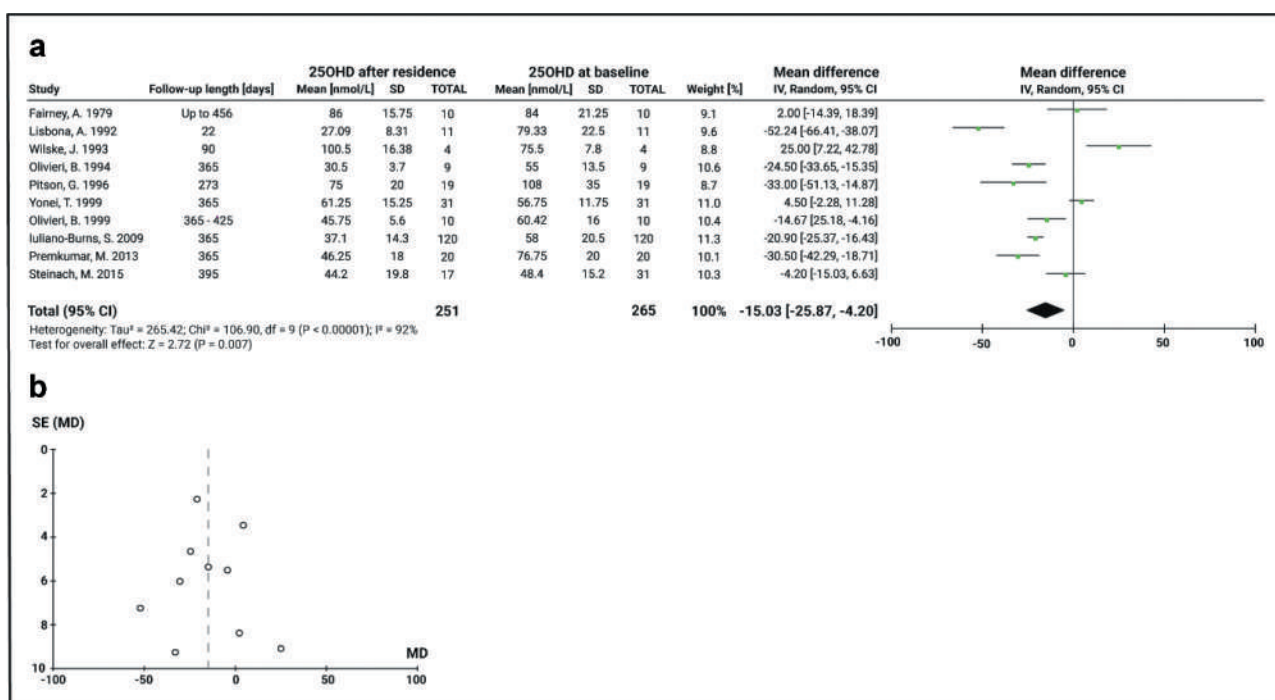


Figure 4. Meta-analysis of 25(OH)D serum change pre- and post- Antarctic residence in non-supplemented subjects. A) Mean difference forest plot of 25(OH)D. The mean differences were calculated based on 25(OH)D serum level at baseline and after a completed stay on the Antarctic or sub-Antarctic bases. The studies of Lisbona, A. 1992 and Luliano-Burns, S. 2012 are included only with the non-interventional group. Values represent the mean effect sizes within a study. B) Funnel plot for publication bias. SE: Standard error of the mean difference.

required to produce sufficient vitamin D levels varies by season, time of the day, and latitude [40]. Previous reports evaluate the association among VD deficiency in populations living in high latitudes due to high solar angles that reduce UVB radiation and climate conditions that the residents oblige to spend more time

indoors. Several studies about seasonal variation analyses demonstrated that serum 25(OH)D levels were lower in winter than in summer in high latitudes [41,42]. Besides, cloudy days and cold climates are associated with higher photoprotection by body clothing coverage, which is related to a lack of sun exposure

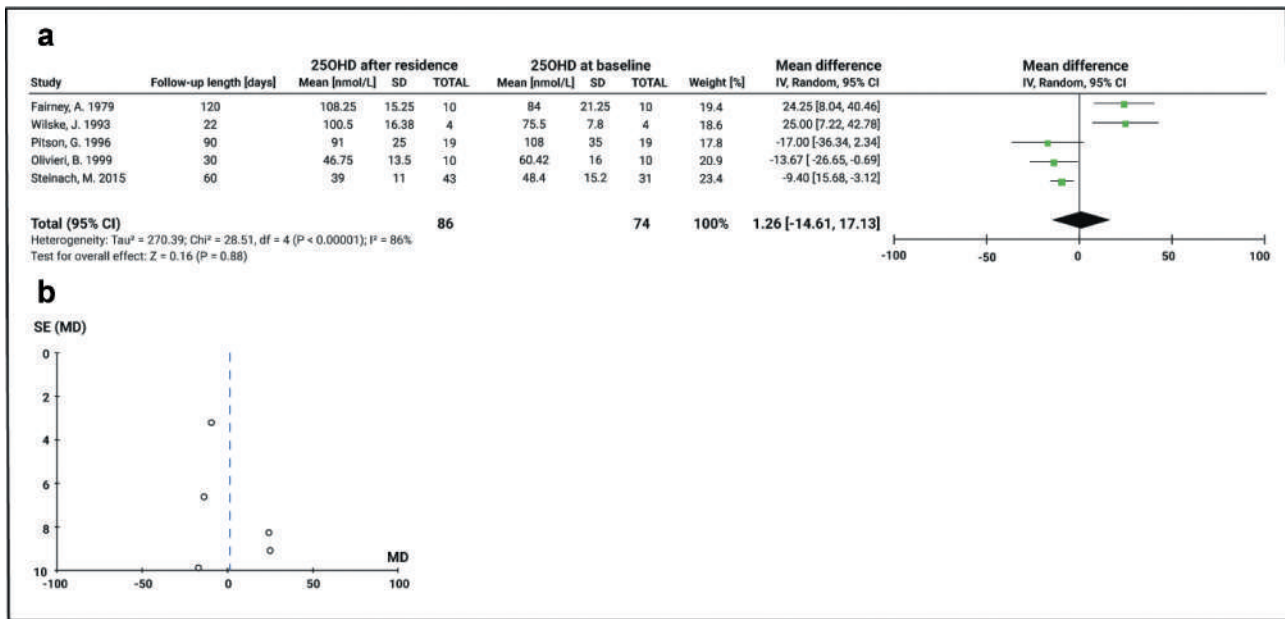


Figure 5. Comparison of 25(OH)D before and after a summer stay in Antarctica in subjects not receiving vitamin D supplementation. A) Mean difference forest plot of 25(OH)D. The mean differences were calculated based on 25(OH)D serum level at baseline and after at least 22 days of stay among December and February. Values represent the mean effect sizes within a study. B) Funnel plot for publication bias. SE: Standard error of the mean difference.

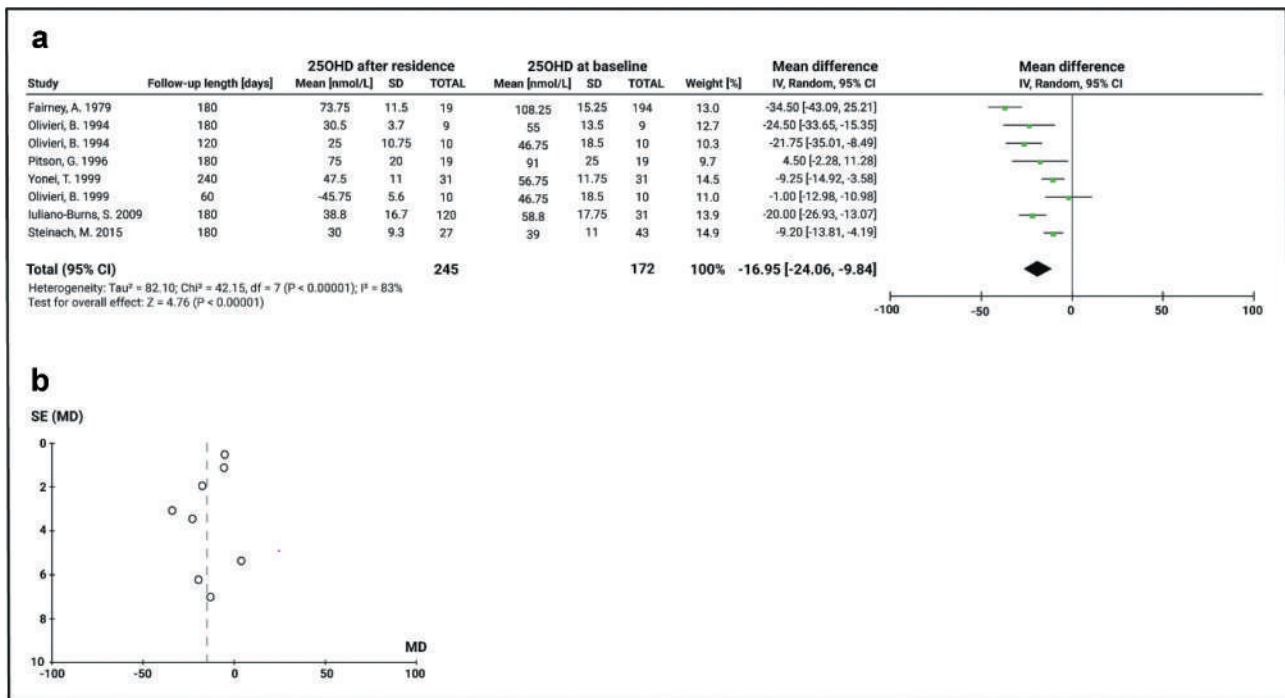


Figure 6. Comparison of 25(OH)D before and after overwintering in Antarctica in subjects not receiving vitamin D supplementation. A) Mean difference forest plot of 25(OH)D. The mean differences were calculated based on 25(OH)D serum level at baseline and after a residence between March and September. Values represent the mean effect sizes within a study. B) Funnel plot for publication bias. SE: Standard error of the mean difference.

[43]. Moreover, the concern about the effects of stratospheric ozone depletion – that is higher in the south pole – has contributed to increase overuse of solar

protection factor (SPF), which alters the incidence of UV radiation on the skin and might decrease VD production [44]. However, the daily SPF use in an adequate

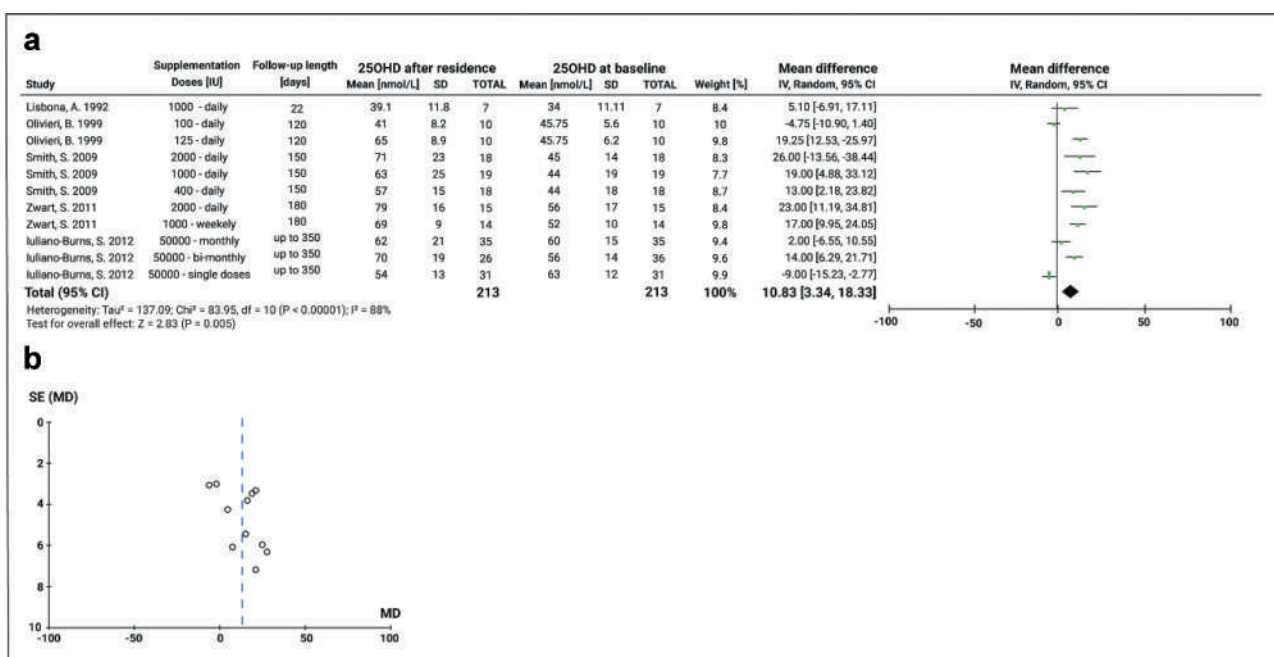


Figure 7. Meta-analysis of the effect of VD supplementation on serum 25(OH)D concentrations during Antarctic residence. A) Mean difference forest plot of the effect of VD supplementation. The mean differences were calculated based on 25(OH)D serum level at baseline and after Antarctic residence in the supplemented groups. Values represent the mean effect sizes within a study. B) Funnel plot for publication bias. SE: Standard error of the mean difference.

dose does not necessarily compromise VD synthesis [45]. Considering this, Antarctica is an ideal ambient to test the association between sun exposure and the risk of generating VD deficiency. Hence, our report is consistent with the previous investigations that concluded an association of living in sun deprivation and worse VD status, highly probably due to factors previously mentioned.

This article is the first report that systematically summarises the sparse literature about the adverse effects of residence in Antarctica on VD status of its transient population. We included the most articles published in order to add strength to our study. However, few data are reported about VD status and stays in Antarctica and even less research with VD supplementation treatment. Despite this limitation, the meta-analysis about completed and winter-stays shows a strong significance and without observable publication bias favouring the association between worsen VD level and sun deprivation in the white continent.

The meta-analyses performed in this review show high heterogeneity due to large clinical variability among studies. The main differences are related to the populations' characteristics involving different baseline VD status, which might differentially change the effect of lack of sunlight exposure on the studies' participants. Regarding the 25(OH)D at baseline, higher baseline VD serum concentrations might protect from

subsequent deficiencies after completing extended stays in Antarctica [30,32,36]. Likewise, deficient and insufficient VD levels might be unfavourable conditions to worsen VD status after living in Antarctica. However, the reported evidence is not enough to get a significant conclusion in a subgroup analysis according to baseline status.

Possible explanations of why summer stays in Antarctica did not significantly affect 25(OH)D levels probably include the higher solar radiation that is proper of this season and the formation of the ozone layer hole every austral spring. UV radiation reaching the surface in the Antarctic summer is highly variable, and UV index in spring and summer may be comparable to that of northern European countries in this same season [46]. This it is possible that summer Antarctic inhabitants from high latitude countries are not affected by a significant change in UV exposure. However, the results of our meta-analysis of 25(OH)D change in summer could also be influenced by the small number of reported investigations, the small size of the studies, and differences in their design. Moreover, the visual analysis of publication bias supports scarcity of information and potential methodological issues. The largest study evaluating change in VD status in summer showed a worsening 25(OH)D concentration after a summer residence in those with VD deficiency [37], dropping from 48.4 ± 15.0 nmol/L to

39.0 ± 10.8 nmol/L in subjects evaluated in January (n = 31) and March (n = 43) of 2007 to 2012. Noteworthy, from January to March VD deficiency increased from 3.2% to 14% in this report. Given the large sample size and the multiple measurements presented in this study, it could be considered strong support to investigate, with the right study design, how seasons and baseline status of populations impact VD status during Antarctic residence and to test the hypothesis of whether a summer residence affects VD status as well.

To prevent the worsening of VD status that is generated by living in Antarctica, oral VD supplementation is an easy, low cost, and effective intervention for this population. Our meta-analysis supports the intervention in people who reside in Antarctica and receive treatment for at least 120 days especially in subjects with low baseline 25(OH)D levels. VD dosing and frequency determine the impact of VD supplementation. Our study did not compare the effect of different doses or dosing regimens in Antarctic population. The optimal dose and frequency of supplementation remain unclear, as the few supplementation studies evaluated are too heterogenous to provide an universally applicable recommendation on VD dosing and frequency for Antarctic inhabitants. Thus, despite the significant result of the meta-analysis regarding the effect of VD supplementation during Antarctic residence, more interventional clinical trials appear necessary. Another alternative to improve VD status of Antarctic residents is increasing their intake of VD-rich foods (i.e. oily fish) or preferentially importing VD-fortified foods to Antarctic bases. Our research did not include the dietary assessments of VD intake because these are not systematically reported in the reviewed studies. Further research on Antarctic residents' diet also seems necessary to address this issue.

Conclusions

This meta-analysis shows that VD status significantly worsens after residence in Antarctica, particularly when over-wintering. Our findings also suggest that supplementation with VD is beneficial to humans in Antarctica by improving VD status and suggests it may be necessary for expeditions to this continent and other places with limited access to UVB light. Besides oral VD supplementation, another strategy that might be considered for preventing VD deficiency in this population, is incorporating VD food fortification to products brought to Antarctica. Likewise, people that will move to this continent might be advised to reach a sufficiency level of 25(OH)D before departure

to avoid unhealthy risk consequences related to VD deficiency. Future studies are needed to clarify the effect of living in Antarctica during summer on VD status, optimal dosing and frequency of VD supplementation, the efficacy of VD treatment related to the length of stay, and the impact of Antarctic residence on the risk of developing VD deficiency-associated conditions.

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