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Review

The Impact of UV-dose, Body Surface Area Exposed and Other Factors on Cutaneous Vitamin D Synthesis Measured as Serum 25(OH)D Concentration: Systematic Review and Meta-analysis

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Abstract. *Background/Aim: To optimize public health campaigns concerning UV exposure, it is important to characterize factors that influence UV-induced cutaneous vitamin D production. This systematic review and meta-analysis investigated the impact of different individual and environmental factors including exposed body surface area (BSA), UVB dose and vitamin D status, on serum 25(OH)D concentration. Materials and Methods: In accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses, and Meta-analysis of Observational studies in Epidemiology guidelines, a systematic literature search was conducted (MEDLINE; 01/1960-07/2016) investigating the impact of these factors on vitamin D status after artificial UV exposure as main outcome measure. Summary mean differences [and 95% confidence interval (CI)] were derived from random-effects meta-analysis to account for possible heterogeneity across studies. Meta-regression was conducted to account for impact of UVB dose, baseline 25(OH)D level and BSA. Results: We identified 15 studies, with an estimated mean 25(OH)D rise per standard erythema dose (SED) of 0.19 nmol/l (95% CI 0.11-0.26 nmol/l). Results from meta-regression suggest a significant impact of UV dose and baseline 25(OH)D concentration on serum 25(OH)D level ($p<0.01$). Single UVB doses between 0.75 and 3 SED resulted in the highest rise of serum 25(OH)D per dose unit. BSA exposed had a smaller, non-proportional, not significant impact. Partial BSA exposure resulted in relatively higher rise compared to whole-body exposure (e.g. exposure of face and hands caused an 8-fold higher rise of serum 25(OH)D concentration/SED/1% BSA compared to whole-body exposure). Our findings support previous reports, estimating that the half-life of serum 25(OH)D varies depending on different factors. Conclusion: Our results indicate that partial BSA exposure (e.g. 10%) with moderate UV doses (e.g. 1 SED) is effective in generating or maintaining a healthy vitamin D status. However, due to limitations that include possible confounding factors such as skin type, which could not be considered, these findings should be interpreted with caution.*

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Although oral vitamin D supplements are easily available, pandemic vitamin D deficiency causes serious health problems worldwide that are still widely under-recognized (1-3). It has been estimated that at present, approximately one billion people are vitamin D-deficient or-insufficient (1). Vitamin D deficiency has not only been associated with problems for bone and muscle function, but also with an increased incidence of and unfavourable outcome for a broad variety of independent acute and chronic diseases including various types of malignancies (*e.g.* colon, skin, and breast cancer), diabetes, autoimmune, infectious, neurocognitive and cardio-vascular diseases (1-3). A recent meta-analysis provided evidence that higher levels of vitamin D are protective against non-melanoma skin cancer [summary relative risk of 1.64 (95% confidence interval (CI)=1.02-2.65) for highest *versus* lowest levels] (4). Clinical and laboratory investigations have demonstrated that vitamin D compounds exert antiproliferative

effects and modulate cell growth and development in many tissues (1). Moreover, vitamin D compounds mediate potent immunomodulatory effects and have been found to be protective against many autoimmune and inflammatory diseases, including those of the central nervous system (1). A recent meta-analysis indicated that vitamin D supplementation prevents respiratory tract infections (5). In pregnancy, a reduced risk of preterm delivery was associated with vitamin D supplementation (6, 7) as well as of asthma and wheezing in children born to mother's with adequate vitamin D intake during pregnancy (8).

It is generally accepted that the best way to assess a person's vitamin D status is measuring the serum 25-hydroxyvitamin D [25(OH)D] concentration (1). Although there is no consensus on the optimal level of circulating 25(OH)D, vitamin D deficiency is defined by most experts as a serum 25(OH)D concentration less than 50 nmol/l (1), with serum concentrations less than 20-25 nmol/l being indicative of severe vitamin D deficiency, which results in rickets and histologically evident osteomalacia. Serum concentrations of 25(OH)D of 50-75 nmol/l and of 75 nmol/l or greater have been reported to indicate a relative insufficiency of vitamin D, and sufficient vitamin D, respectively (1). Vitamin D intoxication has been observed exclusively in otherwise healthy individuals when the serum level of 25(OH)D was greater than 374 nmol/l. These definitions of vitamin D deficiency/sufficiency consider epidemiological, clinical and laboratory investigations. Interestingly, it has been shown that the serum levels of 25(OH)D and parathyroid hormone are inversely associated until the serum level of 25(OH)D reaches 75 to 100 nmol/l (1), a point at which the parathyroid hormone level begins to plateau (at its nadir). Furthermore, intestinal calcium transport has been reported to be increased by 45 to 65% in women when the serum 25(OH)D concentration was elevated from an average of 50-80 nmol/l (1).

Under most living conditions in Europe and North America, up to 90% of the body's requirement of vitamin D has to be fulfilled by the ultraviolet (UV)-induced cutaneous synthesis of this prohormone (1). While UVB has been identified as the UV spectrum required for the induction of vitamin D synthesis in the skin (1), little is known about the impact of different individual and environmental factors including exposed body surface area (BSA), UVB dose and vitamin D status on cutaneous vitamin D production. It was the aim of this systematic review and meta-analysis to evaluate the present knowledge on this topic, in particular by investigating the impact of individual and environmental factors including BSA exposed, UVB dose and vitamin D status on cutaneous vitamin D production, measured as serum 25(OH)D concentration. Additionally, we aimed to estimate the half-life of serum 25(OH)D in the studies that we identified.

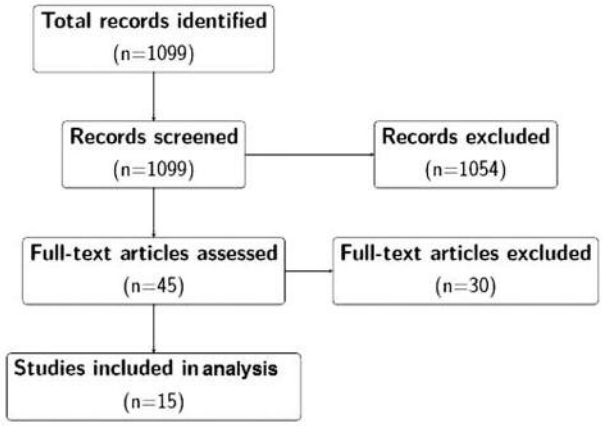

Figure 1. *Flow chart of our literature search process that identified 15 papers [(11-25); 829 participants] published in the past 7 years, that were eligible for meta-analysis.*

Materials and Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses, and the Meta-analysis of Observational studies in Epidemiology guidelines (9, 10).

Search strategy, inclusion/exclusion criteria and outcome measures. A systematic literature search was conducted using MEDLINE (01/1960-07/2016) and cross-referenced studies to investigate the impact of exposure to artificial UV sources on vitamin D status. The following search terms were used (alone and in combination): *UV*, *UV radiation, UVB, ultraviolet, ultraviolet radiation, SED, Standard Erythema Dose, vitamin D, vitamin D_3, vitamin D increase, 25(OH)D_3, 25-hydroxyvitamin D*, and *25-hydroxycholecalciferol*. Article inclusion criteria included: randomized controlled trials (RCTs) and observational studies (OS) that analysed serum 25(OH)D concentration and reported mean values, were performed during wintertime and where UV exposure was reported as SED. Studies that included individuals that were younger than 18 years, or that had taken vitamin D supplements, photosensitizing or cholesterol-lowering medications, or had been on vacation in sunny countries within 3 months prior to the study were excluded. Relevant parameters extracted included the serum 25(OH)D level before and after exposure, time of exposure, UV source, UV dose (in SED), exposed body surface area (BSA), number of individuals included, age and gender.

The main outcome measure was the change in serum 25(OH)D concentration [Δ25(OH)D] after artificial UV exposure.

Statistical analysis. Summary mean differences and 95% CI were derived from random-effects meta-analysis to account for possible heterogeneity across studies. Furthermore, meta-regression was conducted to account for dose (in SED), baseline (initial) level of serum 25(OH)D concentration and BSA exposed. One unit of SED is equivalent to an erythemal effective radiant exposure of 100 J/m^2, whereas the ambient diurnal exposure on a clear summer day in Europe is approximately 30-40 SED (29). Note that some relevant features such as age, body mass index or skin type could not be considered because

Table I. *Characteristics of included studies (n=15), in abecedarian order.*

Study (Ref. no.)	Type of study	Time of intervention	Latitude	Country	No. of participants
Ala-Houhala *et al*. (11)	OS	12/2010-03/2011	61˚N	Finland	33
Biersack *et al*. (12)	OS	10/ 2011-03/2012	52˚N	Germany	20
Bogh *et al*. (13)	RCT	02-03/2008 02-03/2009	56˚N	Denmark	92
Bogh *et al*. (14)	RCT	01-03/2008	56˚N	Denmark	55
Bogh *et al*. (15)	OS	01-03/2008	56˚N	Denmark	96
Bogh *et al*. (16)	RCT	10/2008-02/2009	56˚N	Denmark	55
Chel *et al*. (17)	OS	Not given	52˚N	The Netherlands	8
Datta *et al*. (18)	OS	03-04/2011 02/2012	56˚N	Denmark	29
Karppinen *et al*. (19)	RCT	10/2013-03/2014	61˚N	Finland	34
Lagunova *et al*. (20)	RCT	12/2007-02/2008	59˚N	Norway	11
McKenzie *et al*. (21)	RCT	Winter 2006 and 2007	37˚S	New Zealand	119
Rhodes *et al*. (22)	OS	01-02/2006 01-02/2007	53.3˚N	UK	109
Sallender *et al*. (23)	RCT	12/2011-03/2012	59˚N	Sweden	75
Vähävihu *et al*. (25)	OS	12-03/2004 12-03/2005 12-03/2006	67˚N	Finland	42
Vähävihu *et al*. (24)	OS	01-03/2008 01-03/2009	61˚N	Finland	51

RCT: Randomized controlled trial; OS: observational study; N: north; S: south.

Table II. *Impact of UVB exposure (dose) on vitamin D status [serum 25(OH)D concentration]. Exposure to single UVB doses of 0.75 and 3 standard erythema dose (SED) resulted in a smaller increase of serum 25(OH)D concentration per dose unit compared to exposure with single UVB doses of 1.5 SED. This indicates that UVB exposure with single doses between 0.75 and 3 SED may result in the highest increase in serum 25(OH)D per dose unit.*

Study ref. no.	Single dose (SED)	Total dose (SED)	BSA (%)	Δ25(OH)D (nmol/l)	Δ25(OH)D/SED	Δ25(OH)D/SED/%BSA
13+18	0.75	3	6	6.63	2.21	0.37
13+18	1.5	6	6	16.24	2.7	0.45
13	3	12	6	29.4	2.45	0.41

SED: Standard erythema dose; BSA: Body surface area.

information was missing, incomplete or not comparable. All analyses were performed using the metafor-package in R version 3.2.4 and StatsDirect (StatsDirect Ltd. Statistical Software, UK).

Results

A flow-chart of our literature search process is shown in Figure 1. We identified 15 articles (11-25) published in the past 7 years that were eligible for our meta-analysis. Characteristics of the included studies (n=15, 829 participants) are shown in Table I.

Results from the meta-regression suggest a statistically significant impact of UV dose and baseline serum 25(OH)D concentration on UVB-induced changes of serum 25(OH)D level ($p<0.01$). The mean increase of serum 25(OH)D concentration per single SED applied was estimated to be 0.19 nmol/l (95% CI=0.11-0.26 nmol/l), under these investigative conditions. Our study indicates that single UVB doses between 0.75 and 3 SED are very effective in inducing cutaneous vitamin D synthesis and may result in the highest increase in serum 25(OH)D per dose unit (Table II). Exposure to single UVB doses of 0.75 and 3 SED resulted in a smaller increase of serum 25(OH)D concentration per dose unit compared to exposure with a single UVB dose of 1.5 SED.

Exposed BSA was not statistically significantly associated with UVB-induced change of serum 25(OH)D concentration (Table III), nor was the increase in serum 25(OH)D concentration proportional to the BSA exposed. Partial exposure of the body surface resulted in relatively higher increase of serum 25(OH)D concentration per SED and 1%

Table III. *Impact of UVB-exposed body surface area (BSA) on vitamin D status [serum 25(OH)D concentration]. The UVB-induced increase in serum 25(OH)D concentration was not proportional to the amount of exposed body surface. Partial exposure of the body surface resulted in relatively higher increase of serum 25(OH)D concentration per unit SED and percent BSA compared to exposure of the whole bod, e.g. exposure of face and hands resulted in an 8-fold higher increase in Δ25(OH)D/SED/% BSA compared to whole-body irradiation.*

Study ref. no.	UV source	Total dose (SED)	BSA (%)	Δ25(OH)D (nmol/l)	Δ25(OH)D/SED (nmol/l/SED)	Δ25(OH)D/SED/% BSA (nmol/l SED/% BSA)
13+18	BB-UVB	3	6	6.63	2.21	0.37
13+14	BB-UVB	3	24	20.13	6.71	0.28
12	BB-UVB	3.5	90	13.9	3.97	0.04
25	NB-UVB	13	6	4	0.31	0.05
25	NB-UVB	13	29	11	0.85	0.03
25	NB-UVB	13	100	11.4	0.88	0.009

BB-UVB: Broadband-UVB; NB-UVB: narrowband-UVB (311 nm); SED: standard erythema dose.

Table IV. *Impact of serum 25(OH)D concentration at the time of UVB exposure (baseline) on change in serum 25(OH)D concentration. The baseline serum 25(OH)D concentration is crucial for UVB-induced increase of serum 25(OH)D concentration. The lower the baseline, the greater the increase of serum 25(OH)D concentration after irradiation.*

Study ref. no.	Total dose (SED)	BSA (%)	Baseline 25(OH)D (nmol/l)	Δ25(OH)D (nmol/l)	Δ25(OH)D/SED (nmol/l/SED)	Δ25(OH)D/SED/% BSA (nmol/l/SED/% BSA)
15	12	24	21.3	26.9	2.24	0.093
15	12	24	27.8	25.3	2.1	0.088
14	12	24	31.2	23.9	1.99	0.082
15	12	24	36.5	23.3	1.94	0.080
22	23.4	35	44	26	1.11	0.032
16	12	88	71.9	4.4	0.37	0.004

BSA: Body surface area; SED: standard erythema dose; ΔH-25(OH)D: change in serum 25(OH)D concentration; Δ25(OH)D/SED change in serum 25(OH)D concentration per 1 SED; Δ25(OH)D / SED /% BSA: change in serum 25(OH)D concentration per 1 SED and 1% BSA.

BSA exposed as compared to the whole body, *e.g.* exposure of the face and hands resulted in an 8-fold higher increase in Δ25(OH)D/SED/1% BSA as compared to whole-body irradiation. Notably, our findings demonstrate that the baseline serum 25(OH)D concentration is crucial (Table IV). The lower the baseline, the greater was the increase of serum 25(OH)D concentration after irradiation (Table V).

To gain further insight into the impact of individual factors on vitamin D status, we generated the following formula from meta-regression that enables estimation of the resulting exposure-induced change in serum 25(OH)D concentration [E(Δ25(OH)D)] when the UV dose applied, BSA exposed, and baseline serum 25(OH)D concentration are known:

$$E(\Delta 25(OH)D) = 30.18 + 0.19 \times (\text{UV dose in SED}) - 0.39 \times (\text{baseline serum 25(OH)D concentration}) + 0.05 \times (\text{BSA exposed})$$

As an example of use of this formula, the expected change in serum 25(OH)D concentration in an individual with a baseline serum 25(OH)D concentration of 50 nmol/l, following exposure of 10% BSA to a UVB dose of 1 SED can be estimated as 15.87 nmol/l (Table VI). Estimations that were calculated using this formula underline the relevance of UV dose, BSA exposed, and baseline serum 25(OH)D

Table V. *Spontaneous change in serum 25(OH)D concentration during wintertime. Analysis of non-UV-treated control groups revealed that serum 25(OH)D concentration on average decreased by 0.39 nmol/l per day in these participants. Our findings support previous reports estimating that the half-life of serum 25(OH)D varies depending on different factors, including baseline serum 25(OH)D concentration, but can be assumed to be under distinct circumstances (16) at least about two months.*

Study ref. no.	Baseline 25(OH)D (nmol/l)	Study period (days/weeks)	Δ25(OH)D (nmol/l)	Δ25(OH)D/day (nmol/l/day)
23	39.6	14/2	−1.42	−0.12
16	64.8	112/16	−24.7	−0.22
16	34.2	56/8	−30.6	−0.55
19	76.8	168/24	−11.1	−0.07

Table VI. *Estimated impact of dose, baseline serum 25(OH)D concentration and body surface area exposed (BSA) on UV-induced change in serum 25(OH)D.*

			Baseline 25(OH)D (nmol/l)	
	BSA exposed	SED	50 nmol/l	100 nmol/l
EΔ25(OH)D (nmol/l)	100%	1	15.87	–3.63
	100%	3	16.25	–3.25
EΔ25(OH)D/SED (nmol/l)	100%	1	15.87	–3.63
	100%	3	5.42	–1.08
EΔ25(OH)D/10 nmol/l baseline 25(OH)D nmol/l	100%	1	3.17	–0.36
	100%	3	3.25	–0.33
EΔ25(OH)D (nmol/l)	10%	1	11.37	–8.13
	100%	1	15.87	–3.63
EΔ25(OH)D/1% BSA (nmol/l)	10%	1	1.14	–0.81
	100%	1	0.16	–0.04
EΔ25(OH)D/10 nmol/l baseline 25(OH)D nmol/l	10%	1	2.27	–0.81
	100%	1	3.17	–0.36
EΔ25(OH)D (nmol/l)	10%	1	11.37	–8.13
	100%	1	15.87	–3.63
	10%	3	11.75	
	100%	3	16.25	
EΔ25(OH)D/SED (nmol/l)	10%	1	11.37	–8.13
	100%	1	15.87	–3.63
	10%	3	3.92	
	100%	3	5.42	
EΔ25(OH)D/10% BSA (nmol/l)	10%	1	11.37	
	100%	1	1.59	
	10%	3	11.75	
	100%	3	1.63	

SED: Standard erythema dose. Estimations were calculated using the formula: Expected (E)Δ25(OH)D=30.18+0.19× (UV dose in SED) – 0.39× (baseline serum 25(OH)D concentration) + 0.05× (BSA exposed).

concentration for UV-induced changes in serum 25(OH)D concentration (Table VI).

Finally, analysis of non-UV-treated control groups revealed that serum 25(OH)D concentration on average decreased per day in these participants by 0.39 nmol/l, supporting previous reports, estimating that under distinct conditions the half-life of serum 25(OH)D can be assumed to be at least about 2 months.

Discussion

The results of this meta-analysis and systematic review are in agreement with previous reports demonstrating the relevance of different environmental and individual factors on UVB-induced cutaneous synthesis of vitamin D, and the resulting serum 25(OH)D concentration (13, 14, 18, 21, 26-28).

Under the investigative conditions of the studies analysed in this meta-analysis, the baseline (initial) serum 25(OH)D concentration and UV dose had a statistically significant impact on the change of serum 25(OH)D level following exposure to artificial UVB-emitting devices. The exposed BSA had a smaller impact, which was not statistically significant. These results are well in line with findings reported previously in the literature [reviewed in (28)]. It has been demonstrated convincingly that in response to UV phototherapy, the absolute increase in serum 25(OH)D concentration is correlated inversely to the baseline serum 25(OH)D concentration [reviewed in (28)]. A study reported that the rise in serum 25(OH)D concentration in individuals with baseline 25(OH)D concentrations of less than 25 nmol/l was double that seen in individuals with baseline concentrations greater than 50 nmol/l (28, 30). Furthermore, it was shown that in individuals with baseline serum 25(OH)D concentrations less than 10 nmol/l, UV phototherapy elevated 25(OH)D by 30 nmol/l, but in those with baseline concentrations approaching 50 nmol/l, the rise was negligible (31). These previous findings highlight the significant impact of the baseline serum 25(OH)D concentration on the change of serum 25(OH)D level following exposure to artificial UVB-emitting devices. Our meta-analysis and estimations obtained using the formula we introduced in this study are well in line with these results.

In the report of Cicarma *et al*., 30-60% of the increase in serum 25(OH)D concentration following UVB exposure was estimated to depend on the UV dose (26). Moreover, results of a recent meta-analysis of 18 studies demonstrated a positive correlation between UV dose and increase in serum 25(OH)D concentration (27). However, the correlation between UVB dose applied and resulting change in serum 25(OH)D concentration is not linear. For example, Bogh *et al*. reported a relatively low increase in serum 25(OH)D concentration of 24.7 nmol/l following exposure of 24% BSA to a relatively high UVB dose of 12 SED (14), and Rhodes *et al*. reported a relatively low increase in serum 25(OH)D concentration of 26.0 nmol/l following exposure of 35% BSA to 23.4 SED (22). These findings are well in line with results of this meta-analysis and our estimations obtained using the formula above that we introduced in this study. A reason for this non-linear correlation between UVB dose applied and resulting change in serum 25(OH)D concentration may be that a saturation value is reached. Accordingly, results obtained from meta-regression should be interpreted with caution as a linear effect for UVB dose is generally assumed. This assumption will not be valid for specific thresholds in particular. It has been reported that UV exposure beyond the minimal erythemal dose does not increase serum 25(OH)D concentration further (28). Skin exposure to relatively high UV doses may induce a shift from vitamin D production to production of other biologically less active or inactive vitamin D metabolites, including tachysterol and lumisterol (1, 14, 27, 28). Moreover, the UV-induced synthesis of

vitamin D precursors is counterbalanced by degradation of vitamin D and its precursors [reviewed in (28)].

In conclusion, results of this meta-analysis are in agreement with the concept that partial BSA exposure (*e.g.* 10%) to moderate UV doses (*e.g.* 1 SED, note: the ambient diurnal exposure on a clear sky summer day in Europe is approximately 30-40 SED) is very effective in generating or maintaining a healthy vitamin D status (29). However, due to limitations that include other possible confounding factors, such as skin type, which could not be considered, these findings need to be confirmed and should be interpreted with caution. It has been shown that following UV exposure, the concentration of pre-vitamin D in skin reaches an equilibrium within 20 minutes (28). Interestingly, it has been reported that skin pigmentation does not affect the amount of vitamin D that can be produced by exposure to solar or artificial UV, although it may take 3-6 times longer for pigmented skin to reach the equilibrium concentration of dermal vitamin D [(37), reviewed in (28)]. 7-Dehydrocholesterol (7-DHC) is the substrate needed for cutaneous vitamin D production. Aging reduces the concentration of 7-DHC in skin, and substantially reduces the capacity for vitamin D production [reviewed in (28)].

Furthermore, our findings support previous reports, estimating that the half-life of serum 25(OH)D concentration varies depending on different factors, including baseline serum 25(OH)D concentration, but can be assumed to be under distinct circumstances at least about 2 months (28).

The effects of extensive UV exposure and of UV deprivation have been reviewed elsewhere (2, 28). Notably, exposure to solar or artificial UV has never been reported to induce vitamin D intoxication in healthy individuals. Serum 25(OH)D concentrations of people living or working in sun-rich environments have been published, reporting a farmer in Puerto Rico with a serum 25(OH)D concentration of 225 nmol/l, and three individuals with serum 25(OH)D concentrations >200 nmol/l in a study of 391 that excluded individuals taking calcium or vitamin D supplements. Analysing the effects of artificial UV light treatment sessions on 25(OH)D concentrations, individual 25(OH)D concentrations measured were up to 274 nmol/l (28, 32, 33). Many studies support the concept that one full-body exposure to sunlight can be equivalent to an oral vitamin D intake of at least 250 μg (10,000 IU) [reviewed in (2, 28)]. Holick presented data that compared blood vitamin D concentrations in individuals taking vitamin D orally with those given UV light exposure (34). Phototherapy produced blood vitamin D concentrations comparable with an intake of 250-625 μg (10000-25000 IU) vitamin D/day orally.

Concerning UV deprivation, a percentage decline in serum 25(OH)D concentration was demonstrated in an American submarine crew that was comparable with that of a British crew reported two decades earlier (35, 36). The decline in serum 25(OH)D concentration of 30 nmol/l over 2 months was despite "a standard US Navy diet which included milk and breakfast cereals fortified with vitamin D". The baseline mean 25(OH)D concentration was higher in the American crew than in the British, consistent with lower vitamin D supplies from diet and solar UV exposure in British.

Our results indicate that partial exposure of the skin (*e.g.* 10%) to moderate UV doses (*e.g.* 1 SED) is effective in generating or maintaining a healthy vitamin D status. However, due to limitations that include possible confounding factors such as skin type, which could not be considered, these findings should be interpreted with caution.

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