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ORIGINAL ARTICLE

Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis

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Abstract
Summary We performed a meta-analysis of cross-sectional studies on serum 25(OH)D status globally. Serum 25(OH)D levels on average were 54 nmol/l, were higher in women than men, and higher in Caucasians than in non-Caucasians. There was no trend in serum 25(OH)D level with latitude. Vitamin D deficiency was widespread.
Introduction We studied vitamin D status (expressed as serum 25-hydroxy-vitamin D [25(OH)D]) in native subjects worldwide.
Methods Meta-analysis and meta-regression of studies reporting on 25(OH)D in healthy subjects retrieved from Pubmed, Embase and Web of Science using the terms "serum", "25-hydroxy-vitamin D", "cholecalciferol", and "human". A total of 394 studies were included.
Results The mean 25(OH)D level was 54 nmol/l (95% CI: 52–57 nmol/l). Women had borderline significantly higher 25(OH)D levels than men, and Caucasians had higher levels than non-Caucasians. 25(OH)D levels were higher in subjects aged >15 years than in younger subjects. Unadjusted there was no significant decrease in 25(OH)D with latitude (slope of curve −0.03±0.12 nmol/l per degree latitude north or south of equator, p=0.8). There was a significant decline with latitude for Caucasians (−0.69± 0.30 nmol/l per degree, p=0.02), but not for non-Caucasians (0.03±0.39 nmol/l per degree, p=0.14). After adjustment for age, gender, and ethnicity, no overall correlation was present between 25(OH)D and latitude (−0.29±0.24 nmol/l per degree, p=0.23).
Conclusion There was no overall influence of latitude on 25 (OH)D. However, in separate analyses 25(OH)D decreased with latitude in Caucasians but not in non-Caucasians. A widespread global vitamin D insufficiency was present compared with proposed threshold levels.

Keywords Cholecalciferol · Latitude · Meta-analysis · Serum vitamin D

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Introduction

A large amount of vitamin D is produced in human skin when exposed to ultraviolet light in band B (UVB - 290–315 nm) giving rise to a substantial proportion of the human exposure to vitamin D [1]. The remaining vitamin D is absorbed from the intestine and depends on dietary intake, fortification and supplementation. The production of vitamin D in the skin varies with UVB exposure which may be modifiable through factors such as sun bathing, clothing traditions and use of sun protection, while a number of other factors are not modifiable like age, and skin colour

(pigmentation) [1]. UVB exposure depends on latitude, altitude, clouds and pollution. The UVB exposure decreases markedly from equator towards the polar regions [1], creating a gradient for vitamin D production in the skin, which may have influenced the occurrence of disease and human survival and reproduction.

Ecological studies have disclosed that the prevalence of many diseases like malignancies [2], inflammatory bowel disease [3], multiple sclerosis [4], rheumatoid arthritis [5], type 1 diabetes [6] and osteoporosis show geographic variations with an increase at higher northern or southern latitudes. These observations have led to the suggestions that vitamin D insufficiency may be implicated in their pathogenesis or influence their prognosis [1, 2].

The aim of the present ecologic meta-regression study was to establish an overview of variations in vitamin D status (serum 25hydroxyvitamin D, 25(OH)D) across the world with special emphasis on the influence of latitude, ethnicity (skin colour), age, and sex. The hypothesis was that due to declining sunlight exposure, serum 25(OH)D would decline with increasing latitude.

Subjects and methods

A search was performed of the PubMed, Embase, and Web of Science using the search terms: "serum", "25-hydroxyvitamin D", "cholecalciferol", and "human". Papers in all languages were eligible. Papers in any non-English language were translated where applicable. Only published papers or abstracts were included. It did not change the search to add "calciferol", "plasma" or "25(OH)D" to the search. The search spanned the time interval January 1, 1970 to November 1, 2004 (with the exception of Embase, which was searched from 1974 and onwards) and resulted in 5,855 papers (PubMed with the limitation "human"—5,437 references, ISI Web of science, 266 references, Embase 263 references, combined excluding duplicates 5,855 references). Abstracts of all papers were screened and papers reporting original data on serum vitamin D from cross-sectional studies in all populations were retrieved for further appraisal. Reference lists from these papers were also examined for articles reporting original data on serum vitamin D from cross-sectional studies in all populations. Efforts were made to locate all papers identified to report original data on serum vitamin D from abstracts or reference lists for further study, and all papers selected for such further study were localised in full text. No contact was made with authors of the papers. Inclusion criteria were papers from all over the globe reporting original cross-sectional data on serum 25(OH)D levels in healthy subjects who were native inhabitants of the area where the measurements were performed. Exclusion criteria were immigrants and conditions known to be associated with vitamin D deficiency (e.g., rickets or osteoporosis). Nursing home residents were excluded. In some cases control groups of healthy subjects existed in studies of nursing home residents or subjects with conditions known to be associated with vitamin D deficiency, in these cases the control groups were included in the study. The study outcome was cross-sectional measurements of serum 25(OH)D (expressed as nmol/l or converted from ng/ml to nmol/l) as a continuous variable. The following determining variables for serum 25(OH)D were extracted: latitude, gender, age, skin pigmentation (Caucasian with white skin vs. non-Caucasian with darker skin), and type of vitamin D assay (HPLC or RIA assay). Latitude was determined using the area (city, geographical region) where the study was performed. If a large area was studied, the average latitude for the area in question was used determined from a map. Not all variables were available in each study. We tried to avoid overlap between studies. However, some authors reported different subgroups from the same population in different papers. In the calculations we have tried to avoid overlap by only including one study per calculation (say for the calculations for overall serum vitamin D). This resulted in a reduction in the number of studies available for the different calculations (see the results section). However, we cannot completely exclude overlap, due to differences in the reporting of studies. Regarding the quality of the studies, differences existed. However, no generally accepted scale exists for assessing quality of observational studies.

None of the studies reported random selection of population based participants in all age, gender, and ethnic groups. Some studies reported random selection of participants in selected age and gender strata, but the number of studies was too limited to allow detailed analysis.

The search was performed by TH, RV, TNG, CSP, and PV supported by a research librarian. The papers were screened by TH, RV, TNG, CSP, and PV. Discrepancies in selection were solved by consensus. Tests for publication bias were performed using funnel plots.

Statistics

Mean and standard error of the mean (SEM) were used as descriptive statistics. The meta-analysis was performed using a meta-regression model with between-study variation as a random effect [7, 8]. For each study (i) we have data on study size (N_i), mean value ($\bar{y}_i$), standard error on the mean value ($SE_i = SE(\bar{y}_i)$) and a number of covariates (latitude, gender, age, etc.). The meta-regression of the mean value $\bar{y}_i$ is specified as (using only one covariate x for simplicity): $\bar{y}_i = \alpha + \beta \cdot x_i + e_i$, and the variance on the residuals (e_i) is composed of two variance components: the random between study variation (τ^2) and the within study

variation $\left(\sigma_i^2\right)$, i.e., $Var(\bar{y}_i) = Var(e_i) = \tau^2 + \sigma_i^2/N_i$. Using $\sigma_i^2/N_i = SE^2(\bar{y}_i)$ the only unknown variance component is τ^2. The regression model then corresponds to a weighted regression with weights $w_i = \left(\tau^2 + \sigma_i^2/N_i\right)^{-1}$. Since the between study variation τ^2 is unknown, the regression problem has to be solved by an iterative procedure. We have used the Proc Mixed in SAS, since this procedure can deal with this special form of the variance. For further details on the method see [7].

In this analysis the analyses have been based on a linear curve. It did not change the results of significance or absence of significance with latitude or other parameters to change to other curve forms. The optimal curve fit in most cases was obtained with a linear form.

Results

Effect of sex, age and skin pigmentation

A total of 394 studies with 33,266 subjects from all over the world were included in the study (Table 1). A detailed list of studies included can be found as electronic supplementary material on the journals web page. The mean serum 25 (OH)D level was 54 nmol/l (SEM 1.4 nmol/l, 95% confidence intervals for the mean 52–57 nmol/l). Women tended to have borderline significantly higher mean serum 25(OH)D (56±1.6 nmol/l) than men (50±2.6 nmol/l, p= 0.05, N=382 studies, Table 1). Subjects aged >15 years had higher serum 25(OH)D than subjects ≤15 years (Table 1, p<0.01). Subjects aged >75 years had slightly lower serum 25(OH)D than subjects aged 65–75 years (mean difference 9.3±4.5 nmol/l, p=0.04, Table 1). Caucasians had on average 21.2±5.1 nmol/l higher serum 25(OH)D levels than non-Caucasians (68±3.2 versus 47±4.0 nmol/l, p<0.01, N= 151 studies). Mean values > 100 nmol/l was reported in 4.2% (95% CI: 3.1–5.4%) of the subgroups described by the included studies. Mean values >75 nmol/l were reported in 19.6% (95% CI: 17.5–21.9%) of the studies.

Table 1 Number of studies in different categories with number of participants and average vitamin D status (serum 25-hydroxyvitamin D)

Group	Number of studies	25(OH)D, nmol/l (mean±SEM)
All	394	54±1.4
≤15 years	21	37±5.7
15–65 years	214	57±1.8
>65 years	147	53±2.1
66–75 years	95	57±2.7
>75 years	52	47±3.6
Men	105	50±2.6
Women	277	56±1.6
Caucasians	96	68±3.2
Non-Caucasians	55	47±4.0

A detailed list of studies included can be found as electronic supplementary material on the journals web page

Effect of latitude

Unadjusted, there was no significant trend in serum 25(OH) D with latitude: slope of the curve −0.03±0.12 nmol/l per degree latitude north or south from equator (p=0.80) with very large variations in mean values between studies (Fig. 1). Adjustment for age and gender did not change this association significantly. The change in serum 25(OH) D per degree latitude was now positive (i.e., a small increase in serum vitamin D with latitude), but still not significant: slope of curve 0.02±0.12 nmol/l, p=0.87, N=382 studies, i.e., a slope close to zero. In addition, further adjustment for ethnicity did not change the results (change in serum 25(OH)D per degree latitude: 0.29± 0.24 nmol/l, p=0.23, N=139 studies).

Figure 2 shows that although the serum 25(OH)D levels varied with age, no association with latitude was present in any of the age strata (p-combined = 0.50).

Figure 3 details the effects of skin pigmentation on serum 25(OH)D. Caucasians had higher serum 25(OH)D levels than non-Caucasians, especially at lower latitudes. Unadjusted, there was a significant decline with latitude for Caucasians (−0.69±0.30 nmol/l per degree, p=0.02), but not for non-Caucasians (0.03±0.39 nmol/l per degree, p= 0.90). There was a trend towards a statistically significant difference (p=0.14 for interaction).

Subgroup analysis by continent (slope of regression line for change in serum 25(OH)D (nmol/l) per degree latitude north or south, not adjusted for age or gender: Africa: 0.82±0.57, 2p=0.15, Asia: −0.25±0.22, 2p=0.27, Europe: 0.28±0.16, 2p=0.08, North America: −0.31±0.19, 2p= 0.10, and South America: −0.98±0.28, 2p<0.01) did not change the results of an overall lack of association with latitude. Only in South America, where the number of studies was limited was a significant association seen.

Inclusion of assay type used for determining serum 25 (OH)D did not change the results (p=0.56 for assay type). After adjustment for age, gender, and latitude mean serum 25(OH)D in studies using pure HPLC assays was slightly but insignificantly reduced (6.0±6.3 nmol/l, p=0.34) compared with the mean values from studies using RIA assays for determining vitamin D, while competitive protein binding assays had almost the same mean values for vitamin D as the RIA assays (0.7±3.1 nmol/l higher, p< 0.82). Further adjustment for skin colour besides age and gender did not change the finding that assay type did not influence serum 25(OH)D (p=0.13 for method).

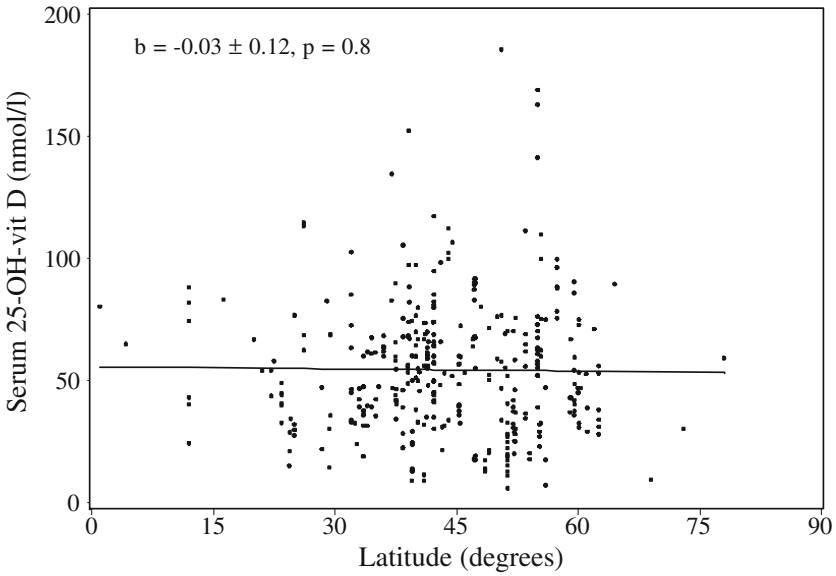

Fig. 1 Crude correlation between latitude and serum 25-OH-vitamin D

Publication year did not influence the results (p=0.36), and this finding was not influenced by age, gender or skin colour. Papers published before 1986 tended to have a little but not significantly lower serum 25(OH)D values (4.1± 3.4 nmol/l lower, p=0.23) than papers published after 1995. Papers published between 1987 and 1994 had almost the same level of 25(OH)D as papers published after 1995 (1.1±3.3 nmol/l higher, p=0.75).

Analyses by season did not change the results, although the number of studies reporting seasonal data was limited. Inclusion of data on vitamin D fortification policy did not change the results. There were no signs of publication bias.

Discussion

Effect of latitude

This study showed no overall effect of latitude on serum 25 (OH)D. Despite large variations probably originating in differences in culture (clothing, time spent outdoors, and sunbathing habits), vitamin D intake (diet, fortification, use of supplements), genetic factors, and study-related factors such as selection of participants, and methods used to determine 25(OH)D etc., the overall levels of vitamin D seemed not to vary with latitude. This is in contrast to a

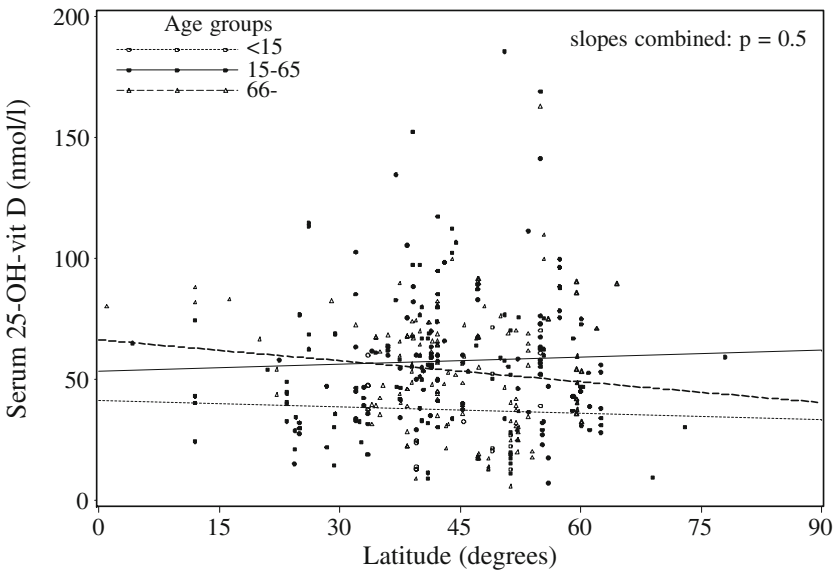

Fig. 2 Effect of age on variation in crude (unadjusted) serum 25-OH-vitamin D with latitude

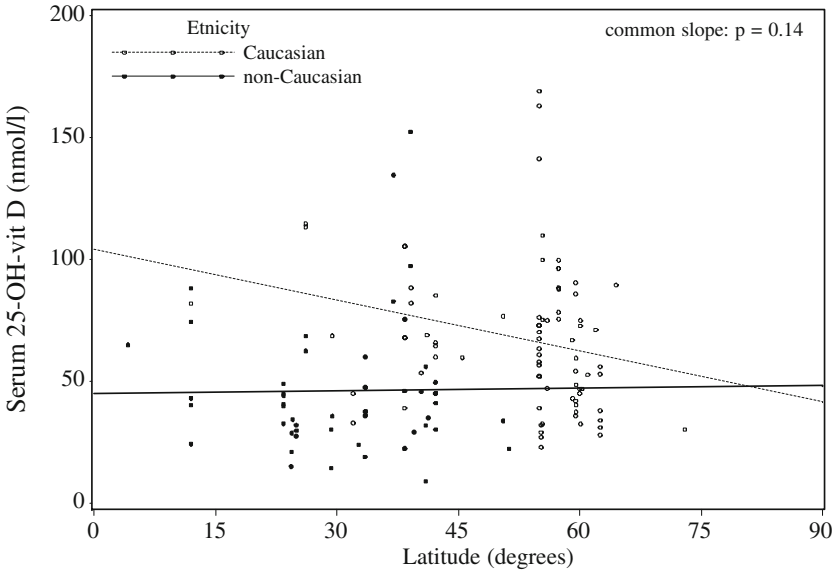

Fig. 3 Effects of ethnicity on variation in crude (unadjusted) serum 25-OH-D with latitude

previous cross-sectional study [9] reporting 25(OH)D levels in 7,564 postmenopausal women from 25 countries on five continents. This study showed a significant relation between serum 25(OH)D and region with the highest levels in Northern Europe and South East Asia and the lowest in Latin America and Southern Europe. A highly significant positive correlation was observed between serum 25(OH)D and latitude in this study (r^2=0.42, p<0.01) in Europe [10]. Another study measuring wintertime plasma 25(OH)D in 824 elderly people in 11 European countries showed a similar relation with lowest values in the southern part of Europe [11]. The first study was based on baseline values from an osteoporosis intervention study [10], and the second on a nutrition study (Euronut-SENECA) [12]. In a subgroup analysis in Europe a non-significant positive correlation with latitude was present in our study, but when extending the perspective to the entire world, no correlation with latitude was present.

Participants in nutrition studies and intervention studies may differ from the general population, as participants in such studies may perhaps be more health orientated with respect to outdoor life, diet, and vitamin D supplementation than the general population. This could have affected the outcomes. The finding that wintertime values increased with latitude in elderly with reduced skin production of vitamin D points towards differences between countries in dietary habits, fortification policy, and supplementation. This interpretation is supported by reviews that report higher plasma 25(OH)D levels among Scandinavian and North American young adults, healthy elderly and institutionalized elderly than in other parts of Europe especially during winter, but also a higher vitamin D intake from fish and fortified food, and a higher proportion taking supplements [13]. In contrast to these studies, an epidemiologic investigation of vitamin D status in the general urban population from twenty French cities between latitude 43° and 51° N reported a significant inverse effect of latitude (r=−0.79, p=0.01) and a positive effect of average hours of sunshine per day (r=0.72, p=0.03) [14]. These findings show that within a more homogenous population with common fortification policies and supplementation traditions the effect of latitude on vitamin D status is more evident as also shown in our study when restricting the analysis to Caucasians between latitudes 30 and 65 degrees.

Analysed separately the decrease with latitude was significant in Caucasians but not in non-Caucasian. It may thus be that the pale skin thus is more adapted to changes in UVB exposure than darker skin. Furthermore, at a high UVB exposure darker skin may offer a better protection from the high exposure, an adaptation also seen with sun tanning in Caucasians. However, the observation that no decrease with latitude was seen in non-Caucasians needs further study, as a decrease with extreme differences in UVB exposure may also have been expected in non-Caucasians. The present finding of a tendency towards a decrease in serum 25(OH)D with latitude among Caucasians may support ecologic studies showing regional differences in cancer-related diseases and mortality patterns in relation to latitude, assuming a biologic relation between vitamin D insufficiency and disease incidence or outcome [1, 15, 16]. Such biological relations include inhibition of cell proliferation by 1α,25$(OH)_2$D, enhancement of differentiation and apoptosis [17], and inhibition of the effects of IGF-I [18]. Grant [2] reported a higher mortality of 14 different solid tumours, including breast cancer, colon cancer and prostate cancer, in the North Eastern part of USA with low sun exposure compared with other more sunny regions. However, more research in the field is needed [19].

Effects of age and sex

Our study showed lower serum 25(OH)D in childhood and adolescence than in adults and higher values in females than in males. We have no ready explanation for these differences from the present investigation since we have insufficient data at individual level. Previous studies have observed inverse relations between serum 25(OH)D and fat mass meaning that more obese subjects have lower serum 25(OH)D levels than non-obese [20, 21]. In children the relationship with the distribution between fat and lean mass may suggest that increases in lean body mass with growth are associated with an increased utilization of 25(OH)D by soft tissue [22].

We observed a decrease in serum 25(OH)D levels in individuals aged 75+ years in our global study. In accordance the dermal production of 25(OH)D is considered to decrease substantially with age leading to deficiency in 25(OH)D and secondary hyperparathyroidism [10]. This effect is apparently not - at least in USA - neutralized by a higher dietary intake or use of supplementation with age [22, 23]. In the last study [23] based on The Third National Health and Nutrition survey (NHANES III) and the Continuing Survey of Food Intakes by Individuals (CSFII 1994–96) adequate dietary intakes of 25(OH)D (> 15 μg/day) were only found in 1–3% of males and in none of the females aged 70+ years. These figures rose to 12% if supplements were also taken into account. These findings thus need further study.

Skin pigmentation

The major dermal histological difference between African, Asian and European populations seems to be the packaging and size of melanosomes in the keratinocytes [24]. Variation in skin colour appears to be a multifactorial trait involving a number of major genes (i.e., MSH cell surface receptor and melanosoma P protein) that regulate the levels and activity of the melanogenic enzyme thyrosinase, thyrosinase-related protein-1 (TRP1) and other proteins [24]. Following the exodus from Africa people who had reduced skin pigmentation and therefore an increased ability to utilise the limited amount of UVB in spite of the need of clothing inhabited the northern latitudes in Europe. These Caucasians have later settled in other temperate areas of the world with limited sun exposure especially during winter. In contrast, people with coloured skin who were displaced to higher latitudes in North America or Europe in recent historic time have a reduced serum 25(OH)D levels compared with their white counterparts because of a reduced dermal vitamin D production rate that have not been compensated for by an increased dietary intake [25]. Furthermore, recent immigrants from Palestine, Pakistan and India to Northern Europe may develop severe deficiency in 25(OH)D with proximal myopathy due to the limited effect of sunshine and a low dietary vitamin D intake [26]. This problem has triggered pharmacological substitution programs with limited effect [27].

Adaption to geography and life styles

Our study suggests that the human race to a large extent have adapted to variations in UVB exposure caused by latitude. One exception may be that Caucasians tend to have improved vitamin D status at lower latitudes. However, great variations were observed between studies within the same range of latitude. These variations may be related to geographic variations in climate (i.e., clouds, pollution) and altitude or variations in age, skin colour, sex, life-style, fortification policy, and supplementation tradition. The overall general adaptation to UVB exposure may be explained by the same factors. Some people tend to avoid extensive sun exposure by staying indoors, by using covering clothes or sun protection. Others develop a tanning that reduces dermal vitamin D production. The moderately pigmented Inuit's during their migration towards the polar regions through millenniums have adapted to a life with sparse solar exposure through a diet of fatty fish and blubber with a high content of animal vitamin D. They tend to develop vitamin D deficiency if the shift to a westernized fare [28]. However, genetic adaptation apart from skin colour may also influence vitamin D metabolism. Inuits appear to have developed an enhanced renal conversion of 25(OH)D to $1,25(OH)_2D$ improving the utilization of available 25(OH)D [28]. In contrast, Asian Indians have developed (or maintained) an increased renal $24,25(OH)_2D$-hydroxylase activity facilitating the production of the inactive $24,25(OH)_2D$ at the expense of $1,25(OH)_2D$ [29].

Global vitamin D status

Our study showed a mean global serum 25(OH)D level of 54±1.3 nmol/l. This is low compared with the proposed threshold levels for vitamin D insufficiency. Based on the development of secondary hyperparathyroidism at lower 25(OH)D levels Lips [9, 30] suggested that 25(OH)D levels <50 nmol/l should be characterized as insufficiency and levels <25 nmol/l as deficiency. Mean values >100 nmol/l was only reported in 4.2% (95% CI: 3.1–5.4%) of the subgroups described by the studies in our meta-analysis. Mean values >75 nmol/l were reported in 19.6% (95% CI: 17.5–21.9%) of the studies. In an evolutionary perspective the widespread insufficient serum 25(OH)D status may be caused by factors that in other ways improve reproduction and survival such as clothing and indoor-life.

Limitations to the study

There are several limitations to our study. In most studies we had to use the latitude of the centre where the study had originated. In larger studies covering greater geographic areas we had to use the average latitude of the area. However, in most cases the distances covered were limited and this may only have introduced a limited bias. A further major source of variation may stem from different assays for determination of vitamin D. However, in a subgroup analysis, assay type did not seem to influence the overall results. We had no information on vitamin D intake from foods and supplements. Furthermore, we had no information on altitude or regional climate and in most studies we had to use pooled 25(OH)D values across seasons. However, this was partly countered by stratified analyses of regions with similar populations and climate. Because of limited information on skin colour we had to dichotomize ethnicity into Caucasians and non-Caucasians. A more detailed categorization would have been preferable. Finally, we had no information on individual life-style variables like clothing tradition, sunbathing, use of sun protection, etc.

The analysis is based on published reports, and from certain regions in the world, especially close to the equator, the number of reports were limited. The conclusions thus are based on the assumption that the reports represent random samples of the populations of interest around the globe. However, if strong correlations with latitude were present these would have materialized from the large statistical power from the number of studies.

In this study we included all types of cross-sectional studies and did not limit the inclusion to say studies who used subjects randomly selected from the background population. This may represent a bias. However, in studies aiming at randomly selected populations, although selection bias may be reduced, it may not be completely be avoided. Some groups may upon invitation to a study be more likely to respond than others. Especially frail elderly subjects from the community who are otherwise characterized as "healthy" may be less likely to participate and the group of younger individuals with good life styles and high serum vitamin D values may be over-represented.

The limited number of studies with randomly selected participants was a limitation, and further population based studies are needed.

Conclusions

The present ecologic meta-regression analysis has shown that vitamin D status globally depend on age, gender and skin colour. There was no overall influence of latitude. However, in separate analyses plasma 25-OHD decreased with latitude in Caucasians but not in non-Caucasians. The study indicates a widespread global vitamin D insufficiency compared with proposed threshold levels.

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Conflicts of interest None.

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