ANTICANCER RESEARCH *42*: 5027-5034 (2022)
doi:10.21873/anticanres.16011

*Review*

# Critique of Public Health Guidance for Vitamin D and Sun Exposure in the Context of Cancer and COVID-19

REINHOLD VIETH

*Department of Nutritional Sciences, and Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada*

**Abstract.** *Official public health pronouncements about sun exposure and vitamin D can be summarized as follows: First, there is no such thing as a safe tan. Therefore, avoid exposing the skin to sunshine. Second, in the absence of sunshine, a daily intake of 800 IU/day (20 mcg/d) vitamin D or less is sufficient for the health needs of almost all members of the population. However, exposure of the skin to sunlight induces multiple mechanisms that lower blood pressure, while also initiating production of vitamin D, which is needed to produce a hormone that regulates multiple systems including the cellular biology that affects cancer mortality. Disease-prevention relationships point to a beneficial threshold for serum 25-hydroxyvitamin D [25(OH)D; the index of vitamin D nutrition] that is at least 75 nmol/l (30 ng/ml). To ensure the threshold for all adults, an average per-day minimum total input of vitamin D3 from sunshine/UVB exposure, and/or from food (natural food like fish or fortified food like milk), and/or vitamin supplementation of at least 4,000 IU/d (100 mcg/d) is required. Strong, although not Level-1, evidence indicates that the maintenance of that threshold will lower mortality overall, lower mortality from cancer, and lower the risk of certain other diseases such as respiratory infection and COVID-19.*

*Correspondence to:* Reinhold Vieth, Ph.D., Department of Nutritional Sciences, and Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Canada. Tel: +1 4169929389, e-mail: reinhold.vieth@utoronto.ca

*Key Words:* Recommended daily intake, RDA, clinical trial study design, evidence-based medicine, public health, primary disease prevention, COVID-19, evolution, primate biology, vitamin D toxicity, review.



The unavoidable complexity for understanding the contributions of sunshine and vitamin D nutrition in relation to health is the fact that official health policies have ignored the scientific reality that most people acquire most of their vitamin D through exposure of their skin to ultraviolet light. According to mainstream dermatology, "there is no such thing as a safe tan" (1) and the public is advised to minimize exposure of skin to sunshine. The American Dermatology Association states that adults should avoid sunshine, and that the general public should simply adhere to the evidence-based advice of the Institutes of Medicine (IOM) (2). The IOM report on vitamin D, last updated in 2011, makes it very clear that it assumes that no vitamin D needs to come from ultraviolet exposure of the skin (3). Despite their expectation of Level 1 evidence for policy, neither the IOM nor any other agency can provide high quality evidence for the long-term serum 25(OH)D response to a daily dose of vitamin D in people who were never exposed to sunshine. Therefore, so far, as officialdom is concerned, the optimal threshold for sunshine and vitamin D can be reached by anyone adhering to official dietary guidance.

It is not plausible that human health can be optimal in the absence of exposure of skin to sunshine, and it is not plausible that, to replace sunshine, the amount of vitamin D required from the diet is an oral intake of 800 IU (20 micrograms) or less. David Sacket who led the group that developed the modern concept of "Evidence-Based Medicine" (EBM), has clarified what he means by EBM.

"Because the randomised trial, and especially the systematic review of several randomised trials, is so much more likely to inform us and so much less likely to mislead us, it has become the "gold standard" for judging whether a treatment does more good than harm. However, some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there" (4).

## Human Biology

The concept underlying evolutionary biology is that the environment during the species' evolution determines its genotype, and from the resulting gene pool, environmental change drives the fine selection of characteristics that determine the phenotype. Evolution involves natural selection in a manner that optimizes the species' biology to suit the environment in which the species arose. Homo sapiens originated in the horn of Africa. Early humans are logically described as nudists whose skin was of type-six, on the 6-point Fitzpatrick skin darkness scale. We are optimized through evolution to inhabit the tropics. The changes that accompanied the millennia-long migrations of homo sapiens across the various global environments resulted in selection – not evolution – of phenotypes that maximize ability to give birth to viable offspring (5-7). There may be disagreement as to the exact geographic region in which the genes for whiter European skin originated (8), but since selection for lighter skin with distance away from the equator happened independently in both hemispheres, lighter skin colour with distance away from the tropics was multi-factorial and driven by the environment (9, 10). The serum 25(OH)D levels that should be regarded as biologically "normal" for humans, is evident from work published by Luxwolda *et al*. They studied groups living traditionally in tropical Africa (11, 12). The results summarized in Figure 1 show data from Africa, and from healthy students at the University of Toronto (13). Serum 25(OH)D concentration is more severely affected by environment and culture than anything else in the bloodstream. This is not like any "normal" blood test. The basic biology of homo sapiens points to our species' "normal" 25(OH)D level as best represented by the Massai data published by Luxwolda *et al*. (11, 12) (Figure 1).

In a review addressing the challenges related to evidence-based nutrition, Blumberg *et al*. pointed out that classic, evidence-based medicine is based on a pharmaceutical model, and that "The level of confidence needed in defining nutrient requirements or dietary recommendations to prevent disease can be different from that needed to make recommendations to treat disease" (14).

The defence for policy makers is logical: nutrient and sun exposure recommendations should require higher confidence than pharmaceutical validation, because public health guidance applies throughout the lifespan, to prevent (*i.e*., lower the risk of) primary disease across the entire population. In contrast, pharmaceuticals are applicable to secondary intervention, that is, once disease exists. The risk/benefit profiles for vitamin D nutrition and sun exposure guidelines are vastly different for primary prevention *versus* secondary prevention of disease. For double-blind, placebo controlled clinical trials, there is a practical time limit to those. Realistically, there is a five-year maximum time-frame that granting agencies are capable of supporting (15). No clinical trials exist with randomized, active-*versus*-placebo intervention beyond 5 years. To show efficacy for osteoporosis, cancer, or mortality, if such randomized clinical trials could happen, they would involve initially healthy members of the general public who are younger than the age of retirement, and they would involve active *vs*. control intervention that would last for decades.

"Because the intakes required to prevent many of the long-latency disorders are higher than those required to prevent the respective index diseases, recommendations based solely on preventing the index diseases are no longer biologically defensible" (16, 17).

If only causal, Level-1 evidence is demanded to affect health policy, then that policy will forever remain blind to the potential benefit of increase in vitamin D consumption or sun-exposure behaviour that is maintained for years.

## Cancer

It has long been clear that either more sunshine or vitamin D derived from it results in lower cancer mortality (18). In 2019, the analysis of the VITAL study for the prespecified primary outcomes was published (19). The primary outcome was the "prevention of occurrence of invasive cancer of any type", and for that result was not statistically significant (19).

The analysis of the VITAL study data regarding an effect of vitamin D did show a lower incidence of advanced (metastatic or fatal) cancer. But that only became clear for the data beyond the 1-year point into the trial (20). It is important to bear in mind the background population for the VITAL study. The best data regarding general population of the USA is represented by the National Health and Nutrition Examination Survey (NHANES) sample, whose subjects were tested between 2001-2006, shortly before the start of VITAL clinical trial. In that NHANES assessment, only 19% of participants had 25(OH)D values ≥30 ng/ml. That context makes it very likely that the VITAL study, with its relatively high mean baseline 25(OH)D levels of 29.3 ng/ml (21) was at least partly affected by a "healthy volunteer selection bias", similar to what has affected other vitamin D studies (22).

The mean 25(OH)D concentration at baseline of participants in the VITAL study was already at the threshold for a vitamin D nutrition optimum that the Endocrine Society has advocated (23). The VITAL study participants randomized to 2,000 IU/day of vitamin D3 had an average serum 25(OH)D concentration at Year 1 of 40.3 ng/ml (101 nmol/l) (21). If 2,000 IU/day of vitamin D3 raised serum 25(OH)D by 11 ng/ml, then how much background vitamin D input must there have been due to sunshine, diet, and supplements in the volunteers for the study to produce their baseline concentration of 29.3 ng/ml (74 nmol/l)? Baseline nutrient was already far more than could be achieved just by vitamin D according to

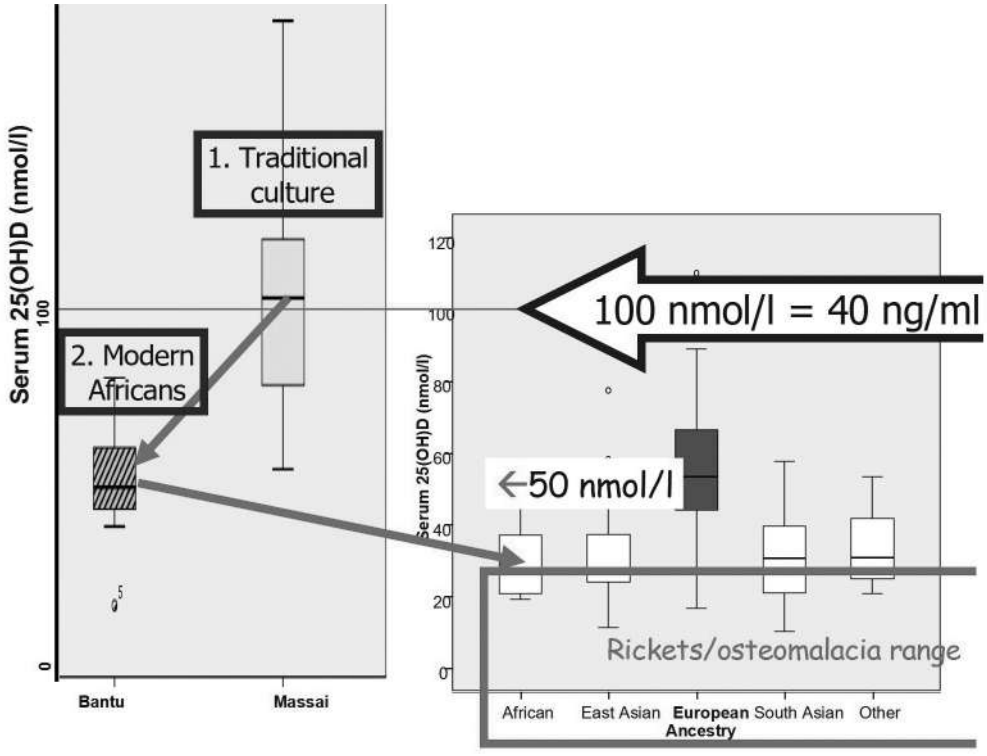


Figure 1. *Boxplots showing serum 25(OH)D nmol/l levels in people from different ancestries in Africa (latitude 0) and during February in Toronto (43N). All results here were assayed with the same Diasorin method. The Africa values are from Luxwolda et al. and Muskeit et al. (11, 12), and refer to traditionally-living Masai, and urban-living Bantu. Since humans originated in Africa, the Masai results logically indicate serum 25(OH)D levels that are "normal" for the human species. Note that the levels of 25(OH)D in urban Africans match those of White Canadians, i.e., of European ancestry. But people of non-European ancestry who live in north Toronto (13) exhibit levels that are half those of urban Africans and those are a fraction of the Masai levels that I contend should be considered the "normal range" for humans. The box at the bottom right highlights 25(OH)D values at or below 25 nmol/l (10 ng/ml), which are regarded as the criterion for a diagnosis that rickets or osteomalacia caused by vitamin D deficiency.*

any dietary guideline of 800 IU/day or less. Based on the treated group's 25(OH)D median for the VITAL study, if development of advanced cancer or cancer mortality over five years in healthy adults is a meaningful objective, then surely, the prevention threshold level for serum 25(OH)D must be at least the 40.3 ng/ml (101 nmol/l) (21).

Similar clinical trials using vitamin D at 2,000 IU/day were reported by Lappe *et al*., albeit in conjunction with calcium supplement (24, 25). Recent meta-analyses have consistently led to the unambiguous conclusion that although vitamin D supplementation does not affect total cancer incidence, they do unambiguously show that mortality from cancer is lower in the vitamin D-supplemented arms of clinical trials (26-28).

The evidence-based conclusion of benefit from double-blind, placebo-controlled clinical trials of vitamin D3 is based on the binary, yes-or-no conclusion of statistical significance. To turn that into practice requires knowledge of how much vitamin D supplementation is needed, or more importantly, what serum 25(OH)D levels should people aim for? Sustaining serum 25(OH)D that is at least at the 25th percentile of the attained level in the treatment arm – *i.e*., 30 ng/ml (75 nmol/l) is a prudent preventive target for healthy adults. Consistent with that value is a cross-sectional analysis of 25(OH)D data from one clinical trial (24) combined with data and a group of self-reported cohort referred to as Grassroots Health (29).

## Mortality

There are consistent epidemiological data that mortality is highest among those people classified into the lowest group for serum 25(OH)D or for sun exposure. Those advocating for higher recommended intakes of vitamin D are told its benefit is due to more active, outdoor lifestyles. Those advocating for health policy that incorporates sun exposure are told to advise vitamin D instead.

Schottker *et al*. conducted a meta-analysis of eight prospective cohort studies from sample populations from Europe and the USA. The analysis was performed by assembling the data on all the 6,685 individual participants of the studies and classifying them into country quintiles of serum

25(OH)D. Mortality was consistently highest for those in the lowest 25(OH)D quartile. The relationship did not differ across countries, sexes, seasons of blood draw, or age groups (30). Despite differences in mean serum 25(OH)D among reported studies, Schottker *et al*. observed that it was always the lowest quantile that showed highest mortality, making it difficult to define a threshold serum 25(OH)D for lower mortality (30). However, there are suggestions of higher mortality for higher serum 25(OH)D quintiles; for example, the Newcastle 85+ Study showed a U-shaped higher mortality relationship (31). But for the latter cohort, the higher mortality in those at the highest category of serum 25(OH)D was no longer significant after statistical adjustment for mental health and morbidity-related variables. That suggests a "confounding by indication" bias, whereby vitamin supplementation is higher because of known risk or presence of disease. A similar analysis has been reported for the Chinese Longitudial Health and Longevity Study (CLHLS). In that study, Mao *et al*. looked at plasma 25(OH)D levels in 2185 Chinese adults older than 79 years (mean 93 yrs) (32). There, all-cause mortality decreased progressively with rising plasma 25(OH)D, with the lowest mortality in those with 25(OH)D at or higher than 75 nmol/l (30 ng/ml). Among 3408 NHANESIII participants, older than 64 y and prospectively followed for a median of 7.3 y, all-cause mortality was highest in those with baseline 25(OH)D levels below 50.0 nmol/l, but the authors concluded that levels of at least 100.0 nmol/l may be necessary for better survival (33). One problem with the available epidemiological data is that very few people have 25(OH)D higher than 75 nmol/l. Sparse numbers of data points result in wide confidence intervals, to the point that some, such as the Institutes of Medicine, interpret the uncertainty of wide confidence bands as indicative of greater risk at higher ranges of 25(OH)D levels (3). Lastly, Ford analyzed data from 7531 participants in an NHANES cohort in the USA further and reported the fully adjusted hazard ratio per 10 nmol/l higher serum 25(OH)D was 0.93 (95%CI=0.86-1.01) (34). These epidemiological survey results on mortality are consistent with the meta-analysis of randomized clinical trials described in the next paragraph.

The key questions remain, "Is mortality lower in healthy subjects who are randomized to higher intake of vitamin D *versus* placebo? And if so, what is the optimal daily intake recommendation?" The first to address these questions were Autier and Gandini, whose meta-analysis consisted of 18 independent randomized controlled trials, involving 57,311 participants (35). The doses used in the clinical trials conducted up to the year 2006 ranged from 300 to 2,000 IU/day (all were vitamin D3). For the pooled vitamin D arm of those trials, the relative risk for mortality from any cause was 0.93 (95% confidence, 0.87-0.99), *versus* placebo, regardless of whether these osteoporosis clinical trials included calcium supplements. The findings of the Autier and Gandini meta-analysis were confirmed in the report done for the Cochrane Collaboration and authored by Bjelakovic *et al*. (36). Clinical trials involving vitamin D2, alfacidol, or calcitriol had no significant effect on mortality (36). The lack of success in clinical trials using vitamin D2 should not come as a surprise to anyone who has compared the characteristics of vitamin D2 *versus* vitamin D3 (37-39). The more recent meta-analysis by Zhang *et al*. included data from long-awaited, large randomized clinical trials, and there, the conclusion was that vitamin D supplementation alone was not associated with all cause mortality in adults compared with placebo or no treatment (26). What makes the recent, large clinical trials relevant, is that subjects were younger and healthier than the subjects in the osteoporosis-focused trials performed earlier. Hence, with the healthy subjects, event rates for death as a proportion of the sample were lower, biasing the results toward a null outcome for overall mortality. Nonetheless, despite no effect on mortality from cardiovascular disease, cerebrovascular disease, or ischaemic heart disease, Zhang *et al*. found that vitamin D supplementation lowered cancer mortality by 16% (95%CI=0.74 to 0.95) (26).

It is not enough to deliver a "threshold" level for serum 25(OH)D. Unlike other vitamins, vitamin D is not a metabolic co-factor. Cholesterol, the precursor substrate for steroid hormones, circulates and is available in millimol-per-liter concentrations. Like cholesterol, vitamin D is the structural precursor for a steroid-like hormone. But unlike cholesterol, the vitamin D and 25(OH)D are available to the body in miniscule, nanomolar concentrations; that is, vitamin D metabolite concentrations are six orders of magnitude less than cholesterol, the paradigm for how the rest of endocrinology functions! The point here is, that nanomolar concentrations of enzyme substrate add unique complexity to the way the synthesis and breakdown of the hormone 1,25-dihydroxyvitamin D are regulated. The enzymes of the vitamin D system function under the unusual circumstance of first-order reaction kinetics. The yield of product is determined not just by the amounts of the hydroxylase enzymes, but also by substrate concentrations as well (40). It takes time for the vitamin D system to adjust to non-physiological, sudden, bolus doses of vitamin D (41, 42). Since vitamin D is normally acquired gradually through long-term exposure of skin to sunshine, acute bolus doses of vitamin D are not physiological. Despite warnings against long dosing intervals for vitamin D in 2009 (41) subsequent clinical trials used them, and the negative clinical outcomes with long dosing intervals have been assimilated into meta-analyses along with trials that used daily-dosing. Distinctions to be considered in meta-analyses must include the form of vitamin D, the daily-equivalent dosage, and the dosage interval (43).

## Cardiovascular

Like tanning, the serum 25(OH)D is regarded as a good, long-term marker of skin exposure to sunshine. Cross-sectionally, higher serum 25(OH)D relates to better cardiovascular health

outcomes (33, 44). Meta-analysis of clinical trials has been highly convincing for the null hypothesis, that vitamin D supplementation at various doses has not lived up to the expectation of cardiovascular benefit (45, 46). Autier *et al*. contend that the survival benefits related to higher serum 25(OH)D are secondary to other factors such as diseases that may keep people less active and indoors, as well as lifestyle. They concluded that "associations between 25(OH)D and health disorders reported by investigators of observational studies are not causal" (47). However, Mendelian randomization analyses do point to a causal connection between serum 25(OH)D and cardiovascular disease risk (48, 49). For vitamin D, the most likely explanation is that the dose response for the cardiovascular benefit with vitamin D is satisfied once serum 25(OH)D reaches 20 ng/ml (50 nmol/l). In other words, most clinical trials of vitamin D probably failed because the participants started with a serum 25(OH)D that was already enough to minimize its role in cardiovascular disease risk.

Sunlight on the skin by itself, has well known cardiovascular health benefits. First, sunshine warms the skin which causes vasodilatation and lowers blood pressure. Second, the skin is a production and storage location for nitric oxide, a potent vasodilator, which is released into the general circulation when the skin is exposed to sunshine. Third, UVA, corresponding to natural sunlight exposure for 30 min at noon on a sunny day at 41 degrees north latitude, vasodilates the arterial vasculature in a way that is independent of nitric-oxide-synthase or skin temperature (50). This complex of mechanisms prompted Liu *et al*. to conclude "We are concerned that well-meaning advice to reduce the comparatively low numbers of deaths from skin cancer may inadvertently increase the risk of death from far higher prevalent CVD and stroke and goes against epidemiological data showing that sunlight exposure reduces all-cause and cardiovascular mortality (51)". The cardiovascular and mortality relationships with skin cancer are consistent with the work of Lindqvist *et al*., who surveyed Swedish women regarding sun avoidance. Lindqvist *et al*. showed that women who minimized their exposure to sunshine exhibited rates of cancer and overall mortality that were comparable to cigarette smoking (52).

## Toxicity

Concern about toxicity of vitamin D that is consumed at 4,000 IU/day is unjustified if one considers that this is well within the amount of vitamin D produced naturally in the skin from sunshine. Serum 25(OH)D, exceeding 30 ng/ml (75 nmol/l), is physiological and normal for humans (11, 12). Experience with randomized clinical trials shows that 48 weeks of vitamin D3 taken at 14,000 IU daily was safe in patients with multiple sclerosis (53-55). I mention the multiple sclerosis clinical trials to confirm that the no observed adverse effect level (NOAEL) for vitamin D3 consumption ranges of up to 10,000 IU/day as specified in earlier reviews including the Institutes of Medicine (3, 56, 57). The application of a safety margin to that NOAEL results in the "Tolerable Upper Intake Level" (UL) that specified by the IOM was 4,000 IU/day. I am not advocating vitamin D intakes beyond 4,000 IU/day, but rather, restating here evidence that there is a wide margin of safety for vitamin D.

## COVID-19

Before the era of COVID-19, observational studies consistently reported that lower serum 25(OH)D was associated with higher risk of upper and lower acute respiratory infections (ARI). For example, among a nationally representative sample of 14,108 adults in the USA, who were asked at the time of testing, 4.8% reported having had an acute respiratory infection in the previous 30 days. After adjusting for season, demographic factors, and clinical data, those people who had serum 25(OH)D below 30 ng/ml (<75 nmol/l) had 58% higher odds of having had a respiratory infection during the previous month, and those rates of respiratory infection increased progressively with declining serum 25(OH)D concentrations (58).

Challenges that are unavoidable when it comes to figuring out whether taking more vitamin D can lower the risk for COVID-19, its risk of infection, or severity, or hospitalization or death are:

1. COVID-19 continues to evolve into multiple variants, causing changes to the nature of the disease itself, and its efficiency of transmission
2. human behaviour, the wearing of masks and physical distancing change during the pandemic
3. vaccination lowers incidence of the disease
4. efficacy of vaccination varies, and it wanes with time

As an interesting example of the challenges listed above, a preprint of a submitted manuscript shows a well conducted clinical trial by Jolliffe *et al*., involving 3,100 participants in the UK (59). That vitamin D clinical trial shows no benefit from 6 months of 3,200 IU vitamin D3 daily. That manuscript has still not been published in peer-reviewed form at the time of this writing July, 2022. The problem was, that by six months into the clinical trial, to June 2021, 89.1% of participants had received one or more doses of a COVID-19 vaccine. The impressive level of vaccination of the participants casts doubts on the validity of this clinical trial and is another example of the "healthy volunteer bias", which poses challenges that must not be ignored when assessing disease-prevention research for nutrition in general.

In April 2022, Villasis-Keever *et al*. published a double-blind, placebo-controlled clinical trial that was conducted from July to December 2020 in hospital workers who were at high exposure to infected patients (60). Of the 192 subjects

completing the 45-day protocol, SARS-CoV-2 infection rate was lower in those randomized to 4,000 IU/day vitamin D3 than in the placebo-treated group. Infection rates were, 6.4% *vs*. 24.5%, respectively, ($p$<0.001). Baseline 25(OH)D was low, at 18.3 (interquartile range=14.6-22.9) ng/ml (median 46 nmol/l), and the level increased by 8.8 ng/ml after 6 weeks of treatment with 4,000 IU/day of vitamin D.

The RCT published by Villasis-Keever is remarkable, because it is a rare clinical trial that met the challenges of the time: it was conducted early in the pandemic, it was not affected by vaccines, and the study population was healthy but did exhibit the expected high rates of infection events because they were front-line medical workers (60). This study can be classified as "Level-1 evidence" for a prophylactic effect of initiating the intake of 4,000 IU/day of vitamin D3. It is possible that this protective effect happened thanks to an acute increase in vitamin D nutritional status, and that a steady-state higher level may not produce the protection observed by Villasis-Keever *et al*. The rationale for why an acute rise in vitamin D status might deliver benefits not observable with a long-term vitamin D status or intake is based on the concept of the first-order reaction kinetics discussed above in this article.

## Conclusion

The biologically justifiable "normal" range for serum 25(OH)D is best represented by levels observed in people traditionally living in Sub-Saharan Africa who obtain their vitamin D through exposure of skin to ultraviolet light. Their serum 25(OH)D levels are at least 30 ng/ml (75 nmol/l) with median values of about 40 ng/ml (100 nmol/l). Most of the evidence supporting a minimum desirable 25(OH)D threshold of 30 ng/ml (75 nmol/l) comes from prospective epidemiological data, not clinical trials. There is no public health guidance for nutrition or for sun exposure that is based on Level-1 evidence for primary disease prevention. It is probably impossible to produce clinical trials pertinent to public health that can match the quality standards of pharmaceutical trials. Therefore, a standard of evidence that is less than "Level 1" may be required. Vitamin D nutrition, whether from sun exposure, diet (including fortification) or supplementation can deliver benefits for musculoskeletal health, cancer mortality, as well as risk of COVID-19 infection, its severity and outcomes. To sustain a 30 ng/ml (75 ng/ml) threshold for serum 25(OH)D in 97.5% of the population requires a combined vitamin D3 supply of 4,000 IU/day (100 mcg/d) *via* UVB exposure, diet, and/or supplement.

## Conflicts of Interest

The Author has no conflicts of interest to declare in relation to this study.

## References


1 Buller MK, Loescher LJ and Buller DB: "Sunshine and skin health": a curriculum for skin cancer prevention education. J Cancer Educ *9(3)*: 155-162, 1994. PMID: 7811604. DOI: 10.1080/08858199409528299

2 American Academy of Dermatology: Vitamin D. Available at: https://www.aad.org/media/stats-vitamin-d [Last accessed on July 27, 2022]

3 Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D and Calcium: The National Academies Collection: Reports funded by National Institutes of Health. In: Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, Taylor CL, Yaktine AL and Del Valle HB (eds.). Washington (DC), National Academies Press (US) National Academy of Sciences, 2011.

4 Sackett DL, Rosenberg WM, Gray JA, Haynes RB and Richardson WS: Evidence based medicine: what it is and what it isn't. BMJ *312(7023)*: 71-72, 1996. PMID: 8555924. DOI: 10.1136/bmj.312.7023.71

5 Vieth R: Weaker bones and white skin as adaptions to improve anthropological "fitness" for northern environments. Osteoporos Int *31(4)*: 617-624, 2020. PMID: 31696275. DOI: 10.1007/s00198-019-05167-4

6 Vieth R: The paleolithic nutrition model in relation to ultraviolet light and vitamin D. Adv Exp Med Biol *1268*: 409-419, 2020. PMID: 32918231. DOI: 10.1007/978-3-030-46227-7_21

7 Jablonski NG and Chaplin G: Human skin pigmentation, migration and disease susceptibility. Philos Trans R Soc Lond B Biol Sci *367(1590)*: 785-792, 2012. PMID: 22312045. DOI: 10.1098/rstb.2011.0308

8 Hanel A and Carlberg C: Skin colour and vitamin D: An update. Exp Dermatol *29(9)*: 864-875, 2020. PMID: 32621306. DOI: 10.1111/exd.14142

9 Relethford JH: Hemispheric difference in human skin color. Am J Phys Anthropol *104(4)*: 449-457, 1997. PMID: 9453695. DOI: 10.1002/(SICI)1096-8644(199712)104:4<449::AID-AJPA2>3.0.CO;2-N

10 Parra EJ: Human pigmentation variation: evolution, genetic basis, and implications for public health. Am J Phys Anthropol *Suppl 45*: 85-105, 2007. PMID: 18046745. DOI: 10.1002/ajpa.20727

11 Luxwolda MF, Kuipers RS, Kema IP, Dijck-Brouwer DA and Muskiet FA: Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. Br J Nutr *108(9)*: 1557-1561, 2012. PMID: 22264449. DOI: 10.1017/S0007114511007161

12 Luxwolda MF, Kuipers RS, Kema IP, van der Veer E, Dijck-Brouwer DA and Muskiet FA: Vitamin D status indicators in indigenous populations in East Africa. Eur J Nutr *52(3)*: 1115-1125, 2013. PMID: 22878781. DOI: 10.1007/s00394-012-0421-6

13 Gozdzik A, Barta JL, Wu H, Wagner D, Cole DE, Vieth R, Whiting S and Parra EJ: Low wintertime vitamin D levels in a sample of healthy young adults of diverse ancestry living in the Toronto area: associations with vitamin D intake and skin pigmentation. BMC Public Health *8*: 336, 2008. PMID: 18817578. DOI: 10.1186/1471-2458-8-336

14 Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM and Zeisel SH: Evidence-based criteria in the nutritional context. Nutr Rev *68(8)*: 478-484, 2010. PMID: 20646225. DOI: 10.1111/j.1753-4887.2010.00307.x

15 Pilz S, Trummer C, Theiler-Schwetz V, Grübler MR, Verheyen ND, Odler B, Karras SN, Zittermann A and März W: Critical appraisal of large vitamin D randomized controlled trials. Nutrients *14(2)*: 303, 2022. PMID: 35057483. DOI: 10.3390/nu14020303
16 Heaney RP: Long-latency deficiency disease: insights from calcium and vitamin D. Am J Clin Nutr *78(5)*: 912-919, 2003. PMID: 14594776. DOI: 10.1093/ajcn/78.5.912
17 Lappe JM and Heaney RP: Why randomized controlled trials of calcium and vitamin D sometimes fail. Dermatoendocrinol *4(2)*: 95-100, 2012. PMID: 22928064. DOI: 10.4161/derm.19833
18 Grant WB: An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer *94(6)*: 1867-1875, 2002. PMID: 11920550. DOI: 10.1002/cncr.10427
19 Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, Friedenberg G, Ridge C, Bubes V, Giovannucci EL, Willett WC, Buring JE and VITAL Research Group: Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med *380(1)*: 33-44, 2019. PMID: 30415629. DOI: 10.1056/NEJMoa1809944
20 Chandler PD, Chen WY, Ajala ON, Hazra A, Cook N, Bubes V, Lee IM, Giovannucci EL, Willett W, Buring JE, Manson JE and VITAL Research Group: Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. JAMA Netw Open *3(11)*: e2025850, 2020. PMID: 33206192. DOI: 10.1001/jamanetworkopen.2020.25850
21 Luttmann-Gibson H, Mora S, Camargo CA, Cook NR, Demler OV, Ghoshal A, Wohlgemuth J, Kulkarni K, Larsen J, Prentice J, Cobble M, Bubes V, Li C, Friedenberg G, Lee IM, Buring JE and Manson JE: Serum 25-hydroxyvitamin D in the VITamin D and OmegA-3 TriaL (VITAL): Clinical and demographic characteristics associated with baseline and change with randomized vitamin D treatment. Contemp Clin Trials *87*: 105854, 2019. PMID: 31669447. DOI: 10.1016/j.cct.2019.105854
22 Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R and Allen NE: Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol *186(9)*: 1026-1034, 2017. PMID: 28641372. DOI: 10.1093/aje/kwx246
23 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM and Endocrine Society: Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab *96(7)*: 1911-1930, 2011. PMID: 21646368. DOI: 10.1210/jc.2011-0385
24 Lappe JM, Travers-Gustafson D, Davies KM, Recker RR and Heaney RP: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr *85(6)*: 1586-1591, 2007. PMID: 17556697. DOI: 10.1093/ajcn/85.6.1586
25 Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, Baggerly K and McDonnell SL: Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. JAMA *317(12)*: 1234-1243, 2017. PMID: 28350929. DOI: 10.1001/jama.2017.2115
26 Zhang Y, Fang F, Tang J, Jia L, Feng Y, Xu P and Faramand A: Association between vitamin D supplementation and mortality: systematic review and meta-analysis. BMJ *366*: l4673, 2019. PMID: 31405892. DOI: 10.1136/bmj.l4673
27 Keum N, Lee DH, Greenwood DC, Manson JE and Giovannucci E: Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. Ann Oncol *30(5)*: 733-743, 2019. PMID: 30796437. DOI: 10.1093/annonc/mdz059
28 Guo Z, Huang M, Fan D, Hong Y, Zhao M, Ding R, Cheng Y and Duan S: Association between vitamin D supplementation and cancer incidence and mortality: A trial sequential meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr: 1-15, 2022. PMID: 35352965. DOI: 10.1080/10408398.2022.2056574
29 McDonnell SL, Baggerly C, French CB, Baggerly LL, Garland CF, Gorham ED, Lappe JM and Heaney RP: Serum 25-hydroxyvitamin D concentrations ≥40 ng/ml are associated with >65% lower cancer risk: pooled analysis of randomized trial and prospective cohort study. PLoS One *11(4)*: e0152441, 2016. PMID: 27049526. DOI: 10.1371/journal.pone.0152441
30 Schöttker B, Jorde R, Peasey A, Thorand B, Jansen EH, Groot Ld, Streppel M, Gardiner J, Ordóñez-Mena JM, Perna L, Wilsgaard T, Rathmann W, Feskens E, Kampman E, Siganos G, Njølstad I, Mathiesen EB, Kubínová R, Pająk A, Topor-Madry R, Tamosiunas A, Hughes M, Kee F, Bobak M, Trichopoulou A, Boffetta P, Brenner H and Consortium on Health and Ageing: Network of Cohorts in Europe and the United States: Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. BMJ *348*: g3656, 2014. PMID: 24938302. DOI: 10.1136/bmj.g3656
31 Granic A, Aspray T, Hill T, Davies K, Collerton J, Martin-Ruiz C, von Zglinicki T, Kirkwood TB, Mathers JC and Jagger C: 25-hydroxyvitamin D and increased all-cause mortality in very old women: the Newcastle 85+ study. J Intern Med *277(4)*: 456-467, 2015. PMID: 24889485. DOI: 10.1111/joim.12273
32 Mao C, Li FR, Yin ZX, Lv YB, Luo JS, Yuan JQ, Mhungu F, Wang JN, Shi WY, Zhou JH, Chen GC, Gao X, Kraus VB, Wu XB and Shi XM: Plasma 25-hydroxyvitamin D concentrations are inversely associated with all-cause mortality among a prospective cohort of Chinese adults aged ≥80 years. J Nutr *149(6)*: 1056-1064, 2019. PMID: 30949685. DOI: 10.1093/jn/nxz041
33 Ginde AA, Scragg R, Schwartz RS and Camargo CA Jr: Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. J Am Geriatr Soc *57(9)*: 1595-1603, 2009. PMID: 19549021. DOI: 10.1111/j.1532-5415.2009.02359.x
34 Ford ES, Zhao G, Tsai J and Li C: Vitamin D and all-cause mortality among adults in USA: findings from the National Health and Nutrition Examination Survey Linked Mortality Study. Int J Epidemiol *40(4)*: 998-1005, 2011. PMID: 21266455. DOI: 10.1093/ije/dyq264
35 Autier P and Gandini S: Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med *167(16)*: 1730-1737, 2007. PMID: 17846391. DOI: 10.1001/archinte.167.16.1730
36 Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M and Gluud C: Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev *(1)*: CD007470, 2014. PMID: 24414552. DOI: 10.1002/14651858.CD007470.pub3
37 Houghton LA and Vieth R: The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr *84(4)*: 694-697, 2006. PMID: 17023693. DOI: 10.1093/ajcn/84.4.694

38 Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, Chope G, Hyppönen E, Berry J, Vieth R and Lanham-New S: Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr *95(6)*: 1357-1364, 2012. PMID: 22552031. DOI: 10.3945/ajcn.111.031070

39 Tripkovic L, Wilson LR, Hart K, Johnsen S, de Lusignan S, Smith CP, Bucca G, Penson S, Chope G, Elliott R, Hyppönen E, Berry JL and Lanham-New SA: Daily supplementation with 15 μg vitamin $D_2$ compared with vitamin $D_3$ to increase wintertime 25-hydroxyvitamin D status in healthy South Asian and white European women: a 12-wk randomized, placebo-controlled food-fortification trial. Am J Clin Nutr *106(2)*: 481-490, 2017. PMID: 28679555. DOI: 10.3945/ajcn.116.138693

40 Vieth R, McCarten K and Norwich KH: Role of 25-hydroxyvitamin D3 dose in determining rat 1,25-dihydroxyvitamin D3 production. Am J Physiol *258(5 Pt 1)*: E780-E789, 1990. PMID: 2185661. DOI: 10.1152/ajpendo.1990.258.5.E780

41 Vieth R: How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. Anticancer Res *29(9)*: 3675-3684, 2009. PMID: 19667164.

42 Vieth R: Chapter 57 - The Pharmacology of Vitamin D. In: Vitamin D (Third Edition). Feldman D, Pike JW and Adams JS (eds.). San Diego, Academic Press, pp. 1041-1066, 2011.

43 Mazess RB, Bischoff-Ferrari HA and Dawson-Hughes B: Vitamin D: Bolus is bogus-a narrative review. JBMR Plus *5(12)*: e10567, 2021. PMID: 34950828. DOI: 10.1002/jbm4.10567

44 Scragg R: Emerging evidence of thresholds for beneficial effects from vitamin D supplementation. Nutrients *10(5)*: 561, 2018. PMID: 29751504. DOI: 10.3390/nu10050561

45 Jenkins DJA, Spence JD, Giovannucci EL, Kim YI, Josse RG, Vieth R, Sahye-Pudaruth S, Paquette M, Patel D, Blanco Mejia S, Viguiliouk E, Nishi SK, Kavanagh M, Tsirakis T, Kendall CWC, Pichika SC and Sievenpiper JL: Supplemental vitamins and minerals for cardiovascular disease prevention and treatment: JACC focus seminar. J Am Coll Cardiol *77(4)*: 423-436, 2021. PMID: 33509399. DOI: 10.1016/j.jacc.2020.09.619

46 Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, Yelangi A, Sundus S, Bachuwa G, Alkotob ML and Manson JE: Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. JAMA Cardiol *4(8)*: 765-776, 2019. PMID: 31215980. DOI: 10.1001/jamacardio.2019.1870

47 Autier P, Boniol M, Pizot C and Mullie P: Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol *2(1)*: 76-89, 2014. PMID: 24622671. DOI: 10.1016/S2213-8587(13)70165-7

48 Emerging Risk Factors Collaboration/EPIC-CVD/Vitamin D Studies Collaboration: Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. Lancet Diabetes Endocrinol *9(12)*: 837-846, 2021. PMID: 34717822. DOI: 10.1016/S2213-8587(21)00263-1

49 Zhou A, Selvanayagam JB and Hyppönen E: Non-linear Mendelian randomization analyses support a role for vitamin D deficiency in cardiovascular disease risk. Eur Heart J *43(18)*: 1731-1739, 2022. PMID: 34891159. DOI: 10.1093/eurheartj/ehab809

50 Liu D, Fernandez BO, Hamilton A, Lang NN, Gallagher JMC, Newby DE, Feelisch M and Weller RB: UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol *134(7)*: 1839-1846, 2014. PMID: 24445737. DOI: 10.1038/jid.2014.27

51 Brøndum-Jacobsen P, Nordestgaard BG, Nielsen SF and Benn M: Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. Int J Epidemiol *42(5)*: 1486-1496, 2013. PMID: 24038635. DOI: 10.1093/ije/dyt168

52 Lindqvist PG, Epstein E, Nielsen K, Landin-Olsson M, Ingvar C and Olsson H: Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort. J Intern Med *280(4)*: 375-387, 2016. PMID: 26992108. DOI: 10.1111/joim.12496

53 Kimball SM, Ursell MR, O'Connor P and Vieth R: Safety of vitamin D3 in adults with multiple sclerosis. Am J Clin Nutr *86(3)*: 645-651, 2007. PMID: 17823429. DOI: 10.1093/ajcn/86.3.645

54 Hupperts R, Smolders J, Vieth R, Holmøy T, Marhardt K, Schluep M, Killestein J, Barkhof F, Beelke M, Grimaldi LME and SOLAR Study Group: Randomized trial of daily high-dose vitamin $D_3$ in patients with RRMS receiving subcutaneous interferon β-1a. Neurology *93(20)*: e1906-e1916, 2019. PMID: 31594857. DOI: 10.1212/WNL.0000000000008445

55 Dörr J, Bäcker-Koduah P, Wernecke KD, Becker E, Hoffmann F, Faiss J, Brockmeier B, Hoffmann O, Anvari K, Wuerfel J, Piper SK, Bellmann-Strobl J, Brandt AU and Paul F: High-dose vitamin D supplementation in multiple sclerosis - results from the randomized EVIDIMS (efficacy of vitamin D supplementation in multiple sclerosis) trial. Mult Scler J Exp Transl Clin *6(1)*: 2055217320903474, 2020. PMID: 32047645. DOI: 10.1177/2055217320903474

56 Vieth R: Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr *69(5)*: 842-856, 1999. PMID: 10232622. DOI: 10.1093/ajcn/69.5.842

57 Hathcock JN, Shao A, Vieth R and Heaney R: Risk assessment for vitamin D. Am J Clin Nutr *85(1)*: 6-18, 2007. PMID: 17209171. DOI: 10.1093/ajcn/85.1.6

58 Monlezun DJ, Bittner EA, Christopher KB, Camargo CA and Quraishi SA: Vitamin D status and acute respiratory infection: cross sectional results from the United States National Health and Nutrition Examination Survey, 2001-2006. Nutrients *7(3)*: 1933-1944, 2015. PMID: 25781219. DOI: 10.3390/nu7031933

59 Jolliffe DA, Holt H, Greenig M, Talaei M, Perdek N, Pfeffer P, Maltby S, Symons J, Barlow NL, Normandale A, Garcha R, Richter AG, Faustini SE, Orton C, Ford D, Lyons RA, Davies GA, Kee F, Griffiths CJ, Norrie J, Sheikh A, Shaheen SO, Relton C and Martineau AR: Vitamin D supplements for prevention of Covid-19 or other acute respiratory infections: a phase 3 randomized controlled trial (CORONAVIT). medExiv, 2022. DOI: 10.1101/2022.03.22.22271707

60 Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, Zurita-Cruz JN, Barrada-Vázquez AS, González-Ibarra J, Martínez-Reyes M, Grajales-Muñiz C, Santacruz-Tinoco CE, Martínez-Miguel B, Maldonado-Hernández J, Cifuentes-González Y, Klünder-Klünder M, Garduño-Espinosa J, López-Martínez B and Parra-Ortega I: Efficacy and safety of vitamin D supplementation to prevent COVID-19 in frontline healthcare workers. A randomized clinical trial. Arch Med Res *53(4)*: 423-430, 2022. PMID: 35487792. DOI: 10.1016/j.arcmed.2022.04.003

*Received July 28, 2022*
*Revised September 5, 2022*
*Accepted September 8, 2022*