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Review

Sunlight exposure: Do health benefits outweigh harm?

Mohammed S. Razzaque, MBBS, PhD[a,b,c,d,*]

[a] Department of Applied Oral Sciences, Forsyth Institute, Cambridge, MA, USA
[b] Department of Pathology, Saba University School of Medicine, Saba, Dutch Caribbean, Netherlands
[c] Department of Oral Health Policy & Epidemiology, Harvard School of Dental Medicine, Boston, MA, USA
[d] Department of Preventive & Community Dentistry, Rwanda University School of Dentistry, Kigali, Rwanda

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ABSTRACT

Vitamin D is a fat-soluble vitamin whose levels within the body are elevated following sunlight exposure. Numerous studies have shown that sunlight exposure can provide protection to a wide variety of diseases, ranging from different types of tumors to hypertension to type 1 diabetes to multiple sclerosis. Moreover, studies have shown that avoiding sunlight may influence the initiation and progression of some of these diseases. Avoidance of sunlight, coupled with the inclination towards consuming supplements, is becoming the primary choice to obtain vitamin D. The purpose of this article is to present evidences from published literature, to show that the expected benefits of vitamin D supplements are minimized by the potential risk of cardiovascular events and beyond. Since hypovitaminosis D status usually reflects reduced sunlight exposure, the obvious primary replacement should be safe sunlight exposure, and not exogenous supplements.

Contents

1. Vitamin D

Vitamin D, also known as the sunshine vitamin, plays an important role in calcium and phosphorous metabolism and skeletal mineralization [1–6]. Vitamin D synthesis is partly triggered when the skin is exposed to ultraviolet (UV) B rays from sunlight. The obtained Vitamin D from sunlight exposure then undergoes two hydroxylations – first in the liver and then in the kidney to produce the physiologically active form 1,25-dihydroxyvitamin D [1,25(OH)2D], which is also known as calcitriol (Fig. 1). It is believed that, in humans, around 10,000 units of vitamin D are generated within 30 min of full body exposure to the sun [7]. Exposure to sunlight is the main source of vitamin D. UVB radiation (wavelength of 290–320 nm) is able to penetrate exposed skin and can convert cutaneous 7-dehydrocholesterol to previtamin D3, which undergoes further hydroxylations in the liver and kidney to produce bioactive vitamin D3 [1]. Several factors influence UVB exposure and subsequent vitamin D synthesis such as the aging process, state of skin pigmentation, application of sunscreen, the time of sunlight exposure during the day, air pollution, and geographical locations (e.g., higher latitude) [8]. Of particular importance, UV energy is significantly reduced when the sun is completely covered by clouds, and the extent of cloud cover (light to very dark) and latitude can also influence the availability of UV energy. Also, shade by severe air pollution can reduce UV energy by 60% [9]. Moreover, indoor exposure of sunlight through a window does not induce dermal vitamin D

* Correspondence to: Department of Applied Oral Sciences, Forsyth Institute, 245 First Street, Cambridge, MA, 02142, USA.
E-mail addresses: mrazzaque@forsyth.org, mrazzaque@hms.harvard.edu (M.S. Razzaque).

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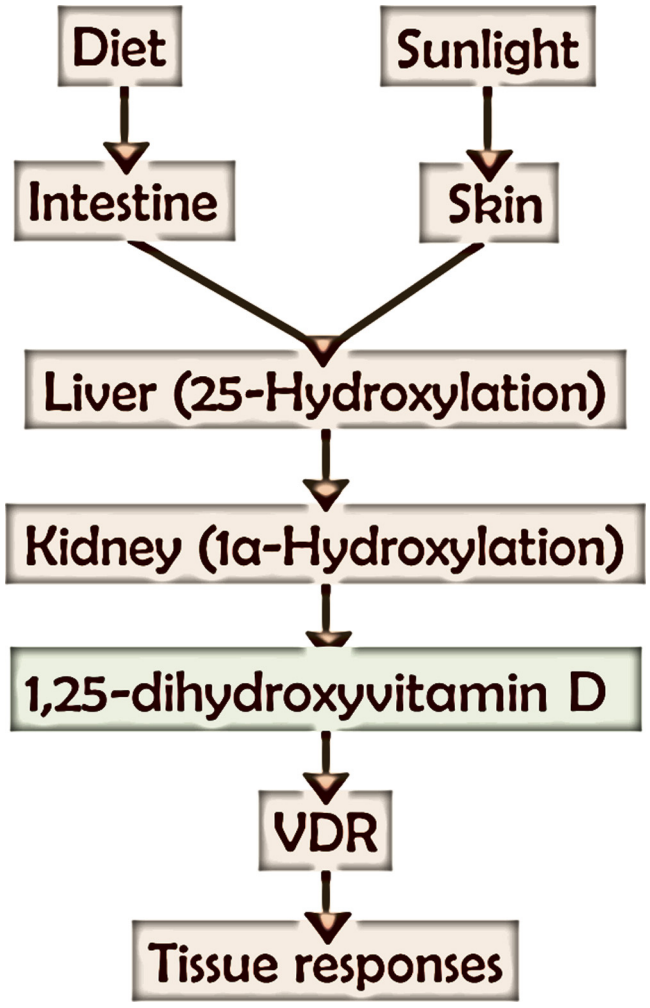

Fig. 1. Simplified diagram of the different stages of vitamin D synthesis, modified from earlier publications [1,69]. For simplicity, only essential steps of vitamin synthesis are included. **VDR**: vitamin D receptor.

synthesis, as UVB radiation is not able to penetrate through glass [10,11].

Though physiologic regulation of calcium and phosphate balance is an important function of vitamin D, the presence of vitamin D receptors (VDR) in the cellular components that are not actively involved in mineral ion metabolism raises the possibility of a wider biological role for vitamin D. In fact, studies have found a vital role for vitamin D in cell growth, immune regulation, and inflammatory modulation [12–17]. Serum level of precursor 25-hydroxyvitamin D [25(OH)D] is usually used to predict vitamin D status, with a circulating half-life of about 15 days [18]. However, serum 25(OH)D levels do not reflect the amount of vitamin D stored in various tissues, particularly in the adipose tissues. Experimental studies have shown that orally administered cholecalciferol rapidly accumulates in adipose tissue, and that it is very slowly released in periods of negative energy balance; the investigators concluded that adipose tissue is likely to act as a 'buffer to functional vitamin D status' by preventing unregulated production of 25(OH)D from dietary vitamin D up to a certain extent, and by slowly releasing vitamin D during fasting conditions [19]. Storage of the lipophilic vitamin D_3 molecule in the adipose tissue, therefore, can reduce the serum bioavailability [20,21]. Moreover, muscle tissue is also an important vitamin D reservoir, perhaps stored as 25(OH)D [22].

Table 1
Recommendations by Endocrine Society and Institute of Medicine (IOM) for vitamin D status by serum 25-hydroxyvitamin D [25(OH)D] levels [8].

	Endocrine Society	IOM
Deficient (ng/mL)	0–20	0–11
Insufficient (ng/mL)	21–29	12–20
Sufficient (ng/mL)	30–100	>20
Adverse effects (ng/mL)	>100	>50

While there is no debate on how inadequate vitamin D levels can induce certain bone diseases, including rickets (in children) and osteomalacia (in adults), there is, however, no general consensus on the optimal levels of vitamin D. According to Institute of Medicine (IOM), 25(OH)D levels of ≥20 ng/mL are considered sufficient, and when serum 25(OH)D levels are 12 ng/mL or less, persons are at risk of developing consequences related to vitamin D deficiency. According to IOM, serum levels >50 ng/mL could exert potential harmful effects as well (Table 1), and studies have shown that serum levels of 30–48 ng/mL can be linked to increase in all-cause mortality, higher risk of tumor formation and cardiovascular disorders, with more falls and fractures among the elderly individuals [8]. A large study conducted on 247,574 patients showed an increased risk for all-cause mortality (HR 1.42, 95%CI 1.31–1.52) above the range of 50–60 nmol/L of 25(OH)D. These authors concluded that 20–24 ng/mL is an optimal level [23], which supports the IOM findings and recommendations. Of relevance, the Vitamin D Council recommends serum 25(OH)D levels of 40–80 ng/mL as sufficient, while the Endocrine Society recommends 30–100 ng/mL as sufficient. It is important and perhaps alarming to note that the recommended upper limit from both expert groups falls into the harmful range of IOM recommended values (Tables 1 and 2).

2. Sunlight and vitamin D synthesis

It is an accepted fact that moderate sun exposure is sufficient to maintain adequate vitamin D levels to protect bones from diseases like rickets and/or osteomalasia [4,9]. Experts believe that approximately 5–30 min of sunlight exposure between 10 a.m. to 3 p.m. in most human populated latitudes, at least twice a week, to the face, arms, legs, or back without sunscreen can provide the required amount of vitamin D [7]. In addition to particular time of the day, seasons, likes winter can also influence production of vitamin D in skin; similarly, in some latitudes, vitamin D is not synthesized even between 10 a.m. to 3 p.m. The influence of time of the day, season, and solar zenith angle in the synthesis of vitamin D are summarized by Engelsen, and interested readers are recommended to that publication for more details [24]. Of relevance, National Health and Nutrition Examination Surveys (NHANES) found serum 25(OH)D levels were higher in blood samples

Table 2
Recommended daily intakes by Endocrine Society and Institute of Medicine (IOM) [8].

	Endocrine Society	IOM
Infants (IU/day)	400–1000	400
Children (IU/day)	600–1000	600
Adults (IU/day)	1500–2000	600 (seniors: 800)

taken during the summer (May to October), as compared to the other months of the year; such higher levels are likely to be related to more outdoor activities and exposure to sunlight during summer. One of the strong arguments of taking vitamin D supplement is that, it can be taken daily, while solar UVB exposure cannot be ensure daily due to unpredictability of the weather. Moreover, use of sunscreen can impact vitamin D synthesis; a sunscreen with a sun protection factor (SPF) of 30 absorbs approximately 95–98% of solar UVB radiation, and markedly reduces the capacity of the skin to generate vitamin D3 [25]. Without the use of sunscreen, cutaneous synthesis of vitamin D by UVB sunlight accounts for more than 80% of required vitamin D in humans. Low sun exposure correlates with increased risks of cardiovascular and brain disorders [26–34]. Conversely, UVB exposure can decrease blood pressure, possibly by increasing 1,25(OH)2D levels [35–37]. Human and experimental studies have provided evidence that vitamin D decreases the activity of the renin-angiotensin-aldosterone system to reduce the blood pressure. For instance, 1-alpha hydroxylase deficient mice that are unable to produce active vitamin D metabolite 1,25(OH)2D, develop high blood pressure and left ventricular hypertrophy [38]. Analyzing the NHANES data of 7561 individuals with available 25(OH)D measurements, studies have found that the lowest 25(OH)D quintile (<13.2 ng/mL) had a systolic blood pressure 3.5 mm Hg higher than those in the highest 25(OH)D quintile (>30 ng/mL) [39]. Some studies linked such lowering of blood pressure to UVA exposure, perhaps by influencing nitric oxide activities [40]. It is, therefore, obvious that UV exposure can have beneficial effects other than vitamin D production, as elaborated recently [41,42]; however reported observational studies, suggesting significant inverse correlations between 25(OH)D concentrations and various health outcomes, need carefully designed clinical trials to validate the notion, as most clinical trials have not been properly designed to assess the findings of observational studies [43].

Excessive UV exposure has some well-known hazards. Malignant melanoma is an aggressive tumor in which UV radiation is believed to be a causative factor [44]. In the United States, of around 1.5 million skin cancers, 10,130 annual deaths are thought to be related to metastatic melanoma, while another 3520 annual deaths are related to other skin cancers [45]. Studies are needed to determine what amount of UVB exposure is needed for the synthesis of vitamin D without increasing the risk of developing skin cancer. In fact, studies have found that most melanoma tumors arise on the least sun-exposed parts of the body, and occupational exposure to sunlight actually diminished the numbers of melanoma-affected patients [46]. In a similar line of observation, patients with early-stage melanoma who continued to receive high sunlight exposure showed an increased survival [47]. It is well-documented that cancer-related death rates decline in the lower latitudes (between 37°N and 37°S) where sunshine is more abundant. Studies have found that women with active sunlight exposure have longer life expectancy than that of women who avoided sun exposure; though risk of skin cancer increased in sunlight exposed group [48].

Of public health importance, prolonged exposure of sunlight, unlike excessive consumption of vitamin D supplements, does not induce vitamin D toxicity because skin has the ability to photodegrade previtamin D3 and vitamin D3 as it is formed. Moreover, the UVB-induced dermal activation of previtamin D_3 can produce multiple non-vitamin D metabolites, such as lumisterol, tachysterol and others, and thereby limit the excessive formation of vitamin D_3 [49]. Similarly, with the exception of food fortified with vitamin D, excessive consumption of dietary vitamin D from natural food is also very unlikely to induce vitamin D toxicity.

3. Consequences of excessive vitamin D consumption

As consumption of supplements usually do not push serum vitamin D levels high enough to be deemed toxic, advocates of vitamin D supplementation want the consumers to believe that it is safe to take higher doses for prolonged periods. A single dose (600,000 IU) of intramuscular injection of vitamin D2 resulted in increased serum levels of phosphate beyond normal range by 4 weeks and persisted till the follow up period of 8 weeks, even when serum 25(OH)D level was below the normal range [50]; of clinical importance, vitamin-D treated hyperphosphatemia can induce numerous short and long-term adverse effects [6,51–54].

Supplement-associated vitamin D toxicity can induce adverse effects, ranging from anorexia to weight loss to polyuria to cardiac arrhythmias. Focusing on the last one, a 2.5-fold increased incidence of atrial fibrillation was reported in patients with high levels of vitamin D (>100 ng/dL) that are difficult to reach without consuming a high dose of vitamin D supplements [55]. Moreover, vitamin D can also elevate serum calcium and phosphate levels to initiate and propagate ectopic calcification in blood vessels, nephrocalcinosis and stone formation [56–58]. When such calcification involves vascular components, particularly coronary arteries, it may lead to fatal consequences [1,57,59]. An increased risk of all-cause mortality and acute coronary syndrome were noted in a cohort of 420,000 patients, when 25(OH)D levels exceeded 36 ng/mL [60]. It is, however, important to remember that vitamin D toxicity from supplement consumption is not always a quantitative problem, but can also be a qualitative issue, and supplement-induced adverse effects can be observed – even in the hypovitaminosis D state. As mentioned, high dose of vitamin D treatment induced hyperphosphatemia despite serum 25(OH)D level stayed below the normal range [50], clearly suggesting that supplement-mediated adverse effects could be induced in the hypovitaminosis D state.

Some experts believe that a daily intake of vitamin D supplements below 10,000 IU/day is unlikely to produce adverse effects [61]; in a vitamin D risk assessment, Hathcock et al. [61] concluded that a reasonable and safe tolerable upper intake level (UL) should be 10,000 IU of vitamin D per day, which corresponds to a serum 25(OH)D concentration of approximately 100 ng/mL. Of relevance, the IOM deems daily uptake of up to 4000 IUs of vitamin D is safe for children and adults [8]. But taking into consideration numerous national survey data and clinical trials, the Food and Nutrition Board concluded that an even lower amount of vitamin D intake by supplementation might have adverse health effects over time. A 17% increase in the risk of kidney stones was found in postmenopausal women, who consumed both calcium (1000 mg/day) and vitamin D (400 IU) supplements for approximately 7 years [62]. Of relevance, some specialists of vitamin D biology believe that the IOM recommended values are too low [63]. Since the purpose of this article is to discuss the utility of solar UVB exposure as a primary source of vitamin D, discussing the long-standing debate of IOM recommendation is beyond the scope of this article.

The acute and chronic toxicity related to extremely high consumption of vitamin D is beyond doubt. For instance, accidental consumption of 600,000 IU vitamin D_2/day for 21 days resulted in nausea, vomiting, and weight loss, thirst, polyuria, and poor mental concentration in a 72-year-old man [64]. Although some analysis found that excessive vitamin D2 might not be as detrimental as D3 [65]. In a separate report, extremely high dose of vitamin D_3 consumption for several months resulted in hypercalcemia, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss [66]. In a similar line of study, 11 patients who were treated with high dose of injectable form of vitamin D (600,000 IU) for various skeletal and metabolic diseases showed

Table 3
Partial list of the symptoms encountered in vitamin D intoxication [18,67,70].

- Anorexia
- Constipation
- Ectopic calcification
- Headache
- Hypercalcemia
- Hypercalciuria
- Hyperphosphatemia
- Hypertension
- Nausea/vomiting
- Polydipsia
- Polyuria
- Renal stones

clinical features of hypervitaminosis D; all the high vitamin D-treated patients developed hypercalcemia, recurrent vomiting, abdominal pain, polyuria, polydipsia, constipation, anorexia and weakness [67] (Table 3). It is commonly believed that there is a U-shaped and/or J-shaped relationships exist between vitamin D status and the health outcome, though some studies suggest that such associations might not always be the case.

4. Conclusions

For most adults, the recommended daily allowance (RDA) is 600 IU/day of vitamin D [Table 2]. This amount is predicted to enable 97.5% of the population to achieve serum 25(OH)D values of 20 ng/mL or more. Despite the efficacy of moderate safe sunlight exposure to ensure adequate vitamin D levels, our dependency on supplements is growing and often becoming our primary choice. Experts recommended that “moderate sun exposure (less than the time required to burn) to the arms, shoulders, trunk, and legs should be sought rather than avoided” [68]. Some studies suggest that it is possible to produce vitamin D by safe sunlight during the spring, summer, and fall months and store it in the liver and fat for use over the winter [8]. As pointed out by Baggerly et al. [68], humans have an innate ability to produce endogenous vitamin D in response to sunlight exposure, and since lower vitamin D status reflects reduced sun exposure, the obvious primary source should be sunlight, and not exogenous supplements.

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References

[1] M.S. Razzaque, The dualistic role of vitamin D in vascular calcifications, Kidney Int. 79 (2011) 708–714.
[2] M.S. Razzaque, The FGF23-Klotho axis: endocrine regulation of phosphate homeostasis, Nat. Rev. Endocrinol. 5 (2009) 611–619.
[3] M.S. Razzaque, FGF23-mediated regulation of systemic phosphate homeostasis: is Klotho an essential player? Am. J. Physiol. Renal. Physiol. 296 (2009) F470–476.
[4] B. Lanske, M.S. Razzaque, Vitamin D and aging: old concepts and new insights, J. Nutr. Biochem. 18 (2007) 771–777.
[5] M.S. Razzaque, R. St-Arnaud, T. Taguchi, B. Lanske, FGF-23, vitamin D and calcification: the unholy triad, Nephrol. Dial. Transplant. 20 (2005) 2032–2035.
[6] R.B. Brown, M.S. Razzaque, Phosphate toxicity: a stealth biochemical stress factor? Med. Mol. Morphol. 49 (2016) 1–4.
[7] M. Wacker, M.F. Holick, Sunlight and vitamin D: a global perspective for health, Dermatoendocrinology 5 (2013) 51–108.
[8] IOM, Institute of Medicine, Food and Nutrition Board, Dietary Reference Intakes for Calcium and Vitamin D, National Academy Press, Washington, DC, 2010 (2010).
[9] B. Wharton, N. Bishop, Rickets, Lancet 362 (2003) 1389–1400.
[10] M.F. Holick, Vitamin D: evolutionary, physiological and health perspectives, Curr. Drug Targets 12 (2011) 4–18.
[11] M.F. Holick, Sunlight, ultraviolet radiation, vitamin D and skin cancer: how much sunlight do we need? Adv. Exp. Med. Biol. 810 (2014) 1–16.
[12] E. Wintermeyer, C. Ihle, S. Ehnert, U. Stockle, G. Ochs, P. de Zwart, I. Flesch, C. Bahrs, A.K. Nussler, Crucial role of vitamin D in the musculoskeletal system, Nutrients (2016), doi:http://dx.doi.org/10.3390/nu8060319.
[13] J.A. Reynolds, I.N. Bruce, Vitamin D treatment for connective tissue diseases: hope beyond the hype? Rheumatology (Oxford) (2016), doi:http://dx.doi.org/10.1093/rheumatology/kew1212.
[14] M. Bscheider, E.C. Butcher, Vitamin D immunoregulation through dendritic cells, Immunology (2016), doi:http://dx.doi.org/10.1111/imm.12610.
[15] R.J. Mellanby, Beyond the skeleton: the role of vitamin D in companion animal health, J. Small Anim. Pract. 57 (2016) 175–180.
[16] C. Mattozzi, G. Paolino, A.G. Richetta, S. Calvieri, Psoriasis, vitamin D and the importance of the cutaneous barrier's integrity: an update, J. Dermatol. 43 (2016) 507–514.
[17] S.Z. Shahrokhi, F. Ghaffari, F. Kazerouni, Role of vitamin D in female reproduction, Clin. Chim. Acta 455 (2016) 33–38.
[18] G. Jones, Pharmacokinetics of vitamin D toxicity, Am. J. Clin. Nutr. 88 (2008) 582S–586S.
[19] D.A. Brouwer, J. van Beek, H. Ferwerda, A.M. Brugman, F.R. van der Klis, H.J. van der Heiden, F.A. Muskiet, Rat adipose tissue rapidly accumulates and slowly releases an orally-administered high vitamin D dose, Br. J. Nutr. 79 (1998) 527–532.
[20] C. Ding, V. Parameswaran, L. Blizzard, J. Burgess, G. Jones, Not a simple fat-soluble vitamin: changes in serum 25-(OH)D levels are predicted by adiposity and adipocytokines in older adults, J. Intern. Med. 268 (2010) 501–510.
[21] I. Barchetta, M. De Bernardinis, D. Capoccia, M.G. Baroni, M. Fontana, A. Fraioli, S. Morini, F. Leonetti, M.G. Cavallo, Hypovitaminosis D is independently associated with metabolic syndrome in obese patients, PLoS One 8 (2013) e68689.
[22] M. Abboud, C. Gordon-Thomson, A.J. Hoy, S. Balaban, M.S. Rybchyn, L. Cole, Y. Su, T.C. Brennan-Speranza, D.R. Fraser, R.S. Mason, Uptake of 25-hydroxyvitamin D by muscle and fat cells, J. Steroid Biochem. Mol. Biol. 144 (Pt. A) (2014) 232–236.
[23] D. Durup, H.L. Jorgensen, J. Christensen, P. Schwarz, A.M. Heegaard, B. Lind, A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: the CopD study, J. Clin. Endocrinol. Metab. 97 (2012) 2644–2652.
[24] O. Engelsen, The relationship between ultraviolet radiation exposure and vitamin D status, Nutrients 2 (2010) 482–495.
[25] M.F. Holick, Vitamin D deficiency, N. Engl. J. Med. 357 (2007) 266–281.
[26] L. Wang, J.E. Manson, Y. Song, H.D. Sesso, Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events, Ann. Intern. Med. 152 (2010) 315–323.
[27] F.C. Griffin, C.A. Gadegbeku, M.R. Sowers, Vitamin D and subsequent systolic hypertension among women, Am. J. Hypertens. 24 (2011) 316–321.
[28] K.A. Young, J.K. Snell-Bergeon, R.G. Naik, J.E. Hokanson, D. Tarullo, P.A. Gottlieb, S.K. Garg, M. Rewers, Vitamin D deficiency and coronary artery calcification in subjects with type 1 diabetes, Diabetes Care 34 (2011) 454–458.
[29] I.H. de Boer, B. Kestenbaum, A.B. Shoben, E.D. Michos, M.J. Sarnak, D.S. Siscovick, 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification, J. Am. Soc. Nephrol. 20 (2009) 1805–1812.
[30] M.F. Holick, Sunlight and vitamin D: both good for cardiovascular health, J. Gen. Intern. Med. 17 (2002) 733–735.
[31] D. Martins, M. Wolf, D. Pan, A. Zadshir, N. Tareen, R. Thadhani, A. Felsenfeld, B. Levine, R. Mehrotra, K. Norris, Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey, Arch. Intern. Med. 167 (2007) 1159–1165.
[32] T.J. Wang, M.J. Pencina, S.L. Booth, P.F. Jacques, E. Ingelsson, K. Lanier, E.J. Benjamin, R.B. D'Agostino, M. Wolf, R.S. Vasan, Vitamin D deficiency and risk of cardiovascular disease, Circulation 117 (2008) 503–511.
[33] J. Hsia, G. Heiss, H. Ren, M. Allison, N.C. Dolan, P. Greenland, S.R. Heckbert, K.C. Johnson, J.E. Manson, S. Sidney, M. Trevisan, Calcium/vitamin D supplementation and cardiovascular events, Circulation 115 (2007) 846–854.
[34] J. Parker, O. Hashmi, D. Dutton, A. Mavrodaris, S. Stranges, N.B. Kandala, A. Clarke, O.H. Franco, Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis, Maturitas 65 (2010) 225–236.
[35] S.G. Rostand, Ultraviolet light may contribute to geographic and racial blood pressure differences, Hypertension 30 (1997) 150–156.
[36] S.G. Rostand, Vitamin D deficiency in the pathogenesis of hypertension: still an unsettled question, Curr. Hypertens Rep. 16 (2014) 464.
[37] S.G. Rostand, Vitamin D, blood pressure, and African Americans: toward a unifying hypothesis, Clin. J. Am. Soc. Nephrol. 5 (2010) 1697–1703.
[38] C. Zhou, F. Lu, K. Cao, D. Xu, D. Goltzman, D. Miao, Calcium-independent and 1,25(OH)2D3–dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice, Kidney Int. 74 (2008) 170–179.
[39] J.L. He, R.K. Scragg, Vitamin D, parathyroid hormone, and blood pressure in the National Health and Nutrition Examination Surveys, Am. J. Hypertens 24 (2011) 911–917.
[40] C. Oplander, C.M. Volkmar, A. Paunel-Gorgulu, E.E. van Faassen, C. Heiss, M. Kelm, D. Halmer, M. Murtz, N. Pallua, C.V. Suschek, Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from

intracutaneous photolabile nitric oxide derivates, Circ. Res. 105 (2009) 1031–1040.
[41] P. Autier, M. Boniol, C. Pizot, P. Mullie, Vitamin D status and ill health: a systematic review, Lancet Diabetes Endocrinol. 2 (2014) 76–89.
[42] M.J. Bolland, A. Grey, G.D. Gamble, I.R. Reid, The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis, Lancet Diabetes Endocrinol. 2 (2014) 307–320.
[43] R.P. Heaney, Guidelines for optimizing design and analysis of clinical studies of nutrient effects, Nutr. Rev. 72 (2014) 48–54.
[44] Y.M. Chang, J.H. Barrett, D.T. Bishop, B.K. Armstrong, V. Bataille, W. Bergman, M. Berwick, P.M. Bracci, J.M. Elwood, M.S. Ernstoff, R.P. Gallagher, A.C. Green, N. A. Gruis, E.A. Holly, C. Ingvar, P.A. Kanetsky, M.R. Karagas, T.K. Lee, L. Le Marchand, R.M. Mackie, H. Olsson, A. Osterlind, T.R. Rebbeck, P. Sasieni, V. Siskind, A.J. Swerdlow, L. Titus-Ernstoff, M.S. Zens, J.A. Newton-Bishop, Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls, Int. J. Epidemiol. 38 (2009) 814–830.
[45] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA Cancer J. Clin. 66 (2016) 7–30.
[46] M.N. Mead, Benefits of sunlight: a bright spot for human health, Environ. Health Perspect. 116 (2008) A160–167.
[47] M. Berwick, B.K. Armstrong, L. Ben-Porat, J. Fine, A. Kricker, C. Eberle, R. Barnhill, Sun exposure and mortality from melanoma, J. Natl. Cancer Inst. 97 (2005) 195–199.
[48] P.G. Lindqvist, E. Epstein, K. Nielsen, M. Landin-Olsson, C. Ingvar, H. Olsson, 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. (2016).
[49] A.R. Webb, B.R. DeCosta, M.F. Holick, Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation, J. Clin. Endocrinol. Metab. 68 (1989) 882–887.
[50] J. Rajah, L. Abdel-Wareth, A. Haq, Failure of alphacalcidol (1alpha-hydroxyvitamin D3) in treating nutritional rickets and the biochemical response to ergocalciferol, J. Steroid Biochem. Mol. Biol. 121 (2010) 273–276.
[51] M.S. Razzaque, Phosphate toxicity and vascular mineralization, Contrib. Nephrol. 180 (2013) 74–85.
[52] S. Osuka, M.S. Razzaque, Can features of phosphate toxicity appear in normophosphatemia? J. Bone Miner. Metab. 30 (2012) 10–18.
[53] M.S. Razzaque, Phosphate toxicity: new insights into an old problem, Clin. Sci. (Lond) 120 (2011) 91–97.
[54] M. Ohnishi, M.S. Razzaque, Dietary and genetic evidence for phosphate toxicity accelerating mammalian aging, FASEB J. 24 (2010) 3562–3571.
[55] M.B. Smith, H.T. May, T.L. Blair, J.L. Anderson, J.B. Muhlestein, B.D. Horne, D.L. Lappe, J.D. Day, B.G. Crandall, P. Weiss, Vitamin D excess is significantly associated with risk of atrial fibrillation, Circulation 124 (2011) A14699.
[56] H. Ketha, R.J. Singh, S.K. Grebe, E.J. Bergstralh, A.D. Rule, J.C. Lieske, R. Kumar, Altered calcium and vitamin D homeostasis in first-time calcium kidney stone-formers, PLoS One 10 (2015) e0137350.
[57] R.B. Brown, A. Haq, C.F. Stanford, M.S. Razzaque, Vitamin D, phosphate, and vasculotoxicity, Can. J. Physiol. Pharmacol. 93 (2015) 1077–1082.
[58] S. Nguyen, L. Baggerly, C. French, R.P. Heaney, E.D. Gorham, C.F. Garland, 25-Hydroxyvitamin D in the range of 20–100 ng/mL and incidence of kidney stones, Am. J. Public Health 104 (2014) 1783–1787.
[59] M.S. Razzaque, B. Lanske, Hypervitaminosis D and premature aging: lessons learned from Fgf23 and Klotho mutant mice, Trends Mol. Med. 12 (2006) 298–305.
[60] Y. Dror, S.M. Giveon, M. Hoshen, I. Feldhamer, R.D. Balicer, B.S. Feldman, Vitamin D levels for preventing acute coronary syndrome and mortality: evidence of a nonlinear association, J. Clin. Endocrinol. Metab. 98 (2013) 2160–2167.
[61] J.N. Hathcock, A. Shao, R. Vieth, R. Heaney, Risk assessment for vitamin D, Am. J. Clin. Nutr. 85 (2007) 6–18.
[62] R.D. Jackson, A.Z. LaCroix, M. Gass, R.B. Wallace, J. Robbins, C.E. Lewis, T. Bassford, S.A. Beresford, H.R. Black, P. Blanchette, D.E. Bonds, R.L. Brunner, R.G. Brzyski, B. Caan, J.A. Cauley, R.T. Chlebowski, S.R. Cummings, I. Granek, J. Hays, G. Heiss, S.L. Hendrix, B.V. Howard, J. Hsia, F.A. Hubbell, K.C. Johnson, H. Judd, J. M. Kotchen, L.H. Kuller, R.D. Langer, N.L. Lasser, M.C. Limacher, S. Ludlam, J.E. Manson, K.L. Margolis, J. McGowan, J.K. Ockene, M.J. O'Sullivan, L. Phillips, R.L. Prentice, G.E. Sarto, M.L. Stefanick, L. Van Horn, J. Wactawski-Wende, E. Whitlock, G.L. Anderson, A.R. Assaf, D. Barad, Calcium plus vitamin D supplementation and the risk of fractures, N. Engl. J. Med. 354 (2006) 669–683.
[63] R.P. Heaney, M.F. Holick, Why the IOM recommendations for vitamin D are deficient, J. Bone Miner. Res. 26 (2011) 455–457.
[64] R.R. Todd, E.A. Bailey, K.L. Espiner, Vitamin D2 for the treatment of chilblains-a cautionary tale, N. Z. Med. J. 100 (1987) 465.
[65] R. Chowdhury, S. Kunutsor, A. Vitezova, C. Oliver-Williams, S. Chowdhury, J.C. Kiefte-de-Jong, H. Khan, C.P. Baena, D. Prabhakaran, M.B. Hoshen, B.S. Feldman, A. Pan, L. Johnson, F. Crowe, F.B. Hu, O.H. Franco, Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies, BMJ 348 (2014) g1903.
[66] R. Vieth, T.R. Pinto, B.S. Reen, M.M. Wong, Vitamin D poisoning by table sugar, Lancet 359 (2002) 672.
[67] S. Sath, A.R. Shah, S. Nadeem, S.N. Rafiq, I. Jeelani, Hypervitaminosis D in Kashmiri population: a case series of 11 patients, SSRG Int. J. Med. Sci. 3 (2016) 1–6.
[68] C.A. Baggerly, R.E. Cuomo, C.B. French, C.F. Garland, E.D. Gorham, W.B. Grant, R. P. Heaney, M.F. Holick, B.W. Hollis, S.L. McDonnell, M. Pittaway, P. Seaton, C.L. Wagner, A. Wunsch, Sunlight and Vitamin D: necessary for public health, J. Am. Coll. Nutr. 34 (2015) 359–365.
[69] R.B. Brown, F. Al Anouti, M.S. Razzaque, Vitamin D supplements: magic pill or overkill? South East Asia J. Public Health 5 (2015) 1–3.
[70] NIH, Vitamin D: Fact Sheet Health Professionals, (2016) . https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/.