Calcif Tissue Int (2013) 92:177–183
DOI 10.1007/s00223-012-9605-6

ORIGINAL RESEARCH

What Is Vitamin D Insufficiency? And Does It Matter?

Robert P. Heaney

Received: 9 January 2012 / Accepted: 27 April 2012 / Published online: 15 May 2012

Abstract The term nutrient "insufficiency," as commonly used, refers to a nutritional status intermediate between classical, severe deficiency, and full normal. As both "deficiency" and "insufficiency" are causes of dysfunction and disease, there is no biological basis for a distinction between them. What is important to note is that, in the case of vitamin D, the preponderance of the evidence indicates that there is real, preventable disease in the range of vitamin D status values now labeled "insufficient."

Keywords Vitamin D · 25(OH)D · Osteomalacia · Vitamin D requirement

Nutrients are substances provided by the environment which an organism needs for normal physiological function. Energy and water were the first two nutrients recognized to serve in this way, and as recently as 90 years ago, they were the *only* substances so recognized. Toward the end of the First World War E. V. McCollum tried to convince two standing committees of the American Medical Association that inadequate intake of two substances (now recognized as vitamin A and thiamine) would lead to explicit disease and suggested that these two were the advance guard of a host of others [1]. His presentation was met with derision. At the time the prevailing medical model was that all disease was caused by external agencies, microbial or toxic. The notion that *not* eating something could make one sick was judged absurd. Nutrition was mainly a matter of taking on enough fuel. If you had enough to sustain your daily work, you were adequately nourished.

Nutrition has come far in the past 90 years, with about 20 substances now recognized as essential, each carrying at least tentative intake recommendations. Moreover, there are 20 or so additional nutrients still inadequately explored. Despite this progress, there still is a general undercurrent in medicine which downplays the importance of nutrition [2] and often fits nutrients into the old disease paradigm, i.e., as potentially toxic (e.g., cholesterol, sodium, saturated fat). This skepticism has contributed to a marginalization of nutrition, where it merges into all kinds of quackery, thereby further justifying medicine's skepticism.

Awareness of this historical background is useful as we attempt to understand current approaches to defining inadequacy, not just for vitamin D but for most other nutrients as well. Vestiges of past attitudes persist into the present.

Deficient, Insufficient, Adequate

Despite the conquest of diseases such as scurvy and beriberi, medicine still seems to operate from the same resistant stance that confronted McCollum. Today, that presumption takes the form of "current diets provide most or all of what a person needs." The notion that not getting enough of nutrient *X* (vitamin D in this case) could cause or increase the risk of disease *Y* is considered unlikely at the very outset. As a consequence, nutrition policy has increasingly been based on an approach that requires proponents of nutrient intakes higher than those prevailing in the population to provide proof that more is better,

The author has stated that there is no conflict of interest.

R. P. Heaney (✉)
Creighton University, 601 N. 30th Street, Suite 4841, Omaha, NE 68131, USA
e-mail: rheaney@creighton.edu

specifically in the form of randomized controlled trials (RCTs). In the absence of such proof, prevailing intakes are deemed adequate, though there is no proof of that, nor even, for most nutrients, any consensus as to what "adequate" means.

This is not to suggest that medicine does not recognize deficiency disease. Pellagra, rickets, beriberi, and scurvy are classic examples. But these were past triumphs; they are caused by intakes of nutrients *below* prevailing diet levels, often far below. Except for continuing sporadic cases, public health measures, such as food fortification, would seem to have taken care of these problems. People who do not have these diseases explicitly are presumed to be ingesting sufficient quantities of the nutrients concerned.

Against this background skepticism, there has been a slowly growing recognition for most nutrients, not just for vitamin D, that intakes lower than average but still above frank deficiency levels could increase the risk or severity of various diseases. Since individuals with these conditions did not have the classical manifestations of "deficiency," their status was labeled not "deficient" but "insufficient." This terminologic distinction is a vestige of the original model for nutrition, i.e., one nutrient–one disease, with which nutritional science began and which has no real biological basis. (Unfortunately, it is a model that is still enshrined in food claim regulations of the US Food and Drug Administration, which, in effect, permit only one disease per nutrient [3].)

We no longer hold that nutrients have but one function or one target organ. Current nutritional science understands that most tissues and body systems have a requirement for most nutrients. As a result, inadequate intake of *any* nutrient must result in some functional impairment of one or more body systems, with those most affected producing the symptom complex that medicine calls "disease." In brief, and ignoring the labels "deficient" and "insufficient," it seems inescapable that any intake/nutrient status that results in preventable dysfunction or disease must be labeled "inadequate."

Defining Adequacy

Aside from simply assuming that current intakes are adequate, what problems come with the current evidence-based nutrition (EBN) approach to defining intake recommendations? And if those problems are not tractable, what alternatives might be considered? The problems have been explored in depth elsewhere [4–7]. They consist basically in the fact that nutrients are not drugs, and approaches based on a drug model (evidence-based medicine [EBM]) fit nutrients poorly. Critical differences consist of (1) often very different dose–response curves (e.g., threshold [or plateau] effect response for nutrients), (2) ethical problems created by placing a contrast group on a low intake of a substance recognized as important for health, (3) critical nutrient–nutrient interactions, (4) absence of a feasible zero-intake contrast group in RCTs, (5) smallness of effect size, and (6) multisystem outcomes. Two of these are of sufficient salience that, by themselves, they show why the newly adopted EBN approach must fail to define adequacy.

Figure 1 represents a typical nutrient response curve and illustrates why the foregoing problems make it difficult to determine adequacy of intake using a typical RCT design. As the figure makes plain, the response is sigmoidal, with a plateau region above which increases in intake produce no further effect. To show a reduction in disease risk in an RCT requires that one contrast group have a low intake/status and the other an intake/status near or above the plateau threshold. (Incidentally, failure to locate the contrasting study intakes relative to the central segment of this sigmoidal curve virtually guarantees a null effect in a clinical trial, a point usually overlooked in systematic reviews and meta-analyses.)

Nevertheless, a properly designed trial, if positive, would indeed serve to establish a causal relationship between the nutrient and a particular health or disease outcome. But it would not thereby define an "adequate" intake/status. As Fig. 1 suggests, the plateau, i.e., the maximum achievable benefit, is approached asymptotically. In theory at least, it could be approximated by a

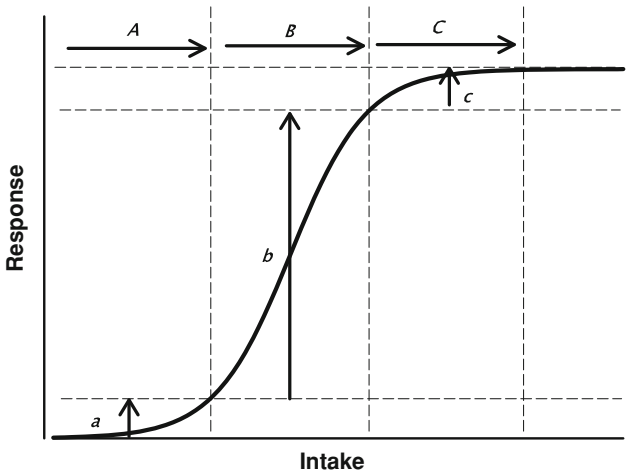

Fig. 1 Typical sigmoidal *curve* showing physiological response as a function of nutrient intake. "Response" refers both to probability of measurable benefit in a population and to the actual values of the physiological variable by which response is assessed in a treated individual. Depicted are the expected responses from *equal* increments in intake, starting from a low basal intake and moving to progressively higher starting levels. Intake increments *A*, *B*, and *C* produce responses, *a*, *b*, and *c*, respectively. Only intakes in the *B* region produce responses large enough to test the hypothesis that the nutrient concerned elicits the response in question (Copyright Robert P. Heaney, M.D., 2010. All rights reserved. Used with permission)

series of paired trials, gradually climbing toward the plateau. If intake *X* is proven to produce a benefit, then use *X* as the control group intake for a second trial, testing *X* plus *Y* intake against *X* alone. And if *X* plus *Y* can be shown to have a benefit, then repeat. The problem, as Fig. 1 shows, is that the incremental benefit is small and gets progressively more so as intake/status rises. Thus, while in theory the RCT can establish *efficacy*, it cannot easily locate the therapeutic threshold above which lies *adequacy*.

Further, in practice, the RCT encounters ethical obstacles since, to establish efficacy for a second or third body system, one contrast group (the controls) must have a low intake/status of the nutrient—somewhere below the midpoint of the rise in Fig. 1. But this guarantees that participants will suffer the effects of inadequate intake/status for at least some body systems (if not the one currently being tested). For example, a control group for a trial testing a putative hypertension end point would have to have a 25(OH)D status well below 20 ng/mL (50 nmol/L) if a possible treatment effect were to be sought and found. The study of Priemel et al. [8] showed that a substantial fraction of individuals exhibit increased osteoid volume at serum 25(OH)D levels below 30 ng/mL (75 nmol/L), and Bischoff-Ferrari and her colleagues showed increased fracture risk in this same range of vitamin D status values [see 41, 42]. Thus, the controls in such a study would be at risk of incurring skeletal abnormality.

In brief, although the RCT is the standard upon which nutrient requirements are now based, it cannot actually establish the point of full adequacy, nor, once one disease outcome has been established, can it ethically test efficacy for most other end points. Clearly, more useful, indeed more intrinsically physiological, criteria are needed. Several have been recently suggested [9], including three that have potential utility for defining vitamin D adequacy. These are (1) a set point criterion, (2) a plateau criterion, and (3) a primitive intake criterion. All three were explored to a limited extent by the Institute of Medicine (IOM) in its document on calcium and vitamin D requirements [10]. Ultimately, however, the expert panel reverted to an empirical (as opposed to physiological), RCT-based conclusion. It is important to note that, with the physiological approach, the presumption of adequacy attaches to and follows from a *physiological* foundation, and firm evidence would be required to show that less was safe. That is the exact opposite of the current empirical approach, which presumes that prevailing intakes are adequate and requires firm evidence to show that more is better.

The contrast between a physiological and an empirical approach is illustrated nicely with respect to the first two of the suggested criteria, i.e., the calcium absorptive plateau and the inverse relation between PTH and serum 25(OH)D. The IOM [10] found the calcium absorptive plateau to occur at lower 25(OH)D concentrations than have others [11]. Similarly, the PTH set point has been found by some to occur at 25(OH)D values ranging from as low as 10 ng/mL (25 nmol/L) [12] to as high as 49 ng/mL (122 nmol/L) [13]. The point here is not to claim one conclusion from the data to be correct and the others not but to assert that, once such a physiological criterion is accepted as the yardstick of adequacy, the location of the plateau or of the set point can be objectively determined using appropriate physiological methods, thus bypassing both of the barriers that frustrate the empirical, RCT-based approach.

The third criterion, i.e., primitive intake, is perhaps less controverted. It is clear that vitamin D is synthesized in the skin on exposure to UV-B radiation. The quantity so synthesized is reasonably well established [14–18], as is the effect of skin pigmentation on that endogenous production [19]. Further, it is generally agreed that *Homo sapiens* evolved in equatorial East Africa, glabrous and wearing little or no clothing. Thus, it is virtually certain that primitive cutaneous production would have been in excess of 5,000 IU/day. Further, as outdoor summer workers can have 25(OH)D values ranging up to at least 90 ng/mL (225 nmol/L), the physiological range must be recognized as extending to that level [20, 21]. In limited measurements in Masai natives, values above 40 ng/mL (100 nmol/L) are the norm [22]. Thus, any value less than 40 ng/mL would have to be considered as below primitive status.

The argument from primitive intake is that this is the intake/status to which human physiology is fine-tuned, and it is thus the intake best suited to normalize the function of the various body systems in which vitamin D plays a role. That is not proof, of course, given drastically changed nutritional and environmental influences over the millennia following the agricultural revolution. But starting at the primitive input does get us back to where we were as a modern species when we crossed over from a hunter–gatherer lifestyle to an agricultural one (a transition that occurred as recently as 3,000 years ago in the Western Hemisphere and about 10,000 years ago in the Fertile Crescent). Any such physiological criterion would thus be given the presumption of correctness until proved otherwise; i.e., it must be shown to be incorrect, rather than the other way about.

The Consequences of Inadequacy

The IOM has defined "deficiency" as a 25(OH)D value below 12 ng/mL (30 nmol/L) and "sufficiency" as values above 20 ng/mL (50 nmol/L) [10]. The IOM report avoids the term "insufficiency," but, as currently employed, the range between 12 and 20 ng/mL (and probably between 12

and 30 ng/mL) would comprise what is usually meant by that term. Setting aside for a moment whether 20 ng/mL (50 nmol/L) is indeed adequate, what is important to note is that there will inescapably be some dysfunction/disability associated with inadequate vitamin D status. Thus, it would seem more straightforward to use the term "inadequate" or "inadequacy" (as the IOM report seemed to favor) for any status associated with dysfunction preventable by a higher vitamin D intake/status.

The range of diseases that have been associated with low vitamin D status extends from the long-recognized rickets/osteomalacia to osteoporotic fractures, hypertension, preeclampsia, low–birth weight newborns, reduced resistance to infection, several forms of cancer, schizophrenia, and autoimmune disorders such as multiple sclerosis and type 1 diabetes, among others [23–27]. This breadth of association is not surprising given the fact that vitamin D is involved in the regulation of gene expression in many tissues, and hence, any inadequacy would be expected to impair to some extent the function of several body systems. It is likely that each of these system responses follows the sigmoid type of curve shown in Fig. 1, and it is also likely that the 25(OH)D value associated with adequacy for a particular end point may well differ from tissue to tissue and from system to system. In this sense, "adequate" for the whole organism would refer to the 25(OH)D status (and the intake required to assure it) that would be above the plateau threshold for the system with the highest apparent requirement.

The evidence for the various disease end points has been extensively reviewed (and debated) elsewhere [10, 23, 27–38] and would be beyond the scope of this essay in any case. Only a few additional points need to be made here.

First, consider the canonical effect of vitamin D on calcium absorption and the consequent skeletal expression of rickets and osteomalacia. Generally, the clinical manifestations of rickets or osteomalacia are obliterated at 25(OH)D levels above 12 ng/mL (30 nmol/L), and it had long been presumed that, accordingly, there were no histological abnormalities above 12 ng/mL as well. However, the recent autopsy study by Priemel et al. [8] showed clearly that definable histological abnormalities persisted up to serum 25(OH)D levels as high as 30–32 ng/mL (75–80 nmol/L) (see Fig. 2). Additionally, their data showed that for the 25-plus individuals in their series with 25(OH)D concentrations of 32 ng/mL (80 nmol/L) or above, the upper limit for osteoid volume (OV/BV) was actually 1 %, not the 2 % used in earlier estimations and not the 1.2 % figure which Priemel et al. themselves suggested might be applied to their data (and which yields virtually the same proportion of abnormality as the 1 % value).

It should be noted that Recker et al. [39], who were among the first to attempt to define the normal range of values for the various histomorphometric measurements,

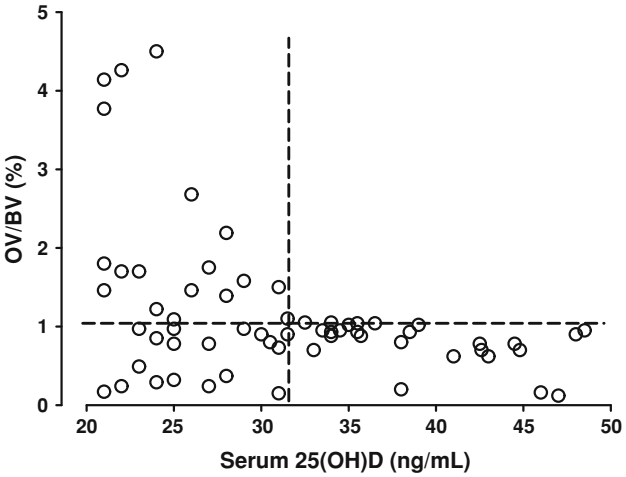

Fig. 2 Osteoid volume (*OV/BV*) expressed as a function of vitamin D status in those individuals in the study of Priemel et al. [8] with serum 25(OH)D values of 50 nmol/L (20 ng/mL) or higher (the level proposed by the IOM as "sufficient"). *Horizontal dashed line* demarcates a plausible normal value for osteoid volume as suggested from the data of Priemel (1 %) and *vertical dashed line*, the 25(OH)D boundary between those individuals with and without values for osteoid volume above the 1 % boundary. Redrawn from the data of Priemel et al. [8] (Copyright Robert P. Heaney, 2011. All rights reserved. Used with permission)

made no reference to the vitamin D status of the subjects providing the biopsies that they used to establish the "healthy" norms. Thus, their estimate of 2–3 % was clearly tentative and, in view of the Priemel et al. data, possibly incorrect. Using the 1 % criterion, about half the individuals in this study with 25(OH)D values in the range of 20–32 ng/mL had increased osteoid volume on bone biopsy, as Fig. 2 shows. Below 20 ng/mL the prevalence of elevated osteoid volume rose to ~68 % (not shown). On the basis of this criterion alone, I believe that serum 25(OH)D values below 30–32 ng/mL (75–80 nmol/L) cannot be considered "normal" or "adequate."

And, lest it be objected that histological abnormality is not of the same import as actual fractures (or other clinically evident disease), there is the evidence, for example, from the RCT of Trivedi et al. [40], demonstrating fracture reduction on elevating serum 25(OH)D within precisely the range now commonly labeled "insufficient." To be sure, not all studies of vitamin D supplementation in this range of 25(OH)D values have produced significant benefit. One would not expect that as studies vary in quality, extent of compliance, and other factors that influence outcomes. Bischoff-Ferrari and her collaborators have, in a series of meta-analyses [e.g., 41,42], shown significant risk reduction for fractures and falls as 25(OH)D rises from 50 to 80 nmol/L (and above). Hence, for two bone end points (increased osteoid volume on bone biopsy and fracture risk) there is clear evidence of increased disease risk in the range of values generally considered "insufficient."

Second is the matter of RCTs. The IOM, and indeed most other comparable bodies, have called for more RCTs to address these questions, simply because such evidence is unarguably the only certain way of establishing efficacy. What is little appreciated is (1) efficacy is not the real issue as all nutrients are essential (and hence efficacious), and the relevant question is not "whether" but "for what and how much?"; (2) as already noted, ethical and feasibility concerns make RCTs inappropriate or impractical; and (3) there are already over 100 RCTs studying various end points, most of which demonstrate benefit for elevated vitamin D status for one or another end point [e.g., 40–51]. Some published trials have produced a null result, whereas two have produced negative results [52, 53]. Both used what I would consider to be a nonphysiological approach to dosing (one dose of 500,000 or 300,000 IU per year). Sanders et al. [52] found increased risk of fractures and falls, while Smith et al. [53] produced a null result for most fractures but a small increase in risk for hip fracture. Both regimens would have resulted in extreme cyclicity of 25(OH)D levels, a phenomenon that had earlier been predicted to counteract any possible beneficial outcome [54]. That the study of Trivedi et al. [40], also using an intermittent dose, was positive may have been due to the fact that the dose was smaller and the dosing more frequent. Certainly, the degree of cyclic variation following a regimen of 100,000 IU doses every 4 months would have been less than with the once-yearly 500,000-IU dose of Sanders et al. [52] and the 300,000-IU dose of Smith et al. [53].

This distinction between null and negative is important as nutrient effects on single-system variables are usually small, and hence, many trials are likely to be inconclusive (i.e., null). But an agent with a truly null effect, while sometimes producing apparent positive outcomes from chance alone, would be expected to produce about the same number of apparently negative outcomes as well. In other words, trial outcomes would be symmetrically distributed around zero effect [55]. That appears not to be the case for vitamin D for most end points (skeletal and non-skeletal alike), for which the distribution of study outcomes is shifted distinctly toward the positive side, thus pointing toward an overall suggestion of multisystem benefit.

Conclusion

The term vitamin D "insufficiency" denotes a vitamin D status above 25(OH)D levels associated with clinically perceptible manifestations of rickets or osteomalacia but below levels judged to be fully adequate. Individuals characterized as "insufficient" have been shown to be at increased risk of osteoporotic fractures and of histological osteomalacia (among many other untoward outcomes). These risks can be reduced by improved vitamin D status. Thus, there is no logical dividing line between a status deemed "deficient" and one deemed "insufficient." Any condition in which disease occurs that is preventable by improved vitamin D status must be judged "D-deficient." While this may seem a semantic quibble, what is important to recognize is that individuals currently labeled as "insufficient" are at risk of real disease.

Additionally, it must be noted in closing that (1) there is no consensus with regard to the vitamin D status that represents true adequacy and (2) there is a substantial and growing body of evidence indicating that the lower end of the adequate range is at least as high as 32 ng/mL (80 nmol/L) and, by some criteria, 40 ng/mL (100 nmol/L). The fact that this value is higher than that recently recommended by the IOM may be due in large part to their use of a drug-based approach to evaluating efficacy, rather than one based on physiological criteria.

References

1. McCollum EV (1918) The "vitamin" hypothesis and the diseases referable to faulty diets. JAMA 71:937–940
2. Goodwin JS, Tangum MR (1998) Battling quackery. Arch Intern Med 158:2187–2191
3. Heaney RP, Roller S (2012) Nutrition, health policy, and the problem of proof. In: Coulston AM, Boushey CJ, Feerruzzi M (eds) Nutrition in the prevention and treatment of disease, 3rd edn. Elsevier, San Diego
4. Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM, Zeisel SH (2010) Evidence-based criteria in the nutritional context. [Appendix: Amplification on certain of the points discussed in the paper (online only).] Nutr Rev 68:478–484
5. Heaney RP, Weaver CM, Blumberg J (2011) EBN (evidence-based nutrition) ver. 2.0. Nutr Today 46:22–26
6. Heaney RP (2008) 2008 W.O. Atwater Memorial Lecture. Nutrients, endpoints, and the problem of proof. J Nutr 138:1591–1595
7. Willett WC (2010) The WHI joints MRFIT: a revealing look beneath the covers. Am J Clin Nutr 91:829–830
8. Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, Proksch N, Pastor F, Netter C, Streichert T, Puschel K, Amling M (2010) Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 25:305–312
9. Heaney RP (2012) The nutrient problem. Nutr Rev 70:165–169
10. IOM (Institute of Medicine) (2011) Dietary reference intakes for calcium and vitamin D. National Academies Press, Washington, DC
11. Heaney RP (2007) The case for improving vitamin D status. J Steroid Biochem Mol Biol 103:635–641
12. Aloia JF, Talwar SA, Pollack S, Feuerman M, Yeh JK (2006) Optimal vitamin D status and serum parathyroid hormone concentrations in African American women. Am J Clin Nutr 84:602–609

13. Kinyamu HK, Gallagher JC, Balhorn KE, Petranick KM, Rafferty KA (1997) Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes. Am J Clin Nutr 67:342–348
14. Webb AR (2006) Who, what, where and when—influences on cutaneous vitamin D synthesis. Prog Biophys Mol Biol 92:17–25
15. Holick MF (1985) The photobiology of vitamin D and its consequences for humans. Ann N Y Acad Sci 453:1–13
16. Webb AR, Kline L, Holick MF (1988) Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab 67:373–378
17. Holick MF, Matsuoka LY, Wortsman J (1989) Age, vitamin D, and solar ultraviolet. Lancet 2:1104–1105
18. Hall LM, Kimlin MG, Aronov PA, Hammock BD, Slusser JR, Woodhouse LR, Stephensen CB (2010) Vitamin D intake needed to maintain target serum 25-hydroxyvitamin D concentrations in participants with low sun exposure and dark skin pigmentation is substantially higher than current recommendations. J Nutr 140:542–550
19. Armas LAG, Dowell MS, Akhter M, Duthuluru S, Huerter C, Hollis BW, Lund R, Heaney RP (2007) Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UV-B dose and skin color. J Am Acad Dermatol 57:588–593
20. Barger-Lux MJ, Heaney RP (2002) Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 87:4952–4956
21. Vieth R (1999) Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 69:842–856
22. Luxwolda ME, Kuipers RS, Kema IP, Dijck-Brouwer DAJ, Muskiet FAJ (2012) Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L. Br J Nutr. doi:10.1017/S0007114511007161
23. Holick MF, Chen TC (2008) Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 87(Suppl):1080S–1086S
24. Holick MF (2008) Vitamin D: a D-lightful health perspective. Nutr Rev 66(Suppl 2):S182–S194
25. Holick MF (2006) High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 81:353–373
26. Peterlik M, Cross HS (2005) Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest 35:290–304
27. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich, Dawson-Hughes B (2006) Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 84:18–28
28. Boucher BJ (2011) The 2010 recommendations of the American Institute of Medicine for daily intakes of vitamin D. Public Health Nutr 14:740
29. Giovannucci E (2011) Vitamin D, how much is enough and how much is too much? Public Health Nutr 14:740–741
30. Gorham ED, Garland CF (2011) Vitamin D and the limits of randomized controlled trials. Public Health Nutr 14:741–743
31. Cannell J (2011) Era or error? Public Health Nutr 14:743
32. Norman AW (2011) Vitamin D nutrition is at a crossroads. Public Health Nutr 14:744–745
33. Grant WB (2011) The Institute of Medicine did not find the vitamin D–cancer link because it ignores UV-B dose studies. Public Health Nutr 14:745–746
34. Schwalfenberg GK, Whiting SJ (2011) A Canadian response to the 2010 Institute of Medicine vitamin D and calcium guidelines. Public Health Nutr 14:746–748
35. Hollis BW, Wagner CL (2011) The vitamin D requirement during human lactation: the facts and IOM's "utter" failure. Public Health Nutr 14:748–749
36. Heaney RP (2011) Finding the appropriate referent for vitamin D. Public Health Nutr 14:749–750
37. Holick MF (2011) The D-batable Institute of Medicine report: a D-lightful perspective. Endocr Prac 7:143–149
38. Heaney RP, Holick MF (2011) Why the IOM recommendations for vitamin D are deficient. J Bone Miner Res 26:455–467
39. Recker RR, Kimmel DB, Parfitt AM, Davies KM, Keshawarz N, Hinders S (1988) Static and tetracycline-based bone histomorphometric data from 34 normal postmenopausal females. J Bone Miner Res 3:133–144
40. Trivedi DP, Doll R, Khaw T (2003) Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. BMJ 326:469–474
41. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav J, Thoma A, Kiel DP, Henschkowski J (2009) Prevention of nonvertebral fractures with oral vitamin D and dose dependency. Arch Intern Med 169:551–561
42. Bischoff-Ferrari HA, Willet WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B (2005) Fracture prevention with vitamin D supplementation. JAMA 293:2257–2264
43. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J (2009) Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomized controlled trials. BMJ 339:b3692
44. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H (2010) Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr 91:1255–1260
45. Bischoff-Ferrari HA, Dawson-Hughes B, Stöcklin E, Sidelnikov E, Willett WC, Orav EJ, Stähelin HB, Wolfram S, Jetter A, Schwager J, Henschkowski J, von Eckardstein A, Egli A (2012) Oral supplementation with 25(OH)D_3 versus vitamin D_3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. J Bone Miner Res 27:160–169
46. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP (2007) Vitamin D and calcium supplementation reduces cancer risk. Am J Clin Nutr 85:1586–1591
47. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C (2001) Effects of a short-term vitamin D_3 and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 86:1633–1637
48. Brooke OG, Brown IRF, Bone CDM, Carter ND, Cleeve HJW, Maxwell JD, Robinson VP, Winder SM (1980) Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. BMJ 15:751–754
49. Nursyam EW, Amin Z, Rumende CM (2006) The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. Acta Med Indones 38:3–5
50. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K (2008) Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med 168:103–108
51. Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM (1998) Ultraviolet-B and blood pressure. Lancet 352:709–710
52. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC (2010) Annual high-dose oral vitamin D and falls and fractures in older women. JAMA 303:1815–1822
53. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C (2007) Effect of annual intramuscular vitamin D on fracture risk in elderly men and women—a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology 46:1852–1857

54. Vieth R (2009) How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. Anticancer Res 29:3675–3684

55. Heaney RP, Rafferty K (2008) The preponderance of the evidence: an example from the issue of calcium intake and body composition. Nutr Rev 67:32–39