Vitamin Supplement

The role of vitamers and dietary-based metabolites of vitamin D in prevention of vitamin D deficiency

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Abstract

There is little doubt that vitamin D deficiency across all age groups in Europe is a problem. Low vitamin D status arises due to limited, if any, dermal synthesis during the winter months at latitudes above 40°N, putting increased importance on dietary supply of the vitamin. However, dietary intakes by most populations are low due to the limited supply of vitamin D-rich foods in the food chain. Thus strategies that effectively address this public health issue are urgently required. It has been emphasized and re-emphasized that there are only a limited number of public health strategies available to correct low dietary vitamin D intake: (1) improving intake of naturally occurring vitamin D-rich foods, (2) vitamin D fortification (mandatory or voluntarily) of food, and (3) vitamin D supplementation. Recent evidence suggests that the levels of vitamin D added to food would need to be high so as to ensure dietary requirements are met and health outcomes optimized. In addition, knowledge of the most effective forms of vitamin D to use in some of these preventative approaches is important. There is still uncertainty in relation to the relative efficacy of vitamin D_2 versus D_3, the two main food derived forms and those used in vitamin D supplements. The major metabolite of vitamin D with biological activity is $1,25(OH)_2D$; however, this is usually used for pharmacological purposes and is not typically used in normal, healthy people. The other major metabolite, 25(OH)D, which has also been used for pharmacological purposes is present in certain foods such as meat and meat products (particularly offal) as well as eggs. This metabolite may have the potential to boost vitamin D status up to five times more effectively that native vitamin D_3 in foods. However, the exact bioactivity of this compound needs to be established.

Keywords: *vitamin D deficiency*; *vitamers*; *metabolites of vitamin D*; *fortification*

Without doubt, vitamin D is the nutrient that has captured the minds and imaginations of the scientific community, authoritative agencies, regulatory bodies, industry, and the public alike in the first decade of the new millennium. It is notable that in the US, the Food and Nutrition Board of the Institute of Medicine (IOM) have very recently released new Dietary Reference Intake (DRI) values for vitamin D (and calcium). The European Food Safety Agency (EFSA) will soon undertake a review of the Population Reference Intake (PRI) values for vitamin D and other micronutrients in Europe. Several EU member states are also re-evaluating their local or regional dietary recommendations for vitamin D.

These activities are not surprising in light of the increasing evidence base during the last decade that potentially links vitamin D to non-skeletal disease (such as cardiovascular disease, diabetes, certain types of cancer, infectious disease, or other autoimmune and inflammatory disease that add greatly to the global burden of disease and total chronic disease deaths) as well as to its more accepted role in metabolic bone disease (rickets, osteomalacia, osteoporosis) risk. An intense research effort has resulted in this increased evidence-base as and has facilitated agencies begin the process of re-evaluation of dietary vitamin D recommendations. However, despite new recommendations, vitamin D deficiency will remain a major public health issue in Europe (and indeed elsewhere), with huge potential cost implications to its health care system and its societies unless effective dietary strategies for prevention of vitamin D deficiency are put in place. The present paper will overview vitamin D deficiency, its prevalence, causes, and health effects, as well as potential dietary strategies for its prevention. In particular it will highlight some existing knowledge gaps in relation to efficacy of different forms of vitamin D that

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would need to be addressed in terms of formulation of effective preventative dietary strategies.

Vitamin D deficiency: a major concern for Europe and the health of its populations

There is little doubt that vitamin D deficiency across all age groups in Europe is a problem, the magnitude of which ranges from significant to pandemic depending on which biochemical definition one uses; that is, what level of serum 25-hydroxyvitamin D [25(OH)D; the nutritional status measure for vitamin D] is used as the cutoff to define deficiency. For example, it is universally accepted that serum 25(OH)D levels should be maintained above an absolute minimum of 25 nmol/L at all times for prevention of osteomalacia in adults and vitamin D-dependent rickets in children (1). Currently in the UK, about 21% of adolescents (2), 25% of adults (3), and 35% of older adults in residential care (4) are clinically vitamin D deficient during wintertime with serum 25(OH)D levels below 25 nmol/L. These UK prevalence data are mirrored in other European countries. For example, Andersen et al. (5) in their study of adolescent girls and elderly women in four Northern European countries showed that 37% of girls and 17% of women had wintertime serum 25(OH)D below 25 nmol/L. The problem of low vitamin D status spreads from Eastern to Western and from Northern to Southern Europe (5–7).

Less severe vitamin D deficiency [represented by a serum 25(OH)D value <50 nmol/L, although values between 30 and 110 nmol/L have been suggested (8–10)] causes secondary hyperparathyroidism and increases bone turnover and bone loss (11, 12). In addition to its well-accepted role in these metabolic bone diseases, a large epidemiological, biologically plausible evidence base has increased exponentially during the last decade linking low vitamin D status [serum 25(OH)D <50 nmol/L] with development of non-skeletal diseases (including the cardiometabolic syndrome, diabetes, selected cancers, respiratory infections, autoimmune and inflammatory diseases, and cognitive decline) (13–15), which collectively make a huge contribution to the global burden of disease and total chronic disease deaths. However, it is worth noting that the evidence basis for some of these outcomes awaits data from randomized clinical trials (RCTs) to prove cause and effect. Currently in the UK, about 40–55% adolescents (2), 70–75% of 19–64-year-old adults (3), and up to 90% of elderly (4) are vitamin D deficient during wintertime using a serum 25(OH)D cutoff of 50 nmol/L. These UK prevalence data are mirrored in other European countries (5–7). For example, Andersen et al. (5) in their study of adolescent girls and elderly women in four Northern European countries showed that 92% of girls and 67% of women had wintertime serum 25(OH)D below 50 nmol/L. Of note this biochemical cutoff for vitamin D deficiency was accepted recently by the Standing Committee of European Doctors (16). Some researchers have suggested that serum 25(OH)D levels need to be in excess of 80–120 nmol/L to optimize health (13, 14). Most European subjects will have serum 25(OH)D levels below this cutoff in winter and a very high proportion will not reach it even in summer (3, 5–7).

Why does vitamin D deficiency occur so commonly in Europe?

In humans, vitamin D is obtained primarily through cutaneous biosynthesis in the presence of ultraviolet blue (UVB) sunlight in summer. During wintertime in latitudes greater than 35°N, the angle of the sun is too oblique for UVB rays to pass through ozone, so little or no vitamin D is dermally synthesized. The duration of this period during which vitamin D can not be synthesized increases with latitude so, for example, human skin exposed to sunlight on cloudless days in Boston (42.2°N) from November through February produced no previtamin D_3. In Edmonton (52°N) this ineffective winter period extended from October through March (17). There are also many reasons why summertime sun exposure may be inadequate. Improved adherence to public health campaigns to promote sun safety and awareness of the links between excessive sun exposure and skin cancer, as well as premature wrinkles, has led to the widespread use of sunscreen and inclusion of sun protection factor (SPF) ingredients in cosmetic products. Correct application of sunscreen with an SPF of 15 reduces cutaneous skin production of previtamin D_3 by 93% (18). Dermal synthesis of vitamin D is a much less efficient process in non-Caucasians than in Caucasians and in older than in younger adults. Discreet clothing habits limit sun exposure particularly in veiled women and long working hours spent indoors mean that most adults rely on vacation to spend time outdoors during the day.

In the absence of sufficient UVB for dermal synthesis, vitamin D becomes an essential nutrient; however, food sources of vitamin D are few and the typical average vitamin D intakes in populations within the EU are generally around 2–5 μg/d (19). There is a significant gap between typical intakes in European populations and the current dietary targets (10 and 15 μg/d for 1–70 years; 10 and 20 μg/d for >70 years; US Estimated Average Requirement and Recommended Dietary Allowance values, respectively (8)). Even these new DRI values are not as high as those proposed by some researchers (22). For example, data from nationally representative surveys shows that 74% of adults in the UK and Ireland are not reaching an intake of 5 μg/d and 90% of older men and women in Ireland are not reaching 10 μg/d (20, 21). The European dietary recommendation (PRI) for vitamin D for adults also reveals considerable uncertainty about the available evidence on which to base a recommended intake, as it ranges from 0 to 10 μg/d to account not

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only for the knowledge gaps but also for the widely varying latitudes that EU citizens live in (35–70°N), assuming a higher dietary requirement in more northerly latitudes but not having data to base a requirement on (23). Two recent controlled, randomized, double-blind vitamin D_3 intervention trials, the first in 245 adults aged 20–40 years (24) and the second in 225 community-dwelling adults over 64 years (25), showed that the estimated dietary requirements (covering needs of 97.5% of population) for vitamin D in men and women (aged 20–40 years and 64+ years) to maintain serum 25(OH)D above 25 nmol/L during winter were 8.6 and 8.7 μg/d, respectively. Using the 50 nmol/L cutoff, the requirements raised to 24.7 and 28.0 μg/d for 20–40 and 64-year-olds, respectively. Estimates of the dietary vitamin D requirement to reach a serum 25(OH)D threshold of 80 nmol/L in adults and elderly range from 41 to 114 μg/d (24–26).

Of particular concern, these new target values (even the lowest ones) are considerably beyond current intakes in adolescent (2, 27) and adult populations (in some cases even the high consumers (reflected by those in the 95 percentile of intake) have vitamin D intakes below 9 μg/d (19). As an example, 84–97% of adolescents (2) and 93% of adults (20) in the UK National Diet and Nutrition Survey do not reach an intake of 5 and 9 μg/d, respectively.

Addressing the low intake and associated vitamin D deficiency

As mentioned already, in humans, vitamin D is obtained primarily through cutaneous biosynthesis in the presence of UVB sunlight in summer. While stores established during summer sun exposure can help reduce the requirement for dietary vitamin D in wintertime, it does not negate this (24, 25). In addition, it is worth noting that population levels of unprotected summer sun exposure may be rapidly declining, as a consequence of public education campaigns in relation to skin cancer (28). Thus, dietary supply of vitamin D is taking on increasing importance not only in winter months but potentially also in summer; however, dietary supply is low for most European populations. It has been emphasized and re-emphasized that there are only a limited number of public health strategies available to correct low dietary vitamin D intake:

1. *Improving intake of naturally occurring vitamin D-rich foods.* However, this is the least likely strategy to counteract low dietary vitamin D intake due to the fact that there are very few food sources that are rich in vitamin D. Furthermore, most of these are not frequently consumed by many in the population (21).
2. *Vitamin D fortification (mandatory or voluntarily) of food.* This has been viewed by some as a feasible and effective measure once applied in an evidence-based approach. In response to concerns about widespread vitamin D deficiency, many countries have implemented either mandatory or discretionary food fortification. Fortification of foods with vitamin D in the US and Canada has an important impact on the mean daily intake of vitamin D by the average adult. Fortified foods constitute the largest contributor (65–87%; and fortified milk alone contributes 40–64%) to dietary vitamin D intake in the US population (29). However, Calvo and Whiting (30) suggest that the current level of fortification in the US and Canada is not effective in reaching the required levels of vitamin D intake (i.e. existing dietary targets, which are much lower than those shown by the recent RCTs described above). This may relate to the level of fortification, types and choice of food vehicles, and the issue of mandatory or optional/voluntary fortification. O'Donnell et al. (31), in their recent systematic review of the efficacy of food fortification on serum 25(OH)D concentrations, showed that of the nine RCTs ($n=889$ subjects, all community-dwelling participants; most used dairy products as the source of vitamin D fortification) that were included, eight consistently showed a significant beneficial effect of food fortification on 25(OH)D concentrations. The authors concluded that their review highlights the need for stronger data on food fortification. Flynn et al. (19) have recently shown that the 95th percentile of intake of vitamin D from voluntary fortified foods in Europe is low. Thus, from a European perspective we need to model European food and vitamin D intake data to ascertain which food vehicles and what level of vitamin D addition will ensure an effective but safe rise in serum vitamin D status in European populations. So there is a need to invest in such research.
3. *Vitamin D supplementation.* Supplementation with vitamin D has been shown to significantly improve vitamin D intake across a variety of age, race, ethnic, and gender groups (30) as well as improving vitamin D status *per se* (efficacy of which dependent on dose) (32). However, evidence seems to suggest that the population intake of vitamin D from supplements is quite low (19). For example, although supplements contribute ~12 and 7% to vitamin D intakes in Irish women and men, respectively (33) and almost a quarter of vitamin D intakes in women and 12% in men in the UK (20), overall intakes are low so these contributions while proportionally high are quantitatively low. This is a function mainly of the relatively low vitamin D content of most supplements in some countries relative to requirement as discussed above. Some are of the view that while not highly

effective at a population level, vitamin D supplementation may be appropriate in high risk groups such as the elderly (16, 34, 35).

Forms of vitamin D and relative efficacy in improving status

While recent evidence suggests that the levels of vitamin D added to food and/or supplements would need to be high so as to ensure dietary requirements are met and health outcomes optimized, knowledge of which are the most effective forms of vitamin D to use in some of these preventative approaches is also important.

Vitamin D_2 versus D_3

While vitamin D_2 and D_3 [the two main food derived forms (although vitamin D_2 only occurs in wild mushrooms) and those used in vitamin D supplements] both unquestionably elevate serum 25(OH)D as evidenced in a recent systematic review of biomarkers of vitamin D status (32), there is still uncertainty in relation to the relative efficacy of these two forms of vitamin D. For several decades, pharmacopoeias have officially regarded these two forms as equivalent and interchangeable, yet the evidence base for this was old and largely based on studies of rickets prevention in infants in the 1930s.

There have been a number of human studies that directly compared the two forms of vitamin D in terms of their potential for raising serum 25(OH)D in adults. Trang et al. (36) compared the ability of an equal molar dose of vitamin D_2 or D_3 [≈4,000 IU (100 μg)/d] to elevate serum total 25(OH)D (via radioimmunoassay) over 2 weeks between February and early May when vitamin D concentrations and solar exposure are minimal in 72 healthy men and women (mean age, 38 years). Both vitamin D_2 and vitamin D_3 increased serum total 25(OH)D concentrations, but the increase in total 25(OH)D was found to be 70% greater (1.7 times) with vitamin D_3 than the increase obtained with vitamin D_2. Armas et al. (37) compared the time course of serum total 25(OH)D (via radioimmunoassays) over a period of 28 days after a single dose of either vitamin D_2 or vitamin D_3 [50,000 IU (1250 μg)] in 20 healthy males (mean age, 33.0 years) in summertime (July) [necessitating the researchers having to account and adjust for increases in serum 25(OH)D due to sun exposure]. Both forms of vitamin D produced similar rises in serum total 25(OH)D concentration over the first 3 d, but serum 25(OH)D continued to rise in the vitamin D_3-treated subjects (peaking by day 14 and remaining above baseline until at least day 28), whereas in the vitamin D_2-treated subjects, serum 25(OH)D concentrations fell rapidly, reaching baseline values by day 14. Interestingly, 25(OH)D concentrations then continued to decline in this group and fell below baseline values by day 28. A comparison of the areas under the curve (concentration versus time) showed a >threefold greater potency with vitamin D_3. A surprising finding was a decline in 25(OH)D_3 concentrations (via HPLC assay) in the vitamin D_2-treated subjects, whereas concentrations rose in the control group (due to sun exposure) (37). Glendenning et al. (38) studied whether 1,000 IU (25 μg)/d of vitamin D_2 and D_3 are equipotent therapies in vitamin D-insufficient [serum 25(OH)D <50 nmol/L] hip fracture patients ($n=95$). Vitamin D_3 supplementation resulted in a 31% greater increase in total HPLC-measured 25(OH)D and 52% greater rise in radioimmunoassay-measured total 25(OH)D than supplementation with an equivalent dose of vitamin D_2 after 3 months. The authors also reported a lack of difference in PTH lowering between the two forms of vitamin D treatments and raised questions about the biological importance of the greater potency with vitamin D_3.

Houghton and Vieth (39), in their review of the available data and evidence, provide a very succinct overview of several biologically plausible mechanisms that could contribute to the greater capacity of vitamin D_3 over D_2 to maintain higher 25(OH)D concentrations over time, including:

1. Serum 25(OH)D_2 has a lower affinity for vitamin D-binding protein (DBP) and results in a shorter circulating half-life than that of 25(OH)D_3.
2. A higher affinity of hepatic 25-hydroxylase for vitamin D_3 than for vitamin D_2.
3. Minor differences in the chemistry of side chains between the two forms of vitamin D result in differences in the site of hydroxylation and leads to the production of unique biologically active metabolites:
   - After 25-hydroxylation, 25(OH)D, and 1,25$(OH)_2$D undergo additional 24-hydroxylation in the kidney to form 24,25$(OH)_2$D and 1,24,25$(OH)_3$D, respectively.
   - The formation of 1,24,25$(OH)_3D_2$ leads to deactivation of the vitamin D_2 molecule, whereas the analogous vitamin D_3 metabolite, 1,24,25$(OH)_3D_3$, must undergo additional side-chain oxidation to be biologically deactivated. 1,24,25$(OH)_3D_3$ has the ability to bind to the vitamin D receptor [VDR; ≈40% more than 1,25$(OH)_2D_3$] and, thus, is able to potentially generate significant biological activity.
   - While 24-hydroxylation of the side chain could occur only after 25-hydroxylation, at least for vitamin D_3, it does not appear to be a prerequisite for vitamin D_2. 1,24$(OH)_2D_2$, formed in the kidney from 24(OH)D_2, has less affinity for VDR than do 1,25$(OH)_2D_3$ and 1,24$(OH)_2D_3$. Binding to VDR represents a molecular event important to the biological action of the vitamin D metabolites.

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The authors concluded that when the data and findings are taken together, the most plausible explanations for the greater bioefficacy of vitamin D_3 are conceivably due to the higher affinities of vitamin D_3 and its metabolites than vitamin D_2 for hepatic 25-hydroxylase, DBP, and VDR and because vitamin D_3 is not directly metabolized to 24(OH)D as is vitamin D_2. Interested readers are referred to this review for a more comprehensive coverage of the potential mechanisms (39).

While the findings from the above studies and possible underlying mechanisms might suggest so, the case for greater bioefficacy of vitamin D_3 over vitamin D_2 is less than clear. Rapuri et al. (40) reported that in a study of elderly women (mean age, 72 years) who self-reported their use of vitamin D_2 and D_3 supplements, the mean serum total 25(OH)D levels (via competitive protein binding assay) were higher in women on vitamin D_2 (33.6 ± 2.1 ng/mL) and vitamin D_3 (29.7 ± 1.8 ng/mL) supplements (mean dose, 401 and 465 IU/d, respectively) compared to unsupplemented women (27.3 ± 0.7 ng/mL) during wintertime. In fact, the difference was only significant for those on vitamin D_2. Holick et al. (41) showed that elevations in serum total 25(OH)D concentrations (via liquid chromatography tandem mass spectroscopy) were identical between healthy adult men and women ($n = 68$; mean age, 38.6 years) given 1,000 IU (25 μg)/d vitamin D_2 or vitamin D_3 or a combination of 500 IU/d of vitamin D_2 plus 500 IU/d of vitamin D_3 (1,000 IU/d in total) in capsule form at the end of the winter for 3 months. Furthermore, the 25(OH)D_3 levels did not change in the group that received 1,000 IU vitamin D_2 daily. Similarly, infants (mean age, 10 months) who received 2,000 IU (50 μg) daily or 50,000 IU (2,000 μg) vitamin D_2 weekly for 6 weeks (throughout the year) experienced an elevation in serum total 25(OH)D concentrations (via a chemiluminescent assay) equivalent to concentrations observed in children who received 2,000 IU vitamin D_3 daily (42). Biancuzzo et al. (43) very recently showed in a study of healthy adult men and women ($n = 105$; mean age, 40.3 years) in late winter that, using analysis of the area under the curve, there was no significant difference in serum total 25(OH)D (via liquid chromatography tandem mass spectroscopy) between subjects who consumed vitamin D_3-fortified orange juice and vitamin D_3 capsules. Similarly, no significant difference in serum 25(OH)D_2 was observed between subjects who consumed vitamin D_2-fortified orange juice and vitamin D_2 capsules. In addition, there was no significant difference in serum total 25(OH)D between subjects who consumed 1,000 vitamin D_2 or D_3 in orange juice or in a capsule. Thus, these latest findings appear to suggest that not only are vitamin D_2 and vitamin D_3 equally bioavailable, they are so from a fortified food source or a capsule.

It is clear that the data are ambiguous and may stem from the fact that the various studies that have compared the two forms of vitamin D have had differences in design (season in which study conducted, age profile of subjects), dose/mode of administration of vitamin D, preparation of vitamin D, as well as method of analysis of serum 25(OH)D, all of which may have contributed to the mixed findings and limit a firm conclusion being drawn at this time.

Vitamin D metabolites

The major metabolite of vitamin D with biological activity is 1,25$(OH)_2$D; however, this is usually used for pharmacological purposes and is not typically used in normal healthy people. The presence of minor amounts of this metabolite in some foods of animal origin (as is the case with 25(OH)D; see below) and its contribution to biological vitamin D activity has not been investigated.

It has been suggested that the other major metabolite, 25(OH)D, which has also been used for pharmacological purposes, may contribute to vitamin D nutriture. This metabolite is present in certain foods of animal origin. Meat, eggs, and to a lesser extent fish have been shown to possess 25(OH)D (44–47). There has been some limited investigation of offal (and in particular liver and kidney), which shows that they contain higher amounts of the metabolite than cuts of meat (which is not surprising as these tissues are where vitamin D is metabolized *in vivo*) (48, 49). For example, pork liver appears to have equivalent amounts of vitamin D_3 and 25(OH)D (0.4 μg per 100 g), while beef liver has more 25(OH)D than vitamin D_3 [<0.05 μg and 0.3 μg 25(OH)D per 100 g, respectively] (45). Chicken also appears to have equivalent amounts of vitamin D_3 and 25(OH)D (0.3 μg and 0.25 μg per 100 g, respectively) (45), while eggs yolk have 3 μg vitamin D_3 and 1 μg 25(OH)D per 100 g, respectively (44).

Meat and meat products as well as egg and egg dishes can make sizeable contributions to the mean daily intake of vitamin D for some populations (20, 21). However, some of this contribution stems from the fact that the UK (and others such as Danish and Swiss) food composition tables suggests that 25(OH)D may possess up to five times the activity of native vitamin D_3 in food (50–52). Thus, in theory, each μg of 25(OH)D consumed in the diet could boost vitamin D status up to five times more effectively compared to each μg of native vitamin D_3 in food. Thus, food-based 25(OH)D may be a very valuable strategy for bridging the gap between current intakes and new dietary targets for vitamin D (9–10 or 15 μg/d; 8, 24,25) (24, 25). For example, if habitual daily intakes of vitamin D in most European populations are in the region of ~ 4 μg (19), then an additional 5 μg/d of vitamin D would need to be achieved via diet to reach a target of 9 μg/d or potentially only an additional 1 μg/d 25(OH)D from food. This would only be the case if the relative potency of 25(OH)D to the native vitamin D is 5, but as Ovesen et al. (48) point out

there is as yet no consensus on the conversion factor that should be used for 25(OH)D to calculate vitamin D activity. Depending on the testing system used, the factor varies from 1.5 to 5 (48). Moreover, Jakobsen et al. (53) recently showed in a 12-week pig feeding trial that in relation to benefits for human nutrition, 25(OH)D in pig feed should be regarded as lower than vitamin D_3, as meat and liver produced by feeding the pigs exclusively 25(OH)D had a significantly low content of vitamin D_3. Priority needs to be given to data from human studies that have experimentally examined this relative potency. Using data from a 1-year intervention study by Rossini et al. (54) in osteopenic/osteoporotic women with hypovitaminosis D, it can be estimated that vitamin D_3 and 25(OH)D may have about equal potency (with the latter being only ~1.4-fold more potent than vitamin D_3). In contrast, in a preliminary publication, Jetter et al. (55) recently showed that healthy postmenopausal women (aged 50–75 years) who were supplemented daily with 20 µg/d of 25(OH)D had more than a twofold greater increase in serum 25(OH)D after 16 weeks compared to those who were supplemented with 20 µg/d of vitamin D_3 over the same time frame. Clearly, further research is needed to better define the relative potency of 25(OH)D present in foods so that food compositional tables can better reflect the true vitamin D nutritive value of meats, fish, and eggs, but also in terms of whether this metabolite is something that could be used for dietary supplementation/fortification purposes.

Conclusion

Without question there is a need to address the shortfall in current intakes of vitamin D in European and other populations relative to existing and potentially new and higher dietary recommendations. Fortification of foods with vitamin D as well as vitamin D supplementation in specific at-risk groups would appear to be likely strategies that may address low vitamin D status at a population level. Further research is needed to clarify whether differences in potency of vitamin D_2 and D_3 really do exist and to ascertain the exact relative potency of 25(OH)D to vitamin D_3. Such research will inform the dietary strategies aimed at prevention of vitamin D deficiency.

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References

1. UK Department of Health. Nutrition and bone health: with particular reference to calcium and vitamin D. Report on Health and Social Subjects (49). London: The Stationary Office; 1998.
2. Gregory J, Lowe S, Bates CJ, Prentice A, Jackson LV, Smithers G, et al. The National Diet and Nutrition Survey: young people aged 4–18 years. Volume 1: Report of the diet and nutrition survey. London: TSO; 2000.
3. Ruston D, Hoare J, Henderson L, Gregory J, Bates CJ, Prentice A, et al. The National Diet and Nutrition Survey: adults aged 19–64 years. London: TSO; 2004.
4. Finch S, Doyle W, Lowe C, Bates CJ, Prentice A, Smithers G, et al. The National Diet and Nutrition Survey: people aged 65 years and over. Volume 1: Report of the diet and nutrition survey. London: TSO; 1998.
5. Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, Chabros E, et al. Teenage girls and elderly women living in northern Europe have low winter vitamin D status. Eur J Clin Nutr 2005; 59: 533–41.
6. van der Wielen RP, Löwik MR, van den Berg H, de Groot LC, Haller J, Moreiras O, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet 1995; 346: 207–10.
7. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med 2006; 260: 245–54.
8. Institute of Medicine Food and Nutrition Board. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academy Press, 2010.
9. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? J Steroid Biochem Mol Biol 2004; 89–90: 611–4.
10. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997; 7: 439–43.
11. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001; 22: 477–501.
12. Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. Vitamin D and bone health in the elderly. Am J Clin Nutr 1982; 36: 1014–31.
13. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003; 89: 552–72.
14. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006; 84: 18–28.
15. Seamans KM, Hill TR, Scully L, Meunier N, Andrillo-Sanchez M, Polito A, et al. Vitamin D status and measures of cognitive function in healthy older European adults. Eur J Clin Nutr 2010; 64: 1172–8.
16. Standing Committee of European Doctors. 2009 Vitamin D nutritional policy in Europe. http://cpme.dyndns.org:591/adopted/2009/CPME_AD_Brd_241009_179_final_EN.pdf [cited 30 June 2010].
17. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988; 67: 373–8.
18. Gilchrest BA. Sun exposure and vitamin D sufficiency. Am J Clin Nutr 2008; 88: 570S–577S.
19. Flynn A, Hirvonen T, Mensink GB, Ocké MC, Serra-Majem L, Stos K, et al. Intake of selected nutrients from foods, from fortification and from supplements in various European countries. Food Nutr Res 2009; 53. DOI: 10.3402/fnr.v53i0.2038.

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20. Henderson L, Irving K, Gregory J, Bates CJ, Prentice A, Perks J, et al. The National Diet and Nutrition Survey: adults aged 19 to 64 years – vitamin and mineral intake and urinary analytes. London: TSO; 2004.
21. Hill TR, O'Brien MM, Cashman KD, Flynn A, Kiely M. Vitamin D intakes in 18–64-y-old Irish adults. Eur J Clin Nutr 2004; 58: 1509–17.
22. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr 2007; 85: 649–50.
23. Commission of the European Communities. Vitamin D. In: Nutrient and energy intakes of the European community. Report of the Scientific Committee for Food (31st series), pp. 132–39, Brussels, Luxembourg, 1993.
24. Cashman KD, Hill TR, Lucey AJ, Taylor N, Seamans KM, Muldowney S, et al. Estimation of the dietary requirement for vitamin D in healthy adults. Am J Clin Nutr 2008; 88: 1535–42.
25. Cashman KD, Wallace JM, Horigan G, Hill TR, Barnes MS, Lucey AJ, et al. Estimation of the dietary requirement for vitamin D in free-living adults >=64 y of age. Am J Clin Nutr 2009; 89: 1366–74.
26. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003; 77: 204–10.
27. Hill TR, Cotter AA, Mitchell S, Boreham CA, Dubitzky W, Murray L, et al. Vitamin D status and its determinants in adolescents from the Northern Ireland Young Hearts 2000 cohort. Br J Nutr 2008; 99: 1061–7.
28. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005; 135: 317–22.
29. Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr 2005; 135: 2478–85.
30. Calvo MS, Whiting SJ. Public health strategies to overcome barriers to optimal vitamin D status in populations with special needs. J Nutr 2006; 136: 1135–9.
31. O'Donnell S, Cranney A, Horsley T, Weiler HA, Atkinson SA, Hanley DA, et al. Efficacy of food fortification on serum 25-hydroxyvitamin D concentrations: systematic review. Am J Clin Nutr 2008; 88: 1528–34.
32. Seamans KM, Cashman KD. Existing and potentially novel functional markers of vitamin D status: a systematic review. Am J Clin Nutr 2009; 89: 1997S–2008S.
33. Kiely M, Flynn A, Harrington KE, Robson PJ, O'Connor N, Hannon EM, et al. The efficacy and safety of nutritional supplement use in a representative sample of adults in the North/South Ireland Food Consumption Survey. Public Health Nutrition 2001; 4: 1089–97.
34. Viljakainen HT, Palssa A, Kärkkäinen M, Jakobsen J, Lamberg-Allardt C. How much vitamin D3 do the elderly need? J Am Coll Nutr 2006; 25: 429–35.
35. McKenna MJ, Freaney R, Byrne P, McBrinn Y, Murray B, Kelly M, et al. Safety and efficacy of increasing wintertime vitamin D and calcium intake by milk fortification. QJM 1995; 88: 895–8.
36. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr 1998; 68: 854–8.
37. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004; 89: 5387–91.
38. Glendenning P, Chew GT, Seymour HM, Gillett MJ, Goldswain PR, Inderjeeth CA, et al. Serum 25-hydroxyvitamin D levels in vitamin D-insufficient hip fracture patients after supplementation with ergocalciferol and cholecalciferol. Bone 2009; 45: 870–5.
39. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 2006; 84: 694–7.
40. Rapuri PB, Gallagher JC, Haynatzki G. Effect of vitamins D2 and D3 supplement use on serum 25OHD concentration in elderly women in summer and winter. Calcif Tissue Int 2004; 74: 150–6.
41. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 2008; 93: 677–81.
42. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, et al. Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab 2008; 93: 2716–21.
43. Biancuzzo RM, Young A, Dibuld D, Cai MH, Winter MR, Klein EK, et al. Fortification of orange juice with vitamin D(2) or vitamin D(3) is less effective as an oral supplement in maintaining vitamin D status in adults. Am J Clin Nutr 2010; 91: 1621–6.
44. Mattila PH, Piironen VI, Uusi-Rauva EJ, Koivistoinen PE. Determination of 25-hydroxycholecalciferol content in egg yolk by HPLC. J Food Comp Anal 1993; 6: 250–5.
45. Mattila PH, Piironen VI, Uusi-Rauva EJ, Koivistoinen PE. Contents of cholecalciferol, ergocalciferol, and their 25-hydroxylated metabolites in milk products and raw meat and liver as determined by HPLC. J Agri Food Chem 1995; 43: 2394–9.
46. Mattila P, Lehikoinen K, Kiiskinen T, Piironen V. Cholecalciferol and 25-hydroxycholcalciferol content of chicken egg yolk as affected by the cholecalciferol content of feed. J Agri Food Chem 1999; 47: 4089–92.
47. Clausen I, Jakobsen J, Leth T, Ovesen L. Vitamin D3 and 25-hydroxyvitamin D3 in raw and cooked pork cuts. J Food Comp Anal 2002; 16: 575–85.
48. Ovesen L, Brot C, Jakobsen J. Food contents and biological activity of 25-hydroxyvitamin D: a vitamin D metabolite to be reckoned with? Ann Nutr Metab 2003; 47: 107–13.
49. Rivera JD, Bachman SE, Hubbert ME, Branine ME, Horst RL, Williams SN, et al. Serum and tissue concentrations of vitamin D metabolites in beef heifers after buccal dosing of 25-hydroxyvitamin D3. J Dairy Sci 2005; 88: 1364–9.
50. McCance and Widdowson's Composition of Foods Integrated Dataset, 2008. http://www.food.gov.uk/science/dietarysurveys/dietsurveys/ [cited 30 June 2010].
51. ETH Zurich and BAG. Swiss Food Composition Database V3.01. http://www.swissfir.ethz.ch [cited 30 June 2010].
52. Saxholt E, Christensen AT, Møller A, Hartkopp HB, Hess Ygil K, Hels OH. Danish Food Composition Databank, revision 7. Department of Nutrition, National Food Institute, Technical University of Denmark; 2008. http://www.foodcomp.dk/ [cited 30 June 2010].
53. Jakobsen J, Maribo H, Bysted A, Sommer HM, Hels O. 25-hydroxyvitamin D3 affects vitamin D status similar to vitamin D3 in pigs—but the meat produced has a lower content of vitamin D. Br J Nutr 2007; 98: 908–13.

54. Rossini M, Viapiana O, Gatti D, James G, Girardello S, Adami S. The long term correction of vitamin D deficiency: comparison between different treatments with vitamin D in clinical practice. Minerva Med 2005; 96: 1–7.
55. Jetter A, Henschkowski J, Dawson-Hughes B, Stahelin HB, Stocklin E, Wolfram S, et al. Plasma pharmacokinetics: comparison between oral supplementation regimens with 25(OH)D and vitamin D3. Poster No. MO0381. 31st Annual Meeting of the American Society for Bone and Mineral Research (ASBMR), Denver, CO; 2009. http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=b02959d0-e015-4e9a-bfec-9f491b4bb71f [cited 1 June 2010].

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