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Recommended intake, dietary intake and upper tolerable levels of vitamin D

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Abstract

The requirement for vitamin D can ideally be met by the amount formed in the skin by sun exposure. However, several studies from the Nordic countries have shown that deficiency occurs when the dietary intake is low. Dietary vitamin D is thus required in addition to that formed in the skin.

Requirement of a nutrient is the lowest amount needed to avoid clinical symptoms while recommended intake includes a security margin to account for individual variability and uncertainties in the data. Former recommendations were based on the minimum amount required to avoid clinical manifestations like rickets or osteomalacia to which was added an amount for security. Vitamin D is converted to 25-hydroxyvitamin D (25(OH)D) in the liver and the concentration of this metabolite in plasma is a marker of vitamin D status. Recommended intakes of vitamin D are now based on the effect on plasma concentration of 25(OH)D. The distribution in a healthy population is in the range 25 to 125 nmol/L. Values of 25(OH)D >50 nmol/L may be considered acceptable, 25-50 as vitamin D insufficient, 12.5-25 as deficiency and <12.5 as serious deficiency. To ensure an acceptable vitamin D status in the population, the recommended dietary intake of vitamin D according to the Nordic Nutrition Recommendations 2004 is 10 µg/d for the age groups 6-23 months and above 61 years and 7.5 µg/d for all other age groups. Dietary intake (supplements excluded) is of the order of 3 to 5 µg /d, somewhat higher in men than in women. There is a large variation in intake, in particular when supplements are included. Only about 40% of the adult Norwegian population do not take cod

liver oil or other supplements. The lowest intake is seen among adolescents. Low levels of serum 25(OH)D have been found in population groups in all the Nordic countries suggesting that the actual intake of vitamin D is lower than desirable. Furthermore, the intake is not sufficient to avoid a drop in 25(OH)D during the winter months. To diminish this seasonal drop the recommended intake for adults has been increased from 5 to 7.5 $\mu\text{g}/\text{d}$.

Large amounts of vitamin D may lead to hypercalcemia, nephrocalcinosis and kidney failure. Infants and children are more sensitive than adults. No clear toxic level has been defined, but based on the effects on serum 25(OH)D and risk of hypercalcemia, the following upper levels of intake have been proposed: for infants and children up to age 10 years 25 $\mu\text{g}/\text{d}$, for adolescents and adults 50 $\mu\text{g}/\text{d}$.

Vitamin D status

Vitamin D₃ or cholecalciferol¹ is a steroid-like molecule that is synthesized from 7-dehydrocholesterol in the skin under the influence of ultraviolet B light (wavelength between 290 nm and 315 nm) (1) (fig. 1).

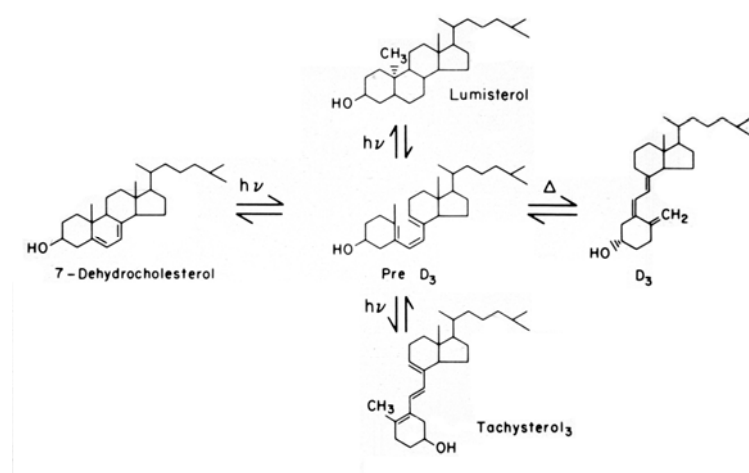


Figure 1. Formation of vitamin D₃ in the skin.

¹ One IU (international unit) corresponds to 0.025 μg vitamin D

It may also be derived from the diet. Sun exposure of the skin is more important than diet and dermal production can totally cover the requirement for the vitamin. A rather modest exposure to sunlight is sufficient to produce a satisfactory amount of vitamin D in the skin (1). Exposure of the face, arms, hands and legs to sunshine for 6-8 minutes 2-3 times a week is more than adequate to satisfy the requirement (2). Experience demonstrates, however, that under Norwegian living conditions and at the latitude of the Nordic countries, vitamin D deficiency may occur if the diet has limited amounts of the vitamin. Infants may develop rickets and elderly people osteomalacia. For this reason vitamin D has to be considered an essential micronutrient.

The liver rapidly takes up vitamin D formed in the skin or absorbed from the gut where it is hydroxylated to 25-hydroxyvitamin D (25(OH)D). This metabolite is transported in plasma bound to the vitamin D binding protein. The circulating concentration of 25(OH)D is a good marker of vitamin D status. The distribution in the healthy population is generally found to be 25 to 125 nmol/L. Vitamin D is also a prohormone because 25(OH)D is further converted to a hormone, 1,25-dihydroxyvitamin D, in the kidney. The main functions of this hormone are to stimulate calcium absorption in the gut, mobilise calcium from bone and to a certain extent stimulate re-absorption of calcium in the kidney. It is now clear that vitamin D also has several other functions related to cellular differentiation and metabolism (3). There is a marked seasonal variation in serum concentrations of 25(OH)D seen both in children (4) and in adults (5) with a marked downward shift during the winter months (fig. 2).

Under Nordic climatic conditions there are indications that exposure to sunlight is insufficient for enough vitamin D to be formed in the skin and for vitamin D status to be maintained during the winter months. A study from northern Finland in 1980 showed that vitamin D status was satisfactory during the summer, but that a large number of the individuals had unsatisfactory vitamin D status during the winter months (6). On the other hand satisfactory serum levels of 25(OH)D and seasonal variation was found among adults in a similar study from Tromsø in northern Norway (7). These studies indicate that light intensity during summer is sufficient at 70 degree north to elicit vitamin D formation in the skin. The explanation for the difference in vitamin D status between the 2 population groups during the winter months is that at the time of these studies the consumption of fish and margarine fortified with vitamin D was much higher in Norway than in Finland. These findings indicate that dietary vitamin D is essential to ensure satisfactory vitamin D status at northern latitudes, in particular during the winter months. The question is how much is needed and what intake should be recommended?

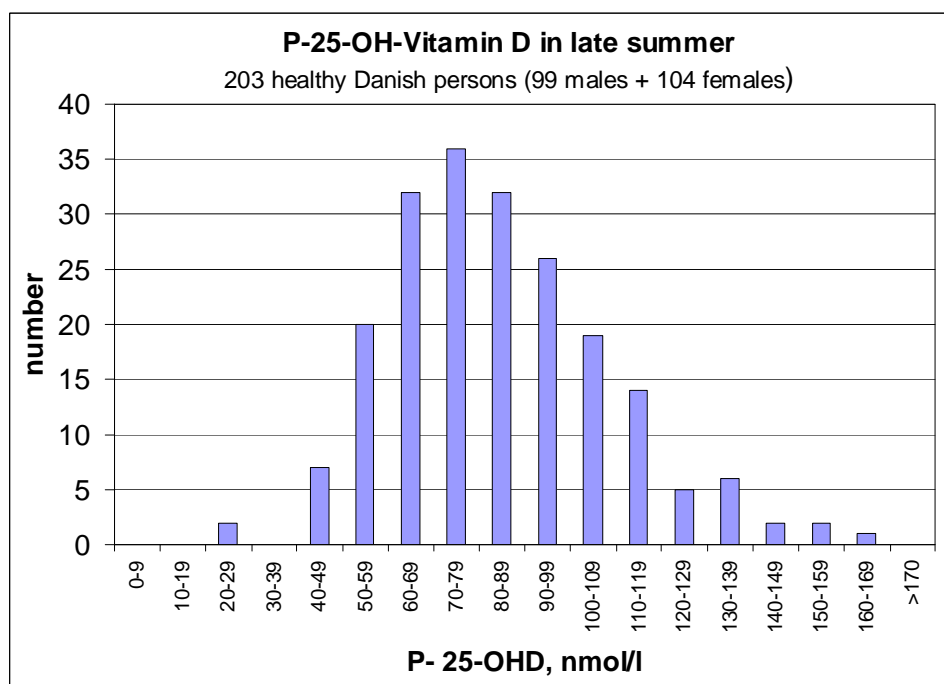
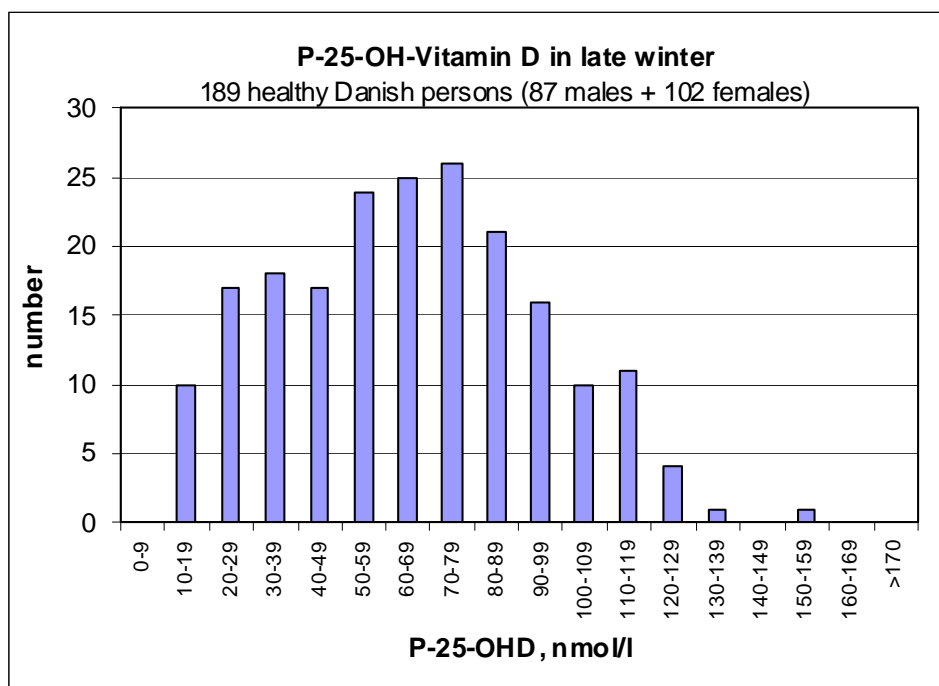


Figure 2. Distribution of plasma 25(OH)D in Danish men and women during winter ($n = 189$, upper panel) and during summer months ($n = 203$, lower panel) (modified from ref. 5 with permission from author and journal).

Recommended intake versus requirement

Recommended intake of a nutrient is not equivalent to requirement. Requirement is the lowest amount needed to avoid clinical symptoms or to avoid physiological or biochemical changes that might indicate suboptimal health. Recommended intake includes a security margin that takes into account individual variability and uncertainties in the data. In the Nordic Nutrition Recommendations 2004 (NNR 2004) the term 'recommended intake' (RI) refers to 'the amount of a nutrient that according to present knowledge can meet the known requirement and maintain good nutritional status among practically all healthy individuals' (8).

Recommended intakes as expressed in the NNR 2004 are primarily valid for groups of healthy individuals and are to be used as a basis for planning of diet.

Problems in setting recommendations

A main problem is to choose the criteria to be used as a basis for the recommendations. Disease states and clinical symptoms were the first to be used, but the health condition may be seriously reduced when clinical symptoms appear. Amounts needed to prevent or cure rickets or osteomalacia were previously used to arrive at recommendations for vitamin D. A daily dose of 2.5 µg of vitamin D was found sufficient to cure or prevent rickets or osteomalacia. Adding what was considered a reasonable margin of safety, a daily intake of 10 µg was recommended for infants and 5 µg for all other age groups.

The effect of dietary vitamin D on the concentration of 25-hydroxyvitamin D in plasma is now the criterion generally used as a basis for recommendations. But this raises a new question, namely what criteria should be used to set reference values for 25(OH)D?

Criteria used for evaluating vitamin D status

Different levels of vitamin D status have been proposed depending on the relation of serum 25(OH)D to:

- Clinical symptoms
 - Rickets is seen at levels < 12 nmol/L
 - Osteomalacia in the range 12-20 nmol/L
 - Histological signs of osteomalacia may be seen at levels <30 nmol/L
- Effect on serum concentration of 1,25(OH)₂D that will increase with serum 25(OH)D up to 40-50 nmol/L
- Absorption of radiocalcium attains a level with serum 25(OH)D at 50 nmol/L
- Increased secretion of parathyroid hormone (PTH). This occurs at low levels of 25(OH)D and the lowest level associated with normal PTH would ideally be the criterion of choice. PTH, however, also depends on other factors like calcium intake and age and therefore variable values of 25(OH)D,

- most in the range 38-80 nmol/L, have been reported not to be associated with hyperparathyroidism (for a critical discussion on this issue see ref 5).
- Associations with different health outcomes in epidemiological studies ("soft" endpoints) have indicated a favorable range of 75-100nmol/L.
 - Results from intervention studies. Randomized control studies would be the ultimate goal on which to base recommendations. Only one relevant such study has been published showing a reduced risk of cancer when the concentration of 25(OH)D was above 80 nmol/L corresponding to a daily intake of 20 µg vitamin D (9).

Reference values of 25(OH)D for evaluation of vitamin D-status in the population

The values given below have been used to evaluate vitamin D status in the population in two recent official reports from Denmark (5,10) and Norway (11).

| Serum or plasma 25(OH)D | Characterization |
|--------------------------------|---|
| > 50 nmol/L | acceptable |
| 25-50 nmol/L | suboptimal – vitamin D insufficiency |
| 12.5-25 nmol/L | vitamin D deficiency |
| < 12.5 nmol/L | serious vitamin D deficiency |

Recommended daily intake of vitamin D

To ensure an acceptable vitamin D status in the population, the recommended daily vitamin D intake according to NNR 2004 (12) is the following:

| Age | µg |
|------------|-----------|
| 6-23 mo | 10 |
| 2-9 yrs | 7.5 |
| 10-60 yrs | 7.5 |
| 61 > yrs | 10 |

Compared to the previous edition of NNR, the recommendation for the age groups 2-60 years has been increased by 50% from 5 µg/d in order to diminish the seasonal drop in plasma 25(OH)D during the winter months. Elderly with little or no sun exposure should in addition receive a supplement of 10 µg/d .

These recommendations were based on the available literature up to 2003. Results from intervention studies with hard endpoints like the one mentioned (9) might require re-evaluation of these figures in the future.

Dietary intake of vitamin D

A recent report on vitamin D status in the Norwegian population from the National Nutrition Council (11) gives an overview of the vitamin D intake in the population as estimated from several dietary surveys. The results are shown in tables 1-2.

Table 1. Dietary intake of vitamin D (supplements excluded), household surveys (from ref 11).

| | 1977-79 | 1986-88 | 1996-98 | 1999-01 | 2001-3 |
|-------------|---------|---------|---------|---------|--------|
| µg/d (mean) | 4.1 | 4.0 | 4.5 | 4.4 | 4.3 |
| µg/10 MJ | 4.0 | 3.9 | 4.9 | 4.7 | 4.6 |

The intake has been low the last 30 years. More than half the individuals in the different age groups are below the recommended intake. Even if supplements are taken into account, the intake is low in many age groups. Most seriously, the intake is very low during adolescence, the period of life when bone formation and need for absorbed calcium is at the highest.

The most important sources of vitamin D in Norway are enriched margarine and fish.

Large variation in intake is found both when considering dietary and total intake when supplements are included (fig. 3). Use of cod liver oil and vitamin supplements is relatively common in Norway. Among adults in the Norkost study 1997 only 38% did not use cod liver oil or other supplements (More women than men used supplements in this survey).

Daily intake of vitamin D (µg) in the Nordic countries

Intake of vitamin D in the Nordic countries is about at the same level as in Norway (11). It is slightly higher in Iceland due to widespread use of cod liver oil, and slightly lower in Denmark because until recently fortification of food has not been used.

Table 2. Mean (SD) intake of vitamin D ($\mu\text{g}/\text{d}$) in different age groups according to a nationwide survey (from ref. 11).

| Age group | n | Vit D without supplement $\mu\text{g}/\text{d}$ | Vit D with supplement $\mu\text{g}/\text{d}$ | Below recommended intake (%) |
|---------------------------|------|--|---|------------------------------|
| 12 months, not breast fed | 1231 | | 9.4 (6.2) | |
| 2 yrs | | | | |
| Girls | 852 | 2.5 (1.2) | 10.0 (7.0) | |
| Boys | 868 | 2.8 (1.5) | 10.4 (7.0) | |
| 4 år yrs | | | | |
| Girls | 185 | 2.4 (1.5) | 7.1 (5.6) | 66 |
| Boys | 206 | 2.7 (2.1) | 6.8 (5.3) | 64 |
| 9 år yrs | | | | |
| Girls | 411 | 2.6 (2.1) | 5.0 | 77 |
| Boys | 404 | 3.1 (3.0) | 6.4 | 69 |
| 13 år yrs | | | | |
| Women | 517 | 2.4 (2.5) | 3.9 | 87 |
| Men | 492 | 2.8 (3.0) | 4.5 | 85 |
| 16-29 yrs | | | | |
| Women | 354 | 3.4 (2.5) | 8.8 (9.0) | 55 |
| Men | 340 | 5.5 (4.1) | 9.8 (10.0) | 54 |
| 30-59 yrs | | | | |
| Women | 774 | 4.2 (2.8) | 10.3 (9.1) | 48 |
| Men | 721 | 5.9 (4.1) | 11.0 (10.9) | 51 |
| 60-79 yrs | | | | |
| Women | 246 | 4.0 (2.2) | 12.5 (10.8) | 47 |
| Men | 237 | 5.8 (3.8) | 13.9 (11.0) | 48 |

Tolerable Upper Intake Level (UL) of Vitamin D

Excessive intake of vitamin D may be toxic. Vitamin D formed in the skin, however, does not reach toxic levels. High levels of 25(OH)D will cause plasma calcium to increase to levels where calcification of soft tissues occurs. Calcification in the kidneys or nephrocalcinosis is the most serious and may lead to kidney failure and death. There are several reports of hypercalcemia in connection with uncritical supplementation of infant foods with vitamin D.

EU Scientific Committee on Food (2002) has recently reviewed the literature and evaluated the risk of high intake of vitamin D (13). The committee concluded that at intake $>100 \mu\text{g}/\text{day}$ and corresponding serum level 25(OH)D of 200 nmol/L there is risk of hypercalcemia and hypercalciuria. This level is

considered as NOAEL (No observed adverse effect level). Using a security factor of 2 results in a UL of 50 $\mu\text{g}/\text{day}$. For children the UL is set at 25 $\mu\text{g}/\text{day}$. Hathcock et al have recently proposed a UL of 250 $\mu\text{g}/\text{day}$ (14). The UL will hardly be reached through dietary intake, only by taking excess supplemental vitamin D.

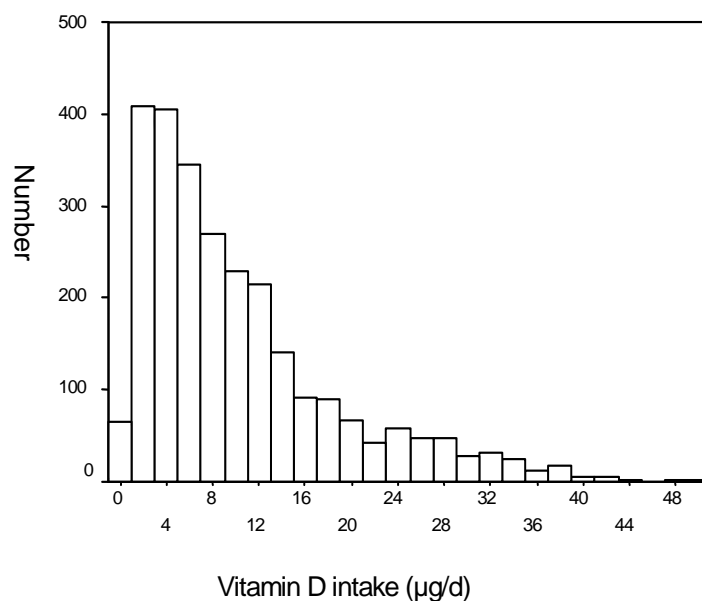


Figure 3. Vitamin D intake including cod liver oil and supplements, 2651 women and men 16-79 yrs (1997). (21 persons with intake >50 μg are not shown on the figure) (from ref. 11).

References

1. Holick MF. Vitamin D: Photobiology, metabolism, and clinical application. In: *The Liver: Biology and Pathobiology*, 3d edn. ed. by Arias IM, Boyer JL, Fausto N, et al. Raven Press, Ltd., New York, 1994 pp. 543-562.
2. Holick MF. Sunlight and vitamin D. Both good for cardiovascular health. *J Gen Intern Med* 2002; 17: 733-5.
3. Humble M D-vitaminbrist kanske vanligare än vi trott. Prevention och behandling skulle kunna ge oanade folkhälsoeffekter. *Läkartidningen* 2007; **104**: 853-857.
4. Poskitt EME, Cole TJ, Lawson DEM. Diet, sunlight, and 25-hydroxy vitamin D in healthy children and adults. *BMJ* 1979; **1**: 221-223.
5. Mosekilde L. Vitamin D-mangel. Definisjon og prevalens i Danmark. *Ugeskr Læger* 2005; **167**: 29-33.

6. Savolainen K, Mäenpää PH, Alhava EM, Kettunen K. A seasonal difference in serum 25-hydroxyvitamin D₃ in a Finnish population. *Med Biol* 1980; **58**: 49-52.
7. Vik T, Try K, Strømme JH. The vitamin D status of man at 70° north. *Scand J Clin Lab Invest* 1980; **40**: 227-232.
8. Nutrition recommendations – background and principles. Chapter 3 in: *Nordic Nutrition Recommendations 2004*, 4th edn. Nord 2004:13. Copenhagen 2004, pp 27-46.
9. Lappe, JM, Travers-Gustafson, D. Davies KM, Recker RR, Heany R. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J clin Nutr* 2007; **85**: 1586-1591.
10. D-vitaminstatus i den danske befolkning bør forbedres. Ministeriet for Fødevarer, Landbrug og Fiskeri, Danmarks Fødevare- og Veterinærforskning, Afdeling for Ernæring Søborg 2004, pp1-80 <http://www.dfvf.dk>
11. Tiltak for å sikre en god vitamin D status i befolkningen. Nasjonalt råd for ernæring. Sosial- og helsedirektoratet, Oslo 2006, pp 1-87. <http://www.shdir.no>
12. Vitamin D. Chapter 17 in *Nordic Nutrition Recommendations 2004*, 4th edition. Nord 2004:13. Copenhagen 2004, pp 241-250.
13. Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable upper intake level of vitamin D. European Commission. Health & consumer protection Directorate-General, Brussels 2002. http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html
14. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Amer J Clin Nutr* 2007; **85**: 6-18.