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REVIEW

The estimated benefits of vitamin D for Germany

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This article gives an overview of the vitamin D status in Germany, provides evidence for an independent association of vitamin D deficiency with various chronic diseases, and discusses preventive measures for improving vitamin D status in Germany. The prevalence of vitamin D insufficiency is 40–45% in the general German population. An additional 15–30% are vitamin D deficient. Vitamin D can prevent falls and osteoporotic fractures in older people. There is also accumulating evidence that vitamin D may prevent excess mortality and may probably prevent some chronic diseases that occur in early life such as type 1 diabetes and multiple sclerosis. Adherence to present sun safety policy (avoidance of the sun between 11 am and 3 pm) and dietary recommendations (5–10 μg daily for adults) would, however, definitively lead to vitamin D deficiency. The estimated cost saving effect of improving vitamin D status in Germany might be up to 37.5 billion € annually. It should be the goal of nutrition and medical societies to erase vitamin D deficiency in Germany within the next 5–10 years. To achieve this goal, the daily production of at least 25 μg of vitamin D in the skin or an equivalent oral intake should be guaranteed.

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1 Introduction

Vitamin D is well known for its effects on calcium and bone metabolism. Vitamin D deficiency results in rickets in infants and small children and in osteomalacia and osteoporosis in adults. However, it is becoming increasingly clear that vitamin D has a much broader range of actions in the human body than believed before. The vitamin D receptor is nearly ubiquitously expressed, and almost all cells respond to vitamin D exposure; about 3% of the human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system [1]. Consequently, vitamin D influences many physiological processes, including muscle function, cardiovascular homeostasis, nervous function, cellular integrity, and the immune response [2]. It is easy to imagine that severe disturbances in these biological systems have serious health effects. The present article gives an overview of the vitamin D status in Germany, provides evidence for an independent association of vitamin D deficiency with chronic diseases, and discusses preventive measures for improving vitamin D status in Germany.

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Abbreviation: RCT, randomized controlled trial

2 Vitamin D metabolism

Solar UVB radiation (290–315 nm) is the major source of vitamin D for humans, whereas dietary vitamin D is a second, less important source. Already, 20 min of a daily whole body exposure to UVB radiation trice a week is able to maintain adequate vitamin D status in people with light skin [3]. However, increased skin pigment can increase exposure time by factor six to achieve a similar effect [4]. Unfortunately, Germany has only a moderate climate and its geographic location (47°16'N to 55°04'N) is relatively northern. Generally, solar UV-B radiation is assumed to be negligible at geographic latitude of 40°N from November until February and at latitude of 50°N from October until April [5].

The UV-index for Rinteln, a small town in Central Germany (geographic latitude: 52°N), is illustrated in Fig. 1

for a whole year and also for 1 day in August. The figure demonstrates that the UV-index is below a value of 3 from the beginning of October until the end of March. As a rule of thumb, one can say that no vitamin D can be produced in the skin if the UV-index is below the value of 3. The UV-index is related to the intensity of UV radiation reaching the surface of the earth at a given point and occupies a spectrum of wavelengths from 290 to 400 nm. The index takes into account that shorter wavelengths are much more significant with respect to skin damage than longer wavelengths, a phenomenon which is seen with respect to skin synthesis of vitamin D as well. It becomes also obvious that even in August an UV index of 3 is only exceeded between 10:30 h and 16:30 h (Fig. 1), indicating that people who do not go out during the day (*e.g.* immobilized persons or office workers) do not produce vitamin D in their skin.

Once in the circulation, vitamin D is metabolized by a hepatic hydroxylase into 25-hydroxyvitamin D (25[OH]D) and by a renal 1α-hydroxylase into the vitamin D hormone 1,25-dihydroxyvitamin D (calcitriol). The latter step is under control of parathyroid hormone. However, in case of vitamin D deficiency/insufficiency, renal synthesis of calcitriol becomes substrate dependent, *i.e.* dependent on the circulating 25(OH)D concentration [6]. In addition, circulating calcitriol is adversely affected by a reduced number of viable nephrons, high serum concentrations of fibroblast growth factor-23, and high levels of inflammatory cytokines [7, 8]. Calcitriol is also produced by local 1α-hydroxylases from its precursor 25-hydroxyvitamin D in various extra-renal cells, including cells from the gastrointestinal tract, skin, vasculature and placenta [9]. There is general agreement that vitamin D status can best be assessed by measuring circulating 25(OH)D concentrations. The following cut-offs are used for different vitamin D stages: <25 nmol/L for deficiency (divide by 2.5 to convert into ng/mL), 25 to 49.9 nmol/L for insufficiency, 50 to 75–99.9 nmol/L for hypovitaminosis, ≥ 100 to 250–500 nmol/L for adequate status, and ≥ 250–500 nmol/L for intoxication (Table 1) [10]. Although there is still some debate on how to classify vitamin D status, the vast majority of vitamin D researchers agree that 25(OH)D levels below 50 nmol/L are insufficient.

Diet contributes only a small percentage to vitamin D supply. Its contribution to circulating 25(OH)D usually does not exceed 10–20% in free-living persons. In Germany, mean daily vitamin D intake in adults is 1–3 μg (1 μg is equivalent to 40 international units) [6, 11]. It has been calculated that 1 μg vitamin D increases circulating 25(OH)D levels by approximately 1 nmol/L [12]. To maintain a serum level above 75 nmol/L in almost all subjects of a group that has mean initial 25(OH)D levels of 30 nmol, a daily intake of approximately 100 μg vitamin D is necessary. If the mean initial circulating 25(OH)D concentration is higher (*e.g.* 50 nmol/L), a daily vitamin D intake of 75 μg is still necessary to maintain a serum level above 75 nmol/L in almost all subjects [13]. In Germany, the vitamin D amount of supplements sold in drugstores is restricted by law to 5 μg *per* tablet. Supplements sold as over the counter products in pharmacies are allowed to contain up to 25 μg *per* tablet. Higher dosages have to be prescribed by physicians. Only a small minority of people take vitamin D supplements in Germany [14]. Together, vitamin D current intake by natural foods and supplements in Germany does not have a significant impact on vitamin D status in the population.

3 Vitamin D status in Germany

In line with the geographic latitude of Germany and the low amount of dietary vitamin D intake, several representative large nationwide studies have demonstrated that a high

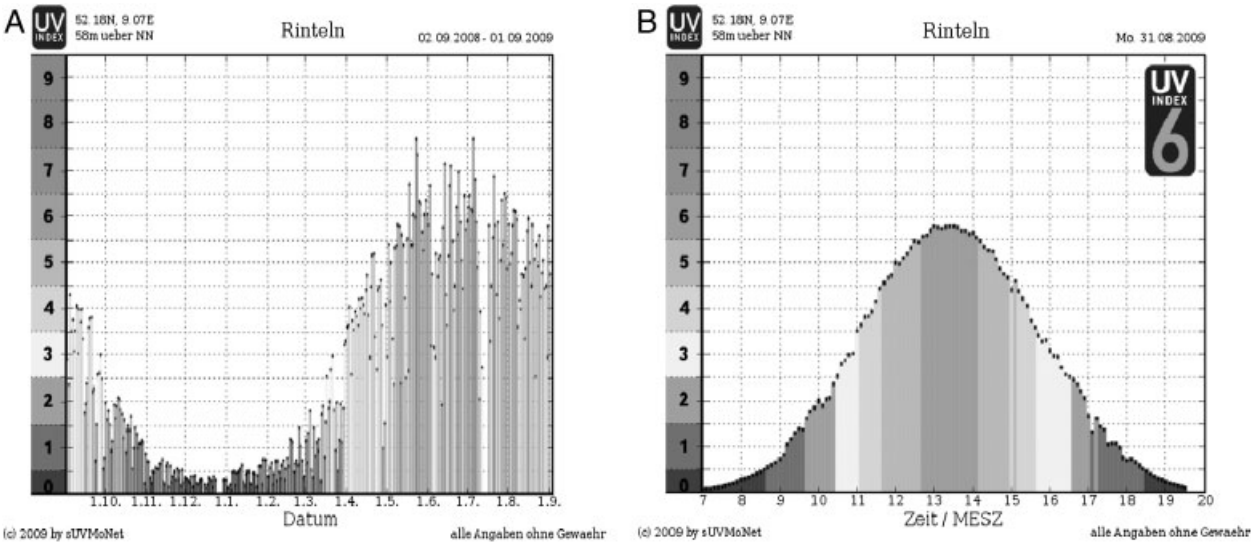

Figure 1. The UV index for Rinteln, a small town in Central Germany at 52°N, from September 2008 until August 2009 (A), and on August 31, 2009 (B) (adopted from www.suvnet.de, accessed 09/02/2009).

percentage of Germans have insufficient and even deficient circulating 25(OH)D concentrations: The German National Health Interview and Examination Survey is a representative study in the entire adult German population [11]. It was conducted from October 1997 to March 1999 and included 7124 men and women, aged 18–79 years. As demonstrated in Table 1, more than 50% of German adults have 25(OH)D concentrations in the insufficiency or even deficiency range. The German National Health Interview and Examination Survey for Children and Adolescents (KiGGS) [15] provides information on the health status of 10 015 children and adolescents in Germany at the national level. It was conducted from May 2003 to May 2006. Data demonstrate that the vitamin D status is deficient or insufficient in more than 60% of nonimmigrant boys and girls (Table 2). It is also obvious that a very high percentage of immigrant girls are in the deficiency range. In immigrant and nonimmigrant boys and girls aged 1–2 years, the situation is much better. This is most probably due to the fact that nearly 30% of immigrant boys and 32% of immigrant girls and also 20% of nonimmigrant boys and 23% of nonimmigrant girls take vitamin D supplements. The intake of vitamin D supplements is recommended in Germany as a measure for preventing rickets in infants and small children. A supplement of 10–12.5 μg vitamin D should be taken daily during infancy and also during the second winter in those infants who are born in winter.

The DEVID (De Vitamin in Deutschland) study is an investigation performed in 1343 adult individuals who had an outpatient visit with their general practitioner [16]. The study was initiated to estimate the percentage of adult German patients with insufficient and deficient vitamin D status. Blood samples were collected in an unselected cohort of patients from 264 general practitioners in all regions of Germany between February 26 and May 25, 2007. Mean 25(OH)D concentrations in the entire study cohort was 41 nmol/L (SD: 22.0 nmol/L). There was a decrease in 25(OH)D concentrations with increasing age. The percentage of individuals with deficient 25(OH)D concentrations was nearly twice as high in individuals 75 years and older compared to younger individuals (Fig. 2). Depending on the age group, between 72 and 85% had deficient or insufficient

Table 1. The different stages of vitamin D status according to circulating 25-hydroxyvitamin D concentrations (adopted from [10], with modifications)

Vitamin D status	25(OH)D concentration	Clinical and biochemical consequences
Deficiency	< 25 nmol/L	Rickets, osteomalacia, severe myopathy, severe hyperparathyreodism, calcium malabsorption, vascular calcification, high infection rates, low circulating calcitriol concentrations
Insufficiciency	25 to 49.9 nmol/L	Osteoporosis, impaired muscle function, elevated PTH concentrations
Hypovitaminosis	50 to 75–99.9 nmol/L	Reduced bodily store of vitamin D, slightly elevated PTH concentrations
Adequacy	100 to 250–500 nmol/L	Adequate vitamin D stores, no disturbances in vitamin D dependent functions
Intoxication	>500 nmol/L	Calcium hyperabsorption, hypercalcemia, vascular calcifications

Table 2. Prevalence of deficient and insufficient vitamin D status in the GNHIES and KiGGS study participants (adopted from [11, 15])

	Vitamin D deficiency < 25λnmol/L	Vitamin D Insufficiency 25–50λnmol/L	Adequate vitamin D status, > 75 nmol/L
GNHIES			
Men	15.50%	41.20%	Not applicable[a)]
Women	17.00%	40.80%	Not applicable[a)]
KiGGs			
1–2 y			
Nonimmigrant boys	7.10%	24.10%	37.80%
Immigrant boys	10.80%	29.70%	34.60%
Nonimmigrant girls	7.10%	29.30%	29.70%
Immigrant girls	17.20%	28.30%	40.20%
3–17 y			
Nonimmigrant boys	17.70%	44.10%	13.40%
Immigrant boys	18.80%	47.10%	8.20%
Nonimmigrant girls	16.80%	46.60%	13.40%
Immigrant girls	31.20%	45.40%	6.40%

Abbreviations: GNHIES, German National Health Interview and Examination Survey KiGGS, German National Health Interview and Examination Survey for Children and Adolescents.
a) The original article did not differ between 25(OH)D concentration of 50–75 nmol/L and >75 nmol/L.

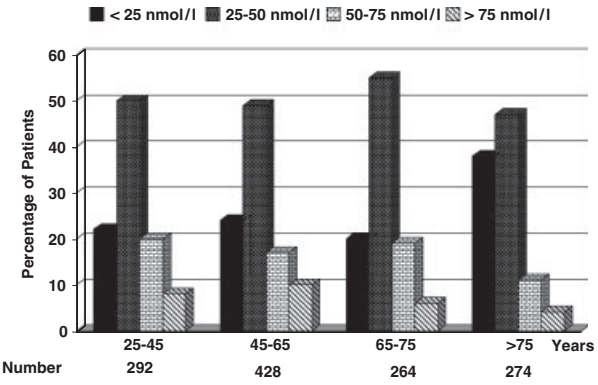

Figure 2. Vitamin D status in German patients having a visit with their general practitioner (254 doctors' offices nationwide) (adopted from reference [16]).

25(OH)D concentrations. Only a minority of individuals had 25(OH)D concentrations above 75 nmol/L in all age groups and this percentage markedly decreased in individuals 75 years and older compared to younger individuals (4% compared to 10%). Several nonrepresentative studies have also demonstrated that a high percentage of specific groups of German patients have circulating 25(OH)D concentrations in the deficiency or insufficiency range (between 65 and 98%). These groups include patients scheduled for coronary angiography [17], congestive heart failure patients [18], organ transplanted patients [19], and obese patients [20].

In a small study in female students of childbearing age [17], it has been demonstrated that mean winter values of circulating 25(OH)D were only slightly above the deficiency range (33 nmol/L). Results fit well together with another study demonstrating that mean 25(OH)D levels were only 25 nmol/L in cord blood samples of newborns who were born in the winter half-year (from October to March) [22]. Although newborns usually receive vitamin D supplements for preventing rickets, possible adverse effects of deficient vitamin D concentrations during fetal development such as increased susceptibility for type I diabetes and multiple sclerosis have to be considered as well [23, 24].

4 Vitamin D deficiency and mortality

Several very large nonrandomized prospective studies were recently published on all-cause mortality and vitamin D status: In a subgroup analysis of 3408 NHANES III participants aged 65 and older [25], the adjusted mortality risk for individuals with 25(OH)D levels of 100 nmol/L or higher compared to individuals with less than 25.0 nmol/L was 83% higher and for levels of 25.0 to 49.9 nmol/L was 47% higher. The LURIC (Ludwigshafen risk and Cardiovascular Health) study investigated a cohort of 3258 consecutive male and female patients scheduled for coronary angiography [17]. Median age varied between 61.5 and 66.3 years, according to 25(OH)D quartile. During a median follow-up of 7.7 years, 737 patients (22.6%) died. In the lower two 25(OH)D quartiles (median, 19.0 and 33.3 nmol/L), multivariate-adjusted all-cause mortality was 128 and 60% higher than in patients belonging to the highest 25(OH)D quartile (median, 71.0 nmol/L). The corresponding values for cardiovascular mortality risk were 122 and 82%, respectively. The LURIC data also demonstrated that deficient 25(OH)D concentrations were independently and significantly related to fatal cancer, fatal stroke, sudden cardiac deaths, and deaths due to heart failure compared with patients who had 25(OH)D concentrations in the adequate 25(OH)D range [26–28]. In a recently published study on 614 older Dutch men and women [29], excess mortality was significantly associated with low 25(OHD) levels as well. Compared with other subjects, in subjects in the lowest 25(OH)D quartile (median:30.6 nmol/L) the unadjusted and multivariable adjusted all-cause mortality risk was 124 and 97% higher. In 2007, Autier and Gandini [30] published a meta-analysis of randomized controlled trials (RCTs) on vitamin D and mortality that were not primarily designed to assess mortality. The authors concluded that vitamin D supplementation is linked to lower all-cause mortality in middle-aged and elderly patients with low serum concentrations of 25-hydroxyvitamin D (25(OH)D) than in unsupplemented subjects. Daily dose of vitamin D ranged between 10 and 50 μg. Risk reduction was 7% during a mean follow-up of 5.7 years. Improving vitamin D status might thus be a promising public health strategy for increasing survival. According to conservative estimations, at least 2.2% of all deaths or 18 300 lives annually could probably be saved by achieving 25(OH)D concentrations of at least 75 nmol/L in the entire German population [16].

5 Vitamin D deficiency and chronic diseases

It is well established and confirmed by meta-analyses that vitamin D can prevent falls and osteoporotic fractures in older people [31, 32]. A daily intake of 20 μg vitamin D is able to prevent nonvertebral fractures by 20%. Approximately 4–8 million Germans suffer from osteoporosis. However, the most important causes of morbidity and mortality in Germany are cardiovascular disease and various kinds of tumours such as lung cancer, breast cancer, and colon cancer. Large US studies indicate that low vitamin D status is an independent predictor of cardiovascular events [33, 34]. Recent RCTs have demonstrated that vitamin D can improve several classical and nonclassical cardiovascular risk markers [20, 35].

In 2008, a WHO report came to the conclusion that there is consistent epidemiological evidence for an inverse association between 25(OH)D and colorectal cancer, and suggested epidemiological evidence for an inverse association between 25(OH)D and breast cancer [36]. A first RCT in

postmenopausal women already provides evidence for a decrease in cancer incidence [37] by improving vitamin D status with 27.5 μg vitamin D daily. It has been estimated that achieving circulating 25(OH)D concentrations of 100–125 nmol/L will reduce the colon cancer incidence by 32% and the breast cancer incidence by 26% in Western and Central Europe [38]. There is also accumulating epidemiological and experimental evidence that low vitamin D status is related to allergic reactions [39], type 1 diabetes [20, 36, 37], multiple sclerosis [23, 42], and infections [43–45]. First, RCTs and an excellent review and meta-analysis also demonstrate beneficial vitamin D effects in type 2 diabetes [35, 46, 47]. Furthermore, there is evidence that vitamin D might protect against arterial hypertension [48].

6 Estimated costs of low vitamin D status in Europe

The economic benefit of improving vitamin D status in Germany is not easy to assess. It has recently been estimated that based on a population of 363 million inhabitants, direct and indirect costs of 187 billion € can be saved in Europe annually by improving vitamin D status to at least 100 nmol/L [49]. The costs of improving vitamin D status would be less than 10% of the costs that can be saved. Considering that these effects are similar for Germany (population: 82 million), approximately 38 billion € could be saved in Germany annually. However, since premature death can also save money, *e.g.* money that has otherwise to be paid for retirement, the cost-saving effects in Germany would be slightly lower than the aforementioned value. Given that at least 20 000 lives can be saved annually by adequate vitamin D intake [16], and that a pension of 20 000 € has to be paid for one person annually on average, the cost saving effect of vitamin D would be reduced by an amount of 0.5 billion €, leading to a total cost saving effect of 37.5 billion € in Germany annually.

7 Preventive measures to improve vitamin D status in Germany

Solely the beneficial effects of vitamin D on falls and osteoporotic fractures and the assumed life-saving effects of vitamin D justify the need for an improvement in vitamin D status in Germany. The accumulating evidence of an increased susceptibility of vitamin D deficient people to chronic diseases that occur in early life such as type 1 diabetes and multiple sclerosis further strengthen the need for effective preventive measures beyond infancy. Vitamin D status can be improved by regular UVB exposure and by higher oral vitamin D intake. As mentioned before, UVB radiation is very effective in producing vitamin D in the human skin. Already, 20 min of whole body exposure trice a week is able to increase circulating 25(OH)D concentrations by approximately 100 nmol/L in light skinned people [3]. At present, however, official German recommendations include sun avoidance at noon in order to protect against skin damage and skin cancer [http://www.sonne-mit-verstand.de; http://www.comet.bayern.de/webservice/stmugv_presse_pdf/pdf_presse.php?tid = 15163]. But this recommendation is in contrast to what would be desirable for improving vitamin D status. According to Holick's rule, exposure of 25% of the body surface to 25% of a minimal erythemal *per* day provides the human body with approximately 25 μg vitamin D. It has been estimated that lunchtime sun exposure is a viable route to produce 25 μg vitamin D in some times of the year if adequate areas of the skin are exposed [50]. For much of the globe and much of the year, however, it is not achievable in a lunchtime hour to produce 100 μg vitamin D and where it is possible large areas of skin must be exposed to prevent erythema. Even if one does not follow the official sun avoidance policy, it would be difficult to achieve amounts of solar UVB that are necessary to produce adequate amounts of vitamin D in spring and fall, when temperatures in Germany are often only modest. In addition, one cannot produce vitamin D in the skin from October to the end of March in most parts of Germany (Fig. 1). Artificial UVB exposure could be an alternative to solar UVB exposure. It is not understandable from the scientific point of view why the use of sun beds should be more dangerous than solar UVB exposure, provided the wavelengths spectrum and radiation intensity of both sources is similar. In addition, there is no scientific evidence that daily exposure to 25% of an erythemal dose would be harmful. Even higher values than 25% of an erythemal dose may be safe. One also has to take into account that a problem arises when one tries to simply estimate the benefit of vitamin D_3 production based on erythemally weighted outdoor doses, since the erythemal action spectrum differs from the previtamin D3 action spectrum and continues throughout the UVA region [51]. Although there is no doubt that UVB can cause skin cancer, cutaneously produced vitamin D may have some beneficial effects on skin cancer [52, 53]. Therefore, the risks and benefits of UV radiation must be well balanced [54]. Consequently, sun safety policy should be changed in Germany and should take into account that artificial UVB exposure can contribute to adequate vitamin D status. Artificial UVB exposure has the advantage that a whole body UVB exposure can easily be performed and that duration time of UVB exposure can easily be limited to 10–20 min. Theoretically, artificial UVB lamps can also be installed in occupational places to offer employees the opportunity for improving their vitamin D status. Generally, it should be made clear in future that UV lamps should not primarily be used for tanning but for improving vitamin D status. Official recommendations should support this point of view. It is not acceptable why children and adolescents should completely avoid artificial UVB exposure, since low vitamin D status during childhood and adolescence may be critical for the development of type

1 diabetes [24] and multiple sclerosis [23, 42, 55]. However, additional scientific research is needed in this field.

Besides UVB exposure, higher oral vitamin D intake is another measure for improving vitamin D status. At present, however, it is the problem that apparently healthy subjects do not have the opportunity to effectively prevent vitamin D deficiency/insufficiency in Germany. The current recommendation of 5–10 μg is irrelevant with respect to improving circulating 25(OH) concentrations [56]. But these recommendations and similar EU recommendations are the basis for the amount of vitamin D that can be put in a supplement that is sold in drugstores. It would therefore be of importance to enhance the reference value for vitamin D to at least 25 μg *per* day. A daily intake of this dose would at least avoid deficient circulating 25(OH)D concentrations. The next step should be the introduction of a more efficient food fortification program in Germany. At present, only margarine and a few other foods are allowed to be fortified with very low vitamin D doses. General considerations concerning the optimal vitamin D fortification strategy are already available. With respect to efficacy and safety, it has been demonstrated that fortification of a wide variety of foods with vitamin D is superior to fortification of only a few foods [57].

In addition to an improvement in vitamin D status in the general population, physicians should be made aware for recognizing people at risk for vitamin D deficiency. Especially, gynecologists should be aware of preventing vitamin D deficiency in women of child-bearing age. A simple blood test of serum 25(OH)D can be used. However, standardization of different test procedures is still necessary [58]. An amount of 100 μg daily should be prescribed in institutionalized people and in people who completely avoid UVB exposure in order to maintain a circulating 25(OHD concentration of at least 75 nmol/L. Oral vitamin intake can be performed on a daily, weekly, or monthly basis without influencing its efficacy and safety [59]. Note that a daily amount of 250 μg vitamin D is safe [60]. This amount is similar to the amount that is produced by daily whole body exposure to UVB radiation [61]. However, at present this is only an expert opinion, so that there is still a need to increase the official recommendations for the upper tolerable intake level of vitamin D from 50 to 250 μg daily.

8 Concluding remarks

Due to the geographic latitude of Germany and the low dietary vitamin D intake, there is a high risk of developing vitamin D insufficiency, at least in the winter half-year. Adherence to present sun safety policy and dietary recommendations would, however, definitively lead to vitamin D deficiency. Large representative surveys confirm the high prevalence of vitamin D insufficiency and even deficiency in the German population. Therefore, there is an urgent need to change current sun safety policy and dietary vitamin D recommendations. It should be the goal of nutrition and medical societies to erase vitamin D deficiency in the general German population and in the majority of patients within the next 5–10 years. Measures for improving vitamin D status are already well established in infants in order to prevent rickets. They included artificial UVB exposure in former decades, and now constitute of daily vitamin D supplementation and fortification of milk formula. Similar measures could be introduced into the adult population as well. A daily intake of 25 μg vitamin D would effectively prevent vitamin D deficiency (25(OH)D concentrations <25 nmol/L) in adults and would also be safe. This amount should be made available in vitamin D supplements sold in drugstores and also in fortified foods. In the meantime, future studies should evaluate more detailed the health effects of higher circulating 25(OH)D concentrations and higher daily oral vitamin D doses.

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