Vitamin D deficiency: Evidence, safety, and recommendations for the Swiss population

Report written by a group of experts on behalf of the Federal Commission for Nutrition (FCN) 2012

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Preface

The present report on “Vitamin D deficiency: Evidence, safety, and recommendations for the Swiss population” has been written by experts in the field of vitamin D upon request of the Federal Office of Public Health and the Federal Commission for Nutrition (FCN). It serves to the Federal Office of Health as a basis for updated recommendations on vitamin D intake in Switzerland.

The writing group was chaired by Heike Bischoff-Ferrari, an internationally known expert in the field of vitamin D.

Vitamin D and calcium are important for normal bone structure and function. Recent data have demonstrated that vitamin D is also essential for muscle health, and vitamin D deficiency has been shown to increase fracture risk and falls. In addition, epidemiological evidence suggests that vitamin D sufficiency plays a role in the prevention of other diseases, such as cardiovascular disorders, certain cancers, infections of the upper respiratory tract, multiple sclerosis, diabetes mellitus, and inflammatory bowel disease.

Recent data have accumulated that optimal vitamin D serum levels have to be higher than previously thought, and thus increased reference intakes have been recommended e.g. by the US “Institute of Medicine” in 2010.

Requirements for adequate vitamin D can be met through oral intake and through endogenous synthesis occurring in the skin during exposure to sunlight. However, oral intake is low in Switzerland because dietary sources of vitamin D are scarce. Sunlight exposure is often insufficient, particularly in winter months, for the major part of the Swiss population. In view of the demographic development of the society and the current lifestyle with most of daily activities taking place indoors, sufficient sun exposure to produce adequate amounts of vitamin D often does not occur. In addition, sun exposure is often avoided because of the fear of developing skin cancer caused by UV B.

Therefore, vitamin D deficiency occurs frequently in all sections of the population. Particularly vulnerable are children below age 3 years, dark-skinned people, women who are pregnant, are breastfeeding or wear a veil, and senior adults age 60 years and older. With age skin production of vitamin D is reduced, and immobile seniors not leaving their homes belong to the highest risk group.

According to the present report, adult subjects who have little sun exposure need vitamin D supplements of 600 IU per day. Senior adults age 60 years and older and subjects at particular risk for osteoporosis or vitamin D deficiency need supplements of 800 IU per day.

This report raises several questions, such as how vitamin D requirements can be met by the whole population. What is the role of the food industry in fortifying food with vitamin D? How can a widespread supplementation be accomplished ? Who pays it? These issues should be addressed in the future.

Nevertheless, the FCN believes that improving the vitamin D status of the Swiss population is an important and feasible measure to improve the health state of the population. The FCN expresses its warmest thanks to the authors for their outstanding contributions.

Basel, January 2012
Prof. Ulrich Keller, President of the FCN

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Executive Summary

Heike A. Bischoff, Zürich

On the basis of an assessment of available data on 25-hydroxyvitamin D (25(OH)D) concentrations in the Swiss population and in neighbouring countries, the panel concludes that about 50% of the Swiss population have serum 25(OH)D concentrations below 50 nmol/l, and less than 30% have 25(OH)D concentrations above 75 nmol/l.

Current evidence supports the notion that 25(OH)D concentrations of at least 50 nmol/l are necessary to support bone health in all adults and muscle health in older adults. As regards bone and muscle health in children and adolescents, as well as other non-skeletal effects of vitamin D in all age groups, more data are needed. In adults up to 59 years of age, a vitamin D intake of 600 IU is recommended, but for the older adult population (≥60 years) the panel strongly recommends a vitamin D supplementation of 800 IU per day, on the basis of evidence from randomized controlled trials (RCTs) showing a reduction of about 20% in the risk of falls and fractures. This recommendation is consistent with those of the Institute of Medicine (IOM, 2010), the International Osteoporosis Foundation (IOF, 2010) and the US Endocrine Society (2011).

Further, the panel concludes that, given the lack of evidence from large clinical trials, health benefits with serum concentrations higher than 50 nmol/l cannot at present be substantiated for endpoints other than bone health in all adults and muscle health in older adults. However, the panel recommends that vitamin D deficiency (i.e. 25(OH)D concentrations < 50 nmol/l) should be corrected in all age groups, as this measure has greater benefits than risks. On the basis of evidence from two meta-analyses of double-blind RCTs in elderly populations, the panel recommends a 25(OH)D threshold of 75 nmol/l for optimal fall and fracture prevention, in agreement with the IOF and the US Endocrine Society.

The panel only recommends screening for vitamin D deficiency, using a high-quality assay, in individuals at high risk for severe vitamin D deficiency, in order to detect a potential need for larger vitamin D doses.

Regarding sources of vitamin D, the panel notes that due to limited sun exposure, widespread use of sun protection, seasonality and very limited nutritional sources, many individuals – particularly those with insufficient sun exposure and most older adults – need vitamin D supplements in the form of drops or tablets, regardless of season, to meet their vitamin D requirements for bone and muscle health.

Table 1: Overview of daily intakes of vitamin D recommended by the panel

Group of subjects	**General Swiss population**	**Patients with severe vitamin D deficiency** (25(OH)D concentrations of < 25 nmol/l)	**Both groups**
	Recommended intake per day	Recommended intake per day	Safe upper intake
Children / Adolescents			
0-6 months	400 IU (10 µg)	400 - 1000 IU (10 – 25 µg)	1000 IU (25 µg)
6-12 months	400 IU (10 µg)	400 - 1000 IU (10 – 25 µg)	1500 IU (37.5 µg)
1-3 yrs	600 IU (15 µg)	600 - 1000 IU (15 – 25 µg)	2500 IU (62.5 µg)
4-8 yrs	600 IU (15 µg)	600 - 1000 IU (15 – 25 µg)	3000 IU (75 µg)
9-18 yrs	600 IU (15 µg)	600 - 1000 IU (15 – 25 µg)	4000 IU (100 µg)
Adults			
19-59 yrs	600 IU (15 µg)	1500 - 2000 IU (37.5 – 50 µg)	4000 IU (100 µg)
60+ yrs	800 IU (20 µg)	1500 – 2000 IU (37.5 – 50 µg)	4000 IU (100 µg)
Pregnant / breastfeeding women			
	600 IU (15 µg)	1500 – 2000 IU (37.5 – 50 µg)	4000 IU (100 µg)

As regards the recommended intake **for the general population**, the panel largely supports the 2010 recommendations of the Institute of Medicine (IOM) [1] with the aim to reduce vitamin D deficiency in all subgroups of the population. However, the panel recommends a daily vitamin D intake of 800 IU starting at age 60 – rather than 70, as suggested by the IOM – to reflect the data from RCTs on fracture and fall prevention [2], and in agreement with the 2010 IOF recommendations [3]. In addition, the panel points out that European recommendations on vitamin D intakes for children are currently being revised. Thus, the panel's recommendations for children and adolescents may be adapted in the future to conform to European standards.

Intake represents the sum of all nutritional sources of vitamin D (diet and supplements), assuming limited sun exposure (i.e. in institutionalized individuals, during the winter season in Switzerland and throughout Europe, under sun protection).

The goal of our recommendations for the general population is to ensure that 25(OH)D concentrations of at least 50 nmol/l are attained in most individuals, so as to improve bone health. With a daily vitamin D intake of 400-600 IU in children and adolescents, and 600-800 IU in adults, more than 97% of individuals will reach a threshold of 50 nmol/l, including pregnant and breastfeeding women, and about 50% will reach a concentration of 75 nmol/l. It is not clear how much vitamin D is needed to reach the 75 nmol/l threshold in 97% of older adults, so as to ensure optimal fall and fracture prevention [2]. However, based on a recent trial

in Swiss hip fracture patients, this threshold may be reached in 93% of older adults with a daily vitamin D intake of 2000 IU [4].

For patients with documented severe vitamin D deficiency (25(OH)D concentrations < 25 nmol/l or < 10 ng/ml), the panel supports the recent recommendations of the US Endocrine Society [5] (see Table 1). These recommendations also apply for subjects at high risk for vitamin D deficiency (Table 2; see full report).

The panel concludes that sunlight as a source of vitamin D is not without risk, nor is it a reliable source of vitamin D due to seasonal variation – sun intensity is insufficient to produce significant amounts of vitamin D between November and the end of April. Accordingly, blood concentrations of 25(OH)D decline by about 20 nmol/l during the winter. In addition, sun protection is widely used in the population, and skin production of vitamin D declines with age. Furthermore, natural nutritional sources of vitamin D are limited. This means that a sufficient vitamin D supply is only achieved in individuals regularly and directly exposed to sufficient sunlight or in those taking **oral supplements**. To ensure effective supplementation, it would be desirable for consumers to have a choice of effective food supplements and fortified foods from retailers, in addition to the vitamin D in drop or tablet form which is currently available over the counter in pharmacies and drugstores.

Summary Report

Heike A. Bischoff-Ferrari, Zürich

1. Summary of recommendations

1.1. Screening: How and in whom and with which assay

The measurement of 25(OH)D reflects vitamin D status. When measurement of 25(OH)D serum concentrations is indicated (Table 2) we recommend the use of a reliable assay (see below) tested against standard methodology (liquid chromatography tandem mass spectroscopy and uniform standards available through the National Institute of Standards and Technology; NIST).

We recommend screening for vitamin D deficiency only in individuals **at high risk for severe vitamin D deficiency** in order assess their potential need for larger vitamin D doses to correct their deficiency (Table 2).

Serum 1,25-dihydroxyvitamin D is not a suitable measure to reflect vitamin D status.

Table 2: Subject groups with high risk for severe vitamin D deficiency in which serum screening is indicated

Bone disorders	Rickets Osteomalacia Osteoporosis Any low trauma fracture Hyperparathyroidism
Older adults	With a history of a fall With a history of low trauma fracture
Obese individuals	Adults (BMI 30 kg/m2 or more) Obese children with additional risk factors/symptoms
Pregnant and lactating women with risk factors or unwilling to take vitamin D supplements	Pregnant women with dark skin tone, obesity, gestational diabetes, minimal sun exposure, pregnant women not taking vitamin D supplements
Children and adults with a dark skin tone	African, Indian or Hispanic ethnicity
Athletes of all ages	Who primarily exercise indoors, or perform their regular outdoor training in early morning or late afternoon hours with minimal sunshine intensity
Chronic kidney disease	
Hepatic failure	
Malabsorption syndromes	Cystic fibrosis Inflammatory bowel disease Crohn's disease Bariatric surgery Radiation enteritis

Medications	Antiseizure medications Glucocorticoids AIDS medications Antifungals cholestyramine
Granuloma-forming disorders	Sarcoidosis Tuberculosis Histoplasmosis Berilliosis Coccidiomycosis

This table has been adapted from the recommendations of the US Endocrine Society [5]. The panel notes that 25(OH)D assessment is subject to variability, and variations and up to 30% have been described [32, 33]. Assay variability is in part explained by different methodologies for 25(OH)D measurement being used, including radioimmunoassay, high-performance liquid chromatography, and liquid chromatography tandem mass spectroscopy [6]. Clearly, efforts to improve assay comparability are important, and uniform standards available through the National Institute of Standards and Technology (NIST) should be used by high quality laboratories.

Regarding cost considerations, the assay cost for 25(OH)D is about 50 CHF, while the cost of supplementation (800 IU vitamin D per day for 1 year) equals about 20 CHF; see Table 5. Therefore, selective testing is recommended among those at high risk of severe vitamin D deficiency.

1.2. Definition of vitamin D deficiency

25(OH)D serum concentrations of less than 50 nmol/l (< 20 ng/ml) are considered as indicative of vitamin D deficiency. Severe vitamin D deficiency is marked by a threshold of less than 25 nmol/l (< 10 ng/ml) [5] and vitamin D insufficiency by concentrations in the range of 25 to 49 nmol/l (10-19 ng/ml). At a concentrations below 25 nmol/l (< 10 ng/ml) adverse effects like rickets and osteomalacia are observed in children and adults, and increased bone resorption and elevated risk for secondary hyperparathyroidism are seen at concentrations between 25 and 49 nmol/l (10-19 ng/ml). The panel recommends a 25(OH)D threshold of at least 50 nmol/l as an adequate 25(OH)D concentration to support bone health in all age groups, consistent with the IOM recommendations.

The panel points out that a 25(OH)D threshold of 75 nmol/l (30 ng/ml) is needed for optimal bone mineral density in younger (age 19-49 yrs) and middle aged adults (age 50+) in the largest population-based study (NHANES III [7]), and fracture and fall prevention in adults age 60 yrs and older based on double-blind randomized controlled trials [2, 8-10]. Therefore, the panel supports a concentration of ≥75 nmol/l (target range 75 to 110 nmol/l; 30 to 44 ng/ml) for optimal bone health in younger and middle-age adults, and fracture and fall reduction in older adults, consistent with the IOF [3] and the US Endocrine Society [5].

Regarding general health endpoints, this panel states in agreement with the US Endocrine Society that evidence from randomized controlled trials is lacking, however, numerous epidemiological studies have suggested that 25(OH)D blood concentrations of 75 to 110 nmol/l (30 to 44 ng/ml) may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease, and infectious diseases [11-15].

Table 3: Serum 25(OH)D concentrations and their interpretation

Classification	Serum 25(OH)D nmol/l (ng/ml)	Clinical implications
Vitamin D deficiency	< 50 nmol/l (< 20 ng/ml)	Summarizes both concentrations of severe deficiency and insufficiency
Severe Vitamin D deficiency	< 25 nmol/l (< 10 ng/ml)	Increased risk of rickets, osteomalacia, secondary hyperpara-thyroidism, myopathy, falls, fractures
Vitamin D insufficiency	25 to 49 nmol/l (10 to 19 ng/ml)	Increased risk of bone loss, secondary hyperparathyroidism, falls, fractures
Adequate Vitamin D threshold concentrations*	50 nmol/l (20 ng/ml)	Low risk for bone loss and secondary hyperparathyroidism, neutral effect on falls and fractures
Desirable Vitamin D threshold concentrations for fall and fracture reduction**	75 nmol/l (30 ng/ml)	Optimal suppression of parathyroid hormone and bone loss; reduction of falls and fractures by about 20%

* Threshold supported by the Institute of Medicine as adequate concentration for most people (97%).

** Threshold supported by the IOF and US Endocrine Society for the reduction of falls and fractures, especially among older adults age 60+ years of age.

Supplementation dose and 25(OH)D concentration response:

Based on a dose-response calculation proposed by Heaney and colleagues, administration of 400 IU is expected to increase 25(OH)D concentrations by about 10.0 nmol/l (4 ng/ml) at the lower end of baseline 25(OH)D concentration distribution, and by 6 nmol/l (2.4 ng/ml) at the upper end [16]. The evidence from randomized trials suggests that the dose of vitamin D supplement needed to bring the large majority of adults to the range of adequate serum 25(OH)D ≥50 nmol/l), is 600 to 800 IU vitamin D, while doses in the range of 1800 to 4000 IU/day [2] would be needed to reach a threshold of 75 nmol/l in the large majority of older adults.

In a double-blind RCT of Swiss hip fracture patients 800 IU vitamin D per day shifted 70% of patients to at least 75 nmol/l, and 2000 IU per day shifted 93% to at least 75 nmol/l at 12 month follow-up [4]. Notably, the supplementation dose needed by individuals is dependent on the body mass index [17], which explains why obese individuals may require up 3-times higher supplement doses to reach the same target 25(OH)D concentration compared to non-obese individuals.

1.3. Vitamin D deficiency, intake recommendations and evidence in different age groups

Children and Adolescents (0 to 18 yrs)

Vitamin D deficiency in children and adolescents age 0-18 yrs:

In one study of 92 boys and 104 girls, aged 11-16 years from the French part of Switzerland, 17% of girls and 15% of boys had serum 25OHD concentrations of < 30 nmol/l, with the highest proportion of insufficiency at Tanner pubertal stages 4-5 (physical development in adolescents) in boys (29%) and at Tanner stage 3 in girls (24%) [18]. In a larger survey of German children age 1 to 17 yrs, median 25(OH)D concentrations were 44 nmol/l among native children, and 35 nmol/l among immigrant children. Concentrations of boys and girls were similar, however, there was a some decline with age with the highest median concentrations measured in the first year of life, likely due to the German supplementation recommendation of 500 IU per day in infants of this age group (KiGGS; Thierfelder et al. 2007). The Optiford study of 4 Northern European countries (Denmark, Finland, Poland, Ireland) included 199 children with a mean age of 12.5 years who had in 30% to 50% of the cases serum 25(OH)D concentrations below 25 nmol/l, and in over 90% of the cases serum concentrations were below 48 nmol/l [19]. The same study also assessed 25(OH)D concentrations in senior adults and suggested that in comparison, vitamin D deficiency was more prevalent in children [19].

Based on these data about 40 to 50% of native Swiss children are expected to be vitamin D deficient (< 50 nmol/l). Notably, 400 IU vitamin D per day will bring most infants (age 0-12 months) to a 25(OH)D threshold above 50 nmol/l [20], however, any lower intake, especially among older children (> 12 months), will not be sufficient to reach this threshold [21, 22]. Therefore, the Institute of Medicine (IOM) increased their recommendation from 200 IU to 600 IU vitamin D per day in all older children and adolescents (age 2 to 18 yrs). The panel notes that children at increased risk for severe vitamin D deficiency (darker skin tone, obesity and decreased playtime outside, use of sunscreen) may need more than 600 IU vitamin D to reach a 25(OH)D threshold of 50 nmol/l. The wide use of sunscreen in children and limited playtime outside, contributes to the high prevalence of vitamin D deficiency among children.

Evidence for bone health in children and adolescents age 0-18 yrs

Rickets is a result from vitamin D deficiency and has a significant impact on growth and bone development [23, 24]. While supplementation with 100, 200, or 400 IU/d of vitamin D resulted in the prevention of rickets in one study [25], vitamin D intakes between 340–600 IU/d have been reported to have the maximum effect on linear growth of infants [26]. A 2011 meta-analysis of 4 double-blind RCTs of vitamin D supplementation in the range of 132 to 2000 IU vitamin D per day compared to control (placebo or lower dose) among a total of 639 children suggested a trend to a small effect on lumbar spine bone mineral density in all treated children (standardized mean difference 0.15, 95% confidence interval −0.01 to 0.31; P=0.07); and a significant benefit of vitamin D supplementation in children with serum 25(OH)D below 35 nmol/l [27]. The effects on total body bone mineral content and lumbar spine bone mineral density were equivalent to a 2.6% and 1.7% percentage point greater change from baseline, respectively, in the supplemented group [27]. Notably, based on one randomized trial among Lebanese girls age 10 to 17 yrs included in this most recent meta-analysis, hip bone density increased more with 14'000 IU vitamin D per week (2000 IU/day) compared to 1400 IU/week (200 IU/day) at 12 month follow-up without any report of toxicity, and irrespective of baseline 25(OH)D concentrations [28].

Evidence for non-skeletal benefits in children and adolescents age 0-18 yrs

In the same randomized trial among Lebanese girls age 10 to 17 yrs there was also a benefit on muscle mass measured by DXA with vitamin D supplementation [28]. This is supported by clinical data as outlined in the adult section of this summary, suggesting that vitamin D deficiency has a direct adverse effect on muscle with the VDR being present in muscle tissue [29]. Further, children with vitamin D deficiency who are hypocalcemic may present with neuro-muscular symptoms such as weakness, tetany, cramps and muscle pain [30]. Regarding other non-skeletal benefits of vitamin D in children, observational data support an inverse relationship between higher 25-hydroxyvitamin D status or vitamin D supplementation and lower incidence of diabetes [31, 32], atopic allergies [33, 34], and upper respiratory infections [35]. However, evidence from clinical trials in children are very limited, and data from Swiss children are entirely lacking. One Finnish birth cohort study suggested that in infants who received ≥2000 IU/d of vitamin D compared to no supplementation during the first year of life, an 86% reduction in their risk of developing type 1 diabetes in the following 31 years, without any reports of toxicity [36]. This pragmatic trial is supported by a recent meta-analysis of four case-control studies of about 6500 infants which found that supplemental vitamin D prevents type 1 diabetes (OR=0.71 [0.60-0.84]), with higher cumulative doses conferring a greater benefit [37]. Regarding infections, one clinical trial in 334 Japanese Children who received 1200 IU vitamin D per day from December through March documented a 42% reduction in influenza A among children randomized to vitamin D when compared to placebo [38]. A secondary analysis documented also an 83% reduction in asthma attacks among children with asthma enrolled in the same trial [38]. For cardiovascular health, one small 4-month trial of 49 black boys and girls with a mean age of 16 years, 2000 IU compared to 400 IU vitamin D per day improved arterial stiffness significantly measured by pulse wave velocity [39].

Intake recommendations

It is not known at this time if 400 to 600 IU/d is enough to provide additional non-skeletal health benefits in children. For bone health, the American Academy of Pediatrics and the Canadian Pediatric Association (Wagner and Greer 2008) recommend 400 IU from age 1 to 18 years and the Institute of Medicine (IOM) recommends 400 IU per day during the first year of life and 600 IU per day for children age 1 to 18 years [1]. The European guidelines will be coordinated but are expected to be in the same range, given the potential benefit, the high prevalence of vitamin D insufficiency in children, and the safety of these recommendations. We therefore recommend for Swiss children an intake of 400 IU per day in the first year of life, and 600 IU per day in all children (age 2 to 18 yrs). A vitamin D prophylaxis until the 3rd birthday is strongly recommended and should be implemented by physicians and infant's health care providers. During the age period 4 to 18 years supplementation is recommended but may not be necessary in healthy children with plenty of outdoor activities. As with the adult recommendations, high risk groups of children (age 0 to 18 yrs) should be tested for their 25(OH)D status and may need vitamin D supplementation at a higher dose. These include dark-skinned children, children on anti-convulsants or on glucocorticoid treatment, children with low-trauma fractures, chronic disorders associated with malabsorption, cerebral palsy or not practicing outdoor activities (also children who perform athlete level in-door sports activities), and also children with non-specific symptoms like poor growth, gross-motor delay, tiredness, irritability or leg pain (see Table 2 on indications for 25(OH)D assessment).

Younger Adults (19 to 49 yrs) and middle-aged adults (50 to 59 yrs)

Vitamin D deficiency in young adults age 19-49 yrs and middle-aged adults age 50-59 yrs

In a large survey in 1992 of 3276 Swiss adults aged 25 to 75 years, 25(OH)D concentrations were relatively stable across age groups. The median concentration was 46 nmol/l, 34% had concentrations below 38 nmol/l, and about 70% had concentrations below 75 nmol/l [40]. These data are largely consistent with other European countries [41] and the US [42].

An adequate 25(OH)D concentration for hip bone density in younger adults has been explored in the large NHANES III population-based study [7]. Compared to the lowest quintile of 25(OH)D, the highest quintile had higher mean bone density by 4.1% in young adults of Caucasian ethnicity (test for trend; $p < 0.0001$), and higher 25(OH)D was associated with higher hip bone density even beyond 100 nmol/l, suggesting a benefit of raising 25(OH)D concentrations beyond the threshold of vitamin D deficiency (50 nmol/l) for bone health in younger adults. Since bone mineral density is generally stable in men and women aged 20 to 40 years, it seems desirable to reach a threshold concentration of 75 nmol/l in view of the fact that higher concentrations may contribute to the development of greater peak bone mass.

The vitamin D intake recommendations for the general population age 19 to 59 yrs defined by the IOM (600 IU per day) and supported by this panel will bring a large majority (97%) of younger adults to a threshold of 50 nmol/l 25(OH)D. Less well defined is the intake needed to bring a large majority of younger and middle-aged adults to a threshold of 75 nmol/l, and a range of 1800 to 4000 IU/day may be needed to reach a threshold of 75 nmol/l in the large majority of younger and middle-aged adults [2]. Mean concentrations of 75 to 100 nmol/l are achieved with intakes of 700 to 1000 IU/d in groups of young and middle-aged adults [43-45].

Evidence for bone health in young adults age 19-49 yrs and middle-aged adults age 50-59 yrs

Vitamin D is essential for bone growth [46, 47] and preservation [48]. While we lack evidence from randomized controlled trials in these age groups, one large observational study (as discussed above [7]) and a large bone biopsy study (see below [49]) support a threshold of at least 75 nmol/l in younger and middle-aged adults. Priemel et al. 2010 examined 675 iliac crest biopsies from male and female Germans (401 men with mean age 58.2 and 270 women with mean age 68.2) [49]. The authors demonstrate that mineralization defects of bone occur in individuals with a serum 25(OH)D below 75 nmol/l and strongly argue that the dose of vitamin D supplementation should ensure that circulating concentrations of 25(OH)D reach a minimal threshold of 75 nmol/l to maintain skeletal health. In contrast, the Institute of Medicine concluded from the same study that a concentration of 25(OH)D of 50 nmol/l (20 ng/ml) was adequate to prevent osteomalacia in at least 97.5% of the population and therefore suggests 50 nmol/l as a threshold in younger and middle-age adults.

Evidence for non-skeletal benefits in younger (age 19-49 yrs) and middle-aged adults (age 50-59 yrs)

Observational studies suggest that vitamin D insufficiency is prevalent in athletes [50] and that vitamin D insufficiency may have a negative impact on athletic performance [51], however no high-quality randomized controlled studies are available. Further, no trial data are available for other non-skeletal endpoints, although observational studies that are supportive of a benefit on cardiovascular health [12] and cancer prevention [52] include younger and middle-aged adults.

Intake recommendations

We suggest that younger adults age 19 to 49 years and middle-aged adults age 50 to 59 years require 600 IU vitamin D per day to prevent vitamin D deficiency and to support their bone health. Higher intakes are likely more advantageous for bone health but randomized controlled trials are lacking in this age group.

Older adults (age 60+ yrs)

Vitamin D deficiency in older adults age 60+ yrs

In addition to the Swiss survey mentioned above which included also older adults up to age 75 yrs [40], there are several data from smaller studies suggesting a high prevalence of vitamin D deficiency in healthy community-dwelling and institutionalized older adults living in Switzerland [53, 54]. In the European SENECA study, 36% of older men and 47% older women had 25(OH)D serum concentrations below 30 nmol/l, and SENECA included participants from Switzerland [55]. Most vulnerable to vitamin D deficiency are Swiss older adults with acute hip fracture who were found to have severe vitamin D deficiency (< 30 nmol/l) in 50% of cases, both in the ambulatory and institutionalized setting [56], and over 80% had 25(OH)D concentrations below 50 nmol/l, while desirable 25(OH)D concentrations of at least 75 nmol/l for fracture prevention were achieved in less than 5 percent of Swiss hip fracture patients age 65 and older [56].

Evidence for bone health in older adults age 60+ yrs

Higher 25(OH)D concentrations are associated with increased hip bone density in younger and older adults [7]. Also, in double-blind RCTs among older men and women, vitamin D supplementation increased bone density and reduced bone loss [57, 58]. Further, for fracture and fall prevention among older adults, there is strong evidence from 2 recent meta-analyses on double-blind RCTs that vitamin D supplementation of 700 to 1000 IU vitamin D per day reduces the risk of any non-vertebral fractures, hip fractures, and falls by about 20% [8, 9, 59]. Based on the achieved 25(OH)D concentration in the treatment groups of these trials, fracture reduction is neutral at a threshold of 50 nmol/l and optimal fracture and fall reduction is achieved with 75 to 110 nmol/l [8, 9]. The panel recommends 800 IU per day in all adults age 60 years and older and supports a concentration of at least 75 nmol/l (target range: 75 to 110 nmol/l; 30-44 ng/ml)in older adults at risk of falls and fractures. Whether 800 IU/d of vitamin D is enough to provide optimal fall and fracture preventionis not known at this time. Notably, 800 IU will raise 25(OH)D concentrations in the majority of older adults to ≥50 nmol/l. According to one double-blind RCT among Swiss hip fracture patients age 65 yrs and older, blood concentrations of 25(OH)D can be raised to at least 75 nmol/l in 93% of the cases with 2000 IU vitamin D per day, while 800 IU per day may achieve this goal only in about 70% of cases [4]. Further, in the same double-blind RCTs 2000 IU vitamin D per day compared to 800 IU vitamin D per day reduced hospital re-admission by 39% over a 12 month follow-up [4]. While 2000 IU compared to 800 IU per day did not reduce the risk of falling in this trial, it did reduce the risk of hospital re-admission due to fall related injury by 60%, primarily repeat fractures [4].

Evidence for non-skeletal benefits in older adults 60+ yrs

Muscle health: Muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency. Clinical findings in vitamin D-deficiency-associated myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [60]. Double-blind RCTs demonstrated that 800 IU/d vitamin D3 resulted in a 4-11% gain in lower extremity strength or function [53, 61], an up to 28% improvement in body sway [61, 62] in adults age 65 years and older after 2–12 months of treatment,

resulting in an up to 72% reduction in the rate of falls [8, 63]. Several meta-analyses of randomized trials confirmed a benefit of vitamin D on fall reduction [8, 64, 65]. In the most recent analysis of 8 double-blind RCTs vitamin D treatment regardless of dose level significantly reduced the odds of falling (OR=0.73 [0.62, 0.87]; p=.0004) [7, 59]. When the model was expanded to capture the impact of both high dose and low dose treatment, high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling (OR=0.66 [0.53, 0.82]; p=.0002), while low dose vitamin D did not (OR=1.14 [0.69, 1.87]; p=.61) [8, 59].

Cardiovascular health: Mechanistic [66] and epidemiologic [14] studies, and small clinical trials [67-69] suggest a benefit of vitamin D on blood pressure, however, data from large clinical trials are missing. Based on data from two large cohorts of men and women, the serum concentration of 25(OH)D that confers the maximum benefit regarding risk reduction of incident hypertension is at least 75 nmol/l (30 ng/ml) [70]. This threshold concentration is supported by large epidemiologic studies on myocardial infarction [12] and cardiovascular death [71] [13] associated with the lowest risk of disease.

Cancer prevention: Mechanistic [72] and epidemiologic [52] studies and a small clinical trial among postmenopausal women [73] support a benefit of vitamin D on cancer prevention, however data from large clinical trials are missing. The strongest epidemiologic data exist for vitamin D-related prevention of colo-rectal cancer. A quantitative meta-analysis of 5 cohorts supports a dose-response association with 75 to 110 nmol/l as the 25(OH)D threshold concentration associated with the lowest risk of this rectal cancer [74].

Mortality: 25-hydroxyvitamin D (25(OH)D concentrations have been inversely associated with mortality in several epidemiologic studies [13, 75-78], most of which suggested a continuous inverse relationship between 25(OH)D concentrations and risk of mortality. This inverse association is supported by a meta-analysis of 9 randomized controlled trials documenting a 7% significant reduction of mortality with vitamin D supplementation compared to control (placebo or calcium) [79]. A similar trend for risk reduction was observed in the large Women's Health Initiative trial (hazard ratio for total mortality: 0.91; 95% confidence interval, 0.83-1.01) [80]. Notably, however, in two observational studies, a U-shaped relationship has been described with an increased risk of mortality both at low (< 50 nmol/l) and very high concentrations of 25(OH)D (> 220 nmol/l) [77, 81]. The threshold concentrations that confer the maximum risk reduction for mortality across all studies was 75 to 110 nmol/l [2].

Other diseases: Weaker data of a beneficial effect of vitamin D exists for other diseases, including upper respiratory tract infections [82], multiple sclerosis [83], tuberculosis [84], insulin resistance [85, 86], other cancers [87-90], osteoarthritis [91, 92] and prevalent hypertension [93-95].

Intake recommendations

We recommend that older adults age 60+ years require 800 IU vitamin D per day to maximize bone health and to reduce their risk of fractures and falls. Our recommendation is consistent with the IOF position statement on vitamin D [3]. The IOM recommends 600 IU vitamin D in all adults up to age 69 years, and 800 IU in adults age 70 and older [1].

While the panel of the present report agrees that all older adults should prevent vitamin D insufficiency and should reach a 25(OH)D concentration of at least 50 nmol/l), it supports a higher target concentration of 75 nmol/l among older adults at risk for falls and fractures. In a recent meta-analysis of double-blind RCTs, a threshold of 50 nmol/l was insufficient for fracture reduction, while trials that reached a higher 25(OH)D

concentration of at least 75 nmol/l in the treatment groups achieved fracture reduction by about 20% both at the hip and at any non-vertebral site [9].

The panel recommends vitamin D supplementation for fall prevention in older adults based on a meta-analysis of double-blind RCTs in 2009 [8] and an update in 2011 [59]. The panel's recommendation is consistent with the 2010 assessment by the IOF [3], the 2011 assessment of the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force [64], the 2010 guidelines of the American and British Geriatric Society, and the 2011 recommendations of the US Endocrine Society [64].

An overall analysis of 12 RCTs by the IOM (n=14,101) showed a significant benefit of vitamin D on fall prevention (OR=0.89; 95% CI 0.80-0.99), as did the majority of their subset analyses, clearly supporting the use of vitamin D in the prevention of falling. However, the IOM synopsis concluded that the data were inconsistent. The set of analyses which showed no benefit were based on only 4 studies, which cannot be considered reliable indicators of true treatment efficacy, as these trials either used low dose vitamin D [96], had less than 50% adherence [97], had a low-quality fall assessment [98], or used one large bolus dose of vitamin D among seniors in unstable health [99].

Therefore, the panel suggests that the evidence of the vitamin D effect on falls has been misinterpreted by the IOM since it disregarded the overall benefit across all trials and the differential efficacy by dose among trials that tested true treatment efficacy in a double-blinded design with high quality fall assessment. Thus, given the available evidence today, vitamin D supplementation for fall prevention should not be delayed among the senior population.

Pregnancy and lactation

Vitamin D deficiency in pregnant women and their offsprings

Severe vitamin D deficiency with 25(OH)D concentrations below 25 nmol/l has been documented in 10 to 30% of pregnant women assessed in Greece [100], Belgium [101], and the Netherlands [102]. In the Dutch study prevalence of severe vitamin D deficiency was observed in 59 to 84% of pregnant women of non-western ethnicity [102]. Notably, the Greek study also reported 25(OH)D concentrations in the newborns and found that their concentrations were strongly correlated with those of their mothers (correlation coefficient = 0.64) [100]. While the threshold of 50 nmol/l was not assessed in the available European studies, the Belgium study documented that 86-88% of pregnant women did not reach 25(OH)D concentrations of at least 75 nmol/l. No data was available from pregnant women in Switzerland. Notably, human milk and colostrum contain only small amounts of vitamin D, on average 15.9 ± 8.6 IU/l [103]. Thus, newborns who are exclusively breast fed and do not receive fortified formula depend on vitamin D supplementation, especially as infants have very limited unprotected sun exposure.

Evidence for bone health in pregnant women and their offsprings

While there is no data on the benefit of vitamin D on the mother's bone health, likely due to the limited opportunities of investigation, observational data suggest that increased vitamin D exposure of the mother during pregnancy correlates with better bone health in the offspring. In a longitudinal study of 198 children in the UK, reduced 25(OH)D concentrations in their mothers during late pregnancy was associated with reduced whole-body (r=0.21, p=0.009) and lumbar-spine (r=0.17, p=0.03) bone-mineral content in children at age 9 years [104].

Evidence for non-skeletal benefits in pregnant women and their offsprings

Several observational studies show either a positive [105-108] or neutral [109-113] association between birth weight and vitamin D exposure during pregnancy. Notably, in a small double-blind randomized controlled trial among 126 Asian women living in London supplementation with 1000 IU vitamin D2 per day in the last trimester of pregnancy led to a greater weight gain in the mothers and reduced the risk of small-for-gestational-age babies (15% versus 29% during placebo) [114]. These findings were supported by another study in Indian women and their offspring comparing a bolus supplementation with 600'000 IU vitamin D in gestational month 7 and 8 and 1200 IU vitamin D per day in the third trimester to placebo, resulting in significantly higher birth weights with supplementation (bolus vitamin D = 3'180g; daily vitamin D = 2'890g; placebo = 2'730g) [115]. No difference in birth weight was found in a smaller open-design trial comparing two treatment regimens with vitamin D to placebo (200'000 IU once during pregnancy or 1000 IU per day during the last three months of pregnancy) [116].

The largest double-blind randomized controlled trial among 494 Caucasian, Hispanic, and African American pregnant women living in South Carolina by Hollis et al. compared 400 IU to 2000 IU and to 4000 IU vitamin D per day [117]. Mean 25(OH)D concentration at baseline were about 60 nmol/l, and there was a significant increase in mean 25(OH)D concentrations with treatment in all groups at 1 month prior to delivery (400 IU = 81.2 nmol/l; 2000 IU=102.6 nmol/l; 4000 IU=114.2 nmol/l). With respect to clinical endpoints, no adverse events occurred with any of the tested doses, and small but non-significant differences in birth weight (400 IU=3'222g; 2000 IU=3360g; 4000 IU=3'285g) and gestational age at birth (400 IU=38.6 weeks ; 2000 IU =38.8 weeks; 4000 IU= 39.1 week) were documented [117].

Further, vitamin D deficiency during pregnancy has been associated with an increased risk of preeclampsia [118, 119], gestational diabetes [120, 121], and caesarian section [100], but data from intervention studies are missing. Notably, in animal experiments the administration of vitamin D and its analogs improved insulin sensitivity and insulin secretion [122, 123] and prevented type 1 diabetes [124-126]. Results of cross-sectional, case-control, cohort, and small intervention studies in healthy and ill populations suggest favourable effects of vitamin D on impaired glucose tolerance, decreased insulin sensitivity or type 2 diabetes [127-130], although this was not observed consistently [131].

Observational data suggest that children exposed to more vitamin D during pregnancy have a lower risk to develop asthma in early life as suggested by two longitudinal studies [132, 133]. Litonjua et al. estimated from two birth cohort studies that the population attributable risk for asthma incidence caused by vitamin D deficiency in pregnancy is about 40% of all cases in children 3 to 5 years old [134].

Notably, in contrast to other findings illustrated above, the increased risk of eczema on examination at 9 months (OR 3.26, 95% CI 1.15-9.29) and asthma at age 9 years (OR 5.40, 95% CI, 1.09-26.65) observed in a smaller cohort study among children of mothers who had 25(OH)D concentrations of 75+ nmol/l compared to children whose mothers had a concentration of < 30 nmol/l during pregnancy may have been influenced by the large loss to follow-up (62%) in this cohort [111].

Intake recommendations

We suggest that pregnant and lactating women require 600 IU vitamin D per day to reduce the risk of vitamin D deficiency and support the health of mother and child. This suggestion is based on the widespread vitamin D insufficiency documented in pregnant women, the potential health benefit for mother and child, and the

safety of vitamin D supplementation demonstrated in pregnant women (see below: the IOM set the safe upper limit for pregnant and lactating women at 4000 IU per day [1]). Consistently, the IOM recommends 600 IU per day in pregnant and lactating women in the general population [1]. Pregnant women with a darker skin tone, obesity, gestational diabetes or minimal sun exposure may need larger doses of vitamin D. The panel suggests pregnant women should receive a vitamin D supplement of 600 IU per day independent of risk factors for vitamin D deficiency. 25(OH)D measurements are recommended in pregnant women with risk factors for vitamin D deficiency (see Table 2) or pregnant women unwilling to take a vitamin D supplement. The panel also recommends that lactating women who breast feed may need 2000 IU vitamin D per day to cover the needs of their infant if the infant does not receive vitamin D supplements.

2. General background on vitamin D (adapted from Holick MF [135]):

2.1. Vitamin D sources

Vitamin D can be made in the skin from exposure to sunlight [136] (see section 3). Alternatively, natural nutritional sources of vitamin D are rare. Vitamin D2 is obtained from the ultraviolet irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. Vitamin D3 is present in fatty fish such as salmon, mackerel, and herring (see section 4). To cover a daily recommended intake of 600 to 800 IU vitamin D, we would need to consume two servings of wild salmon per day (farmed salmon has much less vitamin D) [137], a diet difficult to maintain for the large majority of the population. Commercially available vitamin D3 is synthesized from the cholesterol precursor 7-dehydrocholesterol naturally present in the skin or obtained from lanolin [137]. Both vitamin D2 and vitamin D3 are used for food fortification and in vitamin D supplements. Vitamin D (D represents either D2 or D3, or both) that is taken orally is incorporated into chylomicrons, which are absorbed into the lymphatic system and enter the venous blood. It has been suggested that D2 is less potent than D3 in maintaining 25(OH)D concentrations [138, 139], although this was challenged by a recent trial showing similar potency of daily D2 and daily D3 [140].

2.2. Vitamin D metabolism

Vitamin D that comes from the skin or diet is biologically inert and requires its first hydroxylation in the liver by the 25-hydroxylase to 25(OH)D [135]. However, 25(OH)D requires a further hydroxylation in the kidneys and many other cells by the 1α-hydroxylase to form the biologically active form of vitamin D 1,25(OH)2D [141, 142]. 1,25(OH)2D interacts with its vitamin D nuclear receptor (VDR), which is present in the small intestine, kidneys, muscle and many other tissues [72, 143, 144] and promotes both calcium and phosphate absorption in the intestine [145, 146].

The vitamin D receptor is present in most tissues and cells in the body. 1,25(OH)2D has wide range of biologic actions, including cell differentiation and inhibition of proliferation, inhibition of renin production and angiogenesis, stimulation of insulin production, and stimulation of macrophage cathelicidin production [72, 147, 148]. In addition, 1,25(OH)2D stimulates its own destruction by enhancing the expression of the 25 -24-

hydroxylase to metabolize 25(OH)D and 1,25(OH)2D into water-soluble inactive forms. The paracrine effects of vitamin D are supported by the presence of the VDR and the 1α-hydroxylase in many tissues [141, 142].

3. Solar sources of vitamin D

Solar ultraviolet radiation, UVB in particular, is the main source of vitamin D in humans. However, solar radiation is not a reliable source of vitamin D, and there are associated risks of skin aging and cancer. Notably, all of Europe does not get sufficient UVB irradiation intensity during the months November to end of March, allowing only for minimal skin production of vitamin D during the winter season. Thus, the lowest seasonal 25(OH)D status is reached in March/April. At this nadir 25(OH)D concentrations tend to be in the average 20 nmol/l lower if compared to the end of summer 25(OH)D concentrations. As the half-life of vitamin D is 3 to 6 weeks the seasonal peak of 25(OH)D status in September decreases rapidly with a decline beginning already in November. Additionally, skin production of vitamin D declines with age [149]; seniors have been reported to have a 4-times lower capacity to produce vitamin D in their skin compared to younger adults [137]. Further, seniors tend to avoid direct sun exposure which explains the large segment of seniors with vitamin D deficiency residing in the Mediterranean area of Europe [55].

Further, the use of sunscreen and sun protective clothing reduces skin production of vitamin D, independent of age [150]. Several studies have shown that clothing worn for cultural or religious reasons can have an adverse effect on vitamin D status and bone health [151]. Finally, solar elevation angle (i.e. latitude, and time of day), cloud cover, cloud type, ozone, air pollution, altitude, surface reflexion have an impact on vitamin D production in the skin [152]. Notably, the data from ambient UVB measurements are related to a horizontal plane, while vertical surfaces such as the face, arms and legs receive much lower UVB doses compared to a horizontal plane. Thus, in practice much longer exposure times are needed to produce a certain amount of vitamin D.

Based on a mathematical model, the UVB exposure time needed to produce 1000 IU vitamin D differs by skin type and season [153-155]. For an 8% body surface exposure (face and hands) during midday the exposure time will vary between about 30 minutes to 1 hour in the summer time, and up to about 20 hours in the winter. Notably, a recent randomized trial found that vitamin D supplementation is more effective than advised sunlight exposure for treating vitamin D deficiency in non-western immigrants age 18 to 65 yrs residing in the Netherlands [156].

Tanning beds that provide UVB irradiation are an effective source of vitamin D production- provided that small and repeated doses are used which do not produce erythemas.

We suggest that sunshine exposure is not a reliable source of vitamin D and is not without risk. Therefore, supplementation strategies are important to consider in all age groups.

4. Nutritional sources of vitamin D and supplements

Natural nutritional sources of vitamin D are limited. Larger amounts are only present in fatty fish, such as salmon or sundried shiitake mushrooms (see Table below; sources Holick M et al. [157]; and http://www.swissfir.ethz.ch).

Table 4:

Natural Nutritional Sources	IU vitamin D
Wild salmon	600 to 1000 IU per 100 grams
Farmed salmon	100 to 250 IU per 100 grams
Sardines, canned	300 to 600 IU per 100 grams
Mackerel, canned	250 IU per 100 grams
Tuna, canned	236 IU per 100 grams
Cod liver oil	400 to 1000 IU per table spoon
Shiitake mushrooms, fresh	100 IU per 100 grams
Shiitake mushrooms, sun dried	1600 IU per 100 grams
Egg yolk	20 IU/yolk
Champignons fresh (Switzerland)	76 IU per 100 grams
Butter (Switzerland)	52 IU per 100 grams
Emmentaler Cheese (Switzerland)	44 IU per 100 grams

In Switzerland, few foods such as margarines, some oils, multi-vitamin juices, and few milk products are fortified with small amounts of vitamin D. These can be purchased at any supermarket or food store. For infants, 40 to 44 IU vitamin D per 100 grams of adapted formula milk is available in Switzerland (Hipp, Adapta).

The amount of fortification is regulated by the food law, which only allows a maximum of 200 IU (= 5 micrograms) of vitamin D to be added to a daily serving. The vitamin D dose may be extended to a maximum of 300 IU per day. This is insufficient to meet the daily recommendations of 800 IU vitamin D per day in the older population as suggested in this report.

Medicinal products containing vitamin D for supplementation are regulated by the Swiss law on pharmaceutical products (http://www.swissmedic.ch/rechtstexte/00201/index.html?lang=en). They are available over the counter in Swiss pharmacies and drug stores only. These are in drop form.

Table 5:

Supplements for vitamin D	IU [μg] vitamin D per drop	Cost per month at a supplemental dose of 800 IU per day equivalent to 24'000 IU per month
ViDe3 (Wild) (alcohol-based)	100 IU (2.5 μg)	2.45 CHF (content = 45'000 IU in 10 ml bottle / 4500 IU per ml) (only product which is paid by the health insurance upon prescription)
Vitamin D3 Streuli (alcohol-based)	100 IU (2.5 μg)	2.82 CHF (content = 40'000 IU in 10 ml bottle / 4000 IU per ml)
Vitamin D3 Wild (oil-based)	667 IU (16.7 μg)	2.70 CHF (content = 200'000 IU in 10 ml bottle / 20'000 IU per ml)

The panel notes that child-caring persons need to be well instructed on the dosing of vitamin D. Several cases were reported that led to overdosing due to lack of instruction. Depending on the product of vitamin D drops, the exact number of drops need to be communicated to the mothers for the supplementation regimen of their infants.

For intra-muscular use, one additional product is available on the Swiss market containing 300'000 IU vitamin D3 (Streuli), which has been used by physicians as an oral large-dose bolus. However, this is an off-label application. See recommendations on intermittent large dose supplementation below.

The working group recommends that the food law may need to be revised to allow for a larger fortification dose to meet the vitamin D recommendations for bone health in targeted foods and food supplements. This would be valuable for all segments of the population and would increase consumer choices.

5. Safety, intermittent supplementation, seasonal needs

In a 2010 benefit-risk assessment of vitamin D there was no evidence to suggest a risk of hypercalcemia during daily intakes of vitamin D up to 10'000 IU or serum 25(OH)D up to 240 nmol/l, which are far higher intakes and higher serum concentrations than necessary to achieve benefits [2]. In the current risk assessment, hypercalcemia was chosen as the critical effect, the adverse effect occurring at the lowest intake. The only RCT that documented an increased risk of nephrolithiasis was the Women's Health Initiative (WHI), which tested 400 IU vitamin D in combination with 1000 mg of calcium (hazard ratio,1.17; 95 percent confidence interval, 1.02 to 1.34) [158]. Whether this was the only trial large enough to detect a small risk of nephrolithiasis with vitamin D supplementation or whether this was caused by the substantial calcium supplement intake taken in combination with the vitamin D and/or the additional calcium and vitamin D supplements taken by the majority of participants outside the study protocol in the WHI trial is unclear. However, the low dose vitamin D used in the WHI argues against a causal role of the increased risk of nephrolithiasis.

In the IOM report published in November 2010, safe upper intake concentrations have been defined for all age groups [1]. These may also apply for the Swiss population (see Table 1). The safe upper limit intake recommendation as defined by the IOM are 1000 IU/day from 0 to 6 months, 1500 IU/day from 6 to 12 months, 2500 IU from age 1-3 years, 3000 IU from age 4-8 years, and 4000 IU from age 9 and older, including pregnant and lactating women [1]. The last EFSA (European Food Safety Authority) assessment for vitamin D was in 2008 and reflects data up to 2006, thus is somewhat outdated today (http://www.efsa.europa.eu/en/scdocs/doc/828.pdf).

The safe upper limit is important for clinical practice as adult patients with vitamin D deficiency need to be treated with higher daily doses for 4 to 6 weeks, or a one-time bolus (Stoss Therapie; i.e. 45'000 to 100'000 IU once, then daily maintenance supplementation) to replete their vitamin D stores quickly and efficiently.

Safety and benefit of intermittent vitamin D treatment

While intermittent dosing of vitamin D is attractive to enhance adherence to treatment, it is unclear whether treatment intervals beyond the half-life of vitamin D (3-6 weeks) are beneficial in fracture reduction. One trial found that 100,000 IU vitamin D taken orally every 4 months, reduced 33% of first hip, wrist or forearm fractures[98]. Conversely, two annual treatment trials, one with 300,000 IU vitamin D given as intra-muscular injections[159] and one with 500,000 IU given orally [160], were not successful in reducing fractures, and a potential harmful effect could not be excluded. Thus, high-dose annual vitamin D treatment may not be warranted for fracture reduction. Intermittent treatment weekly doses (5600 to 7000 IU/week is equivalent to 800 to 1000 IU per day) or monthly doses (24'000 to 30'000 IU/month is equivalent to 800 to 1000 IU per day) are useful and raise 25(OH)D concentrations similarly to the daily application of the same dose[161]. During infancy and childhood, treatment of vitamin D deficiency should be combined with calcium supplements to prevent hypocalcemia or tetanic seizures[162]. The panel notes that very large doses of vitamin D (i.e. 300'000 IU as a stoss therapy prophylaxis) in infants (0-12 month) is not recommended due to several observed cases of nephrocalcinosis[163]. Notably, infants will reach significant increases in 25(OH)D concentration with the recommended daily dose of 400 IU per day.

Seasonal fluctuations of 25(OH)D concentrations [164] and influence on needs

30 to 50 percent of children and adults may be in the target range during summer months. However, as the half-life of vitamin D is only 3 to 6 weeks, these concentrations will not sustain during the winter months even in sunny latitudes of Europe[165, 166]. Thus, winter supplementation with vitamin D is needed even after a sunny summer. Furthermore, several studies suggest that many older persons, and especially those with hip fractures, will not achieve optimal serum 25(OH)D concentrations during summer months, suggesting that vitamin D supplementation should be independent of season in older persons[166-168]. Further, children, younger and middle-aged adults who are not outside during the summer months or use sun-protective clothing or sunscreen, will depend of vitamin D supplementation also during the summer months.

Therefore, the working group therefore recommends that vitamin D supplementation should be considered independent of season in the older adult population (age 60+ yrs), but also among younger individuals who wear sunscreen regularly or stay indoors and therefore have minimal sun exposure also during the summer months.

6. Calcium sparing effects of vitamin D

Vitamin D stimulates calcium absorption in the intestine. A calcium sparing effect of vitamin D is supported by two recent epidemiologic studies, suggesting that both PTH suppression[169] and hip bone density[170] are primarily influenced by 25(OH)D concentration independent of calcium intake. The studies further suggested that PTH suppression and hip bone density only correlate with calcium intake at very low 25(OH)D concentrations. Consistently, non-vertebral fracture reduction was 21% with or without additional calcium supplementation for the higher dose of vitamin D in a 2009 meta-analysis of double-blind RCTs[9].

As calcium absorption is improved with higher serum 25-hydroxyvitamin D concentrations [169, 171], the panel notes that with vitamin D supplementation calcium absorption is increased, which may reduce the total calcium intake recommendations from 1000 mg per day to about 800 mg per day.

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Chapters of the Report

1. Vitamin D and pregnancy

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1.1. Physiology

25(OH) vitamin D_3 can pass the placenta and the fetus is completely dependent on the maternal serum for vitamin D supplementation. A small study describes a small decrease of 25(OH) vitamin D_3 during pregnancy [1] and it seems that the 25(OH) vitamin D_3 level is not changing without supplementation or synthesis [2]. Decidual cells express the vitamin D receptor (VDR) and can transform 25(OH) vitamin D_3 into the active form of the hormone by 1α-hydroxylase [3, 4]. Vitamin D is already present at the time of implantation and could influence the congenital immunity at the feto-maternal barrier [5-7]. Several studies describe that the 1,25(OH)D level doubles between the first and second trimester and reaches a maximum in the third trimester compared to non-pregnant women [8-10]. During lactation the 1,25(OH)D level normalizes or decreases below the recommended level. The increase in 1,25(OH)D is mainly necessary to increase absorption of calcium [1].

1.2. Prevalence

Several different definitions of vitamin D deficiency complicate the assessment of prevalence. Currently the most common cut-off level for serum 25(OH) vitamin D_3 deficiency used in publications of this field is < 80 nmol/l (32 ng/ml). Several papers differentiate between an insufficiency and a deficiency. For this review we used the cut-off levels that were mentioned in the respective study.

Worldwide we found a prevalence of vitamin D deficiency during pregnancy between 5 and 84% [11] (Tab. 1): Belgium 21-32% [12], Netherlands 8-50% [13], Norway 71% [14, 15], Greece 20% [16], USA 5-50% [17, 18], Iran 80% [19], India 31-84% [20, 21]. In Switzerland the current prevalence of vitamin D deficiency in pregnant women is not known.

The correlation of skin pigmentation and the vitamin D status has been demonstrated in several studies: van der Meer et al. [13] found vitamin D deficiency in 50% of pregnant women with a dark skin, where only 8% of Caucasian pregnant women had a deficiency (cut-off defined as 25 nmol/l). Because of this conservative interpretation of deficiency a higher prevalence can be assumed [22-24]. Bodnar et al. found similar numbers in the US (5% of Caucasian pregnant women and 29.2% of African-American pregnant women; cut-off level at 37.5 nmol/l). If women with an insufficiency were included the numbers were for Caucasian women 46.2% and for African-American women 83.4% (cut-off for insufficiency: < 80 nmol/l) [17].

Table 1

	Cohort	Cut-off level	% Deficiency
Belgium: Cavalier et al. 2008	pregnant n= 24 women in childbed n=65	< 75 nmol/l (30 ng/ml) < 30 nmol/l (12 ng/ml)	86 - 88 % 21 -32 %
Netherlands: van der Meer et al. 2006	pregnant, 1. pregnancy visit n=105 / Western n=253 / Non-Western	< 25 nmol/l (10 ng/ml)	 8.0% 59 - 84 %
Norway: Markestad et al. 1984 Norway: Viljakainen et al. 2010	pregnant, n=41 pregnant n=125	– < 50 nmol/l	– 71%
Greece: Nicolaidou et al. 2006	pregnant, n=123, at term	< 10 ng/ml	19.50%
USA: Bodnar et al. 2007 USA: Lee et al. 2007	pregnant, at term n=200 / Caucasian n=200 / Afro-American pregnant, at term n=200 / Caucasian n=200 / Afro-American at birth, n=40	< 37.5 nmol/l (15 ng/ml) < 80 nmol/l (32 ng/ml) < 30 nmol/l (12 ng/ml)	 5% 29.2% 46.2% 83.4% 50.0%
Canada: Weiler et al. 2005	at birt, n=72	< 37.5 nmol/l (15 ng/ml)	46.0%
Iran: Bassir et al. 2001 Iran: Maghbooli et al. 2007	pregnant, n=50 at term pregnant, n=741, mid-pregnancy	< 25 nmol/l (10 ng/ml) < 25 nmol/l (10 ng/ml) < 12.5 nmol/l (5 ng/ml)	80% 71% 29%
India: Farrant et al. 2009	pregnant, n=559 30 weeks	< 50 nmol/l (20 ng/ml) < 28 nmol/l (11ng/ml)	66% 31%

In older studies Asian pregnant women showed lower mean 25(OH) vitamin D levels than Caucasian women [25] and specifically Asian vegetarians had lower levels than Asian non-vegetarians [26]. Grover et al. found a prevalence of vitamin D deficiency (< 22.5 nmol/l) of 80% of pregnant women wearing a veil [27].

The season and the latitude have the same influence on vitamin D production as in the general population [28, 29]: lower values in the winter and spring months as well as with increasing latitude [15, 17, 30].

For Switzerland we assume a prevalence of 5 – 40% for Caucasian pregnant women and 29-84% for non-Caucasian women if the vitamin D deficiency is defined as cut-off 10-15 ng/ml. If the deficiency is defined as cut-off 30-32 ng/ml the prevalence of vitamin D for Caucasian women would might be as high as 46-88% and for non-Caucasian women 80-88%.

1.3. Current recommendations for supplementation

The Institute of Medicine (IOM) released new recommendations in November 2009. They suggest 600 IU vitamin D per day and an upper limit (UL) of 4000 IU/d for pregnant and lactating women [31] The authors base their recommendations mainly on the lack of data to support more benefits at a higher dose. The U. S. Endocrine Society recommended in July 2011 that pregnant and lactating women require at least 600 IU/d and recognize that at least 1500-2000 IU/d of vitamin D may be needed to maintain a blood level of 25(OH)D above 30 ng/ml [32]. These authors base their recommendations on two studies showing epidemiologic evidence for an association between low levels of vitamin D and increased risk for preeclampsia [17] as well as cesarean section [33]. The Endocrine Society classifies women during pregnancy and lactation as populations at risk and therefore are candidates for screening.
In the most recent safety trial with 494 pregnant women the vitamin D supplementation of 4000 IU/d was safe [34].

The most common way of supplementation of vitamin D during pregnancy is in a multivitamin tablet. The current dose varies between 200-400 IU/day. Already in 1980 Cockburn et al. [35] assumed this was too low.

In several studies vitamin D has been studied in combination with other vitamins and/or fatty acids [36-38], but the influence of vitamin D alone on single outcomes cannot be determined in these studies.

1.4. Screening for vitamin D deficiency during pregnancy

Instead of a general recommendation for supplementing vitamin D during pregnancy, 25(OH) vitamin D3 could be screened during pregnancy. Mulligan et al. have suggested a list of risk factors [39] which would lead to a serum 25(OH) measurement in pregnant women with one or more of these risk factors. This list is similar to the suggested populations at rist by the U. S. Endocrine Society [32].

List of risk factors:

- Northern latitude, especially during winter and spring
- Limited sun exposure
- Regular use of sunscreen
- Dark skin
- Obesity (BMI > 30 kg/m2)
- Extensive clothing cover

- Malabsorptive syndromes (cystic fibrosis, cholestatic liver disease, inflammatory bowel disease, short gut syndrome)

1.5. Influence of vitamin D deficiency on the mother

Infertility

The two most common reasons for female infertility are endometriosis and polycystic ovarian syndrome (PCOS). We assume that endometriosis is dependent on a defect to recognise endometrial elements in the abdomen which is modulated by the immune system. Somigliana et al. [40] found in women with endometriosis higher levels of 25(OH)D3 than in a control group. The severity of endometriosis was directly correlated to the level of 25(OH)D3. Ferrero et al. [41] detected higher levels of vitamin D binding protein (isoform DBPE) in the peritoneal liquid in patients with endometriosis, but not in the plasma of these patients.

On the other hand, women with PCOS who were treated with metformin, in addition to calcium 1g and vitamin D 400IU per day showed more regular cycles with the development of dominant follicles than compared to women without the therapy [42].

Overall, it seems that vitamin D plays a role in female infertility. A supplementation would not help in all cases, but probably would even be counterproductive as in the case of endometriosis. But these are only preliminary research results and no clinical trials are available.

Gestational diabetes

Vitamin D plays an important role in the balance of glucose tolerance. Gestational diabetes occurs by an increase in insulin resistance during pregnancy. Vitamin D deficiency is significantly correlated with increased insulin resistance and a disturbed insulin secretion in non-pregnant women [43]. Zhang et al. [44] found in a nested case-control study significantly lower 25(OH) levels at 16 weeks of pregnancy in pregnant women who developed gestational diabetes compared to pregnant women who did not develop gestational diabetes. Vitamin D deficiency (< 20 ng/ml) increased the risk for gestational diabetes by 2.66 (CI 1.01-7.02), adjusted for maternal age, origin, history of diabetes in the family and BMI before pregnancy.

Clifton-Bligh et al. found a negative correlation between the 25(OH) vitamin D3 level and fasting glucose levels, but the odds ratio for gestational diabetes in women with 25(OH) vitamin D < 50 nmol/l did not reach statistical significance [45]. Maghbooli et al. found a higher prevalence of severe vitamin D deficiency (< 12.5 nmol/l) in patients with gestational diabetes than in normoglycemic pregnancies (44.2% vs. 23.5%) [46, 47]. One study in India did not find an association between vitamin D deficiency (< 50 nmol/l) and gestational diabetes [20].

In a small supplementation study (n=12) with a single dose of 1,25(OH)D i.v. therapy (Etalpha) and 14 days of oral therapy showed an inverse correlation between 1,25(OH)D and glucose within two days. However, the effect was not constant over a 14 days oral therapy [47].

Vitamin D deficiency (< 20 ng/ml) probably negatively influences the glucose haemostasis during pregnancy. Further investigations are needed to clarify if supplementation has a therapeutic or preventive option. It has to be determined at what gestational age a supplementation is most helpful.

Preeclampsia

Preeclampsia is correlated with hypocalcuria. Already in 1987 Taufield et al. showed that women with preeclampsia have lower levels of calcium in the urine, higher levels of PTH and lower levels of 1,25(OH)D compared to women without preeclampsia [48]. One reason could be the influence of vitamin D on the early placentation period. A defect in the placenta (reduced activity of 1α-hydroxylase [49]) suppresses the synthesis of active vitamin D causing hypocalcemia.

The correlation of vitamin D deficiency and preeclampsia has been demonstrated in several epidemiological studies [50-52]. Similar results can be drawn from seasonality studies: higher levels of vitamin D and lower prevalence of preeclampsia during the summer and autumn and vice versa in the winter and spring months [53, 54].

Already in 1938 [38] a multivitamin and halibut liver oil (900 IU vitamin D), starting at 20 weeks of pregnancy, reduced the odds by 32% to develop preeclampsia. Haugen et al. did find similar numbers in a cohort study in 2009: Pregnant women who took 10-15 µg/d (400-600 IU) daily had a significantly lower odds ratio for developing preeclampsia than women without supplementation (OR 0.73 [0.58-0.92] [37].

Marya et al. showed in 1987 [55] in a randomised trial with 1200 IU vitamin D and 375 mg calcium or no supplementation in 400 pregnant women beginning at 20-24 weeks of gestation that the therapy could reduce significantly hypertension but not the incidence of preeclampsia (6 vs. 9%)

In a cohort study, preconceptional vitamin D supplementation of the mother reduced the risk to develop preeclampsia in the daughter's first pregnancy by 50% [56].

It seems plausible that vitamin D deficiency is associated with preeclampsia, but it is unclear when and how much vitamin D supplementation can reduce the risk for preeclampsia.

Caesarean section

Poor muscular function is an established symptom of vitamin D deficiency in children and adults. Merewood et al. [33] tested this hypothesis in terms of the association between vitamin D deficiency (< 37.5 nmol/l) and primary caesarean section in a cohort of 253 women. They found that 28% of women with deficiency had a caesarean section where as only 14% of women without deficiency had the operation (p=0.012). No other study has confirmed these results so far.

Hollis et al. could not show a difference in mode of delivery at different supplementation levels (400 IU vs 2000 IU vs 4000 IU) in an ethnically diverse group of 494 pregnant women [34].

1.6. Influence of vitamin D defiency on the child

Osteomalacia / Rickets

The best known consequences of vitamin D deficiency are osteomalacia and rickets. Most of the current supplementation recommendations are based on the prevention of these two diseases.

Weiler et al. found that maternal vitamin D deficiency leads to a disturbed mineralisation of the bones of the newborn [57]. Viljakainen et al. confirmed these findings [15].

The maternal vitamin D deficiency during pregnancy is translating into the infant's childhood. Javaid et al. showed a positive correlation of maternal vitamin D status (49% of mothers had a 25(OH) vitamin D level

≤ 20 ng/l) and the bone mineralisation in nine year old children [58]. Reduced concentration of 25(OH)-vitamin D in mothers during late pregnancy was associated with reduced whole-body (r=0.21, p=0.0088) and lumbar-spine (r=0.17, p=0.03) bone-mineral content in children at age 9 years. Both the estimated exposure to ultraviolet B radiation during late pregnancy and the maternal use of vitamin D supplements predicted maternal 25(OH)-vitamin D concentration (p<0.0001 and p=0.0110, respectively) and childhood bone mass (p=0.0267).

Osteomalacia and rickets occur only with extreme vitamin D deficiency and can be prevented with vitamin D supplements of 200-400 IU per day.

There is a hypothesis of a correlation of intrauterine vitamin D deficiency and osteoporosis later in life, which needs further investigation [59].

Birth weight / Small-for-Gestational-Age children (SGA)

The influence of vitamin D on fetal growth is controversial in epidemiologic studies: Two studies from different countries, but both adjusted for confounding factors, suggest a correlation between maternal vitamin D deficiency and birth weight or SGA infants [30, 60]. But four other studies, two of them adjusted for confounding factors, did not find a correlation between 25(OH)D and the mean birth weight or similar outcomes [20, 61-64].

Scholl et al. found that the intake of vitamin D (in diet and as supplementation) is a predictor for birth weight [65]. Sabour et al. could not supported these findings in an Iranian study: Infants of mothers who took the recommended supplementation during pregnancy had not a higher mean birth weight that infants of mothers who did not take supplementation [66].

All except one supplementation studies for improving birth weight are older than 15 years and mainly lack adjustment for confounding factors. In 1980 Brooke et al. found in a double-blind randomised controlled supplementation trial with 1000 IU/day vitamin D given in the third trimester that Asian women had a significantly lower rate of SGA infants if they took the supplementation [67].

Mayra et al. [68] compared in a supplementation study 2x single dose of 600'000 IU (15 mg) vitamin D in gestational month 7 and 8 with 1200 IU/d in the third trimester placebo. They found significantly higher birth weights with supplementation (3’180g and 2’890g vs. 2’730g). In a follow-up study [69] with 2x 600'000 IU in the third trimester compared to placebo they showed a reduction of low birth weight (< 2500g) among 200 Indian pregnant women (4% vs 19%).

Maxwell et al. found in double-blind study only half as many infants < 2500g when mothers took a supplementation of 1000 IU/d during pregnancy compared to no supplementation [70].

In contrast a smaller study (n=77) of Mallet et al. with a randomized study of 200'000 IU p.o. once during pregnancy or 1000 IU p.o. during the last three months of pregnancy or no supplementation did not find any birth weight differences [71]. Hollis et al. could not show a difference in birth weight at different supplementation levels (400 IU vs 2000 IU vs 4000 IU) in an ethnically diverse group of 494 pregnant women [34].

There is some evidence that vitamin D supplementation increases birth weight in certain ethnic groups. But the studies mainly have no adjustments for confounding factors and therefore are not conclusive in detail.

Preterm birth

In a large randomised controlled trial (n=494) in South Carolina first results show an influence of vitamin D on preterm birth. Hollis et al. found that pregnant women who took 4000 IU/d had a lower risk to deliver preterm (< 32 and < 37 weeks of pregnancy) compared to women without supplementation [72] (Dr. Bruce Hollis, personal communication). Other studies on the influence of vitamin D on preterm delivery were not conclusive [63, 73].

Currently not enough data on this association is available for recommendations.

Other health outcomes in children

Gale et al. found in the same cohort as Javaid that children of mothers who had a 25(OH)-vitamin D concentration in pregnancy > 75 nmol/l had an increased risk of eczema on examination at 9 months (OR: 3.26, 95% CI 1.15-9.29, P=0.025) and asthma at age 9 years (OR 5.40, 95% CI, 1.09-26.65, P=0.038) compared to children whose mothers had a concentration of < 30 nmol/l [62]. The study might be biased by a large loss to follow-up (61.8%).

On the other hand Camargo et al. could show at an early age that compared with mothers in the lowest quartile of daily intake (median: 356 IU), those in the highest quartile (724 IU) had a lower risk of having a child with recurrent wheeze (OR: 0.39, 95% CI 0.25-0.62, P< 0.001) [74]. Devereux et al. presented similar results showing significantly increased risks for ever wheeze (OR: 0.48; 95% CI: 0.25-0.91), wheeze in the previous year (OR: 0.35; 95% CI: 0.15-0.83), and persistent wheeze (OR: 0.33; 95% CI: 0.11-0.98) in 5-y-old children comparing the highest and lowest quintiles of maternal total vitamin D intake [75]. Litonjua et al. estimated from these two birth cohort studies that the population attributable risk for asthma incidence caused by vitamin D deficiency in pregnancy is about 40% of all cases in children 3 to 5 years old [76]. But these studies have not investigated the level of 25(OH) vitamin D of the mother during pregnancy.

Data of maternal vitamin D deficiency and atopic outcomes in children point to an association, but further studies have to support the hypothesis that the supplementation changes the prevalence of atopic outcomes, mainly asthma.

Lactation

Human milk and colostrum contain only little amounts of vitamin D, on average 15.7 ± 8.6 IU/l [77]. Newborns that are exclusively breastfed depend on vitamin D supplementation, especially as infants have limited unprotected sun exposure. In Switzerland vitamin D prophylaxis in fully breastfed children should specially be recommended. There is the possibility of supplementing the mother with 4000 IU/d to reach acceptable levels of vitamin D in the breast milk [77, 78].

Vit D dose	Vit D	25(OH)D	25(OH)D
mother	Content breast milk	mothers	babies
2000 IU/Tag	34 IU/liter	88 nmol/l	75 nmol/l
4000 IU/Tag	94 IU/liter	105 nmol/l	75 nmol/l

From: Hollis et al. 2004 Am J Clinic Nutrition

1.7. Summary

The prevalence of vitamin D deficiency in pregnant women in Switzerland is difficult to determine due to the two following reasons:

- Missing of a definition of clinically relevant vitamin D deficiency during pregnancy
- Absence of a previous study on vitamin D deficiency in pregnant women; absence of data on vitamin D content in milk of Swiss lactating women

Acknowledging these missing factors it seems there are several risk factors for vitamin D deficiency. Mulligan [39] presented a list of risk factors as mentioned under point 4:

- Northern latitude, especially during winter and spring
- Limited sun exposure
- Regular use of sunscreen
- Dark skin
- Obesity (BMI > 30 kg/m2)
- Extensive clothing cover (i.e. veil)
- Malabsorptive syndromes (cystic fibrosis, cholestatic liver disease, inflammatory bowel disease, short gut syndrome)

We recommend that pregnant and lactating women should take 600 IU vitamin D per day, as recommended for the general population. For pregnant women with a darker skin tone, obesity, gestational diabetes, minimal sun exposure or other risk factors screening of 25(OH) vitamin D is recommended. If vitamin D deficiency is evident, appropriate supplementation (1500-2000 IU/d) is indicated. Lactating women who breast feed exclusively may need 2000 IU vitamin D per day to cover the needs of their infant if the infant is not separately supplemented.

Open is the question at what point during pregnancy the supplementation should start.

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2. Swiss recommendations on vitamin D prophylaxis in paediatrics[1]

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2.1. Summary

(Refer also to the summary of the EEK Vitamin D working group: VITAMIN D: REPORT ON DEFICIENCY, EVIDENCE, SAFETY, AND RECOMMENDATIONS FOR THE SWISS POPULATION)

In Switzerland, low vitamin D levels are found in 20 to 60% of children and adolescents. Though rickets has become rare, vitamin D deficiency may impair bone density and muscle function also during childhood and adolescence, and negative effects on immune system, diabetes incidence and cardio metabolic function have been shown. Nevertheless, the currently recommended supplementation with 400 IU vitamin D up to the end of the first year of life is implemented in 64% of infants only. Therefore, the implementation of the current recommendations has to be urgently improved. Children at risk should be screened and treated, namely those with dark skin, chronic disorders or not practicing outdoor activities. It has to be examined which measures, e.g. vitamin D fortified dairy products, may assure the suggested vitamin D intake of 600 IU/day after the first year of life.

[1] Citations are classified according to their evidence stages and indicated following the references in the text using the following codes:

Stage of evidence type (in some studies in brackets, still to be added)	
I a	evidence based on (>) meta analyses, randomized, controlled studies
I b	evidence based on at least one randomized controlled study
II a	evidence based on at least one well-designed, controlled study without randomization
II b	evidence based on at least one well-designed, quasi-experimental study
III	evidence based on well-designed, non-experimental, descriptive studies (e.g . comparative clinical trials, correlation studies, case control studies)
IV	evidence based on reports/opinions of expert communities, consensus conferences and/or clinical experience of renown authorities.

(Guideline of the manual of the Association of the Scientific Medical in Germany and Z.Ärztl. Fortbild.Qual.sich (AZO) 2001 (95) Supplement 1, S 41)

2.2. Introduction

Rickets and other manifestations of vitamin D deficiency in the musculo-skeletal system are rare in children in Switzerland and Central Europe. An increased prevalence is known to exist in children of immigrant families, severely handicapped or children treated with the classic anti-epileptics such as phenytoin or carbamazepin (1) (Table 1). In children with chronic diseases of the intestine, liver or kidney (2;3) or during glucocorticoid therapy (4), vitamin D therapy or osteoporosis prophylaxis respectively are a routine measure in the management of the respective condition.

Table 1: Increased risk for vitamin D deficiency in childhood and adolescence:

Breast-fed children without supplementation and/or children of mothers with vitamin D deficiency
Dark skin colour (mainly girls from Africa, Turkey, Near and Middle East as well as from India, Pakistan and Sri Lanka).
Lack of sunlight exposure (wearing veils, indoor sports activities, TV & screen abuse,…)
Immobilisation (cerebral palsy,...)
Chronic diseases such as o malabsorption syndromes (coeliac disease, mucoviscidosis, Morbus Crohn) o liver dysfunction o biliary tract disease o chronic kidney insufficiency o diabetes mellitus
Obesity
Symptoms like o poor growth o gross-motor delay o tiredness o irritability o leg pain
Anti-epileptic or glucocorticoid medication
Constant use of cutaneous sun protection factors
(Phases of accelerated growth during infancy or puberty)

There are guidelines addressed to physicians and summarised in Table 2, on clinical symptoms and diagnostics of rickets and manifest vitamin D deficiency as well as on their treatment under medical supervision (5;6).

In addition, interest in this prohormone has resurged. On the one hand, vitamin D is said to have effects beyond bone health, which were known in paediatrics even before the prophylaxis era or in vitamin D deficiency dependent rickets, i. e. muscle force and resistance to infections (7), as well as prophylaxis against auto-immune diseases.

On the other hand, Vitamin D is a marker of a healthy lifestyle with well-balanced diet and regular outdoor activities, as explained below. For the age of childhood, it is, however, questionable, whether cross-sectional and observational studies not corrected for obesity and lifestyle justify to causally derive beneficial effects on

carcinoma and cardiovascular diseases (8)(Ia) or even on mortality (9)(Ia); (8)(Ia). Due to insufficient data, these efficacy parameters are not given any further consideration in the paediatric chapter.

The following insights serve as a basis for reflections on the introduction of a more comprehensive vitamin D prophylaxis, taking into consideration Swiss and European results to the largest extent possible.

Table 2: Rickets caused by vitamin D deficiency and treatment of symptomatic vitamin D deficiency (5; 6)

Main symptoms	
Skeleton:	Deviations from the axes (knees) distal bowing of the legs (diaphysis) widening fraying or cupping of the metaphyseal growth plates, Harrison's sulci rickety rosary kyphosis and scoliosis craniotabes poor growth
Neurology:	Infants: muscular hypotonia general motor developmental delay All ages: tetany (e.g. sign of Chvostek) hypocalcaemic seizures Adolescents: tiredness cramps in the calf pain in the legs muscle weakness (when climbing stairs, among others)
Other:	Increased susceptibility for infections hypocalcaemic cardiac arrhythmia gingival hyperplasia
Diagnostics	
1. stage:	Serum alkaline Phosphatase (AP) S-calcium (Ca) S-phosphate (P) S-creatinine U-calcium U-phosphate U-creatinine calculation of calcium / creatinine ratio tubular reabsorption of phosphate (TRP) in percent tubular threshold for phosphate (TmP/GFR)
2. stage:	intact parathormone (PTH) 25-Hydroxy vitamin D (25-OHD3) X-ray hand left (age > 12 months), if necessary of a knee joint a.p. (age < 12 months).
3. stage:	1,25-Dihydroxy vitamin D (1,25 (OH)2D3)

Therapy	
age ≤ 4 weeks:	1'000 IU vitamin D3/ay + calcium (80 mg/kg*d for 2 weeks – 30 mg/kg*d up to 12 weeks, then 400-500 IU Vitamin D3 up to the end of the first year of life or longer.
age 4 weeks to 1 year:	3'000 IU vitamin D3/day + calcium (80 mg/kg*d for 2 weeks – 30 mg/kg*d up to 12 weeks, later 400-500 IU vitamin D3 up to the end of the first year of life or longer.
age > 1 year:	5'000 IU vitamin D3 /day + calcium (80 mg/kg*d for 2 weeks – 30 mg/kg*d up to 12 weeks, then continuous prophylaxis according to current recommendations (400-600 IU vitamin D3) and oral Ca intake (e.g. milk)
Stoss therapy in the case of non-compliance:	100'000-600'000 IU vitamin D over 1-5 days calcium 40-80 mg/kg for 12 weeks
	1 ampul vitamin D3 Streuli = 300 000 IU
Monitoring during therapy and follow-up	
After 2, 6 and 12 weeks:	Ca, P, AP, iPTH (only after 2 weeks) U-Ca/crea (kidney ultrasound if for three months > 0,6 mmol/mmol)
After 6 or 12 months	X-ray of the hand or the knee[x], if necessary Ca, P, AP[xx]
	Normalisation of Ca, P and iPTH after 2 to 3 weeks
	If necessary 25-OHD3 after 12 months

[x] AP may remain elevated for several months

[xx] After 6 months healing of bone lesions

2.3. Isufficiency of supplementation in Switzerland and Europe as compared to North America

So far, there was unanimous agreement on a serum level of about 25 nmol/l necessary to prevent rickets and growth failure in infants, attained by supplementation with 400 IU of vitamin D during the first year of life (5;10). There is no consensus on the optimum vitamin D level, because in healthy Caucasian children no correlation between serum levels of vitamin D and clinically relevant signs of bone disease such as increased fracture rate or impairment of growth, were found. In adults, vitamin D insufficiency was defined non-uniformly as serum levels of vitamin D between 25 and 75 nmol/l, and a vitamin D deficiency as serum levels of vitamin D below 25 to 50 nmol/l, based on fracture rate, calcium absorption and parathormone levels. However, it is questioned whether the above mentioned levels of vitamin D deficiency, defined for adults, have the same functional relevance in children (11)(IV), since parathormone levels are physiologically higher during pubertal growth spurt, and whether the levels measured in fact reflect the real efficacy without taking into consideration the metabolism and binding proteins (12)(IIb). There are no outcome parameters for childhood to prove sufficient vitamin D status (11), and the overly optimum serum concentrations were defined based on achieving a steady state of the effect of vitamin D on the calcium phosphate metabolism (5). To date, in children, serum concentration below 37.5 nmol/l has been considered a deficiency, and a value below 50 nmol/l an insufficiency (5)(IV), as measured by clinical signs of rickets or an increase of alkaline phosphatase respectively. This threshold is corroborated by a meta-analysis of 4 randomized

controlled trials reviewing effects of 132 to 2000 IU of vitamin D supplementations per day on muscular-skeletal system, which were significant when initial serum level of less than 35 nmol/l was elevated.

Nevertheless, several paediatric societies did implement guidelines with various definitions as mentioned above, without relying on clinically significant findings. This makes comparison between different regions and ethnicities very difficult.

Table 3: 25-OHD3-levels of the German children's and adolescents' health survey (KIGGS 2007) (16)

25-Hydroxy-vitamin-D_3 serum levels (nmol/l) as median, 5^{th} and 95^{th} percentile						
Age Group	Boys		Girls		Total	
Years	Median	P.5-95	Median	P.5-95	Median	P.5-95
1-2	63.6	20.5-119.0	59.8	19.4-114.0	61.9	19.4-115.0
3-6	44.0	13.9- 97.4	44.1	16.1- 93.6	44.1	15.0- 95.8
7-10	42.9	15.2- 90.8	40.3	14.1- 86.9	41.7	14.8- 89.1
11-13	39.6	14.9- 87.9	35.7	9.0- 74.5	38.0	12.7- 80.9
14-17	36.8	11.9- 88.8	41.1	13.5-104.0	93.3	12.3- 96.3
total	42.4	14.1- 96.2	41.4	13.8- 96.4	41.9	13.9- 96.3
migrants	35.5	10.1- 89.7	34.2	8.0- 94.1	34.8	8.9- 92.5
non-migrants	43.9	15.1-9 7.2	42.9	15.4- 97.0	43.5	15.2- 97.2

The Swiss Paediatric Society (Schweizerische Gesellschaft für Pädiatrie) recommends an administration of daily 400 IU vitamin D up to the end of the first year of life (13)(IV), however, only 64% of infants actually receive that dose as oral medication (14)(III). Children of immigrant communities, in particular premature babies of Arab mothers are considered a risk group, the latter presenting with a high prevalence of vitamin D deficiency (15)(III), as well as their mothers, if they did not take vitamin D during pregnancy despite indicated supplementation. In Germany, similar recommendations for vitamin D prophylaxis have been issued (500 IU/d, 0-12 months), resulting in sufficient vitamin D levels in infants, as shown by the German children's and adolescents' health survey 2007 (Kinder- und Jugendgesundheitssurvey KIGGS) (Table 1) (16). Beyond infancy, over 50% of children and adolescents are affected by a vitamin D deficiency, more often so in puberty and in migrants (16)(III, Table 3).

In Switzerland, in 17% of girls and 15% of boys aged 11 to 16 years, vitamin D deficiency (serum 25OHD < 30 nmol/l) was shown, the prevalence being highest in pubertal stage 4 to 5 (29%) in boys and in pubertal stage 3 (24%) in girls, without any apparent significant association between 25OHD and markers of bone metabolism (17)(III). In a recent study at the Zurich Children's Hospital 60% of 100 healthy children with and without growing pain had 25(OH)vitamin D levels below 50 nmol/l (Bischoff-Ferrari, personal communication). In Swiss children affected by type 1 diabetes aged 3 to 18.6 years, 57% presented with a vitamin D deficiency (< 50 nmol/l); in this group, the parathormone levels were significantly higher compared to vitamin D sufficient patients (18)(IIb), but only in single patients clearly elevated. In contrast, overt vitamin-D deficient rickets is extremely rare among children born and grown up in Switzerland; there was a higher prevalence (2%) among asylum seeker children (19)(III).

In England, vitamin D supplementation is recommended until the third year of life (20)(IIb), but even there, 73% of girls in an urban population consisting predominantly of migrants, are vitamin D deficient until their 15th birthday. French boys of a Jockey school with a low dairy intake showed a vitamin D deficiency only in winter (in 70%) (21)(Ib), which proves that also physically active adolescents in our latitudes may be deficient in vitamin D, if they consume an inadequate amounts of dairy products. In European countries further north, such as Finland (22)(IIb), Denmark, Ireland and Poland, vitamin D status in female adolescents in winter is considered deficient in over a third (< 25 nmol/l) or insufficient (< 50 nmol/l) in almost all and 47% had increased parathormone levels (23)(IIb). Sunlight exposure is too little , e.g. in English girls, mainly in those from immigrant communities (20)(IIb)

According to the ESKIMO and DONALD studies in German youth with nutritional recommendations similar to Switzerland, only 4% of girls and 13% of boys reach the recommended vitamin D intake of 5 micrograms per day (24);(25)(IIb), Thus the cause of vitamin D deficiency also consists of insufficient intake.

In the US, only some 10% of infants are administered vitamin D prophylaxis (26)(III). However, several foodstuffs are enriched with vitamin D (about 400 IU/l). Nevertheless, in adult age, vitamin D deficiency or insufficiency respectively are very common and affect between 9 und 45% (27)(III) (28)(III) and nearly all coloured adolescents are vitamin D deficient (29)(III). In addition, results from a paediatric metabolic bone clinic have shown that all children and adolescents with osteological problems were suffering from vitamin D deficiency (30)(III).

2.4. Bone health in children and adolescents

The significance of peak bone mass, of bone mineral mass gain during the growth phase up to post-pubertal stage (31)(IIb) as a life-long reserve and predictor for bone fractures later in life, is well known. Bone density (BMD) in childhood is predictive for the following years (32;33) (IIb), to identify the „tracking“, measurements must however be taken volumetrically (34)(IIa) or need to be corrected for height (35;36)(III). The issue of bone health has been extended by the geometric aspects of the functional muscle-bone-unit (37)(IIa). Bone strength is essentially influenced by the increase in bone mass and the geometry during childhood and adolescence (34)(IIa) and correlates strongest with the number of hours of physical activity (38)(IIa). Apart from physical activity or weight-bearing muscle training, dairy products and vitamin D have a beneficial influence on bone strength (39)(overview study). Muscle function is better with higher vitamin D levels (40) (IIb), at least in girls. Bone mineral mass gain in adolescents also depends on growth hormone, sex steroids (39) and sunlight exposure (41)(IIb). Bone density (42)(III) and parathormone levels (21) also show seasonal variations.

It remains unclear however, in how far bone density in adolescents is influenced by vitamin D alone. Only in winter and in 12 to 15 years old girls are high vitamin D levels (> 74.1 nmol/l) significantly correlated with greater forearm bone density, lower parathormone and bone turnover markers, but not so in boys in Ireland. (43)(III).

Also in Finland, in 10 to 12 years old girls with vitamin D deficiency (< 25 nmol/l), cortical bone density was lower and parathormone higher than in those with levels exceeding 25 nmol/l (44)(III). Pakistani immigrant girls (10–14.7 years) in Denmark, however, did not show any correlation between vitamin D levels and bone turnover markers (45)(III).

Differences between calcium absorption or BMD respectively and vitamin D levels can be explained by polymorphisms of the vitamin D receptor, e. g. the genotype of Fok1 gen (46)(IIb). Likewise, in Swedish men, an association between better BMD with a higher vitamin D intake was found, which was further improved in the presence of an L/L polyadenosin (A) vitamin D receptor polymorphism (47)(IIb). Similar findings also resulted from the intervention studies following below.

Intervention studies on the effect of vitamin D on the musculo-skeletal system:

Interventions studies are necessary to allow for the evaluation of the role of vitamin D in bone density during childhood and adolescence: In infancy, even after 6-month vitamin D supplementation with 400 IU/d, no difference in bone density (bone mineral density, BMD) as compared to untreated controls was seen (48)(Ib). Accordingly, Vitamin D supplementation (100, 200, or 400 IU/day) during the first 6 months of life could prevent rickets (49)(Ib), but season of birth and dose of vitamin D did not affect the growth rate(50)(Ib). Vitamin D prophylaxis in infancy, however, was associated with a better BMD in prepubertal girls (51)(IIb).

The results of childhood studies are complex. In most cases, only girls were investigated. French boys aged 13 to 16 years were treated with a vitamin D Stoss therapy at a jockey school in winter (3 x 1,000,000 IU p.o every 2 months), and, in comparison to controls, showed a normalisation of vitamin D3 and parathormone levels (21)(Ib). When bone density was measured, it remained unchanged in Lebanese boys aged 10 to 17 years as well as in Finnish girls and boys aged 8 to 10 years during 1 year of vitamin D treatment (52)(Ib), (53)(Ib).

English girls aged 12 to 14 years benefited from a vitamin D supplementation (4 x 150'000 IU/12 months) and normalization of serum vitamin D levels only with regard to muscle jump velocity, not regarding BMD, bone geometry, muscle strength and others (54)(Ib). The best results were achieved by girls with the lowest vitamin D levels initially. In a double blind RCT with a once a week vitamin D therapy (14'000 or 1400 IU), Lebanese girls (10-17 y) showed a dose dependant significantly better lean mass and lumbar spine BMD than with placebo treatment (/week), especially before menarche (52)(Ib). Likewise, in a one-year controlled study in 11.4 ±0.4 years old Finnish girls, the daily administration of 400 IU vitamin D3 showed a higher efficacy than 200 IU in the improvement of bone density of femur and spinal column, but only in the compliance-based evaluation (55)(Ib); serum 25(OH)D concentrations > 50 nmol/l were sufficient for bone mineral gain. In all these studies, sufficient calcium intake had been ensured.

The randomized controlled therapy of Pakistani immigrant girls aged 10 to 15 years with daily 400 or 800 IU vitamin D for one year similarly normalised serum vitamin D levels, as opposed to the untreated controls, but did not result in any changes in bone turnover markers and BMD (56)(Ib). The same working group proved that Caucasian Danish 11 to 12 years old girls showed an improvement of BMD with therapy of daily 200 or 400 IU only when they had a certain vitamin D receptor genotype, even though, in all those treated vitamin D, levels increased regardless of the dose (57)(Ib).

A recent meta-analysis of 6 randomised controlled studies (RCT) showed that vitamin D supplementation (132 to 2000 IU) of deficient children and adolescents (vitamin D < 35 nmol/l) could result in clinically useful improvements in bone density; nevertheless, the results in healthy children and adolescents with normal vitamin D levels on bone density are inconsistent and Vitamin D supplements are unlikely to be beneficial in this group (58)(Ia).

Combined administration of 800 mg calcium and 400 IU vitamin D daily during 12 months in RCT in 12 years old white girls resulted in an improvement of volumetrically determined bone density (59)(Ib).

However, based on current knowledge (Cochrane Review), calcium supplementation alone cannot increase bone density lastingly – with the exception of the upper extremities – and decrease fracture rate (60)(Ia).

2.5. Experimental findings of extraskeletal effects of vitamin D

From the comparison with knock out mice for vitamin D receptor, numerous effects of vitamin D can be anticipated also for humans, even though the functions of the receptor and its activated ligand, the 1,25 dihydroxy vitamin D, are not fully overlapping(61). This applies for instance for the hair cycle, which is only dependent on the receptor, manifesting clinically in form of lacking head hair in type I vitamin D dependent rickets. For keratinocytes' differentiation and an intact skin barrier function, however, activated 1,25 dihydroxy vitamin D is necessary, in this context, vitamin D effects are made use of in psoriasis.

The vitamin D receptor is expressed by all cells of the immune system, also by the antigen presenting cells such as macrophages. Like the activity of 1alpha hydroxylase, the receptor is regulated differentially and antimicrobial innate immune response is strengthened. In macrophages, regulation is effected via interferon gamma and toll-like receptors, which also explains increased vitamin D activity in granulomatous diseases and tuberculosis. These mechanisms help to explain the efficacy of climatic and light cures in tuberculosis. Attenuation of immune response works via activation of suppressor cells, transforming effector cells and modulation of the cytokine profile, refer to type 1 diabetes,(paragraph 8).

In vitro results on the influence of vitamin D on carbohydrate metabolism and the cardiovascular system are less conclusive.

2.6. Vitamin D and resistance to infections in children

Vitamin D deficiency is associated with the same epidemiological pattern as seen in repeated respiratory tract infections or in asthma: namely Afro-Americans, urbanization of lifestyle, low social status and obesity. Thus, results of association studies need to be read with caution, even if experimental evidence suggests a connection between infections and vitamin D deficiency. Respiratory tract epithelia are able to hydroxylate vitamin D and can then activate anti-infectious molecules such as calthelicidin (62). Vitamin D can also contribute to locally inhibit cytokines and thus limit the inflammatory reaction. For the RS virus infection the mechanism is based on a chemo- and cytokine activation through vitamin D (63).

Numerous epidemiological and case control studies (III) reveal that prevalence of infections in young adults with vitamin D deficiency is increased, namely infections of the respiratory tract in the US in recruits (64) and in Finland (65), tuberculosis (66) and infections in the intensive care unit (62).

In children, an association was shown between vitamin D deficiency and obstructions of the lower airways with an aggravated development, as well as need for intensive care (67), or with pneumonias before the fifth birthday in Ethiopia (68)(III).

In Turkish mature newborns with pneumonia, a vitamin D deficiency was found, as also in their mothers, compared to higher levels in control children and mothers that were still largely in the range of vitamin D insufficiency (69)(III). In an American observatory study in infants up to the age of 3 years, with an eczema

or familial asthma anamnesis, more frequent bronchitides were detected, when their mothers had taken less than 400 IU daily during pregnancy, as compared to children, whose mothers had taken more than 700 IU (70)(III).

Randomized controlled intervention studies (RCT) on infect prevention showed contradictory results in adults, but the starting situation was heterogenous (71-73)(Ib;Ib;Ia).

Japanese 8 to 10 year old school children were significantly less frequently affected by influenza infections when substituted with 1200 IU vitamin D in winter, and children with asthma had less exacerbations than untreated controls; children without previous vitamin D supplementation benefited additionally (74)(Ib). In children with pneumonia in Kabul, the risk of a pneumonia relapse could be reduced by a single administration of 100,000 IU of vitamin D in comparison to controls (75)(Ib).

2.7. Vitamin D, obesity and type 2 diabetes

Obese persons have a lower vitamin D levels, probably because vitamin D is sequestered into fat tissue (76). When weight was reduced in children, the corresponding Vitamin D levels did increase again, without any concomitant changes in the calcium phosphate metabolism (77). For supplementation of the frequent vitamin D deficiency in obese children (57 vs. 40%), the administration of 400 IU daily for the duration of one month was not sufficient to normalise these levels (78), but 2000 IU after 4 months did, whereby the slope of the increase was negatively correlated with fat mass (79).

From a clinical perspective, disturbances in bone health are not causally linked to obesity; based on increased muscle mass in obesity and the anabolic effect of insulin and growth factors, BMD is increased compared to age peers and the risk for osteoporosis tends to be lower.

However, there are two associations of vitamin D, namely

1. with insulin resistance (80;81)(III) and intramuscular fat (82)(III) and
2. with insulin secretion. In animal experiments, vitamin D is necessary for insulin secretion (61) and beta cell capacity or insulin secretion capacity respectively in humans with vitamin D deficiency is lower compared to sufficient vitamin D level (83)(III).

Since in Afro-American adolescents, an association between cardiometabolic risk factors and vitamin D status was found, a randomized controlled study was to investigate the effect of daily vitamin D supplementation with 2000 IU. During normalisation of vitamin D levels in the therapy group, a slight decrease in pulse wave velocity as a sign of improved arterial elasticity was seen, as opposed to the untreated controls, where this parameter increased. (79)(IIa). To what extent these results are transferable to Caucasian or Swiss adolescents respectively, remains unclear and requires further intervention studies.

2.8. Vitamin D and prevention of autoimmune diseases such as diabetes mellitus type 1 or multiple sclerosis

A metaanalysis of observatory studies (III) shows a dose-dependent protection against type 1 diabetes manifestation in childhood, when vitamin D was administered in infancy (84), e. g. birth cohort study (85) and vitamin D infants prophylaxis study (86). Furthermore, in Finland, sufficient vitamin D supply during pregnancy led to a reduction of type 1 risk, next to other nutritional conditions (87;88)(III). These data might

not be entirely transferable to other regions, because they were collected among a population with significantly increased risk for diabetes and low sunlight exposure. Though diabetes prevalence is much lower in Swiss children and adolescents, it was tremendously rising in the last 20 years and the prevalence of vitamin D insufficiency in this group was high (18)(IIb)

Vitamin D treatment of children and adults affected by type 1 diabetes manifestation did not lead to any significant improvement of the insulin dose needed and the remaining C peptide secretion (89)(Ib).

Autoimmune mechanisms are thought to have a major role in the pathogenesis of multiple sclerosis (MS) and vitamin D is hypothesised to contribute to disease susceptibility. Several association studies show that HLA-DRB1*15 genotype, previous infection with Epstein-Barr virus and vitamin D insufficiency are susceptibility factors for multiple sclerosis (III)(90;91). Vitamin D supplementation, as provided by a teaspoon cod-liver oil may be protective when sun exposure is low (III)(91). Data is insufficient to prove a causal relationship between Vitamin D and MS.

2.9. Current Swiss recommendations on therapy and prophylaxis in comparison to the US and Canada

For treatment of manifest vitamin D deficiency, e.g. rickets and others (5), Table 2 shows recommendations. On Table 4, available Swiss pharmaceuticals are listed. For prevention and therapy in Canada and in the US (92)(10) and for vitamin D in pregnancy (93;94) there are also recommendations. Guidelines of the American Academy of Pediatrics propose a daily intake of 400 IU of vitamin D3 from birth to the 18th year of life, by supplements or until the child is consuming 1 l of fortified formula or milk daily, and supplementation may be higher for children with additional risk factors (95)(IV).

Currently, for all Swiss children, daily intake of 400 IU vitamin D as a general vitamin D prophylaxis is recommended for the time from the first week of life up to the end of the first year of life. In addition, infant formula and follow-on formula are also fortified with 400 IU (10 microgram) of vitamin D in Switzerland and an intake of 800 IU per day is safe. Calcium intake should be regulated via nutrition and correspond to the DACH nutritional recommendations (Table 5). One to 4 servings a day, according to age, are necessary to supply enough calcium. In children and adolescents active in sports with a physical activity level (PAL) >2, it is crucial to provide the adequate energy intake, besides Vitamin D and calcium, especially in female gymnasts in order to prevent osteoporosis and the female athlete's triad, As vitamin D fortified products only rarely are available, nutritional intake (Table 1) and sunlight exposure cannot supply enough Vitamin D in these children and adolescents, especially during autumn and winter.

Table 4: Vitamin D preparations in Switzerland

Oral:	
○ ViDe 3 Wild drops: Cholecalciferolum and ethanol, 4 drops daily = 400 IU ○ Vitamin D3 Streuli drops: Cholecalciferolum and ethanol, 4 drops daily = 400 IU ○ Vitamin D3 Wild oil: Cholecalciferolum and triglycerides,1 drop daily = 667 IU	
In Germany:	○ Vigantol® Oel: Cholecalciferol & triglycerides, 1 drop daily = 500 IU
In Austria:	○ Oleovit D3: Cholecalciferolum & peanut oil, 1 drop daily = 400 IU CAVE: allergies
Parenteral, Oral:	
○ Vitamin D3 Streuli i.m., p.o., 1 ampule 300 000 IU	
Calcium / Vitamin D preparations	
○ Calcium Sandoz D3 f (500 mg/440 IU), ff (1000 mg/880 IU), instant powder ○ Calcium Sandoz D3 (600 mg/400), forte (1200 mg/800 IU), effervescent tablets ○ Calcimagon D3 (500 mg /400), forte (1000 mg /800 IU) ○ Calperos D3, (500 mg/400 IU) ○ Calcium D3 Mepha (600 mg/400), forte (1200 mg /800 IU) ○ Decalcit Pulver (600 mg/750 IU) in 1 teaspoon = 1g (tasteless)	

Table 5: Recommendations for calcium and energy intake in childhood and adolescence

for children with normal leisure activity[x] and for (semi-)professional sports[xx]

Age	**Kcal/d**		**Kcal/d**		**Calcium**	**Milk**	**Curd**	**Yoghurt**	**Hard cheese**
Years	Competitive sports**		Normally active*		mg/d	Un-skimmed	Medium fat	Natural un-skimmed	Gruyère
	f	m	f	m					
4 - < 7	?	?	1400	1500	700	583	660	507	78
7 - < 10	76/kg	83/kg	1700	1900	900	750	849	652	100
10 - < 13	62/kg	71/kg	2000	2300	1100	917	1038	797	122
13 - < 15	52/kg	63/kg	2200	2700	1200	1000	1132	870	133
15 - < 19	2900	3600	2500	3100	1200	1000	1132	870	133
> 19	2800	3500	2400	3000	1000	833	943	725	111

[x] DACH recommendations 2000,
[xx] physical activity level PAL 2.2 (approx. 7 to 14 hours of sports training/week)

In future, compliant with adult guidelines and with the caveat that we do not know optimal serum 25(OH)D levels for any functional outcome in children, the Swiss Working Groups on Vitamin D (instituted by the Federal Commission on Nutrition, FCN), proposes to define Vitamin D supply as follows:

<25 nmol/l (<10 ng/ml) = severe deficiency

<50 nmol/l (<20 ng/ml) = deficiency (= threshold supported by the Institute of Medicine as the level as adequate level for most people (97%) (IV, IOM (96))

75 nmol/l (30ng/ml) = optimal threshold supported by the IOF and the US Endocrine Society (97).

The evidence that higher levels (75-125 nmol/l) are necessary in children and adolescents for skeletal or extraskeletal effects is weak.

To prevent vitamin D deficiency and to correct insufficient vitamin D supply, a daily intake of 600 IU is recommended after the first year of life up to 18 years (IV, IOM (96) and Endocrine Society (97) and of 400 IU per day during the first year of life. Until the 3rd birthday, this vitamin D prophylaxis is recommended to be thoroughly implemented by physicians and infant's health care providers as mentioned below. These recommendations are valid except when otherwise determined by the future European recommendations.

The recommended vitamin D dose of 400 IU/d (IOM); (96) has been shown to generate serum levels of 76, 97 and 92 nmol/l at 1.5, 3 and 6 months of therapy in breastfed infants, compared to 39, 39 and 59 nmol/l, respectively, in the placebo group (Ib) (11;48), while 200 IU increase a serum level only to about 27 nmol/l. Also in children at age 8 to 15 years, doses between 400 (53)(55)(Ib) and 2000 IU of vitamin D daily for 1 year (52)(Ib) raise serum levels by 12.2 to 49 nmol/l in a positive dose responsive manner.

It would be possible to start supplementation without prior measurement serum levels in breast-fed children without supplementation and in healthy individuals with dark skin colour or lacking sunlight exposure (wearing veils, indoor sports activities, home for the handicapped,…) (Kragstrup 2011) if they have no risk for hypercalcaemia / hypercalciuria (e.g. renal disease, leukaemia, sarcoidosis,…) or chronic disease.

In Finnland, dairy products were moderately fortified with 0.5 µg Vitamin D/100g (20 IU/100g) and margarine with 7,5 to 10 µg Vitamin D/100g (400/per 100g; 0,5 µg Vitamin D per teaspoon (in 2003). Compared to 2001/2002, the nutrient intake of vitamin D by 4 years old children increased significantly from 2,1 to 4,5 µg serum concentration of 25-OHD from 54,7 to 64,9 nmol/l (98). Absorption may be better from dairy products than calculated for other forms of supplementation.

The recommended dose for timely limited treatment of documented vitamin D deficiency may be higher, namely 1000-2000 IU/day (Endocrine Society (97)). In general, in children as well as in adults, the vitamin D level approximately increases 1-2 nmol/l for every 1 µg (40 IU) of daily vitamin D supplementation; therefore, in order to increase serum levels from 30 to >75 nmol/l, a dose of 50 micrograms or 2000 IU/d is necessary(IIa)(99).

Furthermore, there is evidence that in obese adolescents only 2000 IU/day , but not 400 IU, are sufficient to raise vitamin D levels adequately, but this evidence is limited to black individuals(Ib) (79). Therefore, 2- to 3-fold higher doses are suggested for obese children and adolescents as well as those on anticonvulsive or glucocorticoid medication as sequestration into fat tissue or catabolism may be increased(IV) (97). However, It has not yet been verified by scientific evidence, whether for children and adolescents with obesity, chronic

intestine conditions, liver or kidney diseases, an increased dose of vitamin D (800 to 2000 IU daily) should be recommended.

To prevent maternal vitamin D-deficiency and infantile rickets, sufficient vitamin D intake of the pregnant mother has to be ensured; during pregnancy and for mothers during lactation, substitution is to be recommended, with a recommended dose of vitamin D of at least 600 IU daily, an intake of 4000 IU daily would probably be even better (refer to chapter on pregnancy and lactation by Quack-Lötscher in this report).

Sunlight exposure and outdoor physical activity remain the mainstay of paediatric prevention of musculoskeletal disease and obesity, although UVB radiation is critical and cannot be recommended for sole Vitamin D source all over the year in Switzerland, as reviewed in this report in the chapter on UVB radiation by B. Gerber, Only very little UVB is necessary for vitamin D synthesis, this is however dependent on skin type, season, latitude, body size, age and the skin area exposed, weather conditions as well as environmental pollution (100)(IV). The proposal for natural vitamin D formation by sun bathing can no longer be tolerated for young children, as there is evidence for an increased cancerogenic risk due to UVB exposure during the first years of life (101). It was described that with light skin type (I-III) and depending on the season, by means of 5 to 20 minutes of sunlight exposure of arms and face every second day around midday (102) an adequate serum vitamin D level can be obtained naturally, without the risk of sunburn or skin cancer (103-105). But in particular for the malign melanoma, sunburns during childhood are, next to the cumulative UV dose, known to be an important risk factor. A study published recently additionally points out that the suntanning of children of a light skin type is associated with the development of melanocytic nevi, which goes hand in hand with an increased risk for the later formation of melanoma. Therefore, the limit of “safe” sunlight exposure cannot be defined, since immediately with the beginning of the production of vitamin D DNA damage occurs and carcinogenesis sets in.

In particular during pregnancy or in dark skin type migrants (106)(Ib), sufficient vitamin D level cannot be achieved by sunlight exposure. Therefore, increasing vitamin D level by means of generally increased sunlight exposure cannot be recommended by dermatologists based on the current data (100)IV. Whether careful sunlight exposure is able to build up a sufficient vitamin D level in light skin type in Switzerland, is not known, but mainly in infancy, this cannot be assumed based on the recommended sun protection to be used. Hence, avoidance of excess sun exposure must be promoted in paediatrics as well as the correct and frequent application of sunscreen factors. It has to be pointed out that adequate use of sunscreen crèmes inhibits more than 99% of vitamin D formation!

2.10. Safety of vitamin D prophylaxis and therapy during childhood

The dosage for manifest vitamin D deficiency and rickets can be taken from Table 2. A relatively high dose might prove to be necessary to reach the vitamin D level desired (107). Particular attention needs to be paid to hypocalcaemia in infancy and adolescence, since in half of the children with a vitamin D deficiency, rickets is found, but also in therapy, if no extra calcium is administered. Hypocalcemic tetany or epileptic seizures might occur up to adolescence (1). Therefore, a simultaneous adequate calcium administration has to be ensured.

Toxic effects are rare and limited to case reports, in most cases caused by inadvertent overdosing. In Switzerland, a “Stoss”-therapy, e.g. with 300’000 IU every 4 weeks or about 10’000 IU per day, may induce a

vitamin D-intoxication with failure to thrive, hypercalciuria and persistant nephrocalcinosis in infants and young children (108). Only recently have actual Swiss data on toxic effects following chronically increased vitamin D application been published (III)(109); within 18 months, 22 cases of chronic intoxication have been registered by the Toxicological Centre in Zurich (1.1.2009 to 15.5.2010). A clear increase in the last 3 years was due to the availability of a new vitamin D preparation with a 5 fold higher content and a new application system. Thus, 2 cases of nephrocalcinosis were found after cumulative doses of 1.4 million IU in a 1 month old boy and of 2,7 million IU within 12 days in a 1 month old girl. Two other cases with nephrocalcinosis after cumulative doses of 0.6 million units in a 35 days old boy and a 4 month old girl have been described (reviewed in (109)) in addition to 4 less severe cases with symmptoms of nausea, vomiting, constipation, failure to thrive, lethargy, muscle hypotonia and arterial hypertension. The concomitant hypercalcaemia was successfully treated with Furosemide, Calcitonin, Biphosphonates and Corticosteroids. It is advisable to explain carefully the dosage of the vitamin D droplet application and to control the consumption of the medication, in especially of the higher concentrated oily preparation. After the age of 10 years, no side effects need to be expected with several doses below 10'000 IU of vitamin D, which can also be obtained by sunbathing. However, chronic medication with 2000 IU in newborns and infants and 4000 IU in young children may lead to toxic side effects after several years (97), but up to 10'000 IU weekly over 1 year is considered to be safe for adolescents (110). Shorter term intake of 10000 to 40000 IU for 1 to 4 months is safe beyond infancy and can also be obtained by sunbathing. However, the European Recommendations indicated as a maximum upper daily limit for safe administration, for instance by ways of enriched foodstuffs, an amount of 1000 IU for children below 10 years of age and of 2000 IU for children from 11 years on (111). This is overcome by the more recent recommendations of safe upper intake levels by the IOM: is 1000 IU/day from 0 to 6 months, 1500 IU/day from 6 to 12 months, 2500 IU from age 1-3 years, 3000 IU from age 4-8 years, and 4000 IU from age 9 and older(96). It is evident from paediatric experience with vitamin D therapy of rickets during a limited period that, in young children, therapeutic doses of vitamin D (Table 2) may exceed the above mentioned limits of safe upper intake recommended for prevention in general population.

2.11. Conclusion

Prevalence of vitamin D deficiency in children and adolescents in Switzerland and in the neighbouring countries is higher than suspected so far and affects between 15 and 57% of the children between 3 and 18 years of age. The consecutive parathormone increase in some adolescents emphasizes the clinical relevance of vitamin D deficiency. Even young athletes, practicing outdoor sports in winter may suffer from vitamin D deficiency when consuming too little dairy products. Particularly during phases of accelerated growth, from birth up to the third birthday and between the 11th and 16th year of life, the need for calcium and vitamin D is high; thus, vitamin D deficiency is particularly frequent during puberty and prevented by vitamin D prophylaxis during infancy.

Conditions for good bone health in children and adolescents are weight-bearing physical activity, nutrition including sufficient amounts of protein, energy and calcium (or dairy products) as well as sufficient vitamin D levels. Epidemiological studies have shown that these conditions are not fulfilled in risk groups (refer to Table 2), in particular in pubertal immigrant girls. Randomized controlled therapy studies show mainly in these and in Caucasian girls a beneficial effect on muscles, but not always on bone density. In summary,

interventions with vitamin D supplementation in childhood and adolescence have a positive effect on bone mineral gain in girls before the pubertal growth spurt, under the condition of sufficient calcium intake, good compliance and the presence of a certain vitamin D receptor type. There is no proven evidence that all healthy Swiss children and adolescents without an immigration background would need a general vitamin D prophylaxis to ensure bone health. Since infants might be at risk for vitamin D deficiency before birth, and protection against sunlight exposure has a high priority in infancy, it is to be recommended to extend the phase of general vitamin D prophylaxis up to the completion of the fast growth phase, i. e. to the third birthday. This would provide an additional health benefit due to the positive effect of vitamin D on the innate immunity and on resistance against seasonal flue.

With regard to resistance to infections, vitamin D might reduce absenteeism in school and at work, the number of corresponding studies and children is, however, very small, namely 2. They did not show whether other lifestyle measures such as healthy nutrition and outdoor activities had an even greater influence. A targeted vitamin D prophylaxis and monitoring of deficiency are recommended for children with recurrent upper respiratory tract infections.

Prevention of type 1 diabetes by administration of sufficient vitamin D has been suggested by epidemiological studies in Europe. This would again speak for vitamin D prophylaxis during pregnancy and during the first three years. If this finding was to be used as a sole reason for general lifelong vitamin D prophylaxis, it would, however, not be very efficient in view of the low incidence of type 1 diabetes (8:100,000 Swiss).

Vitamin D deficiency in obesity and type 2 diabetes as a secondary phenomenon due to sequestration of vitamin D into fat tissue is basically reversibly by means of weight reduction. The primary efficiency of even minimum measures in children and adolescents to improve quality of nutrition and increase physical activity has been proven. Based on the studies published vitamin D may play, a supporting role for the cardiovascular system and against insulin resistance.

Thus, not all children and adolescents would benefit from a vitamin D prophylaxis, but predominantly those with low sun exposure or dark skin type and girls before puberty until pregnancy. Since no side effects are known for doses below 1000 IU, the daily administration of 400-600 IU vitamin D may be regarded as safe and recommendable.

Two problems arise, 1. compliance and 2. the ethical justification of the administration of medicine not necessary for all:

1. Currently, compliance with regular vitamin substitution is not present in all children and adolescents who would need substitution because of a chronic intestine, liver or kidney condition (Bianchetti 2010); the long-term implementation of vitamin D therapy requires regular checks and motivation, especially in adolescents.

   The low implementation rate of vitamin D prophylaxis recommendation also illustrates the necessity of accompanying measures, in particular for risk groups (young mothers, female migrants, multiparity)
2. The ethical justification of prevention measures in paediatrics, for instance immunizations, lies in the fact that in childhood even highly severe, handicapping or fatal diseases may be avoided, which justifies an intervention also in healthy children. Beyond the age of threatening toddler's rickets, these considerations are less relevant, since osteoporosis or tendency for infections due to vitamin D

deficiency for the most part don't lead to any serious health consequences in childhood. Thus, there will probably be no understanding for and compliance with the measures as long as they are proposed in an untargeted and uncontrolled manner.

2.12. Measures

Prevalence of vitamin D deficiency in northern latitudes and bone fracture rate in elderly people raise the issue of a general vitamin D prophylaxis for the entire Swiss population. Since due to sun protection recommendations and urbanization of lifestyle sunlight exposure alone is no longer sufficient for the production of the amount of vitamin D needed, vitamin D intake by fortified food products or pharmaceutical products are recommended giving special attention to phases of fast growth. This concerns in particular infancy, see below. High risk groups of children should be tested for their 25(OH) vitamin D status and receive vitamin D supplementation, if necessary. These include dark-skinned children, children on anti-convulsants or glucocorticoid treatment, children with low-trauma fractures, children with chronic disorders associated with malabsorption, children with cerebral palsy or not practicing outdoor activities, and also children with non-specific symptoms like poor growth, gross-motor delay, tiredness, irritability or leg pain.

Measures proposed:

1. Improvement of the implementation of the recommendations in force, and
2. Extension of vitamin D prophylaxis to all children in Switzerland up to their third birthday,as in Great Britain (s. (20)). This seems to be realizable in combination with the standard preventive medical examinations. The implementation of a further non-targeted prevention with drops or tablets in youth is not realistic,

Measures 1 and 2 require the training of midwives, parental counselling officers, paediatricians, gynaecologists as well as general practicioners and dieticians. Information campaigns for vitamin D prophylaxis are also feasible.

3. Safe-guarding of a vitamin D intake or prophylaxis of 600 IU /d during puberty to be implied by the school health service (Schulärztlicher Gesundheitsdienst), family doctor or paediatrician:
   During early puberty from the 10th to 11th birthday, sufficient vitamin D levels have to be ensured, since even in Switzerland, 1 out of 3 or 4 adolescents is affected by vitamin D deficiency. A general supplementation of this age group with 600 IU daily could be considered, since potential side effects are negligible, would however be unrealistic due to the low compliance to be expected. Targeted counselling of adolescents not practicing outdoor activities or with high television consumption, affected by overweight, of dark skin type, unexplainable tiredness or chronic diseases should be performed or they should be referred to the family doctor or a paediatrician. Further measures as mentioned above can be considered.
4. Improved medical, health care and lay medical counselling of risk groups, refer to Table 1.
   For practitioners, information on risk groups for vitamin D deficiency and new therapy indications (resistance to infections, type 1 diabetes) is to be broadened.
5. Introduce clearly labeled vitamin D fortified dairy products, explain and promote their use: As practised in Finland, vitamin D fortified dairy products seem ideal, because they strengthen the other benefits of these nutrients. In addition, a better absorption of calcium and Vitamin D from fortified dairy products

can be concluded from the results of the Finn study (98) precise age-dependant servings should be recommended (1 serving with 300 IU 3-5 year old, 2 -3 servings in 6 -18 year old individuals).

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3. Adult bone and muscle effects of vitamin D

Heike A. Bischoff-Ferrari, Zürich & René Rizzoli, Genève

3.1. Abstract

This chapter will summarize the impact of vitamin D deficiency on adult bone and muscle health. Evidence from randomized-controlled trials will be reviewed for fall and fracture prevention based on recent meta-analyses and by dose of vitamin D, type of dwelling, and treatment interval. Finally, trial and epidemiological data will be reviewed to assess desirable serum 25-hydroxyvitamin D levels for optimal bone and muscle health.

3.2. Muscle effects of vitamin D

Four lines of evidence support a role of vitamin D in muscle health. First, proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [1]. Clinical findings in vitamin D deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [2]. Second, the vitamin D receptor (VDR) is expressed in human muscle tissue [3,4] and VDR activation may promote de novo protein synthesis in muscle [5]. Mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life [6,7]. These abnormalities persist after correction of systemic calcium metabolism by a rescue diet [7]. Third, several observational studies suggest a positive association between 25-hydroxyvitamin D and muscle strength or lower extremity function in older persons [8, 9]. Fourth, vitamin D supplementation increased muscle strength and balance [10,11], and reduced the risk of falling in community-dwelling individuals [11-13], as well as in institutionalized individuals [10,14] in several double-blind randomized-controlled trials summarized in a 2009 meta-analysis discussed below [15].

Regarding data from clinical trials, one uncontrolled biopsy trial in postmenopausal women with osteoporosis documented a relative increase in the diameter and number of type II muscle fibers after a 3 month treatment with 1-alpha-calcidiol [5]. These findings were supported by three recent double-blind RCTs with 800 IU vitamin D3 resulting in a 4-11% gain in lower extremity strength or function [10,11], and an up to 28% improvement in body sway [11,13] in older adults age 65+ between 2 to 12 month of treatment

3.3. Vitamin D effects on fall

The effect of vitamin D supplementation on fall prevention was summarized in a 2009 meta-analysis of 8 double-blind RCTs including a total of 2426 individuals age 65 and older [15]. Figure 1A depicts the relative risk of falling from these 8 double-blind RCTs plotted against the treatment dose of vitamin D in the different trials. By visual inspection of Figure 1A, anti-fall benefits of vitamin D started at a dose of 700 IU per day. In the 2011 re-analysis requested by the Institute of Medicine [16], when treatment is the only predictor (regardless of dose level), there is a significant reduction in the odds of falling based on our primary analysis: OR=0.73 [0.62, 0.87]; p=.0004. When the model was expanded to capture the impact of both high dose and low dose treatment, high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling (OR=0.66 [0.53, 0.82]; p=.0002), while low dose vitamin D did not (OR=1.14 [0.69, 1.87]; p=.61). At the

higher dose of 700 to 1000 IU vitamin D, there was a 38% reduction in the risk of falling with a treatment duration of 2 to 5 months and a sustained significant effect of 17% fall reduction with treatment duration of 12 to 36 months. Thus, benefits of 700 to 1000 IU vitamin D per day on fall prevention are rapid and sustained and include all subgroups of the senior population [15].

Figure 1A: Fall reduction by treatment dose of vitamin D

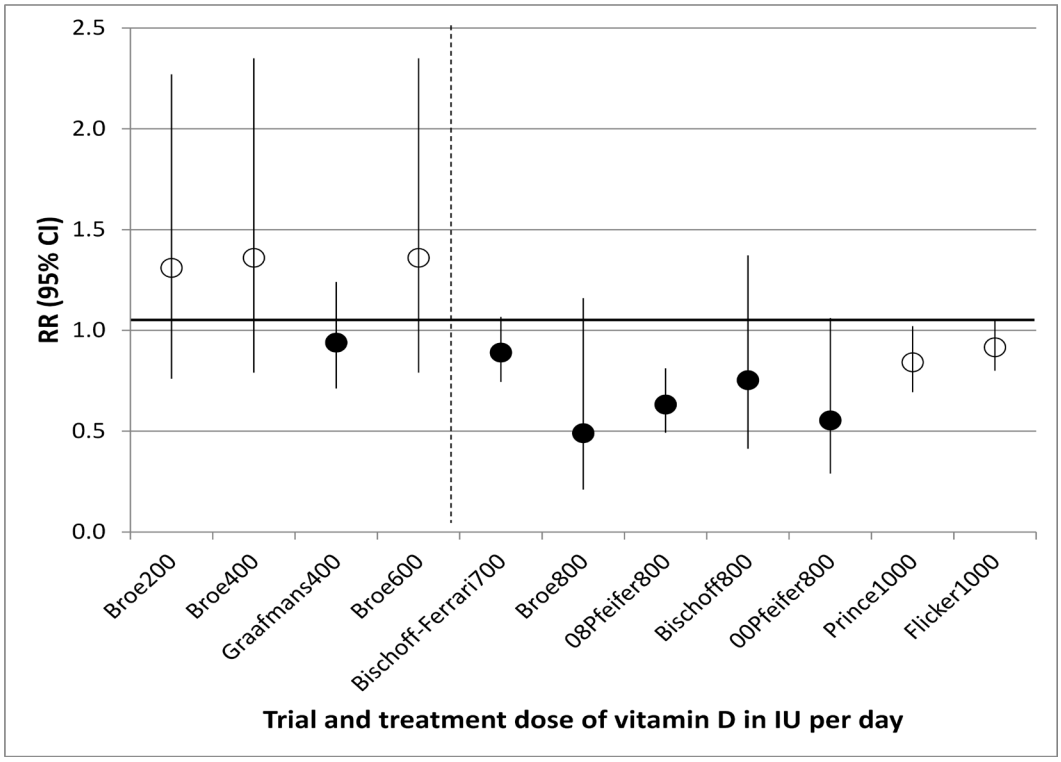


Figure 1A is adapted from Bischoff-Ferrari HA et al. "Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials", Bmj 2009 [15] – update 2011 [16]; 339: b3692, Copyright © (2009), British Medical Journal. All Rights reserved. Triangles indicate trials with D3, circles trials with D2.

3.4. Vitamin D an bone effects

Results from double-blind randomized controlled trials

Vitamin D is essential for bone growth [17,18] and preservation [19], and higher 25-hydroxyvitamin D levels are associated with higher bone density in younger and older adults [20]. Also, in double-blind RCTs, vitamin D supplementation increased bone density and reduced bone loss [21,22]. A 2009 meta-analysis summarized the evidence of 12 double-blind randomized controlled trials and 42,279 individuals age 65 and older on oral vitamin D supplementation. The results show that oral vitamin D supplementation reduces the risk of hip fracture by 18% [23] and the risk of any non-vertebral fracture by 20% [23]. However, similar to fall prevention, the benefit on fracture prevention depended on the dose of vitamin D (see Figure 1B+C). Fracture prevention required a received dose (treatment dose*adherence) of more than 482 IU vitamin D per day. The primary use of received dose (dose*adherence) as opposed to treatment dose from double-blind RCTs allowed for the assessment of anti-fracture efficacy by a dose that accounts for the low adherence in several recent large trials [24, 25]. Any lower received dose than 481 IU per day did not reduce fracture risk at any non-vertebral site or the hip.

Figure 1B: Non-vertebral fracture prevention by received dose (dose*adherence) in the treatment group

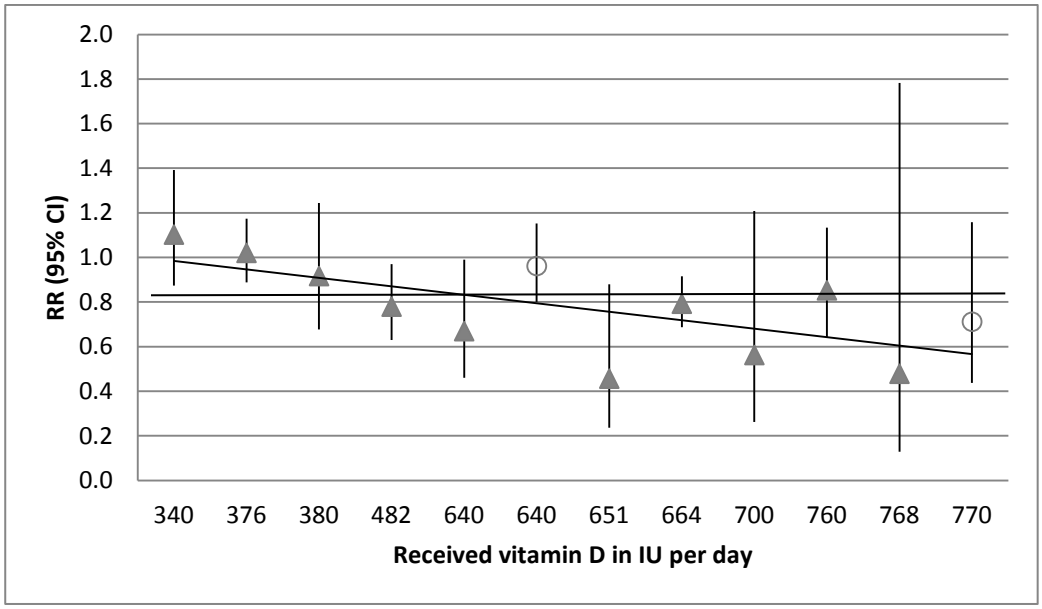


Figure 1B is adapted from Bischoff-Ferrari HA et al. "Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials", Archives of Internal Medicine. 2009 Mar 23;169(6):551-61., Copyright © (2009), American Medical Association. All Rights reserved [23]. It depicts the relative risk of non-vertebral fracture from 12 double-blind RCTs plotted against the received dose of vitamin D in the different trials. For any non-vertebral fractures, anti-fracture efficacy increased significantly with higher received dose (meta-regression: Beta = - 0.0007; p = 0.003). The pooled RR was 0.80 (95% CI, 0.72-0.89) for a received dose of 482 to 770 IU supplemental vitamin D per day, while the pooled RR was 1.02 (95% CI, 0.92-1.15) for received doses of less than 482 IU per day.

Figure 1C: Hip fracture prevention by received dose (dose*adherence) in the treatment group

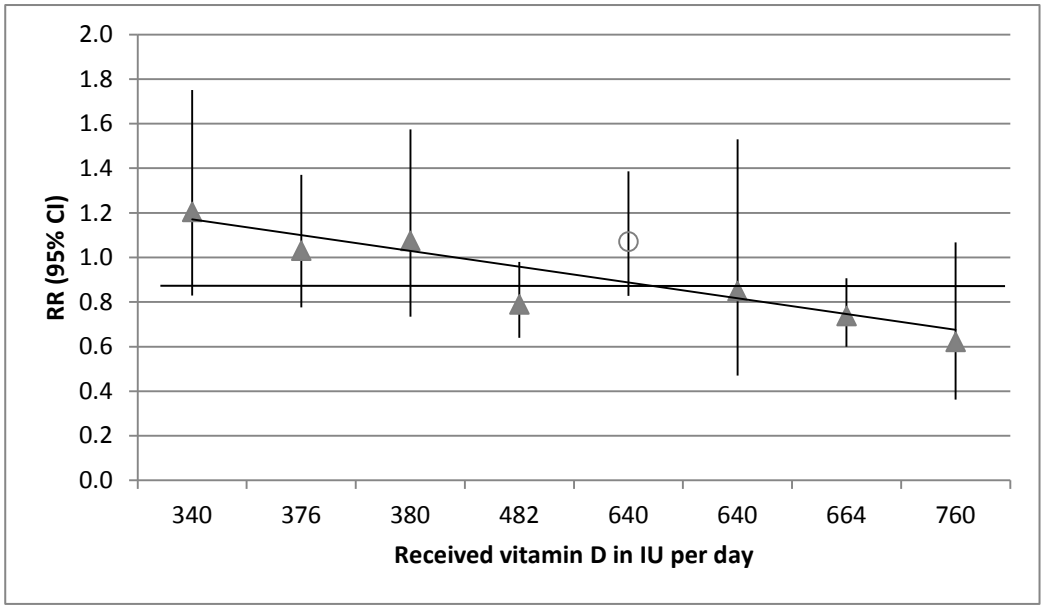


Figure 1C is adapted from Bischoff-Ferrari HA et al. "Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials", Archives of Internal Medicine. 2009 Mar 23;169(6):551-61., Copyright © (2009), American Medical Association. All Rights reserved [23]. Triangles indicate trials with D3, circles trials with D2. Line = Trendline through relative risks from different trials.

Figure 1C depicts the relative risk of hip fracture from 8 double-blind RCTs (n = 42,279 individuals) plotted against the received dose (dose*adherence) of vitamin D in the different trials. For hip fracture, anti-fracture

efficacy increased significantly with higher received dose (meta-regression: Beta = - 0.0009; p = 0.07). The pooled RR was 0.82 (95% CI, 0.69-0.97) for a received dose of 482 to 770 IU supplemental vitamin D per day, while the pooled RR was 1.09 (95% CI, 0.90-1.32) for received doses of less than 482 IU per day.

Similar to the data on fall prevention with vitamin D, at the higher received dose of vitamin D (>482 IU per day) the prevention of non-vertebral fractures was present in all subgroups of the older population independent of age and type of dwelling, and additional calcium supplementation did not further improve anti-fracture efficacy [23]. Notably, there was a suggestion that vitamin D3 was superior to vitamin D2 for both fall and fracture prevention with vitamin D [15, 23].

Results from meta-analyses on fracture prevention that included also open-design trials

In August 2007, a review and meta-analysis commissioned by the US Department of Health and Human Services (HHS) addressed the effect of vitamin D supplementation on all fractures in postmenopausal women and men ages 50 and older [26]. The pooled results for all fractures included 10 double-blinded and 3 open design trials (n = 58,712) and did not support a significant reduction of fractures with vitamin D (pooled odds ratio = 0.90; 95% CI 0.81-1.02). The report suggested that the benefit of vitamin D may depend on additional calcium and may be primarily seen in institutionalized individuals, which is consistent with the meta-analysis of Boonen et al. [27].

One 2010 patient-based meta-analysis included 7 large trials of vitamin D with 68500 individuals age 47 and older [28]. The authors defined criteria that permitted the inclusion of two open design trials [29, 30], one trial with intra-muscular vitamin D, and 4 of the 12 double-blind RCTs included in the 2009 meta-analysis described above (one RCT using intermittent vitamin D2 without calcium [31], one RCT with 400 IU vitamin D3 without calcium [32], one trial with 800 IU vitamin D3 per day with and without calcium and less than 50% adherence [25], and one trial with 400 IU vitamin D with calcium [24]). Based on these criteria, their findings showed a reduced overall risk of fracture (hazard ratio = 0.92; 95% CI 0.86 to 0.99) and a non-significant reduction of hip fractures (hazard ratio = 0.84; 95% CI 0.70 to 1.01) for trials that used vitamin D plus calcium. Vitamin D alone, irrespective of dose, did not reduce fracture risk. The authors concluded that vitamin D, even in a dose of 400 IU vitamin D per day reduces the risk of fracture if combined with calcium. Notably, this regimen was tested in 36,282 postmenopausal women in the Women's Health Initiative Trial over a treatment period of 7 years and did not reduce the risk of fracture [24].

Discussion on the recent meta-analyses that also included open-design trials

In all 3 meta-analyses reviewed under this section, heterogeneity by dose may have been missed due to the inclusion of open design trials plus a dose evaluation that did not incorporate adherence. Biologically, the exclusion of heterogeneity by dose seems implausible even if a formal test of heterogeneity is not statistically significant. A dose-response relationship between vitamin D and fracture reduction as documented for the two 2009 meta-analyses of double-blind RCTs [15,23], is supported by epidemiologic data showing a significant positive trend between serum 25(OH)D concentrations and hip bone density [33] and lower extremity strength [8,9].

Factors that may obscure a benefit of vitamin D are low adherence to treatment [34], low dose of vitamin D, or the use of less potent D2 [35,36]. Furthermore, open design trials [37] may bias results towards the null because vitamin D is available over the counter. Heterogeneity by trial quality is supported by the sensitivity

analyses performed for the two 2009 meta-analyses of double-blind RCTs, where heterogeneity was introduced by open design trials for any dose, and the lower and higher dose of vitamin D [15, 23].

Thus, data on vitamin D recommendations should be based on the highest available evidence, a meta-analysis of double-blind randomized controlled trials.

3.5. Desirable 25-hydroxyvitamin D status for optimal musculoskeletal health

A threshold for optimal serum 25-hydroxyvitamin D concentration and fracture and fall prevention has been addressed in a recent benefit-risk analysis [38] and is illustrated in Figure 2. Based on these data, 75 or better 100 nmol/l (30 or better 40 ng/ml) are suggested as an optimal threshold of 25-hydroxyvitamin D for fall and fracture prevention. The threshold of 75 nmol/l 25-hydroxyvitamin D as desirable for optimal musculoskeletal health is supported by epidemiologic data for hip bone density in younger and older adults [20], as well as lower extremity function for older adults [8,39].

Figure 2: Desirable serum 25-hydroxyvitamin D concentration for fall and fracture prevention

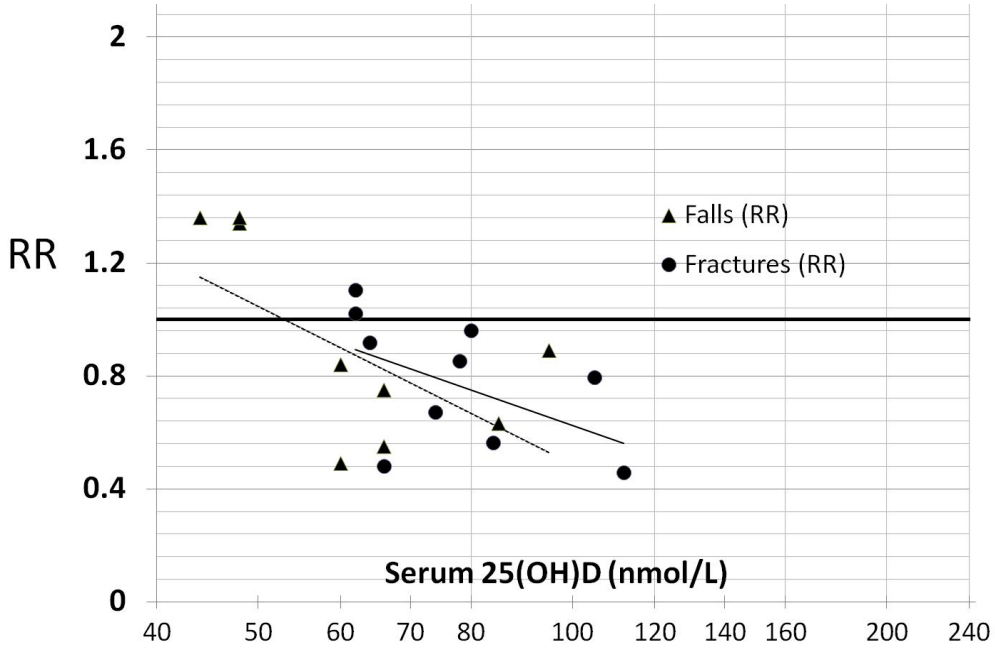


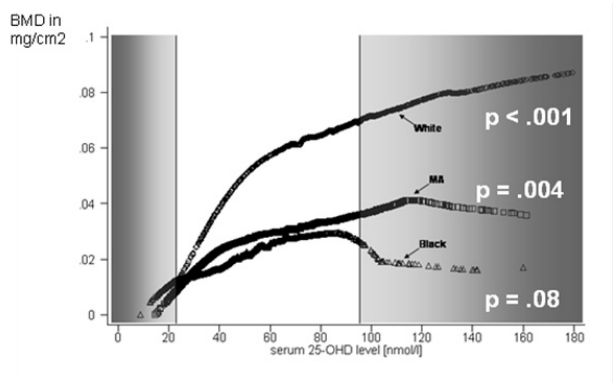
Figure 2 is adapted from Bischoff-Ferrari HA et al. “Benefit-risk assessment of vitamin D supplementation”, Osteoporosis International .2010 Jul;21(7):1121-32. Epub 2009 Dec 3, Copyright © (2010), Osteoporosis International. All Rights reserved [40]. Data points show the relative risk of falls and the relative risk of sustaining any non-vertebral fracture from double-blind RCTs, by achieved 25-hydroxyvitamin D levels in the treatment groups. Data was extracted from two 2009 meta-analyses [15, 23] and summarized in a recent benefit-risk analysis of vitamin D [38]. Based on these data, 75 or better 100 nmol/l (30 or better 40 ng/ml) are suggested as an optimal threshold of 25-hydroxyvitamin D for fall and fracture prevention.

A threshold for optimal 25-hydroxyvitamin D and hip bone density has been addressed among 13,432 individuals of NHANES III (The Third National Health and Nutrition Examination Survey) including both younger (20-49 years) and older (50+ years) individuals with different ethnic racial background [33]. Compared to the lowest quintile of 25-hydroxyvitamin D, the highest quintile had higher mean bone density by 4.1% in younger whites (test for trend; $p < 0.0001$), by 4.8% in older whites ($p < 0.0001$), by 1.8% in younger Mexican Americans ($p = 0.004$), by 3.6% in older Mexican Americans ($p = 0.01$), by 1.2% in

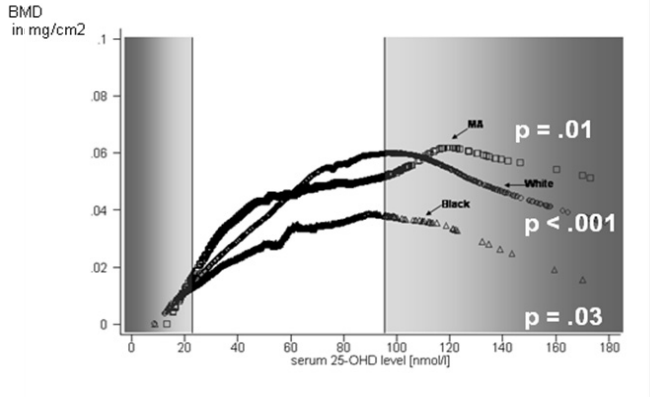
younger blacks (p = 0.08) and by 2.5% in older blacks (p = 0.03). In the regression plots higher serum 25-hydroxyvitamin D levels were associated with higher BMD throughout the reference range of 22.5 to 94 nmol/l in all subgroups (Figure 3 A and B). In younger whites and younger Mexican Americans, higher 25(OH)D was associated with higher BMD even beyond 100 nmol/l.

Figure 3: Desirable serum 25-hydroxyvitamin D concentration for hip bone mineral density in younger and older adults

A) Younger adults (age 20-49)



B) Older adults (age 49+)



Figures 3 A and B are adapted from Bischoff-Ferrari HA et al. “Positive association between 25-hydroxy vitamin d levels and bone mineral density: a population-based study of younger and older adults”, Am J Med 2004, Vol. 116, Issue 9, Page 634-9. Copyright © (2004), American Journal of Medicine. All Rights reserved [33]. Regression plot of difference in bone mineral density by 25(OH)D in younger (20 to 49 years, Figure 3A) and older adults (50+ years, Figure 3B). Symbols represent different ethnicities: circles are Caucasians, squares are Mexican Americans and triangles are African American individuals. The intercept was set to “0” for all race/ethnicity groups to focus on the difference in BMD by 25(OH)D levels, as oppose to differences in BMD by race/ethnicity. The reference range of the 25(OH)D assay (22.5-94 nmol/l) is marked as vertical lines. The reference range of the Diasorin assay has been provided by the company and was established using 98 samples from apparently healthy normal volunteers collected in the south-western United States (high latitude) in late autumn (www.fda.gov/cdrh/pdf3/k032844.pdf).

Regression plots adjust for gender, age, body mass index, smoking, calcium intake, estrogen use, month and poverty income ratio. Weighting accounts for NHANES III sampling weights, stratification and clustering.

The threshold of at least 75 nmol/l for serum 25-hydroxyvitamin D concentrations is supported by the recent IOF position statement on vitamin D for optimal fall and fracture prevention [41].

3.6. Dosing interval of vitamin D and musculoskeletal health

In 2010, a large double-blind RCT by Sanders et al., including 2256 community-dwelling women age 70 years and older, tested the benefit of 500,000 IU vitamin D3 given orally once a year, on fall and fracture prevention [42]. In those women, mean age 76, considered to be at risk of fracture, 500,000 IU vitamin D once a year did not reduce but instead it increased the risk of falls by 15% and the risk of fractures by 26% compared to placebo, with the greatest increase in falls occurring during the first 3 month after dosing. These findings are consistent with another trial that tested 300'000 IU vitamin D2 as an intra-muscular injection once a year [43]. Whether the large dose of vitamin D tested in the Sanders trial was too much of a good thing or not enough to provide a sufficient supply of vitamin D over 12 months is speculative [44]. The temporal pattern of events may suggest that the high dose of vitamin D may have induced a "protective" reaction resulting in an acute decrease in 1,25-dihydroxyvitamin D [45]. Alternatively, the undocumented potential effect of vitamin D on muscle strength [39] and overall health (i.e. less infections and less hospital admissions [46]) in the Sanders trial, may have improved mobility and decreased "down time" , ironically leading to an increased opportunity to fall and fracture. As a result of the Sanders trial and given the half-life of vitamin D is 3 to 6 weeks, a daily, weekly, or monthly dosing interval may be most advantageous and safe [38,47].

How to achieve a serum concentration of at least 75 nmol/l for musculoskeletal health

Studies suggest that 700 to 1000 IU of vitamin D per day may bring 50% of younger and older adults up to 75-100 nmol/l [48-50]. Thus, to bring most older adults to the desirable range of 75-100 nmol/l, vitamin D doses higher than 700-1000 IU would be needed. According to a recent benefit-risk analysis on vitamin D, mean levels of 75 to 110 nmol/l were reached in most RCTs with 1800 IU to 4000 IU vitamin D/d without risk [38]. In a recent trial among acute hip fracture patients, 70% reached the 75 nmol/l threshold with 800 IU vitamin D3 per day, and 93% with 2000 IU vitamin D3 per day, at 12 month follow-up and with over 90% adherence [51].

Consistently, Heaney and colleagues, in a study of healthy men, estimated that 1000 IU cholecalciferol per day are needed during winter months in Nebraska to maintain a late summer starting level of 70 nmol/l, while baseline levels between 20-40 nmol/l may require a daily dose of 2200 IU vitamin D to reach and maintain 80 nmol/l [52,53]. These results indicate that individuals with a lower starting level may need a higher dose of vitamin D to achieve desirable levels, while relatively lower doses may be sufficient in individuals who start at higher baseline levels.

Due to seasonal fluctuations of 25(OH)D levels [54], some individuals may be in the desirable range during summer months. However, these levels will not sustain during the winter months even in sunny latitudes [55,56]. Thus winter supplementation with vitamin D is needed even after a sunny summer. Furthermore, several studies suggest that many older persons will not achieve optimal serum 25(OH)D levels during summer months suggesting that vitamin D supplementation should be independent of season in older persons [56-58]. Even among younger persons, the use of sunscreen or sun-protective clothing may prevent a significant increase in 25-hydroxyvitamin D levels [58].

Most vulnerable to low vitamin D levels are older individuals [56,59], individuals living in northern latitudes with prolonged winters [54,60], obese individuals[61], and individuals of all ages with dark skin pigmentation living in northern latitudes [33,62,63].

Naturally high 25-hydroxyvitamin D levels observed in healthy outdoor workers are 135 nmol/l [64] in farmers and 163 nmol/l [65] in lifeguards. As a first sign of toxicity, only serum 25(OH)D levels of above 220 nmol/l have been associated with hypercalcemia [66, 67].

3.7. In summary

Based on evidence from randomized-controlled trials, oral vitamin D supplementation reduces both falls and non-vertebral fractures, including those at the hip. However, this benefit is dose-dependent and a dose of 700-1000 IU vitamin D per day is required to assure both fall and fracture prevention in older adults. For optimal fall and fracture reduction a serum 25-hydroxyvitamin D concentration of at least 75 nmol/l is required. This threshold may be reached with 800 to 1000 IU vitamin D in 50% of adults, whereas higher doses of vitamin D would be required to shift all adults to this threshold.

3.8. References

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4. Non-skeletal and non-muscle related positive effects of vitamin D in adults and elderlies

Clinical studies

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4.1. Vitamin D and cancer

Introduction

After the observation that the mortality of cancer, cardiovascular diseases and diabetes rise with increasing latitude in North America (1, 2), and that the survival of various cancer diseases is better in summer (3, 4) than in winter, the question rose, if this is in relation with the UV irradiation and by that with the vitamin D status, especially with the serum level of 25OH-vitamin D, which is the main form of circulating vitamin D. It is known that that 25OH-vitamin D is activated (hydroxylated) in many cells, and that the active 1,25 dihydroxy vitamin D3 acts on many cells inducing cell differenciation and angiogenesis , and inhibiting invasive cell growth.

Indeed, ecologic studies have shown that the UVB-irradiation, and by that the production of vitamin D in the skin, or the increased serum levels of 25OH-vitamin D is associated with an increaased mortality of various cancer diseases. The World Health Organization published already in 2008 a review of the relation between vitamin D and cancer (5) and encouraged more studies. In a more recent review it was concluded that there is a large data-base showing a positive effect of vitamin D on breast and colorectal cancer, and that there is good evidence (at least from 3 studies) in cancer of prostate, endometrium, ovaries, oesophagus, stomach, pancreas, urinary bladder and kidneys, as well as in Hodgkin's and non Hodgkin's lymphoma (6). Epidemiologic studies *o*f large cohorts, such as e.g. the Nurses' Health Study, also revealed the association between between vitamin D and colorectal and breast carcinoma, but not for prostata carcinoma (7). A recently published meta-analysis provided further evidence that the UVB irradiation is associated with a decreased risk of several intestinal cancer diseases, which was explained by the production of vitamin D (8). Notably, a recently published double-blind randomized trial showed a significant 60% reduction of total cancer risk among 1179 community-dwelling healthy postmenopausal women treated with vitamin D plus calcium compared to placebo over a 4-year follow-up (32).

Colorectal carcinoma

The search for a positive influence of vitamin D on lowering the risk of colorectal carcinoma was the main interest of numerous clinical and epidemiological studies, which were reviewed already in 2006 (9). A more recent epidemiologic study on over 500'000 subjects (10) allowed a nested case-control approach on 1248 cases of colorectal carcinoma, and showed a linear negative relationship between serum levels of 25OH vitamin D and the cancer risk, the risk beeing increased in the presence of low levels and decreased by 23% when the levels were above 100 nmol/l.

Pancreatic cancer

There is still doubt concerning the positive influence of vitamin D on lowering the risk of pancreas cancer, because not all studies provided conclusive results, although the mortality grew with increasing latitude (11). Some authors even found a decreased risk for pancreas carcinoma in the presence of low 25OH-vitamin D levels (12).

Prostate cancer

For prostata cancer too, a relationship was found with the latitude, and by that with the UV-irradiation (11), but nested case-control studies with measurements of 25OH-vitamin D levels could not confirm that (13).

Intestinal squamous cell carcinoma.

In an analysis of the geographic distribution, a significant relationship with the UVB-irradiation was found for colon-, rectum-, and gastric carcinomas (10).

Endometrial cancer

For endometrial carcinoma too, a negative correlation was found between the IV-irradiation and the cancer incidence (14).

Breast cancer

A recent meta-analsis of 7 prospective studies on mamma carcinoma and 10 studies on colorectal cancer show an exponential negative relationship with the 25OH-vitamin D levels. The risk of breast cancer was found to be reduced in a follow-up study by about 25%, when the level is over 78 nmol/l (15), and that of colorectal cancer too when the levels where above 60 nmol/l, compared to the risk with the lowest vitamin D levels (15).

However, it must be emphasized, that the evidence concerning breast cancer is weaker and mainly concerns elderly patients (16).

Prostate cancer

High vitamin D levels improve the prognosis of prostate cancer (17). Other studies were less conclusive (7).

Conclusions and recommendations

In summary, mechanistic and epidemiologic studies and a small clinical trial among postmenopausal women (32)support a benefit of vitamin D on cancer prevention, however data from large clinical trials are missing. Further, the accumulation of reports showing a correlation between the risk of cancer disease and low 25OH-vitamin D levels allowed some speculations on the optimal serum level. Accordingly, the increase of the level to 40-60 ng/ml (100-150 nmol/l) in the US and in Canada would avoid about 56'000 new cases of breast cancer and 49'000 new cases of colorectal cancers, and would decrease the number of deaths caused by these diseases by 75% (18). However it must be reminded that significant associations between blood levels of 25OH-vitamin D and the risk of any disease or of mortality are not proofs of causal relationships. In addition, for rising the serum level to over 75 nmol/l it would theoretically be necessary, in view of the great variabilityof the individual responsiveness, to take 3800 IU vitamin D daily if the serum level already is above 55 nmol/l, otherwise 5000 IU per day (19).

An increase of the vitamin D intake to some less elevated doses has also been recommended in view of other positive health effects. But it has to be reminded that intake of the recommended 1000 IU daily in adults raises the serum level of 25OH vitamin D only to over 75nmol/l only on average, i.e. in half of the population in a RCT, and that for this reason this dose can not be a valid recommendation of health authorities (9).

4.2. Vitamin D and various chronic diseases

Vitamin D was shown to have probably a protective role in numerous crossectional studies on various cancer diseases, in multiple sclerosis (20, 21), infections of the upper respiratory tract (22), lymphoma, tuberculosis, diabetes, inflammatory bowel diseases, and cardiovascular diseases (23). As for cancer diseases, the bulk of evidence stems from observational studies, where a significant association does not prove a causal relationship. Considering the abundant literature, review articles are quoted here. The one evaluated the degree of evidence for significant relations with various dieases as follows (6) : The evidence seems ot be convincing for colorectal and for breast carcinomas, as of course for osteoporosis, based on prospective, restrospective and cross-sectional studies, large cohort studies and interventional trials. For the following diseases the evidence is considered as fair, based on at least three studies : carcinomas of various organs, cardiovascular diseases, neuromuscular diseases, diabetes type 1, tuberculosis, paradental diseases, loss of teeth. In addition, some relationship with vitamin D was also found for hypertension, metabolic syndrome, and multiple sclerosis. For each disease, the optimal vitamin D levels seems to be different (9).

4.3. Vitamin D and mortality

The relationship between the vitamin D level and cancer and other diseases led to the examination of the influence of vitamin D on mortality. In any event, cardiovascular mortality was found to be vitamin D-dependent. In groups of patients with a relatively high mortality due to cardiac diseases, there was a sigificant influence of the vitamin D level. The mortality of patients with terminal cardiac failure was decreased by 49% when their 1,25 dihydroxy-vitamin D level was in the upper third (24). In a crossectional study on candidates for coronarography, the risk of cardiac mortality was increased by 2.84 when the 25OH vitamin D level was below 10 ng/ml in comparison with patients whose level was above 30 ng/ml (25). Also in patients on renal dialysis the risk of mortality could be related to the vitamin D levels (26). Again, these associations do not shed a light on the eventuality of a causal relationship.

The question of general mortality has been approached by a prospective study in 3258 candidates for coronarography whose vitamin D levels have been measured and whose mortality has been examined during 7.7 years. In comparison to the quart of this population with the highest vitamin D levels, the mortality of the groups with low average levels of 19 and 33 nmol/l was increased by 108%, resp. by 53%, and the cardiovascular mortality even by 122%, resp. 82% (27). The authors were surprised to discover that this observation did depend neither on the coronary disease, nor on the physical activity or on comorbidities.

In the same year the same problem was also investigated in 13'331 adults of the NHANES III statistics. Over 8.7 years in average, the general mortality of the quart of this population with the lowest vitamin D levels (< 17.8 ng/ml) was significantly higher by 26% than the mortality of the quart with the higest levels (28). The slight increase of mortality observed in women with 25OH-levels of > 50 ng/ml was at the edge of significance and needs further confirmation.

All these significant results confer a possible protective role to vitamin D, for so far unknown reasons.

This obviously raises the question, if a substitution with vitamin D can lower mortality. Already in 2007, a meta-analysis was published on the question, if the 9 valid randomized controled trials, which examined the effect of a substitution with vitamin D, resultet in decreased mortality. Indeed, a reduction of the risk of mortality of 7% could be calculated (29). In the frame of the Women's Health Inititative, where 36'282 postmenopausal women of any age were treated with 1 g of calcium and 400 IU vitamin D daily, or a placebo, the mortality over 7 years was reduced by 9%, although this result just missed significance (CI 0.83-1.01)(30). A more recent meta-analysis examined the randomized controled studies in which calcium and vitamin D were given for prevention of hip fracture. Here again, the mortality was significantly reduced by 12%, independently of the incidence of hip fractures. With vitamin D alone the result was not significant (31).

Comment and recommendation

All these studies differ in their selection of patients or groups of subjects, especially concerning the age and the comorbidities, and for that cannot be compared to each other. But most were carefully examined for the eventual influence of life style and comorbidity and represent all together an impressive data-base which speaks for the positive influence of vitamin D on longeivity. But they do not yet provide information on the level of circulating vitamin D which has to be reached for an optimal reduction of mortality. It can only be confirmed that a level of 25OH vitamin D below 24 ng/ml, resp. 62 nmol/l (27), or below 32.1 ng/ml (28) goes along with increased mortality. The reason for this association remains unclear.

But one has to suppose that in view of the international vitamin D deficieny, all these studies were performed in groups of subjects or patients with relatively low vitamin D levels compared to the potentially optimal values. It is therefore possible that the optimal level is even higher than the level of the groups with the highest values in these studies.

The evidence for an eventual causal relationship would be greatly improved by more controlled intervention trials or at least by follow-up studies. As mentioned above, a few such studies resulted in a decrease of mortality, which still leaves open the question by which mechanism this effect could be explained.

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5. UV Radiation and Vitamin D synthesis in the skin

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5.1. Introduction

Solar ultraviolet radiation (UVR) plays an important role for humans. Apart from the well known adverse effects of terrestrial UVR like sunburn in the short-term and skin cancer and photoageing in the long-term, the only established benefit of solar UVR and UVB in particular, is the cutaneous synthesis of vitamin D3. It has been estimated that the majority of vitamin D3 is derived from solar UVB (280–320 nm) exposure [1]. The risks and benefits of solar UVR are therefore of great interest to the dermatology community.

Many variables are of importance in determining the extent of previtamin D3 production in the skin as a result of UVR exposure. These can be summarized in four groups: (1) the intensity of ambient solar UVR, (2) the fraction of ambient exposure received at the anatomical sites, (3) the personal behaviour and time spent outdoors, and (4) the personal characteristics.

5.2. Intensity of ambient solar UVR

The solar elevation angle (SEA i.e. height of the sun), which in turn is dependent on factors such as latitude, season and time of day, have a substantial impact on UVB radiation. The higher the SEA, the higher the UVB irradiance. Also affected by the SEA is the ratio of UVB to UVA, with increasing UVB part to higher SEA. Depending on the degree of cloud cover and cloud type, UVB radiation is attenuated in most cases, but may also be enhanced. Furthermore, ozone concentration (stratospheric and tropospheric) as well as air pollution influences the UVB irradiance dominantly. A Belgian study found (tropospheric) ozone concentration influencing the vitamin D level by comparing urban residents [2]. Finally, altitude and the ground surface have to be mentioned. Solar UVB radiation increases by about 7% per km in altitude and is further enhanced by reflectivity on ground surface. Snow in particular almost doubles UVB radiation due to reflectivity [3].

Summary (1): Solar elevation angle (i.e. latitude, season and time of day), cloud cover, cloud type, ozone, air pollution, altitude, surface reflexion

5.3. Fraction of ambient exposure received at the anatomical sites

Mostly, the data from ambient UVR measurements are related to a horizontal plane. However, vertical surfaces such as the face, arms and legs receive much lower UVR doses compared to a horizontal plane [4,5], which would mean much longer exposure times in practice to receive a certain amount of vitamin D. This aspect is often insufficient considered in vitamin D studies. It is possible that reported vitamin D accumulation is substantially overestimated.

5.4. Personal behaviour and time spent outdoors

Personal behaviour includes clothing, as sun protection or due to temperature, shade and sunscreen use.

Clothing is advocated in photoprotection strategies to reduce UVR exposure. Laboratory in vitro and in vivo studies have shown that clothing in line with UVR inhibits the production of previtamin D and serum vitamin D respectively [6, 7], and that the transmission of previtamin D effective radiation depends on fabric type [7, 8]. Several studies have shown that clothing worn for cultural or religious reasons can have an adverse effect on vitamin D status or its health outcomes [9,10].

The influence to the UVR exposure varies in a wide range by different shade environments. It was found in the shade a higher relative proportion of UVB compared to full sun and therefore a pronounced environment for cutaneous synthesis of vitamin D3 – especially an environment with mostly sub-erythemal UVR exposure [11].

Sunscreen blocks UVB radiation effectively, but at present it is difficult to make a definitive conclusion about the role of sunscreens on vitamin D status. No randomized controlled trials or longitudinal studies have been reported showing that sunscreens significantly suppress cutaneous vitamin D synthesis, but three papers published about 20 years ago provide information that this might be the case [12-14]. Theoretically sunscreens have the potential to reduce vitamin D synthesis but in practice they usually do not, almost certainly because they are not used in the way that their sun protection factor (SPF) is assessed. People normally apply much less sunscreen than used in the testing process to determine a product's SPF [15], and some areas of the skin are mostly left out; absolute full-body coverage of sunscreen is uncommon.

It is evident that there is a variation in the time spent outdoors during a specific exposure period (e.g. summer weekends) by habit. The results obtained from a number of studies in Europe [for example 16-18] indicate that people receive an annual exposure of the order of 200 standard erythema doses (SED), what corresponds to approximately 5% of the total ambient available. This exposure is mainly received from summer weekend and vacational exposure, and principally to the hands, forearms and face. However, on a population basis, annual exposure can vary enormously depending on an individual's propensity for being outdoors. For example, in studies of the solar UV exposure of indoor workers in Denmark [16,18] was measured a range of annual exposures of individuals within the cohort extending from a few tens of SED to several hundred SED.

5.5. Personal characteristics

An individual characteristic is the constitutive skin pigmentation as natural sun protection and potentially as suppression for cutaneous vitamin D synthesis; melanin blocks the UVB radiation from reaching the 7-dehydrocholesterol (7-DHC). It has been hypothesized that maintaining vitamin D status was a major factor in the evolution of the loss of skin colour as humans moved from Africa to less sunny climates [19] because epidermal melanin attenuates the photoconversion of 7-DHC to previtamin D. There is epidemiological evidence that people with skin type V and VI have lower levels of vitamin D than those with white skins under given environmental conditions [20,21], but it is not always easy to dissociate these data from confounding factors. A study in Toronto with people of Asian and European ancestry showed an inverse relationship between winter vitamin D status and skin pigmentation measured by reflectance spectroscopy [22]. However, a different conclusion comes from a study in France that assessed the vitamin D status in

1191 people in relation to skin type and self-assessed sun exposure [23]. Fair skin types I and II had lower vitamin D levels than skin types V and VI. Vitamin D status was positively correlated with sun exposure which was inversely correlated with skin type (i.e. the darker the skin, the more the exposure). A similar observation was made in a recent UK study on 1414 Caucasian women, with Celtic (skin type I) to Mediterranean (skin type IV) skin types, which found a very strong relationship between vitamin D status and tanning (facultative pigmentation) ability [24]. These results may be because fair skin types avoid the sun to reduce their risk of sunburn and skin cancer; in other words their skin type governs their sun exposure behaviour. A study in New Zealand compared vitamin D status in Europeans and Pacific People. The latter had significantly higher values [25]. However, vitamin D status was positively correlated with quantitatively measured facultative but not constitutive pigmentation. This suggests that solar exposure is the main determinant of vitamin D status independent of skin type.

Overall, the relationship between skin type and vitamin D status seems complex. It is difficult to draw a conclusion from the studies that address the role of constitutive pigmentation in vitamin D photosynthesis. There seems to be contradictory data in both the observational and the UVR intervention studies. Single exposure laboratory studies with UVB suggest that melanin is photoprotective [26,27] whereas the repeat exposure studies suggest the opposite [28-30]. Most of the studies have had small numbers of volunteers. Besides skin pigmentation, UVR does increase the thickness of the stratum corneum, but this increase is very modest and offers only very modest protection against erythema [31]. The effect of stratum corneum thickening on vitamin D synthesis has not been determined.

Further individual characteristics like age and obesity have an impact on the vitamin D synthesis. It has been found, that cutaneous synthesis of vitamin D decreases with age (elderly persons are less capable of synthesizing vitamin D [32]), and obesity leeds to a reduced capacity of vitamin D synthesis [33]. Moreover, a recent work [30] has shown that baseline vitamin D is a major determinant of response to UVB, what has not usually been considered in past studies.

It was estimated a 1000-fold variation in daily personal (erythemal) dose throughout the year at latitudes of about 50°N by only the intensity of ambient solar UVR, the fraction of ambient exposure received at the anatomical sites and the time spent outdoors [5]. Considering all other variables mentioned above, it is expected to come to much extended variation.

5.6. UVR exposure in order to obtain 1000 IU of vitamin D

The UVR exposure time needed to obtain a certain amount of vitamin D can be calculated with a mathematical model described in [34] and [35]. Although the model well considered several atmospheric variables and exposed skin area, it does not consider the orientation of the exposed anatomical sites. The UVR irradiance is calculated on a horizontal plane. Moreover, like in many other studies, it has used the original previtamin D action spectrum [36] or its CIE derivative [37] to estimate the effective vitamin D dose. The validity of these previtamin D action spectra has been called into question for a variety of different reasons [38]. One important reason is spectral interaction [39]; i.e. where one part of the solar UVR spectrum modifies the effects on another. So, an incorrect action spectrum would invalidate many of the conclusions derived from its use. With this in mind, also the following calculations should be used carefully.

The UVR exposure time (hours:minutes) for several skin types needed to obtain 1'000 IU of vitamin D is based on the model mentioned above (Table 1). The values in parentheses corresponds to the exposure times, taking the anatomical sites into account (30% relative to a horizontal plane), but not the time course of the day of the UVR irradiance, i.e. exposure times longer than approximately one hour, would be in practise even longer than indicated in Table 1.

To what extend the use of sun beds contributes to the vitamin D synthesis in the skin will strongly depend on the emission spectrum of the sunlamps. These spectra may be very different in the several type of sunlamps and contain in the vast majority of sunlamps an enormous part of UVA (up to fifteen-fold that of the sun). UVA has non ability to synthesize vitamin D in the skin but causes negative effects like premature aging of the skin, erythema and skin cancer. Therefore sun beds contain a poor risk-benefit balance for vitamin D synthesis in the skin.

Table 1: The UVR exposure time (hours:minutes) around midday for several skin types (Fitzpatrick classification scale) needed to obtain 1'000 IU of vitamin D. Parameters: Location 47°N/7.5°E; skin type = various; body exposure 8% (face, hands), unprotected skin; sky condition = cloudless; visibility = 25.00 km; total ozone column = various, according to the time course of the year; surface altitude = 550 m a.s.l., surface type = various, Nov-Feb: snow, Mar-Oct: concrete, lawn, meadow, field, sand (albedo = 0,03). The skin type classification is based on the ability to get a sunburn and a suntan: type I always burns easily, never tans (sensitive); type II always burns easily, tans minimally (sensitive); type III burns moderately, tans gradually (to a light-brown) (normal). About 90% of the Swiss population covers the range of skin type I to III.

Date (mid-month)	Jan.	Feb.	Mar	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Ozon (DU)[a]	340	360	365	365	350	330	315	300	290	285	290	315
Skin type I												
Exposure time around midday (hours:minutes)	4:11 (13:56)	1:19 (4:23)	0:41 (2.16)	0:21 (1:10)	0:14 (0:46)	0:11 (0:36)	0:10 (0:33)	0:12 (0:40)	0:19 (1:03)	0:39 (2:10)	1:31 (5:03)	5:56 (19:46)
Skin type II												
Exposure time around midday (hours:minutes)	∞	1:40 (5:33)	0:52 (2:53)	0:26 (1:26)	0:17 (0:56)	0:14 (0:46)	0:13 (0:43)	0:15 (0:50)	0:23 (1:16)	0:49 (2:43)	1:55 6:23)	∞
Skin type III												
Exposure time around midday (hours:minutes)	∞	2:02 (6:46)	1:02 (3:26)	0:31 (1:43)	0:20 (1:06)	0:16 (0:53)	0:16 (0:53)	0:18 (1:00)	0:28 (1:33)	0:58 (3:13)	2:22 (7:53)	∞

The rudimentary calculation shows even for the skin type I at least half an hour sunlight exposure on face and hands daily needed to obtain 1'000 IU of vitamin D. It is therefore questionable, whether in practice a sufficient vitamin D status is achievable all year around by sunlight only.

5.7. Conclusion

In conclusion, the relationship between solar UVR exposure, sun protection, whether natural or behavioural (including sunscreen use) and vitamin D status is poorly understood. Calculated conclusions may have been confounded by the use of an incorrect action spectrum and other factors like insufficiently considered anatomical sites exposure. There remains much work to be done in risk vs. benefit assessment of UVR exposure, which will depend on individual, demographic, cultural, and geographic factors.

5.8. References

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