Vitamin D in the Healthy European Paediatric Population

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ABSTRACT

In recent years, reports suggesting a resurgence of vitamin D deficiency in the Western world, combined with various proposed health benefits for vitamin D supplementation, have resulted in increased interest from health care professionals, the media, and the public. The aim of this position paper is to summarise the published data on vitamin D intake and prevalence of vitamin D deficiency in the healthy European paediatric population, to discuss the health benefits of vitamin D and to provide recommendations for the prevention of vitamin D deficiency in this population. Vitamin D plays a key role in calcium and phosphate metabolism and is essential for bone health. There is insufficient evidence from interventional studies to support vitamin D supplementation for other health benefits in infants, children, and adolescents. The pragmatic use of a serum concentration >50 nmol/L to indicate sufficiency and a serum concentration <25 nmol/L to indicate severe deficiency is recommended. Vitamin D deficiency occurs commonly among healthy European infants, children, and adolescents, especially in certain risk groups, including breastfed infants, not adhering to the present recommendation for vitamin D supplementation, children and adolescents with dark skin living in northern countries, children and adolescents without adequate sun exposure, and obese children. Infants should receive an oral supplementation of 400 IU/day of vitamin D. The implementation should be promoted and supervised by paediatricians and other health care professionals. Healthy children and adolescents should be encouraged to follow a healthy lifestyle associated with a normal body mass index, including a varied diet with vitamin D–containing foods (fish, eggs, dairy products) and adequate outdoor activities with associated sun exposure. For children in risk groups identified above, an oral supplementation of vitamin D must be considered beyond 1 year of age. National authorities should adopt policies aimed at improving vitamin D status using measures such as dietary recommendations, food fortification, vitamin D supplementation, and judicious sun exposure, depending on local circumstances.

Key Words: adolescents, children, infants, vitamin D deficiency, vitamin D supplementation

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Vitamin D was identified in the early 20th century. It is a nutrient, but can also be synthesised in the human skin by sunlight exposure. The main functions of vitamin D are the regulation of calcium and phosphate metabolism (1). It is therefore essential for the maintenance of bone health (2). If not supplied in adequate amounts during childhood, rickets and osteomalacia will develop (3,4).

Other health effects of vitamin D have been proposed for children and adolescents, including prevention of immune-related diseases (asthma, type 1 diabetes mellitus), infectious diseases (respiratory infections, influenza), and cardiovascular disease (5,6). In adults, vitamin D has also been suggested to have a role in neurophysiological functioning and cancer prevention.

Interest in vitamin D has increased considerably in recent years, among health care professionals, the media, and the public. There have been many reports suggesting that vitamin D deficiency is common worldwide, including the Western world, both among adults and children (7–9).

Clinical research on vitamin D has been stimulated by the discovery that many human cell types carry the vitamin D receptor (VDR), and that vitamin D and VDR may play a role in the regulation of cell proliferation and differentiation (2), for example, in cells of the immune system (T cells, macrophages and monocytes, antigen-presenting cells), and in epidermal keratinocytes. The function of vitamin D in these various cell types, however, is not known.

The aim of this position paper is to summarise available data on vitamin D intake and prevalence of vitamin D deficiency in the European paediatric population, to discuss the health effects of vitamin D, and to provide recommendations for the prevention of vitamin D deficiency. The recommendations made in this article will not cover children with chronic diseases. Recommendations for preterm infants have been published recently (10).

METHODS

To identify relevant publications, the databases of PubMed, ISI Web of Science, and the Cochrane Library were searched up to November 2012.

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ABSORPTION, METABOLISM, AND STORAGE OF VITAMIN D

The term vitamin D (calciferol) refers to a group of fat-soluble secosteroids with endocrine function. The 2 major forms are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). These have different side chains: vitamin D_2 has a double bond between C22 and C23 as well as a methyl group at C24, whereas vitamin D_3 has a single bond between C22 and C23 and no methyl group at C24, There are studies suggesting that vitamin D_2 may be less potent than vitamin D_3 in the human body (11); however, this is controversial (12). Vitamins D_2 and D_3 are produced by photolysis with UVB (wavelength 280–315 nm) from sterol precursors. Certain plants and fungi produce vitamin D_2, whereas vitamin D_3 is synthesised by animals (eg, fish, birds, vertebrates) and within the human skin. Dietary vitamin D_2 and D_3 are absorbed in the small intestine. Absorption is dependent on the presence of dietary fats in the intestine to stimulate the production of pancreatic lipase and bile acids (13). Excretion of vitamin D metabolites takes place mainly through the bile, and to a much lesser extent through the urine.

Vitamins D_2 and D_3 are both inactive prohormones that bind to the vitamin D–binding protein to be transported to the liver, where they are converted to 25-hydroxyvitamin D (25(OH)D) by the enzyme 25-hydroxylase. 25(OH)D undergoes further hydroxylation by the enzyme 1α-hydroxylase in the kidney to become the active metabolite 1,25-dihydroxyvitamin D (1,25(OH)D). This second hydroxylation step is regulated by calcium and phosphate concentrations via parathyroid hormone (PTH). 1,25(OH)D is the active metabolite that is involved in many physiological processes, mainly—but not exclusively—in calcium and phosphate metabolism.

VITAMIN D AND SUN EXPOSURE

Vitamin D status depends not only on oral supply, but also—and to a greater extent for most humans—on sun exposure. The human skin can produce vitamin D by sun exposure (UVB), converting the naturally occurring 7-dehydrocholesterol, found in high concentrations in the human skin, to vitamin D_3. The production is dependent on the amount of UVB reaching the skin, and is therefore influenced by skin pigmentation, use of sunscreen, type of clothing, season of the year, and geographical latitude (14–16). Sun exposure cannot result in toxic vitamin D concentrations (5).

In the United States, national surveys showed low dietary vitamin D intake, whereas serum concentrations of vitamin D are usually above the threshold of 50 nmol/L. This observation suggests that sun exposure is the major contributor to vitamin D status in people in the United States (17); however, the amount of sun exposure may vary considerably from person to person. Determining dietary vitamin D requirement is therefore extremely difficult.

A British study calculated the exposure required to gain a number of proposed oral-equivalent doses of vitamin D as functions of latitude, season, skin type, and skin area exposed. The model showed that a daily synthesis of 400 IU is readily achievable through casual sun exposure of face and hands in the midday lunch hour, with no risk of erythema, for all latitudes some of the year and for the entire year at some (low) latitudes. At the higher proposed vitamin D synthesis of 1000 IU, lunchtime sun exposure is still a viable route, but requires exposing greater areas of skin (18).

In this context, it is noteworthy that—according to a recent clinical trial—vitamin D production may be completely abolished when the amount of sunscreen and sun protection factor (SPF) advised by the World Health Organization is used (19,20). One publication reports on a white child in Canada with clinical, biochemical, and radiological evidence of vitamin D deficiency rickets associated with the use of potent sunscreen (SPF 30) (21).

An extremely important but still open question is the determination—within the European population—of the average percentage of vitamin D arising from skin production compared with vitamin D provided by food.

National health authorities should establish recommendations, based on latitude and climate, to ensure sufficient sun exposure without sunscreen to allow vitamin D synthesis while avoiding the development of erythema/sunburn. Reevaluation of sun protection strategies may be needed.

NUTRITIONAL SOURCES OF VITAMIN D

Dietary sources of vitamin D are scarce and include mainly fatty fish (wild salmon, mackerel, eel, anchovy, sardines, swordfish, tuna), and—to a lesser extent—egg yolk and certain fungi (1,5,17). In some European countries, certain foods are fortified with vitamin D. These include milk, dairy products, margarine, breakfast cereals, and fruit juices.

Vitamin D fortification of infant formula is well established. According to Directive 2006/141/EC of the European Commission, vitamin D content must be 40 to 100 IU/100 kcal in infant formula and 40 to 120 IU/100 kcal in follow-on formula (22). In addition, all European countries recommend oral vitamin D supplementation during infancy, and some countries also recommend oral vitamin D supplementation in children (17,23–26).

VITAMIN D AND ADIPOSE TISSUE

Vitamin D is stored in adipose tissue. The regulation of accumulation to and mobilization from the adipose tissue is presently not known. It has been suggested that vitamin D stores in adipose tissue may not be readily available when needed (27).

Obese children, adolescents, and adults have been reported to have lower 25(OH)D serum concentrations than people with normal BMI, probably because of sequestration of vitamin D in the excess adipose tissue. They may need higher amounts of vitamin D to achieve normal 25(OH)D serum concentration (28–30); however, other studies reported that fat and lean mass were not independently associated with vitamin D status in healthy children and adolescents (31). Lifestyle may be another factor influencing the association between obesity and 25(OH)D serum concentration. Currently, there is no evidence that vitamin D deficiency associated with increased body fat has negative consequences on bone mineral density and bone health in the paediatric age group (29,32).

DEFINITION OF VITAMIN D DEFICIENCY

25(OH)D serum concentrations are presently regarded as the best indicator of vitamin D status as a result of nutritional intake and cutaneous synthesis of vitamin D; however, determining vitamin D serum concentrations is not straightforward: one study reported substantial interassay differences of commercially available 25(OH)D tests (33).

There is only scarce evidence on the correlation of 25(OH) serum concentrations with health outcomes, which makes it challenging to define vitamin D deficiency based solely on 25(OH)D serum concentrations. 1,25(OH)D, which is the active form of vitamin D, is not useful as a marker for vitamin D intake and cutaneous synthesis or for the correlation with health outcomes. The main reasons for this are the short serum half-life and the fact that 1,25(OH)D is not regulated by vitamin D intake, but by other factors such as PTH. Therefore, 1,25(OH)D serum concentrations may be normal or even elevated in vitamin D deficiency as a result of secondary hyperparathyroidism.

Most commonly, vitamin D deficiency is considered to be present at 25(OH)D serum concentrations <50 nmol/L, whereas

severe vitamin D deficiency is defined by a threshold <25 nmol/L (17,34). Other definitions of vitamin D deficiency range from 25(OH)D concentrations <20 to 37 nmol/L (35,36).

The use of a 25(OH)D serum concentrations of 50 nmol/L to indicate sufficiency is supported by studies in adult bone health (osteoporosis, bone mineral content, fractures); however, based on clinical outcomes, a final consensus has not been achieved: the US Endocrine Society and the International Osteoporosis Foundation promote a desirable 25(OH)D threshold of 75 for adults, whereas the Institute of Medicine (IOM) defines a 25(OH)D threshold of 50 as normal (17,37–39). The inverse correlation between PTH and 25(OH)D has also been used to determine vitamin D deficiency (40). Infants and children presenting with adverse effects such as rickets and osteomalacia generally have 25(OH)D concentrations <25 nmol/L; however, data on vitamin D concentrations and rickets are confounded by calcium intake (41), highlighted by reports of children with rickets having 25(OH)D concentrations up to 50 nmol/L (42). Therefore, it is difficult to define a reliable 25(OH)D threshold.

For scientific and clinical purposes, the ESPGHAN Committee on Nutrition recommends the pragmatic use of a 25(OH)D serum concentration >50 nmol/L to indicate sufficiency and a serum concentration <25 nmol/L to indicate severe deficiency.

PREVALENCE OF VITAMIN D DEFICIENCY IN THE EUROPEAN PAEDIATRIC POPULATION

Limited data on vitamin D concentrations and vitamin D deficiency among the European paediatric population are available from several countries, including Denmark, England, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Poland, Spain, Switzerland, and Turkey (Table 1) (43–56). Some of the studies included only small numbers of children. No consistent study design and no consistent definitions of vitamin D deficiency were used. Nevertheless, based on these limited reports, a considerable number of healthy European children and adolescents may be expected to be vitamin D deficient.

Vitamin D deficiency is associated with dark skin, insufficient sun exposure (excessive use of sunscreen with high SPF, staying indoors for much of the day, wearing clothes covering most of the skin, living in northern latitudes during wintertime), obesity, chronic liver diseases, chronic intestinal diseases, chronic renal diseases (57), and the use of certain drugs such as anti-epileptic drugs (phenytoin and carbamazepine) and systemic glucocorticoids (58,59).

VITAMIN D INTAKE IN THE EUROPEAN PAEDIATRIC POPULATION

There are only a limited number of studies addressing vitamin D intake in European children, the most recent studies coming from Germany. The DONALD study showed that approximately 80% of children ages 1 to 12 years in Germany do not reach the nutritional vitamin D supply of 200 IU/day as recommended by the German Society for Nutrition (Deutsche Gesellschaft für Ernährung) (60). The EsKiMo study (Ernährungsstudie als KiGGS-Modul) also showed that nutritional vitamin D supply is much lower than recommended in Germany (mean 76 IU/day, recommended 200 IU/day), in both boys and girls. In adolescent boys, vitamin D supply is slightly higher (mean 100 IU/day), but still not sufficient (61).

A Finnish study (62) investigated vitamin D intake (diet and supplementation) in 1768 children and adolescents ages 3, 6, 9, 12, 15, and 18 years in autumn 1980. The dietary vitamin D intake increased with increasing age, whereas the use of supplements decreased. The total vitamin D intake, including both dietary vitamin D and vitamin D from supplements, was highest in the youngest groups and decreased with age. In all age groups, the mean vitamin D intake was below the recommended dietary allowance. The main dietary sources of vitamin D were fortified margarine, fish and fish products, and eggs, providing together approximately 80% of the total vitamin D intake. With a low daily vitamin D intake ranging from 100 to 200 IU, including supplements, the risk of nutritional rickets should be high; however, rickets was uncommon in these age groups in Finland. The children in this study were healthy, active individuals who were obviously sufficiently exposed to sunshine to absorb enough vitamin D through the skin (62).

A recent cross-sectional observational study among 102 schoolchildren (ages 9–13 years) in Spain reported vitamin D intake (2.83 ± 3.27 μg/day) below recommendation (200 IU/day) in 86.9% of the children (43).

HEALTH EFFECTS OF VITAMIN D IN INFANTS (BIRTH TO 12 MONTHS OF AGE), CHILDREN, AND ADOLESCENTS

Bone Health

Healthy bone development in infants and children requires adequate amounts of vitamin D. 1,25(OH)2D increases calcium and phosphate serum concentrations by stimulating calcium and phosphate absorption in the small intestine, by mobilising calcium from bone, and by reabsorption of calcium by distal renal tubules. Increased calcium and vitamin D concentrations lead to decreased PTH production. Inadequate amounts lead to the development of rickets and osteomalacia (3,4,23,63).

Rickets has been a common disease for many centuries (64); however, data on the prevalence of the disease were not available before the late 19th century. At that time, 63% to 80% of infants and children in northern European countries were affected by rickets, according to 1 publication (65).

After the implementation of vitamin D fortification of infant formula and oral supplementation to breast-fed infants in Europe and the United States, rickets became rare in this age group. Between 1986 and 2003, only 166 cases of rickets have been reported in the United States among infants and children 4 to 54 months of age in 22 publications (66). Most (83%) were described as African American or black and almost all (96%) were breast-fed.

In the United Kingdom and other European countries (Germany, Finland) during the 1980s, rickets and osteomalacia were described mainly in children of immigrant families from Pakistan and other Asian populations (67–70). In a Scottish survey, vitamin D deficiency was most pronounced in adolescent girls of Asian origin ages 13 to 15 years, with rickets occurring in 6% (69). Two and 3 years after the launch of a campaign in Glasgow to supplement children and adolescents at risk with 100 IU vitamin D daily, a considerable reduction in the total prevalence of rickets was achieved. Hospital discharges of Asian children with rickets declined rapidly after the start of the campaign (71). One German publication reported 4 cases of neonatal rickets. The mothers of the affected infants were immigrants from the Middle East and had vitamin D deficiency and osteomalacia (68).

Since the 1980s reports of clinically manifest rickets in healthy infants, children, and adolescents have become rare in Europe, probably primarily because of vitamin D supplementation of infants during the first year of life and systematic vitamin D fortification of infant formula. Some studies reported on rare cases of nutritional rickets predominantly among dark-skinned immigrants in several European countries (72–76). In some areas,

TABLE 1. Vitamin D deficiency in children in European countries

Study (reference)	Country	Calendar months	Subjects	Absolute 25(OH)D concentration, nmol/L	% 25(OH)D							
					<10 nmol/L	<12.5 nmol/L	<20 nmol/L	<25 nmol/L	<27.5 nmol/L	<30 nmol/L	<50 nmol/L	<5 nmol/L
Akman et al (44)	Turkey		849 children 1–16 y								8	25.5
Andersen et al (45)	Denmark, Finland, Ireland, Poland	February–March	199 girls ages 12.5 ± 0.5 y					37			92	
Andersen et al (46)	Denmark	January–November	37 Pakistani immigrant girls ages 10.1–14.7 y (mean 12.2 y)	10.9	46			81			95	
Das et al (47)	England	May	182 girls, median age 15.3 y, range 14.7–16.6 y			17				73		
Ginty et al (48)	Switzerland	September–March	196; 92 boys, 104 girls, ages 11–16 y							17 girls, 15 boys		
Grindulis et al (49)	England	January–December	124 Asian children ages 21–23 mo	31.75 ± 16.25		6		40				
Guillemant et al (50)	France	September and March	54 boys, ages 13.4–16.1 y	71.6 ± 19.9 (September), 20.4 ± 6.9 (March)				1.9 (September), 72 (March)				
Lapatsanis et al (51)	Greece	February–March, September–October	178 children ages 3–18 y	46.25 ± 3.25				February–March 13–14 (3–14 y)–47 (15–18 y); September–October 0				
Lawson and Thomas (52)	England	October–November	213 Asian children ages 2 y			0	0	1			17	64
Lehtonen-Veromaa et al (53)	Finland	February–March	191 girls ages 9–15 y, mean 12.9 ± 1.7 y	34.0 ± 13.2								
Lippi et al (54)	Italy		192 children, mean age 7.2 y, age range 1 wk–17.9 y	121					6.2			
Ostergard et al (55)	Denmark		255 healthy 9-month-old infants	77.2 ± 22.7							11	
Rodriguez-Rodriguez et al (43)	Spain		102 children ages 9–13 y	49.6 ± 15.9						8	51	
Stellinga-Boelen et al (56)	The Netherlands	Mid-spring	112 asylum seekers children ages 2–12 y							13	42	

there was a trend towards an increasing incidence of rickets, mainly among immigrant children from south Asia, Africa, and the Middle East (72). One British survey reported an overall incidence of symptomatic vitamin D deficiency in the British West Midlands of 7.5/100,000 children, with those of south Asian origin having an incidence of 38/100,000 and those of black African or African Caribbean origin having an incidence of 95/100,000. Only 1 child of white ethnic origin was reported, giving an incidence of 0.4/100,000 (76).

A retrospective study in London reported on patients with vitamin D deficiency (defined as 25(OH)D concentrations <25 nmol/L) presenting to several children's hospitals with hypocalcaemia or rickets. In the 5-year observation period, 65 children were identified, 97% of them with black or Asian ethnic background; 74% had clinical and/or radiological evidence of rickets (77). Although accurate numbers are not available from most countries, the present incidence of nutritional rickets in Europe is likely to be extremely low.

Some studies have addressed the effects of vitamin D supplementation on bone mineral content. In a longitudinal randomised double-blind placebo-controlled study of breast-fed infants supplemented with 400 IU/day of vitamin D_2 or placebo, and a third group of infants fed with a standard infant formula, the breast-fed groups did not differ significantly in bone mineral content or serum concentrations in the supplemented human milk group (23.53 ± 9.94 vs 36.96 ± 11.86 ng/mL; $P < 0.01$) (78). In contrast, in an observational study, vitamin D supplementation in infancy was found to be associated with increased bone mineral density at specific skeletal sites later in childhood in prepubertal white girls in Switzerland (79).

Six studies with a total of 343 participants receiving placebo and 541 receiving vitamin D contributed data to a recently published meta-analysis on the effects of vitamin D supplementation on bone density in healthy children (80). In these studies, vitamin D supplementation was provided at different doses, from 132 to 400 IU/day to 1400 to 14,000 IU/week. Vitamin D supplementation had no statistically significant effects on total body bone mineral content or on bone mineral density of the hip or forearm. Effects were similar in studies of participants with high compared with low serum vitamin D concentrations, although there was a trend towards a larger effect in participants with low vitamin D concentrations for total body bone mineral content. The authors of the meta-analysis conclude that it is unlikely that vitamin D supplements are beneficial in children and adolescents with normal vitamin D concentration; however, subgroup analyses suggested that supplementation of vitamin D–deficient children and adolescents could result in clinically useful improvements, particularly in lumbar spine bone mineral density and total body bone mineral content (80).

The findings of randomised controlled trials (RCTs) published subsequent to this review are to a great extent consistent with the review's results. In a 12-month RCT of 200 or 400 IU of vitamin D_3 compared with placebo in 221 relatively vitamin D–deficient girls (baseline mean serum 25(OH)D 43 nmol/L), there was no effect on indices of bone health; however, there was an effect on bone mineral density for a subgroup with the FF VDR genotype, indicating an influence of genotype (81).

In summary, the importance of vitamin D for bone health in infants and children is well established. Based on epidemiological experience, vitamin D supplementation during infancy prevents rickets and osteomalacia and is therefore recommended. Vitamin D supplements in vitamin D–deficient children can result in increased bone mineral density, whereas there is no evidence supporting vitamin D supplementation in children and adolescents with normal vitamin D concentrations to improve bone health and linear growth. Based on the above, the ESPGHAN Committee on Nutrition concludes that at present there is insufficient evidence to support or refute routine supplementation of vitamin D beyond infancy.

Muscle Strength

Infants and children with severe vitamin D deficiency and rickets may present with delayed motor development, muscle hypotonia, and weakness. These clinical findings are often associated with hypocalcaemia, but they may also be present without hypocalcaemia (63,82). In a cross-sectional study in postmenarchal adolescent girls in the United Kingdom, 25(OH)D concentrations were significantly associated with muscle power and force (83).

In summary, although there is a well-known association of vitamin D deficiency with impaired muscle function, the ESPGHAN Committee on Nutrition could not identify relevant evidence for a beneficial effect of vitamin D supplementation on muscle function in healthy infants, children, and adolescents.

Prevention of Infectious Diseases

Several studies suggest that infectious diseases are more prevalent among newborns, infants, and children with vitamin D deficiency. There are also data suggesting that vitamin D supplementation may be associated with a reduced risk of respiratory infections.

A hospital-based case-control study carried out in Turkey suggests that newborns with subclinical vitamin D deficiency may have an increased risk of experiencing acute lower respiratory tract infection (84).

A further study, recruiting children with acute lower respiratory infections, that is, bronchiolitis or pneumonia (455 or 50, respectively), as well as control subjects without respiratory symptoms (492) in Canada found no difference in vitamin D concentrations between the children with acute lower respiratory infections and the control group; however, significantly more children admitted to the paediatric intensive care unit with acute lower respiratory infections had vitamin D serum concentrations <50 nmol/L. These findings suggest that the immunomodulatory properties of vitamin D may influence disease severity of acute lower respiratory infections. Remarkably, children with acute lower respiratory infections were significantly more likely to be of North American Indian ancestry compared with the children in the control group. The increased skin melanin of the former may contribute to the reported higher vitamin D deficiency rate of these children (85). Furthermore, the results may be confounded by socioeconomic factors.

One randomised double-blind placebo-controlled trial comparing vitamin D_3 supplements (1200 IU/day) with placebo in 334 schoolchildren in Japan suggested that vitamin D_3 supplementation during the winter may reduce the incidence of influenza A (primary outcome) (relative risk [RR] 0.58; 95% confidence interval [CI] 0.34–0.99; $P = 0.04$), especially in specific subgroups of schoolchildren who had not been taking other vitamin D supplements (RR 0.36; 95% CI 0.17–0.79; $P = 0.006$) and who started nursery school after age 3 years (RR 0.36; 95% CI 0.17–0.78; $P = 0.005$). Analysis of the secondary outcomes of this study showed, however, an increase in influenza B that was not significant (86).

In an cluster-randomised double-blind trial, 247 Mongolian schoolchildren with low vitamin D serum concentrations (median serum 25(OH)D concentrations 17.5 nmol/L) were assigned to receive either vitamin D–fortified milk (300 IU/day) or standard milk during 3 winter months (January–March). Compared with controls, children with vitamin D deficiency receiving vitamin D

reported significantly fewer acute respiratory infections during the study period (mean 0.80 vs 0.45; $P = 0.047$), with a rate ratio of 0.52 (95% CI 0.31–0.89) (87).

A single high-dose oral vitamin D_3 supplementation (100,000 IU) given to 453 children ages 1 to 36 months, diagnosed as having nonsevere or severe pneumonia along with antibiotic treatment for pneumonia, reduced the occurrence of repeat episodes of pneumonia in a double-blind randomised placebo-controlled trial in a hospital in Kabul (RR 0.78; 95% CI 0.64–0.94; $P = 0.01$) (88).

A further randomised placebo-controlled trial carried out in the same setting compared quarterly bolus doses of 100,000 IU vitamin D to placebo for 18 months in 1524 healthy infants in Kabul; however, in this study, this intervention turned out not to be effective to reduce the incidence of pneumonia in infants (89).

In summary, the evidence correlating vitamin D deficiency to the risk of infections is conflicting. The ESPGHAN Committee on Nutrition concludes that although there is some evidence connecting vitamin D supplementation to prevention of infection, the present data are not sufficient to establish recommendations for vitamin D supplementation to prevent infectious diseases in healthy European infants and children.

Prevention of Allergic Diseases

The randomised double-blind placebo-controlled trial of Urashima et al (86) comparing vitamin D_3 supplements (1200 IU/day) with placebo in 330 schoolchildren in Japan reported that in children with a previous diagnosis of asthma, asthma attacks occurred in 2 children receiving vitamin D_3 compared with 12 children receiving placebo (RR 0.17; 95% CI 0.04–0.73; $P = 0.006$). Asthma attacks were a secondary outcome in this study.

On the contrary, the Finnish birth-cohort study reported an association between vitamin D supplementation in infancy and an increased risk of atopy and allergic rhinitis later in life: The prevalence of atopy and allergic rhinitis at age 31 years was higher in participants who had received vitamin D supplementation regularly during the first year compared with others (odds ratio [OR] 1.46, 95% CI 1.4–2.0, and OR 1.66, 95% CI 1.1–1.6, respectively). A similar association was observed for asthma (OR 1.35, 95% CI 0.99–1.8). These associations persisted after adjustment for a wide range of behavioural and social factors (adjusted OR 1.33 for all; $P = 0.01$ for atopy, $P = 0.001$ for allergic rhinitis, and $P = 0.08$ for asthma) (90,91). The authors discuss a possible long-term effect on immune regulation, perhaps by inducing a shift towards a TH2-dominated immune response. An alternative explanation could be the better hygiene of parents who supplemented their children according to the recommendations, compared with parents who did not (91).

In summary, an RCT suggested that asthma attacks, which were a secondary outcome of the study, were reduced in schoolchildren receiving vitamin D supplements. One observational study, however, reported an association between vitamin D supplementation during infancy and an increased risk of allergic diseases later on in life.

The ESPGHAN Committee on Nutrition concludes that available evidence is insufficient to support a relation between vitamin D supplementation in infants and children and prevention of allergic diseases.

Prevention of Type 1 Diabetes Mellitus

There are immunological and animal studies suggesting the hypothesis that vitamin D supplementation may reduce the incidence of type 1 diabetes mellitus (92–95).

The Finnish birth-cohort study, in which 12,055 pregnant women were enrolled, collected data about frequency and dose of vitamin D supplementation and presence of suspected rickets in the first year of life, and the relation to the cumulative incidence of type 1 diabetes mellitus 31 years later. A dietary vitamin D supplementation of 2000 IU daily, which was the official recommendation in Finland, was associated with reduced risk of type 1 diabetes mellitus. The authors conclude that ensuring a high vitamin D supplementation for infants could help to reverse the increasing trend in the incidence of type 1 diabetes mellitus (90).

A systematic review and meta-analysis of studies investigating vitamin D supplementation in early childhood and risk of type 1 diabetes mellitus identified—up to June 2007—5 observational studies (4 case-control studies and 1 cohort study), but no RCT (96). Meta-analysis of the case-control studies showed that the risk of type 1 diabetes mellitus was significantly reduced in infants who were supplemented with vitamin D compared with those who were not supplemented (pooled OR 0.71, 95% CI 0.60–0.84). The result of the cohort study (90) was in agreement with the case-control studies. There was also evidence for a dose-response effect, with infants receiving higher amounts of vitamin D being at lower risk for developing type 1 diabetes mellitus. The authors conclude that vitamin D supplementation in early childhood may protect against the development of type 1 diabetes mellitus; however, adequately powered RCTs are still needed to establish causality as well as dose and duration of supplementation (96).

In summary, there is limited evidence from 5 observational studies and 1 systematic review and meta-analysis suggesting that vitamin D supplementation during infancy may reduce the risk of type 1 diabetes mellitus during childhood and adolescence. No RCT has ever addressed this question.

The ESPGHAN Committee on Nutrition concludes that there are presently insufficient data to prove or refute a relation between vitamin D supplementation and the risk of type 1 diabetes mellitus.

Prevention of Cardiovascular Disease

In adults, there is evidence from observational studies supporting an inverse relation between serum 25(OH)D concentrations and the presence of cardiovascular disease, but evidence for a causal relation between vitamin D intake and development of disease was not found (17).

In children, however, evidence is scarce and only addresses potential indicators of risk factors for cardiovascular disease. A 16-week RCT showed that 2000-IU daily vitamin D_3 supplementation may be effective in optimising vitamin D status and counteracting the progression of aortic stiffness in black youths. Plasma 25(OH)D concentrations in response to the 2000 IU/day supplementation of vitamin D_3 were negatively modulated by adiposity (97).

In summary, there is some evidence relating vitamin D supplementation to a surrogate marker of cardiovascular risk; however, the ESPGHAN Committee on Nutrition concludes that more studies are needed to make any recommendation on the effect of vitamin D supplementation to prevent cardiovascular disease in later life.

VITAMIN D TOXICITY

Few studies have addressed the safety of vitamin D supplementation. There is no agreement on the amount of vitamin D causing toxicity. Prolonged daily intake of vitamin D up to 10,000 IU or up to serum concentrations of 25(OH)D of 240 nmol/L appears to be safe (17).

Acute vitamin D intoxication is rare and usually results from vitamin D doses much higher than 10,000 IU/day, although a well-defined threshold for acute toxicity has not been established. Resulting vitamin D serum concentrations are >375 nmol/L and associated with acute hypercalcaemia and hyperphosphataemia (5,98).

On the contrary, the long-term effects of supplementation at higher doses of vitamin D are not known. Risks cannot be excluded. In adults, a large RCT (36,282 postmenopausal women enrolled in a Women's Health Initiative clinical trial) documented a significantly increased risk of nephrolithiasis (hazard ratio 1.17; 95% CI 1.02–1.34) in the group receiving 1000-mg calcium carbonate with 400 IU of vitamin D_3 daily (99). Obviously, these findings relate to calcium supplementation more than to vitamin D dosage, but demonstrate that calcium and vitamin D supplementation cannot be assessed independently and emphasise the clinical need to rule out hypercalciuria before calcium supplementation. A recent pooled nested case-control study suggested an association between 25(OH)D serum concentrations >100 nmol/L and an increased risk of pancreatic cancer (100).

Despite a shortage of data on high vitamin D intakes in infants, children, and adolescents, the European Food Safety Authority and the IOM have recently set tolerable upper intake levels. Tolerable upper intake levels identified by the European Food Safety Authority are 1000 IU/day for infants 0 to 12 months, 2000 IU/day for children ages 1 to 10 years, and 4000 IU/day for children ages 11 to 17 years (and adults) (101). Tolerable upper intake levels identified by the IOM are 1000 IU/day for infants ages 0 to 6 months, 1500 IU/day for infants ages 7 to 12 months, 2500 IU/day for children ages 1 to 3 years, 3000 IU/day for children ages 4 to 8 years, and 4000 IU/day for children and adolescents ages 9 to 18 years (and adults) (17).

The ESPGHAN Committee on Nutrition notes that reports on vitamin D intoxication are scarce and that there is no agreement on a vitamin D toxicity threshold.

RECOMMENDATIONS FOR THE PREVENTION OF VITAMIN D DEFICIENCY IN EUROPEAN INFANTS, CHILDREN, AND ADOLESCENTS

Vitamin D in the body may come from dietary vitamin D or from synthesis in the skin by sun exposure. The amount of sun exposure may vary considerably from person to person. Determining optimal oral intake of dietary vitamin D is therefore extremely difficult. Furthermore, intake and metabolism of calcium must also be considered.

In 2011, the IOM published its review *Dietary Reference Intakes for Calcium and Vitamin D* (17). To overcome the challenge of differentiating between dietary vitamin D from vitamin D synthesis in the skin by sun exposure, the IOM's approach was to estimate vitamin D requirements under conditions of minimal sun exposure. This approach is adopted by the ESPGHAN Committee on Nutrition.

Infants

Most European countries as well as the United States and Canada, according to the recent reports of both the American Academy of Paediatrics and the IOM, recommend a daily vitamin D intake of at least 400 IU/day for infants during the first year of life (17,23,102). The Committee on Nutrition of the French Society of Paediatrics, however, recently confirmed their recommendation with higher doses of vitamin D supplementation for infants (breast-fed infants: 1000–1200 IU/day; children younger than 18 months of age receiving milk supplemented with vitamin D: 600–800 IU/day; children younger than 18 months of age receiving milk not supplemented with vitamin D: 1000–1200 IU/day) (24).

The ESPGHAN Committee on Nutrition recommends a daily oral supplementation of 400 IU vitamin D for all infants during the first year of life. This measure will bring most infants (age 0–12 months) to a 25(OH)D concentration of 50 nmol/L and prevent vitamin D deficiency–associated diseases (17). Nevertheless, there is evidence that many infants do not receive the recommended supplementation (66,103). It is therefore important that paediatricians and other health care professionals ensure that these efficient preventive strategies are put into practice and that all infants in Europe receive daily vitamin D supplements appropriate for their age.

Children and Adolescents

A daily supply of 400 IU vitamin D may not be sufficient in children older than 12 months. The IOM has therefore decided to increase the estimated average requirements of 400 IU vitamin D daily for this age group and to propose recommended dietary allowances of 600 IU vitamin D daily to all children and adolescents ages 2 to 18 years (17). Healthy children at increased risk for vitamin D deficiency may even need >600 IU vitamin D to reach a 25(OH)D threshold of 50 nmol/L (12,104). Increased risk in healthy children is associated with dark skin, lack of adequate sun exposure (excessive use of sunscreen with high SPF, staying indoors for much of the day, wearing clothes covering most of the skin, living in northern latitudes during wintertime), and obesity.

The Committee on Nutrition of the French Society of Paediatrics recently recommended supplementing higher doses of oral vitamin D, not only for infants but also for children up to the age of 5 years and adolescents from 10 to 18 years of age (2 doses of 80,000–100,000 IU every winter in November and February) (24).

The ESPGHAN Committee on Nutrition summarises that although available evidence shows low vitamin D intake among European children and adolescents, as well as a high prevalence of low vitamin D serum concentrations (without clinical symptoms), available evidence to support vitamin D supplementation beyond infancy is not strong, with uncertainties regarding cutoff values for defining deficiency and requirements; however, the ESPGHAN Committee on Nutrition recommends that national authorities adopt policies aimed at improving vitamin D status using measures such as dietary recommendations, food fortification, vitamin D supplementation, and judicious sun exposure, depending on local circumstances.

CONCLUSIONS

Vitamin D plays a key role in calcium and phosphate metabolism and is essential for bone health in infants, children, and adolescents.

There is insufficient evidence from interventional studies to support vitamin D supplementation for other health benefits in infants, children, and adolescents.

Vitamin D deficiency occurs commonly among healthy European infants, children, and adolescents, especially in certain risk groups.

Risk groups include breast-fed infants not adhering to the present recommendation of vitamin D supplementation, children and adolescents with dark skin living in northern countries, children and adolescents without adequate sun exposure (excessive use of sunscreen with high SPF, staying indoors for much of the day, wearing clothes covering most of the skin, living in northern latitudes during wintertime), and obese children.

RECOMMENDATIONS

1. The pragmatic use of a serum 25(OH)D concentration >50 nmol/L to indicate sufficiency and a serum concentration <25 nmol/L to indicate severe deficiency is recommended.

2. All infants should receive an oral supplementation of 400 IU/day of vitamin D. The implementation should be ensured and supervised by paediatricians and other health care professionals.
3. In accordance with the European Food Safety Authority, the upper limit of safety is set at 1000 IU/day for infants, 2000 IU/day for children ages 1 to 10 years, and 4000 IU/day for children and adolescents ages 11 to 17 years.
4. Healthy children and adolescents should be encouraged to follow a healthy lifestyle associated with a normal BMI and including a healthy diet with vitamin D–containing foods (eg, fish, eggs, dairy products) and adequate outdoor activities with associated sun exposure.
5. For children in risk groups identified above, oral supplementation of vitamin D must be considered beyond 1 year of age.
6. National authorities should adopt policies aimed at improving vitamin D status using measures such as dietary recommendations, food fortification, vitamin D supplementation, and judicious sun exposure, depending on local circumstances.

REFERENCES

1. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess (Full Rep)* 2009;183:1–420.
2. DeLuca HF, Schnoes HK. Vitamin D: recent advances. *Annu Rev Biochem* 1983;52:411–39.
3. Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? *Am J Clin Nutr* 2004;80 (6 suppl):1725S–9.
4. Thacher TD, Fischer PR, Strand MA, et al. Nutritional rickets around the world: causes and future directions. *Ann Trop Paediatr* 2006;26:1–16.
5. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
6. Christakos S, DeLuca HF. Minireview: vitamin D: is there a role in extraskeletal health? *Endocrinology* 2011;152:2930–6.
7. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008;87:1080S–6.
8. Mithal A, Wahl DA, Bonjour JP, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009;20:1807–20.
9. Rovner AJ, Stallings VA, Kawchak DA, et al. High risk of vitamin D deficiency in children with sickle cell disease. *J Am Diet Assoc* 2008;108:1512–6.
10. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010;50:85–91.
11. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. *Am J Clin Nutr* 2006;84:694–7.
12. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 2008;93:677–81.
13. Haddad JG Jr, Hahn TJ. Natural and synthetic sources of circulating 25-hydroxyvitamin D in man. *Nature* 1973;244:515–7.
14. Gilchrest BA. Sun exposure and vitamin D sufficiency. *Am J Clin Nutr* 2008;88:570S–7S.
15. Matsuoka LY, Ide L, Wortsman J, et al. Sunscreens suppress cutaneous vitamin D3 synthesis. *J Clin Endocrinol Metab* 1987;64:1165–8.
16. Engelsen O, Brustad M, Aksnes L, et al. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem Photobiol* 2005;81:1287–90.
17. Ross AC, Taylor CL, Yaktine AL, et al. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011.
18. Webb AR, Engelsen O. Ultraviolet exposure scenarios: risks of erythema from recommendations on cutaneous vitamin D synthesis. *Adv Exp Med Biol* 2008;624:72–85.
19. Ultraviolet radiation and the INTERSUN Programme. Individual protection against UV. What are simple action steps for sun protection? *http://www.who.int/uv/faq/protect/en*. Accessed May 1, 2013.
20. Faurschou A, Beyer DM, Schmedes A, et al. The relation between sunscreen layer thickness and vitamin D production after ultraviolet B exposure: a randomized clinical trial. *Br J Dermatol* 2012;167:391–5.
21. Zlotkin S. Vitamin D concentrations in Asian children living in England. Limited vitamin D intake and use of sunscreens may lead to rickets. *BMJ* 1999;318:1417.
22. Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. *Official Journal of the European Union* 2006.
23. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142–52.
24. Vidailhet M, Mallet E, Bocquet A, et al. Vitamin D: still a topical matter in children and adolescents. A position paper by the Committee on Nutrition of the French Society of Paediatrics. *Arch Pediatr* 2012;19:316–28.
25. Federal Commission for Nutrition. *Vitamin D Deficiency: Evidence, Safety, and Recommendations for the Swiss Population. Expert Report of the FCN*. Zurich: Federal Office for Public Health; 2012.
26. Arundel P, Ahmed SF, Allgrove J, et al. British paediatric and adolescent bone group's position statement on vitamin D deficiency. *BMJ* 2012;345:e8182.
27. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72:690–3.
28. Blum M, Dallal GE. Dawson-Hughes B Body size and serum 25 hydroxy vitamin D response to oral supplements in healthy older adults. *J Am Coll Nutr* 2008;27:274–9.
29. Kremer R, Campbell PP, Reinhardt T, et al. Vitamin D status and its relationship to body fat, final height, and peak bone mass in young women. *J Clin Endocrinol Metab* 2009;94:67–73.
30. Alemzadeh R, Kichler J, Babar G, et al. Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. *Metabolism* 2008;57:183–91.
31. Weng FL, Shults J, Leonard MB, et al. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. *Am J Clin Nutr* 2007;86:150–8.
32. Lenders CM, Feldman HA, Von Scheven E, et al. Relation of body fat indexes to vitamin D status and deficiency among obese adolescents. *Am J Clin Nutr* 2009;90:459–67.
33. Snellman G, Melhus H, Gedeborg R, et al. Determining vitamin D status: a comparison between commercially available assays. *PLoS One* 2010;5:e11555.
34. Greer FR. 25-Hydroxyvitamin D: functional outcomes in infants and young children. *Am J Clin Nutr* 2008;88:529S–33S.
35. Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 2008;122:398–417.
36. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998;338:777–83.
37. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911–30.
38. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 2010;21:1151–4.
39. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, et al. Benefit-risk assessment of vitamin D supplementation. *Osteoporos Int* 2010;21:1121–32.
40. Weaver CM, Fleet JC. Vitamin D requirements: current and future. *Am J Clin Nutr* 2004;80 (6 suppl):1735S–9.
41. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? *J Steroid Biochem Mol Biol* 2004;89–90:611–4.
42. Molla AM, Badawi MH, Al-Yaish S, et al. Risk factors for nutritional rickets among children in Kuwait. *Pediatr Int* 2000;42:280–4.
43. Rodriguez-Rodriguez E, Aparicio A, Lopez-Sobaler AM, et al. Vitamin D status in a group of Spanish schoolchildren. *Minerva Pediatr* 2011;63:11–8.
44. Akman AO, Tumer L, Hasanoglu A, et al. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. *Pediatr Int* 2011;53:968–73.

45. Andersen R, Molgaard C, Skovgaard LT, et al. Teenage girls and elderly women living in northern Europe have low winter vitamin D status. *Eur J Clin Nutr* 2005;59:533–41.
46. Andersen R, Molgaard C, Skovgaard LT, et al. Pakistani immigrant children and adults in Denmark have severely low vitamin D status. *Eur J Clin Nutr* 2008;62:625–34.
47. Das G, Crocombe S, McGrath M, et al. Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Arch Dis Child* 2006;91:569–72.
48. Ginty F, Cavadini C, Michaud PA, et al. Effects of usual nutrient intake and vitamin D status on markers of bone turnover in Swiss adolescents. *Eur J Clin Nutr* 2004;58:1257–65.
49. Grindulis H, Scott PH, Belton NR, et al. Combined deficiency of iron and vitamin D in Asian toddlers. *Arch Dis Child* 1986;61:843–8.
50. Guillemant J, Le HT, Maria A, et al. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. *Osteoporos Int* 2001;12:875–9.
51. Lapatsanis D, Moulas A, Cholevas V, et al. Vitamin D: a necessity for children and adolescents in Greece. *Calcif Tissue Int* 2005;77:348–55.
52. Lawson M, Thomas M. Vitamin D concentrations in Asian children aged 2 years living in England: population survey. *BMJ* 1999;318:28.
53. Lehtonen-Veromaa MK, Mottonen TT, Nuotio IO, et al. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. *Am J Clin Nutr* 2002;76:1446–53.
54. Lippi G, Montagnana M, Targher G. Vitamin D deficiency among Italian children. *CMAJ* 2007;177:1529–30.
55. Ostergard M, Arnberg K, Michaelsen KF, et al. Vitamin D status in infants: relation to nutrition and season. *Eur J Clin Nutr* 2011;65:657–60.
56. Stellinga-Boelen AA, Wiegersma PA, Storm H, et al. Vitamin D levels in children of asylum seekers in The Netherlands in relation to season and dietary intake. *Eur J Pediatr* 2007;166:201–6.
57. Geary DF, Hodson EM, Craig JC, et al. Interventions for bone disease in children with chronic kidney disease. *Cochrane Database Syst Rev* 2010;1:CD008327.
58. Leonard MB, Feldman HI, Shults J, et al. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. *N Engl J Med* 2004;351:868–75.
59. Wetzsteon RJ, Shults J, Zemel BS, et al. Divergent effects of glucocorticoids on cortical and trabecular compartment BMD in childhood nephrotic syndrome. *J Bone Miner Res* 2009;24:503–13.
60. Kersting M. Die Kalzium- und Vitamin-D-Zufuhr von Kindern. Ausgewählte Ergebnisse der DONALD Studie mit dem Fokus auf den Verzehr von Milchprodukten. *Ernährungs Umschau* 2008;55:5.
61. Mensink GB, Bauch A, Vohmann C, et al. [EsKiMo: the nutrition module in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007;50:902–8.
62. Lamberg-Allardt C, Ojaniemi R, Ahola M, et al. The vitamin D intake of children and adolescents in Finland. *Hum Nutr Appl Nutr* 1984;38:377–82.
63. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116:2062–72.
64. Rajakumar K. Vitamin D, cod-liver oil, sunlight, and rickets: a historical perspective. *Pediatrics* 2003;112:e132–5.
65. Johannessen A. Bemerkungen über das Vorkommen von Rachitis in Norwegen. *Jahrbuch Kinderheilkunde Phys Erziehung* 1898;46:13.
66. Weisberg P, Scanlon KS, Li R, et al. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am J Clin Nutr* 2004;80 (6 suppl):1697S–705S.
67. Ford JA, Colhoun EM, McIntosh WB, et al. Rickets and osteomalacia in the Glasgow Pakistani community, 1961–71. *Br Med J* 1972;2:677–80.
68. Park W, Paust H, Kaufmann HJ, et al. Osteomalacia of the mother—rickets of the newborn. *Eur J Pediatr* 1987;146:292–3.
69. O'Hare AE, Uttley WS, Belton NR, et al. Persisting vitamin D deficiency in the Asian adolescent. *Arch Dis Child* 1984;59:766–70.
70. Robertson I, Glekin BM, Henderson JB, et al. Nutritional deficiencies among ethnic minorities in the United Kingdom. *Proc Nutr Soc* 1982;41:243–56.
71. Dunnigan MG, Glekin BM, Henderson JB, et al. Prevention of rickets in Asian children: assessment of the Glasgow campaign. *Br Med J (Clin Res Ed)* 1985;291:239–42.
72. Ahmed SF, Franey C, McDevitt H, et al. Recent trends and clinical features of childhood vitamin D deficiency presenting to a children's hospital in Glasgow. *Arch Dis Child* 2011;96:694–6.
73. Beck-Nielsen SS, Jensen TK, Gram J, et al. Nutritional rickets in Denmark: a retrospective review of children's medical records from 1985 to 2005. *Eur J Pediatr* 2009;168:941–9.
74. Brok J, Huusom L, Cortes D. [Severe vitamin D deficiency in children born in Denmark of dark-skinned women]. *Ugeskr Laeger* 2011;173:1862–3.
75. Pedersen P, Michaelsen KF, Molgaard C. Children with nutritional rickets referred to hospitals in Copenhagen during a 10-year period. *Acta Paediatr* 2003;92:87–90.
76. Callaghan AL, Moy RJ, Booth IW, et al. Incidence of symptomatic vitamin D deficiency. *Arch Dis Child* 2006;91:606–7.
77. Ladhani S, Srinivasan L, Buchanan C, et al. Presentation of vitamin D deficiency. *Arch Dis Child* 2004;89:781–4.
78. Greer FR, Marshall S. Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements. *J Pediatr* 1989;114:204–12.
79. Zamora SA, Rizzoli R, Belli DC, et al. Vitamin D supplementation during infancy is associated with higher bone mineral mass in prepubertal girls. *J Clin Endocrinol Metab* 1999;84:4541–4.
80. Winzenberg T, Powell S, Shaw KA, et al. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. *BMJ* 2011;342:c7254.
81. Molgaard C, Larnkjaer A, Cashman KD, et al. Does vitamin D supplementation of healthy Danish Caucasian girls affect bone turnover and bone mineralization? *Bone* 2010;46:432–9.
82. David L. Common vitamin-D-deficiency rickets. *Rickets* 1991;21:107–22.
83. Ward KA, Das G, Berry JL, et al. Vitamin D status and muscle function in post-menarchal adolescent girls. *J Clin Endocrinol Metab* 2009;94:559–63.
84. Karatekin G, Kaya A, Salihoglu O, et al. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *Eur J Clin Nutr* 2009;63:473–7.
85. McNally JD, Leis K, Matheson LA, et al. Vitamin D deficiency in young children with severe acute lower respiratory infection. *Pediatr Pulmonol* 2009;44:981–8.
86. Urashima M, Segawa T, Okazaki M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010;91:1255–60.
87. Camargo CA Jr, Ganmaa D, Frazier AL, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics* 2012;130:e561–7.
88. Manaseki-Holland S, Qader G, Isaq Masher M, et al. Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial. *Trop Med Int Health* 2010;15:1148–55.
89. Manaseki-Holland S, Maroof Z, Bruce J, et al. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. *Lancet* 2012;379:1419–27.
90. Hypponen E, Laara E, Reunanen A, et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;358:1500–3.
91. Hypponen E, Sovio U, Wjst M, et al. Infant vitamin D supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann N Y Acad Sci* 2004;1037:84–95.
92. Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. *Annu Rev Nutr* 2003;23:117–45.
93. Mathieu C, Waer M, Laureys J, et al. Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3. *Diabetologia* 1994;37:552–8.
94. Zella JB, DeLuca HF. Vitamin D and autoimmune diabetes. *J Cell Biochem* 2003;88:216–22.

95. Giulietti A, Gysemans C, Stoffels K, et al. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice. *Diabetologia* 2004;47:451–62.
96. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 2008;93:512–7.
97. Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab* 2010;95:4584–91.
98. Rosen CJ. Clinical practice. Vitamin D insufficiency. *N Engl J Med* 2011;364:248–54.
99. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669–83.
100. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: cohort consortium vitamin D pooling project of rarer cancers. *Am J Epidemiol* 2010;172:81–93.
101. EFSA Panel on Dietetic Products NaACA. Scientific opinion on the tolerable upper intake level of vitamin D. *EFSA J* 2012;10:45.
102. Wabitsch M, Koletzko B, Moss A. Vitamin D status in infancy, childhood and adolescence. *Monatsschr Kinderheilkd* 2011;159:1084–184.
103. Dratva J, Merten S, Ackermann-Liebrich U. Vitamin D supplementation in Swiss infants. *Swiss Med Wkly* 2006;136:473–81.
104. Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the lifecycle: physiology and biomarkers. *Am J Clin Nutr* 2008;88:500S–6S.