Vitamin D in the Healthy European Paediatric Population


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 healthcare 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 breastfeeding 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 healthcare 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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METHODS

To identify relevant publications, the databases of PubMed, ISI Web of Science, and the Cochrane Library were searched up to November 2012.
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 D₃. 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).

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)D 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)₂D 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)₂D is not regulated by vitamin D intake, but by other factors such as PTH. Therefore, 1,25(OH)₂D 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 deficiency 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 using 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 (Ermährungstudie 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>
<thead>
<tr>
<th>Study (reference)</th>
<th>Country</th>
<th>Calendar months</th>
<th>Subjects</th>
<th>Absolute 25(OH)D concentration, nmol/L</th>
<th>% 25(OH)D &lt;10 nmol/L</th>
<th>&lt;12.5 nmol/L</th>
<th>&lt;20 nmol/L</th>
<th>&lt;25 nmol/L</th>
<th>&lt;27.5 nmol/L</th>
<th>&lt;30 nmol/L</th>
<th>&lt;50 nmol/L</th>
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<tbody>
<tr>
<td>Akman et al (44)</td>
<td>Turkey</td>
<td>849 children 1–16 y</td>
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<td>Andersen et al (45)</td>
<td>Denmark, Finland, Iceland, Poland</td>
<td>February–March</td>
<td>199 girls ages 12.5 ± 0.5 y</td>
<td>10.9</td>
<td>46</td>
<td>81</td>
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<td>Andersen et al (46)</td>
<td>Denmark</td>
<td>January–November</td>
<td>37 Pakistani immigrant girls ages 10.1–14.7 y (mean 12.2 y)</td>
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<td>73</td>
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<td>Das et al (47)</td>
<td>England</td>
<td>May</td>
<td>182 girls, median age 15.3 y, range 14.7–16.6 y</td>
<td>17 girls, 15 boys</td>
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<td>Ginty et al (48)</td>
<td>Switzerland</td>
<td>September–March</td>
<td>196; 92 boys, 104 girls, ages 11–16 y</td>
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<td>Guillemant et al (50)</td>
<td>France</td>
<td>September and March</td>
<td>54 boys, ages 13.4–16.1 y (September), 20.4 ± 6.9 (March)</td>
<td>1.9 (September), 72 (March)</td>
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<td>Lapatsanis et al (51)</td>
<td>Greece</td>
<td>February–March, September–October</td>
<td>178 children ages 3–18 y</td>
<td>46.25 ± 3.25</td>
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<td>Lawson and Thomas (52)</td>
<td>England</td>
<td>October–November</td>
<td>213 Asian children ages 2 y</td>
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<td>17</td>
<td>64</td>
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<td>Lehtonen-Vesomaa et al (53)</td>
<td>Finland</td>
<td>February–March</td>
<td>191 girls ages 9–15 y, mean 12.9 ± 1.7 y</td>
<td>34.0 ± 132</td>
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<td>Lippi et al (54)</td>
<td>Italy</td>
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<td>192 children, mean age 7.2 y, age range 1 wk–17.9 y</td>
<td>121</td>
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<td>Ostergard et al (55)</td>
<td>Denmark</td>
<td></td>
<td>255 healthy 9-month-old infants</td>
<td>77.2 ± 22.7</td>
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<td>Rodriguez-Rodriguez et al (43)</td>
<td>Spain</td>
<td></td>
<td>102 children ages 9–13 y</td>
<td>40.6 ± 15.9</td>
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<tr>
<td>Stellinga-Boelen et al (56)</td>
<td>The Netherlands</td>
<td>Mid-spring</td>
<td>112 asylum seekers children ages 2–12 y</td>
<td>13</td>
<td>42</td>
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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, 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 D3 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 D3 supplements (1200 IU/day) with placebo in 334 schoolchildren in Japan suggested that vitamin D3 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 D₃ supplementation (100,000 IU) given to 453 children ages 1 to 36 months, diagnosed as having noneurose 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 D₃ 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 D₃ 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/day vitamin D₃ 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 D₃ 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, 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 skin 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


101. EFSA Panel on Dietetic Products NaACA. Scientific opinion on the tolerable upper intake level of vitamin D. EFSA J 2012;10:45.