Check for updates

Vitamin D in pediatric age: Current evidence, recommendations, and misunderstandings

Antonio Corsello[1†], Giulia C. I. Spolidoro[1†], Gregorio P. Milani[1,2*†] and Carlo Agostoni[1,2†]

[1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [2]Pediatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

In recent years vitamin D has been in the spotlight of many researchers for its possible role in various disorders, including autoimmune and infectious diseases. Even if vitamin D deficiency remains a major public health problem, its symptomatic manifestations are less and less common in clinical practice, and pediatric age represents a "gray area" where vitamin D supplementation is often administered in the absence of an effective evaluation of its status. Moreover, a poor knowledge about different definitions of "deficiency," "insufficiency," and similar terms is spread among clinicians, while guidelines are not univocal, especially after the first year of life. The aim of this brief opinion paper is to sum up recent evidence about vitamin D status and its supplementation in pediatrics, in order to better clarify a common definition of its deficiency. The aim of this opinion article is to raise awareness on this topic among clinicians and encourage a discussion on the real need for routine 25-hydroxycholecalciferol serum evaluation and its supplementation.

1. Introduction

The role of vitamin D for calcium metabolism and, especially, for the treatment of rickets was first identified in 1922 by the American biochemist Elmer McCollum (1879–1967) [1]. After his observations, thousands of papers have shed light on its important and multifaceted function for human health, not only regarding the musculoskeletal system [2, 3]. At the same time, several investigators have observed that a surprising number of patients may present deficient levels of this micronutrient, regardless of their age and origin [4–6]. Vitamin D deficiency remains a major public health problem, even after a century since its discovery [7].

At least two under-rated factors might contribute to the persistence of this issue: the lack of a common definition of vitamin D deficiency and the existence of partially contrasting recommendations on vitamin D prophylaxis.

The aim of this opinion article is to highlight recent evidence about vitamin D status and its supplementation in pediatrics, to better clarify a common definition of its deficiency. Our goal is to raise awareness among clinicians of this topic and encourage a discussion on the real need for routine 25-hydroxycholecalciferol serum evaluation and supplementation.

2. The effects in pediatric age: Bone health and immune function

Vitamin D plays an important role in bone growth and remodeling by osteoblasts and osteoclasts and is essential to maintain calcium, phosphate, and magnesium body homeostasis by regulating intestinal absorption, and renal absorption/excretion, alongside the parathyroid hormone (PTH). Plasma calcium and phosphate are mainly influenced by the active form of vitamin D (1α,25-dihydroxyvitamin D) and PTH, while a minor role is also attained by other humoral factors (8).

Magnesium is influenced, though to a lesser degree, by the same factors that control calcium, and it indirectly influences calcium by altering PTH synthesis and secretion in response to hypocalcemia and by assisting in the activation of vitamin D (9). Indeed, magnesium functions as a cofactor in many kidneys and liver enzymatic reactions and it is required by all the enzymes that intervene in vitamin D metabolization (10). Consequently, a lack of magnesium may result in disruption to the calcium/phosphate homestays regulated by active vitamin D/PTH and may cause vitamin D–resistant hypocalcemia (9, 10). On the other hand, vitamin D deficiency or overload may result in hypermagnesemia (magnesium not utilized) or hypomagnesemia (excessive consumption of magnesium).

In the early stages, vitamin D deficiency results in impaired calcium intestinal absorption and consequent low serum calcium levels (hypocalcemia). In turn, hypocalcemia stimulates PTH secretion which acts to normalize serum calcium by reducing renal calcium excretion, increasing renal phosphate excretion, and stimulating renal production of active vitamin D. High levels of PTH (hyperparathyroidism) also boost osteoclast activity which determines bone calcium release. The combination of low serum phosphate levels (hypophosphatasemia) and increased osteoclast activity results in bone demineralization (11).

In children, severe vitamin D deficiency may cause rickets, a childhood metabolic bone disease caused by under-mineralization of the growing bone. Following the growth plate closure, in older children and adults, the term "osteomalacia" is used to describe the demineralization of bone at sites of bone remodeling (12).

Vitamin D positive effects on the innate immune system are well known since the discovery of its historical beneficial effects on mycobacterium tuberculosis infection (13, 14). Vitamin D modulates monocytes, macrophages, dendritic cell responses, and the production of interleukins (15). Autoimmune diseases (ADs) are caused by an erroneous activation of the immune system, with subsequent destruction of tissues by autoreactive immune cells, which can react against self-antigens (16). Among the causes contributing to the development of ADs, an insufficient vitamin D serum concentration might play a significant role, as proven by epidemiologic findings of higher incidences of ADs among countries with lower sun exposures and high prevalence of vitamin D insufficiency (17, 18).

Recent studies found the vitamin D's involvement in the suppression of T lymphocyte proliferation and adaptive immune system, causing a shift from a Th1 to a Th2 phenotype and a subsequent alteration in the differentiation and maturation of T cells, inducing T regulatory cells function and immune self-tolerance (19, 20). Moreover, B lymphocytes have been found to express vitamin D receptors, which, when activated, can inhibit the differentiation into plasma cells and modulate immunoglobulin production (21). All these

effects could explain the possible connection between variable vitamin D serum levels and the probability to develop an AD (22).

Studies conducted among children with type 1 diabetes (T1D) found a significant difference in the incidence of disease according to the gradient of sun exposure in different countries and the seasonal variability (23, 24). Conflicting evidence has been found about the hypothesis that vitamin D supplementation could reduce the probability to develop T1D in early life, even if a protective correlation between minor incidence and higher serum levels has been found in some studies (25–27). Other studies observed a delay in the progression of beta-cells destruction when vitamin D is administered in an early stage of onset and diagnosis (28–30). Two meta-analyses found that the risk of developing T1D was significantly reduced in children supplemented with vitamin D (27, 31). For these reasons, avoiding a vitamin D insufficiency in patients at high risk for developing T1D is suggested, even if evidence for a specific supplementation in these subjects is lacking (17). Concerning other ADs, low 25(OH)D sera levels have been associated with the development of autoimmune thyroiditis, such as Hashimoto's disease and Grave's disease, both in children and adults (32–34).

Vitamin D also acts as an enhancement of the intestinal defense mechanisms, locally regulating the mucosal immune system and preventing harmful microbial proliferation (35, 36). For instance, an association between lower vitamin D concentrations and an increased risk of developing IBD has been suggested (37–40). This evidence can be strengthened by the reduced vitamin receptors expression found in the colon mucosa of mice affected by IBD when compared to healthy controls, with an increased production of Th1 and Th17 lymphocytes and inflammatory cytokines in the gastrointestinal tract (41, 42). For these reasons, according to recent interventional studies, a vitamin D supplementation can be considered a potential effective and safe therapeutic choice in patients with IBD (43–46).

Emerging evidence from various meta-analyses supposes a plausible role of low vitamin D levels in many other ADs, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, and vitamin D receptors polymorphisms have been associated with higher incidences of several ADs (47–51). However, optimal vitamin D concentrations that could reduce the possible occurrence of ADs are not clear yet, even if levels higher than 20 ng/mL (about 50 nmol/L) should be considered sufficient to maintain the physiologic calcemic and non-calcemic functions of vitamin D (52).

3. Deficiency and insufficiency: Words not to be confused

Vitamin D deficiency has been recognized in a wide range of pathological conditions, from allergic to immune-mediated diseases such as diabetes or chronic inflammatory bowel diseases (25, 27, 53–55). More recently, vitamin D deficiency and its eventual supplementation have been even considered linked with COVID-19 symptoms and prevention, generally without any proof of a cause-and-effect relationship, including reverse causality (56–59).

Although cases of rickets and clinical manifestations of symptomatic vitamin D deficiency are actually rare, many studies worldwide have shown high rates of vitamin D deficiency and insufficiency (measured as the serum concentration of

25-hydroxycholecalciferol, 25(OH)D) in the pediatric population, with rates ranging on average between 40 and 75%, even in developed countries (60–63). The low rates of sunlight exposure in Nordic countries and the limited production in Southern ones, related to the natural protection of dark skin phenotypes toward light together with a diffused poor nutritional status, may represent possible cofactors of this evidence (64–66). Variable percentages of insufficiency/deficiency reported in the literature may be linked also to the variability of the screening methods, which often use improper terminologies and cut-offs. The universal application of unnecessary (and expensive) routine supplementations in a healthy population does not have a scientific rationale. Moreover, there is currently no scientific evidence to recommend vitamin D supplementation in the treatment and prevention of diseases like asthma, allergic, or immune disorders (67).

Consequently, it might be considered if and how a vitamin D deficiency may be responsible for so many different diseases. A meaningful point is represented by the lack of knowledge among clinicians about the current reference values of hypovitaminosis, probably related to the frequent and ambiguous use of terms such as "deficiency," "sufficiency," "adequacy," or "insufficiency" (68, 69). As a consequence, surveys conducted on the general population and based on inappropriate cut-off values have sometimes led to unnecessary supplementations in healthy populations (52, 70, 71).

The threshold value about hypovitaminosis (and therefore "deficiency," and not "insufficiency") is debated (72–74), but according to some authorities we suggest considering adequate levels above 30 ng/mL (75 nmol/L). Values included in the range of 20–29 ng/mL (50–74 nmol/L) are then to be considered "insufficient" (Table 1) (75, 76). Furthermore, with the exception of subjects at risk of hypovitaminosis or those who may require supplementation (e.g., inadequate dietary intake), no screening of serum 25(OH)D dosages is recommended, nor an arbitrary or medically unjustified exogenous administration should be generally performed before verifying an effective deficiency/insufficiency (77, 78).

4. Risk factors and current evidence

Several risk factors are associated with vitamin D deficiency in children and may be considered by clinicians upon deciding whether blood serum screening and/or vitamin D supplementation should be started.

The levels of vitamin D may also be influenced by ethnicity, genetic predispositions, and skin types, with darker skin types requiring more sunlight exposure to absorb vitamin D (72, 79–81). Lastly, there is a risk for vitamin D deficiency also for pediatric and adult subjects who are treated with certain medications (e.g., anti-epileptics, and glucocorticoids) and for patients with chronic diseases which prevent vitamin D intestinal absorption, such as celiac disease or cystic fibrosis, but also diseases which impact the

liver, or the kidneys, preventing physiologic vitamin D metabolism (72, 82–85).

Another major risk factor of vitamin D deficiency is the insufficient sunlight exposure, which affects the body's capacity to produce vitamin D (86, 87). Therefore, spending most of the time indoors or living in regions where the weather is mostly cloudy, and cold represents a risk for vitamin D deficiency. Accordingly, other factors such as latitude, and altitude, which directly impact the sun angle and ultraviolet radiations may impact vitamin D status (72).

Another known risk factor for vitamin D deficiency is related to age, with infants being more at risk of developing hypovitaminosis. Under 12 months of age, the risk is even higher for premature babies, who have less vitamin D deposits, and in children who are breastfed (88). Indeed, human breast milk is almost lacking in proper amounts of vitamin D, with concentrations that range from 10 to 80 IU/L in healthy lactating women, depending on the method of measurement (88, 89).

Considering the first 6 months of age, mothers who are lacking in vitamin D, supply even fewer amounts to their infants, while, higher breast milk quantities of vitamin D positively correlate with higher mother 25(OH)D serum levels (90–92). The rapid conversion of cholecalciferol to 25(OH)D in the mother's liver represents another obstacle to a high passage of vitamin D, and it is maybe one of the main reasons for the 0.2 ratio between maternal and breast milk 25(OH)D (93).

The main problem of infants exclusively breastfed by mothers supplemented with 400 IU/day, the typical amount assumed during pregnancy, is the typical deficiency reported in this population (94, 95). Moreover, breastfed infants typically lack in adequate sunlight exposure and the administration could be affected by poor parental compliance (96, 97).

When exclusive breastfeeding is no longer sufficient to meet all the nutritional needs, it is, therefore, necessary to introduce other foods and liquids. This period is known as "complementary feeding" or "weaning," and should generally be started after 6 months of life, with partial breastfeeding that may continue approximately up to 2 years of age (98).

Low dietary intake of vitamin D remains a common reason for vitamin D deficiency even in older children/adolescents, especially in overweight and obese individuals. Moreover, overweight and obese subjects are more at risk of low blood levels of vitamin D, as adiposity may prevent vitamin D release from the deposits in the fatty tissue and therefore its bioavailability (66, 99).

5. International recommendations

For all the mentioned reasons, most international and national guidelines actually recommend vitamin D prophylaxis to all infants during the first year of life, in order to prevent possible deficiency conditions and in consideration of the frequent, unpredictable, and

TABLE 1 Suggested cut-off values for the definition of vitamin D status based on circulating levels of 25(OH)D (74).

	Severe deficiency	Deficiency	Insufficiency	Sufficiency
Serum	<10 ng/mL	<20 ng/mL	20–29 ng/mL	≥ 30 ng/mL
25(OH)D	(<25 nmol/L)	(<50 nmol/L)	(50–74 nmol/L)	(≥ 75 nmol/L)

often insufficient supply typical of the early infancy (73, 74). It has been estimated that infant formulas are able to provide appropriate amounts of vitamin D (400 IU/day) only once an average intake of at least 1 l of milk per day has been reached, which generally takes place when the baby's body weight is more than 6 kg (100). Moreover, even if cholecalciferol (vitamin D_3) seems to be more effective in raising 25(OH)D levels, there is no proven difference between the administration of ergocalciferol (D_2) or D_3 formulation in preventing possible deficiencies (101, 102). Dosages above 400 IU/day did not show significant differences in vitamin D sufficiency rates and bone health during the first year of life (94). Higher intakes have been suggested only in preterm births; in fact, the European Society of Pediatric Gastroenterology, Nutrition, and Hepatology (ESPGHAN) recommends prophylaxis with 800–1,000 IU/day (avoiding a pro kg dosage) during the first months of the preterm, in order to quickly correct the reduced infants' levels of 25(OH)D, thus reducing the risk of symptomatic deficiencies (103). As for breastfeeding, although some recommendations advise for maternal supplementation of 600 IU per day, some data suggest that this practice does not significantly change the concentration of 25(OH)D in breast milk, which is generally poor in vitamin D (93). For this reason, the American Academy of Pediatrics recommends supplementing all breastfed and partially breastfed infants, regardless of maternal supplementation (88). However, adherence to these recommendations is low (104). Furthermore, due to the poor evidence to assess the benefits of supplementation for improving maternal and infant health outcomes, the World Health Organization (WHO) does not recommend routine vitamin D supplementation in pregnant women (105).

In consideration of the low levels of adherence to a daily administration of vitamin D found in many populations that differed for geographic and socioeconomic conditions, alternative approaches to a daily supplementation based on high doses (up to 6,400 IU/day) given directly to fully breastfeeding mothers have been found to be safe and equally effective in maintaining adequate levels of 25(OH)D, as well as monthly administrations of 50,000 IU given directly to infants (94, 104, 106–110).

After 12 months of life, evidence about pediatric vitamin D supplementation needs is less clear and univocal (111–114). A case-by-case evaluation of the toddler, child, and young adult lifestyle has then been recommended, to correct possible modifiable risk factors when present, particularly in adolescents, by virtue of their increased needs related to major skeletal growth and also the pubertal spurt (99). Any supplementation is therefore only indicated in cases of poor sun exposure or in specific conditions (111). This approach is also supported by WHO, which focuses the indication on vitamin D supplementation more on geographical location and sun exposure than on child age (115). As for the administration of fortified foods in early childhood, the consumption of vitamin D-fortified milk between 2 and 6 years may represent a safe and significantly effective nutritional measure in preventing 25(OH)D insufficiency during periods of reduced sunlight exposure (116–119). On the other hand, other societies, such as the Endocrine Society and the Institute of Medicine, recommend an average vitamin D intake of 600–1,000 IU/d between 1 and 18 years of age (120, 121).

Considering these discrepant recommendations, the inconclusive data on this issue, and that universal screening of 25(OH)D serum levels cannot represent a feasible solution, new studies should assess if vitamin D evaluation in selected cases would be more appropriate and cost-effective than a routinary, continued, and widespread supplementation.

As was observed 10 years ago in the Consensus statement by the ESPGHAN Nutritional Committee, data on vitamin D concentration and vitamin D deficiency in healthy pediatric subjects are limited, with a lack of consistency in terms of study design and definition of vitamin D deficiency (72). From the studies examined in the statement, it appears that a considerable number of healthy European children and adolescents may be expected to be vitamin D deficient (122–134).

Besides, routine vitamin D screening in healthy children is currently not recommended by experts globally, which partially explains the lack of data and systematization of literature regarding vitamin D status in healthy subjects (73).

Finally, although there are few reports on possible damages from high levels of exogenous administration of vitamin D for example, in cases of mutation of the 24-hydroxylase gene or in sporadic cases of overdosages, possible conditions such as hypercalcemia and hypercalciuria might occur, leading up to acute symptoms such as pain, fever, chills, anorexia, and later to soft tissue calcification, and related chronic pathologies such as nephrocalcinosis in case of prolonged overdosages (135, 136). The issue is still discussed in the hypothesis of either a rare genetic predisposition, or real differences in comparison with the expected spontaneous epidemiological distribution of cases. Cases of vitamin D intoxication have been described only for serum levels above 150 ng/mL (137).

It should be once more stressed that vitamin D levels can significantly vary depending on the lifestyle and overall exposure to ultraviolet B rays, which is affected by factors such as geographic location, age, skin, and family habits (66, 138, 139). In newborns and infants, other factors may well affect vitamin D status such as season of birth, maternal prophylaxis in pregnancy, type of breastfeeding, human milk variable individual composition, and the family socioeconomic status (140, 141). Recently, the rising rate of obesity and the lipophilic nature of vitamin D have suggested the need for higher quantities of vitamin D for these subjects, up to at least 1,000–1,500 IU/day (99, 142).

The 25(OH)D serum dosage should be cautiously considered in clinical practice. The National Institute for Health and Care Excellence (NICE) guidelines recommend dosing 25(OH)D serum only in patients with signs of hypovitaminosis, or in the presence of documented risk factors that justifies their dosage (143). Instead, a 6-month 25(OH)D dosage may be appropriate in supplemented patients to evaluate its effectiveness or to consider whether to suspend it.

In Table 2, we summarize different guidelines and statements for supplementation.

6. Conclusion

All children during the first year of life should receive an oral supplementation of vitamin D. Beyond this age, geographic and cultural variability should always be considered by clinicians and scientific societies in recommending, or not, the need for

TABLE 2 Different guidelines for vitamin D supplementation.

First author, year	Title	Type	Vitamin D status cut-off values considered	Vitamin D toxicity level considered	Population	Vitamin D supplementation
Munns et al., 2016 (73)	Global Consensus Recommendations on Prevention and Management of Nutritional Rickets	Consensus statement from expert member of various international societies	Sufficiency, >50 nmol/L Insufficiency, 30–50 nmol/L Deficiency, <30 nmol/L	>250 nmol/L, with hypercalcemia, hypercalciuria, and suppressed PTH	Children and adults	Infants (0–12 months) 400 IU/day in the first year of life, independent of their mode of feeding. Subject beyond 12 months of age: 600 up to 2000 IU/day (minimum duration 12 weeks) in children with history of symptomatic vitamin D deficiency requiring treatment or children and adults at high risk of vitamin D deficiency Pregnant women 600 IU/d throughout pregnancy
Pludowski et al., 2022 (76)	Clinical Practice in the Prevention, Diagnosis, and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement	Consensus statement by Eastern European expert	Sufficiency 30–50 ng/mL (75–125 nmol/L) Insufficiency between ≥20 ng/mL (≥50 nmol/L) and <30 ng/mL (<75 nmol/L) Deficiency <20 ng/mL (<50 nmol/L)	>100 ng/mL (250 nmol/L)	Adults	Healthy adults 800 up to 2000 IU/day in: (1) healthy subjects who want to achieve a targeted/measured 25(OH)D concentration, during wintertime (2) subjects >65 years throughout the year (3) Pregnant women or planning a pregnancy Subjects with medical conditions up to 4,000 IU/day
Braegger et al., 2013 (72)	Vitamin D in the healthy European pediatric population	Consensus statement from member of the ESPHGAN Committee of nutrition	Sufficiency >50 nmol/L Severe deficiency <25 nmol/L.	"No agreement on a vitamin D toxicity threshold"	Children	Infants (birth to 12 months) 400 IU/day in the first year of life Beyond 12 months: >600 IU/day supplementation in children from identified risk groups
Saggese et al. 2018 (99)	Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians	Consensus statement form national Pediatric societies in Italy	Sufficiency ≥30 ng/mL (≥75 nmol/L) Insufficiency 20–29 ng/mL (50–74 nmol/L) Deficiency <20 ng/mL (<50 nmol/L) Severe deficiency <10 ng/mL (<25 nmol/L)	Not reported	Children	Preterm infants: (1) 400–800 IU/day for preterm infants with weight ≥ 1,500 g (2) 200–400 IU/day by enteral feeding in preterm infant with weight < 1,500 g Infants: 400 IU/day in all newborns independent of the type of feeding. Subjects beyond 12 months of age: 600 up to 1,000 IU/day in children and adolescents with risk factors for vitamin D deficiency
Agostoni et al. 2010 (103)	Enteral Nutrient Supply for Preterm Infants: Commentary from the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition	Commentary from ESPHGAN Committee of nutrition	N/A	Not reported	Children	Preterm infants 800 up to 1,000 IU/day during the first months of life

(Continued)

TABLE 2 (Continued)

First author, year	Title	Type	Vitamin D status cut-off values considered	Vitamin D toxicity level considered	Population	Vitamin D supplementation
Wagner et al., 2008 (88)	Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents	Guidelines from the American Academy of Pediatrics	"Serum 25-OH-D concentrations in infants and children should be ≥50 nmol/L (20 ng/mL)."	Not reported	Children	Infants 400 IU/day in the first year of life in breastfed or partially breastfed infants, and in non-breastfed infants who are ingesting <1,000 mL/day of vitamin D–fortified formula or milk Older children 400 IU/day in case of diet with <1,000 mL/day of vitamin D–fortified formula or milk Adolescents 400 IU/day in case the individual does not obtain 400 IU of vitamin D per day through vitamin D–fortified milk/vitamin D–fortified foods (e.g., cereals) Children/adolescents with risk factors: 400 IU/day supplement despite a food intake of 400 IU/day
Rogers et al., 2012 (105)	Vitamin D supplementation in pregnant women	WHO guidelines	N/A	Not reported	Pregnant women	Supplementation during pregnancy as part of routine antenatal care not recommended (conditional recommendation) In cases of documented deficiency, vitamin D supplements may be given
Holick et al., 2011 (121)	Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline	Clinical practice guidelines by the Endocrine Society	Insufficiency 21–29 ng/mL (525–725 nmol/L) Deficiency <20 ng/mL (50 nmol/L),	Not reported	Children and adults	Infants aged 0–1 year who are vitamin D deficient 2000 IU/day for 6 weeks followed by maintenance therapy of 400–1,000 IU/day Children aged 1–18 years who are vitamin D deficient 2000 IU/day for at least 6 weeks followed by maintenance therapy of 600–1,000 IU/day Adults who are vitamin D deficient 6,000 IU/day for 8 weeks followed by maintenance therapy of 1,500–2000 IU/day

supplementation. Vitamin D status may be closely connected to social inequities and related diseases. Moreover, constant and unjustified monitoring of vitamin D levels has then been considered unnecessary in the general population. Screening of serum 25(OH)D concentration should be carried out only in selected cases.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. McCollum EV, Simmonds N, Becker JE, Shipley PG. Studies on experimental rickets: XXI an experimental demonstration of the existence of a vitamin which promotes calcium deposition. *J Biol Chem*. (1922) 53:293–312. doi: 10.1016/S0021-9258(18)85783-0

2. Zmijewski MA. Vitamin D and human health. *Int J Mol Sci*. (2019) 20:145. doi: 10.3390/ijms20010145

3. Bendik I, Friedel A, Roos FF, Weber P, Eggersdorfer M. Vitamin D: a critical and essential micronutrient for human health. *Front Physiol*. (2014) 5:248. doi: 10.3389/fphys.2014.00248

4. Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Ann N Y Acad Sci*. (2018) 1430:44–79. doi: 10.1111/nyas.13968

5. Constantini NW, Arieli R, Chodick G, Dubnov-Raz G. High prevalence of vitamin D insufficiency in athletes and dancers. *Clin J Sport Med*. (2010) 20:368–71. doi: 10.1097/JSM.0b013e3181f207f2

6. Holick MF. High prevalence of Vitamin D inadequacy and implications for health. *Mayo Clin Proc*. (2006) 81:353–73. doi: 10.4065/81.3.353

7. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol* (2014) 144PA:138–145. doi: 10.1016/j.jsbmb.2013.11.003, 144

8. Allgrove J. Physiology of calcium, phosphate and magnesium. *Endocr Dev*. (2009) 16:8–31. doi: 10.1159/000223685

9. Uwitonze AM, Razzaque MS. Role of magnesium in Vitamin D activation and function. *J Am Osteopath Assoc*. (2018) 118:181–9. doi: 10.7556/jaoa.2018.037

10. Reddy P, Edwards LR. Magnesium supplementation in Vitamin D deficiency. *Am J Ther*. (2019) 26:e124–32. doi: 10.1097/MJT.0000000000000538

11. Allgrove J, Shaw NJ. A practical approach to Vitamin D deficiency and rickets. *Endocr Dev*. (2015) 28:119–33. doi: 10.1159/000381000

12. Uday S, Högler W. Nutritional rickets and Osteomalacia in the twenty-first century: revised concepts, public health, and prevention strategies. *Curr Osteoporos Rep*. (2017) 15:293–302. doi: 10.1007/s11914-017-0383-y

13. Grad R. Cod and the consumptive: a brief history of cod-liver oil in the treatment of pulmonary tuberculosis. *Pharm Hist*. (2004) 46:106–20.

14. Cervantes JL, Oak E, Garcia J, Liu H, Lorenzini PA, Batra D, et al. Vitamin D modulates human macrophage response to mycobacterium tuberculosis DNA. *Tuberculosis (Edinb)*. (2019) 116:S131–7. doi: 10.1016/j.tube.2019.04.021

15. Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. *Front Immunol*. (2016) 7:697. doi: 10.3389/fimmu.2016.00697

16. Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med*. (2010) 88:441–50. doi: 10.1007/s00109-010-0590-9

17. Altieri B, Muscogiuri G, Barrea L, Mathieu C, Vallone CV, Mascitelli L, et al. Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept. *Rev Endocr Metab Disord*. (2017) 18:335–46. doi: 10.1007/s11154-016-9405-9

18. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients*. (2013) 5:2502–21. doi: 10.3390/nu5072502

19. Bizzaro G, Shoenfeld Y. Vitamin D and autoimmune thyroid diseases: facts and unresolved questions. *Immunol Res*. (2015) 61:46–52. doi: 10.1007/s12026-014-8579-z

20. Dimeloe S, Nanzer A, Ryanna K, Hawrylowicz C. Regulatory T cells, inflammation and the allergic response—the role of glucocorticoids and Vitamin D. *J Steroid Biochem Mol Biol* (2010) 120:86–95. doi: https://doi.org/10.1016/j.jsbmb.2010.02.029

21. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol*. (2007) 179:1634–47. doi: 10.4049/jimmunol.179.3.1634

22. Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. *Nutrients*. (2018) 10:1656. doi: 10.3390/nu10111656

23. Maddaloni E, Cavallari I, Napoli N, Conte C. Vitamin D and Diabetes Mellitus. *Front Horm Res*. (2018) 50:161–76. doi: 10.1159/000486083

24. Moltchanova E V, Schreier N, Lammi N, Karvonen M. Seasonal variation of diagnosis of type 1 diabetes mellitus in children worldwide. *Diabet Med* (2009) 26:673–678. doi: https://doi.org/10.1111/j.1464-5491.2009.02743.x

25. Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. *Am J Clin Nutr*. (2003) 78:1128–34. doi: 10.1093/ajcn/78.6.1128

26. Marjamäki L, Niinistö S, Kenward MG, Uusitalo L, Uusitalo U, Ovaskainen M-L, et al. Maternal intake of vitamin D during pregnancy and risk of advanced beta cell autoimmunity and type 1 diabetes in offspring. *Diabetologia*. (2010) 53:1599–607. doi: 10.1007/s00125-010-1734-8

27. 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. doi: 10.1136/adc.2007.128579

28. Infante M, Ricordi C, Sanchez J, Clare-Salzler MJ, Padilla N, Fuenmayor V, et al. Influence of Vitamin D on islet autoimmunity and Beta-cell function in type 1 diabetes. *Nutrients*. (2019) 11:2185. doi: 10.3390/nu11092185

29. Li X, Liao L, Yan X, Huang G, Lin J, Lei M, et al.. Protective effects of 1-α-hydroxyvitamin D3 on residual β-cell function in patients with adult-onset latent autoimmune diabetes (LADA). *Diabetes Metab Res Rev* (2009) 25:411–416. doi: https://doi.org/10.1002/dmrr.977

30. Ataie-Jafari A, Loke S-C, Rahmat AB, Larijani B, Abbasi F, Leow MKS, et al. A randomized placebo-controlled trial of alphacalcidol on the preservation of beta cell function in children with recent onset type 1 diabetes. *Clin Nutr*. (2013) 32:911–7. doi: 10.1016/j.clnu.2013.01.012

31. Dong J-Y, Zhang W-G, Chen JJ, Zhang Z-L, Han S-F, Qin L-Q. Vitamin D intake and risk of type 1 diabetes: a meta-analysis of observational studies. *Nutrients*. (2013) 5:3551–62. doi: 10.3390/nu5093551

32. Wang J, Lv S, Chen G, Gao C, He J, Zhong H, et al. Meta-analysis of the association between Vitamin D and autoimmune thyroid disease. *Nutrients*. (2015) 7:2485–98. doi: 10.3390/nu7042485

33. Muscogiuri G, Mari D, Prolo S, Fatti LM, Cantone MC, Garagnani P, et al. 25 Hydroxyvitamin D deficiency and its relationship to autoimmune thyroid disease in the elderly. *Int J Environ Res Public Health*. (2016) 13:850. doi: 10.3390/ijerph13090850

34. Sönmezgöz E, Ozer S, Yilmaz R, Önder Y, Bütün I, Bilge S. Hypovitaminosis D in children with Hashimoto's thyroiditis. *Revista Medica de Chile*. (2016) 144:611–6. doi: 10.4067/S0034-98872016000500009

35. Gubatan J, Moss AC. Vitamin D in inflammatory bowel disease: more than just a supplement. *Curr Opin Gastroenterol*. (2018) 34:217–25. doi: 10.1097/MOG.0000000000000449

36. Corsello A, Pugliese D, Gasbarrini A, Armuzzi A. Diet and nutrients in gastrointestinal chronic diseases. *Nutrients*. (2020) 12:2693. doi: 10.3390/nu12092693

37. Lim W-C, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol*. (2005) 2:308–15. doi: 10.1038/ncpgasthep0215

38. Limketkai BN, Mullin GE, Limsui D, Parian AM. Role of Vitamin D in inflammatory bowel disease. *Nutr Clin Pract*. (2017) 32:337–45. doi: 10.1177/0884533616674492

39. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association between inflammatory bowel disease and Vitamin D deficiency: a systematic review and meta-analysis. *Inflamm Bowel Dis*. (2015) 21:2708–17. doi: 10.1097/MIB.0000000000000546

40. Zhao J, Wang Y, Gu Q, Du Z, Chen W. The association between serum vitamin D and inflammatory bowel disease. *Medicine*. (2019) 98:e15233–3. doi: 10.1097/MD.0000000000015233

41. Liu W, Chen Y, Golan MA, Annunziata ML, du J, Dougherty U, et al. Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. *J Clin Invest*. (2013) 123:3983–96. doi: 10.1172/JCI65842

42. Illescas-Montes R, Melguizo-Rodríguez L, Ruiz C, Costela-Ruiz VJ. Vitamin D and autoimmune diseases. *Life Sci*. (2019) 233:116744. doi: 10.1016/j.lfs.2019.116744

43. Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of Vitamin D in inflammatory bowel disease: mechanism to management. *Nutrients*. (2019) 11:1019. doi: 10.3390/nu11051019

44. Dipasquale V, Lo Presti G, Milani GP, Corsello A, Agostoni C, Romano C. Vitamin D in prevention of autoimmune diseases. *Front Biosci*. (2022) 27:288. doi: 10.31083/j.fbl2710288

45. Reich KM, Fedorak RN, Madsen K, Kroeker KI. Vitamin D improves inflammatory bowel disease outcomes: basic science and clinical review. *World J Gastroenterol*. (2014) 20:4934–47. doi: 10.3748/wjg.v20.i17.4934

46. Yang L, Weaver V, Smith JP, Bingaman S, Hartman TJ, Cantorna MT. Therapeutic effect of vitamin d supplementation in a pilot study of Crohn's patients. *Clin Transl Gastroenterol*. (2013) 4:e33–3. doi: 10.1038/ctg.2013.1

47. Wang X-R, Xiao J-P, Zhang J-J, Wu Y-G. Decreased serum/plasma Vitamin D levels in SLE patients: a meta-analysis. *Curr Pharm Des*. (2018) 24:4466–73. doi: 10.217 4/1381612825666190111145848

48. Zhang J, Li W, Liu J, Wu W, Ouyang H, Zhang Q, et al. Polymorphisms in the vitamin D receptor gene and type 1 diabetes mellitus risk: an update by meta-analysis. *Mol Cell Endocrinol* (2012) 355:135–142. doi: https://doi.org/10.1016/j.mce.2012.02.003

49. Feng M, Li H, Chen S-F, Li W-F, Zhang F-B. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. *Endocrine*. (2013) 43:318–26. doi: 10.1007/s12020-012-9812-y

50. Tizaoui K, Kaabachi W, Hamzaoui A, Hamzaoui K. Association between vitamin D receptor polymorphisms and multiple sclerosis: systematic review and meta-analysis of case–control studies. *Cell Mol Immunol*. (2015) 12:243–52. doi: 10.1038/cmi.2014.47

51. Lee YH, Bae S-C. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis. *Clin Exp Rheumatol*. (2016) 34:827–33.

52. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*. (2020) 74:1498–513. doi: 10.1038/s41430-020-0558-y

53. Aranow C. Vitamin D and the immune system. *J Investig Med*. (2011) 59:881–6. doi: 10.231/JIM.0b013e31821b8755

54. Cantorna MT, Vitamin D. Multiple sclerosis and inflammatory bowel disease. *Arch Biochem Biophys*. (2012) 523:103–6. doi: 10.1016/j.abb.2011.11.001

55. Forno E, Bacharier LB, Phipatanakul W, Guilbert TW, Cabana MD, Ross K, et al. Effect of Vitamin D3 supplementation on severe asthma exacerbations in children with asthma and low Vitamin D levels: the VDKA randomized clinical trial. *JAMA*. (2020) 324:752–60. doi: 10.1001/jama.2020.12384

56. Brenner H, Vitamin D. Supplementation to prevent COVID-19 infections and deaths-accumulating evidence from epidemiological and intervention studies calls for immediate action. *Nutrients*. (2021) 13:411. doi: 10.3390/nu13020411

57. Panfili FM, Roversi M, D'Argenio P, Rossi P, Cappa M, Fintini D. Possible role of vitamin D in Covid-19 infection in pediatric population. *J Endocrinol Investig*. (2021) 44:27–35. doi: 10.1007/s40618-020-01327-0

58. Martineau AR, Forouhi NG. Vitamin D for COVID-19: a case to answer? *Lancet Diabetes Endocrinol*. (2020) 8:735–6. doi: 10.1016/S2213-8587(20)30268-0

59. Yisak H, Ewunetei A, Kefale B, Mamuye M, Teshome F, Ambaw B, et al. Effects of Vitamin D on COVID-19 infection and prognosis: a systematic review. *Risk Manag Healthc Policy*. (2021) 14:31–8. doi: 10.2147/RMHP.S291584

60. Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of Vitamin D deficiency among healthy infants and toddlers. *Arch Pediatr Adolesc Med*. (2008) 162:505–12. doi: 10.1001/archpedi.162.6.505

61. Zhu Z, Zhan J, Shao J, Chen W, Chen L, Li W, et al. High prevalence of vitamin D deficiency among children aged 1 month to 16 years in Hangzhou, China. *BMC Public Health*. (2012) 12:126. doi: 10.1186/1471-2458-12-126

62. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-Hydroxyvitamin D deficiency in US children: NHANES 2001–2004. *Pediatrics*. (2009) 124:e362–70. doi: 10.1542/peds.2009-0051

63. Haimi M, Kremer R. Vitamin D deficiency/insufficiency from childhood to adulthood: insights from a sunny country. *World J Clin Pediatr*. (2017) 6:1–9. doi: 10.5409/wjcp.v6.i1.1

64. Engelsen O. The relationship between ultraviolet radiation exposure and Vitamin D status. *Nutrients*. (2010) 2:482–95. doi: 10.3390/nu2050482

65. Dawodu A, Davidson B, Woo JG, Peng Y-M, Ruiz-Palacios GM, de Lourdes Guerrero M, et al. Sun exposure and Vitamin D supplementation in relation to Vitamin D status of Breastfeeding mothers and infants in the global exploration of human Milk study. *Nutrients*. (2015) 7:1081–93. doi: 10.3390/nu7021081

66. Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. *Acta Derm Venereol*. (2011) 91:115–24. doi: 10.2340/00015555-0980

67. Della Giustina A, Landi M, Bellini F, Bosoni M, Ferrante G, Onorari M, et al. Vitamin D, allergies and asthma: focus on pediatric patients. *World Allergy Organ J*. (2014) 7:27–6. doi: 10.1186/1939-4551-7-27

68. Sempos CT, Heijboer AC, Bikle DD, Bollerslev J, Bouillon R, Brannon PM, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the first international conference on controversies in Vitamin D. *Br J Clin Pharmacol*. (2018) 84:2194–207. doi: 10.1111/bcp.13652

69. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc*. (2010) 85:752–8. doi: 10.4065/mcp.2010.0138

70. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D deficiency — is there really a pandemic? *N Engl J Med*. (2016) 375:1817–20. doi: 10.1056/NEJMp1608005

71. Haines ST, Park SK. Vitamin D supplementation: what's known, what to do, and what's needed. *Pharmacotherapy*. (2012) 32:354–82. doi: 10.1002/phar.1037

72. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al. Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr*. (2013) 56:692–701. doi: 10.1097/MPG.0b013e31828f3c05

73. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and Management of Nutritional Rickets. *J Clin Endocrinol Metab*. (2016) 101:394–415. doi: 10.1210/jc.2015-2175

74. Saggese G, Vierucci F, Prodam F, Cardinale F, Cetin I, Chiappini E, et al. Vitamin D in pediatric age: consensus of the Italian pediatric society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians. *Ital J Pediatr*. (2018) 44:51. doi: 10.1186/s13052-018-0488-7

75. Holick MF, Vitamin D. Deficiency. *N Engl J Med*. (2007) 357:266–81. doi: 10.1056/NEJMra070553

76. Kimball SM, Holick MF. Official recommendations for vitamin D through the life stages in developed countries. *Eur J Clin Nutr*. (2020) 74:1514–8. doi: 10.1038/s41430-020-00706-3

77. Pludowski P, Takacs I, Boyanov M, Belaya Z, Diaconu CC, Mokhort T, et al. Clinical practice in the prevention, diagnosis and treatment of Vitamin D deficiency: a central and eastern European expert consensus statement. *Nutrients*. (2022) 14:1483. doi: 10.3390/nu14071483

78. Bleizgys A, Vitamin D. Dosing: basic principles and a brief algorithm (2021 update). *Nutrients*. (2021) 13:4415. doi: 10.3390/nu13124415

79. Martin CA, Gowda U, Renzaho AMN. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: a meta-analysis. *Nutrition*. (2016) 32:21–32. doi: 10.1016/j.nut.2015.07.007

80. Akbari AR, Khan M, Adeboye W, Hai Lee LH, Chowdhury SI. Ethnicity as a risk factor for vitamin D deficiency and undesirable COVID-19 outcomes. *Rev Med Virol*. (2022) 32:e2291. doi: 10.1002/rmv.2291

81. Bahrami A, Sadeghnia HR, Tabatabaeizadeh S-A, Bahrami-Taghanaki H, Behboodi N, Esmaeili H, et al. Genetic and epigenetic factors influencing vitamin D status. *J Cell Physiol*. (2018) 233:4033–43. doi: 10.1002/jcp.26216

82. Cuppari L, Garcia-Lopes MG. Hypovitaminosis D in chronic kidney disease patients: prevalence and treatment. *J Ren Nutr*. (2009) 19:38–43. doi: 10.1053/j.jrn.2008.10.005

83. Shaikh AS, Guo X, Li Y, Cao L, Liu X, Li P, et al. The impact of antiepileptic drugs on Vitamin levels in epileptic patients. *Curr Pharm Biotechnol*. (2018) 19:674–81. doi: 10.2174/1389201019666180816104716

84. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. *Nutr J*. (2010) 9:65. doi: 10.1186/1475-2891-9-65

85. Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D sources, metabolism, and deficiency: available compounds and guidelines for its treatment. *Meta*. (2021) 11:255. doi: 10.3390/metabo11040255

86. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord*. (2017) 18:153–65. doi: 10.1007/s11154-017-9424-1

87. Wacker M, Holick MF. Sunlight and Vitamin D: a global perspective for health. *Dermatoendocrinol*. (2013) 5:51–108. doi: 10.4161/derm.24494

88. Chang S-W, Lee H-C. Vitamin D and health - the missing vitamin in humans. *Pediatr Neonatol*. (2019) 60:237–44. doi: 10.1016/j.pedneo.2019.04.007

89. Wagner CL, Greer FRthe Section on Breastfeeding and Committee on Nutrition. Prevention of rickets and Vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. (2008) 122:1142–52. doi: 10.1542/peds.2008-1862

90. Tsugawa N, Nishino M, Kuwabara A, Ogasawara H, Kamao M, Kobayashi S, et al. Comparison of Vitamin D and 25-Hydroxyvitamin D concentrations in human breast Milk between 1989 and 2016-2017. *Nutrients*. (2021) 13:573. doi: 10.3390/nu13020573

91. Anusha K, Hettiaratchi U, Gunasekera D, Prathapan S, Liyanage G. Maternal Vitamin D status and its effect on Vitamin D levels in early infancy in a tertiary Care Centre in Sri Lanka. *Int J Endocrinol*. (2019) 2019:9017951–6. doi: 10.1155/2019/9017951

92. Jan Mohamed HJ, Rowan A, Fong B, Loy S-L. Maternal serum and breast milk vitamin D levels: findings from the Universiti Sains Malaysia pregnancy cohort study. *PLoS One*. (2014) 9:e100705–5. doi: 10.1371/journal.pone.0100705

93. Wagner CL, Taylor SN, Johnson DD, Hollis BW. The role of vitamin D in pregnancy and lactation: emerging concepts. *Women's Health (Lond Engl)*. (2012) 8:323–40. doi: 10.2217/whe.12.17

94. Hollis BW, Wagner CL, Howard CR, Ebeling M, Shary JR, Smith PG, et al. Maternal versus infant Vitamin D supplementation during lactation: a randomized controlled trial. *Pediatrics*. (2015) 136:625–34. doi: 10.1542/peds.2015-1669

95. Corsello A, Milani GP, Giannì ML, Dipasquale V, Romano C, Agostoni C. Different Vitamin D supplementation strategies in the first years of life: a systematic review. *Healthcare*. (2022) 10:1023. doi: 10.3390/healthcare10061023

96. Meena P, Dabas A, Shah D, Malhotra RK, Madhu SV, Gupta P. Sunlight exposure and Vitamin D status in breastfed infants. *Indian Pediatr*. (2017) 54:105–11. doi: 10.1007/s13312-017-1010-9

97. Bae YJ, Kratzsch J. Vitamin D and calcium in the human breast milk. *Best Pract Res Clin Endocrinol Metab*. (2018) 32:39–45. doi: 10.1016/j.beem.2018.01.007

98. Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, et al. Complementary feeding: a position paper by the European Society for Paediatric Gastroenterology, hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. (2017) 64:119–32. doi: 10.1097/MPG.0000000000001454

99. Zakharova I, Klimov L, Kuryaninova V, Nikitina I, Malyavskaya S, Dolbnya S, et al. Vitamin D insufficiency in overweight and obese children and adolescents. *Front Endocrinol (Lausanne)*. (2019) 10:103. doi: 10.3389/fendo.2019.00103

100. Dalle Carbonare L, Valenti MT, Del Forno F, Caneva E, Pietrobelli A. Vitamin D: Daily vs. Monthly use in children and elderly-what is going on? *Nutrients*. (2017) 9:E652. doi: 10.3390/nu9070652

101. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr*. (2012) 95:1357–64. doi: 10.3945/ajcn.111.031070

102. Bilezikian JP, Formenti AM, Adler RA, Binkley N, Bouillon R, Lazaretti-Castro M, et al. Vitamin D: dosing, levels, form, and route of administration: does one approach fit all? *Rev Endocr Metab Disord*. (2021) 22:1201–18. doi: 10.1007/s11154-021-09693-7

103. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, 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. doi: 10.1097/MPG.0b013e3181adaee0

104. Perrine CG, Sharma AJ, Jefferds MED, Serdula MK, Scanlon KS. Adherence to vitamin D recommendations among US infants. *Pediatrics*. (2010) 125:627–32. doi: 10.1542/peds.2009-2571

105. World Health Organization. *Guideline: vitamin D supplementation in pregnant women*. Geneva: World Health Organization (2012).

106. Wheeler BJ, Taylor BJ, Herbison P, Haszard JJ, Mikhail A, Jones S, et al. High-dose monthly maternal cholecalciferol supplementation during Breastfeeding affects maternal and infant Vitamin D status at 5 months postpartum: a randomized controlled trial. *J Nutr*. (2016) 146:1999–2006. doi: 10.3945/jn.116.236679

107. Ahrens KA, Rossen LM, Simon AE. Adherence to Vitamin D recommendations among US infants aged 0 to 11 months, NHANES, 2009 to 2012. *Clin Pediatr (Phila)*. (2016) 55:555–6. doi: 10.1177/0009922815589916

108. Hemmingway A, Fisher D, Berkery T, Murray DM, Kiely ME. Adherence to the infant vitamin D supplementation policy in Ireland. *Eur J Nutr*. (2021) 60:1337–45. doi: 10.1007/s00394-020-02334-w

109. O'Callaghan KM, Taghivand M, Zuchniak A, Onyovwi A, Korsiak J, Leung M, et al. Vitamin D in breastfed infants: systematic review of alternatives to Daily supplementation. *Adv Nutr*. (2020) 11:144–59. doi: 10.1093/advances/nmz098

110. Tan ML, Abrams SA, Osborn DA. Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. *Cochrane Database Syst Rev* (2018) 2018:CD013046. doi: 10.1002/14651858.CD013046

111. Day RE, Krishnarao R, Sahota P, Christian MS. We still don't know that our children need vitamin D daily: a study of parents' understanding of vitamin D requirements in children aged 0-2 years. *BMC Public Health*. (2019) 19:1119. doi: 10.1186/s12889-019-7340-x

112. Martini L, Pecoraro L, Salvottini C, Piacentini G, Atkinson R, Pietrobelli A. Appropriate and inappropriate vitamin supplementation in children. *J Nutr Sci*. (2020) 9:e20. doi: 10.1017/jns.2020.12

113. Taylor SN. Vitamin D in toddlers, preschool children, and adolescents. *Ann Nutr Metab*. (2020) 76:30–41. doi: 10.1159/000505635

114. Patseadou M, Haller DM. Vitamin D in adolescents: a systematic review and narrative synthesis of available recommendations. *J Adolesc Health*. (2020) 66:388–407. doi: 10.1016/j.jadohealth.2019.08.025

115. World Health Organization (2005). Vitamin and mineral requirements in human nutrition. Available at: https://apps.who.int/iris/handle/10665/42716

116. Akkermans MD, Eussen SR, van der Horst-Graat JM, van Elburg RM, van Goudoever JB, Brus F. A micronutrient-fortified young-child formula improves the iron and vitamin D status of healthy young European children: a randomized, double-blind controlled trial. *Am J Clin Nutr*. (2017) 105:391–9. doi: 10.3945/ajcn.116.136143

117. Verduci E, Di Profio E, Corsello A, Scatigno L, Fiore G, Bosetti A, et al. Which Milk during the second year of life: a personalized choice for a healthy future? *Nutrients*. (2021) 13:3412. doi: 10.3390/nu13103412

118. Houghton LA, Gray AR, SzymLek-Gay EA, Heath A-LM, Ferguson EL. Vitamin D-fortified milk achieves the targeted serum 25-hydroxyvitamin D concentration without affecting that of parathyroid hormone in New Zealand toddlers. *J Nutr*. (2011) 141:1840–6. doi: 10.3945/jn.111.145052

119. Hower J, Knoll A, Ritzenthaler KL, Steiner C, Berwind R. Vitamin D fortification of growing up milk prevents decrease of serum 25-hydroxyvitamin D concentrations during winter: a clinical intervention study in Germany. *Eur J Pediatr*. (2013) 172:1597–605. doi: 10.1007/s00431-013-2092-6

120. Institute of Medicine (US) (2011). Committee to review dietary reference intakes for Vitamin D and calcium. *Dietary reference intakes for calcium and Vitamin D*. AC Ross, CL Taylor, AL Yaktine and ValleHB Del, Washington (DC): National Academies Press (US).

121. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. (2011) 96:1911–30. doi: 10.1210/jc.2011-0385

122. Akman AO, Tumer L, Hasanoglu A, Ilhan M, Caycı B. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. *Pediatr Int*. (2011) 53:968–73. doi: 10.1111/j.1442-200X.2011.03486.x

123. Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, Chabros E, 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. doi: 10.1038/sj.ejcn.1602108

124. Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman KD, Jakobsen J, et al. Pakistani immigrant children and adults in Denmark have severely low vitamin D status. *Eur J Clin Nutr*. (2008) 62:625–34. doi: 10.1038/sj.ejcn.1602753

125. Das G, Crocombe S, McGrath M, Berry JL, Mughal MZ. Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Arch Dis Child*. (2006) 91:569–72. doi: 10.1136/adc.2005.077974

126. Ginty F, Cavadini C, Michaud P-A, Burckhardt P, Baumgartner M, Mishra G-D, 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. doi: 10.1038/sj.ejcn.1601959

127. Grindulis H, Scott PH, Belton NR, Wharton BA. Combined deficiency of iron and vitamin D in Asian toddlers. *Arch Dis Child*. (1986) 61:843–8. doi: 10.1136/adc.61.9.843

128. Guillemant J, Le HT, Maria A, Allemandou A, Pérès G, Guillemant S. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. *Osteoporos Int*. (2001) 12:875–9. doi: 10.1007/s001980170040

129. Lapatsanis D, Moulas A, Cholevas V, Soukakos P, Papadopoulou ZL, Challa A. Vitamin D: a necessity for children and adolescents in Greece. *Calcif Tissue Int*. (2005) 77:348–55. doi: 10.1007/s00223-004-0096-y

130. Lawson M, Thomas M. Vitamin D concentrations in Asian children aged 2 years living in England: population survey. *BMJ*. (1999) 318:28. doi: 10.1136/bmj.318.7175.28

131. Lehtonen-Veromaa MKM, Möttönen TT, Nuotio IO, Irjala KMA, Leino AE, Viikari JSA. 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. doi: 10.1093/ajcn/76.6.1446

132. Lippi G, Montagnana M, Targher G. Vitamin D deficiency among Italian children. *CMAJ*. (2007) 177:1529–30; author reply 1530. doi: 10.1503/cmaj.1070102

133. Østergård M, Arnberg K, Michaelsen KF, Madsen AL, Krarup H, Trolle E, et al. Vitamin D status in infants: relation to nutrition and season. *Eur J Clin Nutr*. (2011) 65:657–60. doi: 10.1038/ejcn.2010.285

134. Stellinga-Boelen AAM, Wiegersma PA, Storm H, Bijleveld CMA, Verkade HJ. 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. doi: 10.1007/s00431-006-0221-1

135. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Płudowski P, Jones G. Vitamin D toxicity-a clinical perspective. *Front Endocrinol (Lausanne)*. (2018) 9:550. doi: 10.3389/fendo.2018.00550

136. Dinour D, Beckerman P, Ganon L, Tordjman K, Eisenstein Z, Holtzman EJ. Loss-of-function mutations of CYP24A1, the vitamin D 24-hydroxylase gene, cause long-standing hypercalciuric nephrolithiasis and nephrocalcinosis. *J Urol*. (2013) 190:552–7. doi: 10.1016/j.juro.2013.02.3188

137. Muneer S, Siddiqui I, Majid H, Zehra N, Jafri L, Khan AH. Practices of vitamin D supplementation leading to vitamin D toxicity: experience from a low-middle income country. *Ann Med Surg*. (2022) 73:103227. doi: 10.1016/j.amsu.2021.103227

138. Rabufetti A, Milani GP, Lava SAG, Edefonti V, Bianchetti MG, Stettbacher A, et al. Vitamin D status among male late adolescents living in Southern Switzerland: Role of body composition and lifestyle. *Nutrients*. (2019) 11:2727. doi: 10.3390/nu11112727

139. Milani GP, Simonetti GD, Edefonti V, Lava SAG, Agostoni C, Curti M, et al. Seasonal variability of the vitamin D effect on physical fitness in adolescents. *Scientific reports*. (2021) 11:182. doi: 10.1038/s41598-020-80511-x

140. Fink C, Peters RL, Koplin JJ, Brown J, Allen KJ. Factors affecting Vitamin D status in infants. *Children (Basel)*. (2019) 6:7. doi: 10.3390/children6010007

141. Viljakainen HT, Saarnio E, Hytinantti T, Miettinen M, Surcel H, Mäkitie O, et al. Maternal vitamin D status determines bone variables in the newborn. *J Clin Endocrinol Metab*. (2010) 95:1749–57. doi: 10.1210/jc.2009-1391

142. Castaneda RA, Nader N, Weaver A, Singh R, Kumar S. Response to Vitamin D3 supplementation in obese and non-obese Caucasian adolescents. *Horm Res Paediatr*. (2012) 78:226–31. doi: 10.1159/000343446

143. NICEOverview | Vitamin D: Supplement use in specific population groups | guidance. Avilable at: https://www.nice.org.uk/guidance/ph56 (Accessed September 20, 2022).