Comparative analysis of nutritional guidelines for vitamin D

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Abstract | Vitamin D is essential for calcium and bone homeostasis. Humans are largely dependent on UVB-radiation-induced photosynthesis of vitamin D, as few foods contain vitamin D. However, the same radiation that produces vitamin D is also carcinogenic, albeit with a long lag time, and causes DNA damage. In view of the increasing life expectancy, avoiding excessive sun exposure is prudent. Several groups of people have a shortfall between their requirements for vitamin D and their combined endogenous synthesis and intake from natural foods, and therefore need vitamin D supplementation. Governments and scientific societies are regularly updating their recommendations for intake of vitamin D, especially for groups that should (infants) or prefer to (especially elderly individuals) avoid direct sunlight. An overview of such guidelines is presented in this Review. A fairly large consensus exists that all infants should receive 400 international units (IU) (10 μg) daily during their first year of life and that elderly individuals should have access to vitamin D supplementation (at recommended dosages varying from 400 IU to 800 IU daily in most governmental guidelines but at higher dosages in other guidelines). All guidelines unanimously agree that serum levels of 25-hydroxyvitamin D (25OHD) <25 nmol/l (10 ng/ml) should be avoided at all ages. Children and adults who have limited sun exposure should receive vitamin D supplementation, but the recommended doses vary widely (from 200 IU to 2,000 IU daily), in line with disagreement regarding the minimal desirable serum concentration of 25OHD (which varies from 25 nmol/l to >100 nmol/l).

Vitamin D is essential for calcium and bone homeostasis and might have other health effects[1–5]. Vitamin D has a dual origin: as nutritional intake of vitamin D is usually low, the main source is photosynthesis in the skin during exposure to UVB irradiation by sunlight. A large number of individuals around the world have both a low intake of vitamin D and low exposure to sunlight, and therefore need vitamin D supplementation to avoid vitamin D deficiency-related health problems. Rapid recent progress in understanding the metabolism of vitamin D and its actions has resulted in a large number of scientific or governmental nutritional guidelines for vitamin D. Here, I review the vitamin D guidelines from more than 40 countries, focusing on the fairly large consensus in defining vitamin D requirements for infants, in contrast to the wide discrepancy in recommendations for adults and the elderly population.

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Historical perspective

The essential role of vitamin D in the integrity of the skeleton was discovered about a century ago (reviewed elsewhere[6]). Vitamin D became important early in the evolution of vertebrates, to optimize supply of calcium for bone and especially to maintain extracellular calcium homeostasis[1]. Clinical manifestations of vitamin D deficiency are rather rare in vertebrates living in their natural environment. Few reports on rickets have been documented in human history or in archaeological examinations of skeletons[6]. Rickets was endemic in the seventeenth century in several industrialized countries or cities[7]; however, it took several centuries before the link between rickets and vitamin D deficiency (due to lack of exposure to UVB rays of sunlight) was identified. Rickets was also highly prevalent in dark-skinned children living in New York[8], in upper caste Indian children[9,10] and in animals kept in captivity. With hindsight, this of course is all due to limited exposure to sunlight. The widespread use of vitamin D supplements has virtually eliminated rickets caused by vitamin D deficiency in countries with a policy of prophylactic use of vitamin D in infants and children; nevertheless, rickets remains a frequent problem in countries, or subpopulations, where such a policy is not implemented[11,12]. As our understanding of the complex metabolism, transport and action of

Key points

- Modern humans can expect to live a long life and therefore need to make a balanced choice between exposure to carcinogenic UVB radiation and maintaining an optimal vitamin D status
- Most countries and many scientific societies have prepared or updated guidelines for vitamin D supplementation, with recommended dosages higher than before
- All infants need a daily supplement of vitamin D (preferably 400 international units (IU) per day) during at least their first year of life; however, full implementation of this guideline is problematic in many countries around the world
- A large consensus exists that nearly all elderly individuals need a vitamin D supplement; however, disagreement endures with regard to dosage or optimal concentration of 25-hydroxyvitamin D, and implementation is problematic
- All children or adults lacking sufficient exposure to sunlight need a vitamin D supplement; however, no agreement has been reached regarding dosage, and implementation is poor
- The WHO, supported by its member states, should implement a strategy to eradicate vitamin D (and calcium) deficiency-associated rickets

vitamin D has increased, together with the availability of sophisticated techniques to measure vitamin D metabolites in serum, it has become apparent that the vitamin D endocrine system has an essential role in bone and calcium homeostasis, and perhaps also in many extra-skeletal targets throughout life, such as muscle, the immune and the cardiovascular systems, and in the control of cell proliferation and differentiation[2–4]. Therefore, vitamin D deficiency might have implications for global health well beyond those of bone and teeth.

All vitamin D_3 derives from the transformation of 7-dehydrocholesterol (and thus from *de novo* synthesis of cholesterol) into pre-vitamin D and vitamin D upon exposure to UVB rays of sunlight. The same holds true for the origin of vitamin D_2 via synthesis of ergocalciferol in yeast, fungi and plants; however, as fungi and yeast usually inhabit sun-deprived environments, their natural content of vitamin D is low. This photochemical reaction does not require specific enzymes and can be found early in the evolution of unicellular organisms such as plankton, in which this reaction was probably an important mechanism to protect DNA against photodamage[5]. During evolution, the end product, vitamin D, was largely inactive, but, early in the evolution of vertebrates (after whole-genome duplication), a true vitamin D endocrine system developed with specific enzymes responsible for a complex metabolism, a specific plasma transport system and a dedicated vitamin D receptor, which functions as a transcription factor regulating a remarkably large number of genes (from about 3% of all genes in mice and humans to 10% in zebrafish[13]). On the basis of *in vitro* and *in vivo* studies, a strong dogma exists that only UVB light (wavelength: 280–315 nm) is able to generate vitamin D; however, some data in fish seem to indicate that under specific circumstances blue light (wavelength: ~475 nm) might also be able to generate vitamin D[14].

During the whole of mammalian evolution and 99% of human evolution, access to vitamin D-rich food was limited (few food items apart from oily fish have a high content of vitamin D); consequently, endogenous synthesis of vitamin D must have been the rule with few exceptions. For most adults, UVB-induced synthesis in skin is the major source of vitamin D (estimated at >80% of requirements). However, several factors exist that can limit cutaneous synthesis such as the high melanin content of the skin, deliberately limiting exposure to sunlight (as a result of cultural, religious or other reasons), living in areas of the world with low availability of sun or migration of people with dark skin to geographical areas with limited sun exposure. In addition, we now know that the same UVB light that is essential for the synthesis of vitamin D is also a well-established photocarcinogen that increases risk of basal cell and squamous carcinomas and especially dangerous melanomas. Unsurprisingly, the highest rate of such skin cancers can be found in New Zealand and Australia owing to migration of fair-skinned Europeans into a tropical or a subtropical climate. Infants and children are especially sensitive to UVB-induced DNA damage and later risk of skin carcinomas. Early in human evolution, this risk was minimal as mean life expectancy did not exceed 35 years (such as 2,000 years ago in the Roman Empire) or 45 years (in affluent countries in Western Europe in the nineteenth century). A lag time of a few decades between UVB-induced DNA damage and clinical manifestation of skin cancer is no longer just a hypothetical problem for most humans owing to current lifespans. The close link between UVB damage and synthesis of vitamin D is also relevant to the production of endogenous endorphins and a state of euphoria (at least in mice) produced by exposure to sunlight, as these phenomena are linked to ultraviolet-induced activation of p53 (REF. 15).

Vitamin D status

Nutrition

As most foods have a low natural content of vitamin D (apart from oily fish), the dietary intake of vitamin D is low in most countries, except in those where oily fish is consumed in high quantities. A large survey in several European countries revealed that the mean intake of vitamin D is <5 μg per day in most countries, with the exception of Scandinavian countries[16]. The mean intake of vitamin D is even lower in children and elderly individuals[16]. Similarly, the mean total intake of vitamin D, including that from vitamin D-enriched food items, in North America is considerably lower than 10 μg per day[16].

Endogenous production

The amount of vitamin D that is produced by exposure to sunlight is highly controversial. On the basis of *in vitro* data obtained by UVB irradiation of skin samples, large amounts of vitamin D can be produced by whole-body irradiation, with one erythemal dose of vitamin D being able to produce ~20,000 international units (IU) of vitamin D_3 (REF. 17). However, other studies have demonstrated a lower efficacy, as a similar increase in serum levels of 25-hydroxyvitamin D (25OHD) is induced by total-body UVB exposure three times per week or by an oral daily intake of 800 IU of vitamin D[18]. Such dose–response effects have been confirmed in young Danish women (exposed to daily sunlight during a one-week

winter holiday in the Canary Islands), in whom serum levels of 25OHD increased by 21 nmol/l (equivalent to ~800 IU of oral vitamin D per day)[19]. Several guidelines recommend a daily sunlight exposure of 7–30 minutes (depending on latitude, skin colour and season) for hands, arms and the face to generate sufficient vitamin D and maintain serum levels of 25OHD above the minimal threshold required to maintain normal bone health[20–23]. As extended exposure to sunlight increases DNA damage and the synthesis of vitamin D rapidly reaches a plateau, more-frequent short-term exposures are always preferred over longer exposures. Production of vitamin D in skin is lower when dark-skinned individuals (Fitzgerald score: 4–5) are exposed to sunlight, as overall they need sixfold longer exposure to produce the same amount of vitamin D than do white-skinned individuals (Fitzgerald score: 1–3)[24]. Irrespective of the length of exposure to UVB sunlight, DNA damage occurs in the skin (as measured by levels of thymidine dimers)[19]. Many societies warn against too much sun exposure, and in 2014 the US Surgeon General issued a call-to-action to reduce ultraviolet exposure, whether from sunlight or from tanning booths, to reduce the burden of skin cancers[25].

Genetic determinants

Several twin studies have suggested that the vitamin D status as measured by serum levels of 25OHD is strongly (>50%) defined by genes[4]. Several genome-wide association studies have identified a few genes involved in the synthesis, metabolism or transport of vitamin D that are collectively able to explain not more than 5–10% of the variation in vitamin D status[26,27]. This variation is small (at most, comparable to seasonal variations) in comparison with the wide variation in serum levels of 25OHD between different populations around the world and even within homogenous populations. A polymorphism in the gene encoding vitamin D-binding protein (DBP) is the main driver of known genetic variation in levels of 25OHD[26,27]; however, the physiologic or clinical implications of this polymorphism are not known.

Nutritional guidelines for vitamin D

Two partially overlapping strategies have been used to define nutritional guidelines for vitamin D. The first strategy is based on randomized clinical trials (RCTs) that try to define the efficacy and safety of different dosages of vitamin D in different target populations by studying different end points. The second strategy is based on serum concentrations of 25OHD that are linked to specific health or disease outcomes in different target populations.

Early during the twentieth century, the amount of cod-liver oil necessary for prevention or cure of rickets was empirically defined (one teaspoon), and this was subsequently incorporated into guidelines in the form of a recommended daily intake of vitamin D (400 IU per day)[4,8–10]. More recently, this general approach was used to generate guidelines for older children, adults and elderly individuals. The later guidelines are based on well-documented, extensive literature surveys that pay special attention to RCTs, rather than to observational studies, to define the dose of vitamin D supplementation[20–22,28,29]. However, the most recent guidelines increasingly rely on results of a large number of studies that link ranges or thresholds of serum concentrations of 25OHD with musculoskeletal or extra-skeletal outcomes[20–22,28,29]. Using data from many studies that looked at the increase in serum levels of 25OHD in response to increasing oral doses of vitamin D, one can then try to calculate the minimal intake of vitamin D that is required to reach a specified 25OHD target[30,31].

The serum concentrations of 25OHD used to define vitamin D deficiency vary widely as described below. For reasons of simplicity, I define severe vitamin D deficiency as serum levels of 25OHD below 25–30 nmol/l (10–12 ng/ml) and vitamin D deficiency as serum levels of 25OHD below 50 nmol/l (20 ng/ml).

Infants and children

Vitamin D deficiency-associated rickets was highly endemic in many parts of the world at the beginning of the twentieth century. In 1917, all black children living in New York were reported to have some degree of rickets[8]. Before the discovery of vitamin D, the frequency of mild and severe rickets found at autopsy of young children from Dresden, Germany, between 1901 and 1908, was 94% and 45%, respectively[32]. Also based on autopsy data, 56% and 72% of all white and black children (aged 0–2 years), respectively, had some form of rickets, and 8% and 33%, respectively, had severe rickets in Baltimore, Maryland, USA, between 1926 and 1942 (REF. 33). Rickets is still endemic in certain areas of the world, especially in Mongolia and Northern China, Northern India and some Middle East or Gulf states[11], whereas the incidence is low (≤10 cases per 100,000 in children aged 0–2 years) in Canada[34] and New Zealand[35]. Overall, the incidence of rickets is low in most Western countries where vitamin D supplementation is well introduced. In these countries, rickets is only found in children not receiving vitamin D supplements and mostly in children with known risk factors for vitamin D deficiency. The vitamin D supplementation policy, where introduced, has undoubtedly been extremely effective in eradicating most cases of rickets.

A large consensus exists that infants should not be exposed to direct sunlight to avoid skin damage early in life, which might have long-term consequences for skin ageing and skin cancer[25,36,37]. Indeed, the skin of infants and toddlers is thinner and allows deeper penetration of ultraviolet light than that of older children or adults[37]. The advice of the Surgeon General, WHO and many dermatology and paediatric societies is simple: sun avoidance is the first-line strategy for infants, as their skin is especially permeable and prone to adverse effects when exposed to solar ultraviolet radiation[37]. When infants need exposure to light to prevent bilirubin encephalopathy, ultraviolet-free light sources are used even in dark-skinned infants[38]. The pool of vitamin D in newborn infants (as estimated from cord serum concentrations of 25OHD) is small in comparison with that in adults[39]. Indeed, the cord serum concentration of 25OHD is

strongly correlated with the maternal concentration of 25OHD but is only ~50–60% of the maternal concentration, probably as a result of the very low concentration of DBP in fetal serum in comparison with the high concentration of DBP in maternal serum[40]. Life therefore starts with a limited reserve of vitamin D. Moreover, human breast milk has a low content of vitamin D except when the maternal intake of vitamin D is unusually high owing to pharmacologic supplementation (at levels of 6,400 IU per day)[41]. Intestinal absorption of calcium is already dependent on vitamin D early in the life of humans, in contrast to rodents, in which intestinal absorption of calcium is largely vitamin D independent during lactation[42]. A good vitamin D status is therefore essential for the high positive calcium balance that is needed during the rapid growth phase early in life.

Infants should receive vitamin D supplementation from birth until the time in life that exposure to (limited) sunlight is safe and sufficient to maintain a normal vitamin D status. As rickets was a major public health problem in the past, in the mid-twentieth century most authorities and scientific organizations proposed clear guidelines for vitamin D supplementation of infants. To date, only one major randomized controlled trial, conducted in an area of Turkey with a high frequency of rickets, has demonstrated that vitamin D (at a dose of 400 IU per day) can protect against rickets[43]. However, many careful observational studies, initiated in the early twentieth century[8], have demonstrated that >200–400 IU of vitamin D_3 or vitamin D_2 can prevent vitamin D deficiency-associated rickets[44]. A more generous supply of vitamin D to infants in the UK in the 1950s (cumulative intake was frequently 4,000 IU per day) was linked with a high rate of infantile hypercalcaemia[45]. Although this small epidemic is now largely explained by genetic defects (such as those associated with Williams syndrome or mutations in *CYP24A1*, which encodes 1,25-dihydroxyvitamin D_3 24-hydroxylase[46], the enzyme responsible for the degradation of vitamin D metabolites), vitamin D supplementation of food was transiently prohibited in several countries, albeit later reintroduced. An overview of current and older guidelines for intake of vitamin D, generated by several countries and organizations, for infants and children is shown in TABLE 1.

The median dose of vitamin D that is recommended during the first year of life, as derived from guidelines from ~40 countries or authorities (TABLE 1), is ~400 IU per day (varying from 200 IU per day in many older guidelines to 850 IU per day in France). The distribution of recommended doses in the old and new guidelines is presented in FIG. 1 (the median dose is 300 IU per day, and the 25th and 75th percentiles for all 35 countries combined are 200 IU per day and 400 IU per day, respectively). Most guidelines advocate this amount of vitamin D for children aged 1–3 years; however, the Institute of Medicine (IOM)[29] recommends 600 IU per day, the DACH guidelines[21] (for German speaking countries: Germany, Austria and Switzerland) recommend 800 IU per day and the French guidelines recommend 1,000–1,200 IU per day[47]; the WHO still recommends 200 IU per day (TABLE 1). Although most guidelines now advocate 400 IU of vitamin D per day, a dose of 200 IU per day might nonetheless protect the large majority of infants and young children, based on case studies conducted during the First World War and the Second World War (now known as the inter-war years) and on the duration of such a recommendation in many Western countries.

These doses are recommended systematically for all infants (aged 0–1 years) and usually also for children aged 1–3 years (FIG. 1; TABLE 1), and can either be given as a supplement or in formulae once the daily milk intake of infants increases. Children with diseases affecting intestinal absorption or with disorders of calcium or vitamin D metabolism require an appropriate dose. Vitamin D should only be avoided in the case of rare biallelic mutations in *CYP24A1*, which can cause infantile hypercalcaemia or adult-onset nephrocalcinosis[46,48].

Most guidelines do not provide advice for premature babies. The American Academy of Pediatrics (AAP) recommends doses between 200 IU and 400 IU per day[49], whereas some European or US experts recommend 800–1,000 IU per day[50,51]. Such high doses in small infants might however result in high serum concentrations of 25OHD (>280 nmol/l in 10% of cases) and an increased calcium to creatinine ratio but without hypercalcaemia[52].

Only a limited number of studies on the health benefits of vitamin D supplementation have been conducted in older children. A meta-analysis found no significant effect of vitamin D supplementation in children on bone mass or BMD, except for a modest effect in truly vitamin D-deficient children[53]. Nevertheless most countries recommend vitamin D supplementation of older (usually defined as >3 years of age) children. The median recommendations, based on older and newer guidelines of all countries (TABLE 1), are 200 IU per day but vary between 100 IU (older guidelines for the Russian Federation), 600 IU (USA and Canada) or 800 IU per day (DACH countries). France has a fairly unique policy and recommends two doses of 80,000–100,000 IU (one in November and one in February) for children aged 18 months until 18 years of age[47]. Although the recommended daily dosage has increased in many countries, an exception is Korea, where the dose was reduced from 400 IU to 200 IU per day in 2010 (REF. 54). Most guidelines state that the combination of food-derived vitamin D and endogenous synthesis can provide this amount of vitamin D in older children and that this dose should only be given as a supplement in cases of limited effective exposure to sunlight (such as dark-skinned children living in moderate climate zones and fair-skinned children with limited solar UVB exposure).

The recommended doses, mentioned above, are usually labelled as recommended dietary allowance (RDA)[29], reference nutritional intake (RNI) or 'safe intake' (when data are insufficient to define a RNI)[28], but are all intended to cover the needs of 97.5% of the target population.

The guidelines formulated by government organizations (TABLES 1,2) are very much in line with most guidelines formulated by scientific societies. The AAP increased its previous recommendation of 200 IU per day

Table 1 | **Guidelines for intake of vitamin D in infants, children and pregnant or lactating women**

Authority and/or country (year)	Recommended intake of vitamin D (IU per day)				
	Age 0–1 years	Age 1–3 years	Age 4–18 years	Pregnancy	Lactation
*New guidelines**					
IOM (2010)[29]	400	600	600	600	600
Australia–New Zealand (2013)[23]	400	600	600	600	600
DACH (2012)[21]	400	800	800	800	800
Nordic countries (2012)[20]	400	400	400	400	400
WHO–FAO (2003/2012)[84]	200	200	200	200	200
UK (SACN 2016)[28]	340–400	400	400	400	400
Netherlands (2012)[22]	400	400	400	400	400
Belgium (2009)[74]	400	400	400	800	800
France (Société Française de Nutrition; 2012)[47]	800–1,000	400	80,000–100,000 twice a year	400	400
Endocrine society (2011)[69]	400–1,000	400–1,000	400–1,000	600–2,000	600–2,000
EFSA draft version (2016)[61]	400	600	600	600	600
Older guidelines‡					
Albania	200	200	200	200	200
Bosnia and Herzegovina (entity: Federation of Bosnia and Herzegovina)	300	400	400	300	400
Bosnia and Herzegovina (entity: Republika Srpska)	200	200	200	200	200
Brazil	200	200	200	200	200
Bulgaria	200	200	200	200	200
China	400	400	200	340	400
Croatia	ND	400	300	400	400
Estonia	ND	300	300	400	400
European Community (1993)	280–340	400	0–400	400	400
European Community	ND	400	300	400	400
Greece	ND	400	300	400	400
Hungary	400	400	400	400	400
Ireland	340	400	300	400	400
Italy	ND	400	300	400	400
Japan	180	120	160	300	300
Latvia	400	400	400	400	400
Lithuania	400	400	200	400	400
Macedonia (former Yugoslav Republic of Macedonia)	300	400	400	400	400
Mexico	200	200	200	200	200
Montenegro	200	200	200	200	200
Poland	200	200	200	200	200
Portugal	200	200	200	200	200
Romania	400	400	300	ND	ND
Russian Federation	400	400	100	500	500
Serbia	ND	400	400	ND	ND
Slovakia	300	400	400	400	400
Slovenia	300	400	400	200	200
South Korea	200	400	400	400	400
Southeast Asia region	200	200	200	200	200
Spain	400	400	200	400	400
WHO–FAO	200	200	200	200	200

This table shows the recommended intake of vitamin D in guidelines updated in the past 10 years (new guidelines) and in older guidelines. Most of the values are either recommended dietary allowance (RDA) or reference nutrient intake (RNI). However, for infants, the Institute of Medicine (IOM) and the Scientific Advisory Committee on Nutrition (SACN) use adequate intake or 'safe intake', respectively, owing to a lack of sufficient data to define a RDA or a RNI. *Data from new guidelines are obtained from elsewhere[20–23,28,29,47,61,69,74,84]. ‡Data from older guidelines are obtained from the EURRECA Micronutrient database — Serbian Nutrition database, using the Nutri-RecQuest search engine[143]. DACH, Deutschland (Germany), Austria and Confoederatio Helvetica (Switzerland); EFSA, European Food Safety Authority; FAO, Food and Agriculture Organization of the United Nations; IOM, Institute of Medicine; IU, international units; ND, not determined; SACN, Scientific Advisory Committee on Nutrition.

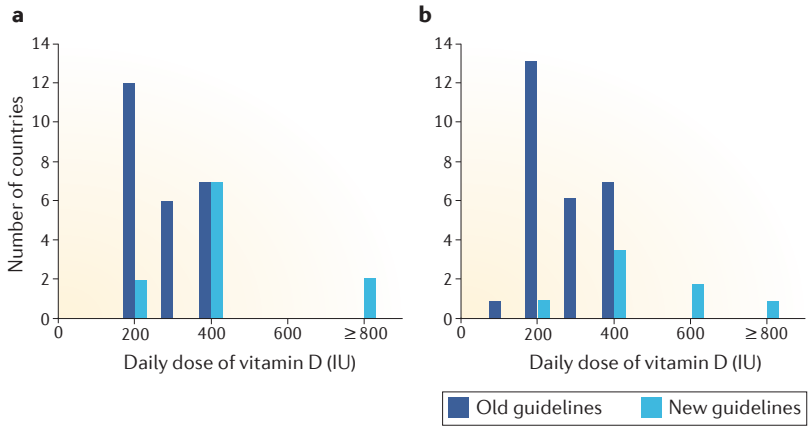

Figure 1 | **Recommended daily dose of vitamin D supplementation in children.** The graphs show vitamin D recommendations in old and new guidelines for children aged 0–1 years (part **a**) and for children aged 4–18 years (part **b**), grouped by number of countries recommending a specific dose of vitamin D. Most guidelines for children aged 1–3 years are very similar to those for infants. IU, international units.

to 400 IU per day in 2008 because of potential broader effects of vitamin D beyond prevention of rickets[55]. This dose is in fact in line with historical empirical data that one teaspoon of cod-liver oil per day (equivalent to 400 IU of vitamin D_3) is safe and efficient at preventing and even curing rickets[56]. Other major societies[57] or expert committees[12,58–60] recommend the same dosages to be given systematically to all infants. The Lawson Wilkins Pediatric Endocrine Society also recommends 400 IU per day for all breastfed infants from within days of birth until they ingest at least 1 litre of vitamin D-fortified milk[51]. The European Food Safety Authority (EFSA) announced in 2016 (in a draft version) that they also recommend a daily intake of 400 IU of vitamin D_3 for infants, whereas they recommend a daily intake of 600 IU for older children so that their serum concentrations of 25OHD reach ≥50 nmol/l. The EFSA defines these amounts as adequate intake, as it considers that insufficient data exist to define a validated populated reference intake[61].

In contrast to recommendations for older individuals (discussed in the following sections and represented in FIG. 2), vitamin D supplementation early in life has historically been largely based on selecting the dose rather than the serum level of 25OHD. An extensive discussion presented in the Scientific Advisory Committee on Nutrition (SACN) 2016 analysis[28] concluded that serum levels of 25OHD >25–30 nmol/l are a safe threshold to prevent rickets or osteomalacia and are supported by all other guidelines and expert groups[58] (FIG. 3). This concentration also corresponds to the threshold below which intestinal absorption of calcium is impaired[62,63]. Unfortunately, most immunoassays are not able to reliably measure such low concentrations of 25OHD owing to analytical problems, and consequently some discrepant values[64] are sometimes found in children with obvious rickets and sufficient calcium intake. Studies looking at the dose–response curve have shown that 400 IU per day is largely sufficient to bring serum levels of 25OHD well above 25 nmol/l in nearly all infants and otherwise healthy children. For example, 400 IU of vitamin D_3 or vitamin D increased serum levels of 25OHD above 50 nmol/l when given to breastfed infants from the first month of life onwards until 12 months of life[65], whereas 1,600 IU per day was discontinued owing to extremely high levels of 25OHD (>180 nmol/l at 3 months). Earlier studies also reported that doses above 1,800 IU per day might impair infant growth[66]. High-pulse doses (>100,000 IU) of vitamin D can also increase serum levels of 25OHD well above the normal range and can sometimes cause hypercalcaemia[67,68].

Most guidelines (including those of the IOM[29] and those of Nordic (Sweden, Finland, Norway, Denmark and Iceland)[20] and DACH countries[21]) recommend serum levels of 25OHD >50 nmol/l in children (FIG. 3), whereas the SACN considers a serum level of 25OHD >25 nmol/l to be sufficient for infants, children and all adults[28]. Scientific groups also support this recommendation, with the AAP[55] supporting serum levels of 25OHD of 50 nmol/l (REF. 57). By contrast, the Endocrine Society task group[69] recommends an optimal serum concentration of 25OHD of >75 nmol/l in children (as they do in adults). Despite this divergence in 25OHD targets, a dose of 400 IU per day for infants and 400–600 IU per day (with one exception of 800 IU per day in the DACH countries) for older children is fairly unanimously recommended (TABLE 1).

Of course, all experts also recommend an age-dependent minimum intake of calcium to avoid calcium deficiency-associated rickets[58]. Some data suggest that a high vitamin D status during the perinatal period might decrease the risk of immune or other diseases in offspring, such as asthma, diabetes mellitus and multiple sclerosis[70–72]. This plausible hypothesis is based on the effects of vitamin D on the deletion of autoreactive T cells or similar immune effects; however, as the efficacy and long-term safety of such a strategy is not known, doses higher than what is generally recommended and certainly doses higher than the upper limit (2,000 IU per day for infants and up to 4,000 IU per day for older children or adults[73]) should not be used beyond the confines of clinical trials.

Pregnant and lactating mothers

The demand for calcium increases substantially during pregnancy and especially during lactation; levels of DBP also double during pregnancy. This combination leads to marked increases in serum levels of total 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) throughout pregnancy and in free 1,25$(OH)_2$D at the end of pregnancy[40], without a consistent change in serum levels of 25OHD. As requirements for vitamin D do not seem to change during pregnancy or lactation, most agencies, except that of Belgium[74] (TABLE 1), conclude that the RDA or the RNI are not different from those for the adult population. France has a long-standing tradition of recommending a loading dose of 80,000–100,000 IU of vitamin D during the third trimester of pregnancy[47], which results in a mean cord concentration of 25OHD of 20 ng/ml (REF. 75).

Table 2 | **Guidelines for intake of vitamin D in adults and elderly individuals**

Authority and/or country (year)	Recommended intake of vitamin D (IU per day)			
	Age 20 years	Age 50 years	Age 65 years	Age >75 years
New guidelines*				
IOM (2010)[29]	600	600	600	800
Australia–New Zealand (2013)[23]	600	600	600	800
DACH (2012)[21]	800	800	800	800
Nordic countries (2012)[20]	400	400	400	800
WHO–FAO (2003/2012)[84]	200	200	200	200
UK (SACN; 2016)[28]	400	400	400	400
Netherlands (2012)[22]	400	400	800	800
Belgium (2009)[74]	400	400	400	800
France (Société Française de Nutrition; 2012)[47]	200	200	400–600	400–600
Endocrine Society (2011)[69]	600–2,000	600–2,000	600–2,000	800–2,000
EFSA draft version (2016)[61]	600	600	600	600
***Older guidelines**‡*				
Albania	400	400	ND	600
Bosnia and Herzegovina (entity: Federation of Bosnia and Herzegovina)	400	200	200	200
Bosnia and Herzegovina (entity: Republika Srpska)	200	200	600	600
Brazil	200	200	200	200
Bulgaria	200	200	400	500
China	200	300	400	400
Croatia	200	200	200	200
Estonia	300	300	400	400
European Community	200	200	400	400
Greece	200	200	400	400
Hungary	200	220	220	220
Ireland	400	400	600	600
Italy	200	300	400	400
Japan	200	200	200	200
Latvia	200	200	200	200
Lithuania	200	200	ND	ND
Macedonia (former Yugoslav Republic of Macedonia)	300	200	200	200
Mexico	200	200	400	600
Montenegro	200	200	400	600
Poland	200	200	400	600
Portugal	200	200	500	600
Romania	200	200	200	200
Russian Federation	100	100	100	100
Slovakia	300	233	200	200
Slovenia	200	200	250	300
South Korea	200	400	400	400
Southeast Asia Region	200	200	500	600
Spain	200	400	600	600
WHO–FAO	200	200	500	600

This table shows the recommended intake of vitamin D in guidelines updated in the past 10 years (new guidelines) and in older guidelines. *Data from new guidelines are obtained from elsewhere[20–23,28,29,47,61,69,74,84]. ‡Data from older guidelines are obtained from the EURRECA Micronutrient database — Serbian Nutrition database, using the Nutri-RecQuest search engine[143]. DACH, Deutschland (Germany), Austria and Confoederatio Helvetica (Switzerland); EFSA, European Food Safety Authority; FAO, Food and Agriculture Organization of the United Nations; IOM, Institute of Medicine; IU, international units; ND, not determined; SACN, Scientific Advisory Committee on Nutrition.

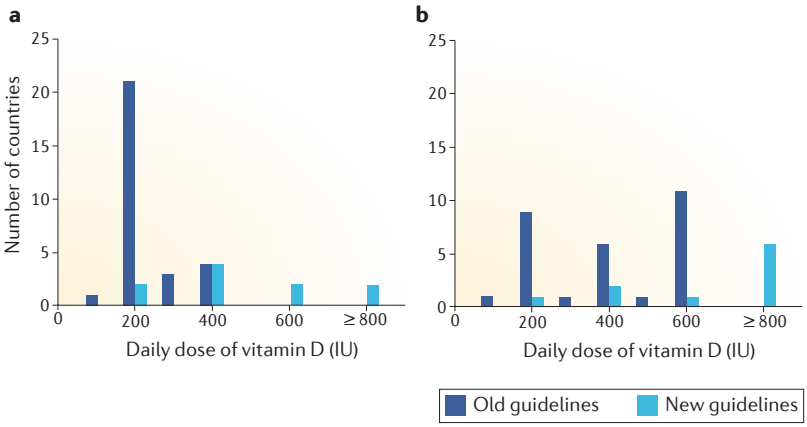

Figure 2 | **Recommended daily dose of vitamin D supplementation in adults.** The graphs show vitamin D recommendations in old and new guidelines for adults (part **a**) and for elderly individuals (part **b**), grouped by number of countries recommending a specific dose of vitamin D. IU, international units.

Many pregnant women around the world have suboptimal or poor vitamin D status[76–78]. In a meta-analysis of 31 studies, low serum concentrations of 25OHD were associated with increased risk of gestational diabetes mellitus, pre-eclampsia and having an infant born small for gestational age[78]. Poor maternal vitamin D status is also associated with a wide range of diseases in offspring, such as low bone mass at age 9 years, as well as with a high risk of schizophrenia, type 1 diabetes mellitus, multiple sclerosis or atopic diseases[79,80]. An extensive Cochrane analysis of 15 vitamin D-supplementation studies[80] and other intervention studies using 1,000 IU per day[79] or 4,000 IU per day[81,82] during pregnancy demonstrated improved vitamin D status of the mother and infants, with some benefits in mothers who were severely vitamin D deficient at baseline. However, the overall beneficial effects were not consistent for the mothers or their offspring. Two recent studies published after the publication of the guidelines described in TABLES 1,2 found marginal effects of vitamin D supplementation in pregnant women on the risk of asthma in their offspring[70,71]; however, an editorial comment clearly noted that these data were insufficient for formulating new guidelines for vitamin D supplementation during pregnancy[83]. In any case, the guidelines from different governmental organizations (in general, published before these recent intervention studies) concluded that insufficient evidence exists to define an optimal intake of vitamin D or serum concentration of 25OHD specifically for pregnant or lactating women. Therefore, the guidelines for pregnant or lactating women do not differ from those for other adults. However, it might be wise to pay greater attention to women of reproductive age to ensure optimal compliance with existing guidelines for micronutrient and macronutrient intake during pregnancy and lactation[12]. In 2016, the EFSA announced (in a draft version) a recommended daily intake (defined as adequate intake) of 600 IU of vitamin D_3 for pregnant and lactating women to achieve serum levels of 25OHD of 50 nmol/l (REF. 61).

Overall, fairly large agreement exists that pregnant or lactating women do not need more vitamin D than do other adult women. The dosage recommended in most recently updated guidelines varies between 400 IU and 800 IU per day, but, again, the WHO is an outlier with a recommendation of 200 IU per day[84]. Moreover, the guidelines are probably not strictly implemented, and this should be better respected and supported to avoid increased short-term and long-term risks for both mothers and their offspring.

Adults

Many adults frequently have a mild or even severe chronic vitamin D deficiency as a result of their low serum concentration of 25OHD. This deficiency is due to many factors such as geography (latitude and climate), behaviour (exposure to sunlight), skin colour, genes and body weight. In several worldwide overviews, the mean concentration of 25OHD in adults was not much higher than 50 nmol/l (REFS 85,86). In two large cohorts of adult or elderly men in North America (the Osteoporotic Fractures in Men study) and Europe (the European Male Ageing Study), the mean serum concentration of 25OHD was 62.5 nmol/l (REFS 87,88). The optimal vitamin D status is defined, and certainly interpreted, in different ways, and this defines the frequency of what is called severe or modest vitamin D deficiency. Severe vitamin D deficiency (defined as serum levels <25 nmol/l) is very common in many developing countries (affecting up to 50% of the population)[89], whereas it is less common in the USA (affecting 6% of the population, according to the latest National Health and Nutrition Examination Survey (NHANES) study, which used standardized measurements of 25OHD[90]). Such low serum concentrations of 25OHD are virtually non-existent in black people living closer to the equator[91,92]. Defined as serum levels of 25OHD between 25 nmol/l and 50 nmol/l, modest vitamin D deficiency affects more than a quarter of all humans around the world[85,86]. According to some criteria, serum levels of 25OHD should be >75 nmol/l, which would mean that the vast majority of mankind can be considered to have vitamin D 'insufficiency' (REF. 93). Some grassroots organizations and vitamin D experts[94,95] recommend a serum concentration of 25OHD >100 nmol/l (40 ng/ml) in all adults or elderly individuals, levels found in Africans living in the Palaeolithic age. However, such concentrations are found in less than a few percent of the apparently healthy US or European population, who are not taking high-dose vitamin D supplements[90].

As few long-term intervention studies with vitamin D supplementation have been conducted in adults, in contrast to studies in elderly individuals, defining evidence-based guidelines for intake of vitamin D in adults is extremely difficult. The frequency of osteomalacia (a sign of very severe and long-term vitamin D deficiency) in adults is also controversial, as most experts consider this condition to occur very rarely in otherwise healthy individuals[96,97], although a slightly higher prevalence (2–4%) has been found in young Pakistani women[98]. However, one large-scale study in Germany came to a totally different conclusion[99]. On the basis of

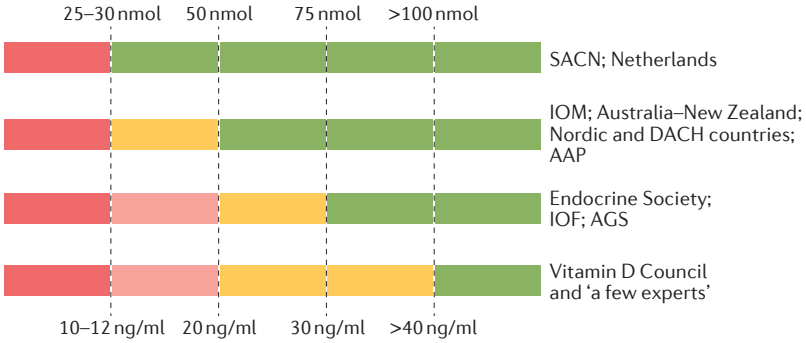

Figure 3 | **Recommendations for interpreting serum levels of 25OHD.** A schematic representation of how different agencies and countries interpret serum levels of 25-hydroxyvitamin D is shown. Colour code: red denotes a state of severe deficiency (danger) that has to be corrected without exception; orange denotes a state of mild deficiency (modest concern), in which intervention is desirable; green denotes a state of sufficient supply that does not benefit from additional supplementation. AAP, American Academy of Pediatrics; AGS, American Geriatrics Society; DACH, Deutschland (Germany), Austria and Confoederatio Helvetica (Switzerland); IOF, International Osteoporosis Foundation; IOM, Institute of Medicine; SACN, Scientific Advisory Committee on Nutrition.

autopsy data on bone from German adults who died accidentally, histologic signs of severe osteomalacia (osteoid/total bone volume >5%) were found in 5% of individuals, and up to 25% showed signs of modest osteomalacia. This population was also severely vitamin D deficient, as the mean serum concentration of 25OHD was slightly below 25 nmol/l. No cases of severe osteomalacia were found in individuals with serum concentrations of 25OHD >75 nmol/l (REF. 99). However, this study has been seriously criticized, as the criteria for the definition of osteomalacia might have been too lax and serum measurements of 25OHD in post-mortem blood samples were done using immunoassays prone to matrix effects[62,100]. Overall, owing to a lack of solid data, defining bone and health implications of vitamin D status in adults around the world is extremely difficult.

This difficulty is also reflected in the range of recommended doses of vitamin D (TABLE 2). The mean recommended intake of vitamin D based on old and new guidelines is 200 IU per day (25th and 75th percentiles being 200 IU and 400 IU per day, respectively) (FIG. 2), whereas most recently updated guidelines recommend ≥600 IU per day for adults with minimal exposure to sunlight (TABLE 2). The UK is an exception and still recommends only 400 IU per day. Little agreement exists between the recommended vitamin D-supplementation guidelines by government organizations and recommendations by scientific societies. Some organizations (UK[28] and Netherlands[22]) just recommend to avoid severe vitamin D deficiency (defined as serum levels of 25OHD <25 nmol/l) and thus conclude that 400 IU per day is sufficient to reach this level in most individuals. Other organizations advocate maintaining serum concentrations of 25OHD above 50 nmol/l (REFS 20,21,29) (FIG. 3) and thus recommend an intake of 600 IU or 800 IU per day when exposure to sunlight is limited. The Australian–New Zealand guidelines[23] also recommend maintaining serum concentrations of 25OHD above 50 nmol/l in all older children and adults around the year; however, to safeguard such levels in late winter and spring, they recommended that summer values of 25OHD should be 10–20 nmol/l higher than the 50 nmol/l threshold.

The National Osteoporosis Foundation (NOF) 'supports' the IOM guidelines but nevertheless recommends an intake of 800–1,000 IU of vitamin D per day for adults aged ≥50 years[101]. Other science organizations or expert groups advocate maintaining serum concentrations of 25OHD >75 nmol/l (FIG. 3) and therefore recommend much higher dosages of vitamin D. These recommendations are usually not based on results from randomized controlled trials but derived from observational studies linking vitamin D status with musculoskeletal and especially non-skeletal outcomes. The Endocrine Society guidelines are complex, recommending a 75 nmol/l target while endorsing the IOM recommendation but then recommending a higher intake (up to 2,000 IU per day or higher until the target level is reached) for a long list of individuals at increased risk of vitamin D deficiency[93]. Very recently, the EFSA announced (in a draft version) that they also recommend a daily intake (defined as adequate intake) of 600 IU per day of vitamin D_3 to enable adults to reach serum concentrations of 25OHD of 50 nmol/l. If the target group has sufficient endogenous production of vitamin D as a result of sun exposure, the nutritional requirement can be decreased to nill[61].

Elderly individuals

Although vitamin D deficiency-associated rickets was endemic at the beginning of the twentieth century and was nearly eradicated in most Western societies by the midst of that century, by the end of the twentieth century vitamin D deficiency was endemic in most elderly individuals in large parts of the world. Low serum concentrations of 25OHD in elderly individuals and the 'old-old' (>85-years-old individuals) have been demonstrated again and again[85,102–104] in countries with moderate climates, as well as in very sunny countries[105]. Intestinal absorption of vitamin D is unlikely to be a contributor to the low vitamin D status, as it is not markedly impaired by old age[106]. The deficiency is probably largely due to low nutritional intake of vitamin D and especially due to sun-avoidance behaviour, which is aggravated by a modestly decreased synthetic capacity of the skin when exposed to sunlight[107].

The consequences of this deficiency are not obvious, as mild osteomalacia is less easily visible than signs and symptoms of rickets. Despite the high frequency of low concentrations of 25OHD, the prevalence of clinical osteomalacia in elderly individuals with normal renal and gastrointestinal function is low. However, vitamin D deficiency in elderly individuals is a contributing factor to the increased risk of osteoporosis and low trauma fractures, as it has been demonstrated in a large number of observational (cross-sectional and prospective) studies and, more convincingly, in intervention trials. A large number of meta-analyses (about the same number as the number of primary RCTs) of the intervention trials in elderly individuals have been performed, and the majority of such studies confirm a modest (10–20%)

decrease in risk of fracture in those individuals receiving ~800 IU of vitamin D_3 per day[62,108–110] when combined with a good intake of calcium.

This reduction in risk of fracture is particularly noticeable in individuals with a poor vitamin D status before supplementation (such as those in institutional care). In an extensive trial sequential meta-analysis, combined supplementation of vitamin D and calcium was found to modestly decrease the risk of all fractures (−8%) and hip fractures (−16%), whereas vitamin D monotherapy had no skeletal benefits[111]. Oral vitamin D_2 has less-convincing effects, and high-dose (>300,000 IU) intermittent administration of vitamin D can even result in a transient increase in the risk of fractures and falls[112–114]. The link between vitamin D deficiency and muscle function is debated; however, muscle weakness, especially of the proximal skeletal muscles in cases of severe $1,25(OH)_2D$ deficiency (as in 25-hydroxyvitamin D_3 1α-hydroxylase deficiency or severe chronic renal failure), is clinically obvious and rapidly improves after correction of the deficiency[4]. Correction of severe vitamin D deficiency (defined as baseline concentrations of 25OHD <25 nmol/l) can improve (proximal) muscle strength and decrease the risk of falls in elderly individuals when physiological doses are used[115]; however, higher doses can be detrimental[116]. The beneficial effects of supplementation in individuals with less severe vitamin D deficiency are disputed[28,29,115]. Extraskeletal benefits of vitamin D supplementation in elderly individuals beyond the musculoskeletal system are plausible (as deduced from many observational studies), especially in severely vitamin D-deficient individuals; however, so far, these benefits have not been well established by large-scale intervention studies[62,111,117,118]. The many ongoing randomized studies (which include >100,000 individuals) can be expected to answer this question in the next 5 years[62,119–121].

On the basis of the high frequency of low serum levels of 25OHD and the positive, albeit modest, overall effects of vitamin D supplementation on the musculoskeletal system, it is not surprising that a fairly large consensus exists among all guidelines that vitamin D supplementation is needed or desirable for all elderly individuals (TABLE 2). However, the recommended dosages are quite different. The older guidelines recommend a median dose of 400 IU per day for those individuals aged >65 years or for those aged >75 years (TABLE 2), varying from 100 IU per day in the Russian Federation to 600 IU per day in many European countries and according to the joint WHO and Food and Agriculture Organization of the United Nations (FAO). Most guidelines from countries with a more recent (<10 years) update recommend ~800 IU per day for elderly individuals (>75 years); one major exception is the UK[28], which only recommends 400 IU per day (TABLE 2). In 2016, the EFSA announced a recommended adequate intake of 600 IU per day for adults, with no increase in dose with advancing age[61]. In most guidelines, this dose is recommended in situations of limited exposure to UVB sunlight, but, as such exposure is generally very low in elderly individuals, it is implicitly or explicitly recommended that such an intake should be reached by nearly systematic supplementation. Many expert groups[122], the standing committee of medical doctors[123], as well as several scientific societies (such as the International Osteoporosis Foundation (IOF)[124] and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)[125]) agree on a consensus for 800 IU of vitamin D per day for elderly individuals with limited exposure to sunlight (that is, nearly all elderly people). The European Menopause and Andropause Society (EMAS)[126] recommends 800–1,200 IU of vitamin D per day to achieve serum levels of 25OHD of 75–225 nmol/l (and, if needed, doses up to 10,000 IU per day), whereas the American Geriatrics Society (AGS)[127] recommends at least 1,000 IU per day for musculoskeletal benefits. In the same document, the AGS also recommends achieving serum concentrations of 25OHD >75 nmol/l and suggests either at least 4,000 IU per day for all elderly individuals or the use of an individualized stepwise increase in intake of vitamin D until such a concentration is reached[127]. The median recommended intake from all countries combined is 400 IU per day (25th and 75th percentiles being 200 IU per day and 600 IU per day, respectively), but most recently updated guidelines recommend 800 IU per day for those aged >75 years (FIG. 2; TABLE 2).

Using a full dose–response curve, several studies have defined the oral dose of vitamin D that is needed to reach a set point in 97% of the target population (>600–800 IU per day)[30,31,128]; however, this dose might not be suitable for individuals with severe obesity[129]. Most studies agree that defining a suitable dose for reaching serum concentrations of 25OHD ≥75 nmol in 97.5% of the target population is impossible without increasing serum concentrations of 25OHD to the supraphysiological range in a large subset of individuals, owing to large inter-individual differences and to the plateau of serum concentrations of 25OHD that is frequently observed with high intake of vitamin D[30].

Vitamin D toxicity

Vitamin D toxicity due to intake of natural foods or excessive sun exposure is exceptionally rare[130], probably because of the extensive set of mechanisms that protect people from overexposure to UVB light[4]. However, as with other fat-soluble vitamins, toxicity can be serious and even lethal when children or adults are exposed (repeatedly) to pharmacologic amounts of vitamin D. Apart from hypercalcaemia and kidney stones, ectopic calcifications of soft tissues and vasculature can be devastating. The final proof of toxicity is that vitamin D is used as an efficient rat poison. No consensus has been reached about the dosages causing toxicity or about the upper safe limit of levels of 25OHD. However, it should be remembered that no individuals living in East African 'natural world conditions' have serum levels of 25OHD >250 nmol/l (REF. 91). The guidelines of the IOM[29] and EFSA[73] are very straightforward in recommending an upper daily dose of 2,000 IU per day for infants and 4,000 IU per day for adults. Despite this clear agreement, some grassroots organizations and companies recommend or provide formulae for daily use of 5,000–10,000 IU per day. In addition, polymorphisms in *CYP24A1* influence serum concentrations of 25OHD[26],

and some mutations have major effects on the toxicity of smaller dosages of vitamin D[46,48]. With hindsight, these polymorphisms are probably one of the major reasons for the small epidemic of infantile hypercalcaemia in England in the 1950s[45]. Indeed, the combined effects of supplements added to different foods can lead to an overall intake of as much as 4,000 IU per day and result in symptomatic vitamin D-induced hypercalcaemia in some children with increased sensitivity to vitamin D (probably attributable to *CYP24A1* mutations)[131,132].

Conclusions

Worldwide awareness of vitamin D deficiency and its consequences is at an all-time high. Substantial harmony exists in all guidelines that serum concentrations of 25OHD <25–30 nmol/l should be avoided in all age groups, as low levels are a risk factor for rickets and osteomalacia. Virtually no individuals of African descent living close to the equator have such low serum levels of 25OHD, whereas this low concentration is found in 6% and 36% of black individuals living in South Africa and the USA, respectively[92]. About 5% of participants in the US NHANES study had serum concentrations of 25OHD <25 nmol/l (REFS 133,134), and ~13% of Europeans have average annual serum levels of 25OHD <30 nmol/l (measured using a 25OHD assay calibrated according to the Vitamin D Standardization Program)[103]. A good strategy is therefore needed to correct this severe deficiency. Serum concentrations of 25OHD between 25 nmol/l and 50 nmol/l are highly prevalent and are frequently considered as a deficiency state that needs correction. Individuals with such serum concentrations should not be considered to have an active disease but rather to be at increased risk of musculoskeletal diseases, similar to the increased risk of cardiovascular events with hypercholesterolaemia or the increased risk of goitre or hypothyroidism with modest iodine deficiency. Moreover, the IOM and most other guidelines conclude that serum levels of 25OHD >50 nmol/l are sufficient for 97.5% of the general population. This conclusion suggests that serum levels of 25OHD between 25 nmol/l and 50 nmol/l are not necessarily a deficiency for everybody. For example, according to the IOM, serum levels of 25OHD of 40 nmol/l are sufficient for half of the population of the USA. Therefore, if at a population level the mean concentration of 25OHD is 40 nmol/l, 50% of that population is vitamin D replete[135]. Nevertheless, on an individual level, defining who needs >40 nmol/l is not currently possible. A wise strategy is therefore to use a combination of safe sun exposure, vitamin D-rich or vitamin D-fortified foods and, if needed, vitamin D supplements to achieve serum levels of 25OHD >50 nmol/l for most of the year.

Most countries have detailed nutritional guidelines for vitamin D, and these guidelines have been updated during the past 10 years in many countries (TABLES 1,2). Some notable exceptions exist, as few African countries have specific guidelines, and India does not even mention vitamin D in its nutritional guidelines[136], despite the frequency of very-low vitamin D status in many Northern Indian states. Japan is also an outlier, as no real government guidelines are available apart from a description of the mean intake at different ages (used to define dietary reference intakes for Japanese people), which seems to be regarded as 'sufficient' without further action. The dosage varies in Japan from 100 IU per day to 140 IU per day for infants and children, up to ~200 IU per day for adolescents, adults and elderly individuals[137]. Finding pharmaceutical preparations of vitamin D in Japan also seems to be difficult. However, the joint committee of the Japanese Society for Bone and Mineral Research (JSBMR), The Japan Endocrine Society (JES) and the Expert Panel supported by the Japanese Ministry of Health, Labor and Welfare is preparing a new document that defines serum levels of 25OHD for the Japanese population much in line with the recommendations of the Endocrine Society[138].

A large consensus exists around the world that infants (up to 1 years of age) should not be exposed to sunlight and thus require systematic vitamin D supplementation. The average recommended dose (FIG. 1; TABLE 1) is 400 IU per day, with some exceptions in older guidelines (TABLE 1) and notably also in the WHO and FAO recommendations (200 IU per day). For children aged >1 year and adults, most guidelines assume that the combination of dietary vitamin D and 'prudent or wise' sun exposure should be sufficient to maintain a normal vitamin D status. No guidelines mention tanning booths to correct vitamin D deficiency. Moreover, many experts, especially those from the dermatology or cancer fields, warn against using tanning booths during adulthood and insist on absolute prohibition of their use during childhood. If people have limited access to sunlight (according to their skin phenotype), vitamin D supplementation is recommended in all guidelines (TABLES 1,2). However, the recommended dose is highly controversial. The UK[28] and Netherlands[22] consider 400 IU per day to be sufficient to maintain serum levels of 25OHD >25 nmol/l and thus protect against mineralization defects. In line with the wording of the SACN, "it is recommended that the serum 25(OH)D concentrations of all individuals in the UK should not fall below 25 nmol/l at any time of the year." (REF. 28) This threshold is considered to represent a 'population-protective level', that is, a concentration below which a risk of poor musculoskeletal health exists and above which the risk is decreased at a population level (for all age groups). However, most other recently updated guidelines[20,21,23,29] recommend 600 IU (or even 800 IU) per day to reach serum concentrations of 25OHD of 50 nmol/l in 97.5% of the target population (FIG. 3). No governmental organizations recommend higher intakes of vitamin D to achieve 75 nmol/l (or higher), unlike the Endocrine Society, the IOF and the EMAS. Some experts or grassroots organizations even recommend that all adults should aim for serum levels of 25OHD of ≥125 nmol/l, as found in African individuals living in conditions similar to our Palaeolithic ancestors. This discrepancy is probably largely due to the high degree of reliance on RCTs (or meta-analyses of such RCTs) by governmental organizations, whereas several experts and some science organizations (such as the Endocrine Society) also include epidemiologic and/or observational data in their final analysis. The superiority of clear positive or negative results obtained by RCTs is hardly debated, but several epidemiologists and vitamin D

Box 1 | **Research agenda and recommendations**

- The mode of action of vitamin D on absorption of calcium in the intestine, which is the major target of vitamin D, is not completely understood and requires further research
- The definition of vitamin D deficiency is still unclear, and a marker of vitamin D deficiency (such as TSH for thyroid hormone deficiency) would be most welcome. Indeed, high levels of parathyroid hormone (secondary hyperparathyroidism) would be expected to be a good marker for a low vitamin D status, but in reality this is not the case. Consequently, a better marker than serum levels of 25-hydroxyvitamin D (25OHD) is needed to diagnose vitamin D deficiency
- The health benefits (and thresholds) of vitamin D beyond those on the skeleton need clarification; appropriate randomized controlled trials are needed to define which dosages or serum concentrations of 25OHD are desirable to achieve these benefits
- The role of extra-renal 1α-hydroxylation of 25OHD and, similarly, the relative importance of free versus total 25OHD (or other metabolites) should be resolved

experts prefer long-term observational data over short-term 'null results' obtained from RCTs[139–141]. Although agreeing that well-documented long-term observational data can generate very plausible hypotheses, I can only state that the authors of most governmental guidelines gave priority to RCTs over observational data, and this opinion seems to be strengthened by the simple fact that about ~3,000 RCTs on vitamin D supplementation are ongoing (for further details, see ClinicalTrials.gov).

For pregnant and lactating women, most authorities or societies do not recommend intakes of vitamin D higher than those for otherwise healthy adults. However, in view of the possible consequences of vitamin D deficiency during pregnancy on maternal health or of the long-term consequences on health of the fetus, neonate and, later, of the offspring, it is highly desirable that pregnant and lactating women should be vitamin D replete, and this requires some vitamin D supplementation, especially in groups at risk of vitamin D insufficiency.

A larger consensus exists regarding the need for vitamin D supplementation in elderly individuals, as they usually have very limited exposure to sunlight, and several intervention studies have demonstrated that vitamin D supplementation (in combination with good intake of calcium) can modestly reduce the risk of musculoskeletal problems (such as falls and fractures). The recommended dose is again, as in adults, largely dependent on the recommended 25OHD target concentration, which is 400 IU per day in the UK[28] and in many older guidelines; most recently updated guidelines nearly unanimously support a daily intake of 800 IU per day (TABLE 2).

Although vitamin D was discovered about a century ago, many essential gaps exist in our understanding of the biology and clinical implications of vitamin D (BOX 1). Although sunlight was the main source of vitamin D during more than 99% of human evolution, it is now clear that, mainly owing to the enormously increased longevity, we need to strive for a delicate balance between limited exposure to sunlight (to avoid skin damage) and optimal vitamin D status. In many cases, this balance implies that vitamin D supplementation is needed. Consequently, vitamin D is probably the most commonly used 'drug' in the world. Health authorities and scientific societies have now generated a wealth of guidelines to prevent or correct vitamin D deficiency worldwide.

Guidelines always need an implementation strategy that is optimized for each target group. As example, only a minority of children in the USA met the AAP 2008 guidelines, and this is especially true for breastfed children (<15% met the 2008 guidelines or even the lower 2003 guidelines)[142]. Similarly, <50% of elderly Europeans, even in institutional care, take vitamin D supplements, let alone the recommended dosage. The WHO, supported by its member states, should take up its essential role in defining a strategy to eliminate vitamin D deficiency-associated rickets worldwide. Similarly, in line with its essential role, the WHO should define and implement a research agenda to better define the role of vitamin D during reproduction and the perinatal period (BOX 1). In the meantime, the WHO should strive to convince its member states to implement strategies to optimize the vitamin D status of pregnant and lactating women. In general, health authorities around the world should monitor the correct implementation of their nutritional guidelines in their population and especially in those subgroups at the highest risk of vitamin D deficiency. Countries or major organizations that have not updated their guidelines in the past 10 years should do so in the near future, which can easily be done using the extensive documents generated by major governmental organization such as, but not limited to, the SACN, the IOM and the Nordic countries.

Currently, far too many people do not receive the amount of vitamin D that they need, despite updated guidelines for intake of vitamin D in many countries. In addition, a small group of people and 'addicts' take too much vitamin D as a result of the misconception that 'more of a good thing should be better'; experience with other micronutrients has amply proved that such high dosages are not necessarily more efficient or even safe. Although many gaps still exist in our understanding of the physiology and clinical implications of vitamin D, progress made over the past decades has made an impression. The ongoing attention means that the future for vitamin D is 'sunny'.

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FURTHER INFORMATION
American Academy of Pediatrics (AAP): https://www.aap.org/
American Geriatrics Society (AGS): http://www.americangeriatrics.org/
ClinicalTrials.gov: https://clinicaltrials.gov/
European Food Safety Authority (EFSA): https://www.efsa.europa.eu/
European Menopause and Andropause Society (EMAS): http://www.emas-online.org/
European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO): http://www.esceo.org/
Endocrine Society: https://www.endocrine.org/
Food and Agriculture Organization of the United Nations (FAO): http://www.fao.org/
Institute of Medicine (IOM): http://www.nationalacademies.org/hmd/
International Osteoporosis Foundation (IOF): https://www.iofbonehealth.org/
Japan Endocrine Society (JES): http://square.umin.ac.jp/endocrine/english/
Japanese Society for Bone and Mineral Research (JSBMR): http://jsbmr.umin.jp/en/
National Osteoporosis Foundation (NOF): https://www.nof.org/
Nutri-RecQuest: http://www.serbianfood.info/eurreca/index.php
Scientific Advisory Committee on Nutrition (SACN): https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition
Vitamin D Council: https://www.vitamindcouncil.org/
WHO: http://www.who.int/

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