Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society

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(Dedicated to the memory of Prof. Steven Boonen and Prof. Silvano Adami)

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Abstract

Vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) <50 nmol/L or 20 ng/mL) is common in Europe and the Middle East. It occurs in <20% of the population in Northern Europe, in 30–60% in Western, Southern and Eastern Europe and up to 80% in Middle East countries. Severe deficiency (serum 25(OH)D <30 nmol/L or 12 ng/mL) is found in >10% of Europeans. The European Calcified Tissue Society (ECTS) advises that the measurement of serum 25(OH) D be standardized, for example, by the Vitamin D Standardization Program. Risk groups include young children, adolescents, pregnant women, older people (especially the institutionalized) and non-Western immigrants. Consequences of vitamin D deficiency include mineralization defects and lower bone mineral density causing fractures. Extra-skeletal consequences may be muscle weakness, falls and acute respiratory infection, and are the subject of large ongoing clinical trials. The ECTS advises to improve vitamin D status by food fortification and the use of vitamin D supplements in risk groups. Fortification of foods by adding vitamin D to dairy products, bread and cereals can improve the vitamin D status of the whole population, but quality assurance monitoring is needed to prevent intoxication. Specific risk groups such as infants and children up to 3 years, pregnant women, older persons and non-Western immigrants should routinely receive vitamin D supplements. Future research should include genetic studies to better define individual vulnerability for vitamin D deficiency, and Mendelian randomization studies to address the effect of vitamin D deficiency on long-term non-skeletal outcomes such as cancer.

European Journal of Endocrinology
(2019) **180**, P23–P54

European Journal of Endocrinology

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-18-0736

Published by Bioscientifica Ltd.

Introduction

The clinical practice committee of the European Calcified Tissue Society (ECTS) met during the European Calcified Tissue Symposium at Stockholm in May 2012. The different guidelines of the Institute of Medicine (IOM) and the Endocrine Society (1, 2) were discussed, including their different scopes, the many uncertainties surrounding the required circulating 25-hydroxyvitamin D (25(OH)D) concentrations, supplementation doses and extra-skeletal effects of vitamin D (3). While the IOM's recommendations were directed at population health, the Endocrine Society guidelines aimed at a clinical care perspective. The members agreed that a European statement outlined in a position paper would be appropriate. A working group was established to prepare a position statement regarding various aspects of vitamin D deficiency and prevention for Europe and the Middle East. Such a document should be appropriate following the recent reports of the IOM, the guidelines of the Endocrine Society, the statement of the Standing Committee of European Doctors and reports from the Scientific Advisory Committee on Nutrition (SACN) (https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report) in the UK, the European Food Safety Authority (EFSA) (https://www.efsa.europa.eu/en/efsajournal/pub/4547) for Europe as well as the ongoing discussions in the American, European and international journals.

The present position paper discusses assessment of vitamin D status and standardization of measurement of 25(OH)D concentration. It includes an overview of the vitamin D status and vitamin D intake in different European and Middle East countries, the prevalence of vitamin D deficiency according to different thresholds, the required circulating 25(OH)D concentrations and required vitamin D intake (from food and/or supplements) to prevent vitamin D deficiency and possible impact on skeletal and non-skeletal outcomes. The perspective of the ECTS Working Group was the whole population, including risk groups such as children, older persons and immigrants. Data on food fortification policy and the use of supplements in risk groups are included. The ECTS Working Group discussed strategic options and proposes possible implementation strategies for adults and elderly subjects in Europe and the Middle East. Finally recommendations and a research agenda are presented.

Assessment of serum 25-hydroxyvitamin D

There is a general consensus, also adopted by the ECTS, that the serum/plasma 25(OH)D concentration is the best indicator of vitamin D nutritional status, as it reflects the contributions from diet and dermal production in response to ultraviolet B (UVB) sunlight exposure (4). It is not surprising therefore that serum/plasma 25(OH)D was used as an indicator of vitamin D status recently by several authorities in North America and Europe who were commissioned to establish dietary reference intake values for vitamin D.

The circulating concentration of total 25(OH)D (i.e. comprising the sum of $25(OH)D_2$ and $25(OH)D_3$) is used diagnostically and clinically as well as in the derivation of dietary reference values for vitamin D. While vitamin D_3 comes from skin synthesis or animal sources, vitamin D_2 is derived from supplements or irradiated foods. As the biological activity of the C3 epimer of serum 25(OH)D is low and its concentration in adults represents only a small fraction of the total 25(OH)D concentration, its separate measurement is not a priority, certainly not in adults. Ideally, measurement of serum 25(OH)D should have a minimal interference from $24,25(OH)_2D$ – the vitamin D metabolite with the highest concentration apart from $25(OH)D_3$ (5, 6, 7). Separate measurement of $24,25(OH)_2D$ may be important in case of suspected genetic CYP24A1 deficiency (8, 9). Measurement of serum $1\alpha,25(OH)_2D$ can be important for establishing the etiology of hyper- or hypocalcemia and some metabolic bone diseases but not for the general assessment of the vitamin D status in a population or individual. Serum $1\alpha,25(OH)_2D$ may be high in patients with inflammatory and granulomatous diseases and lymphoproliferative disorders (10, 11).

The impact of pre-analytical factors (e.g. serum versus plasma, fasting versus non-fasting state, or time of day) on circulating 25(OH)D is not fully defined. Several assay types are currently in use for measurement of circulating 25(OH)D, each with strengths and weaknesses (12). The two most common types of assays are (1) antibody-based methods, which use a kit or an automated clinical chemistry platform; and (2) liquid chromatography (LC)-based methods with either UV or mass spectrometric (MS) detection. While they will both provide a measure of total serum 25(OH)D, mass spectrometry can allow for the separate estimation of $25(OH)D_2$ and $25(OH)D_3$ (and in some cases the C-3 epimers and $24,25(OH)_2D$) from serum samples. The antibody-based methods lack the features that allow them to distinguish between $25(OH)D_2$ and $25(OH)D_3$ (4, 7, 10, 13). Various commercial assays differ because of the nature of the antibody used, some claiming an advantage that they do not discriminate between $25(OH)D_2$ and $25(OH)D_3$ (13), whereas others in fact do underestimate the $25(OH)D_2$ component and therefore

provide correction factors to compensate for high 25(OH)D_2 content (2, 14). It is important to note that the majority of the data collected over the past 20–30 years have been analyzed using antibody-based assays. LC-based assays using a tandem mass spectrometer (LC–MS/MS) allow the analyst to discriminate between 25(OH)D_2 and 25(OH)D_3 and other compounds by their unique molecular masses and mass fragments (12). The potential advantages of LC-based assays include high specificity, high sensitivity and better reproducibility (<10%). The consensus among analysts is that LC–MS/MS assays will become the 'gold standard' for assay performance in the future (15). However, LC–MS/MS will not be available everywhere, and antibody-based assays are still being improved and cross-calibrated against LC–MS/MS, so that smaller labs will be able to perform adequate measurements provided they participate in a quality control program. In the circulation, 25(OH)D is bound to serum proteins, and unbound or free 25(OH)D constitutes <1% of the total concentration. As only free 25(OH)D can enter the cell for further intra/paracrine production of the active metabolite 1,25$(OH)_2$D, it is plausible that free 25(OH)D is more important for local actions than total 25(OH)D. The free 25(OH)D concentration can either be calculated (based on vitamin D-binding protein (DBP), albumin and total 25(OH)D concentrations and the affinity between both components) or can be directly measured. Whether free 25(OH)D is a better predictor for clinical outcomes than total 25(OH)D is presently unclear (16).

Standardization of the measurement of serum 25(OH)D

Standard reference materials, inter-laboratory collaboration and quality assurance schemes are important aspects of overcoming the challenges that the assay methodologies present. An external quality assurance scheme, the Vitamin D External Quality Assurance Scheme (or DEQAS) (www.deqas.org, Charing Cross Hospital in London, UK), exists since the early 1990s and it has grown steadily, such that it now serves as a quarterly monitor of performance of analysts and 25(OH)D analytical methods for more than 1000 laboratories worldwide (5, 17, 18, 19, 20). The introduction of the National Institute of Standards and Technology (NIST) reference standards, calibrated using a reference LC–MS/MS procedure, offers hope that the variability of all methods will be diminished in the future. Recent data suggest that an improvement is already occurring (18) but there is still a long way to go for general implementation of well-validated and accurate measurements of vitamin D metabolites (20, 21, 22).

For reasons of pre-analytical as well as analytical factors, as outlined above, inter-laboratory variation in serum 25(OH)D may be high (17, 18, 19, 23, 24, 25). The international standardization of serum 25(OH)D measurement is also promoted by the Vitamin D Standardization Program (VDSP) – a collaborative initiative between the Office of Dietary Supplements of the National Institutes of Health and the Centers for Disease Control and Prevention (CDC), NIST and a number of the national health surveys around the world (21, 26). The international quality assurance/collaboration schemes, such as DEQAS and VDSP, as well as existing and next generation standard reference materials for 25(OH)D, can further limit inter-laboratory differences. The impact of standardization to NIST standards has been amply demonstrated by recalibration of the (US) NHANES data (27), whereby the J-shaped increased mortality in subjects with high serum 25(OH)D concentration disappeared simply because very few subjects had 'corrected' 25(OH)D levels above 100 nmol/L. Similarly, a recalibration of European studies in the framework of the EU Framework 7-funded ODIN project (food-based solutions for optimal vitamin D nutrition and health through the life cycle; http://www.odin-vitd.eu/) markedly changed the number of vitamin D deficient subjects (28).

Definitions

An international consensus on the definition of vitamin D deficiency and sufficiency is lacking. The IOM has defined a serum 25(OH)D concentration of 30 nmol/L (divide by the conversion factor 2.496 to obtain 12 ng/mL) as the threshold below which clinical vitamin D deficiency may occur (2, 14, 19). It has defined a 25(OH)D concentration of 50 nmol/L (20 ng/mL) as the threshold of sufficiency, that is sufficient for 97.5% of the population in terms of bone health, a definition also recently adopted by the EFSA (29). The serum concentration of 40 nmol/L fits with the estimated average requirement (EAR), that is sufficient for 50% of the population. Serum 25(OH)D levels between 30 and 50 nmol/L (12 and 20 ng/mL), referred to by the IOM as 'inadequacy', represent an uncertain range and can be sufficient or not for a certain individual (Table 1).

The Endocrine Society has defined serum 25(OH)D of 50 nmol/L (20 ng/mL) as the threshold for deficiency and 75 nmol/L (30 ng/mL) as the threshold for sufficiency, that is sufficient for 97.5% of the population (1). The 2016 UK

Table 1 Definitions of vitamin D deficiency and sufficiency according to different advisory bodies.

Serum 25(OH)D concentration (nmol/L)	**Institute of Medicine** (2)	**Endocrine Society** (1)	**EFSA** (29)	**SACN** (27)	**ECTS** (this paper)
<25/30	Deficient	Deficient	Deficient	Deficient	Severely deficient
25–50	Uncertain*	Deficient	Deficient		Deficient
50–75	Sufficient	Insufficient	Sufficient		Sufficient
>75		Sufficient			

*According to the IOM serum 25(OH)D 30–50 nmol/L can be adequate or inadequate.

SACN guidelines defined serum 25(OH)D concentrations below 25 nmol/L as being deficient for all age groups but concluded that there was insufficient evidence to define a higher 25(OH)D being optimal for bone or global health (30).

The ECTS Working Group defines vitamin D deficiency as a serum 25(OH)D concentration below 50 nmol/L. A serum 25(OH)D level below 30 nmol/L is considered severe vitamin D deficiency. A serum 25(OH)D concentration of 50 nmol/L and above is considered sufficient.

A problem with these definitions is that they heavily rely on the accuracy of serum 25(OH)D measurement. The latter depends on standardization and the discussions on this subject have not been finalized (28).

In this review, results for serum 25(OH)D are reported in nmol/L (1 nmol/L = 0.4 ng/mL). Vitamin D intake can be presented in IU/day or in µg/day (1 µg = 40 IU). While clinicians often use IU/day, nutritionists usually prefer µg/day. We have chosen the use of µg/day, with frequent reference to the conversion factor for ease of the reader.

Vitamin D status and prevalence of vitamin D deficiency in Europe

Vitamin D status has been studied in many European countries in various age groups. Since different studies use different laboratories and different assays, the data should be compared with caution because, as mentioned above, the inter-laboratory variation may be high (19, 23). Another point is the study population which may be either a population sample (31) or a convenience sample (32). Data from various studies in different European countries are summarized in Table 2. Recent reviews on vitamin D status in Europe or worldwide were published by Spiro and Buttriss, Wahl *et al*. and Hilger *et al*. (33, 34, 35).

The ODIN project (28) as well as a small project funded by the Nordic Council of Ministers (36) have recently allowed for the generation of standardized serum 25(OH)D data which facilitates estimating and comparing the prevalence of vitamin D deficiency in various European countries. These projects utilized available biobanks from national nutrition and health surveys and cohorts in Europe and used a centralized laboratory LC–MS/MS analytical platform for 25(OH)D, which is traceable to the two higher order reference measurement procedures (NIST, VDSP) and certified by the Centres for Disease Control and Prevention (CDC). The data from these projects together with data from other studies in different countries in Europe and the Middle East is summarized in Table 2. We have selected studies from the last 10 years, and, where available, prioritized population-based studies having standardized serum 25(OH)D values according to the VDSP program.

Northern Europe

The prevalence of serum 25(OH)D <30 nmol/L ranged from 0.4 to 8.4%, and <50 nmol/L from 6.6 to 33.6% in adults, according to standardized data from the ODIN study, and some Nordic studies (28, 36, 37, 38, 39). However, vitamin D status was poor in teenagers in Norway and Denmark with serum 25(OH)D <30 nmol/L at 39% and 51% respectively (40, 41). Vitamin D status was also poor in immigrants (42, 43), and in older persons, especially residents of nursing homes (44, 45). The generally adequate vitamin D status in the Nordic countries is due to the use of cod liver oil and supplements (46) and vitamin D fortification, leading to a great improvement in Finland during the last decade (47).

Western Europe

The prevalence of serum 25(OH)D <30 nmol/L ranged from 4.6 to 30.7% and <50 nmol/L from 27.2 to 61.4% according to standardized data from ODIN (28). Vitamin D status generally was worse in the UK (30.7% < 30 nmol/L and 61.4% < 50 nmol/L) than in other countries (25, 28, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62), and recently a rise in the incidence of rickets was observed (63). A poor vitamin D status was observed in black and Asian people in the UK, in teenagers and adolescents in the UK (25, 48), in (pregnant) non-Western immigrants (64, 65) and in general in older persons (66).

Table 2 Vitamin D status in adults and children in different European countries.

Country	Comments	Study population	*n*	Age (years)	25(OH)D			References
					Mean ± s.d. (nmol/L)	<25 nmol/L (%)	<50 nmol/L (%)	
Iceland (Reykjavik)	Latitude 64° Regionally representative	Adult men and women	5519	66–96	57.0 ± 17.8	4.2	33.6	**Cashman *et al.* 2016 (28)**
Norway (Tromso)	Latitude 69° Regionally representative	Adult men and women	12 817	30–87	65.0 ± 17.6	0.3	18.6	**Cashman *et al.* 2016 (28)**
Norway (Oslo)	Latitude 60°	Adult men and women	866	30–76	71.0 ± 19.5 (white)	0.1 (white)	14.9 (white)	**Cashman *et al.* 2015 (36)**
Sweden	Latitude 58°	Older men	1194	71	68.7 ± 19.1	0.8	17	Melhus *et al.* 2010 (38)
Sweden	Latitude 56°	OPRA women	995	80 (80–81)	78 ± 30	0 ???	16	Buchebner *et al.* 2014 (37)
Finland	Latitude 60–70° Nationally representative	Adult men and women	4102	29–77	67.7 ± 13.2	0.2	6.6	**Cashman *et al.* 2015 (36) Jaaskelainen *et al.* 2017 (47)**
Denmark (Copenhagen)	Latitude 56° Regionally representative	Adult men and women	3409	19–72	65.0 ± 19.2	0	23.6	**Cashman *et al.* 2015 (36)**
UK	Latitude 50–59° Nationally representative	Children, teens and adults	1488	1.5–91	47.4 ± 19.8	15.4	56.4	**Cashman *et al.* 2016 (28)**
Northern Ireland	Latitude 55°	Girls and boys	1015	12 and 15	66.2	16.7	66.2	**Carson *et al.* 2015 (48)**
Ireland	Latitude 51–54°	Adults (national representative sample)	1118	18–84	56.4 ± 22.2	6 (year round)	45 (year round)	**Cashman *et al.* 2013 (56)**
Netherlands	Latitude 52° Nationally representative	LASA 2009	915	61–99	64.7 ± 22.6	2.4	28.5	**Cashman *et al.* 2016 (28)**
Netherlands	Latitude 52° Regionally representative	Adults	2625	40–66	59.5 ± 21.7	4.9	33.6	**Cashman *et al.* 2016 (28)**
Belgium	Latitude 51°	Adults	697	42.7 (32–53)	49.3 (35–65)	7.3	51.1	Hoge *et al.* 2015 (51)
Germany	Latitude 47–55° Nationally representative	Adults	6995	18–79	50.1 ± 18.1	4.2	54.5	**Cashman *et al.* 2016 (28)**
Germany	Latitude 48–52° Nationally representative	Children and adolescents	10 015	1–17	54.0 ± 19.2	6.0	44.5	**Cashman *et al.* 2016 (28)**
France	Varieté study Latitude 43–49°	Men and women	892	18–89	60 ± 20	6.3	34.6	Souberbielle *et al.* 2016 (54)

(*Continued*)

Table 2 Continued.

Country	Comments	Study population	*n*	Age (years)	25(OH)D			References
					Mean ± s.d. (nmol/L)	<25 nmol/L (%)	<50 nmol/L (%)	
Switzerland	Latitude 47°	MONICA	3276	25–74	46 (median)	6 (<20)	>50	Burnand *et al.* 1992 (55)
	Latitude 47°	Nursing home	Women 246 Men 103	85 ± 7 81 ± 8	23 ± 18 26 ± 21	65 48		Krieg *et al.* 1998 (58)
	Latitude 47°	Non-institut. Elderly	193	80 ± 9	18 ± 18	90		Theiler *et al.* 1999 (57)
Spain								
Italy	Latitude 38–45°	Postmenop. women	570	59 ± 8	45 ± 20	28		Bettica *et al.* 1999 (69)
Italy	Latitude 38–45°	Multicenter	700	60–80		76		Isaia *et al.* 2003 (70)
Greece	Latitude 35–40° Regionally representative	Adolescents	806	9–14	47.3 ± 12.5	2.2	62.4	**Cashman *et al.* 2016 (28)**
Greece	Latitude 37° Regionally representative	Children	222	3–6	54.3 ± 15.7	1.4	40.5	**Cashman *et al.* 2016 (28)**
Poland	Warsaw	Postmenop. women	65	72 ± 1	32.5	25	92	Andersen *et al.* 2005 (41)
	Regionally representative	Girls	61	12.6 ± 0.5	30.6	33	87	
Estonia	59° winter	Women Men	200 167	49 ± 12 49 ± 12	44.6 ± 15.8 42.7 ± 14.0	8	73	Pludowski *et al.* 2014 (72) Kull *et al.* 2009 (74)
	Summer	Women Men	200 167	49 ± 12 49 ± 12	58.4 ± 17.7 60.5 ± 18.5	1	29	
Czech Republic	50°	Women Men	321 239	53 ± 14	62.5 ± 10			Mayer *et al.* 2012 (75)
Slovakia	49°	Women	162	32.7 ± 4.4	81.5 ± 31.5		15	Pludowski *et al.* 2014 (72)
Slovenia	Latitude 46°		448	17–89		30.5	66.4	Kocjan *et al.* 2006 (76)
Hungary	47°	Women	319	65 (41–91)	48.4 (12.5–135)		56.7 (w + m)	Bhattoa *et al.* 2004 (78)
		Men	206	60 (51–81)	72.8 (11–185)			Bhattoa *et al.* 2013 (79)
Croatia	Latitude 45°	Postmenop. women	120	61.1 ± 8.8	46.9 ± 16.8	14.2 (<30)	63.3	Laktasic *et al.* 2010 (80)
Belarus	53°	Women Men Women Women	168 176 178 101	45–55 55–65 65–75 >75	72 ± 37 67 ± 35 65 ± 35 46 ± 22			Pludowski *et al.* 2014 (72)
Ukraine	44–52°	Women Men Women Men	649 129 711 86	47 (20–59) 44 (20–59) 69 (60–95) 71 (60–91)	29 ± 15 27 ± 14 26 ± 14 19 ± 9			Pludowski *et al.* 2014 (72)

Country	Comments	Study population	*n*	Age (years)	25(OH)D			References
					Mean ± s.d. (nmol/L)	<25 nmol/L (%)	<50 nmol/L (%)	
Russia		Older persons Hip fracture patients	97 63	70.2 68.8	28 ± 10 22 ± 11	47 65		Bakhtiyarova *et al.* 2006 (81)
Russia	57–67°	Northern indigenous	178	17–59	39.7–47.7	2–53	8–84	Kozlov *et al.* 2014 (82)
Vitamin D status in adults and children in different Middle East countries								
Turkey	Manisa		119 M 272 F	45 ± 17 45 ± 17	51.8 ± 38.7 38.1 ± 28.7		66 79	Hekimsoy *et al.* 2010 (93)
Turkey	Istanbul	students	100 F	21 ± 2	65.7 ± 25 Covered: 52 ± 20 Uncovered: 74 ± 8		34	Buyukuslu *et al.* 2014 (94)
Turkey	Kahramanmaras	Pregnant women newborns, 97 pairs	97 women 97 neonates	27 ± 5 0	12.5 ± 8 10.7 ± 6	85 93	98 100	Parlak *et al.* 2015 (95)
Turkey	Trabzon	Schoolchildren	397 M 349 F	14.6 ± 1.9 14.6 ± 1.8	37.3 ± 20.8 31.3 ± 17.3	28 42	78 87	Karaguzel 2014 (96)
Iran	Shiraz (latitude 30°N)	Selected by postal code number	520 M	20–74	35 ± 17	33.7	29.9 (<35 nmol/L)	Masoompour *et al.* 2008 (97)
Iran	Tehran (latitude 35°N)	Controls from lipid and glucose Study	251 M + F	56.7 ± 11.7	45 (26–77)	19.1	54 (<37.5 nmol/L)	Hosseinpanah *et al.* 2011 (99)
Iran	Zahedan (latitude 30°N)	NA	431 M 562 F	20–88	34.4 ± 29.4	NA	85.2	Kaykhaei *et al.* 2011 (100)
Iran	Tehran	Pregnant women	149	27.9 ± 4.3	38.9 ± 16.6	38% <30		Naseh *et al.* 2018 (102)
Iran	Tehran	Pediatric clinic	286	4.5 ± 2.8	50 ± 38	<2 year: 8 >2 year: 43		Torkaman *et al.* 2016 (103)
Syria	Damascus (33°N)	Healthy volunteers	372	34.1 ± 10.0	24.7 ± 16.9	61		Sayed-Hassan *et al.* 2014 (104)
Israel	Population based (31°N)	Clalit Health Services	198 834 M F	0 to >80 median 60	51.9 ± 24.5	14.4	49.8	Saliba *et al.* 2012 (105)
Israel	Retrospective Population based (31°N)	Maccabi healthcare services	8175 M 26 699 F	F 55 ± 15 M 55 ± 17	M 60 ± 25 F 56.6 ± 24.7	NA	NA	Steinvil *et al.* 2011 (106)
Israel	(31°N)	Volunteers	95 M 100 F	All ages	57.15 ± 25.2	27.2	78	Oren *et al.* 2010 (107)
Israel	Jerusalem	Healthy children primary care	247	1.5–6	64.2 ± 25.0		28.3	Korchia *et al.* 2013 (108)
Jordan	Population based	National sample	4590	41.9 ± 13.4	M 183.3 ± 73.3 F 99.5 ± 51.7		1.5 14.2	Batieha *et al.* 2011 (109)
Jordan	National Micronutrient Survey	Al Basheer Hospital	2032 F	15–49	Median 27.5	60% <30 nmol/L	95	Nichols *et al.* 2012 (110)
Jordan	National Micronutrient Survey	Al Basheer Hospital	1077	1–5	Median 45 nmol/L	20% <30 nmol/L	56.5	Nichols *et al.* 2015 (111)

(*Continued*)

Table 2 Continued.

Country	Comments	Study population	*n*	Age (years)	25(OH)D			References
					Mean ± s.d. (nmol/L)	<25 nmol/L (%)	<50 nmol/L (%)	
Jordan	Healthy volunteers		M 99 F 201	29 32	M 44 ± 10 F western 40 ± 8 F hijab 31 ± 6 F niqab 28 ± 4	0 0 4 9	76 90 98 100	Mallah *et al.* 2011 (112)
Jordan	Neonates	Al Bashir Government Hospital Amman	3731	0	Median 21.5	±90	94%	Khuri-Bulos *et al.* 2013 (113)
Lebanon	Beirut	Hospital database			2008		2002 2008	Hoteit *et al.* 2014 (114)
		2000–2004 and 2007–2008	349 3024 1762	12.2 ± 4.5 49.5 ± 11.6 72.7 ± 5.7	F 42.7 M 48.2 F 57.0 M 54.0 F 59.0 M 54.5		63 58 60 44 62 40	
Lebanon	Population based Beirut (34°N)	Home-dwelling ambulatory subjects	157 M 286 F	65–85 Mean 73 years	25.7 (10–96.7) M 30.2 F 27.3	37 56	94 95	Arabi *et al.* 2010 (115)
Kuwait	Schoolchildren		199	7–9.5	Median 30 M 34; F 27			Alyahya 2017 (116)
Kuwait	Mothers and neonates	Al Adan and maternity hospitals	128 pairs	27	Mothers 36.5 Neonates 20.5	40 65	76 96	Molla *et al.* 2005 (117)
Saudi Arabia	Riyadh	Pregnant women	160	20–49	49.9 (IQR 28)	18	50	Al-Faris 2016 (120)
Saudi Arabia	Population based Jeddah (22°N)	40 (PHCCs)	M < 50: 550 M > 50: 284	20–74	31.3 ± 17.5 26.8 ± 15.0	52.6 41.9	89.9 83.8	Ardawi *et al.* 2012 (118)
Saudi Arabia	Schools all over country	School children	1013 M 1097 F	6–15	28 ± 11	M 25 F 64	M 93 F 98	Al Shaikh *et al.* 2016 (119)
United Arab Em	Abu Dhabi	University students	70 M 208 F	21 ± 4	M 27.3 ± 15.7 F 24.2 ± 14.9		94	Al Anouti *et al.* 2011 (122)
United Arab Em	Abu Dhabi	Pediatric outpatients	183	5.3 ± 3.7	53.6 ± 33.4	17	±57	Rajah *et al.* 2012 (121)
Bahrein	Manama	Blood donors	500	33.7 ± 10.1	27.9 ± 19.3	49.4	86.4	Golbahar *et al.* 2014 (123)
Qatar	Doha	Retrospective study in 547 hospital patients	547	49 ± 13	36.0 ± 27.5	46		El-Menyar *et al.* 2012 (124)
Egypt	Cairo and Port Said	Women	Lactating 51 Pregnant 50 Non pregnant 208 Elderly 38 Geriatric 57	26 ± 5 26 ± 5 31 ± 8 58 ± 4 76 ± 7	30 37 27 66 37	73 54 72 40 77		Botros *et al.* 2015 (125)

Country	Comments	Study population	*n*	Age (years)	25(OH)D			References
					Mean ± s.d. (nmol/L)	<25 nmol/L (%)	<50 nmol/L (%)	
Tunisia	Tunis	Mothers and newborns	87 mothers 87 neonates	31 ± 5 0	17 ± 13 15 ± 4	87 (<30) 78 (<30)	97 98	Ayadi *et al.* 2016 (126)
Algeria	Tizi-Ouzou	Healthy children	435	5–15	Sept: 71.4 March: 52.9	8.1 (<30) 17.4 (<30)	29.9 41.4	Djennane *et al.* 2014 (127)
Morocco	Rabat	Postmenopaual women	178	58.8 ± 8.2	39.5 ± 29.0	51.6		El Maghraoui *et al.* 2012 (128)
Vitamin D status in different European countries: immigrants. Included studies which use standardized serum 25(OH)D data have the references highlighted in bold								
Norway (Oslo)	latitude 60°	Norwegian Pakistani	866 176	30–76	71.0 ± 19.5 27.6 ± 12.3	0.1 52.3	14.9 92.0	**Cashman *et al.* 2015 (36)**
Finland	Latitude 60–63° Representative of immigrant populations	Ethnic (all): White Russian Kurdish Somalian	1310 466 500 364	18–64	45.5 ± 21.9 62.8 ± 21.0 33.7 ± 15.6 40.5 ± 16.6	18.2 2.5 34.2 15.7	63.7 28.7 85.6 76.4	**Cashman *et al.* 2016 (28)**
Finland	Latitude 60	Bangladeshi Somali Finnish	34 48 61	20–48	42.9 ± 16.1 36.8 ± 11.8 54.1 ± 19.1	0 8.3 3.3	70.6 81.3 44.3	Islam *et al.* 2012 (84)
Denmark	Latitude 55	Pakistani	Children 37 Premenopausal women 115 Men 95	12.2 36.2 38.3	10.9 12.0 20.7	81 84 65	95 97 95	Andersen *et al.* 2008 (43)
Netherlands		Adult women and men	613: Dutch Turkish Moroccan Surinam Asian Surinam Creole African	18–65	 67 27 30 24 27 33	 6 41 37 51 45 19		Van der Meer *et al.* 2008 (64)

Included studies are from the last 10 years, nationally or regionally representative and use standardized serum 25(OH)D data, when possible. The references highlighted in bold refer to studies in which the serum 25(OH)D data was standardized. Results for serum 25(OH)D are reported in nmol/L, to convert to ng/mL the value should be divided by 2.496.

Southern Europe

Standardized data from adults are not available. An older European population-based study in older persons, the Seneca study, showed a mean serum 25(OH)D of 26 nmol/L in Spain, 39 nmol/L in Portugal, 28 nmol/L in Italy and 25 nmol/L in Greece while it was around 45 nmol/L in the Nordic countries (31). Other studies in these countries usually show mean serum 25(OH)D concentrations below 50 nmol/L and higher percentages of serum 25(OH)D <30 nmol/L than in Northern and Western Europe (67, 68, 69, 70, 71). Standardized data from infants and children in Greece (ODIN) showed serum 25(OH)D <30 nmol/L in 4.2–6.9%, and <50 nmol/L in 40.5–62.4% (28).

Eastern Europe

Standardized data from adults are not available. In general, a review and individual studies showed a mean serum 25(OH)D usually lower than 50 nmol/L, and a poorer vitamin D status than in Northern and Western Europe (72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82).

Immigrants in Europe

Studies from Norway, Finland, Denmark and the Netherlands confirm a very poor vitamin D status in non-Western immigrants in European countries, in comparison with the locally born and with people in their country of origin (43, 64, 65, 83, 84, 85). A study in Dutch general practices showed a mean serum 25(OH)D of 30 nmol/L or lower in Turkish, Moroccan and Surinamese people in comparison with a mean serum 25(OH)D of 67 nmol/L in locally born people (64).

European population studies

As mentioned early, the Seneca study was performed in eight countries but serum 25(OH)D was measured in one central laboratory to avoid variation between different laboratories (31). Some studies reporting baseline data from randomized clinical trials in patients with osteoporosis also used a central laboratory facility, making comparisons between countries more reliable (raloxifene and bazedoxifene studies) (86, 87). A general trend in these data is that vitamin D status usually is much better in Nordic countries than around the Mediterranean. The European ODIN study used standardized data from epidemiological studies in Europe. Severe vitamin D deficiency (serum 25(OH)D <30 nmol/L) was observed in 12.5% of the participants and 40% was deficient (serum 25(OH)D <50 nmol/L) (28).

Vitamin D status and prevalence of vitamin D deficiency in the Middle East

Population-based studies are rare. The prevalence of vitamin D deficiency and rickets is high in the Middle East despite abundant sunshine (25, 88, 89, 90, 91, 92) (Table 2). The median or mean serum 25(OH)D in almost all surveys was between 25 and 50 nmol/L, with lower values in women than in men, that also depend on clothing style (93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131). In a recent systematic review, the prevalence of vitamin D deficiency in the Middle East varied between 30 and 90% depending on the type of study, country, age group and assay used (92). Vitamin D status was poor in several surveys in Saudi Arabia (118, 119), probably due to a very traditional lifestyle. Vitamin D status is better in Israel.

In general, vitamin D deficiency is much more prevalent in the Middle East than in Northern and Western Europe. Risk groups for severe deficiency include children, adolescents and pregnant women.

Determinants of vitamin D status and risk groups for vitamin D deficiency

Demographic, anthropometric and lifestyle factors are robust predictors of rickets and poor vitamin D status worldwide in general, and in the Middle East in particular (Fig. 1). Sunshine exposure and vitamin D intake are the main determinants, but these are modified by other factors. Vitamin D status deteriorates with aging above 70 years due to decreased sun exposure and cutaneous synthesis (132), and is poor in the institutionalized, 75% of them being severely vitamin D deficient (serum 25(OH)D <25 nmol/L), and in patients with hip fracture (66, 133). The good vitamin D status in the Nordic countries is explained by the frequent consumption of cod liver oil and vitamin D supplements (134, 135). Furthermore, fortification of milk and milk products over the last 10 years has considerably improved vitamin D status in Finland (47). On the other side, strong sunshine in Southern Europe and the Middle East may lead to decreased exposure (136), and skin pigmentation

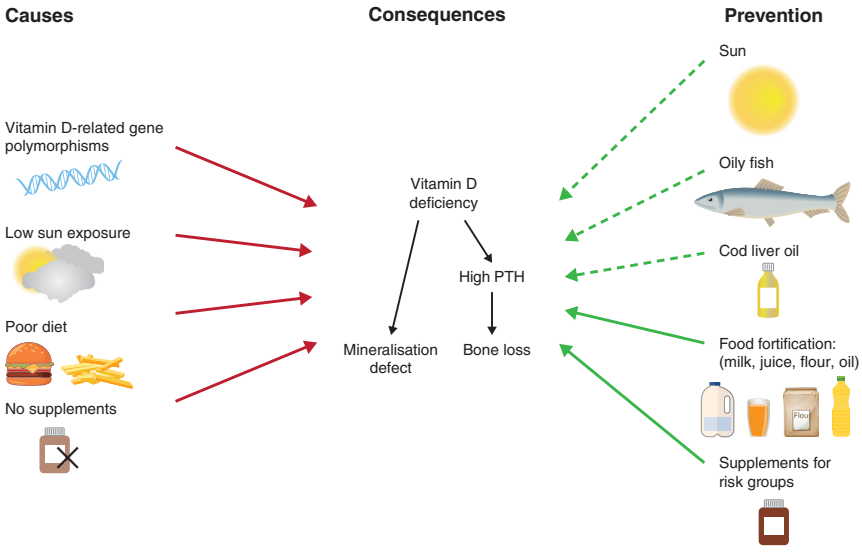

Figure 1
Causes, consequences and prevention of vitamin D deficiency. The red arrows lead to vitamin D deficiency, the green arrows can prevent it. Vitamin D-related gene polymorphisms indicate gene polymorphisms in the vitamin D metabolic pathway that decrease vitamin D bioavailability. Low sun exposure may also be due to clothing style, skin pigmentation and sunscreen use. Poor diet means no fish, no dairy products, no vitamin D-fortified foods. A full color version of this figure is available at https://doi.org/10.1530/EJE-18-0736.

decreases vitamin D synthesis (137). Vitamin D status in the Middle East is strongly dependent on clothing style, with decreasing vitamin D status going from Western-style clothing to hijab and niqab (129, 130, 131). A low calcium intake is common in the Middle East (92). It increases the risk of rickets, and it leads to secondary hyperparathyroidism and bone loss. Pollution and urban living are other factors.

Risk groups for vitamin D deficiency are children, adolescents, pregnant women and older persons. Vitamin D status usually is very poor in immigrants from non-Western countries, compared with native people (28, 64, 83, 84, 85), fatty fish and supplements being the most important determinants (64). This is even worse in pregnant non-Western immigrants, who displayed mean serum 25(OH)D concentrations around 25 nmol/L (65).

Vitamin D intake in Europe and the Middle East

Measurements of vitamin D content of food requires special expertise due to its low concentration, the possible presence of vitamin D esters with uncertain bioavailability, and the presence of 25(OH)D in some food items. Most of the data presented below is based on methodology which estimated vitamin D only. Studies on vitamin D intake in Europe have been nicely summarized by Spiro and Buttriss (33), and Kiely and Black (138). An overview of the data is presented in Table 3.

Northern Europe

The mean intake of vitamin D in Northern Europe varies between 4 and 14 µg/day (41, 43, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149), with high values found in Norway, due to the consumption of oily fish and cod liver oil. In Iceland, the difference between users and non-users of cod liver oil was more than 9 µg/day. In Sweden, fish and fortified milk products were important sources. In Finland, the fortification of fluid milk products was recently increased to 10 µg/L. Vitamin D supplement of 10 µg/day was recommended for children younger than 3 years, and 7.5 µg/day for children and adolescents aged 3–18 years. The recent Finrisk–Findiet survey has shown that the dietary vitamin D intake has increased to above 10 µg/day in men and nearly as much in women (47, 147). The mean dietary vitamin D intake was around 3 µg/day in Denmark.

Western Europe

The mean vitamin D intake in Western Europe varies between 1.5 and 5 µg/day, far below the EAR of 10 µg/day (150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161).

Southern Europe

Food consumption surveys presented in Table 3 showed vitamin D intakes from below 1 µg/day to about 3 µg/day in Italy, Spain and Portugal.

Table 3 Vitamin D intake in European and Middle East countries.

Country	Study population	*n*	Age (years)	Vitamin D intake (µg/day)	References
Iceland				3.9 µg 13.5 µg (with cod liver oil)	Thorgeirsdottir *et al*. 2012 (139)
Norway	Volunteers Norkost	32		9.6 µg M: 15 µg F: 12.9 µg	Brustad *et al*. 2004 (134) Norkost (144)
Sweden	Riksmaten			7.1 µg	Riksmaten (145)
Finland	National Diet Survey Findiet	1708	25–74	M: 11 µg F: 9 µg OM: 14 µg OW: 19 µg	Helldán *et al*. 2013 (147)
Denmark	Dan Nat Survey			3.9 3.1	
United Kingdom	NDNS rolling survey (2008/2009 to 2009/2010)	M: 210 M: 238 M: 346 M: 96 F: 213 F: 215 F: 461 F: 128	4–10 11–18 19–64 >65 4–10 11–18 19–64 >65	2.2 (median) 2.1 2.8 3.9 2 1.7 2.6 3.1 (median)	Department of Health 2011 (153)
Ireland	National Adult Nutrition Survey	1274	18–64	3.5 (median) 6.4 (mean)	Black *et al*. 2015 (151)
Ireland	Irish Preschool Children Survey	500	1–4	2–2.5 µg (median)	Hennessy *et al*. 2016 (152)
Ireland	Irish Children's and Teens' National Nutrition Surveys	594 441	5–8 9–12 13–17	1.9 (median) 2.1 (median) 2.4 (median)	Black *et al*. 2014 (150)
Netherlands	Hip fract pat controls Food cons survey	125 74	75.9 75.6	2.8 2.9 M: 4.8 F: 3.6	Lips *et al*. 1987 (156)
Germany	Nat Nutr Survey			M: 4.4 F: 3.4	
Portugal	Epiporto			M: 3.4 F: 3.3	Spiro & Buttriss 2014 (33)
Spain	ENCAT 2002–2003			M: 0.7 F: 0.7	Spiro & Buttriss 2014 (33)
Italy	INN-CA 1996			M: 2.5 F: 2.4	Spiro & Buttriss 2014 (33)
10 European countries (EPIC)	European Prospective Investigation into Cancer and Nutrition (EPIC) study	M: 13 025 F: 23 009	35–74 35–74	5.5 3.6	Jenab *et al*. 2009 (163)
Southern		M: 4530 F: 7372	35–74 35–74	4.2 5.1	
Central		M: 3807 F: 8561	35–74 35–74	4.7 3.4	
Northern		M: 4688 F: 7076	35–74 35–74	7.4 5.0	
Middle East					
Turkey	Mining facility	135 coal miners	32.6 ± 7.4	2.1 ± 1.3	Bilici *et al*. 2016 (164)
Iran	Tehran Lipid and Glucose Study	5524	18–70	M: 2.5 ± 4.3 F: 3.8 ± 3.1	Ejtahed *et al*. 2016 (165)
Iran	Iranian Multicentric Osteoporosis Study	F: 581	42.4 ± 12.2	1.5 ± 1.2	Khashayar *et al*. 2017 (166)
Iran		Pregnant women		2.3±1.9	Sabour *et al*. 2006 (167)
Iran		Children		1.4	Feizabad *et al*. 2017 (168)

(*Continued*)

Table 3 Continued.

Country	Study population	*n*	Age (years)	Vitamin D intake (µg/day)	References
Iran		100 children	4–10	11.7	Kelishadi *et al*. 2014 (169)
Kuwait	Repres. national sample	1049		1–2.9	Zaghloul *et al*. 2013 (170)
Lebanon	Beirut	F	39.4 ± 5.6	2.2 ± 1.5	Gannage-Yared *et al*. 2000 (171)
		M	41.3 ± 5.5	3.2 ± 2.0	
Lebanon		128 pregnant women		10.6 ± 10.9 (FFQ) 8.9 ± 2.5 (24 h recall)	Papazian *et al*. 2016 (172)
Qatar		60 young women	29	3.0	Salameh *et al*. 2016 (173)
United Arab Emirates		350 adolescent females	15.3 ± 2	8.5	Narchi *et al*. 2015 (174)
Saudi Arabia	University students Tabuk		19–25	53% < 15 µg/day	Alzaheb & Al-Amer 2017 (175)
Tunisia		225 boys		8	Bezrati *et al*. 2016 (176)
Tunisia		87 pregnant women		2.2	Ayadi *et al*. 2016 (126)

M, male; F, female; OM, older male; OF, older female.

Eastern Europe

The mean vitamin D intake varied between 2 and 5 µg/day, according to a recent review (162).

European studies

National dietary and food consumption surveys as well as smaller studies use various methods of data collection, analysis and reporting, making meaningful comparison of vitamin D intakes problematic (155). Some studies compared different countries with the same methods. A European study done in Denmark, Finland, Ireland and Poland found a mean vitamin D intake of 2.4–5.0 µg/day in girls and 3.4–9.5 µg/day in older women (41)

The European Prospective Investigation into Cancer and Nutrition (EPIC) compared vitamin D intakes in ten European countries. The mean vitamin D intake was 5.5 and 3.6 µg/day in men and women respectively with the highest intake in the Northern countries (163).

In conclusion, mean vitamin D intake in most European countries is rather low, in most countries less than 5 µg/day (200 IU/day). Vitamin D intake is highest in the Nordic countries and poor in Southern Europe.

Vitamin D intake in the Middle East

Population-based studies on vitamin D intake are scarce. The used food frequency and 24 h recall questionnaires varied and these tools were mostly validated in Western populations, with little or no adaptation to the Mediterranean/Middle Eastern diet. Vitamin D fortification varies widely between countries, as detailed in the section on Food fortification with vitamin D. These drawbacks may explain the wide variability between countries and the lack of a consistent pattern by age. The mean vitamin D intake ranged between 1 and 4 µg/day, with some exceptions in selected groups of children, adolescents and pregnant women, probably due to vitamin D supplements (126, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176). These intakes are well below the RDA of 10–20 µg/day, depending on age and reproductive stage (2, 177).

Genetic factors

Genetic factors may contribute to up to 28% of inter-individual variability in serum 25(OH)D concentrations, while clinical correlates such as season, vitamin D intake and waist circumference explain another 24% of variability (178). Studies have applied the candidate gene approach to relatively common single nucleotide polymorphisms which play an important biological role in vitamin D metabolism, transport, degradation and downstream pathways, to evaluate their impact on circulating 25(OH)D concentrations (Fig. 1). These include genes involved in cholesterol synthesis (DHCR7), 1-α-hydroxylase (CYP27B1), 25-hydroxylase (CYP2R1), vitamin D transport (GC (group specific component), identical to DBP) and to a lesser extent also 24-hydroxylase (CYP24A1) (179, 180, 181, 182). Similar effects of polymorphisms of these genes (especially DBP/GC) were confirmed in several studies (183). The combined effects of these genes do not explain more than about 5% of the variability and considerably less than the seasonal variation in serum 25(OH)D (179, 184).

25(OH)D and all other metabolites of vitamin D are bound to a high capacity, high affinity serum DBP or GC. A smaller proportion is loosely bound to albumin. Therefore the free concentration of 25(OH)D represents less than 0.1% of the total concentration. Genetic polymorphisms of DBP are associated with different DBP concentrations but this depends on the antibody used for measuring DBP. When polyclonal anti-DBP antibodies are used, subjects with GC2 genotype have a slightly lower DBP concentration compared to others (185), associated with lower 25(OH)D concentrations. A monoclonal antibody method found much (about 50%) lower DBP concentrations in GC 1f–1f homozygotes (mainly African-Americans) than in subjects with other genotypes (186). Subsequent studies using mass spectrometry to measure serum DBP, however, did not find a significant difference in DBP according to race (187, 188), creating serious doubt (189) on the conclusions based on the monoclonal antibody (186). As the free concentration of 25(OH)D is dependent on both DBP concentration and affinity it is yet not possible to conclude whether clinical correlates and thresholds for vitamin D deficiency depend on genetic polymorphisms of DBP. An assay to measure the free 25(OH)D concentration is available, but currently it is uncertain whether the measurement of this metabolite in its free state has clinical implications (189, 190).

Impact of vitamin D on bone

A beneficial effect of vitamin D on musculoskeletal health is well established, as severe vitamin D deficiency causes rickets in children and osteomalacia in adults. While rickets is rare in almost all European countries, it is still reported in the Middle East, in some Asian countries and in immigrants of those countries in Europe (88). In general, rickets in Europe is mostly reported in non-Western immigrants, mainly coming from Africa and Asia and in persons consuming macrobiotic or vegan diets (191, 192). This can be explained by the fact that oily fish and dairy products are the major dietary source of vitamin D and calcium, both being absent in these diets. Milder vitamin D deficiency results in secondary hyperparathyroidism, increased bone turnover and accelerated bone loss, osteoporosis and fractures (66). The vitamin D endocrine system primarily tries to maintain a normal serum calcium homeostasis whereby its role on bone can be either beneficial or deleterious depending on calcium intake and availability (193, 194). Many cross-sectional studies and especially randomized controlled trials have demonstrated a beneficial role of vitamin D supplementation, in a sufficient dose of daily 20 µg (800 IU) vitamin D (195, 196, 197) and in combination with calcium supplements (198, 199), among seniors (institutionalized and community-dwelling) at risk for vitamin D deficiency and with a lower than recommended calcium intake, showing a reduction of falls as well as hip and other fractures (3, 195, 196, 197, 200). This conclusion has been reached in most (195, 201) but not all meta-analyses (202, 203, 204). Whether such supplements would be beneficial for bone health in adolescents and non-elderly adults requires additional controlled intervention studies. The 2018 meta-analysis on the musculoskeletal benefits of vitamin D monotherapy on BMD, fractures and falls by Bolland

Table 4 Dietary reference intakes for vitamin D in µg/day according to different European countries, the Institute of Medicine and the Endocrine Society.

	<1 year	1–3 years	4–10 years	11–18 years	Adults	Older	Pregnant	References*
Nordic NR	10	10	10	10	10	20	20	NORDEN 2014 (144)
UK	8.5–10	10	10	10	10	10	10	SACN 2015 (30)
Ireland	7.0–8.5	10	0–10	0–15	0–10	10	10	FSAI 1999***
Netherlands	10	10	0–10	0–10	0–10	20	10	Weggemans *et al*. 2013 (249)
Belgium	10	10	10	10–15	10–15	15	20	Spiro and Buttriss 2014 (33)
France	20–25	10	5	5	5	5	10	Spiro and Buttriss 2014 (33)
DACH	10	20	20	20	20	20	20	Spiro and Buttriss 2014 (33)
Spain	10	15	15	15	15	20	15	Spiro and Buttriss 2014 (33)
Central Europe	10	15–25	15–25	15–25	20–50	20–50	20–50	Pludowski *et al*. 2013 (269)
EFSA 2016	10	15	15	15	15	15	15	EFSA 2016 (29)
Institute of Medicine	10	15	15	15	15	20	15	IOM 2011 (2)
Endocrine Society	10–25	15–25	15–25	15–25	37.5–50	37.5–50	15–25** 37.5–50	Holick *et al*. 2011 (1)

Partly adapted from Spiro and Buttriss (33).
*The required serum 25(OH)D concentration should be higher than 50 nmol/L in most guidelines. The Endocrine Society recommends a serum 25(OH)D >75 nmol/L and the Central European guideline recommends 75–125 nmol/L; **pregnant 14–18 year 15–25 µg/day. ***Food Safety Authority of ireland

and colleagues suggests no benefit on these outcomes, but they did not analyze clinical trials with vitamin D and calcium vs double placebo (205).

Extra-skeletal health

The presence of the vitamin D receptor (VDR) in most cells and tissues, as well as the expression of the 1α-hydroxylation enzyme CYP27B1 in many cells and the large number of genes under the control of 1α,25(OH)$_2$D suggest a broader role of the vitamin D endocrine system beyond bone and calcium homeostasis (206, 207, 208). Moreover, such potential effects on non-classical or non-skeletal outcomes are in line with data from association studies between low vitamin D status and cardiovascular diseases, diabetes and the metabolic syndrome, inflammatory, infectious and immune disorders, as well as a variety of cancers. A low vitamin D status was also associated with increased mortality risks as extensively reviewed (3, 27, 206, 209). Whether skeletal or cardiac muscles are target tissues for the vitamin D endocrine system has been debated. The presence of the VDR in skeletal muscle tissue has been questioned recently by Wang and DeLuca suggesting that the VDR is undetectable in muscle tissue (210), in contrast with many earlier studies (211, 212, 213, 214, 215), including the most recent one using a new multi-step immunofluorescent technique to detect the VDR in muscle biopsy tissue from older female subjects (216). Recently, others found VDR to be expressed albeit at low (mRNA and protein) levels (217). VDR null mice (systemic or cardiac muscle-specific deletion), however, show a clear muscle phenotype and many *in vitro* studies also show clear coherent positive effects of 1α,25(OH)2D on muscle cell precursors. Severe vitamin D deficiency is frequently associated with muscle weakness/hypotonia and an increased risk of falling (218). Several double-blind intervention studies also show a significant average reduction of 19% in fall frequency when elderly vitamin D deficient subjects receive a vitamin D supplement, but meta-analyses of these studies came to divergent conclusions depending on the quality of fall assessment, and the inclusion of trials with or without blinding (2, 219, 220). The overall interpretation of the presently available data suggest that correction of severe vitamin D deficiency improves muscle function and reduces the risk of falls (3, 220). High intermittent dosing of vitamin D or doses resulting in high serum 25(OH)D levels (above 125 nmol/L, 50 ng/mL) may, however, result in increased risk of falls (221, 222) so that the therapeutic range for serum 25(OH)D and fall prevention may be between 50 and 75 nmol/L (20 and 30 ng/mL) for optimal fall prevention (222). Based on current evidence, this range is safely reached with a vitamin D intake of 20 µg (800 IU) per day (223) or 600 µg (24 000 IU) per month (222, 224). Among somewhat younger postmenopausal women (mean age 66 year), a most desirable range of serum 25(OH)D for optimal fall prevention was suggested to be 80–95 nmol/L (32–38 ng/mL) based on a multidose vitamin D trial (225). Notably, both trials suggested that a serum 25(OH)D higher than 113 nmol/L (45 ng/mL) was associated with a significantly increased risk of falling compared to a 25(OH)D range of 80–95 nmol/L (221).

An additional aspect with potential impact on muscles and falls as well as bone density is the relationship between vitamin D status and sex steroid levels in men with a parallel seasonal variation of both hormones (226, 227, 228, 229). While it has been demonstrated that vitamin D increases testosterone production in human primary testicular cells (230), clinical trials were controversial (231, 232) and a pooled analysis did not show an increase (233). Meta-analyses of RCTs on cardiovascular outcomes, and glycaemic control and type 2 diabetes have shown disappointing effects (208, 234, 235, 236). This was confirmed by a Mendelian randomization study (237). However, a recent meta-analysis of RCTs of vitamin D on acute respiratory infection showed that vitamin D in a daily or weekly dose reduced the risk of acute respiratory infection by 12%, the results being larger in those with baseline serum 25(OH)D <25 nmol/L (238). A large 4 year RCT of vitamin D 2000 IU/day and calcium 1500 mg/day in postmenopausal women showed a borderline (P=0.06) decrease in cancer incidence (239). A recent Mendelian randomization study showed an association between genetically lowered serum 25(OH)D concentrations and higher ovarian cancer susceptibility (240).

In Mendelian randomization studies, the use of 25(OH)D measurements in relation to GC, CYP2R1, DHCR7 genotypes and a binary study outcome variable such as mortality has revealed associations of genotypes with 25(OH)D concentrations, and of 25(OH)D concentrations and mortality, but the statistical association of genotypes and binary outcome mortality was ambiguous (241). Thus, a direct influence of genotypes on clinical outcomes was not always visible (208). Further studies on mortality causes and low vitamin D status showed an association with cancer and all-cause mortality but not with cardiovascular mortality (241).

Recently, the results of two megatrials have become available. The VIDA trial in 5110 subjects compared

vitamin D 100 000 IU/month with placebo and found no effect of vitamin D on cardiovascular disease (242). The VITAL trial comparing vitamin D 2000 IU/day with placebo in more than 25 000 subjects, concluded that vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo (243). The baseline mean serum 25(OH)D was rather high in these trials, 63 and 75 nmol/L, respectively. From all this data, it can be concluded that the prevention of chronic diseases is not a reason to start vitamin D supplementation in a vitamin D replete population (244).

Optimal levels of 25-hydroxyvitamin D

Although a great degree of consensus exists concerning the essential role of vitamin D on bone health, and some controversy on its effect on muscle strength and falls, there is less consensus about the optimal or required concentration of 25(OH)D to achieve these effects. As there is no proven causality for the frequent association between vitamin D status and many other extra-skeletal effects, no threshold concentration can be defined for these putative protective effects.

The ECTS Working Group has defined severe vitamin D deficiency as a serum 25(OH)D lower than 30 nmol/L (12 ng/mL) as such concentrations and even more so concentrations below 15 nmol/L are associated with rickets or osteomalacia (245). The ECTS has defined vitamin D deficiency as a serum 25(OH)D concentration below 50 nmol/L, a concentration that according to the IOM covers the needs of nearly all healthy individuals in the population in relation to bone health (2) (see 'Definitions' section), similar to the EFSA (29). In contrast, an extensive analysis in the UK (30) concluded that serum 25(OH)D concentrations should be above 25 nmol/L at all ages as to avoid rickets or osteomalacia, and that these concentrations can be achieved in all otherwise healthy subjects, even when deprived from sunlight, by a daily vitamin D intake of 10 µg (30). These experts did not find sufficient hard data to define higher serum 25(OH)D or recommend higher vitamin D intake as to improve bone quality or provide extra-skeletal health benefits.

At the other end of the spectrum, a 25(OH)D concentration of 75 nmol/L (30 ng/mL) or higher is recommended by the Endocrine Society (1). Regarding general health endpoints, the Endocrine Society states that while evidence from RCTs is lacking, numerous epidemiological studies have suggested that a serum 25(OH)D concentration of 75 nmol/L (30 ng/mL) and above may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease and infectious diseases (246, 247, 248). In contrast, the IOM concludes that there is no evidence that a 25(OH)D threshold greater than 50 nmol/L (20 ng/mL) has any additional benefit to health (2), based on the results of RCTs. More recently several other organizations (249), including the European Standing Committee of Medical Doctors (250) and several scientists (3) supported the conclusions of IOM on optimal 25(OH)D concentrations being ≥50 nmol/L. This conclusion is based on RCTs looking at surrogate endpoints such as the level of 25(OH)D needed to normalize serum $1,25(OH)_2D$ or PTH concentrations, intestinal calcium absorption or bone mineral density. The required intake of vitamin D to achieve such serum 25(OH)D concentrations has been evaluated in numerous studies and an intake in the range of 600–1000 IU of vitamin D_3 per day (15–25 µg/day) is adequate for achieving concentration levels of ≥50 nmol/L in more than 97% of postmenopausal Caucasian or Afro-American women (223). Similar results were found in some European RCTs of young children, children, teenagers, young adults and older adults (251, 252, 253, 254, 255, 256). Whether a higher dosage is needed for populations with lower baseline 25(OH)D concentrations has not yet been established but evidence from two randomized clinical trials from Lebanon, one in children and another in elderly, suggest that this is the case for countries in the Middle East (257, 258). However, calculations of the required vitamin D to replace the daily metabolic clearance of 25(OH)D suggest that 600–1000 IU/day should be sufficient to maintain serum 25(OH)D concentrations above 50 nmol/L (3). An intake of 800 IU/day (20 µg/day) has also been proven to be efficient in reducing the risks of fractures and falls in elderly Caucasian women (3, 196, 200, 218). The recent individual participant data meta-analysis in the ODIN study concluded that higher doses are required in order to reach a serum 25(OH)D concentration of 50 nmol/L in 97.5% of the population (259).

Whether higher concentrations of 25(OH)D would translate into additional skeletal and extra-skeletal effects as suggested by some cross-sectional or observational studies needs to be investigated in additional RCTs. The presently available usually small RCTs using doses of vitamin D above 2000 IU/day, however, have not proven additional benefits so far (3). Fortunately, several large scale, long-term RCTs are ongoing (Table 5) and are expected to better define efficacy and optimal dosages of vitamin D for a variety of other major non-skeletal

outcomes (3, 260). The negative results of the VIDA and VITAL trials suggest that vitamin D is not effective with regard to cardiovascular disease and cancer when baseline 25(OH)D is high (242, 243). Very high dosages of vitamin D or very high serum 25(OH)D concentrations may be detrimental. First, vitamin D toxicity can occur (261, 262, 263), characterized by increased urinary calcium excretion, hypercalcemia and ectopic soft tissue calcification, but only exists as a iatrogenic disease when serum 25(OH)D exceeds 250 nmol/L. However, large, intermittent pulse doses of vitamin D (300 000 IU or more) have been found to be associated with increased risks of fractures and falls (221, 264). In cross-sectional studies a U-shaped relationship has been found between serum 25(OH)D concentrations and cancer or mortality whereby not only low but also the highest concentrations were found to pose risks (209). Therefore as has been observed for other fat-soluble vitamins too much as well as too little has to be avoided. Also, vitamin D hypersensitivity due to mutation in the gene encoding for the vitamin D catabolizing enzyme 24-hydroxylase (CYP24A1) should not be neglected (265, 266).

A recent review (267) proposes a desirable concentration range of 50–100 nmol/L (20–40 ng/mL), provided precise and accurate assays are used. This range allows practitioners to tailor treatment, taking into account season, lifestyle factors and individual vitamin D intake. Most children reach the desirable target concentrations by a daily intake of 400–600 IU (10–15 µg/day), and adults by an intake of 800 IU/day (20 µg/day). This is in line with results from randomized dose-ranging clinical trials (223, 251). Additional data is needed to validate the above proposed concentration range and vitamin D doses, especially in children, pregnant women and non-Caucasian populations.

Recommendations on vitamin D intake in Europe and the Middle East

As stated in the Introduction, the focus of guidelines may be different, varying from public health, as in the IOM guidelines, to individual patients, as in the Endocrine Society guideline. Most national guidelines are made from a public health perspective. A summary of guidelines and recommendations is presented in Table 4. Recently, a more detailed overview of present guidelines for more than 40 countries was published (268).

Most guidelines resemble those of the IOM. The guideline of Central Europe was made by professional societies and resembles the Endocrine Society guideline (269). When recommended intakes are compared with the actual intake, the values only approach each other in the Nordic countries, Norway, Sweden and Finland (144, 147).

Recommendations for supplement use have explicitly been made for small children in the Nordic countries, the DACH countries, the UK, Ireland, the Netherlands and Turkey. Specific recommendations for supplement use in other age groups have been made in Finland and the Netherlands. Two guidelines, from Saudi Arabia and United Arabic Emirates, recommended 800–2000 IU/day, depending on age category and reproductive status (270, 271). The former was developed with the ESCEO group, and both were exclusively based on expert opinion and review of the evidence from studies conducted in Western populations. The actual use of supplements is high in the Nordic countries and very low in Southern Europe (33) and the Middle East (177).

Strategic options

The principal goal of a strategy aiming to improve vitamin D status is to prevent vitamin D deficient bone disease, for example rickets in children and fractures in adults and older persons. Strategic options may vary between nihilism and interventions to achieve a serum 25(OH)D level above a threshold. The null option to prevent fractures in adults was advocated by the US Preventive Services Task Force (272). This was based on the opinion of the task force that the evidence for an effect of vitamin D on fracture prevention in older persons was insufficient (273). The IOM has set the required serum 25(OH)D level at 50 nmol/L (20 ng/mL) (2). The corresponding required intake (required daily allowance RDA) of vitamin D to achieve 50 nmol/L was therefore defined at 15 µg (600 IU) for 1–70 year olds and 20 µg (800 IU) for older subjects per day, when sun exposure is minimal. The mean vitamin D intake in most European countries with the exception of the Nordic countries is well below the minimal requirement to achieve the 25(OH)D threshold of 50 nmol/L unless there is regular access to sunlight or to vitamin D supplements including cod liver oil (Table 3). Depending on the lifestyle and nutritional habits, the required vitamin D supplementation may vary for different segments of the population and for different countries. For example, in Norway, vitamin D status is adequate in a large part of the population, due to sun exposure on a skin with little pigment, high consumption

Table 5 Megatrials with multiple outcomes with expected results in the coming 5 years.

Consortium	Number of subjects	Study design	Dose	Outcome	Results	References
VIDA	5110	DB, two groups	100 000 IU/month	Fract, CVD, ARI	No effect on falls and fractures, CVD	Khaw *et al.* 2017 (298) Scragg *et al.* 2017 (242)
VITAL	28 875	Factorial design 2/2	2000 IU/day/fish oil/placebo	Cancer, CVD	No effect on CVD and cancer	Bassuk *et al.* 2016 (299) Manson *et al.* 2018 (243)
TIPS-3	5500	Factorial design 2/2/2	60 000 IU/month/polycaps/aspirin	CVD, fract, cancer	Jan 2019	NCT01646437*
FIND	18 000		3200 vs 1600 IU/day vs placebo	CVD, cancer	Dec 2019	NCT01463813*
DO-HEALTH	2152	Factorial design 2/2/2	2000 IU/omega-3/physical exercise	Fract, functional decline, blood pressure, cognitive decline, infection		NCT01745263*
D-HEALTH	25 000		60 000 IU/month	CVD, DM, cancer		Neale *et al.* 2016 (300)
VIDIKids	5400 children	DB, two groups	10 000 IU/week	Tuberculosis, astma, acute resp infection	2022	NCT02880982*

Results are expected between 2015 and 2020. Investigators: R Scragg, JE Manson, S Yusuf, TP Tuomainen, H Bischoff-Ferrari, R Neale, A Martineau.
*Clinical Trials Registry at clinicaltrials.gov. DB, double blind; ARi, acute respiratory infection.

of fish and cod liver oil and adequate dietary calcium intake. In contrast, vitamin D status in Southern Italy may be poor due to low sun exposure on a more pigmented skin, little access to vitamin D-rich food (oily fish or cod liver oil), and a low dietary calcium intake. This means that implementation strategies have to be tailored to the local situation in different countries.

The Endocrine Society has set the required serum 25(OH)D level at 75 nmol/L (30 ng/mL), leading to higher recommendations for vitamin D intake (1) up to 37.5–50 µg/day (1500–2000 IU/day) in adults (Table 4). The ECTS Working Group does not support this option for the general European population.

Implementation strategies

Several concepts on implementation exist based either on individual responsibility or on public responsibility. In the first situation this may lead to vitamin D supplementation on an individual basis, based on requirements as stated by national regulatory bodies or professional societies. In the second situation, a more active public health approach, supported by the ECTS, is required involving recommendations for lifestyle including sunshine exposure, healthy nutrition, food fortification and vitamin D supplementation. Implementation can occur through guidelines, professional organizations, special clinics for young children or other risk groups, and publications in the lay press. Providing vitamin D supplements for free is a very effective implementation strategy, as has been shown in Turkey, where children received a free supplement leading to near eradication of rickets within a few years (274).

Vitamin D can be supplemented as vitamin D_3, vitamin D_2 and 25-hydroxyvitamin D (calcifediol). In three clinical trials, using assays that well differentiated D_2 and D_3 metabolites, vitamin D_3 appeared to be somewhat more effective than vitamin D_2 in increasing serum 25(OH)D (275, 276, 277). Most RCTs have used vitamin D_3 and currently this is more readily available. Regarding calcifediol, this metabolite appears 2–3 times more effective in increasing serum 25(OH)D than vitamin D_3 (224). Calcifediol might be of value in patients with gastro-intestinal disorders, such as celiac disease, serious liver disease or after gastric bypass surgery, but it is not widely available.

Vitamin D supplements have been dosed daily, weekly, monthly and with larger intervals up to one year. Daily, weekly and monthly doses have been compared in two studies. In one of these, in 48 women serum 25(OH)

D was similar after 2 months in all dosing groups (278). The other study in 338 nursing home residents showed a similar increase of serum 25(OH) D with daily or weekly doses, while monthly doses were less effective (279). A yearly dose of 500 000 IU was given in an Australian clinical trial to prevent hip fractures, but the fall and fracture incidence in the vitamin D group were higher than in the placebo group (221). A yearly intramuscular dose of vitamin D (300 000 IU) given in a UK study also was not effective (264).

Absorption with a meal containing some fat appears to improve vitamin D absorption (280). While loading doses have been recommended in case of deficiency by some experts, there is no evidence of the clinical value of such loading doses.

Public health options

The use of cod liver oil was very common in Western Europe to prevent rickets, and still is very widespread in the Nordic countries. A recent meta-analysis demonstrated that at a dose as low as 400 IU/day (10 µg/day) vitamin D prevents the occurrence of rickets (281). The advice to use vitamin D drops 10 µg/day (400 IU/day) in infants and children below 4 years was and still is common practice in the Netherlands and several other Western European countries in special children consultation clinics visited by a great majority of young children. Rickets was an important public health problem in Turkey, leading to the institution of a population-based preventive program in 2005 (274). The free distribution of vitamin D drops to all newborn infants visiting primary care facilities in Turkey has decreased the prevalence of rickets from 6% in 1998 to 0.1% in 2008 in children under 3 years of age (274, 282). A similar experience has been reported from Finland, Canada and New Zealand (47, 283, 284).

The IOM increased its RDAs for vitamin D 7 years ago, ranging from 10 to 20 µg/day, considerably lower than those of the Endocrine Society (1, 14). There were also recent global consensus recommendations on prevention and management of nutritional rickets (285): supplementation with 10 µg/day (400 IU/day) is adequate to prevent rickets and is recommended for all infants from birth to 12 months of age, independent of their mode of feeding. Beyond 12 months of age, all children and adults need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 15 µg/day (600 IU/day), similar to the recommendation of the IOM. The global consensus of rickets also recommends an intake of 15 µg/day for pregnant women (285). Based on a Cochrane meta-analysis, the WHO recommends against routine vitamin D supplementation in pregnancy (286). A more recent update of the Cochrane analysis was more positive about potential benefits of vitamin D supplementation in pregnancy, but the authors concluded that evidence is not sufficient yet for a general supplementation advice in pregnancy (287). Recommendations from a WHO-sponsored symposium during the 2015 Vitamin D Workshop (288) endorsed a correction of widespread vitamin D deficiency of pregnant women in line with the recommendations for all adult females (10–15 µg/day), as part of antenatal care in general. Special risk groups such as pregnant women in the Middle East and pregnant non-Western immigrant women in Europe probably require a vitamin D supplement (65, 85). Some randomized vitamin D trials revealed that the majority of mothers failed to achieve the required serum 25(OH)D level even with doses by far exceeding current recommendations (92). However, it is questionable whether vitamin D doses of 15–20 µg/day (600–800 IU/day) actually are too low, or rather that compliance to these doses may not have been adequate. In a recent dose-finding trial, doses of 600–800 IU/day were sufficient to achieve a 25(OH)D concentration of more than 50 nmol/L in 97% of postmenopausal women (223) similar to findings in an earlier study in Dutch institutionalized elderly (251).

Food fortification with vitamin D

As mentioned above, the dietary intakes of children and adults in European countries, as well as beyond Europe, have been comprehensively reviewed recently (33, 138, 289). In brief, intakes of vitamin D in national surveys throughout Europe (e.g. UK, Ireland, Denmark and France) are typically below 5 µg/day, except for the Nordic countries, and vary according to contribution from nutritional supplements, country-specific fortification practices, sex and age; with the nutritional supplements being the main source of variation. Overall, it is clear that the current dietary supply of vitamin D makes it unfeasible for most children and adults in Europe to meet the IOM's EAR of 10 µg/day (400 IU/day), let alone the RDA of 15 µg/day (600 IU/day), which were established on the assumption of minimal or absent UVB-induced dermal supply. It has been emphasized that there is only a limited number of public health strategies available to correct low dietary vitamin D intake (289, 290). A brief overview will be provided here:

1. *Improving intake of naturally occurring vitamin D-rich foods*. This is the least likely strategy to increase dietary vitamin D intake because there are very few food sources that are rich in vitamin D, such as oily fish, with limited availability. Furthermore, most of these are not frequently consumed by many in the population (290).
2. *Vitamin D supplementation*. Supplementation with vitamin D has been shown to significantly improve vitamin D intake across a variety of age, race, ethnic and gender groups as well as improving vitamin D status *per se*. However, the population intake of vitamin D from supplements is quite low (291). This is mainly due to the relatively low vitamin D content of most supplements compared to the requirement as discussed earlier. While not highly effective at a population level due to the low percentage of compliance in the general population for most European countries, vitamin D supplementation may be appropriate in high-risk groups such as infants and young children, pregnant women and older persons (250). Actually, vitamin D supplements are systematically recommended for young children from 0 to 3 years in several countries and also for all institutionalized elderly subjects (249).
3. *Vitamin D fortification (mandatory or voluntarily) of food*. While supplements are an effective method for individuals to increase their intake, food fortification represents the best opportunity to increase the vitamin D supply to the population (138, 289, 292). Fortification of foods with vitamin D in the United States and Canada has an important effect on the mean daily intake of vitamin D by the average adult, but it does not yet reach the required levels of vitamin D intake (293). This may relate to the level of fortification, types and choice of food vehicles and the issue of mandatory or optional/voluntary fortification. It was recently demonstrated that the 95th percentile of intake of vitamin D from voluntary fortified foods in Europe is low (291). Finland has focused on improving vitamin D status in the whole population by extensive fortification. In April 2010, The National Nutrition Council launched a new recommendation that the earlier fortification levels should be doubled to 1.0 µg/100 g (40 IU/100 g) for all fluid milk products and that 20 µg/100 g (800 IU/100 g) should be used for spreadable fats. These recommendations were based on simulations of the effect of fortification. Especially the dairy industry responded immediately and almost all fluid milk products were fortified, with the exception of ecological products. This fortification has had a positive impact on the vitamin D intake and status in adults, whose mean vitamin D intake now is about 10 µg, where close to 40–50% comes from fortified milk products (147). The vitamin D status has also improved as demonstrated recently when a comparison of standardized serum 25(OH) D data from two nationally representative surveys of Finnish adults 11 years apart showed that less than 6% had a 25(OH)D concentration lower than 50 nmol/L in the autumn/early winter months in 2011 compared to the situation in 2000 when about 50% had concentrations lower than 50 nmol/L (47). Also of note, the prevalence of severe vitamin D deficiency (<30 nmol/L) decreased from 13% to 0.6% over the 11 year period (47).

The ECTS Working Group acknowledges the valuable contribution of fortified milk to vitamin D intakes, particularly in children, and the continued need for fortification of milk and other dairy products. However, fortification, including bio-fortification, of a wider range of foods offers more possibilities. Well-designed sustainable fortification strategies, which use a range of foods to accommodate diversity, have the potential to increase vitamin D intakes across the population distribution and minimize the prevalence of a low serum 25(OH)D concentration (294, 295). To provide evidence, we need to model European food and vitamin D intake data to ascertain which food vehicles and what level of vitamin D addition will ensure an effective but safe rise in serum 25(OH)D concentration in all segments of the European population. The benefits and limitations of bio-fortification of various foods are investigated in the EU Framework 7 ODIN project. This includes plant and animal-based food via UVB irradiation of yeast and mushrooms (296), and addition of the most effective forms of vitamin D (vitamin D_3 or calcifediol in some cases) to the feeds of the animals with ultimate inclusion in the tissue for use as foods. Data from the project suggests that a combination of traditional fortification of dairy foods together with the newer approach of bio-fortification of foods with vitamin D can allow for an mean intake within the population of 10 µg/day conforming to the EAR (2) as published by the IOM.

In Middle East countries food fortification is sporadic and the use of supplements is low (177). Furthermore, dairy products are only consumed by a minority of the population. Fortification of wheat flour may have potential to alleviate vitamin D deficiency in countries

such as India and Jordan, where pasteurized milk is not widely consumed (297). The Gulf Countries Council mandates a wheat flour standard (GS194) that includes vitamin D fortification of flour, and several countries have initiated it. These include Jordan, Palestine and Saudi Arabia that initiated flour fortification with vitamin D at 13.8 µg (550 IU) per kg of flour, a very cost-effective public health intervention to prevent rickets, estimated to incur a cost of 0.04–0.05 US$ per metric ton of flour (Personal communication Quentin Johnson, Food Fortification Initiative, www.ffinetwork.org and Ayoub Al Jawaldeh WHO Eastern Mediterranean Region). The United States Agency for International Development adds 13.8 µg (550 IU) of vitamin D/kg of vegetable oil standard, 0.4–0.6 µg (16–23 IU) per g of oil for their food aid programs. Such initiatives will help countries like Yemen, Iraq and now Syrian refugees in Lebanon, Jordan, Iraq and Turkey. World Food Program standards include vitamin D in both cereal flours and vegetable oil for their emergency programs, an important point in the Middle East refugee context. While these initiatives will undoubtedly help boost serum 25(OH)D concentrations in these regions, their impact on attaining serum 25(OH)D target concentrations, if higher than very conservative ones, is less clear. In addition, vegetable oil and milk standards may include vitamin A and D, but these are mostly voluntary or by covenant at the moment. More on micronutrient fortification of foods in developing countries can be found on http://www.gainhealth.org/programs/initiatives/#global-tracking.

Recommendations

The ECTS Working Group recommends the following:

- **A reliable estimation of vitamin D status**, such as performed in the ODIN project, should be performed in all European countries and the Middle East (28). This requires utilization of protocol to conduct retrospective standardization of the available serum 25(OH)D data as well as a greater effort to standardize assays for accurate measurement of 25(OH)D into the future. All publications and reports on vitamin D status should include such standardized data.
- **Fortification of foods is the preferred strategy to increase vitamin D** intake and status over all segments of the population, provided that adequate quality assurance monitoring is performed. Milk, yogurt and other milk products are to be fortified with around 10 µg/L (400 IU/L). Other options such as fortification of flour and oil with vitamin D as well as bio-fortification of animal-derived food products, such as eggs, red meats and cultured fish, should be considered carefully as additional means of increasing vitamin D intake in the population.
- **Vitamin D supplements are recommended for special risk groups** in order to increase the serum 25(OH)D concentration above 50 nmol/L in all countries of Europe and the Middle East.
- **A vitamin D supplement of 10 µg/day (400 IU/day) is advised for all children of 0–1 year** and preferably 0–3 year to eradicate rickets.
- **A vitamin D supplement of 10–15 µg/day (400–600 IU/day) is advised for all pregnant women**.
- **A vitamin D supplement of 10–20 µg/day (400–800 IU/day) is advised- to all older institutionalized subjects** and should be considered for all older persons above 70 year.
- A vitamin D supplement of 10 µg/day (400 IU/day) should be considered for non-Western immigrants and refugees.

Research agenda

- Effects of food fortification (milk, oil, flour/bread, juice, bio-fortified foods) have to be studied per fortified food item in different countries with regard to different risk groups in the population such as young children, pregnant women, older persons and non-Western immigrants and compared with the effects of vitamin D supplementation.
- Further study is needed on vitamin D requirement in the Middle East (257, 258) and on measures to prevent vitamin D deficiency.
- The impact of individual participant data (IPD) meta-regression analysis on the required vitamin D intake compared to standard meta-regression has to be studied, as the latter suggests that the requirement may be higher (259). The IPD approach could be applied to other population subgroups, such as pregnant women and ethnic groups.
- Regular monitoring of vitamin D intake (using comprehensive vitamin D food composition data) and vitamin D status by standardized 25(OH)D assays should be organized in all European and Middle East countries and should guide future intervention strategies.
- The occurrence of rickets should be monitored in all European and Middle East countries.

- When the results of ongoing large randomized vitamin D trials (Table 5) become available, the optimal serum 25(OH)D concentration and the corresponding vitamin D intake should be adjusted.
- Genetic studies are recommended to investigate the individual vulnerability for vitamin D deficiency. Mendelian randomization studies can elucidate the long-term impact of vitamin D deficiency on cancer and autoimmune disease outcomes, as to guide clinical decision-making in case RCTs are not available and cannot be performed for whatever reason.

Conclusion

In order to compare vitamin D status between different countries and to get a reliable estimate of the prevalence of vitamin D deficiency, standardized 25(OH)D assays should be used in population-based surveys. This should include all ongoing studies and whenever possible, also representative samples of older major published surveys and trials. The prevalence of a low serum 25(OH)D concentration (<50 nmol/L) is high, that is more than 50% during winter, in many European and Middle East countries. Even more worrying is the presence of severe vitamin D deficiency (below 25/30 nmol/L) in specific risk groups. The spectrum ranges from adequate vitamin D status in the Nordic countries to severe deficiency in the Middle East. Vitamin D status usually is poor in non-Western immigrants. According to current evidence, the desirable serum 25(OH)D concentration is set at 50 nmol/L or higher. While most experts agree on this concentration, it is uncertain whether higher concentrations provide additional benefit. When the results of ongoing randomized clinical trials are available, the required serum 25(OH)D concentration may have to be modified, depending on the outcome. It will require a tremendous effort to improve vitamin D status in Europe and the Middle East and reduce the percentage of the population with a serum 25(OH)D concentration below 50 nmol/L. This may translate into targeted approaches such as prudent sun exposure, adequate nutrition, food fortification policy and vitamin D supplementation for high-risk groups. Elimination of nutritional rickets should receive the highest priority. As there is near universal agreement that serum 25(OH)D concentrations should exceed 25/30 nmol/L; at whatever age, strategies to eliminate this deficiency, particularly in children, pregnant women, older persons and immigrants, should receive the highest priority by public health authorities and health care providers.

Declaration of interest

Paul Lips: He received lecture fee from Abiogen. He chaired the vitamin D Workshop in 2015. Kevin D Cashman: He was a member of the UK SACN vitamin D working group. Heike Annette Bischoff-Ferrari: During the last 3 years HABF received investigator-initiated grant support from DSM Nutritional Products and WILD, received speaker fees from Pfizer, Roche Diagnostics, Meda, Sandoz and Sanofi. Maria Luisa Bianchi: She received consultancy honoraria from Alexion Pharmaceuticals and Kyowa Kirin. Roger Bouillon: He received lecture fees (over the last 2 years) from Abiogen, l'Oreal and FAES (Spain) and Fresenius, and is co-owner of an university patent on vitamin D analogs, licensed to Hybrigenix (France); he is member of the organizing committee of the Vitamin D Workshop. The other authors have nothing to disclose.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 4 September 2018
Revised version received 11 December 2018
Accepted 31 January 2019