Review

Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement

Pawel Pludowski [1,*], Istvan Takacs [2], Mihail Boyanov [3], Zhanna Belaya [4], Camelia C. Diaconu [5], Tatiana Mokhort [6], Nadiia Zherdova [7], Ingvars Rasa [8], Juraj Payer [9] and Stefan Pilz [10]

1   Department of Biochemistry, Radioimmunology and Experimental Medicine, The Children's Memorial Health Institute, 04-730 Warsaw, Poland
2   Department of Internal Medicine and Oncology, Faculty of Medicine, Semmelweis University, 1085 Budapest, Hungary; takacs.istvan@med.semmelweis-univ.hu
3   Department of Internal Medicine, Clinic of Endocrinology and Metabolism, University Hospital Alexandrovska, Medical University of Sofia, 1, G. Sofiyski Str., 1431 Sofia, Bulgaria; mihailboyanov@yahoo.com
4   The National Medical Research Center for Endocrinology, 117036 Moscow, Russia; jannabelaya@gmail.com
5   Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, 050474 Bucharest, Romania; drcameliadiaconu@gmail.com
6   Department of Endocrinology, Belarussian State Medical University, 220116 Minsk, Belarus; tatsianamokhort@gmail.com
7   Department of Diagnostics and Treatment of Metabolic Diseases, Center for Innovation Medical Technology, The National Academy of Science of Ukraine, 01030 Kiev, Ukraine; nadejda05.1977@gmail.com
8   Centre for Continuing Education, Riga Stradins University, LV-1002 Riga, Latvia; dr.irasa@inbox.lv
9   Department of Internal Medicine, Comenius University Faculty of Medicine, University Hospital Bratislava, 826 06 Bratislava, Slovakia; payer@ru.unb.sk
10 Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria; stefan.pilz@medunigraz.at
*   Correspondence: p.pludowski@ipczd.pl

Abstract: Vitamin D deficiency has a high worldwide prevalence, but actions to improve this public health problem are challenged by the heterogeneity of nutritional and clinical vitamin D guidelines, with respect to the diagnosis and treatment of vitamin D deficiency. We aimed to address this issue by providing respective recommendations for adults, developed by a European expert panel, using the Delphi method to reach consensus. Increasing the awareness of vitamin D deficiency and efforts to harmonize vitamin D guidelines should be pursued. We argue against a general screening for vitamin D deficiency but suggest 25-hydroxyvitamin D (25(OH)D) testing in certain risk groups. We recommend a vitamin D supplementation dose of 800 to 2000 international units (IU) per day for adults who want to ensure a sufficient vitamin D status. These doses are also recommended for the treatment of vitamin D deficiency, but higher vitamin D doses (e.g., 6000 IU per day) may be used for the first 4 to 12 weeks of treatment if a rapid correction of vitamin D deficiency is clinically indicated before continuing, with a maintenance dose of 800 to 2000 IU per day. Treatment success may be evaluated after at least 6 to 12 weeks in certain risk groups (e.g., patients with malabsorption syndromes) by measurement of serum 25(OH)D, with the aim to target concentrations of 30 to 50 ng/mL (75 to 125 nmol/L).

Keywords: vitamin D; recommendations; guidelines; supplementation; cholecalciferol; treatment

1. Introduction

Vitamin D is crucial for musculoskeletal health, as it plays an important role in the regulation of bone and mineral metabolism, and it can prevent and cure nutritional rickets and osteomalacia [1,2]. In addition, vitamin D receptor (VDR) expression in almost all human

cells suggests, or even documents, a more widespread role of vitamin D for overall health, a notion that is supported by several experimental and epidemiological studies [1,3–8]. While there still exist knowledge gaps and controversy regarding potential extra-skeletal effects of vitamin D, there is a wide consensus that the high worldwide prevalence of vitamin D deficiency is of concern and requires actions to improve this situation [2,7,9]. Addressing this issue has to consider the unique metabolism of vitamin D, which is mainly synthesized in the skin stimulated by ultraviolet-B (UV-B) exposure, whereas nutrition is usually only a minor source of vitamin D [10]. Vitamin D from all different sources is metabolized to 25-hydroxyvitamin D (25(OH)D, calcifediol) in the liver, which is the main circulating vitamin D metabolite that is determined to assess vitamin D status. Further hydroxylation of 25(OH)D in the kidneys or certain extra-renal tissues results in the formation of 1,25-dihydroxyvitamin D (1,25(OH)2D, also called calcitriol), which exerts endocrine, autocrine, and paracrine effects as a steroid hormone [10]. Heterogeneous recommendations, regarding several issues in the practical management of vitamin D deficiency, represent a challenge for clinicians and health authorities on how to deal with this public health problem [11–22]. In this context, systematic evaluations of current vitamin D guidelines did, not only, observe a great heterogeneity of the recommendations, but it also reported a low quality score regarding the methodological processes for the majority of these vitamin D guidelines [17,18]. Tables 1 and 2 provide an overview of selected guideline recommendations, with a focus on Central and Eastern European countries, for prevention and treatment of vitamin D deficiency, respectively.

Table 1. Selected guideline recommendations for prevention of vitamin D deficiency in adults with a focus on Central and Eastern European countries, published since 2010.

Authority and/or Country or Region (Year)	Target Population	Age (Years)	Oral Vitamin D (IU)	Reference
Endocrine Society (2011) USA	General population Pregnant and lactating women Obese individuals/Patients on anticonvulsants, glucocorticoids, antifungals, AIDS medications	19–70 >70	600–2000/day 800–2000/day 600–2000/day 2–3 times more	Holick et al. [14]
DACH (2012) Germany/Austria/Switzerland	General population	>18	800/day	DGE [23]
EVIDAS (2013) Central Europe	General population Obese individuals and elderly Prevention of pregnancy and fetal development complications Night workers and dark skin pigmentation	>18 >16	800–2000/day 1600–4000/day 1500–2000/day 1000–2000/day	Płudowski et al. [21]
EFSA (2016) Europe	General population	>18	600/day	EFSA [24]
Russia (2016)	General population Pregnant women	>18	800–1000/day 800–2000/day	Pigarova et al. [25]
Poland (2018)	General population Obese individuals General population Obese individuals Pregnant and lactating women	19–75 19–75 >75 >75	800–2000/day 1600–4000/day 2000–4000/day 4000–8000/day 2000/day	Rusińska, Płudowski et al. [26]
Belarus (2013)	General population	>18	800–2000/day	Rudenko [27]
Hungary (2012)	General population Pregnant and lactating women	>18	1500–2000/day 1500–2000/day	Takács et al. [22]
Bulgaria (2019)	General population Pregnant and lactating women Patients on anticonvulsants, glucocorticoids, antifungals	>19	600–2000/day 600–2000/day 2–3 times more	Borisova et al. [28]
Slovakia (2018)	Postmenopausal osteoporosis patients	>50	800–1000/day	Payer et al. [29]

Table 2. Selected guideline recommendations for treatment of vitamin D deficiency in adults with a focus on Central and Eastern European countries, published since 2010.

Authority and/or Country or Region (Year)	Target Population	Oral Vitamin D for Treatment (IU)	Treatment Duration	25(OH)D Target Concentration nmol/L (ng/mL)	Oral Vitamin D for Maintenance (IU)	Reference
Endocrine Society (2011) USA	General population	50,000/week or 6000/day	8 weeks	75 (30)	1500–2000/day	Holick et al. [14]
	Obese individuals/Patients on anticonvulsants, glucocorticoids, antifungals, AIDS medications	2–3 times more; at least 6000–10,000/day			3000–6000/day	
EVIDAS (2013) Central Europe	General population	50,000/week or 7000–10,000/day	4–12 weeks	75–125 (30–50)	a maintenance dose may be instituted	Płudowski et al. [21]
Italy (2018)	General population	50,000/week or 5000/day	8 weeks	>75 (>30)	50,000 IU twice per month or 1500–2000 IU/day	Cesareo et al. [30]
Russia (2016)		25(OH)D < 50 nmol/L (<20 ng/mL): 50,000/week or 200,000/month or 150,000/month or 6000–8000/day	8 weeks 2 months 3 months 8 weeks		1000–2000/day or 6000–14,000/week	Pigarova et al. [25]
		25(OH)D < 75 nmol/L (30 ng/mL): 50,000/week or 200,000 or 150,000 or 6000–8000/day	4 weeks single dose single dose 4 weeks			
Poland (2018)	General population	6000/day	12 weeks or until a 25(OH)D concentration of 75 nmol/L (30 ng/mL) is reached	>75–125 (>30–50)	maintenance dose i.e., a prophylactic dose recommended for the general population (see Table 1)	Rusińska, Płudowski et al. [26]
Belarus (2013)	General population	25(OH)D < 25 nmol/L (<10 ng/mL): 2000 to 10,000/day	4–12 weeks	75–200 (30–80)	800–2000 IU/day	Rudenko [27]
		25(OH)D 25–50 nmol/L (10–20 ng/mL): 800 to 4000/day	1 year			
Hungary (2012)	General population	50,000/week or 30,000/week or 2000/day	4–8 weeks 6–12 weeks 12 weeks	75 (30)	1500–2000/day	Takács et al. [22]
Bulgaria (2019)	General population	To maintain bone health: 1000–2000/day	/	50 (20)	maintenance dose i.e., a prophylactic dose recommended for the general population (see Table 1)	Borisova et al. [28]
		For extra–skeletal effects: 2000–4000/day	/	75–110 (30–44)		

In clinical practice, a great variability and controversy is reported regarding vitamin D testing and supplementation, thus requiring an improved guidance for clinicians [31]. Therefore, we aimed to draft an expert consensus statement covering important aspects of the clinical practice in the prevention, diagnosis, and treatment of vitamin D deficiency of adults. Rather than covering all of the above-mentioned vitamin D issues in great and extensive detail, we aimed to provide a simple, easy-to-follow guidance for clinicians. Respective data and recommendations regarding these issues in children can be found elsewhere [14,21,26,32–34].

2. Consensus Development Process

A European expert panel with 10 members and a focus on physicians from Eastern Europe, who are usually underrepresented in such groups, was established by selecting clinicians and key opinion leaders with expertise in vitamin D and related topics from their respective countries. The first and senior authors (P.P. and S.P.) of this article served as the chairs of this expert panel, who selected and invited the other panel members. The consensus-reaching process itself was conducted by using the Delphi method, which is a widely accepted tool for clinical consensus statements [35,36]. The Delphi method was

applied by using SurveyMonkey® for voting on various statements on a 9-point scale with the following numeric (and descriptive) anchors: 1 (strongly disagree), 3 (disagree), 5 (neutral), 7 (agree), and 9 (strongly agree). It was pre-specified that a consensus will be established, in the case that ≥75% of the participants agree with the statement, by a voting scale of 7 or above. In case of failing to reach a consensus according to this criterion, it was planned to repeat these surveys after group discussions and statement modifications, if necessary, until a consensus is reached.

After the alignment of the scope of this consensus document and recruitment of the 10 members of the expert panel, the detailed process of this work started with drafting various questions on practical issues regarding vitamin D, which were exclusively discussed and fine-tuned by the chairs. These questions were subsequently used in a first survey round in September 2021. All panel members were involved in this survey, and their answers, along with the existing literature on vitamin D, served as the basis to formulate respective statements by the chairs. At a hybrid meeting in Darmstadt, Germany on the 20 November 2021, the results of the first survey round, along with the subsequently formulated statements, were presented by the chairs. At the same meeting, each statement was subject to a group discussion and a Delphi voting round to reach consensus, which was finally successful for all statements. The 10 authors of this paper are the 10 experts who participated in the Delphi voting rounds. Each voting round was performed for the whole content of each Table or Figure, respectively. Group discussions before each voting round, however, were used to fine tune the statements according to the opinions and recommendations of the panel members. The work on this consensus document was funded and organized by Wörwag Pharma (Böblingen, Germany). The sponsor provided financial and logistic support but did not actively participate in the scientific discussions and consensus-reaching processes.

3. Consensus Recommendations

The final consensus statements with the level of agreement within the expert group are subsequently presented below. The evidence and considerations underpinning each statement are also outlined. It was our aim to base our work on the totality of available evidence by considering the established hierarchy of evidence levels. The expert panel group was encouraged to perform systematic literature reviews on the topics of this consensus document, but we have to acknowledge that this gathering of information did not follow a pre-specified structured process.

3.1. Current Situation of Vitamin D Deficiency Diagnosis, Prevention and Treatment

Epidemiological studies have documented a high prevalence of vitamin D deficiency worldwide [37]. Data from Europe showed that 25(OH)D concentrations below 20 ng/mL (50 nmol/L) and below 12 ng/mL (30 nmol/L) are observed in 40.4% and 13.0% of the general population, respectively [9]. Therefore, a huge gap exists between the recommendations of nutritional societies regarding dietary reference intakes, as well as target 25(OH)D concentrations, and the actual situation, as documented in large population surveys [38]. Public health actions are, therefore, required to improve the vitamin D status in the general population, but regional differences in vitamin D status, related to factors such as latitude, genetics, lifestyle, body composition, or dietary intake have to be considered [9,38–41]. A major issue to achieve this task is to harmonize the current heterogeneous efforts and guideline recommendations (Table 3).

Table 3. Statement regarding the current situation of vitamin D deficiency diagnosis, prevention, and treatment.

Consensus Statement	Consensus Voting Scale	Level of Agreement
To ensure an adequate screening, prevention and treatment of vitamin D deficiency in the clinical practice, it is necessary to increase the awareness and improve education in the public and medical community. Moreover, national and international guidelines/recommendations should be precise regarding the risk groups that need to be screened, the adequate dosages for prevention and treatment of vitamin D deficiency, the treatment regimen as well as the follow-up to allow transfer into clinical practice.	9 (strongly agree)	80%
	8	0%
	7 (agree)	20%
	6	0%
	5 (neutral)	0%
	4	0%
	3 (disagree)	0%
	2	0%
	1 (strongly disagree)	0%
Overall agreement 100%, consensus endorsed		

3.2. Screening of Vitamin D Deficiency in Adults

No published study evaluated the effects of a screening program for vitamin D deficiency in the general population, so the evidence is insufficient to balance the benefits and harms of such a screening [42,43]. Accordingly, we stress that it is currently not justified to recommend a general screening for vitamin D deficiency by measuring 25(OH)D concentrations in the whole general population. Nevertheless, considering that certain groups of individuals or patients are particularly prone to vitamin D deficiency and/or may particularly benefit from vitamin D treatment, we suggest, in line with the Endocrine Society, that 25(OH)D measurements should be considered in these groups, as listed in Table 4 [14].

Total serum 25(OH)D concentration, i.e., the sum of $25(OH)D_3$ and $25(OH)D_2$, is the accepted marker for the assessment of vitamin D status, as it best reflects vitamin D supply by all different sources, i.e., endogenous vitamin D synthesis in the skin, diet, supplements, and mobilization from tissue stores. Previous reports on a relatively high inter-assay and inter-laboratory variability of 25(OH)D measurements underscore the need for assay standardization and laboratory quality assurance [44,45]. In patients with vitamin D deficiency and certain related health issues, e.g., bone diseases, it should be considered to measure additional laboratory parameters, including serum calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), creatinine (to calculate the estimated glomerular filtration rate), and magnesium, as these laboratory markers may be useful to guide further diagnostics and treatment of these patients. Measurements of, e.g., serum calcium and creatinine are, however, also advised in patients with 25(OH)D concentrations above 100 ng/mL (250 nmol/L), as vitamin D oversupply/toxicity may lead to hypercalciuria, followed by hypercalcemia, potential acute kidney disease, and vascular calcification. Hypercalcemia does, however, usually not occur at 25(OH)D concentrations below 150 ng/mL (375 nmol/L) [46]. There are hardly any contraindications to correct vitamin D deficiency by vitamin D supplementation (e.g., kidney stones are *per se* no contraindication) except of rare conditions with an increased sensitivity to vitamin D treatment, such as inherited 24-hydroxylase-deficiency [47]. This is a rare genetic disorder in which catabolism of vitamin D metabolites is impaired, leading to hypercalcemia, low PTH concentrations, and relatively high serum 25(OH)D concentrations along with an increased risk of nephrolithiasis [47]. If such a disease is suspected, the measurement of 24,25-dihydroxyvitamin D, in a specialized laboratory, aids in the diagnosis as a high ratio of 25(OH)D to 24,25-dihydroxyvitamin D suggests this disease that is further confirmed by genetic analyses [47].

Classification of vitamin D status and its terminology, according to 25(OH)D concentration, remains a controversial issue in the scientific literature [7,16,21]. Being aware that it is an individual continuum from vitamin D deficiency to a sufficient and optimal vitamin D status, as well as to vitamin D toxicity, we suggest a classification system, as indicated in Table 4. It should be kept in mind that such a general classification of vitamin D status

cannot take into account variations in the individual sensitivity to vitamin D effects that may be due to genetic polymorphisms, epigenetic or nutritional factors (e.g., magnesium status), as well as co-morbidities or medications [48–52].

Table 4. Statement regarding screening of vitamin D deficiency in adults.

Consensus Statement	Consensus Voting Scale	Level of Agreement
Screening of vitamin D deficiency should be considered in the following patients/individuals or conditions: Osteoporosis; Osteomalacia; Musculoskeletal pain; Chronic kidney disease; Hepatic failure; Malabsorption syndromes (e.g., cystic fibrosis, inflammatory bowel diseases, bariatric surgery, radiation enteritis); Hyperparathyroidism; Chronic treatment with medications that influence vitamin D metabolism (e.g., antiseizure medications, glucocorticoids, AIDS-medications, antifungal agents, cholestyramine); Chronic autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis); Pregnant and lactating women; Institutionalized or hospitalized patients; Older adults (>65 years) in general; Older adults with history of falls or nontraumatic fractures; Granuloma-forming disorders (e.g., sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidiomycosis); Obesity (BMI $\geq$ 30kg/m^2); dark skin pigmentation. 25(OH)D is recommended as a laboratory marker for the diagnosis of vitamin D deficiency. In patients with diagnosed vitamin D deficiency (25(OH)D < 20 ng/mL (<50 nmol/L)) and suspected related health issues, serum calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), creatinine, and serum magnesium levels should be considered for evaluation; in particular in individuals with a 25(OH)D concentration of <10 ng/mL (<25 nmol/L). A 25(OH)D concentration of <20 ng/mL (<50 nmol/L) is considered as vitamin D deficiency A 25(OH)D concentration of $\geq$20 ng/mL ($\geq$50 nmol/L) and <30 ng/mL (<75 nmol/L) is considered as vitamin D insufficiency A 25(OH)D concentration of 30–50 ng/mL (75–125 nmol/L) is considered as vitamin D sufficiency A 25(OH)D concentration of >50–60 ng/mL (125–150 nmol/L) is considered as safe but not as a target level A 25(OH)D concentration of >60–100 ng/mL (150–250 nmol/L) is considered as area of uncertainty with potential benefits or risks. A 25(OH)D concentration of >100 ng/mL (250 nmol/L) is considered as oversupply/vitamin D toxicity	9 (strongly agree) 8 7 (agree) 6 5 (neutral) 4 3 (disagree) 2 1 (strongly disagree)	50% 20% 30% 0% 0% 0% 0% 0% 0%
Overall agreement 100%, consensus endorsed		

3.3. Prevention of Vitamin D Deficiency in Adults

Most nutritional vitamin D guidelines conclude that vitamin D requirements are met for the vast majority (i.e., 97.5%) of the population when achieving a target 25(OH)D concentration of at least 20 ng/mL (50 nmol/L) [11,12]. Recommended dietary reference intakes for vitamin D usually range from 600 to 800 international units (IU) (40 IU are equal to 1 μg) per day and should ensure a sufficient vitamin D status under conditions of minimal-to-no sunlight exposure [11–13,16,53,54]. These vitamin D intake doses were calculated according to meta-regression analyses of so called "winter RCTs" to estimate the dose-response curve of vitamin D intakes and achieved serum 25(OH)D concentrations without relevant endogenous vitamin D synthesis in the skin [11]. It is a major limitation of most nutritional vitamin D guidelines that they performed meta-regression analyses based on aggregate data because such an approach does not adequately capture between person variability in the treatment response [53,54]. Using individual participant data instead of aggregate data for meta-regression analyses, as a superior methodological approach, results in significantly higher vitamin D intakes to achieve certain target 25(OH)D concentrations [53,54]. Individual participant data meta-regression analyses and single RCTs suggest that an overall vitamin D intake of about 1000 IU of vitamin D per day is

required to maintain 25(OH)D concentrations of, at least, 20 ng/mL (50 nmol/L) in 97.5% of the population [54,55]. Therefore, we recommend a vitamin D supplement dose of at least 800 IU per day when targeting a sufficient vitamin D status, i.e., a 25(OH)D concentration of at least 20 ng/mL (50 nmol/L). We can, of course, improve and maintain vitamin D status by consuming natural or fortified food sources, but vitamin D intake by diet is usually in the range of about 100 to 200 IU per day in the general population [37,56].

In detail, we recommend a vitamin D supplementation dose of 800 to 2000 IU per day for adults who want to ensure a sufficient vitamin D status, with up to 4000 IU per day for certain groups, particularly for patients with obesity and malabsorption syndromes, as well as for individuals with a dark skin pigmentation (see Table 5). The relatively wide dose ranges for vitamin D account for various differences in the dose-response relationship for a given supplemental vitamin D dose and the achieved 25(OH)D concentration with higher dose requirements with increasing body weight and vice versa [57–64]. If a clinician is asked by a random individual which vitamin D dose is safe and very likely avoids vitamin D deficiency, a dose of 800 to 1000 IU per day should fulfill these criteria for the vast majority, even if individual characteristics, including the 25(OH)D status, is unknown. It should, however, also be noted that a few health authorities and experts consider a 25(OH)D concentration, of at least 10–12 ng/mL (25 to 30 nmol/L), as a reasonable treatment target that can be achieved by supplementation of 400 IU of vitamin D per day [11,13,16,53].

Table 5. Statement regarding prevention of vitamin D deficiency in adults.

Consensus Statement	Consensus Voting Scale	Level of Agreement
In healthy adults without other risk factors, a supplementation of 800–2000 IU/day, for those who want to achieve a targeted/measured 25(OH)D concentration, should be considered during wintertime (mainly November-April) due to insufficient endogenous dermal vitamin D synthesis and depending on the body weight.	9 (strongly agree)	30%
	8	20%
	7 (agree)	50%
	6	0%
Due to decreased skin synthesis in elderly (>65 years), a supplementation of 800–2000 IU/day is recommended throughout the year.	5 (neutral)	0%
	4	0%
In hospitalized/institutionalized individuals, a supplementation of 800–2000 IU/day is recommended throughout the year.	3 (disagree)	0%
	2	0%
Women planning a pregnancy should start or maintain the vitamin D supplementation as recommended for healthy adults without other risk factors (800–2000 IU/day). The vitamin D supplementation should be continued throughout pregnancy and lactation.	1 (strongly disagree)	0%
In certain patients/individuals or conditions 2–3 times higher vitamin D dosages, without using vitamin D doses above the UL of 4000 IU/day, are recommended for prevention compared to healthy adults without other risk factors: Malabsorption (e.g., cystic fibrosis, inflammatory bowel diseases, bariatric surgery, radiation enteritis) Obesity (BMI $\geq$ 30 kg/m^2) Dark skin pigmentation		
As vitamin D metabolites are stored in fat and other tissues and gradually released into the blood circulation, a daily or weekly or monthly supplementation regimen is equally effective and safe, if monthly doses are not exceedingly high, for the prevention of vitamin D deficiency.		
A tailored approach for vitamin D administration, involving the patients' preferences of the supplementation regimen (daily, weekly, monthly) might enhance the adherence to preventive vitamin D supplementation.		
For the prevention of vitamin D deficiency, the supplementation of oral cholecalciferol (vitamin D3) is recommended.		
Overall agreement 100%, consensus endorsed		

Daily, weekly, or monthly vitamin D supplementation, at equivalent doses, lead to similar increases in 25(OH)D serum concentrations, when measured after 2 to 3 months [65–67]. Adherence may be better with intermittent vitamin D dosing, but there are also concerns

that high intermittent vitamin D doses may be less beneficial or might even be harmful in certain settings [67–69]. In view of the available evidence from clinical vitamin D trials and some pathophysiological considerations (e.g., altered vitamin D metabolism with high intermittent vitamin D doses), a daily vitamin D dosing schedule should rather be preferred, but when exceedingly high intermittent vitamin D doses are avoided, a weekly or monthly dosing schedule can also be applied [66,67]. The panel members could not reach a clear consensus on a clear cut-off for exceedingly high vitamin D doses, but single doses above about 50,000 IU of vitamin D should rather be avoided. Due to superior evidence regarding clinical benefits and dose-response, we rather prefer vitamin D3 (cholecalciferol) over vitamin D2 (ergocalciferol) for the prevention of vitamin D deficiency [51,70].

3.4. Treatment of Vitamin D Deficiency in Adults

Individuals with a measured 25(OH)D concentration below 20 ng/mL (50 nmol/L) should be treated with vitamin D supplementation, because their vitamin D requirements may not be met [11,12]. There is controversy in the scientific literature whether 25(OH)D concentrations between 20 ng/mL (50 nmol/L) and <30 ng/mL (75 nmol/L) justify vitamin D supplementation [71,72]. The recommended dose range of 800 to 2000 IU per day is a reflection of various considerations underlying such treatment goals (see Table 6). When aiming for a minimum 25(OH)D concentration of at least 20 ng/mL (50 nmol/L), a daily vitamin D supplement dose of about 800 IU per day is sufficient for almost all individuals, even during the winter season, in Europe [54,55]. Data are less clear on which vitamin D doses are required to achieve a 25(OH)D concentration of ≥30 ng/mL (75 nmol/L) in almost all patients, but doses may be in the range of about 1500 to 2000 IU per day or even higher [14,21,26–28]. The classic rule of thumb that 100 IU of vitamin D per day increases serum 25(OH)D concentrations by about 1 ng/mL (2.5 nmol/L) seems to be a useful approximation, but several factors modulate the individual treatment response [73,74]. For example, increases in 25(OH)D are relatively high at low vitamin D supplement doses and low baseline 25(OH)D concentrations, whereas the dose-response curve flattens with higher vitamin D supplement doses and higher baseline 25(OH)D concentrations [73,74]. Evaluations of treatment success, by measurements of 25(OH)D, may be considered in certain patients, such as those with e.g., malabsorption or questionable adherence, but this should not be done earlier than 6 to 12 weeks after starting vitamin D supplementation, as this is about the time that it takes to reach a steady-state in serum 25(OH)D concentrations [2]. Although there is, of course, a seasonal variation in serum 25(OH)D concentrations, usually with higher levels during summertime, as a consequence of endogenous vitamin D synthesis in the skin, we do, in general, recommend continuous and, usually, fixed doses of vitamin D supplementation throughout the year. The decrease in serum 25(OH)D during winter season is, in many patients, significant, but it is less than could be expected by the half-life of serum 25(OH)D concentrations of about 2 to 3 weeks because of a mobilization of vitamin D and its metabolites from various tissue stores (e.g., adipose tissue and muscle) [75].

If a rapid correction of vitamin D deficiency is clinically indicated, a regimen with a higher initial vitamin D dose, i.e., 6000 IU per day, and in certain cases, even up to 10,000 IU per day, followed by a maintenance dose with 800 to 2000 IU per day is recommended (Table 6). Such doses of 6000 IU, or even up to 10,000 IU, per day for several weeks are usually safe and ensure a more rapid correction of vitamin D deficiency compared to lower doses [14,76,77]. Daily vitamin D doses are generally preferred over intermittent dosing schedules [67]. The clinical indications for a rapid correction of vitamin D are, beyond osteomalacia, not clearly defined but may, according to our opinion, involve conditions such as extremely low 25(OH)D concentrations, osteoporosis patients with a very high fracture risk, patients with secondary hyperparathyroidism, and/or reduced serum calcium concentrations.

Regarding treatment of vitamin D deficiency and its prevention, we want to emphasize that promoting a healthy lifestyle by preventing or reducing obesity, regular physical

activity with moderate (cautious) sunlight exposure, and a healthy balanced diet are also effective measures to improve both vitamin D status and overall health. Promoting such lifestyle measures is, of course, also highly recommended, and it should accompany any vitamin D treatment.

As for the prevention of vitamin D deficiency, we recommend vitamin D3 (cholecalciferol) over vitamin D2 (ergocalciferol) for its treatment. Although parenteral, particularly intramuscular, vitamin D treatment can be considered in patients with malabsorption, e.g., inflammatory bowel disease, we primarily suggest to increase the oral vitamin D dose in such settings [78]. Clinicians have to consider that patients with inflammatory bowel disease frequently require higher vitamin D doses, but with daily oral vitamin D supplementation of about 5000 to 10,000 IU, even these patients usually achieve their 25(OH)D target concentrations [78]. If intermittent intramuscular vitamin D injections (e.g., 100,000 IU all three months) are used, the doses are roughly similar and slightly more efficient for intramuscular compared to oral doses, in terms of raising serum 25(OH)D concentrations, but the increase in serum 25(OH)D is slower for intramuscular versus oral vitamin D supplementation [78–81].

Some experts argue that calcifediol (=25(OH)D3, calcidiol) may also be used to correct vitamin D deficiency in certain conditions. The use of calcifediol seems to be more justified in obese people, people with malabsorption syndromes, people with liver disease, patients suffering from chronic kidney disease (stage 3 or 4), and those in all conditions where rapid correction of vitamin D deficiency is required [82–84]. Furthermore, calcifediol use may also be beneficial in patients taking medications that disrupt the hepatic cytochrome P-450 enzyme system, including those taking glucocorticoids, anticonvulsants, anticancer drugs, or antiretroviral drugs [82–85]. The increase in serum 25(OH)D is markedly reduced in patients with obesity (high BMI) and in patients with malabsorption syndromes treated with cholecalciferol, but with calcifediol, the 25(OH)D increase is not significantly different according to BMI or according to the presence, or absence, of malabsorption syndromes. Moreover, the increase in serum 25(OH)D is faster, and the dose-response curve is more linear with the use of calcifediol versus vitamin D3, and when stopping treatment, the decline in 25(OH)D concentration is faster after calcifediol compared to vitamin D3 [75,82–84]. While accumulating evidence suggests that calcifediol may be an attractive alternative to "native" vitamin D, due to the lack of experience with this molecule in Central and Eastern European countries, at this stage, we continue to recommend vitamin D3 (cholecalciferol) [75]. Cholecalciferol and calcifediol appear, so far, as equal molecules in the fight with vitamin D deficiency. However, RCT data are still missing on the superior benefit of calcifediol versus vitamin D, with reference to hard clinical outcomes, but more data on this topic may be available in the future [75,84,85].

Calcitriol (=1,25(OH)2D) and its analogues are used at much lower doses compared to vitamin D3, have a relatively high risk of hypercalcemia and a relatively narrow therapeutic window, and are not recommended for the treatment of common vitamin D deficiency [64]. Therefore, active vitamin D treatment is only indicated in certain diseases, such as chronic hypoparathyroidism, chronic kidney disease, or mineral and bone disorders (CKD-MBD) [64,86].

Table 6. Statement regarding treatment of vitamin D deficiency in adults.

Consensus Statement	Consensus Voting Scale	Level of Agreement
It is recommended to initiate a vitamin D deficiency treatment at a 25(OH)D concentration of <20 ng/mL (<50 nmol/L). At a concentration of <30 ng/mL (<75 nmol/L) a treatment may be considered.	9 (strongly agree)	60%
Individuals with diagnosed vitamin D deficiency can be initially treated with higher vitamin D dosages compared to the preventive dosages recommended for the general population, if a rapid correction of the 25(OH)D concentration is clinically indicated. As initial dose for the treatment of vitamin D deficiency in patients without other risk factors, a dosage of 6000 IU, equivalent to a daily dosage, is recommended.	8	10%
In certain individuals or conditions, higher vitamin D dosages, up to 10,000 IU, equivalent to a daily dosage, are recommended for treatment compared to healthy adults without other risk factors (Endocrine Society recommendation) [14]:	7 (agree)	30%
-Malabsorption (e.g., cystic fibrosis, inflammatory bowel diseases, bariatric surgery, radiation enteritis)	6	0%
-Chronic treatment of medications that influence vitamin D metabolism (e.g., antiseizure medications, glucocorticoids, AIDS-medications, antifungal agents, cholestyramine)	5 (neutral)	0%
-Obesity (BMI $\geq$ 30 kg/m^2)	4	0%
A treatment duration of 4–12 weeks is recommended, depending on the severity of vitamin D deficiency.	3 (disagree)	0%
A tailored approach for vitamin D administration, involving the patients' preferences of the treatment regimen (daily, weekly, monthly) might enhance the adherence to the therapy.	2	0%
As soon as a 25(OH)D concentration of 30–50 ng/mL (75–125 nmol/L) is achieved, a maintenance dose of 800–2000 IU/day is recommended, that can also be used as an initial treatment dose if there is no requirement for a rapid correction of vitamin D deficiency.	1 (strongly disagree)	0%
Approx. 6–12 weeks after start of the treatment, the effectiveness may be evaluated by measurement of the 25(OH)D concentration particularly in certain risk groups with e.g., malabsorption syndrome.		
For the treatment of vitamin D deficiency in adults, oral cholecalciferol (vitamin D3) is preferred.		
Calcifediol may be used instead of vitamin D in certain conditions, including obesity or malabsorption.		
Calcitriol and active vitamin D analogues may be considered in special patient groups.		
In certain risk groups (e.g., patients with severe malabsorption), parenteral vitamin D treatment can be considered.		
Overall agreement 100%, consensus endorsed		

3.5. Vitamin D in Musculoskeletal Disorders

While older meta-analyses of vitamin D RCTs showed a significant reduction in fractures by vitamin D supplementation at a daily dose of about 800 to 2000 IU per day, these data have recently been challenged by updated meta-analyses, suggesting no significant effect on fractures and falls [5,87,88]. Nevertheless, major osteoporosis guidelines recommend vitamin D treatment in osteoporosis patients, and some studies indicate that sufficient 25(OH)D concentrations are required for optimal bisphosphonate treatment efficacy [51,89]. While it is beyond the scope of our work to release detailed recommendations regarding calcium supplementation in osteoporosis patients, we wish to point out that a recent RCT with the bisphosphonate zoledronate showed excellent anti-fracture effects in patients using pure vitamin D supplementation without additional calcium supplements but consuming 1g of calcium daily by a usual diet [90]. These data may suggest that, even in osteoporosis patients, vitamin D treatment without additional calcium supplements may be sufficient in the case of adequate dietary calcium intake, but this issue is still not clarified in the scientific community, since it is challenging to disentangle the effects of

vitamin D and calcium with regards to bone health [5,88,90–92]. Of note, increasing calcium and protein intake by milk, yoghurt, and cheese significantly reduces the risk of falls and fractures in aged care residents [93]. Calcium supplementation is, however, generally indicated in patients with osteoporosis and an insufficient dietary calcium intake. In this context, it should be stressed that most RCTs on osteoporosis drugs were conducted under the conditions of combined calcium plus vitamin D supplementation, thus supporting the use of calcium supplementation, in addition to vitamin D for osteoporosis treatment. Being aware of the uncertainties regarding vitamin D, in the context of osteoporosis, we nevertheless strongly argue to ensure a sufficient vitamin D status in patients with an increased risk of fractures and falls (Table 7). With reference to falls, some studies suggest that high-dose intermittent vitamin D supplementation may even be detrimental so that we prefer daily doses at the lower end of the dosing range of 800 to 2000 IU per day, in this setting [67,85,94]. Therefore, vitamin D overdosing must particularly be avoided in older and severely ill patients [94,95].

Table 7. Statement regarding vitamin D in musculoskeletal disorders.

Consensus Statement	Consensus Voting Scale	Level of Agreement
In osteoporosis patients, a supplementation of 800–2000 IU/day, with oral cholecalciferol (vitamin D3) is recommended in combination with calcium, if indicated. Vitamin D deficiency may impair the response to the osteoporosis treatment, thus screening of the 25(OH)D level and correction of vitamin D deficiency before starting the osteoporosis treatment with antiresorptive medications is recommended. In patients with an increased risk of falls or fractures, a supplementation of 800–2000 IU/day is recommended.	9 (strongly agree)	30%
	8	10%
	7 (agree)	60%
	6	0%
	5 (neutral)	0%
	4	0%
	3 (disagree)	0%
	2	0%
	1 (strongly disagree)	0%
Overall agreement 100%, consensus endorsed		

3.6. Extra-Skeletal Actions of Vitamin D in Adults

The expression of the VDR and of vitamin D-metabolizing enzymes in almost all human tissues and cells suggests a widespread role of vitamin D for overall human health [1,10]. In line with this, numerous epidemiological studies documented that low 25(OH)D concentrations are associated with an increased risk of all-cause mortality and major acute and chronic diseases, such as cancer, cardiovascular and autoimmune diseases, as well as infections (see Table 8) [1,3,4,6,8,92,96–100]. Confounding and reverse causation may, however, explain parts of these associations so that cause and effect relationships are not yet fully established for several of the above mentioned diseases [101].

Meta-analyses of vitamin D RCTs suggest that vitamin D supplementation may reduce the incidence of acute respiratory infections, cancer mortality, as well as asthma and chronic obstructive pulmonary disease (COPD) exacerbations [5,96,102–108]. Considering the totality of evidence regarding vitamin D and a variety of extra-skeletal diseases, we are of the opinion that it is justified to consider screening and preventive vitamin D supplementation in certain populations at risk (see Table 8). The general dilemma with potential extra-skeletal health benefits of vitamin D in the context of vitamin D guidelines is that vitamin D requirements for skeletal health, such as for the prevention of rickets and osteomalacia, may be met at lower 25(OH)D concentrations than the requirements for certain extra-skeletal health benefits [1,14]. Of note, recent large vitamin D RCTs failed to document significant benefits regarding their primary outcomes, such as mortality, cancer, or cardiovascular diseases, but these trials enrolled populations that were, by the vast majority, not vitamin D deficient [109,110].

Numerous studies have been published on vitamin D, in the context of the Coronavirus Disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [111–113]. While there is accumulating evidence suggesting potential benefits of vitamin D or calcifediol, for the prevention and treatment of COVID-19,

this hypothesis still requires confirmation in large clinical trials [111–113]. Fortunately, due to the efficacy of vaccines and natural immunity of individuals who recovered from SARS-CoV-2 infections, the COVID-19 pandemic has already been significantly mitigated in early 2022, with expected further improvements in the near future [114–116].

Table 8. Statement regarding extra-skeletal actions of vitamin D in adults.

Consensus Statement	Consensus Voting Scale	Level of Agreement
Results from observational studies consider a low 25(OH)D concentration as a potential risk marker for several diseases such as cancer incidence and mortality, cardiovascular diseases, diabetes mellitus and its comorbidities, chronic autoimmune diseases, metabolic syndrome, acute respiratory tract infections, neurological diseases and total mortality. Results from meta-analyses of RCTs suggest that beyond musculoskeletal-effects, vitamin D supplementation may have beneficial extra-skeletal effects regarding acute respiratory tract infections and cancer mortality. In patients with or at risk of different types of cancer, certain cardiovascular diseases, diabetes mellitus and its comorbidities, chronic autoimmune diseases, certain neurological diseases and recurrent acute respiratory tract infections, a screening of vitamin D deficiency should be considered, and preventive vitamin D supplementation may be considered.	9 (strongly agree)	60%
	8	10%
	7 (agree)	30%
	6	0%
	5 (neutral)	0%
	4	0%
	3 (disagree)	0%
	2	0%
	1 (strongly disagree)	0%
Overall agreement 100%, consensus endorsed		

3.7. Development of a Vitamin D Deficiency Screening and Treatment Algorithm

Based on our consensus statements, we developed an algorithm for the prevention and treatment of vitamin D deficiency that was also subject to a Delphi voting round, with the following point scale results: 9 points (20% of panel members), 8 points (30%), and 7 points (50%) (see Figure 1).
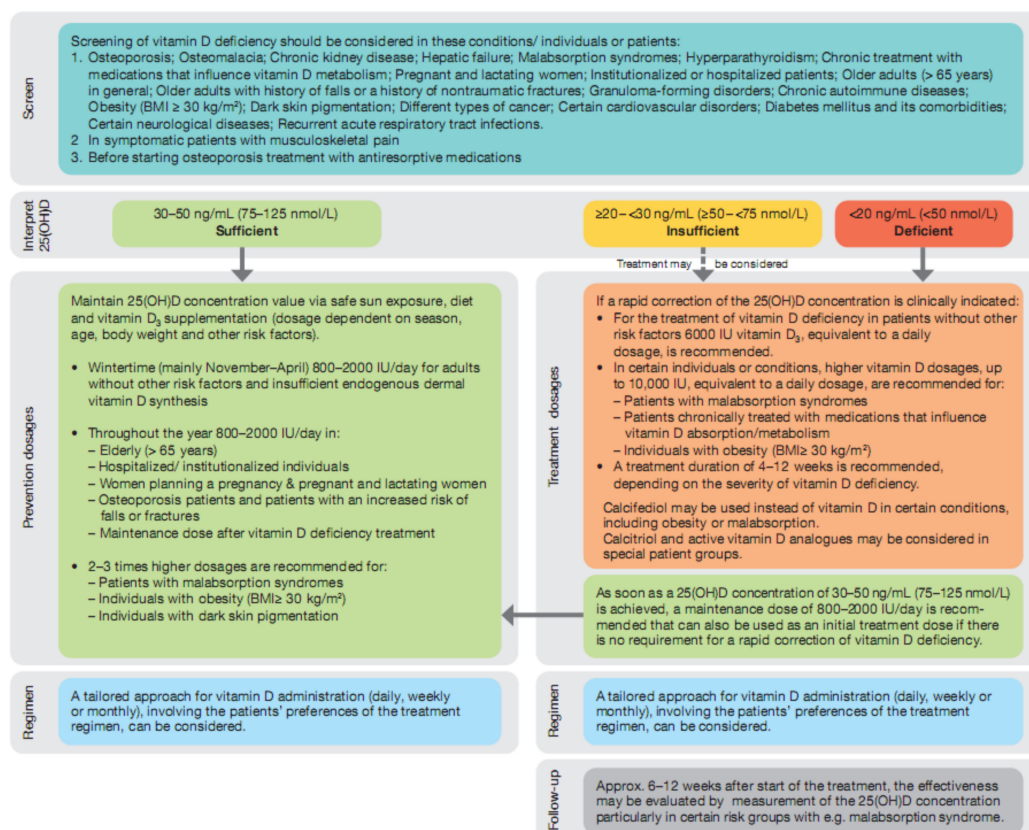

Figure 1. Algorithm for vitamin D deficiency screening and treatment.

4. Strengths and Limitations

As a potential limitation, the financial and logistic support by an industry sponsor (Wörwag Pharma) must be acknowledged. Despite no involvement of the sponsor in the scientific group discussions and consensus reaching processes, we cannot totally exclude some sort of funding bias [17,18]. Moreover, this consensus document was not informed by an a priori structured and pre-registered systematic review of the evidence. A definite strength of our work is the a priori structured process for developing this document, based on the Delphi method for reaching consensus. The number of 10 participants for using the Delphi voting rounds may be considered as too low, but such a group size is not uncommon and, thus, is generally accepted in the scientific literature on this methodology [35]. The involvement of several colleagues from Eastern Europe, who are usually underrepresented in European expert groups, and the well-balanced gender distribution of this panel, may also be regarded as a strength of our work.

5. Conclusions

This consensus statement covers various statements with relevance for the clinical practice in the prevention, diagnosis, and treatment of vitamin D deficiency. We highlighted the relevance of vitamin D for public health and provided guidance regarding this issue by considering the totality of the available scientific evidence, including our personal experience and opinions.

We consider that our work adds to the existing literature by providing a useful and evidence-based guidance for clinicians and health-care workers regarding several relevant and partially controversial topics for the practical management, with reference to vitamin D. In addition, we also addressed various issues with relevance for public health authorities and individuals from the general population that will, hopefully, help to reduce the global health burden of vitamin D deficiency.

Author Contributions: Writing—original draft preparation, P.P. and S.P. Writing a final review and final editing, I.T., M.B., Z.B., C.C.D., T.M., N.Z., I.R., J.P., P.P. and S.P. All authors have read and agreed to the published version of the manuscript.

References

1. Bouillon, R.; Marcocci, C.; Carmeliet, G.; Bikle, D.; White, J.H.; Dawson-Hughes, B.; Lips, P.; Munns, C.F.; Lazaretti-Castro, M.; Giustina, A.; et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. *Endocr. Rev.* **2019**, *40*, 1109–1151. [CrossRef] [PubMed]
2. Pilz, S.; Zittermann, A.; Trummer, C.; Theiler-Schwetz, V.; Lerchbaum, E.; Keppel, M.H.; Grubler, M.R.; Marz, W.; Pandis, M. Vitamin D testing and treatment: A narrative review of current evidence. *Endocr. Connect.* **2019**, *8*, R27–R43. [CrossRef]
3. Maretzke, F.; Bechthold, A.; Egert, S.; Ernst, J.B.; Melo van Lent, D.; Pilz, S.; Reichrath, J.; Stangl, G.I.; Stehle, P.; Volkert, D.; et al. Role of Vitamin D in Preventing and Treating Selected Extraskeletal Diseases—An Umbrella Review. *Nutrients* **2020**, *12*, 969. [CrossRef] [PubMed]
4. Zittermann, A.; Trummer, C.; Theiler-Schwetz, V.; Lerchbaum, E.; Marz, W.; Pilz, S. Vitamin D and Cardiovascular Disease: An Updated Narrative Review. *Int. J. Mol. Sci.* **2021**, *22*, 2896. [CrossRef] [PubMed]
5. Bouillon, R.; Manousaki, D.; Rosen, C.; Trajanoska, K.; Rivadeneira, F.; Richards, J.B. The health effects of vitamin D supplementation: Evidence from human studies. *Nat. Rev. Endocrinol.* **2021**, *18*, 96–110. [CrossRef]
6. Pilz, S.; Zittermann, A.; Obeid, R.; Hahn, A.; Pludowski, P.; Trummer, C.; Lerchbaum, E.; Perez-Lopez, F.R.; Karras, S.N.; Marz, W. The Role of Vitamin D in Fertility and during Pregnancy and Lactation: A Review of Clinical Data. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2241. [CrossRef]
7. Holick, M.F. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev. Endocr. Metab. Disord.* **2017**, *18*, 153–165. [CrossRef]

8.   Gaksch, M.; Jorde, R.; Grimnes, G.; Joakimsen, R.; Schirmer, H.; Wilsgaard, T.; Mathiesen, E.B.; Njolstad, I.; Lochen, M.L.; Marz, W.; et al. Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. *PLoS ONE* **2017**, *12*, e0170791. [CrossRef]

9.   Cashman, K.D.; Dowling, K.G.; Skrabakova, Z.; Gonzalez-Gross, M.; Valtuena, J.; De Henauw, S.; Moreno, L.; Damsgaard, C.T.; Michaelsen, K.F.; Molgaard, C.; et al. Vitamin D deficiency in Europe: Pandemic? *Am. J. Clin. Nutr.* **2016**, *103*, 1033–1044. [CrossRef]

10.   Saponaro, F.; Saba, A.; Zucchi, R. An Update on Vitamin D Metabolism. *Int. J Mol. Sci.* **2020**, *21*, 6573. [CrossRef]

11.   Pilz, S.; Trummer, C.; Pandis, M.; Schwetz, V.; Aberer, F.; Grubler, M.; Verheyen, N.; Tomaschitz, A.; Marz, W. Vitamin D: Current Guidelines and Future Outlook. *Anticancer Res.* **2018**, *38*, 1145–1151. [CrossRef]

12.   Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 53–58. [CrossRef]

13.   Buttriss, J.L.; Lanham-New, S.A.; Steenson, S.; Levy, L.; Swan, G.E.; Darling, A.L.; Cashman, K.D.; Allen, R.E.; Durrant, L.R.; Smith, C.P.; et al. Implementation strategies for improving vitamin D status and increasing vitamin D intake in the UK: Current controversies and future perspectives: Proceedings of the 2nd Rank Prize Funds Forum on vitamin D. *Br. J. Nutr.* **2021**, 1–21. [CrossRef]

14.   Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M.; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 1911–1930. [CrossRef]

15.   Giustina, A.; Bouillon, R.; Binkley, N.; Sempos, C.; Adler, R.A.; Bollerslev, J.; Dawson-Hughes, B.; Ebeling, P.R.; Feldman, D.; Heijboer, A.; et al. Controversies in Vitamin D: A Statement from the Third International Conference. *JBMR Plus* **2020**, *4*, e10417. [CrossRef]

16.   Bouillon, R. Comparative analysis of nutritional guidelines for vitamin D. *Nat. Rev. Endocrinol.* **2017**, *13*, 466–479. [CrossRef]

17.   Fraile Navarro, D.; Lopez Garcia-Franco, A.; Nino de Guzman, E.; Rabassa, M.; Zamanillo Campos, R.; Pardo-Hernandez, H.; Ricci-Cabello, I.; Canelo-Aybar, C.; Meneses-Echavez, J.F.; Yepes-Nunez, J.J.; et al. Vitamin D recommendations in clinical guidelines: A systematic review, quality evaluation and analysis of potential predictors. *Int. J. Clin. Pract.* **2021**, *75*, e14805. [CrossRef]

18.   Dai, Z.; McKenzie, J.E.; McDonald, S.; Baram, L.; Page, M.J.; Allman-Farinelli, M.; Raubenheimer, D.; Bero, L.A. Assessment of the Methods Used to Develop Vitamin D and Calcium Recommendations—A Systematic Review of Bone Health Guidelines. *Nutrients* **2021**, *13*, 2423. [CrossRef]

19.   Rosen, C.J.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; Kovacs, C.S.; et al. IOM committee members respond to Endocrine Society vitamin D guideline. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 1146–1152. [CrossRef]

20.   Pludowski, P.; Holick, M.F.; Grant, W.B.; Konstantynowicz, J.; Mascarenhas, M.R.; Haq, A.; Povoroznyuk, V.; Balatska, N.; Barbosa, A.P.; Karonova, T.; et al. Vitamin D supplementation guidelines. *J. Steroid Biochem. Mol. Biol.* **2018**, *175*, 125–135. [CrossRef]

21.   Pludowski, P.; Karczmarewicz, E.; Bayer, M.; Carter, G.; Chlebna-Sokol, D.; Czech-Kowalska, J.; Debski, R.; Decsi, T.; Dobrzanska, A.; Franek, E.; et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe—Recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. *Endokrynol. Pol.* **2013**, *64*, 319–327. [CrossRef]

22.   Takacs, I.; Benko, I.; Toldy, E.; Wikonkal, N.; Szekeres, L.; Bodolay, E.; Kiss, E.; Jambrik, Z.; Szabo, B.; Merkely, B.; et al. Hungarian consensus regarding the role of vitamin D in the prevention and treatment of diseases. *Orv. Hetil.* **2012**, *153* (Suppl. 2), 5–26. [CrossRef]

23.   German Nutrition Society (DGE). New reference values for vitamin D. *Ann. Nutr. Metab.* **2012**, *60*, 241–246. [CrossRef]

24.   EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies). Scientific opinion on dietary reference values for vitamin D. *EFSA J.* **2016**, *14*, 4547. [CrossRef]

25.   Pigarova, E.A.; Rozhinskaya, L.Y.; Belaya, J.E.; Dzeranova, L.K.; Karonova, T.L.; Ilyin, A.V.; Melnichenko, G.A.; Dedov, I.I. Russian Association of Endocrinologists recommendations for diagnosis, treatment and prevention of vitamin D deficiency in adults. *Probl. Endocrinol.* **2016**, *62*, 60–84. (In Russian) [CrossRef]

26.   Rusinska, A.; Pludowski, P.; Walczak, M.; Borszewska-Kornacka, M.K.; Bossowski, A.; Chlebna-Sokol, D.; Czech-Kowalska, J.; Dobrzanska, A.; Franek, E.; Helwich, E.; et al. Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland-Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel with Participation of National Specialist Consultants and Representatives of Scientific Societies—2018 Update. *Front. Endocrinol.* **2018**, *9*, 246. [CrossRef]

27.   Rudenko, E. *National Regulation about Methods of Diagnosis, Prevention and Differentiated Treatment of Vitamin D Deficiency*; Ministry of Health of the Republic of Belarus: Minsk, Belarus, 2013.

28.   Borissova, A.-M.; Boyanov, M.A.; Popivanov, P.R.; Kolarov, Z.; Petranova, T.P.; Shinkov, A.D. *Recommendation for Diagnosis, Prevention and Treatment of Vitamin D Deficiency*; Bulgarian Society of Endocrinology: Sofia, Bulgaria, 2019.

29.   Payer, J.; Killinger, Z.; Jackuliak, P.; Kužma, M. Postmenopausal osteoporosis: Standard diagnostic and therapeutic practice. *Clin. Osteol.* **2018**, *23*, 18–27.

30.   Cesareo, R.; Attanasio, R.; Caputo, M.; Castello, R.; Chiodini, I.; Falchetti, A.; Guglielmi, R.; Papini, E.; Santonati, A.; Scillitani, A.; et al. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. *Nutrients* **2018**, *10*, 546. [CrossRef]

31. Rockwell, M.; Kraak, V.; Hulver, M.; Epling, J. Clinical Management of Low Vitamin D: A Scoping Review of Physicians' Practices. *Nutrients* **2018**, *10*, 493. [CrossRef]
32. Zittermann, A.; Pilz, S.; Berthold, H.K. Serum 25-hydroxyvitamin D response to vitamin D supplementation in infants: A systematic review and meta-analysis of clinical intervention trials. *Eur. J. Nutr.* **2020**, *59*, 359–369. [CrossRef]
33. Munns, C.F.; Shaw, N.; Kiely, M.; Specker, B.L.; Thacher, T.D.; Ozono, K.; Michigami, T.; Tiosano, D.; Mughal, M.Z.; Makitie, O.; et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 394–415. [CrossRef] [PubMed]
34. Grossman, Z.; Hadjipanayis, A.; Stiris, T.; Del Torso, S.; Mercier, J.C.; Valiulis, A.; Shamir, R. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). *Eur. J. Pediatr.* **2017**, *176*, 829–831. [CrossRef] [PubMed]
35. Diamond, I.R.; Grant, R.C.; Feldman, B.M.; Pencharz, P.B.; Ling, S.C.; Moore, A.M.; Wales, P.W. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. *J. Clin. Epidemiol.* **2014**, *67*, 401–409. [CrossRef] [PubMed]
36. Rosenfeld, R.M.; Nnacheta, L.C.; Corrigan, M.D. Clinical Consensus Statement Development Manual. *Otolaryngol. Head Neck Surg.* **2015**, *153*, S1–S14. [CrossRef]
37. Cashman, K.D. Global differences in vitamin D status and dietary intake: A review of the data. *Endocr. Connect.* **2022**, *11*, e210282. [CrossRef]
38. Lips, P.; Cashman, K.D.; Lamberg-Allardt, C.; Bischoff-Ferrari, H.A.; Obermayer-Pietsch, B.; Bianchi, M.L.; Stepan, J.; El-Hajj Fuleihan, G.; Bouillon, R. 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. *Eur. J. Endocrinol.* **2019**, *180*, P23–P54. [CrossRef]
39. Płudowski, P.; Ducki, C.; Konstantynowicz, J.; Jaworski, M. Vitamin D status in Poland. *Pol. Arch. Med. Wewn.* **2016**, *126*, 530–539. [CrossRef]
40. Avdeeva, V.A.; Suplotova, L.A.; Pigarova, E.A.; Rozhinskaya, L.Y.; Troshina, E.A. Vitamin D deficiency in Russia: The first results of a registered, non-interventional study of the frequency of vitamin D deficiency and insufficiency in various geographic regions of the country. *Probl. Endokrinol.* **2021**, *67*, 84–92. [CrossRef]
41. Nikolova, M.G.; Boyanov, M.A.; Tsakova, A.D. Correlations of Serum Vitamin D with Metabolic Parameters in Adult Outpatients with Different Degrees of Overweight/Obesity Coming from an Urban Community. *Acta Endocrinol.* **2018**, *14*, 375–383. [CrossRef]
42. Burnett-Bowie, S.M.; Cappola, A.R. The USPSTF 2021 Recommendations on Screening for Asymptomatic Vitamin D Deficiency in Adults: The Challenge for Clinicians Continues. *JAMA* **2021**, *325*, 1401–1402. [CrossRef]
43. US Preventive Services Task Force; Krist, A.H.; Davidson, K.W.; Mangione, C.M.; Cabana, M.; Caughey, A.B.; Davis, E.M.; Donahue, K.E.; Doubeni, C.A.; Epling, J.W., Jr.; et al. Screening for Vitamin D Deficiency in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* **2021**, *325*, 1436–1442. [CrossRef]
44. Macova, L.; Bicikova, M. Vitamin D: Current Challenges between the Laboratory and Clinical Practice. *Nutrients* **2021**, *13*, 1758. [CrossRef]
45. Binkley, N.; Dawson-Hughes, B.; Durazo-Arvizu, R.; Thamm, M.; Tian, L.; Merkel, J.M.; Jones, J.C.; Carter, G.D.; Sempos, C.T. Vitamin D measurement standardization: The way out of the chaos. *J. Steroid Biochem. Mol. Biol.* **2017**, *173*, 117–121. [CrossRef]
46. Marcinowska-Suchowierska, E.; Kupisz-Urbanska, M.; Lukaszkiewicz, J.; Pludowski, P.; Jones, G. Vitamin D Toxicity—A Clinical Perspective. *Front. Endocrinol.* **2018**, *9*, 550. [CrossRef]
47. Cappellani, D.; Brancatella, A.; Morganti, R.; Borsari, S.; Baldinotti, F.; Caligo, M.A.; Kaufmann, M.; Jones, G.; Marcocci, C.; Cetani, F. Hypercalcemia due to CYP24A1 mutations: A systematic descriptive review. *Eur. J. Endocrinol.* **2021**, *186*, 137–149. [CrossRef]
48. Carlberg, C. Vitamin D: A Micronutrient Regulating Genes. *Curr. Pharm. Des.* **2019**, *25*, 1740–1746. [CrossRef]
49. Hanel, A.; Neme, A.; Malinen, M.; Hamalainen, E.; Malmberg, H.R.; Etheve, S.; Tuomainen, T.P.; Virtanen, J.K.; Bendik, I.; Carlberg, C. Common and personal target genes of the micronutrient vitamin D in primary immune cells from human peripheral blood. *Sci. Rep.* **2020**, *10*, 21051. [CrossRef]
50. Krasniqi, E.; Boshnjaku, A.; Wagner, K.H.; Wessner, B. Association between Polymorphisms in Vitamin D Pathway-Related Genes, Vitamin D Status, Muscle Mass and Function: A Systematic Review. *Nutrients* **2021**, *13*, 3109. [CrossRef]
51. Bilezikian, J.P.; Formenti, A.M.; Adler, R.A.; Binkley, N.; Bouillon, R.; Lazaretti-Castro, M.; Marcocci, C.; Napoli, N.; Rizzoli, R.; Giustina, A. Vitamin D: Dosing, levels, form, and route of administration: Does one approach fit all? *Rev. Endocr. Metab. Disord.* **2021**, *22*, 1201–1218. [CrossRef]
52. Kupisz-Urbanska, M.; Pludowski, P.; Marcinowska-Suchowierska, E. Vitamin D Deficiency in Older Patients—Problems of Sarcopenia, Drug Interactions, Management in Deficiency. *Nutrients* **2021**, *13*, 1247. [CrossRef]
53. Cashman, K.D. Vitamin D Requirements for the Future-Lessons Learned and Charting a Path Forward. *Nutrients* **2018**, *10*, 533. [CrossRef]
54. Cashman, K.D.; Ritz, C.; Kiely, M.; Odin, C. Improved Dietary Guidelines for Vitamin D: Application of Individual Participant Data (IPD)-Level Meta-Regression Analyses. *Nutrients* **2017**, *9*, 469. [CrossRef]
55. Pilz, S.; Hahn, A.; Schon, C.; Wilhelm, M.; Obeid, R. Effect of Two Different Multimicronutrient Supplements on Vitamin D Status in Women of Childbearing Age: A Randomized Trial. *Nutrients* **2017**, *9*, 30. [CrossRef]
56. Calvo, M.S.; Whiting, S.J. Public health strategies to overcome barriers to optimal vitamin D status in populations with special needs. *J. Nutr.* **2006**, *136*, 1135–1139. [CrossRef]
57. Mo, M.; Wang, S.; Chen, Z.; Muyiduli, X.; Wang, S.; Shen, Y.; Shao, B.; Li, M.; Chen, D.; Chen, Z.; et al. A systematic review and meta-analysis of the response of serum 25-hydroxyvitamin D concentration to vitamin D supplementation from RCTs from around the globe. *Eur. J. Clin. Nutr.* **2019**, *73*, 816–834. [CrossRef]

58. Bacha, D.S.; Rahme, M.; Al-Shaar, L.; Baddoura, R.; Halaby, G.; Singh, R.J.; Mahfoud, Z.R.; Habib, R.; Arabi, A.; El-Hajj Fuleihan, G. Vitamin D3 Dose Requirement That Raises 25-Hydroxyvitamin D to Desirable Level in Overweight and Obese Elderly. *J. Clin. Endocrinol. Metab.* **2021**, *106*, e3644–e3654. [CrossRef]

59. Zittermann, A.; Ernst, J.B.; Gummert, J.F.; Borgermann, J. Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: A systematic review. *Eur. J. Nutr.* **2014**, *53*, 367–374. [CrossRef] [PubMed]

60. Autier, P.; Gandini, S.; Mullie, P. A systematic review: Influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 2606–2613. [CrossRef] [PubMed]

61. Cashman, K.D.; Ritz, C.; Adebayo, F.A.; Dowling, K.G.; Itkonen, S.T.; Ohman, T.; Skaffari, E.; Saarnio, E.M.; Kiely, M.; Lamberg-Allardt, C. Differences in the dietary requirement for vitamin D among Caucasian and East African women at Northern latitude. *Eur. J. Nutr.* **2019**, *58*, 2281–2291. [CrossRef] [PubMed]

62. Cashman, K.D.; Kiely, M.E.; Andersen, R.; Gronborg, I.M.; Tetens, I.; Tripkovic, L.; Lanham-New, S.A.; Lamberg-Allardt, C.; Adebayo, F.A.; Gallagher, J.C.; et al. Individual participant data (IPD)-level meta-analysis of randomised controlled trials to estimate the vitamin D dietary requirements in dark-skinned individuals resident at high latitude. *Eur. J. Nutr.* **2021**, *61*, 1015–1034. [CrossRef] [PubMed]

63. Mazahery, H.; von Hurst, P.R. Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. *Nutrients* **2015**, *7*, 5111–5142. [CrossRef]

64. Ramasamy, I. Vitamin D Metabolism and Guidelines for Vitamin D Supplementation. *Clin. Biochem. Rev.* **2020**, *41*, 103–126. [CrossRef]

65. Ish-Shalom, S.; Segal, E.; Salganik, T.; Raz, B.; Bromberg, I.L.; Vieth, R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 3430–3435. [CrossRef]

66. Takacs, I.; Toth, B.E.; Szekeres, L.; Szabo, B.; Bakos, B.; Lakatos, P. Randomized clinical trial to comparing efficacy of daily, weekly and monthly administration of vitamin D3. *Endocrine* **2017**, *55*, 60–65. [CrossRef]

67. Mazess, R.B.; Bischoff-Ferrari, H.A.; Dawson-Hughes, B. Vitamin D: Bolus Is Bogus—A Narrative Review. *JBMR Plus* **2021**, *5*, e10567. [CrossRef]

68. Jorde, R.; Grimnes, G. Serum cholecalciferol may be a better marker of vitamin D status than 25-hydroxyvitamin D. *Med. Hypotheses* **2018**, *111*, 61–65. [CrossRef]

69. Rothen, J.P.; Rutishauser, J.; Walter, P.N.; Hersberger, K.E.; Arnet, I. Oral intermittent vitamin D substitution: Influence of pharmaceutical form and dosage frequency on medication adherence: A randomized clinical trial. *BMC Pharmacol. Toxicol.* **2020**, *21*, 51. [CrossRef]

70. Tripkovic, L.; Lambert, H.; Hart, K.; Smith, C.P.; Bucca, G.; Penson, S.; Chope, G.; Hypponen, E.; Berry, J.; Vieth, R.; et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: A systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2012**, *95*, 1357–1364. [CrossRef]

71. Bjelakovic, G.; Gluud, L.L.; Nikolova, D.; Whitfield, K.; Wetterslev, J.; Simonetti, R.G.; Bjelakovic, M.; Gluud, C. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst. Rev.* **2008**, CD007470. [CrossRef]

72. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 1153–1158. [CrossRef]

73. Heaney, R.P.; Armas, L.A. Quantifying the vitamin D economy. *Nutr. Rev.* **2015**, *73*, 51–67. [CrossRef] [PubMed]

74. Pludowski, P.; Socha, P.; Karczmarewicz, E.; Zagorecka, E.; Lukaszkiewicz, J.; Stolarczyk, A.; Piotrowska-Jastrzebska, J.; Kryskiewicz, E.; Lorenc, R.S.; Socha, J. Vitamin D supplementation and status in infants: A prospective cohort observational study. *J. Pediatr. Gastroenterol. Nutr.* **2011**, *53*, 93–99. [CrossRef] [PubMed]

75. Vieth, R. Vitamin D supplementation: Cholecalciferol, calcifediol, and calcitriol. *Eur. J. Clin. Nutr.* **2020**, *74*, 1493–1497. [CrossRef] [PubMed]

76. Billington, E.O.; Burt, L.A.; Rose, M.S.; Davison, E.M.; Gaudet, S.; Kan, M.; Boyd, S.K.; Hanley, D.A. Safety of High-Dose Vitamin D Supplementation: Secondary Analysis of a Randomized Controlled Trial. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 1261–1273. [CrossRef]

77. Vieth, R. Vitamin D and cancer mini-symposium: The risk of additional vitamin D. *Ann. Epidemiol.* **2009**, *19*, 441–445. [CrossRef]

78. Nielsen, O.H.; Hansen, T.I.; Gubatan, J.M.; Jensen, K.B.; Rejnmark, L. Managing vitamin D deficiency in inflammatory bowel disease. *Frontline Gastroenterol.* **2019**, *10*, 394–400. [CrossRef]

79. Masood, M.Q.; Khan, A.; Awan, S.; Dar, F.; Naz, S.; Naureen, G.; Saghir, S.; Jabbar, A. Comparison of Vitamin D Replacement Strategies with High-Dose Intramuscular or Oral Cholecalciferol: A Prospective Intervention Study. *Endocr. Pract.* **2015**, *21*, 1125–1133. [CrossRef]

80. Wylon, K.; Drozdenko, G.; Krannich, A.; Heine, G.; Dolle, S.; Worm, M. Pharmacokinetic Evaluation of a Single Intramuscular High Dose versus an Oral Long-Term Supplementation of Cholecalciferol. *PLoS ONE* **2017**, *12*, e0169620. [CrossRef]

81. Gupta, N.; Farooqui, K.J.; Batra, C.M.; Marwaha, R.K.; Mithal, A. Effect of oral versus intramuscular Vitamin D replacement in apparently healthy adults with Vitamin D deficiency. *Indian J. Endocrinol. Metab.* **2017**, *21*, 131–136. [CrossRef]

82. Sosa Henriquez, M.; Gomez de Tejada Romero, M.J. Cholecalciferol or Calcifediol in the Management of Vitamin D Deficiency. *Nutrients* **2020**, *12*, 1617. [CrossRef]

83. Quesada-Gomez, J.M.; Bouillon, R. Is calcifediol better than cholecalciferol for vitamin D supplementation? *Osteoporos. Int.* **2018**, *29*, 1697–1711. [CrossRef]

84. Perez-Castrillon, J.L.; Duenas-Laita, A.; Brandi, M.L.; Jodar, E.; Del Pino-Montes, J.; Quesada-Gomez, J.M.; Cereto Castro, F.; Gomez-Alonso, C.; Gallego Lopez, L.; Olmos Martinez, J.M.; et al. Calcifediol is superior to cholecalciferol in improving vitamin D status in postmenopausal women: A randomized trial. *J. Bone Miner. Res.* **2021**, *36*, 1967–1978. [CrossRef]

85. Bischoff-Ferrari, H.A.; Dawson-Hughes, B.; Orav, E.J.; Staehelin, H.B.; Meyer, O.W.; Theiler, R.; Dick, W.; Willett, W.C.; Egli, A. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. *JAMA Intern. Med.* **2016**, *176*, 175–183. [CrossRef]

86. Bollerslev, J.; Rejnmark, L.; Zahn, A.; Heck, A.; Appelman-Dijkstra, N.M.; Cardoso, L.; Hannan, F.M.; Cetani, F.; Sikjaer, T.; Formenti, A.M.; et al. European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders. *Eur. J. Endocrinol.* **2022**, *186*, R33–R63. [CrossRef]

87. Bischoff-Ferrari, H.A.; Willett, W.C.; Orav, E.J.; Lips, P.; Meunier, P.J.; Lyons, R.A.; Flicker, L.; Wark, J.; Jackson, R.D.; Cauley, J.A.; et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N. Engl. J. Med.* **2012**, *367*, 40–49. [CrossRef]

88. Bolland, M.J.; Grey, A.; Avenell, A. Effects of vitamin D supplementation on musculoskeletal health: A systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol.* **2018**, *6*, 847–858. [CrossRef]

89. Carmel, A.S.; Bockman, R.S. Vitamin D and bisphosphonate response. *Osteoporos. Int.* **2014**, *25*, 2155. [CrossRef]

90. Reid, I.R.; Horne, A.M.; Mihov, B.; Stewart, A.; Garratt, E.; Wong, S.; Wiessing, K.R.; Bolland, M.J.; Bastin, S.; Gamble, G.D. Fracture Prevention with Zoledronate in Older Women with Osteopenia. *N. Engl. J. Med.* **2018**, *379*, 2407–2416. [CrossRef]

91. Li, S.; Xi, C.; Li, L.; Long, Z.; Zhang, N.; Yin, H.; Xie, K.; Wu, Z.; Tian, J.; Wang, F.; et al. Comparisons of different vitamin D supplementation for prevention of osteoporotic fractures: A Bayesian network meta-analysis and meta-regression of randomised controlled trials. *Int. J. Food Sci. Nutr.* **2021**, *72*, 518–528. [CrossRef]

92. Ganmaa, D.; Enkhmaa, D.; Nasantogtokh, E.; Sukhbaatar, S.; Tumur-Ochir, K.E.; Manson, J.E. Vitamin D, respiratory infections, and chronic disease: Review of meta-analyses and randomized clinical trials. *J. Intern. Med.* **2021**. [CrossRef]

93. Iuliano, S.; Poon, S.; Robbins, J.; Bui, M.; Wang, X.; De Groot, L.; Van Loan, M.; Zadeh, A.G.; Nguyen, T.; Seeman, E. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: Cluster randomised controlled trial. *BMJ* **2021**, *375*, n2364. [CrossRef]

94. Appel, L.J.; Michos, E.D.; Mitchell, C.M.; Blackford, A.L.; Sternberg, A.L.; Miller, E.R., 3rd; Juraschek, S.P.; Schrack, J.A.; Szanton, S.L.; Charleston, J.; et al. The Effects of Four Doses of Vitamin D Supplements on Falls in Older Adults: A Response-Adaptive, Randomized Clinical Trial. *Ann. Intern. Med.* **2021**, *174*, 145–156. [CrossRef]

95. Zittermann, A.; Ernst, J.B.; Prokop, S.; Fuchs, U.; Dreier, J.; Kuhn, J.; Knabbe, C.; Birschmann, I.; Schulz, U.; Berthold, H.K.; et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): A 3-year randomized clinical trial with 4000 IU vitamin D daily. *Eur. Heart J.* **2017**, *38*, 2279–2286. [CrossRef]

96. Gnagnarella, P.; Muzio, V.; Caini, S.; Raimondi, S.; Martinoli, C.; Chiocca, S.; Miccolo, C.; Bossi, P.; Cortinovis, D.; Chiaradonna, F.; et al. Vitamin D Supplementation and Cancer Mortality: Narrative Review of Observational Studies and Clinical Trials. *Nutrients* **2021**, *13*, 3285. [CrossRef]

97. Charoenngam, N.; Holick, M.F. Immunologic Effects of Vitamin D on Human Health and Disease. *Nutrients* **2020**, *12*, 2097. [CrossRef]

98. Hajhashemy, Z.; Shahdadian, F.; Moslemi, E.; Mirenayat, F.S.; Saneei, P. Serum vitamin D levels in relation to metabolic syndrome: A systematic review and dose-response meta-analysis of epidemiologic studies. *Obes. Rev.* **2021**, *22*, e13223. [CrossRef]

99. Han, J.; Guo, X.; Yu, X.; Liu, S.; Cui, X.; Zhang, B.; Liang, H. 25-Hydroxyvitamin D and Total Cancer Incidence and Mortality: A Meta-Analysis of Prospective Cohort Studies. *Nutrients* **2019**, *11*, 2295. [CrossRef]

100. Hahn, J.; Cook, N.R.; Alexander, E.K.; Friedman, S.; Walter, J.; Bubes, V.; Kotler, G.; Lee, I.M.; Manson, J.E.; Costenbader, K.H. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* **2022**, *376*, e066452. [CrossRef]

101. Autier, P.; Boniol, M.; Pizot, C.; Mullie, P. Vitamin D status and ill health: A systematic review. *Lancet Diabetes Endocrinol.* **2014**, *2*, 76–89. [CrossRef]

102. Jolliffe, D.A.; Camargo, C.A., Jr.; Sluyter, J.D.; Aglipay, M.; Aloia, J.F.; Ganmaa, D.; Bergman, P.; Bischoff-Ferrari, H.A.; Borzutzky, A.; Damsgaard, C.T.; et al. Vitamin D supplementation to prevent acute respiratory infections: A systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol.* **2021**, *9*, 276–292. [CrossRef]

103. Sluyter, J.D.; Manson, J.E.; Scragg, R. Vitamin D and Clinical Cancer Outcomes: A Review of Meta-Analyses. *JBMR Plus* **2021**, *5*, e10420. [CrossRef] [PubMed]

104. Scragg, R.; Sluyter, J.D. Is There Proof of Extraskeletal Benefits from Vitamin D Supplementation from Recent Mega Trials of Vitamin D? *JBMR Plus* **2021**, *5*, e10459. [CrossRef] [PubMed]

105. Jolliffe, D.A.; Greenberg, L.; Hooper, R.L.; Mathyssen, C.; Rafiq, R.; de Jongh, R.T.; Camargo, C.A.; Griffiths, C.J.; Janssens, W.; Martineau, A.R. Vitamin D to prevent exacerbations of COPD: Systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax* **2019**, *74*, 337–345. [CrossRef]

106. Li, X.; He, J.; Yu, M.; Sun, J. The efficacy of vitamin D therapy for patients with COPD: A meta-analysis of randomized controlled trials. *Ann. Palliat. Med.* **2020**, *9*, 286–297. [CrossRef] [PubMed]

107. Forno, E.; Bacharier, L.B.; Phipatanakul, W.; Guilbert, T.W.; Cabana, M.D.; Ross, K.; Covar, R.; Gern, J.E.; Rosser, F.J.; Blatter, J.; et al. Effect of Vitamin D3 Supplementation on Severe Asthma Exacerbations in Children with Asthma and Low Vitamin D Levels: The VDKA Randomized Clinical Trial. *JAMA* **2020**, *324*, 752–760. [CrossRef]

108. Zittermann, A.; Pilz, S.; Hoffmann, H.; Marz, W. Vitamin D and airway infections: A European perspective. *Eur. J. Med. Res.* **2016**, *21*, 14. [CrossRef] [PubMed]

109. Pilz, S.; Trummer, C.; Theiler-Schwetz, V.; Grubler, M.R.; Verheyen, N.D.; Odler, B.; Karras, S.N.; Zittermann, A.; Marz, W. Critical Appraisal of Large Vitamin D Randomized Controlled Trials. *Nutrients* **2022**, *14*, 303. [CrossRef]

110. Neale, R.E.; Baxter, C.; Romero, B.D.; McLeod, D.S.A.; English, D.R.; Armstrong, B.K.; Ebeling, P.R.; Hartel, G.; Kimlin, M.G.; O'Connell, R.; et al. The D-Health Trial: A randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol.* **2022**, *10*, 120–128. [CrossRef]

111. Zemb, P.; Bergman, P.; Camargo, C.A., Jr.; Cavalier, E.; Cormier, C.; Courbebaisse, M.; Hollis, B.; Joulia, F.; Minisola, S.; Pilz, S.; et al. Vitamin D deficiency and the COVID-19 pandemic. *J. Glob. Antimicrob. Resist.* **2020**, *22*, 133–134. [CrossRef]

112. Smaha, J.; Kuzma, M.; Jackuliak, P.; Payer, J. Vitamin D supplementation as an important factor in COVID-19 prevention and treatment: What evidence do we have? *Vnitr. Lek.* **2020**, *66*, 494–500. [CrossRef]

113. Stroehlein, J.K.; Wallqvist, J.; Iannizzi, C.; Mikolajewska, A.; Metzendorf, M.I.; Benstoem, C.; Meybohm, P.; Becker, M.; Skoetz, N.; Stegemann, M.; et al. Vitamin D supplementation for the treatment of COVID-19: A living systematic review. *Cochrane Database Syst. Rev.* **2021**, *5*, CD015043. [CrossRef]

114. Liu, Q.; Qin, C.; Liu, M.; Liu, J. Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: A systematic review and meta-analysis. *Infect. Dis. Poverty* **2021**, *10*, 132. [CrossRef]

115. Pilz, S.; Chakeri, A.; Ioannidis, J.P.; Richter, L.; Theiler-Schwetz, V.; Trummer, C.; Krause, R.; Allerberger, F. SARS-CoV-2 re-infection risk in Austria. *Eur. J. Clin. Investig.* **2021**, *51*, e13520. [CrossRef]

116. Pilz, S.; Theiler-Schwetz, V.; Trummer, C.; Krause, R.; Ioannidis, J.P.A. SARS-CoV-2 reinfections: Overview of efficacy and duration of natural and hybrid immunity. *Environ. Res.* **2022**, *209*, 112911. [CrossRef]