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REVIEW

Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: a systematic review

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Abstract
Purpose There is considerable variation in incremental circulating 25-hydroxyvitamin D (25OHD) levels on vitamin D supplements, even when similar age groups and identical vitamin D doses are compared. We therefore aimed to investigate the importance of body weight for the dose–response relation in circulating 25OHD.
Methods We performed a systematic review of randomized placebo-controlled vitamin D supplementation trials in all age groups ≥10 years to clarify the influence of body weight and other parameters on incremental circulating 25OHD levels (difference between baseline and in-study values) in vitamin D-deficient and non-deficient individuals.
Results We included 144 cohorts from 94 independent studies, published from 1990 to November 2012, in our systematic review. There was a logarithmic association between vitamin D dose per kg body weight per day and increment in circulating 25OHD. In multivariable regression analysis, vitamin D dose per kg body weight per day could explain 34.5 % of variation in circulating 25OHD. Additional significant predictors were type of supplement (vitamin D_2 or vitamin D_3), age, concomitant intake of calcium supplements and baseline 25OHD, explaining 9.8, 3.7, 2.4 and 1.9 %, respectively, of the variation in circulating 25OHD.
Conclusions This systematic review demonstrates that body weight is an important predictor of variation in circulating 25OHD in cohorts on vitamin D supplements. Our model provides an estimate of the daily vitamin D dose that is necessary for achieving adequate circulating 25OHD levels in vitamin D-insufficient or vitamin D-deficient individuals/cohorts with different body weights and ages.

Keywords Vitamin D · Body weight · 25-Hydroxyvitamin D · Supplementation · Age · Calcium supplements

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Introduction

Vitamin D deficiency is a re-emerging health problem globally, which is primarily due to inadequate exposure to solar UVB radiation [1]. According to the Institute of Medicine (IOM) classification [2], vitamin D status is deficient in approximately 8 % of the general US population [i.e. 25-hydroxyvitamin D (25OHD) levels below 30 nmol/l] and inadequate in an additional 23 % (i.e. 25OHD levels between 30 and 50 nmol/l). Representative surveys in German children and adults report a prevalence of 15–17 % for those with 25OHD levels <25 nmol/l [3, 4]. In the Middle East, up to 80 % of adolescent girls and up to 60–65 % of elderly people have 25OHD in the deficiency range [5]. Oral vitamin D intake is an inexpensive, effective and easy-to-handle measure for preventing vitamin D deficiency and inadequacy.

Daily vitamin D doses of 10–20 μg (to convert into international units multiply by factor 40) are age-dependently recommended for healthy individuals with insufficient or absent skin synthesis of vitamin D [6, 7]. However, there is an ongoing discussion on the adequate daily vitamin D dose.

Doses of 20–50 μg per day have been demonstrated to prevent osteoporotic fractures in elderly people [8], and amounts of up to 250 μg daily are considered to be safe in osteoporotic patients [9]. Since vitamin D may exert various non-classical actions [1, 10] and may reduce mortality risk in elderly people [11], certain non-governmental organizations recommend daily vitamin D doses of 125 μg [12]. Some studies have already used vitamin D doses of up to 250 μg daily for improving vitamin D status in adults [13, 14].

The IOM [6] considers circulating 25OHD levels above 125 nmol/l as potentially harmful, a statement that has been supported by several recently published cohort studies [15–17] and controlled trials [18, 19]. Thus, the benefits of supplementary vitamin D have to be weighed against its potentially harmful effects. Ideally, a daily oral vitamin D supplement should guarantee a circulating 25OHD level within the adequate range. Whereas the IOM considers values of 50–125 nmol/l as adequate [6], some clinical practice guidelines recommend a target range of at least 75–100 nmol/l [20, 21].

Recently, Autier et al. [22] published a systematic review concerning the influence of vitamin D supplements on circulating 25OHD levels. That review, which was restricted to Caucasians aged 50 years and over, demonstrated for similar doses increases in 25OHD levels three to four times higher in some trials than in other trials. The absolute between-study variation in circulating 25OHD levels was as much as 62.5 nmol/l, even at identical doses.

Usually, vitamin D recommendations do not or only roughly take into account inter-individual factors. Some factors such as body weight (BW) have a profound effect on blood volume and the amount of adipose and muscle tissue and may therefore influence the distribution volume of vitamin D. Evidence is indeed emerging that BW can substantially influence the serum 25OHD response to oral vitamin D administration [23, 24]. To clarify the importance of BW for the dose–response relation in circulating 25OHD, we performed a systematic review of vitamin D supplementation studies. In addition, we aimed to calculate for vitamin D-deficient individuals with different body weights the daily vitamin D dose that is necessary to achieve adequate circulating 25OHD levels. We also explored the effect of various potential mediators such as age, baseline 25OHD levels, concomitant diseases, and type and duration of the vitamin D supplement on weight-adjusted dose–response relationships in circulating 25OHD.

Methods

We planned, conducted and reported this systematic review based on a protocol, which was developed in accordance with the QUOROM statement [25].

Search strategy

We performed a systematic literature search from 1975 to November 2012 in several databases such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://www.embase.com) and ISI Web of Science (apps.webofknowledge.com) using the following search terms: [vitamin D or cholecalciferol or ergocalciferol] and [supplementation]. We searched for the keywords in the headers and in the abstract, when available. We also manually searched references that were cited in the selected articles and in a recently published systematic review [22]. Two academic investigators carried out the literature search independently. Group discussion resolved any disagreement about article selection.

Selection

We selected publications that met the following prespecified inclusion criteria: (1) trials with a control group receiving a placebo instead of vitamin D, (2) trials that reported information on circulating 25OHD concentrations for each study cohort separately, (3) trials that presented body weight data and (4) trials that were independent. When the results of the same study were published in more than one article, we used only the most recent or the one with the largest sample of individuals.

We excluded studies when (1) compounds other than vitamin D_2 or vitamin D_3 were tested, (2) only one bolus dose of vitamin D was administered, (3) vitamin D was not administered orally, and (4) studies were performed in infants. We applied no language restrictions.

Data extraction

We selected a list of demographic characteristics prior to conducting the data searches. This list was constructed as a series of records and included information about the study participants' characteristics and dose–response relationships. In brief, we recorded study characteristics such as date of publication, country of origin and the number of study participants. We also extracted data about the study participants such as age, gender, ethnicity, BW and diseases. We documented dose, frequency, duration, type of vitamin D supplement (D_2 or D_3) and vitamin D producer. In case vitamin D was not administered daily, we calculated the daily dose by dividing the administered dose by its frequency (i.e. 350 μg weekly represents a daily dose of 50 μg). In a number of trials, the vitamin D intervention was combined with a calcium supplement, was part of a multivitamin supplement or was given as fortified food, and we abstracted this information. Finally, we recorded

the method of 25OHD measurement. With regard to dose–response information, we recorded the 25OHD concentration (expressed as nmol/l) given at baseline and in-study. If 25OHD levels were presented as ng/ml, we used a correction factor of 2.496 to convert 25OHD concentrations to nmol/l.

Statistical analysis

We included only randomized controlled trials in our systematic review. We assessed absolute variations in serum 25OHD levels between initial and last measurements in the vitamin D and control groups, and evaluated the average variations between intervention and control groups. We calculated the body-weight-adjusted daily dose (expressed as μg vitamin D per day per kg BW) by dividing the daily vitamin D dose by the average body weight of the respective study group. When differences between study groups were reported as median and range, we used the formula by Hozo et al. [26] to estimate mean and SD. We plotted summary estimates of variation in serum 25OHD level by pooling study-specific estimates. We performed multivariate meta-regression analysis for prediction of variation in 25OHD levels. We calculated summary estimates according to daily supplement dose per kg BW. We tested in the multivariate meta-regression analysis the influence of various covariates such as age, ethnicity, diseases, frequency and duration of intake, type of vitamin D supplement, baseline 25OHD level, vitamin D producer, method of 25OHD measurement and co-administration of calcium supplement or other nutrients on BW-adjusted dose–response relationships. We then generated a model for calculating the increment in circulating 25OHD in cohorts on vitamin D supplements. Covariate selection was based on the clinical, nutritional and analytical reason. Some of the aforementioned parameters such as type of vitamin D supplement (D_2 or D_3) and co-administration of calcium supplements have already been identified as modifiers of circulating 25OHD [22]. Since a significant percentage of studies were performed in males and females and only few studies were performed solely in males (see below), gender was not included in the multivariate analysis.

In additional tests, we restricted our analyses to the subgroup of cohorts receiving vitamin D_3. We also checked our model for secular trends by analysing the effect of different publication periods on study results. For assessing interrelationships between variables, we used Pearson's correlation coefficient. We considered a P value <0.05 as statistically significant. Analyses were performed using the statistical software package IBM SPSS, version 20 (IBM Corp, Armonk, NY, USA).

Results

Study selection and data extraction

The detailed steps of our systematic literature search are shown in Fig. 1. We identified 5,649 abstracts in PubMed, 3,285 abstracts in EMBASE and 7,867 abstracts in ISI Web of Science. Of these 16,801 abstracts, we excluded 16,482 on the basis of screening or titles because they were not RCTs or were not relevant for the endpoint of the review, which left 319 articles to source in full text. We identified no additional references from a search of reference lists of the 319 full-text articles. After further inspection, we excluded 225 articles from the 319 full-text articles. One hundred and seven studies gave no information on body weight, 86 studies provided no or no group-specific data on 25OHD concentrations, and 32 studies did not meet other inclusion criteria. Thus, we could include 94 independent studies in the systematic review (supplemental material, Table 1). Our search did not identify articles of interest for our review in languages other than English. Moreover, our literature search did not find studies in pregnant women or patients with chronic kidney disease (CKD), which met our inclusion and exclusion criteria.

Study characteristics

The characteristics of the 94 studies that we included in the final analysis are shown in Table 1. All studies were published between 1990 and 2012. The trials included 9,766 control group subjects and 11,566 intervention group subjects, and the latter were allocated to 144 intervention cohorts. Twenty studies were conducted in North America, five in South America/Antarctica, twelve in Asia and ten in Australia or New Zealand. Forty-six studies were European, and one study was African. Twenty-five cohorts consisted of patients (osteoporosis, heart failure, mixed, HIV, others), and 90 cohorts comprised apparently healthy subjects. In the remaining cohorts, the health status of the participants was not specified. The average age of the study participants ranged from 10 to 92 years (median 57.0 years), and average BW varied between 29.0 kg and 101.9 kg (median 68.0 kg). Nineteen trials tested the vitamin D_2 and 125 trials the vitamin D_3. Study duration comprised a median of 274 days (range 21–1,825 days). The daily vitamin D dose ranged from 5 μg to 250 μg (median 20 μg) and from 0.07 μg to 3.89 μg per kg BW (median 0.26 μg). In 48.6 % of the trials, calcium and vitamin D supplements were tested simultaneously. In 122 cohorts, daily vitamin D doses were tested, whereas in the remaining 22 cohorts, vitamin D doses were tested less frequently (weekly, fortnightly, monthly, bimonthly, trimonthly, four monthly). Measurement of 25OHD was

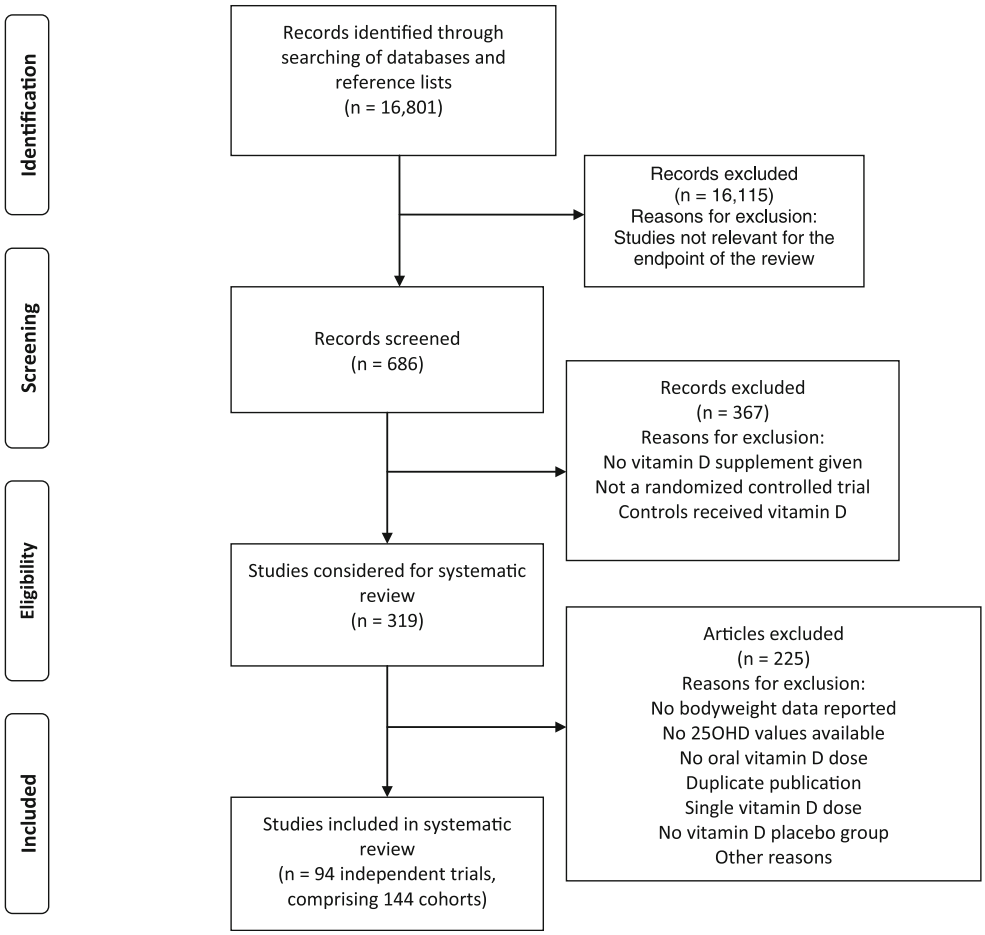

Fig. 1 Flowchart of study selection for inclusion in the systematic review

taken by LC tandem mass spectrometry in 12 cohorts (8.3 %), DiaSorin RIA kits in 51 cohorts (35.4 %), HPLC in 20 cohorts (13.9 %), IDS-Elisa kits in 20 cohorts (13.9 %), protein-binding assays in 20 cohorts (13.9 %), other methods in 17 cohorts (11.8 %) and unknown methods in 4 cohorts (2.8 %). In 30 out of the 144 cohorts, the name of the vitamin D producer was not given (mostly trials with vitamin D-fortified foods). In the remaining 114 cohorts, vitamin D was provided by 43 different companies.

Effects of study variables on variation in circulating 25-hydroxyvitamin D

Figure 2 illustrates the graphical exploration of intervention results. Data demonstrate a nonlinear, logarithmic association between daily vitamin D dose per kg BW and incremental circulating 25OHD. All four cohorts showing a decline in circulating 25OHD [27, 28] received daily vitamin D_2 doses (8.8–28.2 μg). In the 3 cohorts where $25OHD_2$ or $25OHD_3$ were measured separately [28], the decline in total 25OHD was associated with a significant increment in $25OHD_2$, but also with a marked decline in $25OHD_3$.

In the control groups, the median in study change in circulating 25OHD was −1.4 nmol/l (range −40.8 nmol/l to +19.7 nmol/l, data not shown). Ln Vitamin D dose per kg BW per day was highly inter-correlated with Ln dose per day ($R^2 = 0.9140$; $P < 0.001$).

Predictors of variation in circulating 25OHD are presented in Table 2. Summary estimates from this model demonstrate a significant association between supplement dose per kg BW per day and the increment in 25OHD. In addition, each year of age is associated with an increase in 25OHD of 0.22 nmol/l on average. Compared with vitamin D_2, vitamin D_3 is also associated with a significant increase in 25OHD (20.19 nmol/l on average). In contrast, concomitant intake of calcium supplements is associated with a significant decrease in 25OHD (6.34 nmol/l on average). Moreover, higher baseline 25OHD levels decrease the increment in 25OHD significantly.

A total of 54.0 % of the variation in 25OHD was explained by the multivariate model, with vitamin D intake per kg BW per day being by far the strongest predictor

Table 1 Characteristics of trials on vitamin D supplements

	Number	Percent
Intervention groups	144	–
Subjects		
Intervention groups	11,566	–
Placebo groups	9,766	–
Gender		
Men	11	7.6
Women	76	52.8
Mixed	57	39.6
Health status		
Apparently healthy	90	62.5
Patients[a]	25	17.4
Not specified	29	20.1
Study duration (year)		
<1	75	52.1
≥1	69	47.9
Baseline 25OHD (nmol/l)		
<25	21	14.6
25–50	67	46.5
>50	56	38.9
Dose per kg body weight per day (μg)		
>0.0–0.25	69	47.9
>0.25–0.5	41	28.5
>0.5–1.0	21	14.6
>1.0	13	9.0
Age (years)		
10–18	21	14.6
>18–65	71	49.3
>65	50	34.7
Not specified	2	1.4
Body weight (kg)		
<40	8	5.5
40–70	75	52.1
>70	61	42.4
Type of supplement		
D_2	19	13.2
D_3	125	86.8
Frequency of intake		
Daily	122	84.7
Weekly	6	4.2
Monthly	7	4.9
Others (fortnightly, trimonthly, four monthly)	9	6.2
Co-administration of other nutrients		
None	37	25.7
Calcium supplement	70	48.6
Other vitamins (multivitamins)	13	9.0
Calcium and other vitamins (multivitamins)	4	2.8
Part of fortified foods	20	13.9

[a] (osteoporosis, heart failure, mixed, HIV, others)

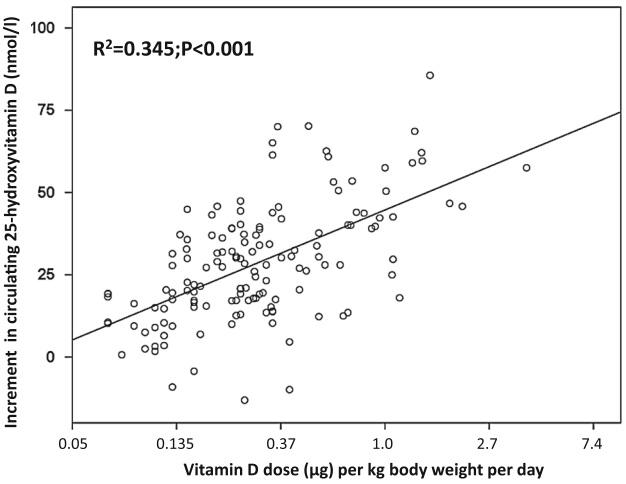

Fig. 2 Summary estimates of increments in circulating 25-hydroxyvitamin D in 144 cohorts on vitamin D supplements. The x-axis is presented on a log-scale

Table 2 Determinants of change in circulating 25-hydroxyvitamin D (in nmol/l) in 144 cohorts on vitamin D

Variables	Regression coefficient	95 % confidence interval		*P* value
		Lower bound	Upper bound	
Intercept	49.4	42.5	56.2	<0.001
Ln dose in μg/kg body weight/day	16.03	13.3	18.8	<0.001
Age (years)	0.22	0.12	0.31	<0.001
Type of supplement				
D_2	−20.19	−26.4	−14.0	
D_3	Ref.			<0.001
Calcium supplements				
No	Ref.			
Yes	−6.34	−10.9	−1.75	0.007
Baseline 25OHD (per nmol/l)	−0.13	−0.23	−0.03	0.012

Variables included in analysis: age, ethnicity, diseases, Ln vitamin D dose, frequency and duration of intake, type of vitamin D supplement, method of 25OHD measurement, baseline 25OHD level, co-administration of calcium supplement or other nutrients and vitamin D producer

(semi-partial R^2 34.5 %). Type of supplement, age, concomitant intake of calcium supplements and baseline 25OHD levels explained 9.8, 3.7, 2.4 and 1.9 %, respectively, of the variation in 25OHD. Our multivariable analysis showed no association between ethnicity, the presence or absence of diseases, frequency and duration of vitamin D intake, method of 25OHD measurement, vitamin D producer and administration of vitamin D with nutrients other than calcium or as fortified food. The incremental change in 25OHD can be calculated as follows:

Table 3 Calculated daily vitamin D_3 dose for achieving in vitamin D-deficient individuals a target 25-hydroxyvitamin D level of 50 nmol/l and 75 nmol/l, respectively

	30-year-old person	70-year-old person
Baseline 25OHD level 25 nmol/l; target 25OHD level 50 nmol/l		
50 kg body weight	9 μg (360 IU)	5 μg (200 IU)
75 kg body weight	13.5 μg (540 IU)	7.7 μg (308 IU)
100 kg body weight	18 μg (720 IU)	10 μg (400 IU)
Baseline 25OHD level 25 nmol/l; target 25OHD level 75 nmol/l		
50 kg body weight	42 μg (1,680 IU)	24 μg (960 IU)
75 kg body weight	63 μg (2,520 IU)	36.5 μg (1,460 IU)
100 kg body weight	84 μg (3,360 IU)	49 μg (1,960 IU)

IU international unit

incremental change in nmol/l = 49.4 + 16.03 × Ln vitamin D dose (μg per kg body weight per day) + 0.22 × age (years) − 20.19 (if vitamin D_2, otherwise = 0) − 6.34 (if calcium is co-administered, otherwise = 0) − 0.13 × baseline 25OHD (nmol/l).

The number of cohort participants was not a significant predictor of the increment in circulating 25OHD, even if cohorts were stratified into subgroups according to the categories of daily vitamin D dose per kg BW per day listed in Table 1 (data not shown). Additional analyses demonstrate that the association between Ln vitamin D dose per kg BW per day improved when the analysis was restricted to cohorts receiving vitamin D_3 ($R^2 = 0.426$; $P < 0.001$). However, the predictive value of our multivariable regression model, which also includes age, concomitant calcium intake and baseline 25OHD levels, was not improved in this subgroup (data not shown). No secular trends according to publication period were observed (data not shown).

Table 3 demonstrates that the calculated daily vitamin D_3 dose that is necessary for achieving adequate circulating 25OHD levels in vitamin D-deficient individuals differs substantially according to body weight, age and target 25OHD value.

Discussion

This systematic review demonstrates that BW is an important predictor of incremental 25OHD in individuals on vitamin D supplements. The daily vitamin D dose that is necessary for achieving adequate circulating 25OHD levels varies substantially according to BW. Results are of practical relevance since current vitamin D recommendations [6, 7] do not take into account these associations.

Our review extends the knowledge provided in a systematic review by Autier et al. [22] because (1) we could demonstrate that BW is a modifier of incremental 25OHD in individuals on vitamin D supplements, (2) our review was not restricted to specific ethnic and age groups, (3) our results show a significant age-dependent effect on incremental circulating 25OHD, and (4) we could confirm that baseline 25OHD and concomitant calcium administration indeed have a significant effect on incremental 25OHD.

Several earlier studies in specific age groups [23, 24, 29] have also demonstrated a BW-dependent increment in 25OHD by vitamin D supplements. Importantly, the study by Heaney et al. [23] showed that body fat mass was not superior in predicting incremental 25OHD compared with BW. In line with the aforementioned findings by Heaney et al., it has recently been suggested that dose–response curve variations are due to differences in volume distribution and not body fat [30]. Usually, BW is relatively closely associated with fat mass and fat-free mass [31, 32], and absolute BW is usually a better predictor of fat-free mass compared with BMI [30]. With our formula, the increment in circulating 25OHD on vitamin D supplements can easily be calculated if BW, age and baseline 25OHD levels are known. Our model demonstrates that at low oral vitamin D doses, the increment in circulating 25OHD is relatively strong, whereas the required oral vitamin D dose per kg BW increases exponentially if high increments in 25OHD are to be reached. With respect to the daily upper tolerable intake level of vitamin D_3, which is according to the IOM 100 μg [6], it can be assumed that in a 70-year-old person with baseline 25OHD level of 50 nmol/l and a BW of 75 kg, this dose will lead to an absolute 25OHD level of approximately 113 nmol/l on average.

Our calculations support the recommendation of some European Nutrition Societies for daily oral vitamin D intake [7], which is set at 20 μg for all age groups beyond infancy with absent cutaneous vitamin D synthesis. Based on our calculations and the assumption that a target 25OHD level of 50 nmol/l is sufficient, even in vitamin D-deficient individuals with a body weight of 100 kg, the required daily oral vitamin D intake dose is on average below 20 μg. However, the required daily dose would be much higher if a target 25OHD value of 75 nmol/l should be achieved.

In our multivariable model, BW accounted for more than one-third of the variance in the incremental 25OHD and 54 % of the variance was explained when all significant parameters were included in the model. Note that in the cohorts of our review, adherence was rarely reported and was surely a strong source of between-trial variability. Imprecision of the 25OHD and BW measurements, solar ultraviolet B-induced skin synthesis of vitamin D and genetic effects on circulating 25OHD are additional factors that may contribute to the unexplained between-trial variance in incremental 25OHD.

Interestingly, age was positively correlated with incremental 25OHD. It is well known that calcium demands are highest during infancy and adolescence. Moreover, circulating levels of the hormonal form of vitamin D, 1,25-dihydroxyvitamin D, are highest in these age groups [33, 34], whereas adults aged 75 years and over have lower 1,25-dihydroxyvitamin D levels compared with adults <65 years of age [35]. This latter finding may, at least in part, be due to an age-dependent decline in kidney function. Experimental studies demonstrate that circulating 25OHD levels are reduced in case of high circulating 1,25-dihydroxyvitamin D levels and vice versa [36]. Therefore, it can reliably be assumed that age-dependent differences in calcium and vitamin D physiology can in part explain the age-related effects of vitamin D supplements on circulating 25OHD.

Our study has the limitation that the number of trials using >1.5 µg vitamin D per kg BW per day was small and so was the number of cohorts with infrequent vitamin D intake (i.e. intakes less frequent than daily). Our formula should therefore be restricted to individuals on daily vitamin D supplements of up to 1.5 µg per kg BW. Another limitation is that the cohorts that were used to generate our model did not include infants and children who were younger than 10 years, pregnant women and CKD patients. In future, it may therefore be useful to develop specific formulas for these groups. Special attention should also be paid to study adherence.

In summary, BW, age, baseline 25OHD, the type of vitamin D supplement (D_2 or D_3) and concomitant calcium intake are important modifiers of the increment in circulating 25OHD. These parameters should be taken into account in individuals with deficient or insufficient circulating 25OHD levels to estimate the daily vitamin D dose that is necessary for achieving adequate circulating 25OHD levels, i.e. concentrations between 50 and 125 nmol/l.

Conflict of interest AZ has received speaker honoraria from DiaSorin, Germany, and Abbott, Germany, two companies that provide test kits for 25-hydroxyvitamin D measurement. None of the other authors has a conflict of interest to declare.

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