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REVIEW ARTICLE

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

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Abstract

Background/Objectives Optimal doses of vitamin D (VitD) supplement in different populations are unclear. We aim to evaluate the relationship between VitD supplementation and post-intervention serum 25-hydroxyvitamin D [25(OH)D] concentration, to provide a recommended dosage of VitD for achieving an optimal 25(OH)D concentration for different populations.

Subjects/Methods Literature search was conducted in Embase, etc. Randomized controlled trials about VitD supplemental intakes and their effect on 25(OH)D concentration were enrolled. The effect on 25(OH)D concentration between different supplementation doses in each population group was compared by meta-analysis. Multivariate meta-regression model is utilized to establish reference intake dosage of VitD.

Results A total of 136 articles were included about children (3–17 years), adults (18–64 years), postmenopausal women, the elderly (>64 years), pregnant, or lactating women. Overall, intervention groups obtained higher 25(OH)D concentration than controls and there was obvious dose–response effect between intake dose and 25(OH)D concentration. Baseline 25(OH)D concentration and age were significant indicators for 25(OH)D concentration. To reach sufficient 25(OH)D concentration (75 nmol/L), the recommended VitD supplemental intakes was 1340 and 2250 IU/day for children and pregnant women, 2519 and 797 IU/day for European adults aged 18–64 and 65–85 years, 729, 2026, and 1229 IU/day for adults in North America, Asia and Middle East and Africa, respectively.

Conclusions Regional- and age-specific recommended dosages of VitD supplements for population to achieve optimal 25 (OH)D concentrations have been suggested.

Introduction

Vitamin D (VitD) deficiency (25-hydroxyvitamin D [25 (OH)D] concentration < 50 nmol/L) is a widespread public health problem in all populations [1] as currently defined and the recommendations on VitD deficiency (25(OH)D concentration < 50 nmol/L) and insufficiency (25(OH)D concentration: 50–75 nmol/L) [2–4], VitD deficiency is highly common even in regions with abundant sunshine [5]. It has been estimated that 34–86% of Asian, Indian, and United Arab Emirates (UAE) adults and 40.4% of Europeans are VitD deficient and dark-skinned ethnic subgroups shared 3- to 71-fold prevalence than the White populations [6–11]. Pregnant women and children are also at risk of deficiency and insufficiency similarly. In a meta-analysis consisted of 13 cohort studies in seven countries, the prevalence of VitD deficiency during pregnancy varied from 13.2 to 77.3% [12]. In China, 23.3% of children and 38.7% of preterm infants suffered from insufficient VitD status [13, 14]. Due to reduced estrogen levels and other hormonal changes, postmenopausal women are particularly

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prone to develop low serum 25(OH)D concentrations [15, 16]. The prevalence of VitD deficiency in postmenopausal women has been reported to be between 31 and 70% [17]. Data from arid and semi-arid regions also serve to strengthen the notion that, in postmenopausal women, the abundance of sunlight does not prevent VitD deficiency irrespective of age group [18]. Experimental data from randomized controlled trials (RCTs) also showed that there may be a gender difference of the effect of VitD supplementation on bone loss [19–21].

The vast majority of VitD come from the cutaneous synthesis by sun exposure [22], inadequacy of sunlight exposure counts for the major cause of low VitD status. Meanwhile, other factors are also significantly associated with VitD deficiency, such as female gender, older age, low economic class, non-white ethnicity, high latitude, obesity, less outdoor activity, low income support, and dietary intake [9, 23, 24]. Baseline 25(OH)D concentration and geographical region are significantly associated with the effects of VitD supplementation on achieved 25(OH)D concentration [25]. A review focused on VitD status based on serum concentrations of 25(OH)D including 117 studies from 27 regions found large regional variations in young adults and the elderly [26]. However, relationship between 25(OH)D concentration and northern latitude was controversial [27]. In Thailand, subjects residing in the southern parts of the country had lower 25(OH)D concentrations than those residing in the northern region. The finding conflicts with a European study that showed a positive relationship between 25(OH)D concentration and latitude that subjects residing in southern parts had higher 25(OH)D concentration [27, 28]. Insufficient 25(OH)D concentration (50–75 nmol/L) can cause rickets in children and osteomalacia in adults. In addition, it also increased the risk of diabetes, depression, preterm birth, asthma, schizophrenia, and autoimmune disorders [29–34]. So far, VitD supplementation is an appropriate approach to prevent or correct VitD deficiency [35]. However, in spite of the high prevalence of VitD deficiency, an escalating trend for hypervitaminosis D has been disclosed in both developed and developing countries [6, 36, 37], which is adding to the difficulties of solving, or at least minimizing this global health issue. Hence, identification of optimal supplemental dosages of VitD is a key point.

The guidelines of dietary reference intakes of VitD for adequacy constructed by many organizations, such as Institute of Medicine (IOM) [38] and the Endocrine Society Clinical Practice Guidelines [39] developed for Americans and Canadians, are based on the dose–response relationships for VitD and bone health. However, one review conducted by Seamans and Cashman [40] suggested that whole-body or lumbar spine bone mineral density (BMD) may be a useful biomarker in older people but not in adolescents, which may suggest that bone health is not an ideal biomarker of VitD status. Meanwhile, there are many reviews that have evaluated the effect of supplementation with different VitD doses on the change of 25(OH)D concentration in different population groups [38, 39, 41–47]. However, most of them focus on the population in a certain region, age-bracket and latitude, and few of them have provided the optimal VitD supplementation dose for different population. To our knowledge, there is no study that has investigated optimal VitD supplementation doses for different populations worldwide and existing guidelines for VitD supplementation are based merely on single specific health issue, for instance, bone health and cancer; also, studies included in those reviews were not exclusively RCTs, while reviews of RCTs are best able to generate the information needed.

In this systematic review, we aimed to identify relevant RCTs of VitD supplementation and analyze the association between VitD dose and serum 25(OH)D concentration, to estimate optimal supplemental doses of $VitD_3$ for achieving sufficient circulating 25(OH)D concentrations (75 nmol/L) and prevent VitD deficiency for different populations at the global and regional levels. Furthermore, the effect of latitude, season, age, body mass index (BMI), the type of VitD given ($VitD_2$ or D_3, with or without calcium supplementation) and frequency of VitD supplements, duration of administration on serum 25(OH)D concentration were investigated.

Methods

Search strategy

The protocol used was based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [48]. The methodology implemented in this systematic review and meta-regression study was in accordance with the general methods in the Cochrane group guidelines [49]. A comprehensive literature search was conducted in databases including Embase, PubMed, Cochrane library, Popline, and Global Index Medicus up to October 2018 without language restriction (appendix 3). MeSH terms and keywords related to VitD and RCT were applied. Additional trials were identified by searching trial registries, including the WHO International Clinical Trials Registry (ICTRP) and the ClinicalTrials.gov, and the references lists of recent systematic reviews on VitD trials were also screened.

Eligibility criteria

Inclusion criteria: RCTs conducted in apparently healthy, community-dwelling individuals of both sexes, including children, pregnant or lactating women and adults, or patients with mild diseases with no known effects on VitD metabolism; RCTs administering $VitD_2$ or D_3, of any dose, with or without calcium supplementation, with intervals of VitD intake of <1 month, and for a minimum duration of 8 weeks were included in our study. Exclusion criteria: studies conducted in children with rickets or in adults with osteomalacia, or in individuals with chronic diseases (chronic kidney disease, liver disease and heart failure), or with conditions or drug therapy that might affect VitD metabolism, VitD binding proteins or VitD metabolism; studies administering VitD supplementation intervals longer than 1 month, in fortified foods, as activated metabolites, or given intramuscularly were excluded.

Data extraction and quality assessment

A data extraction record form was prepared and used to document the key information, including first author, journal name, year of publication, setting, location (country, city, and latitude), intervention details (type of VitD use, dose, frequency, start time/season, and end time/season, duration), concomitant calcium supplementation or not, number of participants per arm, age, BMI, baseline and post-intervention 25(OH)D concentration and assay method. For pregnant women, gestational week was identified. Corresponding means and standard deviations (SDs) of each arm were also extracted. Other statistical variable data like median and interquartile range (IQR) were converted to means and SDs [49]. For studies with large sample and data of symmetric distribution, the median is very similar to the mean and the width of the quartile spacing is about 1.35 times of SD. For studies with small sample size or data of asymmetric distribution, several formulas were used to estimate the mean and SD for different sample size from median, range, and IQR [50]. The Jadad scale was used to assess the quality of included studies in three domains (randomization, blinding and withdrawals and dropouts) [51].

Covariates assessment

Covariates were assessed by the following methods: season was divided into five categories according to changes in sunshine intensity from abundance to scarcity, and from scarcity to abundance for of both the season of starting and ending the supplementation. If the study started and ended in seasons with abundant sunshine (summer and autumn), they were assigned a value of "1"; for studies carried out from abundant to inadequate sunshine, "2", from inadequate to abundant sunshine, "3", and from inadequate to inadequate, "4". With missing data, either for season of starting, stopping or both, they assigned a "5". For supplementation frequency, the assigned value for "daily" was "1" and others, "0". Concomitant Ca supplementation was assigned "1", whereas no Ca supplementation was "0". Latitude was classified into three classes of low (≤23.5°), medium (23.5°–40°) and high (≥40°). For pregnant women, the gestational stage at which supplementation began and ended were noted using the relevant trimester. Producing five categories [first trimester to delivery, second to third trimester, second trimester to delivery, second trimester to postpartum and third trimester to delivery], numbered "1" to "5", respectively. 25(OH)D concentrations that were reported in ng/mL were transformed into nmol/L [1 ng/mL = 4 nmol/L] and VitD dose was recorded as IU according to IOM usage. Full-text references for inclusion, data extraction, and quality assessment were screened by a team of three reviewers (Minjia Mo, Shijie Wang, Zun Chen) in duplicate and independently. Discrepancies were resolved by discussion or in consultation with an independent expert (Yunxian Yu).

Statistical analysis

We conducted a random meta-analysis with at least two studies included in each population for the outcome of post-intervention 25(OH)D concentration. Weighted mean difference (WMD) and 95% confidence interval (CI) were calculated and presented as forest plots. The heterogeneity between studies was assessed using I^2. The degree of heterogeneity was classified as low ($I^2 < 25\%$), moderate (I^2 25–75%), or high ($I^2 > 75\%$), respectively. For comparison purposes, we calculated the weighted mean (WM) of the VitD dose and 25(OH)D concentrations for different dosage groups.

The baseline VitD status was classified as sufficiency (25(OH)D concentration ≥ 75 nmol/L), insufficiency (25(OH)D concentration: 50–75 nmol/L), and deficiency (25(OH)D concentration < 50 nmol/L) according to recent definitions and guidance [2–4]. Subgroup meta-analysis was conducted within each baseline VitD status of potential sources of heterogeneity: intervention dose, defined as low vs. moderate, moderate vs. high and low vs. high. As the supplementary dose varied in different studies, as well as dosing frequency, it was calculated in days and divided into three categories. With low (<800 IU), moderate (800–1600 IU), or high (>1600 IU) daily dose of VitD for children and low (<1500 IU), moderate (1500–3000 IU), or high (>3000 IU) for adults (including pregnant and lactating women, postmenopausal women, adults and elderly). Additional covariates included different population groups (children and

pregnant and lactating women, postmenopausal women, adults and elderly) and geographical region (Asia, Europe, Middle East and Africa, Latin America, North America, Oceania, and Polar).

When more than one intervention arm from the same trial and same dosage group appeared in the meta-analysis, we aggregated them and used them as one intervention–control comparison according to the Cochrane Collaboration's tool. To compare the effect of VitD supplementation on 25(OH)D concentration in different dosages among the same population group, we calculated the increment of achieved 25(OH)D concentration (nmol/L) per 100 IU/day VitD in the low-, moderate-, and high-dose groups based on the WM of both VitD dose and baseline 25(OH)D concentration.

To recommend optimum supplementary doses of VitD to achieve sufficient VitD status [25(OH)D concentrations of 75 nmol/L], we fitted meta-regression models with adjustment for multiple covariates for the prediction of linear change in 25(OH)D concentration from at least 10 studies (study or study arms) in analysis [52]. Summary estimates using supplementation doses and other significant covariates were estimated and linear relationships of supplemental VitD dose and other predictive indicators (such as age, baseline 25(OH)D concentration) to achieved 25(OH)D concentration were produced. The influence of various covariates such as mean age, supplementation duration and baseline 25(OH)D concentration on heterogeneity and summary results were also tested through meta-regression [53]. Selection of the better models for these estimates were based on both statistical and clinical factors; statistical selection was based on changes in residual between-study variance [53], with the lowest Akaike information criterion indicating greatest explanation of the total variability in data [54]. On the clinical side, a predictive model had to include the baseline 25(OH)D concentration because changes in concentrations are usually smaller in subjects with higher baseline concentrations [55]. Standard error (SE) was used to gauge within-study variability based on SD data for each study arm. With the meta-regression model, we evaluated the relationship between VitD dose and achieved 25(OH)D concentration, as well as comparing the effect of latitude, season, age, BMI, concomitant Ca supplementation, VitD given (D_3 OR D_2), frequency, and duration of supplemented VitD on achieved 25(OH)D concentration. Through meta-regression, equations based on the linear relationship between achieved 25(OH)D concentration and other covariates such as mean age, supplementation dosage and baseline 25(OH)D concentration were produced for different populations and geographical regions. Recommended dietary intakes or daily doses of VitD for different populations or regional groups were estimated from the equations resulting from the use of inverse regression.

Sensitivity analysis was conducted according to age, location, latitude, VitD supplementation dose, and baseline 25(OH)D concentration. In addition, for each analysis with at least 10 studies, publication bias was assessed by visual inspection of funnel plots (Figure S1–S4; appendix 1). All statistical analyses were processed with Stata 12.0 and the results were considered significant at a p-value < 0.05

Results

In total, 102,781 articles were identified through the stated search strategy, and 84,178 remained after removal of duplicates. After screening, the titles and abstracts of 1209 references were selected, using the stated inclusion and exclusion criteria, as potentially eligible studies. Finally, 136 RCTs including 20,884 participants were enrolled in this study (Fig. 1). The basic characteristics of the 136 RCTs are listed in Supplementary Table 1 (Table S1). There were 19 studies in children (mean age 3–17 years), 68 in adults (mean age 18–64 years), 16 in postmenopausal women, 14 in the elderly (mean age >64 years), 5 in lactating women, 12 in pregnant women, 1 in both children and adults, and 1 in both adults and the elderly. Based on the latitude and sun exposure, the studies were from seven regions, including Asia ($n = 17$), Europe ($n = 52$), Middle East and Africa ($n = 14$), Latin America ($n = 5$), North America ($n = 32$), Oceania ($n = 15$), and Polar ($n = 1$).

The effect on post-intervention serum 25(OH)D concentration among children (3–17 years)

Eight trials [56–63] had been performed in Europe, five [64–68] in North America, three [69–71] in Middle East and Africa, one [72] in Australia, and three [73–75] in Asia. The number of participants was 880 and 2958 in the control and intervention groups, respectively. The WM doses of low, moderate, and high-dose groups were 403.5, 938.9, and 2235.6 IU/day (Table 1). The WM baseline 25(OH)D concentrations and WM increments in 25(OH)D concentration per 100 IU/day VitD were 60.6, 46.7, 69.1 nmol/L, and 1.6, 2.1, 1.4 nmol/L in the low, moderate, and high-dose groups, respectively (Table 1). There were obvious dose–response effects for intake doses of VitD on blood 25(OH)D concentration. In sub-analyses, similar results were observed (Figure S1–S8; appendix 2).

The effect on post-intervention serum 25(OH)D concentration among adults (18–64 years)

Totally 68 studies were eligible including 8 [76–83] in China, India, Japan, and Malaysia; 29 [61, 84–111] in Europe; 7 [112–118] in Iran and UAE; 15 [119–133] in the

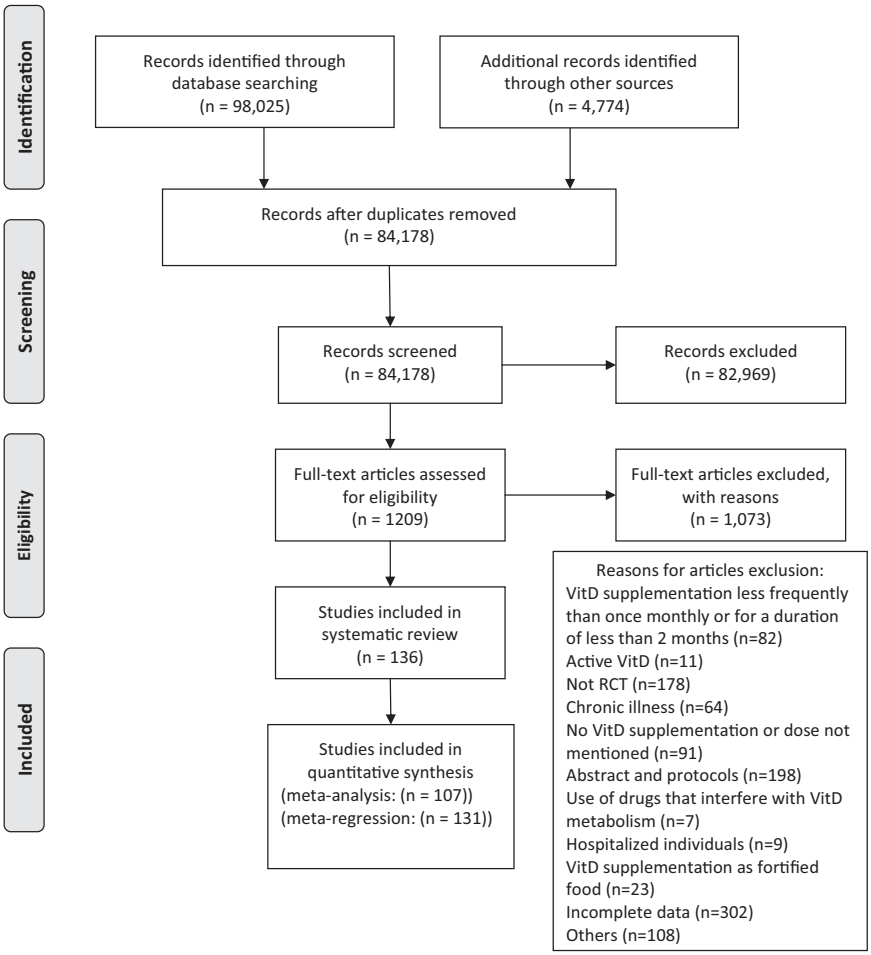

Fig. 1 The review flow diagram

United States (US) and Canada; 8 [134–141] in Australia and New Zealand, and 1 [142] in Antarctica. Total number of participants in the control, low-, moderate-, and high-dose groups were 2734, 1571, 1482, and 1240, respectively. A dose–response effect was also observed between intake doses of VitD and serum 25(OH)D concentration (Figure S9–S21; appendix 2). The WM baseline 25(OH)D concentration and dose were 51.9, 47.9, and 39.9 nmol/L and 737.2, 2213.9, and 4332.7 IU/day for the low-, moderate- and high-dose groups, respectively (Table 1). The WM increments in serum 25(OH)D concentration per 100 IU/day VitD were 2.1, 1.8, and 1.3 nmol/L in these three groups, respectively (Table 1).

A comparison between low dose vs. placebo in subjects with 25(OH)D concentration defining deficiency at baseline was performed and the effect at different latitudes were evaluated by subgroup meta-analysis. The WM difference of achieved 25(OH)D concentration between low dose vs. placebo was 30.4 (95% CI: 25.7, 35) nmol/L ($I^2 = 96.7\%$, $p < 0.001$). And for subjects in moderate and high latitude regions, the WM difference was, respectively, 24.9 (95% CI: 16.4, 33.4) nmol/L ($I^2 = 81.4\%$, $p = 0.005$) and 31.6 (95% CI: 24.1, 39.1) nmol/L ($I^2 = 97.5\%$, $p < 0.001$) (Figs. 2, 3).

The effect on post-intervention serum 25(OH)D concentration among postmenopausal women

Sixteen eligible studies with 1920 participants in the control and 2935 in intervention groups were identified with two in Asia [143, 144], three in Latin America [145–147], six in Europe [148–153], and five in North America (US) [154–158]. In general, the results for increases in serum 25(OH)D concentration were similar to those of children, as well as adults (Figure S22 and S23; appendix 2). Significant heterogeneity was found in the comparison of low dose vs. placebo with deficient baseline 25(OH)D concentration. The WM dose of low, moderate and high groups were 902.74, 1852, and 4310.87 IU/day, respectively (Table 1). The WM dose was 878.9, 1968.5, and 5917.1 IU/day in low, moderate and high groups, respectively. The WM baseline 25(OH)D concentration and the WM increment in 25(OH)D concentration per 100 IU/day VitD were, respectively, 58.3, 79.2, and 60.2 nmol/L, and 2.8, 1.3, and 1.5 nmol/L for the three groups (Table 1).

Table 1 Summary of results from different populations

Age category	Dose category	*N* arms	Dose, IU/day[a]	Number of subjects	Baseline 25 (OH)D, nmol/L[b]	WMD	Increment, nmol/L[c]
Children (6–17 years)	Low	13	404	1210	61	7	1.6
	Moderate	12	939	636	47	20	2.1
	High	6	2236	752	69	31	1.4
Adults (18–64 years)	Low	41	737	1571	52	16	2.1
	Moderate	31	2214	1482	48	41	1.8
	High	32	4333	1240	40	56	1.3
Postmenopausal women	Low	16	879	1374	58	24	2.8
	Moderate	5	1969	1174	79	25	1.3
	High	5	5917	387	60	88	1.5
Elderly (>64 years)	Low	18	606	911	52	20	3.3
	Moderate	5	1952	349	55	44	2.2
	High	4	3900	331	51	67	1.7
Pregnant women	Low	13	752	1033	48	16	2.1
	Moderate	4	2000	233	53	34	1.7
	High	5	4975	315	50	57	1.2
Lactating women	Low	2	1000	125	43	44	4.4
	Moderate	5	2000	143	47	31	1.6
	High	2	4000	22	76	33	0.8
All adults (including postmenopausal women, adults, and elderly)	Low	75	757	3856	54	20	2.6
	Moderate	41	2088	3005	61	35	1.7
	High	41	4573	1958	46	64	1.4

25(OH)D 25-hydroxyvitamin D, *WMD* weighted mean difference

[a]Supplemented dose of participants if one study arm identified or weighted mean dose of studies included in the meta-analysis

[b]Baseline concentration of participants if one study arm identified or weighted mean baseline concentration of studies included in the meta-analysis

[c]Increment in 25(OH)D concentration per 100 IU/day vitamin D (nmol/L): calculated as follows: [(WM 25 (OH)D concentration achieved–WM 25(OH)D concentration at baseline)/vitamin D dose IU/day)] × 100

The effect on post-intervention serum 25(OH)D concentration among the elderly (>64 years)

Seventeen eligible studies performed in the elderly were identified. Eight trials were performed in Europe [102, 159–165]; one in Japan [166]; two in Australia [167, 168]; and two in New Zealand [169, 170]; three in US [171–173] and one in Chile [174]. Overall, the results were similar to those in adults (Figure S24–S26; appendix 2). The WM doses and baseline 25(OH)D concentration were 606.1, 1952.1, and 3900.3 IU/day and 52.4, 54.6, and 51.1 nmol/L, respectively (Table 1). The WM increments in serum 25(OH)D concentrations per 100 IU/day of supplemental VitD intake were 3.3, 2.2, and 1.7 nmol/L, respectively, in the low-, moderate- and high-dose groups (Table 1).

The effect on post-intervention serum 25(OH)D concentration among pregnant women

Twelve eligible studies were identified with one in Bangladesh [175], two in the United Kingdom (UK) [176, 177], three in Iran [178–180], one in Canada [181], one in Brazil [182], one in Australia [183], one in Turkey [184], one in India [185] and one in the US [186]. Totally 608 and 1581 subjects in control and intervention groups were included. Overall, results were similar to those in adults (Figure S27–S32; appendix 2). The WM dose for the low-, moderate-, and high-dose groups were, respectively, 752.4, 2000, and 4974.6 IU/day (Table 1). The WM baseline 25 (OH)D concentrations and increments in 25(OH)D concentration per 100 IU/day VitD were 48.2, 52.9, and 49.8

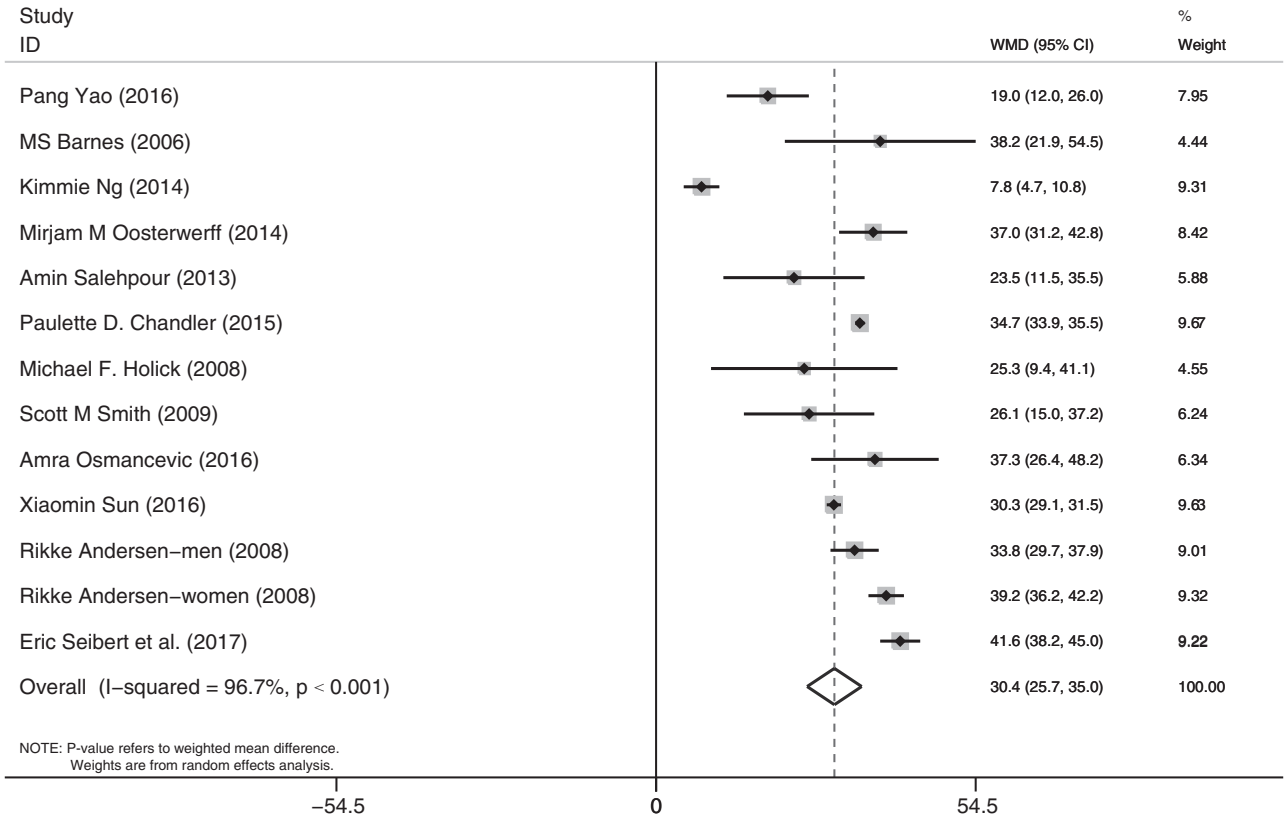

Fig. 2 Low dose (< 1500 IU) vs. placebo in adult subjects with baseline 25(OH)D concentration < 50 nmol/L

nmol/L and 2.1, 1.7, and 1.2 nmol/L in the three groups, respectively (Table 1).

The effect on post-intervention serum 25(OH)D concentration among lactating women

In total, five trials were included with one in India [187], two in the US [188, 189], one in New Zealand [190], and one in the UAE [191]. The total number of lactating women were 125, 143, and 22 in the low-, moderate- and high-dose groups, respectively. The WM dose and baseline 25(OH)D concentrations were 1000, 2000, and 4000 IU/day and 43.02, 46.97, and 75.75 nmol/L (Table 1). The WM increments in 25(OH)D concentration per 100 IU/day VitD were 4.43, 1.55, and 0.83 nmol/L in the three groups (Table 1). Overall, these results are similar to those found in pregnant women. Two trials conducted in the US were included in the comparison of high vs. moderate doses, and the WM difference was 21.25 (95% CI: 14.39, 28.10) nmol/L ($I^2 = 0.0\%$, $p = 0.862$) (Figure S33; appendix 2).

The effect of covariates on post-intervention serum 25(OH)D concentration

Multivariate meta-regression analysis was performed only when there were at least 10 studies in each sub-population, so we could only make these assessments in children (3–17 years), pregnant women and all adults (including post-menopausal women, the elderly (>64 years), and adults (18–64 years)). Multivariate meta-regression was conducted in the final model including variables significantly associated with 25(OH)D concentration after removing insignificant variables, such as intervention duration, latitude, gestation period (in pregnant women), the type of VitD given (D_3 OR D_2), Ca supplementation, BMI (in adults), and season. VitD dose and baseline 25(OH)D concentration were consistently and significantly associated with achieved 25(OH)D concentration in three of these populations. In the final model, the increment in 25(OH)D concentration was 1.6, 1.1, and 1.3 nmol/L per 100 IU/day VitD and 0.7, 0.9, and 0.6 nmol/L per 1 nmol/L increase in baseline 25(OH)D

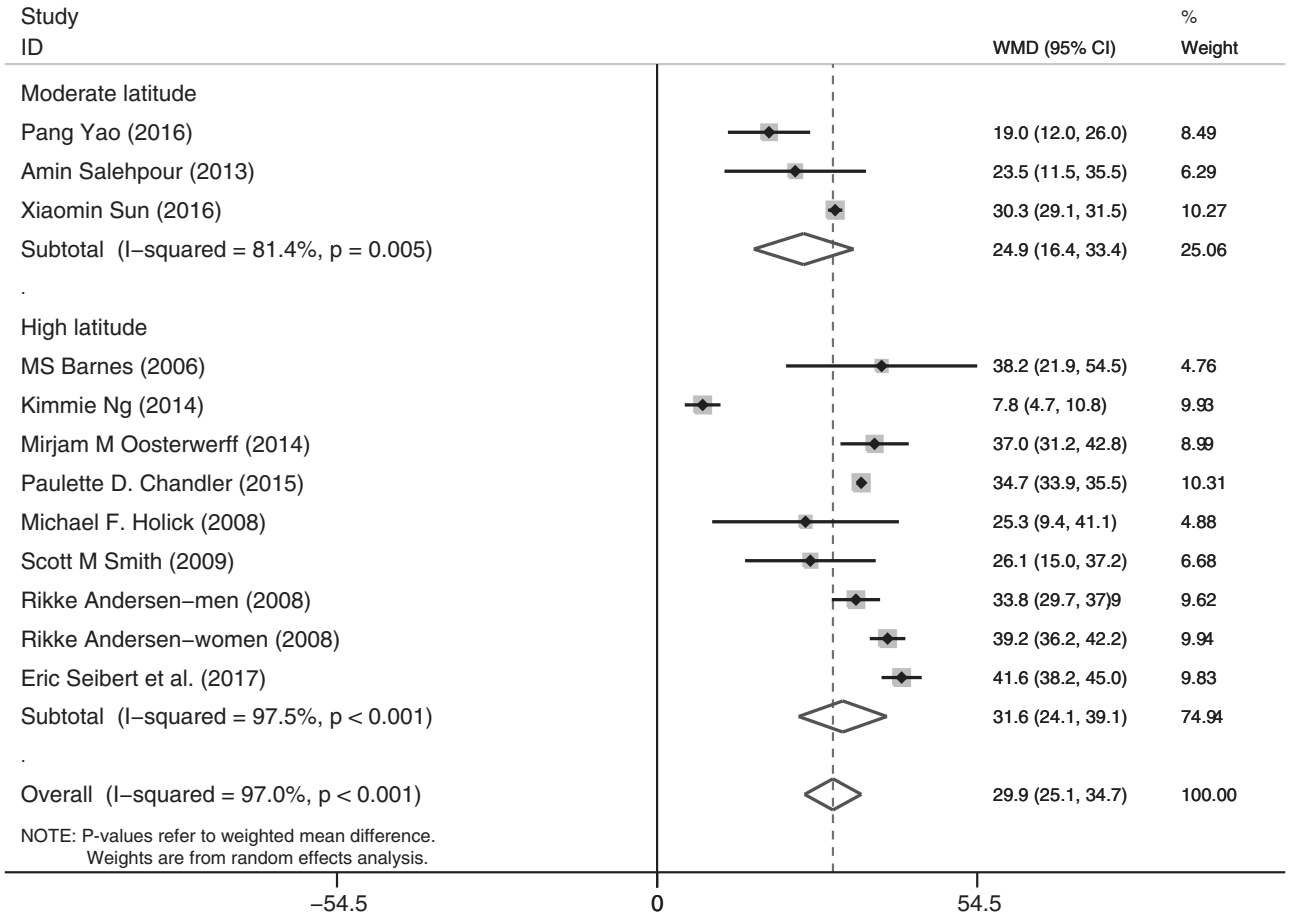

Fig. 3 Low dose (< 1500 IU) vs. placebo in adult subjects with baseline 25(OH)D concentration < 50 nmol/L from different latitudes

concentration for children, pregnant women, and all adults, respectively (Table 2). In addition, age was significantly associated with 25(OH)D concentration at + 0.3 nmol/L per year of age. In contrast to $VitD_3$ administration, the association between $VitD_2$ and achieved 25(OH)D concentration was negative with −16.4 nmol/L in 25(OH)D concentration per 100 IU/day dosage, and this effect was persistently significant in the daily dosing arms (Tables 3a, b). The effect of $VitD_3$ on 25(OH)D concentration was 1.3 nmol/L per 100 IU/day $VitD_3$ in adults and in that model it predicted, 81.2% of the variability in 25(OH)D concentration (Table 4).

Regional meta-regressions were performed separately in adults from Europe, North America, Asia and Middle East and Africa. VitD dose and baseline 25(OH)D concentration were persistently significantly associated with the achieved 25(OH)D concentration in each regional population. The increments in 25(OH)D concentration were 1.4, 1.3, 1.6, and 1.2 nmol/L per 100 IU/day of $VitD_3$; and 0.6, 0.7, 0.8, and 1.1 nmol/L per 1 nmol/L increase in baseline 25(OH)D concentration of Europeans, North Americans, Asians and Middle eastern and Africans (Table 5). Furthermore, age

Table 2 Association between independent variables and achieved 25 (OH)D concentration (in nmol/l) in pregnant women, children, and all adults

Independent variable	β (SE)	95% CI of β		Model characteristics		
				N [a]	I^2	R^2
Pregnant women						
Vitamin D dose (100 IU/day)	1.1 (0.2)	0.8	1.4	27	0	0.98
Baseline 25(OH)D (nmol/l)	0.9 (0.1)	0.6	1.2			
Children						
Vitamin D dose (100 IU/day)	1.6 (0.2)	1.2	2.1	48	0.6	0.93
Baseline 25(OH)D (nmol/l)	0.9 (0.1)	0.7	1.1			
All adults						
Vitamin D dose (100 IU/day)	1.3 (0.7)	1.1	1.4	236	0.6	0.8
Baseline 25(OH)D (nmol/l)	0.6 (0.1)	0.5	0.7			
Age	0.3 (0.1)	0.2	0.4			

Multivariate random-effect meta-regression model

25(OH)D 25-hydroxyvitamin D, I^2, I-squared_res, R^2 adjusted R-squared, *N* number of observations, *CI* confidence interval

[a]Study arms

was also associated with achieved 25(OH)D concentration, which increased by 0.4 nmol/L with each year of increases in age in Europeans.

Recommended dietary allowance (RDA) (IU/day) for achieving a serum 25(OH)D value of at least 75 nmol/L

With meta-regression models, linear relationships of total VitD supplemental dose, baseline 25(OH)D concentration, and age (for specific continents) vs. achieved 25(OH)D concentration in different populations (adults, children, and pregnant women) and geographical region (Middle East and Africa, Asia, Europe and North America) were produced (mean (95% lower CI) serum 25(OH)D (nmol/L) = β_0 (VitD dose (100 IU/day)) + β_1 (baseline 25(OH)D concentration (nmol/L)) + β_2 (age (1-year-old)) + increment). As the baseline, 25(OH)D concentration of adults varied significantly across three different continents, which was an important factor in prediction of achieved 25(OH)D concentration. Based on the calculations made using multivariate meta-regression modeling, RDA, (the recommended VitD supplement dose needed to reach sufficient 25(OH)D concentrations (of 75 nmol/L)), were established for different populations across different continents for adults. The WM of baseline 25(OH)D concentration was 54.8 nmol/L for children and the estimated achieved 25(OH)D concentration was 63.2 nmol/L with 600 IU/day VitD supplementation. We also estimated intakes of $VitD_3$ at a recommended 1340 (95% CI: 1044, 1887) IU/day to achieve adequate 25(OH)D concentrations in children. For pregnant women with a WM baseline of 25(OH)D of 48.2 nmol/L, 2250 (95% CI: 1765, 3100) IU/day VitD were recommended for achieving sufficiency. Because the increased 25(OH)D concentrations after supplemental VitD varied markedly with ages in European adults, RDAs were provided for each age group. While the WM for a baseline 25(OH)D concentration of 50.9 nmol/L, the RDAs were 2519 (95% CI: 2202, 2943) and 797 (95% CI: 697, 931) U/day for adults aged 18–64 years and 65–85 years, respectively. For adults in North America and the Middle East and Africa with the WM baseline 25(OH)D concentrations of 65.6 and 45.5 nmol/L, the RDAs were 729 (95% CI: 582, 984) and 1229 (95%CI: 739, 3656) IU/day. With WM baseline of 25(OH)D concentration in Asian adults of 36.5 nmol/L, the RDA was 2026 (95% CI: 1522, 3030) IU/day.

Discussion

In this systematic review, data from 136 VitD supplementation RCTs with 20,884 participants from different populations worldwide was examined. There were obvious dose–response effects between intake doses of VitD and achieved serum 25(OH)D concentrations in each subpopulation. Meanwhile, the highest supplemental doses (at >4000 IU/day) resulted in hypervitaminosis D, as defined by 25(OH)D concentrations >125 nmol/L [38] in adults, though there was no reported evidence of toxicity. The effect of $VitD_3$ supplementation on serum 25(OH)D concentration was higher than that of $VitD_2$. Baseline 25(OH)D concentration and age were significant predictors of achieved 25(OH)D concentration. In addition, based on meta-regression modeling, RDAs for $VitD_3$ were provided for children, pregnant women, adults from Middle East and Africa, Asia, North America, and age-specific Europeans in the present study.

In the analysis of dose-dependent increases in 25(OH)D concentration per 100 IU/day VitD of three different supplemental doses, the increases in serum 25(OH)D concentration decreased from lower to higher supplemental doses. A meta-analysis by Chakhtoura et al. [42] in the Middle East and North Africa demonstrated a similar dose-dependent relationship. Furthermore, previous meta-regression analyses performed in Europe and by the IOM showed that the intake–status data from the RCTs accounted for the more blunted response of serum 25(OH)D concentration to higher intakes of VitD by applying curvilinear Ln model [38, 46, 192]. These results demonstrably supported the expectation that a plateau of the increments in 25(OH)D concentration will be reached with increasingly high doses. The biphasic relationship between VitD supplementation dose and 25(OH)D concentration maybe due to the fact that hepatic 25-hydroxylase becomes saturated and the reaction switches from first to zero order, which is consistent with standard enzyme kinetics [193]. Our findings demonstrate that long-term low-dose VitD supplements are more effective than short-term high-dose supplements, which should be taken into consideration when policies or specifications for guidelines for RDAs are being formulated.

In the present meta-regression analysis of pregnant women and children, as well as adults, baseline 25(OH)D concentration was identified as a significant predictor of achieved 25(OH)D concentrations. The increment in 25(OH)D concentration ranges from 0.6 to 0.9 nmol/L per 1

Table 3A Compare the effectiveness between vitamin D_2 and vitamin D_3 of all adults in achieved 25(OH) D concentration (in nmol/L)

Independent variable	β (SE)	95% CI of β		Model characteristics		
				N^a	I^2	R^2
Vitamin D dose (100 IU/day)	1.0 (0.1)	0.8	1.2	154	0.56	0.71
Vitamin D_2[b]	−16.4 (5.9)	−28	−4.7			

Table 3B Compare the effectiveness between vitamin D_2 and vitamin D_3 of all adults on daily vitamin D supplements in achieved 25(OH) D concentration (in nmol/L)

Independent variable	β (SE)	95% CI of β		Model characteristics		
				N^a	I^2	R^2
Vitamin D dose (100 IU/day)	1.0 (0.1)	0.8	1.2	132	0.23	0.8
Vitamin D_2[b]	−15.8 (5.8)	−27.3	−4.3			

Multivariate random-effect meta-regression model

25(OH)D 25-hydroxyvitamin D, I^2 I-squared_res, R^2 adjusted R-squared, *N* number of observations, *CI* confidence interval

[a]Study arms

[b]Compared with vitamin D_3

Table 4 Association between independent variables of all adults with vitamin D_3 and placebo administration with achieved 25(OH) D concentration (in nmol/L)

Independent variable	β (SE)	95% CI of β		Model characteristics		
				N^a	I^2	R^2
Vitamin D dose (100 IU/day)	1.3 (0.1)	1.2	1.5	225	0.6	0.81
Baseline 25(OH)D (nmol/L)	0.6 (0.1)	0.5	0.7			
Age	0.3 (0.1)	0.1	0.4			

Multivariate random-effect meta-regression model

25(OH)D 25-hydroxyvitamin D, the sum of both 25(OH)D_2 and 25(OH)D_3,; I^2 I-squared_res, R^2 adjusted R-squared, *N* number of observations, *CI* confidence interval

[a]Study arms

Table 5 Multivariate random-effect meta-regression on adults from Europe, North America, Asia, Middle East, and Africa with vitamin D_3 supplementation

Independent variable	β (SE)	95% CI of β		Model characteristics		
				N^a	I^2	R^2
Europe						
Vitamin D dose (100 IU/day)	1.4 (0.1)	1.2	1.6	104	0.41	0.88
Baseline 25(OH)D (nmol/l)	0.6 (0.1)	0.4	0.8			
Age	0.4 (0.1)	0.3	0.6			
North America						
Vitamin D dose (100 IU/day)	1.3 (0.2)	0.9	1.6	55	0.54	0.75
Baseline 25(OH)D (nmol/l)	0.7 (0.1)	0.4	1			
Asia						
Vitamin D dose (100 IU/day)	1.6 (0.3)	1.1	2.2	26	0.5	0.84
Baseline 25(OH)D (nmol/l)	0.8 (0.3)	0.3	1.4			
Middle East and Africa						
Vitamin D dose (100 IU/day)	1.2 (0.3)	0.4	2	10	0.56	0.77
Baseline 25(OH)D (nmol/l)	1.1 (0.4)	0.1	2.1			

Multivariate random-effect meta-regression model

25(OH)D 25-hydroxyvitamin D, I^2, I-squared_res R^2 adjusted R-squared, *N* number of observations, *CI* confidence interval

[a]Study arms

nmol/L increase in baseline 25(OH)D concentration, which is similar to a preview systematic review with 0.8 ng/mL per 1 ng/mL increase in baseline 25(OH)D concentration [42]. The subgroup dose–response analyses in adults in different regions found that Asian adults, whose baseline 25(OH)D concentrations were much lower than those of North Americans and Europeans, the increment in 25(OH)D concentration per 100 IU/day VitD was highest, which is consistent with previous studies [194, 195]. However, a meta-analysis of changes in 25(OH)D concentration associated with VitD supplementation in Caucasian subjects over 50 years old, however, found that higher concentrations at baseline were not associated with lower increases in achieved 25(OH)D concentrations [54]. The heterogeneity between studies maybe related to variation in age and ethnicity.

In addition, we also identified the type of VitD given as an important factor affecting achieved 25(OH)D concentration. Both $VitD_2$ and $VitD_3$ function as prohormones and the only difference between them is the structure of their side chains. There is still a controversy about the comparative efficacy of between $VitD_2$ and $VitD_3$ for obtaining optimum 25(OH)D concentrations. Some studies found the two types were equivalent in raising 25(OH)D concentration [128, 196, 197], while others found that $VitD_2$ was rather less effective [54, 198–200] than $VitD_3$ when given in daily doses. However, our results showed that compared with $VitD_3$, $VitD_2$ was considerably less effective than $VitD_3$, in raising serum 25(OH)D concentration [by –16.4 nmol/L] per 100 IU/day when taken as a daily supplement. As reported by Horst et al. [201], the difference between $VitD_2$ and $VitD_3$ is due to the fact that once 1,24,25$(OH)_3D_2$ is formed, this change is irreversible and this metabolite is inactive, and while 1,24,25$(OH)_3D_3$ is an active form of VitD [202]. Furthermore, the half-life of 25$(OH)D_2$ in the circulation is shorter than that of 25(OH)D_3, which some people suggest is because it is destroyed or not bound to VitD binding proteins but others suggest that more of it gets into target cells than of the 25$(OH)D_3$ metabolite. It is of note that the side chain of $VitD_2$ would not preclude the activation of the molecule in the 25- or 1α-hydroxylation position or inactivation. However, of the present conflict between findings from different studies may reflect differences in sample size and supplemental dosages [203]. Overall, our findings suggest that $VitD_3$ should be a better option for VitD supplementation than $VitD_2$.

Another finding of our study was that age is a significant predictor of the response to $VitD_3$ supplementation. The

increment in 25(OH)D concentration was 0.3 nmol/L per + 1-year in age, older participants showing a superior response to $VitD_3$ supplementation, independent of baseline 25(OH)D concentration or dose. Barger-Lux [195] has reported similar findings, where age independently influenced VitD responses at + 0.42 nmol/L per + 1-year in age. Though aging is not necessarily accompanied by intestinal malabsorption of VitD [204], the decreased synthetic capacity of the skin with increasing age has been related to the deficiency of VitD due; on the one hand to falls in skin 7-dehydrocholesterol concentrations, and on the other hand to of alterations in skin morphology [205]. The high prevalence of VitD deficiency in the elderly may well contribute to the greater effects reported [206, 207]. There was also an obvious trend for the achieved increment to be relatively higher with smaller doses than with larger dose among elderly. Moreover, the achieved increment in 25 (OH)D concentration per 100 IU/day VitD among elders was higher with lower dose supplementation (3.3 nmol/L), compared with those in adults (18–64 years) (2.1 nmol/L) even though the WM baseline 25(OH)D concentration of the elders (>64 years) in the current meta-analysis was higher than that seen in the adults (18–64 years). Seamans et al. [102] also reported similar results that daily supplementation with same dose of $VitD_3$ increased 25(OH)D concentration over winter concentrations in ≥64-year-old adults, while it diminished the decline in 25(OH)D concentration in 20- to 40-year-old adults.

In addition to VitD dose, baseline 25(OH)D concentration, age and type of VitD given, other factors have been reported to be associated with VitD supplementation and influence the 25(OH)D concentration, including season, latitude, concomitant calcium supplementation, BMI, and frequency [176, 207–210]. However, none of them reached statistical significance as predictors of achieved 25(OH)D in our study. One possible reason maybe that the recruitment of participants was conducted across different seasons and that participants were enrolled into the cohort at different time points [149, 156, 157]. Other studies report that VitD deficiency was more common in those respondents whose blood samples were collected in autumn or winter rather than in those collected in spring or summer [207]. In addition, the inter-individual difference in blood sample collecting times may further weaken the seasonal effect.

Existing evidence for defining an optimal intakes of VitD for pregnant women has been inadequate, and the guidelines from different governmental organizations do not differ from those for other adults [194]. European Food Safety Authority-Draft scientific opinion recommends 600 IU/day of $VitD_3$ for pregnant and lactating women, which is far below our estimated RDA of $VitD_3$ of 2250 IU/day. As shown in a trial by Nancy et al. [181], the prevalence of VitD sufficiency using 2000 IU/day of $VitD_3$ supplementation reached >97%, which provides evidence that supports our specific recommendation for pregnant women as being both appropriate and adequate. The recommended doses from different governmental organizations vary widely in both children and adults with limited sun exposure, from 200 to 2000 IU/day, which is partly due to disagreements on the minimum desirable 25(OH)D concentration [194]. We recommended children with low baseline 25(OH)D concentration (54.8 nmol/L) and insufficient sun exposure, to receive a RDA of 1340 IU/day of $VitD_3$. One RCT conducted by Rajakumar et al. [66] showed that to maintain 25(OH)D concentrations at 20 ng/mL (50 nmol/L), 1543 IU/day VitD was needed, which approximates our recommendation. We recommended 2519 and 797 IU/day for European adults aged 18–64 and 65–85 years, respectively, to reach a sufficient 25(OH)D concentration of 75 nmol/L. Healthy Somali women living in Sweden aged 32–36 years were treated with 1600 IU/day for 3 months and increased 25 (OH)D concentration by 29 nmol/L, which showed a dose-dependent increase from very low levels to sufficient serum 25 (OH)D concentration [98]. In a trial in free-living adults ≥64 years of age, >99% of the participants reached 25(OH)D concentration of 50 nmol/L with supplementation at 600 IU $VitD_3$ per day after a 22-week intervention [163]. Another RCT conducted in Finland also found that with 800 IU/day supplements, all the participants reached the 25(OH)D concentration of 50 nmol/L [164], while recommend, respectively, 729, 2026, and 1229 IU/day for adults in North America, Asia and Middle East and Africa to reach a sufficient 25(OH)D concentration of 75 nmol/L. However, a 6-month RCT of $VitD_3$ supplementation among 138 White and African Americans aged 18–65 years suggested 3800 IU/day for those above a 25(OH)D threshold of 55 nmol/L and 5000 IU/day for those below that threshold [211]. A RCT conducted among Chinese adults with VitD supplementation of 2000 IU/day, 86% of the subjects achieved 25(OH)D concentrations ≥75 nmol/L [81], which supports our estimate of 2026 IU/day VitD supplementation, as adequate for the majority of adults in Asia for achieving a status of sufficiency. Another 12-week double-blind RCT in healthy overweight and obese Iranian women found that with $VitD_3$ supplementation at 1000 IU/day, serum 25(OH)D significantly increased in the VitD group compared with the placebo group (38.2 ± 32.7 nmol/L vs. 4.6 ± 14.8 nmol/L; $p < 0.001$), which further suggests that our recommendation of 1229 IU/day will be adequate. Differences exists between the present recommendations and other reports, probably related to the diverse and comprehensive factors we have included in the analyses of factors predicting achieved 25 (OH)D concentration, rather than, solely VitD dose, such as baseline 25(OH)D concentration and age and regional- and age-specific populations. Experimental data from recent RCTs mentioned above also provide evidence to support the results. However, more RCTs of larger population samples from wide areas are needed to verify our findings.

There are several strengths in our study. This is the first systematic review to assess the dose–response to VitD supplementation of different populations across seven regions. Based on dose–response relationship analysis, optimal dosage of $VitD_3$ for achieving sufficient circulating 25(OH)D concentrations and prevent VitD deficiency in different populations at the global and regional level were estimated. Furthermore, the effect of latitude, season, age, BMI, the type of VitD use and frequency of VitD supplements, and duration of administration on 25(OH)D concentration has been investigated. However, limitations still existed. First, we did not explore the effect of sex and ethnic diversity because the participants of most studies were of same sex or ethnicity and other studies did not report result by sex or ethnicity separately. Second, we could not exclude the influences from sun exposure, skin characteristics, dietary intake, and VitD intake because these confounding factors were not assessed in the available RCT data. Third, high heterogeneity was detected in some meta-analyses, which may be related to the differences of baseline characteristics of the included subjects, supplementation dose, frequency and duration, supplementation type of VitD use. In addition, serum 25(OH)D concentration was measured by different standard or nonstandard assays, which would contribute to the high heterogeneity we found and lead to the reduction of the value of the evidence used in our meta-analysis of RCT data [212]. In the present meta-analysis, a total of 29 (21%) studies used high performance liquid chromatography (HPLC) tandem mass spectrographic assay, which is the "gold standard" for 25(OH)D measurement. As some studies measured both 25$(OH)D_2$ and 25$(OH)D_3$, some measured 25$(OH)D_3$ alone, and many provided assay data that were very different from HPLC data on the same samples. From a harmonization study between liquid chromatography–tandem mass spectrometry (LC-MS/MS) and Diasorin RIA for measurement of 25(OH)D concentrations in a large population survey, concentrations measured by LC-MS/MS were much higher than those measured by Diasorin RIA, with a mean difference of 51.6 nmol/L [213]. Precision testing showed that the Roche Elecsys Vitamin D Total competitive protein-binding assay, standardized against HPLC tandem mass spectrographic assays within-run coefficient of variations (CVs) of ≤ 7%, within-laboratory CVs of < 9.5%, between-laboratory precision CVs of ≤ 10.1%, and a functional sensitivity below 9.8 nmol/L (at CV 12.9%) [214]. And the intraassay and inter-assay CVs for the enzyme-linked immunosorbent assay (ELISA) method were 5.9 and 6.6%, respectively. Method-related differences in results of total serum 25(OH)D from different studies have confounded international efforts to develop evidence-based guidelines for the evaluation of VitD status. Further relevant studies are needed to resolve these problems in the future. Finally, as the results of meta-analysis were derived from pooled data from different studies, ecological bias may be present that we could not adjust for since details for individuals were not available.

Conclusions

This study found that there were clear and consistent positive dose–response relationships between VitD supplemental dose and achieved serum 25(OH)D concentration in each population that baseline 25(OH)D concentration and age were significant predictors for achieved 25(OH)D concentration and that $VitD_3$ had higher effects on serum 25(OH)D concentration than did $VitD_2$. We have, therefore, recommended $VitD_3$ for supplementation, and provided population-specific and regional recommendations for intakes of $VitD_3$ necessary to achieve optimal 25(OH)D concentrations examined, except for pregnant women and children where there were insufficient data due to the limited numbers of studies available for analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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