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REVIEW

Oral vitamin D supplementation and body weight in children and adolescents: a systematic review and meta-analysis of randomized controlled trials

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Abstract

This study was designed to ascertain whether oral vitamin D supplementation (oral supplementation and fortified foods) is associated with changes in body weight measures in children and adolescents, using a systematic review and meta-analysis of randomized controlled trials (RCTs). PubMed, Scopus, Cochrane, and Web of Science databases were searched from inception to October 28, 2022. The mean difference and corresponding 95% confidence interval (CI) of interested outcomes were pooled using a random-effects model. Twenty-one RCTs were included in the meta-analysis, and the results showed a significant decrease in body mass index (BMI) following vitamin D supplementation in children and adolescents ($n=9$ studies, 1029 participants; weighted mean difference: -0.43 kg/m^2, 95% CI: $-0.79, -0.08$; $P=0.02$; $I^2=58.5\%$). Overall, oral vitamin D supplementation had no significant effect on body weight and other anthropometric indices, including fat mass, lean mass, waist circumference, BMI *Z*-score, and height. Although results of body weight changed to significant after sensitivity analysis (WMD = 0.39 kg, 95% CI = 0.01, 0.78; $P=0.04$; $I^2=0\%$, *P*-heterogeneity = 0.71), we also found significant weight gain in healthy pediatric population, and when the dose of vitamin D supplementation was up to 600 IU/day, the certainty of evidence was very low for weight, moderate for height and BMI, and low for the remaining outcomes.

Conclusion: Our results suggest that vitamin D supplementation may lead to a statistically significant weight gain in children and adolescents, while BMI was reduced. Although no significant change was observed in height, it seems vitamin D supplementation may elicit these changes by increasing skeletal growth; however, this remains to be verified. Further high-quality RCTs, with longer duration and larger sample sizes, are needed to yield more certain evidence in this regard.

What is Known:

- *Available evidence indicates an inverse association between body weight/fat mass and vitamin D status in children and adolescents; however, findings regarding the effect of vitamin D supplementation on anthropometric measurements in children are controversial.*

What is New:

- *Our results showed a significant decrease in BMI following vitamin D supplementation in children.*
- *A significant weight gain also was observed after sensitivity analysis, and in healthy pediatric population, and when the dose of vitamin D supplementation was up to 600 IU/day.*

Keywords Vitamin D · Weight · Meta-analysis · Children · Obesity

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
CI	Confidence interval
FMI	Fat mass index
FFMI	Fat-free mass index
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IGF	Insulin-like growth factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
VDBP	Vitamin D-binding protein
WMDs	Weighted mean differences

Introduction

Vitamin D inadequacy is a global public health concern in all age groups [1]. The prevalence of vitamin D deficiency among children varies by geographic region and is relatively high in the Middle East, South America, and Africa [1]. Vitamin D, as a fat-soluble hormone, has important biologic effects in the modulation of endocrines, the immune system, and cell proliferation, beyond its classic influence on calcium homeostasis and bone health [2]. Fatty fish and fish liver oils, as well as egg yolk, are known as dietary sources of vitamin D [3]; although vitamin D is only found in small amounts in these foods [4], moreover, despite that sunlight is a major source for endogenous vitamin D synthesis, many people might still require dietary supplements or food fortification to meet their vitamin D requirements [5–7].

Poor vitamin D status is associated with many health problems in children and adolescents, including increased risk of rickets [8], asthma [9], attention deficit hyperactivity disorder (ADHD) [10], autism spectrum disorder [11, 12], infections [9, 13], and type 1 diabetes [14]. Vitamin D supplementation has also been shown to have beneficial effects in the prevention and/or improvement of most of these conditions [15–19].

Childhood overweight and obesity also remain major health issues worldwide [20, 21]. Childhood obesity predicts adult obesity and morbidity and needs special consideration [21–23]. There are published meta-analyses of observational studies indicating an inverse association between body weight/fat mass and vitamin D status in both the general population [24, 25] and children [26, 27].

Considering the possible role of vitamin D in the regulation of adipogenesis [28], such an association could be plausible. However, the susceptibility of observational studies to a reverse causality relationship cannot be ignored. Indeed, some explanations, including lower vitamin D intake, lower outdoor activities and sun exposure [29], impaired hepatic hydroxylation [30], altered gene expression of vitamin D metabolizing enzymes [31], and lower bioavailability of vitamin D in obese individuals, due to the trapped vitamin D in fat deposits [32], have been hypothesized in this regard. Also, previous meta-analyses of randomized controlled trials (RCTs) reported no significant effect of vitamin D supplementation on weight loss in adults, [29, 33, 34]. However, these assumptions may not apply to children; indeed, a previous meta-regression analysis indicated that the association between vitamin D supplementation and body weight was attenuated with increasing age [30]. There are also some RCTs indicating that vitamin D supplementation may increase body weight [35], and decrease fat mass, in children [36], although some other studies found no significant effect [29, 37].

Thus, given the current gap in meta-evidence, the aim of the present systematic review and meta-analysis of RCTs was to determine the effect of vitamin D supplementation on anthropometric measures in a pediatric population.

Methods

The present meta-analysis was conducted and reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [38]. The study protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42020214497) [39].

Search strategy

We initially searched PubMed, Scopus, Cochrane, and Web of Science databases for relevant studies, published from inception until 14 of March 2021; with no restriction on language, using a combination of selected keywords relevant to "vitamin D" and anthropometric measures. Details on the applied search strategy are described in Supplemental Table 1. The literature search strategy was also finally updated on 28 October 2022. Potentially relevant studies were identified through checking review articles and the references of the retrieved articles.

Inclusion and exclusion criteria

The title and abstract of retrieved studies were independently screened by two reviewers (SS and SB) and were retained if they met the following criteria: (1) studies were randomized controlled (parallel/cross-over), (2) participants with a mean age of 2–18 years old, (3) intervention duration of at least 1 week, (4) investigated the effect of oral vitamin D supplementation or fortified foods compared with a control group/or non-fortified food, and (5) reported mean and standard deviation (or standard error) of changes for any body composition or anthropometric measures in the intervention and control groups or provide sufficient data to estimate change values.

We excluded studies if (1) they were an in vivo or in vitro study; (2) they were observational study, review article, study protocol, conference abstract, or case report; (3) they applied intravenous or intramuscular vitamin D administration; (4) the control group received vitamin D or were exposed to light therapy; (5) used vitamin D as a multicomponent supplement in either intervention or control groups; and (6) if they did not provide data needed for the analysis [mean and SD for pre- and post-values or changes form baseline to estimate effect size], even after contacting the corresponding author. Any discrepancies were resolved using a consensus discussion.

Data extraction

The following information was extracted from each study and cross-checked (SB and SS): first author, publication year, study design [parallel or cross-over], geographic location, the season in which the study was conducted, number of participants in either intervention or control groups, study duration, type and dosage of vitamin D, and any other intervention in both groups. The characteristics of participants (age, sex, health status, vitamin D deficiency), and mean and standard deviation (SD) of changes from baseline for interested outcome were also extracted. In the case of trials that investigated multiple doses of vitamin D supplementation, pooling estimates were calculated using a fixed-effects model, before inclusion in the final analysis.

Risk of bias

Two reviewers (SS, SB) evaluated the study's risk of bias using the Cochrane Risk of Bias tool [40], based on the seven criteria, including sequence generation, allocation concealment, blinding of participants, blinding of personnel, outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Studies were rated as good quality if all criteria were low risk of bias, fair quality if one domain was high risk of bias or two domains were unclear, or poor quality if two or more domains were assigned as high or unclear risk of bias. Disagreements were resolved through group discussion.

Quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to measure the strength of study evidence. Evidence from RCTs receives a default grade of "high" quality but may be downgraded on the basis of risk of bias (according to the Cochrane Risk of Bias tool), inconsistency (unexplained heterogeneity between studies; $I^2 \geq 50\%$, $P < 0.10$), indirectness (presence of limitation to generalize the results), impression (the 95% CI for effect estimates were wide or crossed a minimally important difference), and publication bias. The quality of evidence was classified as high, moderate, low, and very low [41, 42].

Statistical analysis

The mean differences and SD change between the vitamin D supplementation and control groups were calculated for the outcomes of interest. If change from baseline values were missing, we imputed SD values according to the formula provided in the Cochrane Handbook of Systematic Reviews [43], where the r coefficient was considered 0.5 for all outcomes. All analyses were also conducted with correlation coefficients of 0.2 and 0.8, to ensure the result of analyses were not sensitive to the selected correlation coefficient. Weighted mean differences (WMDs) and their corresponding standard errors (SEs) were pooled using the DerSimonian and Laird random-effects model [44]. The between-study heterogeneity was assessed using the Cochran Q statistic (significance set at $P < 0.1$) and quantified by the I^2 values [45]. The source of potential heterogeneity was determined by the predefined subgroup analyses for sex (boys, girls, both), continent of origin, vitamin D type (D2, D3), study duration (≤ 24 weeks, > 24 weeks), vitamin D deficiency (yes, no), calcium supplementation (yes, no), vitamin D fortification (yes, no), dose of vitamin D (≤ 600 IU/day, > 600 IU/day), health status of participants, consideration for the seasonality of interventions (yes, no), and study quality. Subgroup analysis also was performed even little or no heterogeneity was observed, as it is clinically important to estimate treatment effectiveness for specific subgroups. To determine a statistically significant subgroup effect, P value for between-groups considered less than 0.1. Sensitivity analysis was also performed to examine the impact of individual studies on the overall result. Publication bias was tested by the Egger's test [46] and visual inspection of Begg's test funnel plots [47], if there were ≥ 10 studies available for each outcome. Analyses were conducted with Stata 13 software (StataCorp, College Station, TX, USA), and a 2-tailed $\alpha < 0.05$ was considered statistically significant.

Results

Study selection and characteristics

The initial search retrieved 4550 references. After excluding duplicates and title/abstract screening, 311 studies were selected for full-text checking. Twenty-one studies fulfilled the inclusion criteria and were included in the systematic-review [36, 37, 48–66]. Five studies were excluded due to

insufficient data needed for the analysis [49, 52, 53, 56, 65]. Five studies were also added after the last update [67–71], where studies were included that assessed the effect of vitamin D supplementation on body weight ($n=8$), BMI ($n=9$), BMI *Z*-score ($n=6$), fat mass (%, kg) ($n=6$), waist circumference ($n=4$), height ($n=9$), and lean mass (kg) ($n=6$) (Fig. 1). Excluded studies, as well as the reasons for exclusion, are provided in Supplemental Table 2.

The characteristics of the 21 studies are presented in Table 1. Included studies were published between 1998 and 2022 and were carried out in Europe [36, 37, 60, 61, 63, 64, 69, 70], Asia [48, 50, 57–59, 66, 68, 71], the USA [54, 62], Canada [51], Brazil [67], and Africa [55]. All of the included studies applied a parallel randomized controlled design, except one [67]. Participants included exclusively girls in three studies [59, 60, 64], and exclusively boys in one study [50], whereas the others included both sexes. Seven studies enrolled vitamin D-deficient children [36, 48, 50, 55, 66–68, 71], and the others did not apply any inclusion criteria for baseline levels of serum 25 (OH) D concentration. Most of the included studies recruited healthy children [37, 48, 51, 57, 59–64, 71], while other studies enrolled children with autism spectrum [50], leukemia [54], irritable bowel syndrome [55], metabolic syndrome [58], non-alcoholic fatty liver (NAFLD) [68], hypertriacylglycerolemia [67], and obesity [36, 66]. The duration of the interventions ranged from 10 to 144 weeks, and the dose of vitamin D3 supplemented varied from 10 to 2000 IU per day or a high dose (150,000 IU) of vitamin D2 [62]. Vitamin D was administered via nutritional supplement in most of the included studies, but four studies utilized D3-fortified foods [51, 67, 69, 70], and another study assessed the effect of both D3-fortified food or vitamin D capsules [48], where the vitamin D supplements, in comparison with placebo, were considered for overall analysis. Calcium supplementation was given in both intervention and comparison groups in two studies [54, 59], and the remaining studies used solo vitamin D supplementation. The form of vitamin D was D2 in four studies [37, 59, 62, 66] and D3 in the rest of the studies. Anthropometric characteristics were measured by a member of research team in all the included studies.

Risk of bias and quality of evidence

The methodological quality of included studies was assessed, and studies scored as good [36, 55, 66, 68–71], poor [37, 48, 50, 51, 54, 57, 61], or fair quality [58–60, 62–64, 67], based on Cochrane Risk of Bias criteria. The most common bias was related to the lack of explanation of randomization and concealment processes. Two studies were at high risk of bias in blinding of participant's domain, because of the different interventional strategies [48, 50] (Supplemental Table 3). Using the GRADE summary of evidence, the certainty of evidence was very low for weight, and low for BMI *Z*-score, fat mass (%, kg), lean mass, and waist circumference, and moderate for height and BMI, respectively (Supplemental Table 4).

Meta-analysis

Body weight Pooling data from eight studies did not show any significant effect in body weight following vitamin D supplementation in children and adolescents [37, 51, 54, 57, 59, 60, 64, 67] ($n=756$ participants; WMD = 0.22 kg, 95% CI = −0.11, 0.55; $P=0.19$; $I^2=0.0\%$) (Table 2, Fig. 2a). Although there was no between-study heterogeneity, subgroup analysis was performed and showed that vitamin D supplementation leads to a significant weight gain in healthy children (WMD = 0.40 kg, 95% CI = 0.02, 0.78; $P=0.04$; $I^2=0.0\%$, *P* between-groups = 0.07), in studies that considered seasonal variation (WMD = 0.39 kg, 95% CI = 0.01, 0.78; $P=0.04$; $I^2=0.0\%$, *P* between-groups = 0.07), and in studies that applied standard dose supplementation (600 IU/day or less) (WMD = 0.55 kg, 95% CI = 0.04, 1.07; $P=0.03$; $I^2=0.0\%$, *P* between-groups = 0.09) (Table 3).

BMI Pooling data from nine studies showed a significant decrease in BMI in children, following vitamin D supplementation [36, 48, 50, 57–59, 62, 67, 68], with moderate evidence of between-study heterogeneity ($n=1092$ participants; WMD = −0.43 kg/m^2, 95% CI = −0.79, −0.08; $P=0.02$; $I^2=58.5\%$) (Table 2, Fig. 2b). The decrease in BMI following vitamin D supplementation was evident in studies with good quality based on Cochrane tools (WMD = −0.96 kg/m^2, 95% CI = −1.51, −0.41; $P=0.001$; $I^2=31.8\%$, *P* between-groups = 0.02).

BMI *Z*-score was also assessed in six studies, and no significant change was observed after vitamin D supplementation [36, 55, 63, 67, 70, 71] ($n=9435$ participants; WMD = 0.00, 95% CI = −0.02, 0.02; $P=0.82$; $I^2=0.0\%$, *P*-heterogeneity = 0.54) (Table 2, Supplemental Fig. 1).

Height Nine studies examined the effect of vitamin D supplementation on height, and no significant change was found ($n=1088$ participants; WMD = 0.12 cm, 95% CI = −0.06, 0.30; $P=0.21$; $I^2=41.4\%$, *P*-heterogeneity = 0.08) [37, 51, 57, 59–61, 64, 67, 69] (Supplementary Fig. 2). The results of subgroup analysis are shown in Supplementary Table 6.

Fat mass Six studies examined the effect of vitamin D supplementation on fat mass, and our meta-analysis found no significant change in fat mass percentage [36, 54, 59, 67, 71] ($n=9075$ participants; WMD = −0.54%, 95% CI = −1.40, 0.31; $P=0.21$; $I^2=44.5\%$, *P*-heterogeneity = 0.12) or kilograms ($n=9138$ participants; WMD = 0.02 kg, 95%

Table 1 The characteristics of eligible randomized controlled trials investigating the effect of vitamin D supplementation on anthropometric measures in children[a]

Author, year	Country	Participants, sex	Age	Participants health status/obesity status (yes, no)	Seasonal variation consideration	Vitamin D deficiency (25 OHD)	Intervention/co-intervention	Other intervention	Dose per day (IU)	Duration (week)	Outcome
Alahouhala et al. [37]	Finland	51, both	8–10	Healthy/no	Yes	No	D2/No	No	400	24–52	Weight
Al-Daghri et al. [48]	Saudi Arabia	530, both	14.8	Healthy/no	Yes	Yes (< 50 nmol/L)	D3-fortified milk, or D3 tablet/no	No	1000	24	BMI
Ansari et al. [50]	Iran	20, boys	6–14	ASD/no	No	Yes (20–30 and < 20 ng/mL)	D3/no	No	7000	10	BMI
Alves et al. [67]	Brazil	44, both	4–11	Hypertriacylglycerolemia/yes	No	Yes (20–30 and < 20 ng/mL)	D3-fortified sunflower oil/sunflower oil	No	1000	12	BMI, weight, BMI *Z*-score, body fat, fat-free mass, waist circumference, height, skinfold indices
Brett et al. [51]	Canada	49, both	5	Healthy/no	Yes	No	D3-fortified food/no	No	400	24	Weight
Brzeziński et al. [36]	Poland	118, both	10.7	Healthy/yes	Yes	Yes (< 30 ng/mL)	D3/no	Weight reduction diet	1200	26	BMI, lean mass, FM, BMI (*Z*-score)
Diaz et al. [54]	Chile	13, both	5.5	Leukemia/no	Yes	No	D3/Ca[b]	No	10–20	48	Weight, FM, lean mass,
El Amrousy et al. [55]	Egypt	112, both	16.2	IBS/no	Yes	Yes (< 20 ng/mL)	D3/no	No	2000	24	BMI (*Z*-score)
El Amrousy et al. [68]	Egypt	100, both	7.1–17.5	NAFLD/yes	Yes	Yes (< 20 ng/mL)	D3/no	No	2000	24	BMI, waist circumference, HC
Ganmaa et al. [57]	Mongolia	117, both	13.1	Healthy/no	Yes	Yes (< 20 ng/mL)	D3/no	No	1800	24	Weight, BMI
Ganmaa et al. [71]	Mongolia	8851, both	6–13	Healthy/no	Yes	Yes (< 20 ng/mL)	D3/no	No	2000	144	FM, lean mass, BMI (*Z*-score)
Kelishadi et al. [58]	Iran	43, both	10–16	Metabolic syndrome/yes	No	No	D3/no	No	50,000	12	BMI, WC
Khadilkar et al. [59]	India	49, girls	14.6	Healthy/no	Yes	No	D2/Ca[b]	No	820	48	Weight, BMI, FM, lean mass

Table 1 (continued)

Author, year	Country	Participants, sex	Age	Participants health status/ obesity status (yes, no)	Seasonal variation consideration	Vitamin D deficiency (25 OHD)	Intervention/co-intervention	Other intervention	Dose per day (IU)	Duration (week)	Outcome
Molgaard et al. [60]	Denmark	221, girls	11.4	Healthy/no	Yes	No	D3/ No	No	200	48	Weight
Mortensen et al. [61]	Denmark	117, both	6.6	Healthy/no	Yes	No	D3/no	No	400	20	FM, lean mass
Shah et al. [62]	USA	28, both	13.6	Healthy/yes	Yes	No	D2/no	No	150,000	24	BMI
Samaranayake et al. [66]	Sri Lanka	96, both	5–15	Healthy/yes	Yes	Yes (< 20 ng/ml)	D2/no	Structured diet + Physical activity	7100–350	24	BMI SD score, waist, fat mass (%), waist Z-score
Smith et al. [63]	Denmark	110, both	16	Healthy/no		No	D3/no	No	400–800	20	BMI (Z-score), WC
Stounbjerg et al. [69]	Denmark	200, both	6–8	Healthy/no	Yes	No	High and normal yogurt plus vitamin D3/high and normal yogurt	No	800	24	Height, height for age
Thams et al. [70]	Denmark	200, both	6–8	Healthy/no	Yes	No	High and normal yogurt plus vitamin D3/high and normal yogurt	No	800	24	BMI (Z-score), FMI, FFMI
Viljakainen et al. [64]	Finland	212, girls	11.5	Healthy/no	Yes	No	D3/no	No	200–400	48	Weight

ASD autism spectrum disorders, *BMI* body mass index, *FM* fat mass, *FMI* fat mass index, *FFMI* fat-free mass index, *IBS* irritable bowel syndrome, *IU* international unit, *P* parallel, *USA* United states of America, *WC* waist circumference, *NM* not mention

[a]All the included studies are parallel randomized controlled trial

[b]Calcium was supplemented in both groups

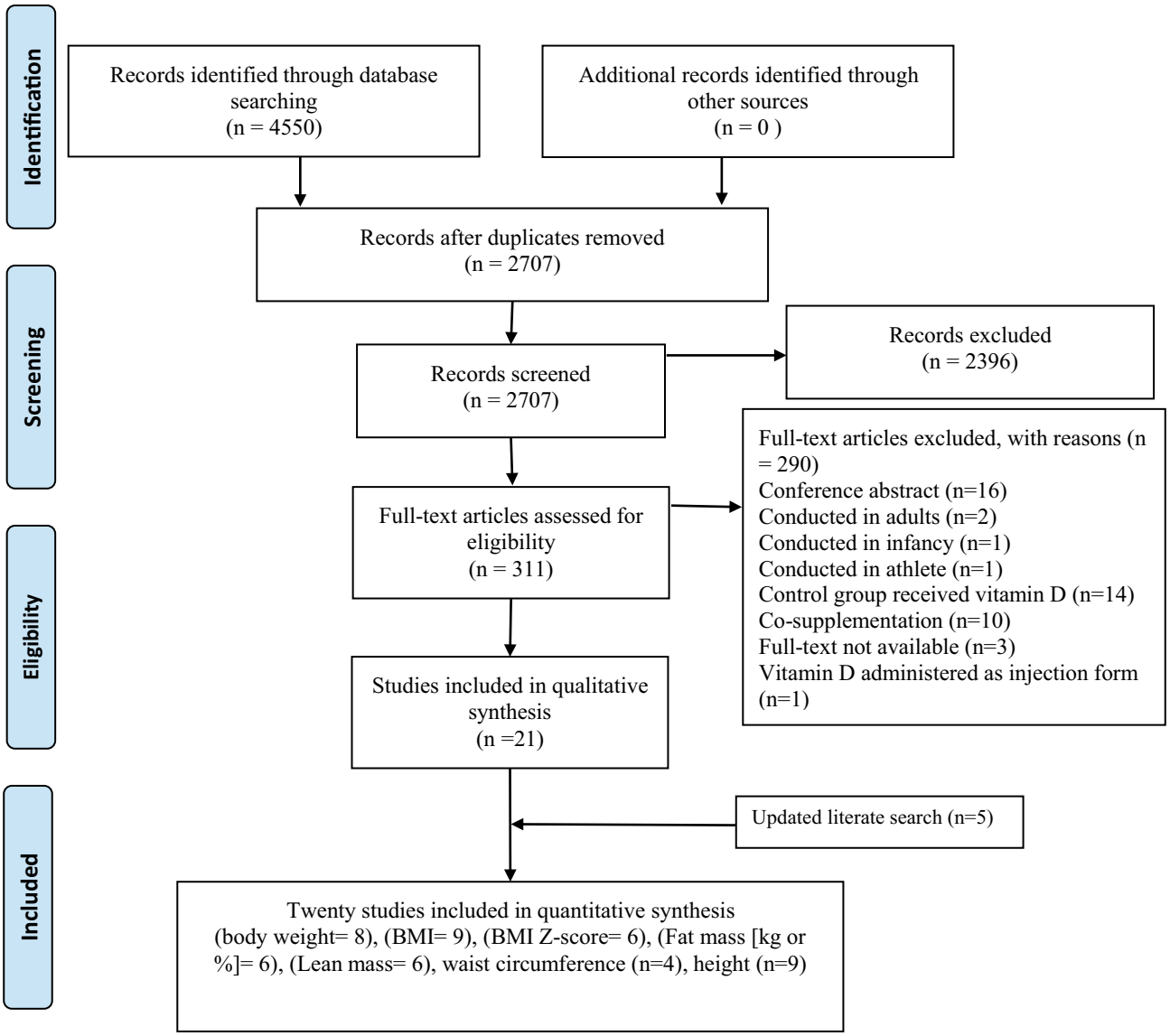

Fig. 1 Study screening process

Table 2 Meta-analysis showing the overall analysis

Outcome	Number of studies	Meta-analysis		Heterogeneity		
		WMD[a] (95% CI)	*P* effect	*Q* statistic	*P* within group	I^2 (%)
Weight (kg)	756 (8)	0.22 (−0.11, 0.55)	0.19	6.86	0.44	0
BMI (kg/m^2)	1029 (9)	−0.43 (−0.79, −0.08)	0.02	19.27	0.01	58.5
BMI *Z*-score	9435 (6)	0.00 (−0.02, 0.02)	0.82	4.14	0.54	0
Fat mass (kg)	9138 (4)	0.02 (−0.05, 0.08)	0.61	0.42	0.48	0
Fat mass (%)	9075 (5)	−0.54 (−1.40, 0.31)	0.21	3.8	0.12	44.5
Lean mass (kg)	9192 (6)	−0.01 (−0.25, 0.23)	0.92	4.43	0.25	24.2
Height (cm)	1088 (9)	0.12 (−0.06, 0.30)	0.21	15.36	0.08	41.4
Waist circumference (cm)	297 (4)	−0.37 (−1.25, 0.51)	0.41	1.50	0.68	0

[a]*WMD* weighted mean difference

BMI body mass index

Table 3 Meta-analysis showing the effect of vitamin D supplementation on body weight (kg) by subgroups

Study group	Number of Studies	WMD[1] (95% CI)	*P* effect	*Q* statistic	*P* within	I^2 (%)	*P* between-group
Sex							0.11
Girls	3	0.56 (0.001, 1.13)	0.050	2.18	0.34	8.3	
Both	5	−0.003 (−0.43, 0.42)	0.99	2.02	0.73	0	
Continent							0.22
Asia	2	0.19 (−0.38, 0.77)	0.50	0.01	0.923	0	
Europe	3	0.57 (0.03, 1.11)	0.04	2.10	0.35	4.7	
South US	1	−4.26 (−15.27, 6.70)	0.45	0	–	–	
North US	2	−0.26 (−0.90, 0.38)	0.43	0.28	0.60	0	
Vitamin D type							0.891
D2	2	0.25 (−1.89, 2.39)	0.82	0.03	0.868	0	
D3	6	0.24 (−0.18, 0.67)	0.26	6.83	0.23	26.8	
Study duration							0.11
Short period (≤24 weeks)	3	0.001 (−0.42, 0.43)	0.99	1.40	0.70	0	
Long period (>24 weeks)	5	0.54 (0.03, 1.05)	0.04	2.93	0.57	0	
Vitamin D deficiency							0.11
Yes	2	−0.02 (−0.50, 0.46)	0.93	1.21	0.27	17.4	
No	6	0.54 (0.04, 1.05)	0.03	2.94	0.71	0	
Calcium supplementation							0.72
Yes	2	−0.34 (−3.57, 2.89)	0.83	0.54	0.463	0	
No	6	0.25 (−0.14, 0.64)	0.22	6.20	0.29	19.4	
Vitamin D fortification							0.09
Yes	2	−0.26 (−0.90, 0.38)	0.43	0.28	0.60	12.4	
No	6	0.39 (−0.01, 0.77)	0.04	3.67	0.60	0	
Vitamin D dose							0.09
Low dose (≤600 IU/day)	5	0.55 (0.04, 1.06)	0.03	2.85	0.58	0	
High dose (>600 IU/day)	3	−0.02 (−0.44, 0.41)	0.94	1.21	0.55	0	
Health status							0.07
Healthy participants	6	0.40 (0.02, 0.78)	0.04	3.01	0.70	0	
Unhealthy	2	−0.30 (−0.95, 0.35)	0.36	0.5	0.48	0	
Seasonal variation consideration							0.07
Yes	7	0.39 (0.01, 0.78)	0.04	3.70	0.72	0	
No	1	−0.29 (−0.94, 0.36)	0.38	0	–	–	
Study quality							0.87
Fair	4	0.28 (−0.36, 0.92)	0.39	6.13	0.11	0	
Poor	4	0.21 (−0.35, 0.77)	0.46	0.73	0.87	0	

CI = −0.05, 0.08; $P = 0.61$; $I^2 = 0.0\%$, *P*-heterogeneity = 0.48) [36, 51, 61, 71] (Table 2, Supplemental Fig. 3). Subgroup analyses were not performed due to the small number of effect sizes.

Lean mass Meta-analysis of six studies found vitamin D supplementation had no significant effect on lean body mass [36, 51, 54, 61, 67, 71] ($n = 9192$ participants; WMD = −0.01 kg, 95% CI = −0.25, 0.23; $P = 0.92$; $I^2 = 24.2\%$, *P*-heterogeneity = 0.25) (Table 2, Supplemental Fig. 4a). Subgroup analyses were not performed due to the small number of effect sizes.

Waist circumference Meta-analysis of four studies showed vitamin D supplementation had no significant effect on waist circumference ($n = 297$ participants; WMD = −0.37 cm; 95% CI = −1.25, 0.51; $P = 0.41$; $I^2 = 0.0\%$; *P*-heterogeneity = 0.68) [58, 63, 67, 68] (Table 2, Supplemental Fig. 4b). Subgroup analyses were not performed due to the small number of effect sizes.

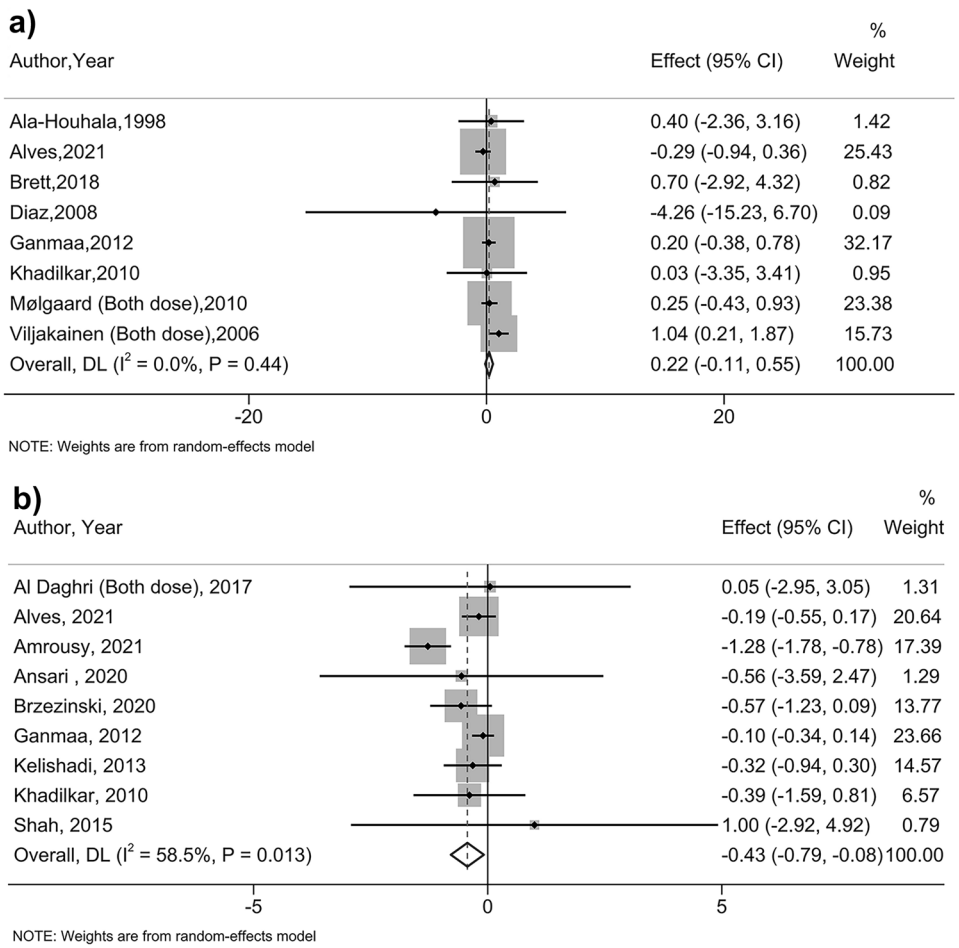

Fig. 2 Meta-analysis showing the effect of vitamin D supplementation on **a** weight (kg) and **b** BMI (kg/m^2) in children and adolescent (all analyses were conducted using a random-effects model). Both dose: high and low dose were combined

Sensitivity analysis and publication bias

Sensitivity analysis showed that the effect of vitamin D supplementation on body weight was sensitive to the study by Alvez et al. [67]. Omitting this study from the main analysis led to an increase in body weight following vitamin D supplementation (WMD = 0.39 kg, 95% CI = 0.01, 0.78; $P = 0.04$; $I^2 = 0\%$, P-heterogeneity = 0.71). The assessment of publication bias was not performed due to the low number of studies (< 10 studies).

Qualitative analysis

Three studies examined the effect of vitamin D supplementation on fat mass index (FMI) [70], fat-free mass index (FFMI) [70], height for age Z-score [69, 71], hip circumference [68], waist-to-height ratio [67], skinfold indices [67], waist-to height ratio Z-score [71], and waist circumference Z-score [66] in children. These parameters were not significantly changed in the vitamin D treatment group in comparison to the placebo [66–71].

Discussion

The findings of the present systematic review and meta-analysis showed that vitamin D supplementation significantly decreased BMI, while it had no significant effect on height, fat mass, and lean body mass, in a pediatric population. Vitamin D supplementation also showed a non-significant increase in body weight, which was significant when Alves et al. [67] was removed from the analysis. Subgroup analyses also indicated that an increase in body weight was evident in studies enrolled healthy children, studies that controlled for seasonal fluctuation, and when dosage of vitamin D supplementation was administered up to 600 IU/day.

The exact biological pathway through which vitamin D affects growth is not clear; however, the link between vitamin D and GH/IGF-1 may explain the effect of vitamin D on growth [72]. Vitamin D seems to increase the hepatic secretion of IGF-1 and its binding protein (IGFBP-3) and the expression of IGF-1 receptors in different tissues [73, 74]. It has also been posited that vitamin D may stimulate GH

secretion through modulating the expression of genes related to skeletal growth [75]. Sensitivity analysis revealed that the Alvez et al. study affected the results of overall analysis for body weight, as removing this study changed the overall effect size from non-significant to a significant increase in body weight. This study was conducted among obese vitamin D-deficient children with hypertriacylglycerolemia. As shown in the forest plot (Fig. 2a), only in two studies [54, 67] did vitamin D supplementation elicit a decrease in body weight. Both of these studies [54, 67] were conducted among participants suffering from a non-communicable disease (leukemia in Diaz et al. study [54] and hypertriacylglycerolemia in Alves et al. study [67]), while participants of the other included RCTs were healthy. Therefore, as confirmed by subgroup analysis, although vitamin D supplementation could yield a significant increase in body weight in a healthy pediatric population, the presence of a concurrent health problem seems to interfere with this effect. Also, the presence of obesity and vitamin D deficiency in the Alvez et al. study makes the situation more complicated and may also have a role in the different results.

Although change in body weight may be used as a proxy of change in body fat in adults, it is not applicable in children and adolescents [72], largely because they are experiencing physiological growth which is accompanied by a simultaneous increases in weight and height. The observed increased body weight in the current study mainly seems to be associated with increased skeletal weight. Although we did not find any significant change in height, a previous meta-analysis also showed no significant change in linear growth following vitamin D supplementation in children under 5 years of age [73]; however, length/height-for-age Z-score was improved slightly, which was not examined in the present study due to inadequate data. Nevertheless, it should be noted that, in RCTs, raw measures could also be acceptable, as the anthropometric measures are compared with a standard control group. It may be that a longer period of supplementation is needed to observe significant increases in linear growth. Moreover, it has been reported that single micronutrient supplementation can result in non-significant benefits on linear growth [74]. On the other hand, linear growth rate differs in various age groups [75]. However, in our study, we found no significant association between the age of participants and our outcome measures, as inferred by meta-regression analysis (data not shown).

Interestingly, we found a decreasing effect of vitamin D on BMI. This finding may be associated with the BMI formula, where body weight (kilograms) is divided by height squared (meters) and gives greater prominence to height. In contrast, we found no significant change in BMI *Z*-score. Altogether as no comparisons were judged to have a high-quality of evidence, a firm conclusion cannot be drawn, and further studies may change the present results.

We also found that vitamin D supplementation could increase body weight in studies used lower doses of vitamin D. All of the studies in this subgroup recruited children with adequate baseline vitamin D, suggesting that supplementation with the recommended dose of vitamin D (600 IU) or lower is sufficient to exert its beneficial effects on the growth in children and adolescents with normal vitamin D status. However, the smaller number of trials contributed data to the higher dose of vitamin D supplementation subgroup (3 trials) than to the lower dosage subgroup (5 trials), meaning that the analysis is unlikely to produce useful findings.

Seasonal fluctuation was controlled in all the included studies investigating the effect of vitamin D supplementation on body weight, except one [67]. Some evidence has suggested that the expression of receptors and vitamin D-modulated genes displays a seasonal variability [76–78]. The gene expression associated with vitamin D receptor is at its lowest level in winter [76]. Moreover, there is some evidence indicating seasonal variation in PTH, where in colder environments, it was increased [79–81]. Our subgroup analysis also showed a significant increase in body weight if seasonal fluctuation was controlled. However, one trial contributed data to the second subgroup (the study that did not control seasonal fluctuation), so the covariate distribution is concerning for this subgroup analysis.

To our knowledge, this is the first meta-analysis investigating the effect of oral vitamin D supplementation on anthropometric measures in children and adolescents. We did not define prespecified outcomes to ensure we retrieved all relevant publications. The quality of methodology and evidence was also assessed using standard tools. Furthermore, the between-study heterogeneity was low for the most outcomes, indicating lack of serious inconsistency in our findings.

There are also some limitations that should be kept in mind while interpreting the findings. One limitation was the low methodological quality of some included RCTs, mostly due to lack of information for allocation concealment, blinding, and sequence generation.

Furthermore, anthropometric measures were reported as a secondary outcome in most of the included trials [48, 50, 54, 55, 57–63], potentially making it difficult to detect a significant difference. The change in levels of serum 25 (OH) D was not measured throughout the included studies, thereby precluding identification of whether the 25OHD level actually changed in response to vitamin D supplementation. Finally, some potential confounder variables, for example, baseline weight status, physical activity, and intake of other micronutrients that influence growth (zinc, iron, calcium), were not reported in some of the included studies, rendering it impossible to perform subgroup analysis in this regard.

Conclusion

The findings of the present systematic review and meta-analysis suggest that vitamin D supplementation may lead to a statistically significant weight gain in children and adolescents, while BMI was reduced. Although no significant change was observed in height, it seems that vitamin D supplementation may elicit changes by increasing skeletal growth, although this remains to be verified. Further high-quality RCTs, including more detailed anthropometric measures and growth indices, are needed to yield more certain evidence in this regard.

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Authors' contributions SS and SA: designed the review; SS and SBR: conducted major database search according to search strategy; SRB and SA did data extraction; SS and SA: performed analysis; MA and SS and CC and SA: wrote the manuscript's draft; and all authors: evaluated the final version of the manuscript precisely and approved it.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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