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Review

Effects of vitamin D supplementation in obese and overweight children and adolescents: A systematic review and meta-analysis

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ABSTRACT

Due to the lipophilic nature of vitamin D, overweight and obese patients have an increased risk of inadequate circulating 25-hydroxy-vitamin D (25(OH)D) concentrations. Vitamin D deficiency has in turn several consequences especially among children and adolescents. Therefore, a few supplementation strategies of vitamin D for pediatric subjects with an excessive body weight have been proposed, but their efficacy remains controversial. The aim of this systematic review and meta-analysis was to evaluate the effect of vitamin D supplementation in overweight and obese children and adolescents. Three databases (PubMed, Embase and Web of Science) were searched to collect trials on the effect of vitamin D supplementation in the pediatric overweight or obese population. Twenty-three studies were included in the systematic review. Results on modification of metabolic or cardiovascular outcomes were controversial. On the other hand, the meta-analysis showed a mean difference by 1.6 ng/ml in subjects supplemented with vitamin D as compared to placebo. In conclusion, vitamin D supplementation slightly increases 25(OH)D levels in pediatric subjects with overweight and obesity. However, the effects on metabolic and cardiovascular outcomes remain controversial. New efforts should be devoted to promoting effective interventions to improve the health of children and adolescents with overweight and obesity.

1. Introduction

Obesity has a significant impact on vitamin D status and metabolism, and obese children and adolescents are known to be at risk of vitamin D insufficiency or deficiency [1]. Research has shown an inverse relationship between circulating 25-hydroxy-vitamin D (25(OH)D), which is currently used to denote overall vitamin D status, and body composition [2,3]. This relationship is mainly due to the lipophilic nature of this hormone, which causes its dilution in the adipose tissue and unavailability for biological functions [2,4]. Other possible mechanisms for low 25(OH)D circulating levels in obese children include insufficient dietary intakes, and especially reduced sun exposure, impaired renal function and increased catabolism caused by hepatic steatosis [2,3,5].

In turn, hypovitaminosis D may worsen the metabolic profile of obese children and adolescents. Circulating 25(OH)D is positively correlated with insulin sensitivity. As a result, it is plausible that obese children who have a poor vitamin D status could be more susceptible to the development of impaired glucose metabolism [1]. Furthermore, circulating 25(OH)D levels seem to be inversely related to the prevalence of hypertension, dyslipidemia and atherosclerosis, factors directly associated with the risk of a subsequent metabolic syndrome [6,7].

It is unclear whether routine supplementation of vitamin D is capable of restoring normal circulating 25(OH)D levels in obese individuals [9–11]. Moreover, inconsistent results on the relationship between

Abbreviations: 25(OH)D, 25-hydroxy-vitamin D.

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vitamin D supplementation and the decrease of cardiovascular risk factors (e.g. elevated inflammatory markers) in childhood obesity are available [7,9,10]. Accordingly, there are no univocal recommendations for vitamin D supplementations in these subjects [9,10].

The primary aim of this study was to assess the effect of vitamin D supplementation on vitamin D status in overweight and obese children and adolescents. The secondary aim was to systematically evaluate the effect of vitamin D supplementation on health outcomes of these patients.

2. Materials and methods

This review was performed according to the 2020 PRISMA guidelines [11] and preregistered on PROSPERO database (CRD42022370699). Differently from the original protocol, we included a few additional secondary outcomes, and sub-analyses were modified according to data available after article selection and their quality assessment. The detail on the differences (and reasons for deviations) between the original pre-registered protocol and the current review are reported in the supplementary online material (supplementary Table 1). The literature search was conducted in three different databases (PubMed, Embase and Web of Science), using the following search string: (Vitamin D OR 25 (OH)D OR cholecalciferol) AND (obese OR overweight) AND (randomized OR trial OR RCT OR intervention) AND (children OR infant OR pediatric OR adolescent).

2.1. Systematic review

Eligible were interventional trials evaluating the effects of vitamin D supplementation in obese or overweight children and adolescents, in any formulation and regardless of the dose or duration. We excluded studies including subjects < 1 year of age, with < 15 subjects or not reporting data on the changes in 25(OH)D circulating levels. Studies focused on individuals with acute or chronic conditions (e.g., endogenous obesity associated to Cushing's disease) were also excluded.

The following data were extracted from each included study: first author, year of publication, country of the trial, study design, sample size, characteristics of the participants (including obese/overweight/normal weight status of participants), dose, formulation and duration of vitamin D supplementation, duration of follow-up, outcomes. The 25 (OH)D circulating levels at the baseline and after intervention, the mean differences and standard deviation were also collected. Definitions of overweight and obesity provided by the original reports were retained.

Researchers in pairs independently assessed for eligibility relevant articles, extracted data and evaluated the quality of the included studies using the Cochrane Risk of Bias Tool [12]. Controversies in study selection, data extraction and quality assessment were resolved by discussion, or involving third researcher if consensus was not reached.

2.2. Meta-analysis

A formal meta-analysis including only randomized and placebo-controlled trials with mean 25(OH)D levels at baseline and at the end of the intervention was conducted. In case of missing data relevant for the meta-analysis, the corresponding author of the paper was tentatively contacted by email. Studies comparing overweight/obese children with normal weight children were not included in the meta-analysis.

Data extracted for the meta-analysis included the number of arms and participants per each arm, the dose of the intervention, vitamin D baseline levels and after the intervention in each arm.

The comparison of mean vitamin D values among the intervention group and the placebo group was expressed as standardized mean difference from the retrieved articles and a pooled standardized mean difference was calculated for mean vitamin D value at baseline and after intervention among the groups. The standardized mean difference serves as a summary statistic in meta-analyses of continuous data, where homogeneity in outcomes is anticipated, but differences in measurement are likely. Under such conditions, it is crucial to normalize the study findings to a common scale before integrating them. Consequently, the standardized mean difference is favored over the mean difference.

A random effects model was used for statistical pooling of data. Pooled data represented weighted averages which were mainly related to the sample size of the individual studies. Pooled results were presented with 95% confidence intervals (95%CI) and displayed using forest plots. Subgroup analyses taking into account different vitamin D dose (limited to studies providing $\leq$2000 IU/d of vitamin D) and risk of bias assessment (limited to studies with low risk of bias) were carried out. An I-square test was also performed to test for heterogeneity between studies (significant heterogeneity was defined for a I-square value was $> 50\%$). For publication bias evaluation, Egger's test was used ($p < 0.05$ = significant publication bias). Statistical analyses were performed using OpenMeta(analyst) statistical software (Brown University, Providence, RI, USA).

The certainty of evidence (high, moderate, low, and very low) obtained through the meta-analysis was rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

3. Results

The literature search process is reported in Fig. 1.

3.1. Systematic review

Table 1 reports the characteristics of the 23 articles included in our systematic review. The studies included were conducted in the following countries: eleven in the United States of America (USA), three in Iran, two in India and one in each other single country (Finland, France, Greece, Italy, Korea, Poland, and Sri Lanka).

Thirteen studies investigated the supplementation of vitamin D exclusively in adolescents [8,13,15,21–25,27,30,31,33,34], while one study involved only children [26]. Seven studies included both children and adolescents [14,17–19,28,29,32]. Two studies included both adolescents and young adults [16,20]. Based on the findings from the 23 studies, the total sample size consisted of 1959 participants. Six studies included > 100 subjects [14,17,19,27,31,33]. Ten out of the twenty-three studies compared one or more vitamin D supplementations to placebo [8,15–17,20,23,25,29,30,34], while the remaining studies compared different amounts of supplementation or just evaluated a single dosage.

Six studies compared overweight/obese to normal-weight subjects in their final analysis, finding substantial differences in term of treatment response in the two groups [13,18,20,26,31,32]. Seven studies included both obese and overweight patients [8,14,16–18,27,28], while the other sixteen studies involved only obese patients.

Twelve studies considered vitamin D deficiency or insufficiency as inclusion criterion [8,16,18,19,24,26–32]. Most of the studies provided only mean values of 25(OH)D levels, while one provided only median values [34]. After being contacted, the corresponding author of this article provided mean values at baseline and at end of the intervention. Two studies analyzed data on the change in vitamin D in each group, but not baseline and post treatment values [21,25].

Several types of vitamin D supplementation dosages and posology were used. Sixteen studies provided a daily administration of vitamin D, while other studies compared weekly, monthly or single administrations. Among their intervention groups, thirteen studies provided an amount of vitamin D $>$ 20,000 IU per week [8,15,16,22,23,28–34]. Apart from one study [8], all trials providing a mean amount of vitamin D $>$ 20,000 IU per week found a relevant increase in 25(OH)D levels among obese subjects. No adverse effects directly relatable to any supplementation were reported.

In addition to the vitamin D/calcium status, most studies included other metabolic or cardiovascular outcomes among their main

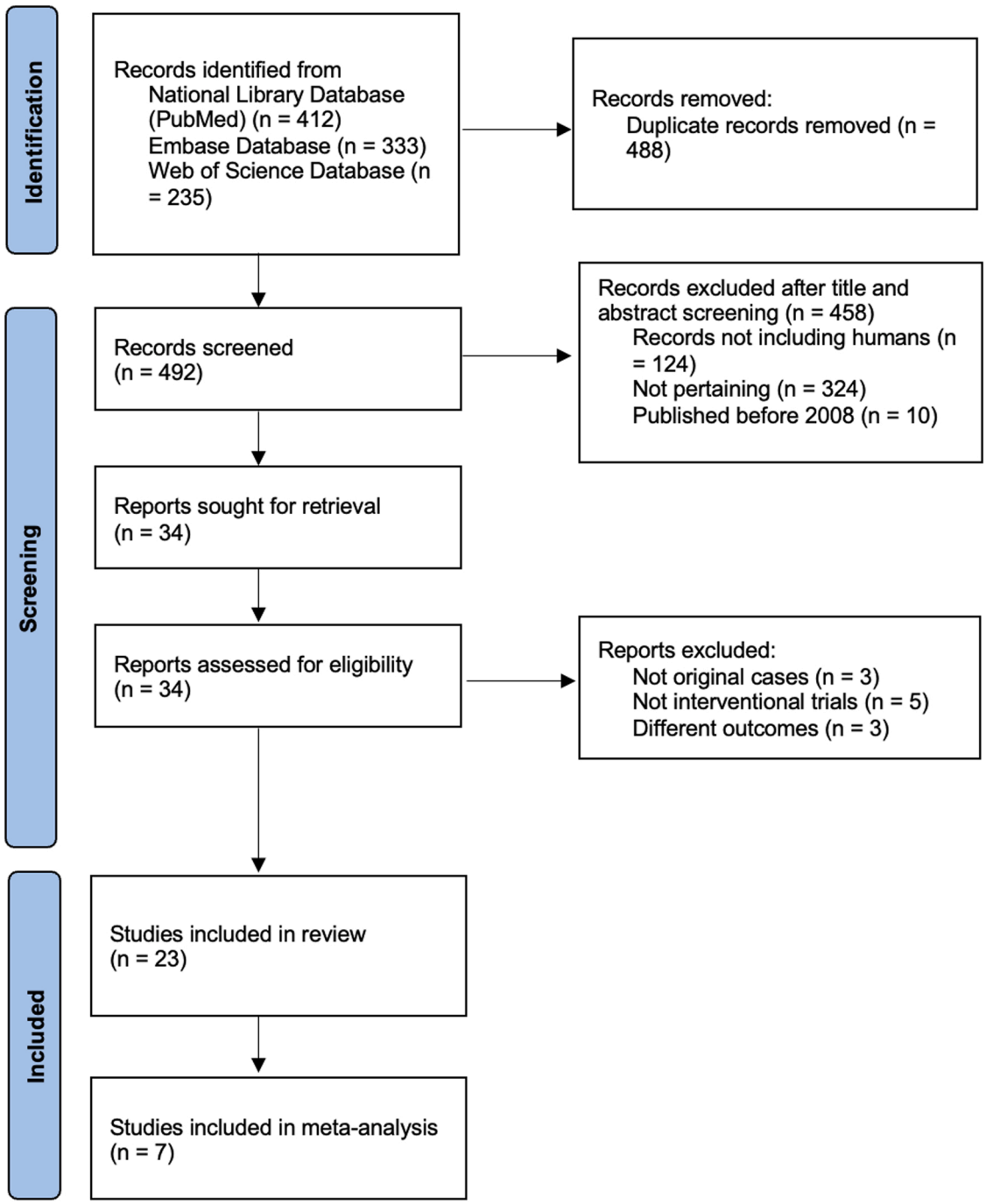

Fig. 1. PRISMA flow diagram.

endpoints. A comparison of cardiovascular risk markers and an evaluation of the lipid status at the end of the intervention was performed in sixteen trials [8,17–19,21–25,27–30,32–34]. Insulin sensitivity/resistance, fasting circulating insulin or homeostasis model assessment for insulin resistance (HOMA-IR) index were evaluated in 13 studies [15,19,21–25,27–30,33,34]. Among these studies, six of them found a positive effect of vitamin D supplementation on fasting insulin or HOMA-IR [15,23,27,28,30,34]. The results of risk of bias assessment are given in the supplementary online material. Six studies presented a low risk of bias [8,18,20,22,29,32] (Supplementary Table 2).

3.2. Meta-analysis

A total of seven studies were included in meta-analysis. At baseline, as expected, there was not a significant difference in the mean vitamin D values among the treatment group and the placebo group (−0.252 ng/l; 95%CI: −0.653 to 0.150; Supplemental Fig. 1). After the intervention, the pooled circulating vitamin D standardized mean difference among treatment and control groups was 1.596 ng/l (95%CI: 0.598–2.595, Fig. 2). A significant heterogeneity was found (>90%), while no significant publication bias based on Egger's test was observed ($p > 0.05$).

A sub-analysis with the exclusion of groups receiving ≤ 2000 IU/d of vitamin D was conducted to assess the wide heterogeneity of the studies. Fig. 3 shows that this heterogeneity also persists in this sub-analysis

Table 1
Studies investigating vitamin D supplementation in obese/overweight children and adolescents.

References (authors, year of publication, country)	Subjects/Study design	Intervention (vitamin D supplementation or placebo)	Total duration of supplementation / follow-up[a]	Main findings
Aguirre Castaneda et al. 2012, USA [13]	36 adolescents (n = 18 obese, n = 18 normal weight) / open label non-randomized trial	2000 IU/d	12 weeks / 12 weeks	The mean baseline 25(OH)D level was higher in the normal weight compared to obese individuals. The increase in 25(OH)D levels following vitamin D supplementation was significantly lower in adolescents with obesity. Circulating phosphorus and parathyroid hormone levels did not change. A not clinically meaningful change in circulating calcium levels was observed.
Asghari et al. 2021, Iran [14]	378 overweight/obese children and adolescents (n = 120 group 1, n = 127 group 2, n = 131 group 3) / randomized controlled trial	600 IU/d (group 1), 1000 IU/d (group 2), 2000 IU/d (group 3)	12 months / 12 months	After 12 months, increases in 25(OH)D concentrations were greater in participants with overweight compared to those with obesity. Serum 25(OH)D concentrations were significantly higher in group 2 and 3 than in group 1 at both 6 and 12 months (both p values < 0.01). Furthermore, there were significant differences in 25(OH)D concentrations between group 2 and group 3. No effect on calcium, phosphorus, iPTH suppression, and ALP was found.
Belenchia et al. 2013, USA [15]	35 obese adolescents (n = 18 group 1, n = 17 placebo group) / randomized controlled trial	4000 IU/d (group 1), or placebo	6 months / 6 months	After 3 months, no subjects in group 1 had vitamin D deficiency. At six months, 93% of subjects in group 1 had sufficient levels of vitamin D. In placebo group, the 25(OH)D levels did not significantly increase over time. Group 1 showed lower levels of insulin (but not of glucose and glycosylated hemoglobin) at six months as compared to placebo group. No difference in BMI, and inflammatory markers was found.
Bhagatwala et al. 2015, USA [16]	70 overweight/obese adolescents and young adults with vitamin D deficiency (n = 17 group 1, n = 18 group 2, n = 18 group 3, n = 17 placebo group) / randomized controlled trial	600 IU/d (group 1), 2000 IU/d (group 2), 4000 IU/d (group 3), or placebo	16 weeks / 16 weeks	Monthly supplementation with both 2000 IU and 4000 IU of vitamin D appeared to be comparable and effective in achieving a 25(OH)D level of 30 ng/ml, unlike a daily dose of 600 IU. Supplementation with 4000 IU resulted in a more rapid optimization of vitamin D status. Modification in parathyroid hormone levels were observed but not in fibroblast growth factor-23, phosphorus and urinary calcium.
Brzeziński et al. 2020, Poland [17]	152 overweight and obese children and adolescents (n = 85 group 1, n = 67 placebo group) with vitamin D insufficiency / randomized control trial	1200 IU/d (group 1), or placebo	26 weeks / 12 months	Although the supplementation had an impact on 25(OH)D levels, only six patients in the intervention group achieved a level above 30 ng/ml at the end of follow-up. No effect was observed on BMI.
Chung et al. 2019, Korea [18]	62 children and adolescents (n = 21 obese/overweight, n = 41 normal weight) with vitamin D deficiency / single arm trial	2000 IU/d	8 weeks / not specified	Supplementation with 2000 IU/d was sufficient to overcome vitamin D deficiency in normal-weight and overweight children without any complications. However, 64% in normal weight vs 48% in overweight group reached sufficient levels of vitamin D. In the overweight group, circulating levels of phosphorus and BMI-z score decreased after intervention, but no difference was found for calcium, PTH, total cholesterol, triglycerides, HDL and LDL blood levels.
De Cosmi et al. 2022, Italy [19]	108 obese children and adolescents with vitamin D deficiency. They all received dietary guidance and were randomized in 2 groups to receive or not also docosahexaenoic acid supplementation	1200 IU/d in both groups	6 months / 6 months	More than 50% of the subjects showed an improvement in their vitamin D status. Fat mass percentage and body mass index were reduced in both groups after the intervention.
Holmlund-Suila et al. 2016, Finland [20]	18 obese and 24 normal-weight adolescents and young adults (n = 19 group 1, n = 21 placebo group)	2000 IU/d or placebo	12 weeks / 12 weeks	Obese young adults exhibited lower total and free 25(OH)D concentrations. The response of free 25(OH)D to supplementation did not differ between obese and normal-weight subjects, while total 25(OH)D was significantly lower in the obese group. No effects in vitamin D binding protein, parathormone, calcium, phosphate and osteocalcin circulating levels were observed.

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Table 1 (*continued*)

References (authors, year of publication, country)	Subjects/Study design	Intervention (vitamin D supplementation or placebo)	Total duration of supplementation / follow-up[a]	Main findings
Javed et al. 2015, USA [21]	51 obese adolescents (n = 25 group 1, n = 26 group 2) with vitamin D insufficiency / randomized controlled trial	400 IU/d (group 1) or 2000 IU/d (group 2)	12 weeks / 12 weeks	There was a modest but significant increase in 25(OH)D concentration in the group 2, but not in the group 1. Four subjects in group 1 and 6 in group 2 achieved 25(OH)D levels ≥ 30 mg/L. No effect was observed on insulin action and β-cell function
Javed et al. 2016, USA [22]	19 obese adolescents with vitamin D insufficiency / single arm trial	100,000 IU once a month	3 months / 3 months	The supplementation was effective in increasing 25(OH)D levels in obese adolescents but did not influence endothelial function. No changes in circulating and urinary calcium levels were found
Kelishadi et al. 2014, Iran [23]	43 obese adolescents (n = 21 group 1, n = 22 placebo group) / randomized controlled trial	25,000 IU once a week (group 1) or placebo	12 weeks / 12 weeks	After the supplementation, only the group receiving vitamin D showed a significant increase in vitamin D levels. Furthermore, circulating triglyceride and insulin decreased. No difference was observed for total cholesterol, LDL-C, HDL-C, fasting blood glucose, and blood pressure.
Magge et al. 2018, USA [24]	26 obese adolescents (n = 12 group 1, n = 14 group 2) with vitamin D deficiency / randomized controlled trial	1000 IU/d (group 1), 5000 IU/d (group 2)	12 weeks / 12 weeks	Circulating 25(OH)D increased less in group 1 than in group 2 (30% vs 83%, respectively, reached levels ≥ 20 ng/ml). No difference in mineral metabolites or cardiometabolic risk markers were observed after the intervention.
Nader et al. 2014, Greece [25]	58 obese adolescents (n = 20 group 1, n = 24 placebo group) / randomized controlled trial	2000 IU/d (group 1) or placebo	12 weeks / 12 weeks	Vitamin D supplementation resulted in a modest (median 6 ng/ml), but significant increase in 25(OH)D levels. Circulating glucose, insulin, lipids and highly sensitive C-reactive protein were not modified after intervention.
Rajakumar et al. 2008, USA [26]	41 children (n = 21 obese, n = 20 normal weight) with vitamin D deficiency / non-randomized pre-post intervention	400 IU/d	1 month / 1 month	Treatment response effects were different in obese and in normal-weight cohorts. In obese children with vitamin D deficiency, the intervention did not raise blood levels of 25 (OH)D to levels ≥ 30 ng/ml. No difference in circulating calcium, phosphorus, albumin, parathormone, bone-specific ALP was observed.
Rajakumar et al. 2020, USA [27]	225 overweight/obese adolescents (n = 76 group 1, n = 74 group 2, n = 75 group 3) with vitamin D deficiency / randomized controlled trial	600 IU/d (group 1), 1000 IU/d (group 2), 2000 IU/d (group 3)	6 months / 6 months	A dose-response in vitamin D levels was observed at 3 and 6 months. PTH concentrations were lower at 3 months in group 1, at 6 months in group 2, and at 3 and 6 months in group 3. The three regimens of supplementation did not influence endothelial function, arterial stiffness, systemic inflammation, or lipid profile, but resulted in lower blood pressure and glucose levels and higher insulin sensitivity.
Rostampour et al. 2020, Iran [28]	53 overweight/obese children and adolescents with vitamin D deficiency / single arm trial	50,000 IU weekly for 8 weeks, and then 1000 IU/d for 3 months.	5 months / 5 months	The intervention significantly increased circulating vitamin D levels in obese and overweight children. BMI and circulating glucose but not insulin resistance decreased after the intervention.
Samaranayake et al. 2020, Sri Lanka [29]	96 obese children and adolescents (n = 32 group 1, n = 33 group 2, n = 31 placebo group) with vitamin D deficiency / randomized controlled trial	50,000 IU per week (group 1), 2500 IU per week (group 2), placebo (group 3)	24 weeks / 24 weeks	Baseline to 6 months increase in vitamin D levels in group 1 was significantly higher than that of group 2 and group 3. There was no significant difference in vitamin D levels between group 2 and 3. A significant, dose-dependent, effect was observed in the reduction of biceps SFT. Baseline to 6 months BMI-SD score, triceps and suprailiac SFT, WC-SD score, percentage fat mass, serum parathyroid hormone, LDL, AST, AST/ALT ratio and insulin resistance showed no statistical difference.
Sethuraman et al. 2018, USA [30]	29 obese adolescents (n = 15 group 1, n = 14 placebo group) with vitamin D deficiency / randomized controlled trial	50,000 IU per week (group 1) or placebo	12 weeks / 12 weeks	A significant increase in vitamin D levels in the interventional group compared to placebo was observed, but no difference was observed for insulin- or lipid-related parameters.
Shah et al. 2015, USA [8]	31 overweight/obese adolescents (n = 17 group 1, n = 14 placebo group) with vitamin D insufficiency / randomized controlled trial	150,000 IU at baseline and after 12 weeks (group 1) or placebo	12 weeks / 24 weeks	Supplementation with vitamin D did not increase circulating 25(OH)D or influence inflammatory and cardiovascular markers. No effect was observed on BMI, ALP and iPTH.

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Table 1 (*continued*)

References (authors, year of publication, country)	Subjects/Study design	Intervention (vitamin D supplementation or placebo)	Total duration of supplementation / follow-up[a]	Main findings
Talib et al. 2016, USA [31]	40 obese and 82 normal-weight adolescents (n = 39 group 1, n = 41 group 2, n = 42 group 3) with vitamin D deficiency / randomized controlled trial	50,000 IU per week (group 1), 5000 IU/d (group 2), 1000 IU/d (group 3)	8 weeks / 8 weeks	Both high-dose treatments (group 1 and 2) were more effective than low dose (group 3) to increase 25(OH)D levels to ≥ 20 ng/ml. In group 1 and 2 > 80% of participants were not vitamin D deficient after supplementation (vs 60% in group 3).
Tayde et al. 2021, India [32]	44 normal weight and obese children and adolescents (n = 22 obese, n = 22 normal-weight) with vitamin D deficient / non randomized trial	150,000 IU, single oral dose	Single dose / 1 month	Obese children have a 2.2 times lower rise in circulating 25(OH)D levels as compared with the normal BMI children. No significant effect on iPTH levels was observed, but ALP levels were higher in obese children.
Varshney et al. 2019, India[33]	189 obese adolescents (n = 96 group 1, n = 93 group 2) / randomized controlled trial	120,000 IU one a month (group 1), 12,000 IU once a month (group 2)	12 months / 12 months	Higher dose of vitamin D was associated with a higher increase in circulating 25(OH)D levels. Vitamin D deficiency persisted in 32% subjects in group 1% and 90% in group 2. No relevant effect was observed on β cell function, cardiovascular risk factors, circulating PTH, glucose and insulin.
Vinet et al. 2021, France [34]	26 obese adolescents (n = 13 group 1, n = 13 placebo; a lifestyle program was proposed to both groups) 23 normal-weight adolescents / randomized controlled trial	4000 IU/d (group 1), or placebo	3 months / 3 months	Circulating 25(OH)D concentrations raised above 20 ng/ml in all obese adolescents, especially in those receiving vitamin D supplements. Insulin resistance decreased more in group 1 than in placebo group, while C-reactive protein decreased similarly in the two groups. Endothelium- dependent microvascular reactivity increased only in group 1.

25(OH)D = 25-hydroxy-vitamin D; iPTH = intact parathyroid hormone; BMI= body mass index; SD = standard deviation; HDL= high-density lipoprotein; LDL= low-density lipoprotein, ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine transaminase; SFT = skinfold thickness; WC = Waist circumference.

[a] Duration of follow up- after the first administration of the supplementation/placebo.

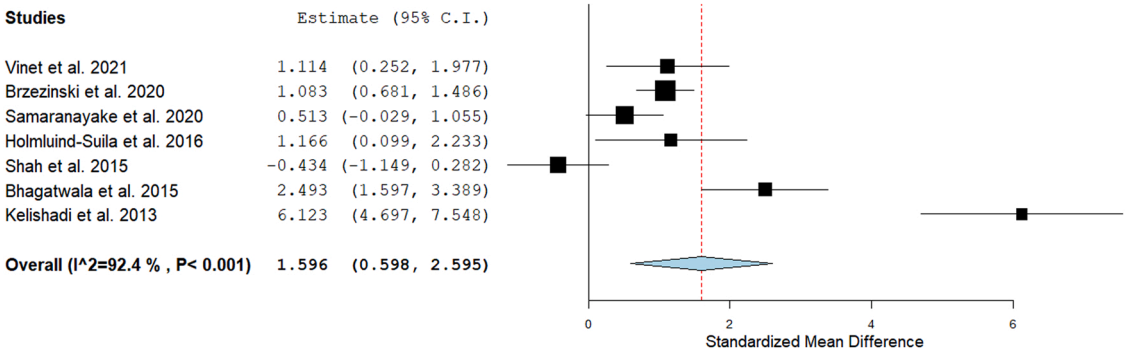

Fig. 2. Meta-analysis and forest plot about pooled standardized mean difference of circulating vitamin D values between treatment group and control group after the intervention. The area of the squares indicates the weight of each study in the analysis.

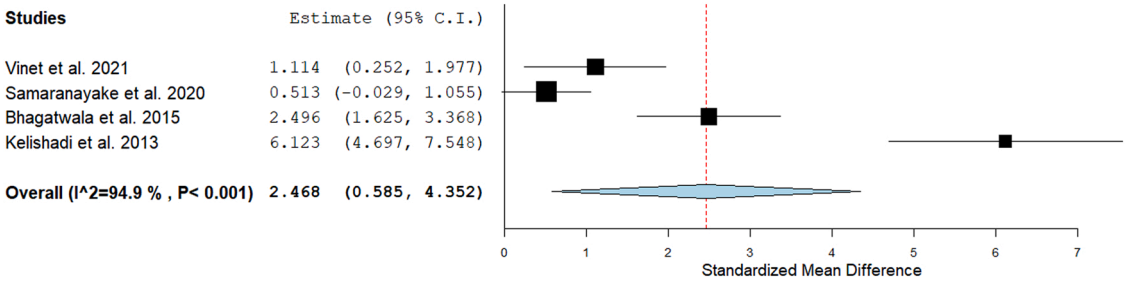

Fig. 3. Subgroup meta-analysis and forest plot (excluding arms providing ≤2000 IU/d of vitamin D) about pooled standardized mean difference of circulating vitamin D values between intervention group and control group after treatment. The area of the squares indicates the weight of each study in the analysis. The present sub-analysis included only one of the three intervention arms investigated by Bhagatwala et al., as the daily dosage of vitamin D supplementation was limited to ≤ 2000 IU in the other two arms.

considering a reduced variety of supplementations as well, and that just a slight reduction of the I^2 was observed.

Similarly, a relevant heterogeneity (70%) persisted limiting the meta-analysis to the studies with low risk of bias (supplementary Fig. 2).

The results of GRADE are provided within the online supplementary material (supplementary Table 3).

4. Discussion

This study investigated the effects of vitamin D supplementation on children and adolescents with overweight or obesity. This analysis found a mean increase by 1.6 ng/ml in vitamin D levels in subjects treated with a vitamin D supplementation as compared to controls. On the other hand, data on the clinical effects of vitamin D supplementation (e.g., on the reduction of cardiovascular risk) appear inconclusive.

A previous similar systematic review on the role of vitamin D supplementation in deficient children with and without obesity conducted in 2017 and including a total of six studies, did not find any evidence of vitamin D improvement among children treated with a vitamin D supplementation vs placebo [35]. Conversely, vitamin D supplementation was notably more effective in non-obese than in obese children [35]. This analysis revealed that vitamin D supplementation effectively raised vitamin D levels in overweight and obese children and adolescents. On the other hand, the clinical relevance of such an increase deserves some further considerations. Despite the statistically significant difference of 1.6 ng/ml in vitamin D levels after supplementation, the percentage of obese children who transitioned to a vitamin D sufficiency condition was relatively low in some of the included studies. In one study [13], only 50% of obese children (against 89% of non-obese) experienced normalization of vitamin D values. Similarly, in another study [18], after 8 weeks of treatment with 2000 UI/d, only 48% of overweight children achieved vitamin D sufficiency, compared to the 62% of normal-weight ones. By contrast, in another study [14], more than 90% of obese children who received 2000 IU/d achieved a vitamin D level $>$ 20 ng/ml. Similarly, another study including subjects with vitamin d deficiency found that 83% of subjects supplemented with 5000 IU/d and 30% of those supplemented with 1000 IU/d for 3 months reached levels of 25 (OH)D $\geq$ 20 ng/ml [24]. Finally, supplementations with 50,000 IU/week and 5000 IU/d were both effective in increasing above 20 ng/ml, the levels of 25(OH)D in over 80% of participants, with 72% and 56% of individuals in the respective groups achieving levels above 30 ng/ml [31].

According to the Italian Pediatric Society guidelines [36], vitamin D supplementation in obese children and adolescents should be performed at higher doses than those recommended for age (1000–1500 IU daily) from the end of fall to the beginning of spring, or throughout the year in case of reduced summer sun exposure. These recommendations are partially supported by some of the studies included in this systematic review.

To further explore both the heterogeneity observed in our meta-analysis and the possible role of the dosage of vitamin D used for supplementation, we performed a sub-analysis of the studies providing $>$ 2000 IU of vitamin D per week. This analysis did not significantly reduce the heterogeneity. Yet, it found that the mean difference between subjects treated with vitamin D and placebo increased up to 0.8 ng/ml, thus suggesting a role, despite limited, of the dosage chosen for the supplementation.

Several hypotheses might explain the difficulty of increasing vitamin D levels in these subjects. The supplemented vitamin D might dilute in adipose tissue [1,2]. Moreover, the limited sunlight exposure and low consumption of vitamin D-rich food products that frequently occur in this population, might further contribute keeping low levels of circulating 25(OH)D levels [1,2].

Inadequate levels of vitamin D have the potential to impact various aspects of health, including cardiovascular well-being [37]. Studies evaluating cardiovascular risk markers first assumed that improving vitamin D levels could reduce this risk [8,17–19,21–25,27–30,32–34]. One of the studies included in this review found that participants receiving 4000 IU/d of vitamin D for 6 months had significant improvements in HOMA-IR and Quantitative Insulin-Sensitivity (QUICKI), considered as two surrogate markers of insulin resistance and sensitivity [15]. Similarly, serum insulin and triglyceride concentrations, as well as HOMA-IR and C-Met, decreased significantly in another supplemented group [23]. In another study [27], there were reductions in BP and fasting glucose concentration, with improvements in the insulin sensitivity. By contrast, two studies found no detectable changes in cardiovascular risk factors including inflammatory markers [25,33].

A positive impact of vitamin D supplementation on insulin homeostasis was found in six studies [15,23,27,28,30,34]. These results are in line with some data from adults, which suggest an inverse correlation between 25(OH)D serum levels and insulin resistance [38,39]. Inflammatory cytokine production, which is considered one of the main mechanisms influencing insulin resistance, might be modulated by circulating vitamin D. Moreover, vitamin D seems to be involved in insulin secretion and function [38].

A previous analysis pooling data from normal weight and obese individuals with and without comorbidities, pointed out a potential effect of vitamin D supplementation on body weight and body mass index of children and adolescents [40]. The results of our review are partially inconsistent on this issue. Brzeziński et al. found no effect of vitamin D supplementation on body weight reduction in children with vitamin D insufficiency undergoing a weight management program [17]. By contrast, Chung et al. [18] found that BMI, BMI z-score, and body fat markers improved after intervention. De Cosmi et al. [19] also found that fat mass percentage was significantly reduced in supplemented patients, while body mass index improved in both groups, even if all the subjects were still obese at the end of the study.

The main limitation of this review was the heterogeneity and low number of included studies. These factors preclude the possibility of further exploring the potential role of other factors such as the age of the subjects, the severity of overweight/obesity, and the role of seasonal variations, which could potentially affect the results of vitamin D supplementation [41,42]. A further limitation is related to the fact that two studies included also young adults [16,20]. However, a sub analysis excluding these studies did not show any relevant difference on the effect of vitamin D supplementation (data not shown).

5. Conclusions

This is the most updated systematic review and meta-analysis on the effects of vitamin D supplementation in children and adolescents with obesity and overweight. Supplementation with vitamin D significantly increases 25(OH)D levels, but its effect appears of limited clinical relevance. Data on the effects on metabolic and cardiovascular outcomes remain controversial.

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CRediT authorship contribution statement

Antonio Corsello: Conceptualization, Methodology, Investigation, Writing – original draft. **Marina Macchi:** Methodology, Investigation, Writing – original draft. **Veronica D'Oria:** Investigation. **Chiara Pigazzi:** Investigation. **Ilaria Alberti:** Significant contribution in their area of expertize, Writing – review & editing. **Giorgio Treglia:** Methodology. **Valentina De Cosmi:** Significant contribution in their area of expertize, Writing – review & editing. **Alessandra Mazzocchi:** Significant contribution in their area of expertize, Writing – review & editing. **Carlo Agostoni:** Conceptualization, Writing – review & editing,

Supervision. **Gregorio Paolo Milani:** Conceptualization, Methodology, Writing – original draft, Supervision. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.106793.

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