

Review Paper

Effect of Vitamin D Supplementation on Serum Lipid Profiles in Children and Adolescence: A Meta-analysis



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ABSTRACT

Background: Vitamin D deficiency is an important risk factor for some chronic diseases. Some reports suggested that there is an interrelationship between lipids and cholecalciferol.

Objectives: This meta-analysis was conducted to summarize the existing evidence of randomized controlled trials (RCTs) to evaluate the effect of vitamin D supplementation on lipid profiles in children and adolescents.

Methods: In this systematic review and meta-analysis, databases, such as Web of Science, PubMed, Scopus, Google Scholar, EMBASE, ScienceDirect, Magiran, and SID were searched for studies up to December 21, 2019. This study was conducted according to PRISMA guidelines. I-square was used to measure the existing heterogeneity through included articles. Considering heterogeneity among articles, random-effect models were applied to pool Standardized Mean Differences (SMD) as overall effect size. Study eligibility criteria included children and adolescents (<18 years) and evaluation of the association between vitamin D and lipid profile. A $P < 0.05$ was considered statistically significant and the analyses were conducted by STATA 14.0.

Results: A total of 13 trials (number of participant=173) were included in the current meta-analysis. The SMD was 0.23, the vitamin D supplementation was associated with a significant slight increase in high-density lipoproteins (HDL) levels in children and adolescents (SMD 0.23; 95% CI, 0.02, 0.45, $P=0.036$; $I^2=57.7\%$, Egger's $P=0.554$). We found no significant association between vitamin D supplementation and LDL-cholesterol (SMD -0.10; 95% CI, -0.29, 0.09, $P=0.310$; $I^2=0.0\%$, Egger's $P=0.689$), total cholesterol (SMD -0.01; 95% CI, -0.20, 0.18, $P=0.926$; $I^2=0.0\%$, Egger's $P=0.005$), and triglycerides (SMD -0.10; 95% CI, -0.22, 0.02, $P=0.093$; $I^2=0.0\%$, Egger's $P=0.160$) levels.

Conclusions: Vitamin D can marginally increase HDL levels, without any significant effect on LDL-C, TG, and TC levels.

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1. Introduction

Chronic diseases and their nascent risk factors begin in the early years of life; thus, early prevention of disease from childhood could halt the nascent activity (1). Amongst non-communicable diseases, cardiovascular diseases display significant morbidity and mortality (2). The early onset of atherosclerosis in addition to the other risk factors of cardiovascular diseases, such as dyslipidemia will continue to persist in adulthood, and cause a host of other diseases (3). Due to continued lipid deposition and proliferation of smooth muscle and connective tissue, fatty streaks and fibrous plaques increase in size and extent and some undergo qualitative changes (4). The most serious change is rupture, which exposes the blood to lipid-rich thrombogenic material and precipitates an occlusive thrombus, which in turn leads to myocardial infarction or sudden cardiac death (5).

Vitamin D deficiency is a major global health problem and is an important risk factor for diabetes, cancer, dyslipidemia, and Cardiovascular Disease (CVD) (6-8). Hypovitaminosis D is a risk factor for glucose intolerance and the impairment in the functional regulation of pancreatic β -cells. Vit D supplementation in early infancy can reduce the subsequent risk of type 1 diabetes by about 30% (9, 10). Vitamin D has a significant role in children and adolescents, including the prevention of infectious diseases, immune-related diseases (type 1 diabetes and asthma), cardiovascular disease, and the onset of osteomalacia and rickets (11). Vitamin D receptors exist in more than 36 tissues of the body; hence, vitamin D actions will expand over almost all cell systems and organs (e.g., immune cells, brain, colon, prostate, and breast) (12). Vitamin D regulates phosphorus and calcium homeostasis, regulates blood pressure, and modification of immune competence, and minimizes the propensity for autoimmune diseases, infectious diseases, and risk of cancer (13). Some reports suggested that there is an interrelationship between lipids and cholecalciferol. A pathway that produces a common substrate 7-dehydrocholesterol (7-DHC) in the skin, synthesizes Cholecalciferol and cholesterol. After exposure to sunlight, 7-DHC is converted to previtamin D3 and then by a heat-dependent process to cholecalciferol. On the other hand, 7-DHC by the enzyme, 7-dehydrocholesterol reductase converts into cholesterol (14, 15). It is important to identify dyslipidemia early to stop the progression of cardiovascular disease and protect the future health of children (16). It is still difficult to find a strong theory for such a relationship, except if we know vitamin D supplementation's effect on serum lipids in placebo-controlled randomized cases.

Unfortunately, the associated studies had different consequences, which some indicate a positive effect (17), and others show a negative effect (14). To the best of our knowledge, there is no systematic review and meta-analysis of randomized controlled trials (RCTs) on the effect of vitamin D supplementation on serum lipid profiles in children and adolescents. This meta-analysis was conducted to summarize the existing evidence of RCTs to evaluate the impact of vitamin D supplementation on lipid profiles in children and adolescents.

2. Material and Methods

Databases and search strategy

This study was conducted according to PRISMA guidelines (18), and the study protocol was submitted to the Birjand University of Medical Sciences, Iran (Code: Ir.bums.REC.1398.68).

PICO question: children or adolescent (P), vitamin D (I), control group (C), lipids (Chol, LDL, VLDL, HDL, TG) (O), clinical trial (S)

For this systematic review and meta-analysis, an electronic search of the literature published up to December 21, 2019, was conducted in the English databases (i.e., Web of Science, PubMed, Scopus, Google Scholar, EMBASE, ScienceDirect, and Persian databases (i.e., Magiran, Scientific Information Database (SID)) by two authors (A.B & R.SM) independently, to identify all articles related to RCTs examining the effect of vitamin D supplementation on the blood lipid profile using the following search terms: Vitamin D or 25-hydroxyvitamin D or Vitamin D3 or Cholecalciferol or Ergocalciferol or Calcitriol or Calcidiol and Lipids or Cholesterol or Triglycerides or HDL or LDL or VLDL. Medical Subject Headings (MESH) and Embase Subject Headings (EMTREE) were used to developing a search strategy and for each database, the strategy was revised. Search strategies are detailed in Tables 1-5 (Supplementary).

Eligibility Criteria

Clinical trials were considered eligible if they were conducted among children and adolescents (<18 years), and had evaluated the association between vitamin D and lipid profile.

Study selection

Based on the eligibility criteria, two authors (A.B & R.SM) independently reviewed the titles and abstracts of search results. Any disagreements were resolved by

discussion. After the removal of duplicates, the full-text articles of potentially relevant publications were assessed to determine the final list of included studies. The excluded full-text articles were archived with the reasons for exclusion. The flow of the records was depicted in a PRISMA diagram.

Data extraction

Characteristics of the included studies were assessed by two authors (A.B & R.SM) independently using a standardized data collection form. The following data were extracted from the previous studies: first authors, year of publication, country, Follow-up (per week), age, gender, study design, the dosage of vitamin D supplementation, the sample size in control and intervention groups, comparison groups, and lipid profiles (i.e., total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG)).

Risk of bias assessment

We used the JBI (Joanna Briggs Institute) guidelines to evaluate the risk of bias in the included study by two authors (A.B & R.SM) independently. Any incongruities were resolved by discussion. The JBI guidelines have a total of 13 questions and the response options for each field were yes, no, unclear, and not available (NA) (19). Quality assessment of clinical trial studies concerning method and risk of bias included sequence generation, blinding, incomplete outcome data, allocation concealment, selective outcome reporting, and other sources of bias. Articles with quality scores <60% were considered with a high risk of bias and excluded.

Data synthesis and analysis

Measurement of the treatment effect

Random-effects meta-analysis models were used to estimate pooled standardized mean differences (SMDs) and 95% confidence intervals (CIs) for all outcomes, such as HDL, LDL, TG, and total cholesterol. The SMD was calculated by $(\mu_1 - \mu_2) / SD$, where μ_1 is the mean of the intervention group, μ_2 is the Mean of the control group, and SD is the pooled standard deviation. The standardized mean differences serve as an easy method to judge the magnitude of the effect, considering the general rules of thumb described by Cohen that suggest that SMD values of 0.2–0.5 are considered small, values of 0.5–0.8 are considered medium, and values >0.8 are considered large (20).

Assessment of heterogeneity

Statistical heterogeneity among studies was evaluated by statistical tests (i.e., Cochran Q and I² statistics). I² statistics is between 0 and 100 percent, and values of 60% or more were considered heterogeneous (21, 22).

Subgroups analysis, meta-regression, and sensitivity analysis

Subgroup analysis was performed on healthy and obese groups. Meta-regression analysis was conducted to explore covariates that might explain the heterogeneity between clinical trials (23). Meta-regression was conducted for qualitative covariates, such as daily intake of Vit D, publication year, and sample size. Sensitivity analyses were carried out for assessing the robustness of the findings based on primary analyses of data. We evaluated the influence of key assumptions, such as different methods of analysis, population study, protocol deviations, and outliers on the overall conclusions in all lipid profiles. The analyses were conducted by STATA 12.0 (Stata Corporation, College Station, TX, USA). All Statistical tests were two-sided, and a P<0.05 was considered statistically significant.

Assessment of publication biases

Publication bias was investigated by Egger's test to judge publication bias for each outcome.

3. Results

Characteristics of included studies

We identified 3931 publications after a thorough search of Web of Science, PubMed, Scopus, Google Scholar, EMBASE, ScienceDirect, Magiran, and SID databases. After screening titles and abstracts and removing duplicates, we reviewed the remaining 46 full-text articles for eligibility. Subsequently, 33 articles were excluded for the following reasons: only abstract available (n=5), data not usable (n=13), non-original studies e.g. reviews, letters, case reports, etc. (n=9), inappropriate design (n=2), and inappropriate outcomes (n=4). Lastly, 13 articles were retained for the analysis in our meta-analysis. Publication years of articles ranged from 2014 to 2019. Two articles had been conducted in Iran, one article in Saudi Arabia, two articles in America, three articles in Argentina, four articles in Denmark, and one article in Egypt. All trials had been conducted using parallel design. The sample size varied from 11 to 189 participants with an overall number of 1173 subjects. Characteristics

Table 1. Characteristics of the included studies in the meta-analysis

Author (Ref)	Publication Year	Country	Study Design	Dose	Gender	Age	Control	Outcomes	Treatment (n)	Control (n)	Quality Score (%)
Sethuraman et al. (28)	2018	America	Parallel	50000 weekly	Both	15.1±1.4	Placebo	Chol,LDL,HDL,TG	15	14	92.3
Magge et al. (45)	2018	America	Parallel	5000_1000 daily	Both	12-17.9	1000 unit	Chol,LDL,HDL,TG	14	10	100.0
Tavakoli et al. (46)	2016	Iran	Parallel	1000 daily	Both	11.5±1.7	Placebo	HDL	24	20	100.0
Al-Daghri et al. (47)	2019	Saudi Arabia	Parallel	1000 daily	Both	14.9±1.9	Placebo	HDL, TG	166	158	84.6
Hafez et al. (48)	2019	Egypt	Parallel	4000 daily	Both	12.7±3.6	Control	Chol,LDL,HDL,TG	30	20	84.6
Hirschler et al. (49)	2016	Argentina	Parallel	50000 monthly-2 months	Both	9.7±2.1	Control	TG,HDL	70	17	84.6
Hirschler et al. (49)	2016	Argentina	Parallel	50000 monthly-2 months	Both	9.7±2.1	Control	TG,HDL	25	11	92.3
Namakin et al. (50)	2015	Iran	Parallel	1000 daily	Both	10-14	Placebo	Chol , HDL,LDL	20	20	92.3
Smith et al. (51)	2018	Denmark	Parallel	400 daily	Both	14-18	Placebo	Chol, HDL,LDL	35	38	84.6
Smith et al. (51)	2018	Denmark	Parallel	800 daily	Both	14-18	Placebo	Chol, LDL,HDL	36	38	92.3
Hauger et al. (52)	2018	Denmark	Parallel	400 daily	Both	4-8	Placebo	Chol, LDL,HDL	42	41	76.9
Hauger et al. (52)	2018	Denmark	Parallel	800 daily	Both	4-8	Placebo	Chol, LDL,HDL	43	41	76.9
Hirschler et al. (53)	2014	Argentina	Parallel	100000_50000 monthly-2 months	Both	8.8±1.7	50000 unit	HDL,TG	189	36	76.9

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of the included studies are summarized in Table 1. Also, the study selection process by to the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA) is shown in Figure 1.

High-density lipoprotein cholesterol (HDL-C)

Twelve papers reported the HDL-C level of participants. Three studies showed a statistically significant increase in HDL-C levels with vitamin D supplementation. Also, four studies showed a not statistically significant reduction in HDL-C levels, and four studies did not show a sta-

tistically significant increase in LDL-C levels with vitamin D supplementation (Figure 2B). Using a random-effects model, the pooled results for lipid profiles showed that Vit D supplementation significantly increased HDL-C levels (SMD 0.23; 95% CI: 0.02, 0.45) (Table 2). As the heterogeneity of studies was moderate, we conducted a subgroup analysis between HDL-C levels among the healthy group and the obese group. The results demonstrated a constant trend in HDL-C levels by use of vitamin D supplementation. Besides, the results of subgroup analysis showed a significant increase in HDL-cholesterol levels among the healthy group (SMD 0.26; 95%

Table 2. The effects of vitamin D supplementation on lipid profiles with CI 95% using subgroup analysis

Variables	N	SMD (95% CI)	I2 (%)	Egger's P	P
TC	8	-0.01(-0.20-0.18)	0	0.005	0.926
LDL-C	7	-0.10(-0.29-0.09)	0	0.689	0.310
HDL-C	12	0.23(0.02-0.45)	57.7	0.554	0.036
TG	11	-0.10(-0.22-0.02)	0	0.160	0.093

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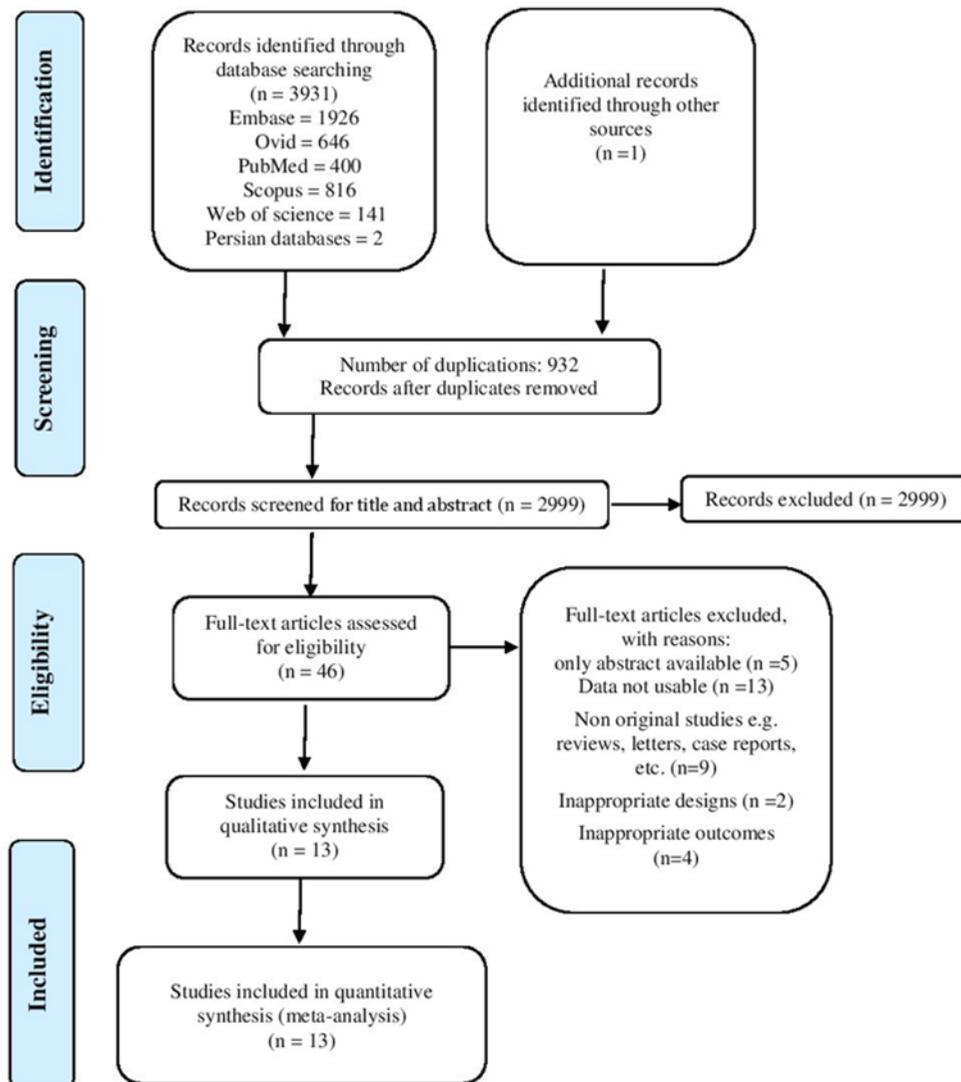


Figure 1. PRISMA flow diagram for exclusion and inclusion of studies in the meta-analysis

CI: 0.01, 0.50) than the obese group (SMD 0.23; 95% CI: 0.02, 0.45) (Figure 2C). Moreover, the meta-regression analysis demonstrated no significant association between the dosage of Vit D supplementation and HDL-C level ($b=-0.00005$, $P=0.38$) (Figure 3).

Low-density lipoprotein cholesterol (LDL-C)

Seven papers reported the LDL-C level of participants. Six studies disclosed a no significant reduction in LDL-C levels and one study no statistically significant increase in LDL-C levels with vitamin D supplementation (Figure 2A). We found no significant association between Vit D supplementation and LDL-C levels (SMD -0.10; 95% CI: -0.29, 0.09) (Table 2) Using the random-effect model. Furthermore, the meta-regression analysis demonstrated no significant association between the dosage of Vit D supplementation and LDL-C levels ($b=-0.00006$, $P=0.264$).

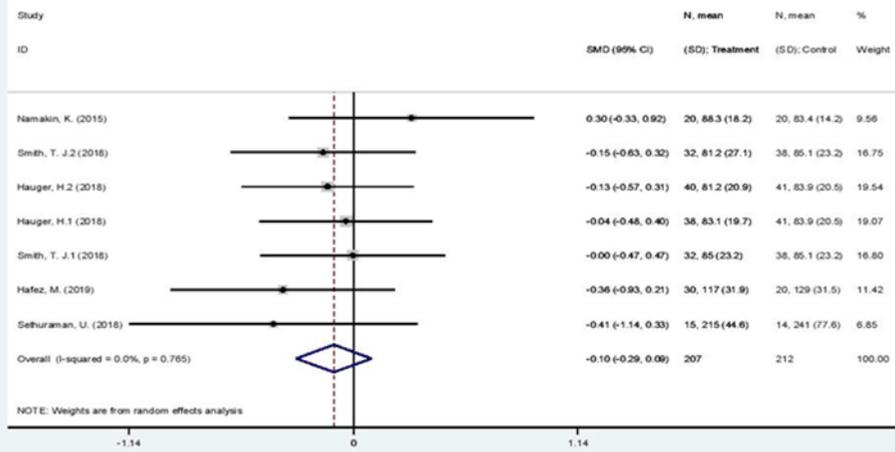
Total cholesterol (TC)

Eight papers reported the TC level of participants. Three studies showed no statistically significant reduction in TC levels and five studies showed no statistically significant increase in TC levels with vitamin D supplementation (Figure 2D). The result showed no significant association between Vit D supplementation and TC levels (SMD -0.01; 95% CI, -0.20, 0.18) using the random-effects model. Also, the meta-regression analysis demonstrated no significant association between the dosage of Vit D supplementation and TC levels ($b=0.00007$, $P=0.196$).

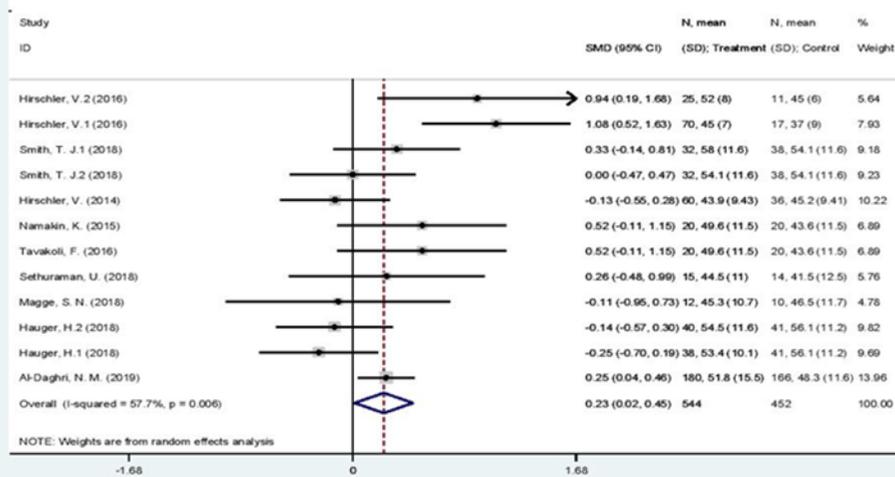
Triglycerides (TG)

Eleven papers reported on the TG level of participants. Eight studies showed a not statistically significant reduction in TG levels and three studies showed a statis-

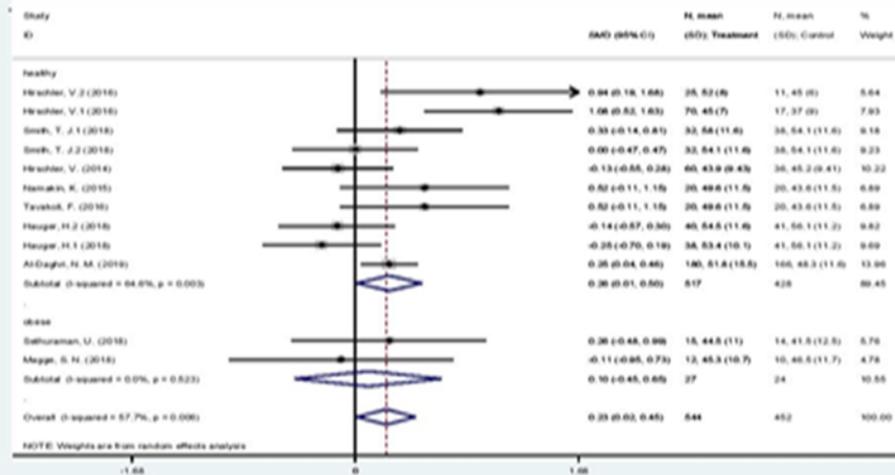
A-LDL



B-HDL



C-HDL



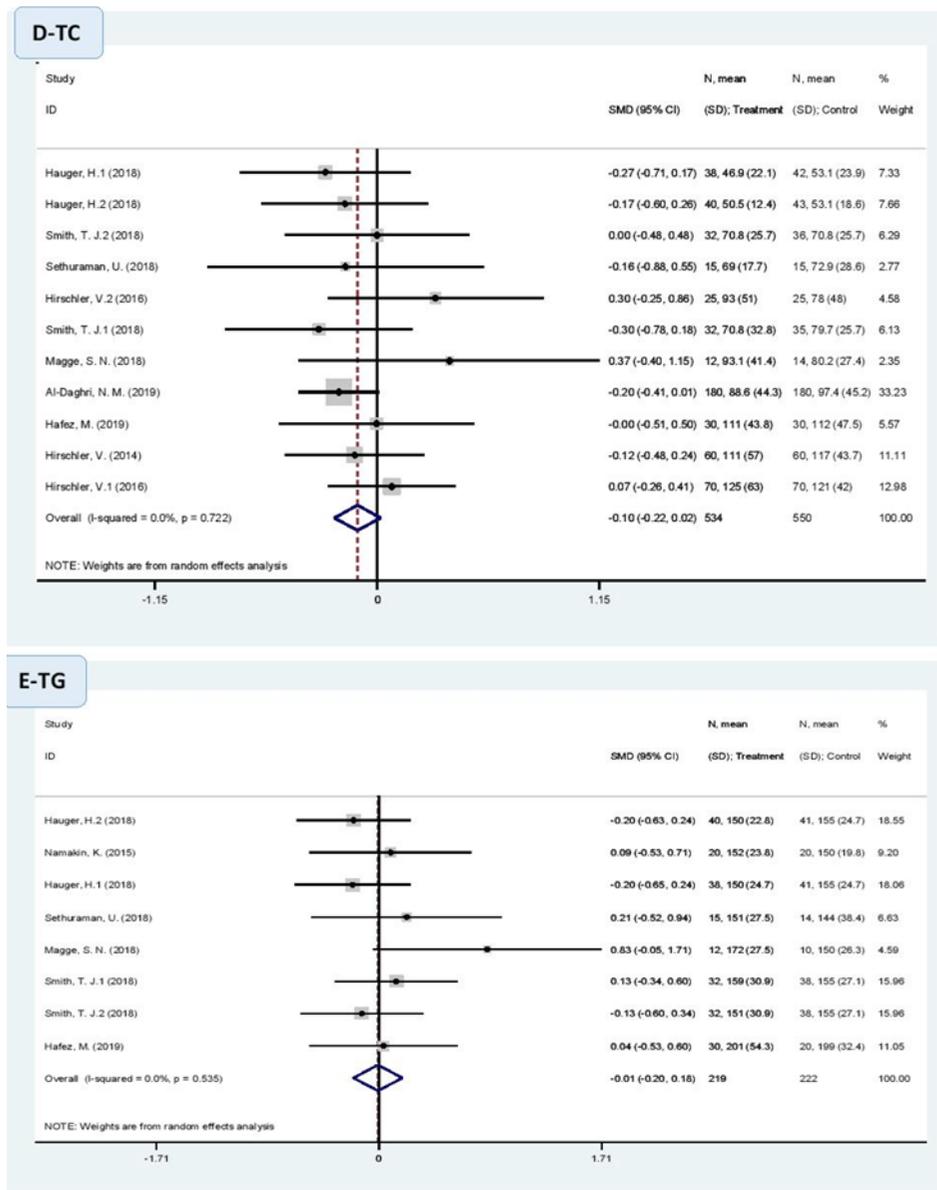


Figure 2. Meta-analysis of lipid profiles' standardized mean difference estimates (A) LDL-cholesterol, (B) HDL-cholesterol, (D) HDL-cholesterol between obese and healthy groups, (D) total cholesterol, and (E) triglycerides in the treatment and control groups (CI=95%). N: total sample size. Values are expressed as Mean±SD.

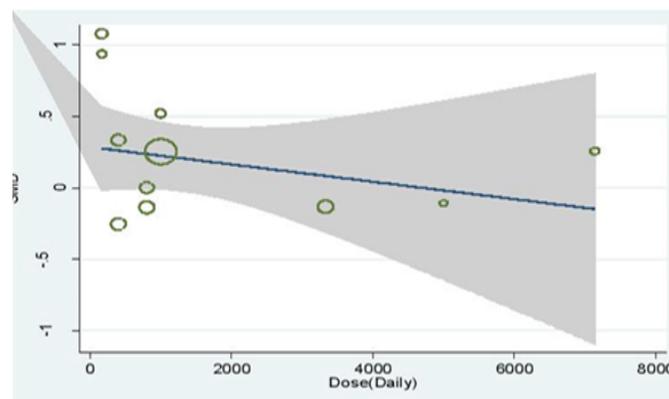


Figure 3. Meta-regression analysis of HDL-cholesterol in dosage of vitamin D supplementation

Table 1 (Supplementary). Search strategy in Web of Science database

Row	Search strings	Items found
#1	TS=(ketocholesterol*) OR TS=(hydroxycholesterol*) OR TS=(oxysterol*) OR TS=(cholesterol ester*) OR TS=(azacosterol) OR TS=(19 iodocholesterol) OR TS=(cholesterol*)OR TS=(triolein) OR TS=(triacetin) OR TS=(triglyceride*) OR TS=(HDL3 lipoprotein*) OR TS=(HDL2 lipoprotein*) OR TS=(pre beta high density lipoprotein*) OR TS=(HDL cholesterol*) OR TS=(HDL lipoprotein*) OR TS=(high density lipoprotein*) OR TS=(HDL) OR TS=(LDL lipoprotein*) OR TS=(LDL cholesterol) OR TS=(low density lipoprotein*)OR TS=(LDL) OR TS=(VLDL lipoprotein*) OR TS=(VLDL cholesterol*) OR TS=(very low density lipoprotein*) OR TS=(VLDL) OR TS=(LIPID*) OR TS=(lipid profile)	878,501
#2	TS=(vitamin D supplement*) OR TS=(vitamin D3) OR TS=(dihydroxycholecalciferol) OR TS=(hydroxycholecalciferol*) OR TS=(hydroxycholecalciferol) OR TS=(colecalfiferol) OR TS=(ergocalciferol*) OR TS=(ergocalciferol) OR TS=(25 hydroxyvitamin D3) OR TS=(25 hydroxyvitamin d2) OR TS=(vitamin D)	102,193
#3	TS=(neonate) OR TS=(TEEN*) OR TS=(teenager) OR TS=(children) OR TS=(toddler) OR TS=(preschool) OR TS=(adolescent) OR TS=(newborn) OR TS=(infant) OR TS=(child*) OR TS=(pediatric*)	2,401,441
#4	TS=(Clinical trial*) OR TS=(Randomized controlled trial*) OR TS=(Clinical study) OR TS=(Random allocation) OR TS=(Randomization)	2,139,644
#5	TS=(vitamin D supplement*) OR TS=(vitamin D3) OR TS=(dihydroxycholecalciferol) OR TS=(hydroxycholecalciferol*) OR TS=(hydroxycholecalciferol) OR TS=(colecalfiferol) OR TS=(ergocalciferol*) OR TS=(ergocalciferol) OR TS=(25 hydroxyvitamin D3) OR TS=(25 hydroxyvitamin d2) OR TS=(vitamin D) AND TS=(ketocholesterol*) OR TS=(hydroxycholesterol*) OR TS=(oxysterol*) OR TS=(cholesterol ester*) OR TS=(azacosterol) OR TS=(19 iodocholesterol) OR TS=(cholesterol*)OR TS=(triolein) OR TS=(triacetin) OR TS=(triglyceride*) OR TS=(HDL3 lipoprotein*) OR TS=(HDL2 lipoprotein*) OR TS=(pre beta high density lipoprotein*) OR TS=(HDL cholesterol*) OR TS=(HDL lipoprotein*) OR TS=(high density lipoprotein*) OR TS=(HDL) OR TS=(LDL lipoprotein*) OR TS=(LDL cholesterol) OR TS=(low density lipoprotein*)OR TS=(LDL) OR TS=(VLDL lipoprotein*) OR TS=(VLDL cholesterol*) OR TS=(very low density lipoprotein*) OR TS=(VLDL) OR TS=(LIPID*) OR TS=(lipid profile) AND TS=(neonate) OR TS=(TEEN*) OR TS=(teenager) OR TS=(children) OR TS=(toddler) OR TS=(preschool) OR TS=(adolescent) OR TS=(newborn) OR TS=(infant) OR TS=(child*) OR TS=(pediatric*) AND TS=(Clinical trial*) OR TS=(Randomized controlled trial*) OR TS=(Clinical study) OR TS=(Random allocation) OR TS=(Randomization)	141

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tically insignificant increase in TG levels with vitamin D supplementation (Figure 2E). The results show that, no significant association between Vit D supplementation and TG level (SMD -0.10; 95% CI, -0.22, 0.02) (Table 2) using a random-effects model. Also, The meta-regression analysis demonstrated no significant association between the dosage of Vit D supplementation and TG level (b=0.00001, P=0.791).

4. Discussion

Supplementation of Vit D can be effective on serum lipid profiles through direct and indirect mechanisms (14, 24). It has been suggested that vitamin D has a link to the onset of cardiovascular diseases, such as hypertension (HTN), and CVD through its diverse role in blood pressure control, endothelial function, calcification of the coronary vessels, and increased vascular resistance (25-27). This study was conducted to evaluate the effect of Vit D supplementation on lipid profiles in children and adolescents. The findings of the current systematic review and meta-analysis showed that Vit D supplementation had an increasing effect on HDL-C levels in children and adolescents, which was in line with the study by Sethuraman et al. (28). A systematic review and meta-analysis that examined the effect of calcium and Vit D co-supplementation on lipids concentrations in overweight/obese subjects revealed that Vit D and calcium

co-supplementation increased the blood concentrations of HDL-C (29). Another systematic review and meta-analysis conducted on adults indicated that lower doses of Vit D supplementation alone were effective in increasing HDL-C levels in a short period (30). A meta-analysis in 2017 among women with gestational diabetes revealed that Vit D supplementation had a beneficial effect on the levels of serum LDL; however, no effect was seen in the total cholesterol, HDL-C, or TG (31).

A meta-analysis of 17 cross-sectional studies noted that higher circulating levels of 25(OH) D are associated with a more favorable lipid profile in the pediatric group (32). Jorde et al. cross-sectional study on 8018 nonsmoking participants revealed significant positive associations between serum 25(OH)D and HDL-C, LDL-C, TC levels, and a significant negative association between serum 25(OH)D and TG levels after adjustment for age, gender, BMI, and month of blood sampling (33). Saedisomeolia et al. assessed 108 participants with T2D and demonstrated that serum levels of 25OHD had an inverse, but no significant association with TC and TG levels and a positive correlation with LDL-C and HDL-C levels after adjusting for confounding variables (25).

These studies are heterogeneous concerning the characteristics of subjects, Vit D dose, and study duration. Also, some common causes may be attributed to both

Table 2 (Supplementary). Search strategy in PubMed database

Row	Search strings	Items found
#1	TITLE-ABS-KEY (lipid*) OR TITLE-ABS-KEY (lipid AND profile) OR TITLE-ABS-KEY (vldl) OR TITLE-ABS-KEY (very AND low AND density AND lipoprotein*) OR TITLE-ABS-KEY (vldl AND cholesterol) OR TITLE-ABS-KEY (vldl AND lipoprotein*) OR TITLE-ABS-KEY (ldl) OR TITLE-ABS-KEY (low AND density AND lipoprotein*) OR TITLE-ABS-KEY (ldl AND cholesterol) OR TITLE-ABS-KEY (ldl AND cholesterol*) OR TITLE-ABS-KEY (ldl AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND lipoprotein*) OR TITLE-ABS-KEY (hdl) OR TITLE-ABS-KEY (high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND cholesterol*) OR TITLE-ABS-KEY (pre AND beta AND high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl2 AND lipoprotein*) OR TITLE-ABS-KEY (hdl3 AND lipoprotein*) OR TITLE-ABS-KEY (triglyseride*) OR TITLE-ABS-KEY (triacetin) OR TITLE-ABS-KEY (triolein) OR TITLE-ABS-KEY (cholesterol*) OR TITLE-ABS-KEY (19 lodocholesterol) OR TITLE-ABS-KEY (azacosterol) OR TITLE-ABS-KEY (cholesterol AND ester*) OR TITLE-ABS-KEY (oxysterol*) OR TITLE-ABS-KEY (hydroxycholesterol*) OR TITLE-ABS-KEY (ketocholesterol*)	1251688
#2	TITLE-ABS-KEY (vitamin AND d) OR TITLE-ABS-KEY (25 hydroxyvitamin AND d2) OR TITLE-ABS-KEY (coledalciferol) OR TITLE-ABS-KEY (25hydroxyvitamin AND d3) OR TITLE-ABS-KEY (hydroxycholecalciferol*) OR TITLE-ABS-KEY (ergocalciferol*) OR TITLE-ABS-KEY (dihydrotachystrol) OR TITLE-ABS-KEY (vitamind3) OR TITLE-ABS-KEY (vitamin AND d AND supplement*)	82859
#3	TITLE-ABS-KEY (pediatric*) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY (children) OR TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (adolescent) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (preschool) OR TITLE-ABS-KEY (toddler) OR TITLE-ABS-KEY (teenager) OR TITLE-ABS-KEY (teen*) OR TITLE-ABS-KEY (neonate)	3921254
#4	TITLE-ABS-KEY (clinical AND trial*) OR TITLE-ABS-KEY (randomized AND controlled AND trial*) OR TITLE-ABS-KEY (clinical AND study) OR TITLE-ABS-KEY (random AND allocation) OR TITLE-ABS-KEY (randomization)	5310025
#5	(TITLE-ABS-KEY (vitamin AND d) OR TITLE-ABS-KEY (25 hydroxyvitamin AND d2) OR TITLE-ABS-KEY (coledalciferol) OR TITLE-ABS-KEY (25hydroxyvitamin AND d3) OR TITLE-ABS-KEY (hydroxycholecalciferol*) OR TITLE-ABS-KEY (ergocalciferol*) OR TITLE-ABS-KEY (dihydrotachystrol) OR TITLE-ABS-KEY (vitamind3) OR TITLE-ABS-KEY (vitamin AND d AND supplement*)) AND (TITLE-ABS-KEY (lipid*) OR TITLE-ABS-KEY (lipid AND profile) OR TITLE-ABS-KEY (vldl) OR TITLE-ABS-KEY (very AND low AND density AND lipoprotein*) OR TITLE-ABS-KEY (vldl AND cholesterol) OR TITLE-ABS-KEY (ldl) OR TITLE-ABS-KEY (low AND density AND lipoprotein*) OR TITLE-ABS-KEY (ldl AND cholesterol) OR TITLE-ABS-KEY (ldl AND cholesterol*) OR TITLE-ABS-KEY (ldl AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND lipoprotein*) OR TITLE-ABS-KEY (hdl) OR TITLE-ABS-KEY (high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND cholesterol*) OR TITLE-ABS-KEY (pre AND beta AND high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl2 AND lipoprotein*) OR TITLE-ABS-KEY (hdl3 AND lipoprotein*) OR TITLE-ABS-KEY (triglyseride*) OR TITLE-ABS-KEY (triacetin) OR TITLE-ABS-KEY (triolein) OR TITLE-ABS-KEY (cholesterol*) OR TITLE-ABS-KEY (19 lodocholesterol) OR TITLE-ABS-KEY (azacosterol) OR TITLE-ABS-KEY (cholesterol AND ester*) OR TITLE-ABS-KEY (oxysterol*) OR TITLE-ABS-KEY (hydroxycholesterol*) OR TITLE-ABS-KEY (ketocholesterol*)) AND (TITLE-ABS-KEY (pediatric*) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY (children) OR TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (adolescent) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (preschool) OR TITLE-ABS-KEY (toddler) OR TITLE-ABS-KEY (teenager) OR TITLE-ABS-KEY (teen*) OR TITLE-ABS-KEY (neonate)) AND (TITLE-ABS-KEY (clinical AND trial*) OR TITLE-ABS-KEY (randomized AND controlled AND trial*) OR TITLE-ABS-KEY (clinical AND study) OR TITLE-ABS-KEY (random AND allocation) OR TITLE-ABS-KEY (randomization))	394

the high serum Vit D levels and favorable lipid profile. Individuals who exercise routinely and eat nutritious food would have increased Vit D levels, and also, may have other healthy habits that could positively affect lipid profiles. The widespread difference in the quantity and formulation of supplemental Vit D may be the most important contributor to the heterogeneity found in our results (34, 35).

In our study, there was no significant association between Vit D supplementation and LDL-C, TC, and TG levels, while our results are not similar to other findings. A meta-analysis of RCTs that evaluated the effects of vitamin D supplementation on blood lipids, showed that Vit D supplementation provided a statistically sig-

nificant increase in LDL-C. There was also a tendency to an increase in TC with supplementation of Vit D and the reductions in HDL-C and TG both were non-significant (35). Another meta-analysis in type 2 diabetics showed that Vit D supplementation lowered LDL-c and total cholesterol levels but had no positive effect on HDL-C and TG levels (36). Al-Daghri et al. demonstrated that Vit D supplementation lowered TG, LDL-C, and total cholesterol levels (37), whereas Manoy et al. reported that HDL-C and LDL-C improved after supplementation but total cholesterol and TG were not different (38). According to Zitterman et al. and Martins et al., Vit D might decrease serum TG and it is well-identified that the clearance of VLDL may lead to increased levels of LDL-C and HDL-C. Moreover, it is possible that the binding of

Table 3 (Supplementary). Search strategy in Scopus database

Row	Search strings	Items found
#1	TITLE-ABS-KEY (lipid*) OR TITLE-ABS-KEY (lipid AND profile) OR TITLE-ABS-KEY (vldl) OR TITLE-ABS-KEY (very AND low AND density AND lipoprotein*) OR TITLE-ABS-KEY (vldl AND cholesterol) OR TITLE-ABS-KEY (vldl AND lipoprotein*) OR TITLE-ABS-KEY (ldl) OR TITLE-ABS-KEY (low AND density AND lipoprotein*) OR TITLE-ABS-KEY (ldl AND cholesterol) OR TITLE-ABS-KEY (ldl AND cholesterol*) OR TITLE-ABS-KEY (ldl AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND lipoprotein*) OR TITLE-ABS-KEY (hdl) OR TITLE-ABS-KEY (high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND cholesterol*) OR TITLE-ABS-KEY (pre AND beta AND high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl2 AND lipoprotein*) OR TITLE-ABS-KEY (hdl3 AND lipoprotein*) OR TITLE-ABS-KEY (triglyseride*) OR TITLE-ABS-KEY (triacetin) OR TITLE-ABS-KEY (triolein) OR TITLE-ABS-KEY (cholesterol*) OR TITLE-ABS-KEY (19 lodocholesterol) OR TITLE-ABS-KEY (azacosterol) OR TITLE-ABS-KEY (cholesterol AND ester*) OR TITLE-ABS-KEY (oxysterol*) OR TITLE-ABS-KEY (hydroxycholesterol*) OR TITLE-ABS-KEY (ketocholesterol*)	1,139,965
#2	TITLE-ABS-KEY (vitamin AND d) OR TITLE-ABS-KEY (25 hydroxyvitamin AND d2) OR TITLE-ABS-KEY (coledalciferol) OR TITLE-ABS-KEY (25hydroxyvitamin AND d3) OR TITLE-ABS-KEY (hydroxycholecalciferol*) OR TITLE-ABS-KEY (ergocalciferol*) OR TITLE-ABS-KEY (dihydrotachystrol) OR TITLE-ABS-KEY (vitamind3) OR TITLE-ABS-KEY (vitamin AND d AND supplement*)	139,253
#3	TITLE-ABS-KEY (pediatric*) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY (children) OR TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (adolescent) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (preschool) OR TITLE-ABS-KEY (toddler) OR TITLE-ABS-KEY (teenager) OR TITLE-ABS-KEY (teen*) OR TITLE-ABS-KEY (neonate)	5,101,677
#4	TITLE-ABS-KEY (clinical AND trial*) OR TITLE-ABS-KEY (randomized AND controlled AND trial*) OR TITLE-ABS-KEY (clinical AND study) OR TITLE-ABS-KEY (random AND allocation) OR TITLE-ABS-KEY (randomization)	7,012,722
#5	(TITLE-ABS-KEY (vitamin AND d) OR TITLE-ABS-KEY (25 hydroxyvitamin AND d2) OR TITLE-ABS-KEY (coledalciferol) OR TITLE-ABS-KEY (25hydroxyvitamin AND d3) OR TITLE-ABS-KEY (hydroxycholecalciferol*) OR TITLE-ABS-KEY (ergocalciferol*) OR TITLE-ABS-KEY (dihydrotachystrol) OR TITLE-ABS-KEY (vitamind3) OR TITLE-ABS-KEY (vitamin AND d AND supplement*)) AND (TITLE-ABS-KEY (lipid*) OR TITLE-ABS-KEY (lipid AND profile) OR TITLE-ABS-KEY (vldl) OR TITLE-ABS-KEY (very AND low AND density AND lipoprotein*) OR TITLE-ABS-KEY (vldl AND cholesterol) OR TITLE-ABS-KEY (vldl AND lipoprotein*) OR TITLE-ABS-KEY (ldl) OR TITLE-ABS-KEY (low AND density AND lipoprotein*) OR TITLE-ABS-KEY (ldl AND cholesterol) OR TITLE-ABS-KEY (ldl AND cholesterol*) OR TITLE-ABS-KEY (ldl AND lipoprotein*) OR TITLE-ABS-KEY (hdl AND lipoprotein*) OR TITLE-ABS-KEY (hdl) OR TITLE-ABS-KEY (high AND density AND lipoprotein*) OR TITLE-ABS-KEY (pre AND beta AND high AND density AND lipoprotein*) OR TITLE-ABS-KEY (hdl2 AND lipoprotein*) OR TITLE-ABS-KEY (hdl3 AND lipoprotein*) OR TITLE-ABS-KEY (triglyseride*) OR TITLE-ABS-KEY (triacetin) OR TITLE-ABS-KEY (triolein) OR TITLE-ABS-KEY (cholesterol*) OR TITLE-ABS-KEY (19 lodocholesterol) OR TITLE-ABS-KEY (azacosterol) OR TITLE-ABS-KEY (cholesterol AND ester*) OR TITLE-ABS-KEY (oxysterol*) OR TITLE-ABS-KEY (hydroxycholesterol*) OR TITLE-ABS-KEY (ketocholesterol*)) AND (TITLE-ABS-KEY (pediatric*) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY (children) OR TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (adolescent) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (preschool) OR TITLE-ABS-KEY (toddler) OR TITLE-ABS-KEY (teenager) OR TITLE-ABS-KEY (teen*) OR TITLE-ABS-KEY (neonate)) AND (TITLE-ABS-KEY (clinical AND trial*) OR TITLE-ABS-KEY (randomized AND controlled AND trial*) OR TITLE-ABS-KEY (clinical AND study) OR TITLE-ABS-KEY (random AND allocation) OR TITLE-ABS-KEY (randomization))	816

25-OH-D to LDL-C could result in a reduction in LDL-C clearance (39, 40). The inconsistencies of these studies might be partially explained by differences in age groups and eating nutritious food (41).

Several mechanisms can explain the effect of vitamin D on lipids. In vitro, Vit D metabolites can affect lipoprotein lipase (42), lower TG, and increase HDL levels. Vit D has anti-inflammatory effects and may reduce insulin resistance by reducing low-grade chronic inflammation (43, 44), thereby increasing HDLC and lowering TG levels.

Strengths and limitations

This systematic review and meta-analysis have several strengths. First, this is the first meta-analysis to assess

the effect of Vit D supplementation on serum lipid profiles in children and adolescents. The inclusion of data from 13 RCTs provided enough power and robustness to detect the effect of Vit D on serum lipid profiles. Lastly, the source of heterogeneity and publication bias was not observed and sensitivity analysis was performed for the robustness of the finding. Additionally, this study has several limitations that must be acknowledged: First, the season of data collection was not available in trials; thus, examination of the role of Vit D on serum lipid profile by season was not possible. Second, no included studies had assessed potential differences regarding the impact of Vit D supplementation based on race and gender. Finally, the dietary pattern had not been mentioned in some included studies; however, nutrition training was similar in the intervention and control groups.

Table 4 (Supplementary). Search strategy in Ovid database

Row	Search strings	Items found
#1	"ketocholesterol".ti,kw,ab. OR "hydroxycalciferol".ti,kw,ab. OR "oxysterol".ti,kw,ab. OR "cholesterol ester".ti,kw,ab. OR 19-iodocholesterol.ti,kw,ab. OR Azacosterol.ti,kw,ab. OR "cholesterol".ti,kw,ab. OR triolein.ti,kw,ab. OR triacetin.ti,kw,ab. OR "triglyceride".ti,kw,ab. OR "hdl3 lipoprotein".ti,kw,ab. OR "hdl2 lipoprotein".ti,kw,ab. OR "pre beta high density lipoprotein".ti,kw,ab. OR "hdl lipoprotein".ti,kw,ab. OR "high density lipoprotein".ti,kw,ab. OR "hdl cholesterol".ti,kw,ab. OR hdl.ti,kw,ab. OR "ldl lipoprotein".ti,kw,ab. OR "ldl cholesterol".ti,kw,ab. OR "low density lipoprotein".ti,kw,ab. OR ldl.ti,kw,ab. OR "vldl lipoprotein".ti,kw,ab. OR "vldl cholesterol".ti,kw,ab. OR "very low density lipoprotein".ti,kw,ab. OR vldl.ti,kw,ab. OR lipid profile.ti,kw,ab. OR "lipid".ti,kw,ab. OR exp Ketocholesterols/OR exp Hydroxycholesterols/OR exp Cholesterol Esters/OR exp 19-Iodocholesterol/OR exp Cholesterol/OR exp Triolein/OR exp Triacetin/OR exp Triglycerides/OR exp Lipoproteins, HDL3/OR exp Lipoproteins, HDL2/OR exp High-Density Lipoproteins, Pre-beta/OR exp Lipoproteins, HDL/OR exp Cholesterol, HDL/OR exp Lipoproteins, LDL/OR exp Cholesterol, LDL/OR exp Lipoproteins, VLDL/OR exp Cholesterol, VLDL/OR exp Lipids/	86609
#2	"vitamin d supplement".ti,kw,ab. OR vitamin d3.ti,kw,ab. OR dihydrotachysterol.ti,kw,ab. OR "hydroxycalciferol".ti,kw,ab. OR "ergocalciferol".ti,kw,ab. OR 25 hydroxyvitamin d3.ti,kw,ab. OR 25 hydroxyvitamin d3.ti,kw,ab. OR "cholecalciferol".ti,kw,ab. OR 25 hydroxyvitamin d2.ti,kw,ab. OR vitamin d.ti,kw,ab. OR exp Dihydrotachysterol/OR exp Ergocalciferols/OR exp Cholecalciferol/OR exp 25-Hydroxyvitamin D 2/OR exp Vitamin D/	12075
#3	neonate.ti,kw,ab. OR "teen".ti,kw,ab. OR teenager.ti,kw,ab. OR toddler.ti,kw,ab. OR preschool.ti,kw,ab. OR adolescent.ti,kw,ab. OR newborn.ti,kw,ab. OR children.ti,kw,ab. OR infant.ti,kw,ab. OR "child".ti,kw,ab. OR "pediatric".ti,kw,ab. OR exp Child, Preschool/OR exp Infant, Newborn/OR exp Adolescent/OR exp Infant/OR exp Child/OR exp Pediatrics/	259598
#4	"trial".ti,kw,ab. OR "clinical trial".ti,kw,ab. OR "random".ti,kw,ab. OR exp Clinical Trials as Topic/OR exp Random Allocation/	1102790
#5	"vitamin d supplement".ti,kw,ab. OR vitamin d3.ti,kw,ab. OR dihydrotachysterol.ti,kw,ab. OR "hydroxycalciferol".ti,kw,ab. OR "ergocalciferol".ti,kw,ab. OR 25 hydroxyvitamin d3.ti,kw,ab. OR 25 hydroxyvitamin d3.ti,kw,ab. OR "cholecalciferol".ti,kw,ab. OR 25 hydroxyvitamin d2.ti,kw,ab. OR vitamin d.ti,kw,ab. OR exp Dihydrotachysterol/OR exp Ergocalciferols/OR exp Cholecalciferol/OR exp 25-Hydroxyvitamin D 2/OR exp Vitamin D/AND "ketocholesterol".ti,kw,ab. OR "hydroxycalciferol".ti,kw,ab. OR "oxysterol".ti,kw,ab. OR "cholesterol ester".ti,kw,ab. OR 19-iodocholesterol.ti,kw,ab. OR Azacosterol.ti,kw,ab. OR "cholesterol".ti,kw,ab. OR triolein.ti,kw,ab. OR triacetin.ti,kw,ab. OR "triglyceride".ti,kw,ab. OR "hdl3 lipoprotein".ti,kw,ab. OR "hdl2 lipoprotein".ti,kw,ab. OR "pre beta high density lipoprotein".ti,kw,ab. OR "hdl lipoprotein".ti,kw,ab. OR "high density lipoprotein".ti,kw,ab. OR "hdl cholesterol".ti,kw,ab. OR hdl.ti,kw,ab. OR "ldl lipoprotein".ti,kw,ab. OR "ldl cholesterol".ti,kw,ab. OR "low density lipoprotein".ti,kw,ab. OR ldl.ti,kw,ab. OR "vldl lipoprotein".ti,kw,ab. OR "vldl cholesterol".ti,kw,ab. OR "very low density lipoprotein".ti,kw,ab. OR vldl.ti,kw,ab. OR lipid profile.ti,kw,ab. OR "lipid".ti,kw,ab. OR exp Ketocholesterols/OR exp Hydroxycholesterols/OR exp Cholesterol Esters/OR exp 19-Iodocholesterol/OR exp Cholesterol/OR exp Triolein/OR exp Triacetin/OR exp Triglycerides/OR exp Lipoproteins, HDL3/OR exp Lipoproteins, HDL2/OR exp High-Density Lipoproteins, Pre-beta/OR exp Lipoproteins, HDL/OR exp Cholesterol, HDL/OR exp Lipoproteins, LDL/OR exp Cholesterol, LDL/OR exp Lipoproteins, VLDL/OR exp Cholesterol, VLDL/OR exp Lipids/AND neonate.ti,kw,ab. OR "teen".ti,kw,ab. OR teenager.ti,kw,ab. OR toddler.ti,kw,ab. OR preschool.ti,kw,ab. OR adolescent.ti,kw,ab. OR newborn.ti,kw,ab. OR children.ti,kw,ab. OR infant.ti,kw,ab. OR "child".ti,kw,ab. OR "pediatric".ti,kw,ab. OR exp Child, Preschool/OR exp Infant, Newborn/OR exp Adolescent/OR exp Infant/OR exp Child/OR exp Pediatrics/AND "trial".ti,kw,ab. OR "clinical trial".ti,kw,ab. OR "random".ti,kw,ab. OR exp Clinical Trials as Topic/OR exp Random Allocation/	646

5. Conclusion

The result of this study indicated that Vit D supplementation could increase HDL levels with low effect size, but does not appear to significantly affect LDL-C, TG, and TC levels. Therefore, it is important to report that higher serum Vit D is correlated with a more positive effect on HDL levels in children and adolescents. In future research, higher doses of Vit D should be considered.

Summary of evidence

Our study did not find a significant relationship between Vit D supplementation and LDL levels. Vit D supplementation significantly increased HDL levels. There was no significant relationship between Vit D supplementation and the levels of TC and TG. Finally, due to

the very low impact of Vit D consumption on the lipid profile of children and adolescents, health policymakers should look for the effect and study other compounds.

Ethical Considerations

Compliance with ethical guidelines

The research was approved on October 14, 2019 by Birjand University of Medical Sciences (IR.BUMS. REC.1398.215).

Funding

This study did not receive any specific funding from the public, commercial or non-profit financial sectors.

Table 5 (Supplementary). Search strategy in Embase database

Row	Search strings	Items found
#1	'lipid'/exp OR 'lipid' OR 'lipids' OR 'very low density lipoprotein'/exp OR 'vldl' OR 'lipoproteins, vldl' OR 'very low density lipoprotein' OR 'very low density lipoprotein cholesterol'/exp OR 'cholesterol, vldl' OR 'lipoproteins, vldl cholesterol' OR 'very low density lipoprotein cholesterol' OR 'vldl cholesterol' OR 'low density lipoprotein cholesterol'/exp OR 'ldl cholesterol' OR 'cholesterol, ldl' OR 'lipoproteins, ldl cholesterol' OR 'low density lipoprotein cholesterol' OR 'low density lipoprotein'/exp OR 'ldl' OR 'lipoprotein, low density' OR 'lipoproteins, ldl' OR 'low density lipoprotein' OR 'high density lipoprotein cholesterol'/exp OR 'hdl cholesterol' OR 'cholesterol, hdl' OR 'high density lipoprotein cholesterol' OR 'lipoproteins, hdl cholesterol' OR 'high density lipoprotein'/exp OR 'hdl' OR 'high density lipoprotein' OR 'lipoprotein, high density' OR 'lipoproteins, hdl' OR 'pre alpha lipoprotein' OR 'very high density lipoprotein' OR 'high density lipoprotein 3'/exp OR 'hdl 3' OR 'hdl3' OR 'hdl3 lipoprotein' OR 'high density lipoprotein 3' OR 'high density lipoprotein hdl3' OR 'lipoprotein hdl3' OR 'lipoproteins, hdl3' OR 'triacylglycerol'/exp OR 'fatty acid triglyceride' OR 'triglyceride' OR 'triglycerides' OR 'tryglyceride' OR 'triacetin'/exp OR 'triacetin' OR 'triacetine' OR 'triolein'/exp OR 'triolein' OR 'cholesterol'/exp OR 'cholesterol' OR 'azacosterol'/exp OR 'azacosterol' OR 'cholesterol ester'/exp OR 'cholesterol ester' OR 'cholesterol esters' OR 'cholesterolester' OR 'cholesteryl ester' OR 'oxysterol'/exp OR 'oxysterol' OR 'oxysterols' OR 'hydroxycholesterol'/exp OR ketocholesterol	1,948,470
#2	'vitamin d'/exp OR 'vitamin d' OR 'd vitamin deficiency'/exp OR 'd vitamin deficiency' OR 'd hypovitaminosis'/exp OR 'd hypovitaminosis' OR 'd hypo-vitaminosis'/exp OR 'd hypo-vitaminosis' OR 'calciferol deficiency'/exp OR 'calciferol deficiency' OR 'cholecalciferol deficiency'/exp OR 'cholecalciferol deficiency' OR 'colecalfiferol deficiency'/exp OR 'colecalfiferol deficiency' OR 'ergocalciferol deficiency'/exp OR 'ergocalciferol deficiency' OR 'hypovitaminosis d'/exp OR 'hypovitaminosis d' OR 'hypovitaminosis d'/exp OR 'hypovitaminosis d' OR 'vit. d deficiency'/exp OR 'vit. d deficiency' OR 'vitamin d deficiency'/exp OR 'vitamin d deficiency' OR 'vitamin d2 deficiency'/exp OR 'vitamin d2 deficiency' OR 'vitamin d3 deficiency'/exp OR 'vitamin d3 deficiency' OR 'vitamin d supplementation'/exp OR 'vitamin d supplementation' OR '25 hydroxyvitamin d'/exp OR '25 hydroxyvitamin d' OR 'vitamin d, 25 hydroxy'/exp OR 'vitamin d, 25 hydroxy' OR '25 hydroxyvitamin d2'/exp OR '25 hydroxyvitamin d2' OR '25 hydroxyvitamin d3'/exp OR '25 hydroxyvitamin d3' OR 'cholecalciferol'/exp OR 'cholecalciferol' OR 'cholecalciferols'/exp OR 'cholecalciferols' OR 'colecalfiferol'/exp OR 'colecalfiferol' OR 'vitamin d3'/exp OR 'vitamin d3' OR 'vitamin d 3'/exp OR 'vitamin d 3' OR 'ergocalciferol'/exp OR 'ergocalciferol' OR 'ergocalciferols'/exp OR 'ergocalciferols' OR 'vitamin d2'/exp OR 'vitamin d2' OR 'vitamin d 2'/exp OR 'vitamin d 2' OR 'hydroxycholecalciferol'/exp OR 'hydroxycholecalciferol' OR 'hydroxycholecalciferols'/exp OR 'hydroxycholecalciferols' OR 'hydroxycolecalfiferol'/exp OR 'hydroxycolecalfiferol' OR dihydrota OR 'dihydrotachysterol'/exp OR 'dihydrotachysterol' OR 'dihydrotachysterol 2'/exp OR 'dihydrotachysterol 2' OR 'dihydrotachysterol 3'/exp OR 'dihydrotachysterol 3'	162,122
#3	'pediatrics'/exp OR 'paediatrics' OR 'pediatrics' OR 'child'/exp OR 'child' OR 'children' OR 'infant'/exp OR 'infant' OR 'adolescent' OR 'adolescent' OR 'teenager' OR 'newborn'/exp OR 'child, newborn' OR 'human neonate' OR 'human newborn' OR 'infant, newborn' OR 'neonate' OR 'newborn' OR 'newborn baby' OR 'newborn child' OR 'newborn infant' OR 'preschool'/exp OR 'preschool child'/exp OR 'child, preschool' OR 'pre-school child' OR 'preschool child' OR 'toddler'/exp OR 'toddler' OR 'toddlers' OR neonate	4,793,333
#4	'clinical study'/exp OR 'clinical study' OR 'medical trial' OR 'controlled clinical trial'/exp OR 'clinical trial, controlled' OR 'controlled clinical study' OR 'controlled clinical trial' OR 'randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'randomization'/exp OR 'random allocation' OR 'randomisation' OR 'randomization'	9,809,978
#5	'lipid'/exp OR 'lipid' OR 'lipids' OR 'very low density lipoprotein'/exp OR 'vldl' OR 'lipoproteins, vldl' OR 'very low density lipoprotein' OR 'very low density lipoprotein cholesterol'/exp OR 'cholesterol, vldl' OR 'lipoproteins, vldl cholesterol' OR 'very low density lipoprotein cholesterol' OR 'vldl cholesterol' OR 'low density lipoprotein cholesterol'/exp OR 'ldl cholesterol' OR 'cholesterol, ldl' OR 'lipoproteins, ldl cholesterol' OR 'low density lipoprotein cholesterol' OR 'low density lipoprotein'/exp OR 'ldl' OR 'lipoprotein, low density' OR 'lipoproteins, ldl' OR 'low density lipoprotein' OR 'high density lipoprotein cholesterol'/exp OR 'hdl cholesterol' OR 'cholesterol, hdl' OR 'high density lipoprotein cholesterol' OR 'lipoproteins, hdl cholesterol' OR 'high density lipoprotein'/exp OR 'hdl' OR 'high density lipoprotein' OR 'lipoprotein, high density' OR 'lipoproteins, hdl' OR 'pre alpha lipoprotein' OR 'very high density lipoprotein' OR 'high density lipoprotein 3'/exp OR 'hdl 3' OR 'hdl3' OR 'hdl3 lipoprotein' OR 'high density lipoprotein 3' OR 'high density lipoprotein hdl3' OR 'lipoprotein hdl3' OR 'lipoproteins, hdl3' OR 'triacylglycerol'/exp OR 'fatty acid triglyceride' OR 'triglyceride' OR 'triglycerides' OR 'tryglyceride' OR 'triacetin'/exp OR 'triacetin' OR 'triacetine' OR 'triolein'/exp OR 'triolein' OR 'cholesterol'/exp OR 'cholesterol' OR 'azacosterol'/exp OR 'azacosterol' OR 'cholesterol ester'/exp OR 'cholesterol ester' OR 'cholesterol esters' OR 'cholesterolester' OR 'cholesteryl ester' OR 'oxysterol'/exp OR 'oxysterol' OR 'oxysterols' OR 'hydroxycholesterol'/exp OR ketocholesterol AND 'vitamin d'/exp OR 'vitamin d' OR 'd vitamin deficiency'/exp OR 'd vitamin deficiency' OR 'd hypovitaminosis'/exp OR 'd hypovitaminosis' OR 'd hypo-vitaminosis'/exp OR 'd hypo-vitaminosis' OR 'calciferol deficiency'/exp OR 'calciferol deficiency' OR 'cholecalciferol deficiency'/exp OR 'cholecalciferol deficiency' OR 'colecalfiferol deficiency'/exp OR 'colecalfiferol deficiency' OR 'ergocalciferol deficiency'/exp OR 'ergocalciferol deficiency' OR 'hypovitaminosis d'/exp OR 'hypovitaminosis d' OR 'hypovitaminosis d'/exp OR 'hypovitaminosis d' OR 'vit. d deficiency'/exp OR 'vit. d deficiency' OR 'vitamin d deficiency'/exp OR 'vitamin d deficiency' OR 'vitamin d2 deficiency'/exp OR 'vitamin d2 deficiency' OR 'vitamin d3 deficiency'/exp OR 'vitamin d3 deficiency' OR 'vitamin d supplementation'/exp OR 'vitamin d supplementation' OR '25 hydroxyvitamin d'/exp OR '25 hydroxyvitamin d' OR 'vitamin d, 25 hydroxy'/exp OR 'vitamin d, 25 hydroxy' OR '25 hydroxyvitamin d2'/exp OR '25 hydroxyvitamin d2' OR '25 hydroxyvitamin d3'/exp OR '25 hydroxyvitamin d3' OR 'cholecalciferol'/exp OR 'cholecalciferol' OR 'cholecalciferols'/exp OR 'cholecalciferols' OR 'colecalfiferol'/exp OR 'colecalfiferol' OR 'vitamin d3'/exp OR 'vitamin d3' OR 'vitamin d 3'/exp OR 'vitamin d 3' OR 'ergocalciferol'/exp OR 'ergocalciferol' OR 'ergocalciferols'/exp OR 'ergocalciferols' OR 'vitamin d2'/exp OR 'vitamin d2' OR 'vitamin d 2'/exp OR 'vitamin d 2' OR 'hydroxycholecalciferol'/exp OR 'hydroxycholecalciferol' OR 'hydroxycholecalciferols'/exp OR 'hydroxycholecalciferols' OR 'hydroxycolecalfiferol'/exp OR 'hydroxycolecalfiferol' OR dihydrota OR 'dihydrotachysterol'/exp OR 'dihydrotachysterol' OR 'dihydrotachysterol 2'/exp OR 'dihydrotachysterol 2' OR 'dihydrotachysterol 3'/exp OR 'dihydrotachysterol 3' AND 'pediatrics'/exp OR 'paediatrics' OR 'pediatrics' OR 'child'/exp OR 'child' OR 'children' OR 'infant'/exp OR 'infant' OR 'adolescent' OR 'adolescent' OR 'teenager' OR 'newborn'/exp OR 'child, newborn' OR 'human neonate' OR 'human newborn' OR 'infant, newborn' OR 'neonate' OR 'newborn' OR 'newborn baby' OR 'newborn child' OR 'newborn infant' OR 'preschool'/exp OR 'preschool child'/exp OR 'child, preschool' OR 'pre-school child' OR 'preschool child' OR 'toddler'/exp OR 'toddler' OR 'toddlers' OR neonate AND 'clinical study'/exp OR 'clinical study' OR 'medical trial' OR 'controlled clinical trial'/exp OR 'clinical trial, controlled' OR 'controlled clinical study' OR 'controlled clinical trial' OR 'randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'randomization'/exp OR 'random allocation' OR 'randomisation' OR 'randomization'	1,926

Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no competing of interests.

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