

RESEARCH ARTICLE

Association between vitamin D status and lipid profile in children and adolescents: a systematic review and meta-analysisRoya Kelishadi¹, Ziba Farajzadegan², and Maryam Bahreynian³¹Department of Pediatrics, Faculty of Medicine, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, ²Department of Community Medicine, Faculty of Medicine, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, and ³Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran**Abstract**

This systematic review and meta-analysis was performed on the relationship of serum 25-hydroxy-vitamin D [25(OH)D] and lipid profile in the pediatric age group. Electronic search was conducted in international databases. Our search yielded to 3213 articles, with initial searching of title and abstracts, 3192 of them were excluded and 21 remained. A meta-analysis of 17 cross-sectional studies, including 25 394 subjects, was conducted according to Strobe guideline. We found an inverse weak significant association between 25(OH)D and triglycerides ($r = -0.135$, CI: $-0.243, -0.025$), total cholesterol ($r = -0.086$, CI: $-0.0205, 0.035$) and LDL-C ($r = -0.025$, CI: $-0.22, 0.17$), and direct association with HDL-C ($r = 0.156$, CI: $-0.021, 0.324$). In the pooled analysis, we used a random effects model as the heterogeneity between studies was significant ($I^2 = 97.04\%$, $p < 0.001$ for triglycerides; $I^2 = 96.09\%$, $p < 0.001$ for total cholesterol; $I^2 = 96.14\%$, $p < 0.001$ for LDL-C; $I^2 = 99\%$, $p < 0.001$ for HDL-C). This study indicates that higher serum 25(OH)D is related to a more favorable lipid profile in the pediatric age group.

Keywords

Adolescents, children, lipid profile, meta-analysis, vitamin D

History

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Introduction

Non-communicable diseases, notably cardiovascular diseases (CVDs) and type 2 diabetes, are considered as common cause of disability and death worldwide (Despres et al., 2008). Dislipidemia and obesity are of major risk factors for CVDs (Grundy, 2008). A growing body of evidence suggests that vitamin D deficiency may have a role in the development of dislipidemia (Potenza & Mechanick, 2009). According to previous studies, vitamin D deficiency is prevalent among 30–50% of adults (Lee et al., 2008; Tangpricha et al., 2002). Hypovitaminosis D is reported among 74% of obese children, and in 32% of the pediatric population (Johnson et al., 2010).

Vitamin D status is usually considered as the level of 25-hydroxy-D [25(OH)D]; since this form has long half-life includes vitamin D of sunlight exposure besides daily diet (Potenza & Mechanick, 2009). Although it is not well defined, values less than 20 ng/mL of serum 25(OH)D is known to be as deficiency state and the level of 20–29 ng/mL as insufficiency (Brannon et al., 2008). Lower vitamin D status is reported to be concurrent with higher prevalence of metabolic disorders, high blood pressure, dislipidemia and CVD (Ashraf et al., 2011).

Many studies conducted among adult populations support the inverse association of vitamin D with cardiometabolic risk factors,

as obesity (Parikh & Yanovski, 2003; Snijder et al., 2005; Teegarden, 2003), dyslipidemia (Botella-Carretero et al., 2007), high blood pressure (Vaidya & Forman, 2010), insulin resistance (Boucher et al., 1995), metabolic syndrome (Botella-Carretero et al., 2007; Boucher et al., 1995; Chiu et al., 2004; Ford et al., 2005; Scragg et al., 2004) and CVDs (Pittas et al., 2007, 2010).

It is well documented that adult diseases and their risk factors origin from early-life (Nilsson et al., 2013), considering the high prevalence of hypovitaminosis D in children and adolescents (Lamberg-Allardt, 2012), and the growing prevalence of cardio-metabolic risk factors in the pediatric age group (Gupta et al., 2013; Kelishadi, 2007), evaluating the relationships of these disorders in early life can help in providing a better understanding of underlying mechanisms, and in conducting action-oriented interventions for primordial and primary prevention of many chronic diseases.

Limited information is available regarding the association of vitamin D and cardiometabolic risk factors in the pediatric population (Nam et al., 2012; Williams et al., 2012). This study aims to systematically review the current published papers with cross-sectional designs on the relationship of serum 25(OH)D levels with lipid profile in children and adolescents.

Methods

A systematic review and meta-analysis was performed on papers that assessed the relation between vitamin D levels and lipid profile, as serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C), among children and adolescents. The 25(OH)D level was considered as vitamin D status.

Search strategy

MEDLINE, Pubmed, ISI Web of Science, ISI Web of Knowledge, and Scopus were used as the main sources to access the relevant papers published until May 2013 (without limiting the time). All cross-sectional data were selected except than one letter (Alam et al., 2012), one report of conference meeting (Challa, 2012) and one longitudinal study (Williams et al., 2013). Search terms as blood lipids OR lipid profile OR lipids* OR triglycerid* OR trigly* OR triacylglycerol OR LDL OR HDL OR VLDL OR cholesterol OR metabolic syndrome OR metabolic syndrome* OR metabolic syndrome X in combination with vitamin D OR cholecalci* OR vit D OR 25-hydroxy-vitamin D and child* OR student* OR pediater* OR school-aged OR (school aged) OR schoolaged OR school-going OR schoolgoing OR youth OR teenager OR adolescen* OR boy OR girl in the form of Medical Subject Headings (MeSH) and truncations were used. Relevant articles were obtained without any language restriction. In case of not having access to the full text versions, we contacted to the email of the corresponding author.

Study selection and eligibility criteria

Having removed duplicates, the relevant papers were selected in three phases. In the first and second phases, titles and abstracts of papers were screened and irrelevant papers were excluded. In the last phase, the full text of recruited papers was explored deeply to select only relevant papers. For any additional relevant studies, the reference list of all reviews and relevant papers were screened as well.

Studies were included if they fulfilled the following criteria: (i) observational cross-sectional design, (ii) case-control studies with target group among the whole population of children and adolescents, (iii) measurement of 25(OH)D concentration as an index for vitamin D status, (iv) any language and (v) reporting the correlation coefficient of 25(OH)D with lipid profiles in the pediatric population.

Quality assessment

Strobe checklist was used to define the most relevant papers for observational studies (von Elm et al., 2007). Two independent reviewers (MB and RK) evaluated the methodological quality of each study and identified the literature searches for their potential relevance or assessed the full text for inclusion in the review. Discrepancies were resolved by consultation and consensus.

Data extraction and abstraction

Two reviewers extracted the data independently using a data collection form including first author name, publication year, sample size and study design, as well as age, gender and ethnicity of participants, geographic setting and techniques measuring serum 25(OH)D, statistical analysis and the variables adjusted in the analyses.

Statistical analysis

Results were pooled using a random effects model with considering the publication bias. Tests for heterogeneity and sub-group analysis were not undertaken because of the large variation between studies for age categories. Results were expressed as pooled correlation coefficients. We pooled the correlation coefficients of serum 25(OH)D with blood lipids. In case of presenting data as odds ratio or odds of having metabolic syndrome, the studies were omitted from the analysis. I square statistic was reported showing the percentage of variation results from the heterogeneity. We evaluated publication bias

using a funnel plot and Kendall test to find out whether there was a bias during search process. All analyses were conducted by using Comprehensive Meta-analysis Software (CMA) version 2.0 (Biostat, Englewood, NJ).

Results

We initially retrieved 3213 articles in the database search. Figure 1 represents the flowchart summarizing the search results. With initial searching of title and abstracts, 3192 articles were excluded and 21 remained. No additional references were identified through checking the reference lists of selected papers. A further four papers were not included in the pooled analysis because their results were not presented in a format that allowed us to combine the results with other papers (Brenner et al., 2011; Kumar et al., 2011; Lee et al., 2013; Williams et al., 2011). Studies that presented the results in the most similar way to other studies were included for the pooled analysis.

The main characteristics of the 21 studies included in the systematic review are demonstrated in Table 1. Overall, the studies reported data on 32 724 subjects. All studies were published between 2009 and 2013. Five studies were conducted in Europe, five in Asia, 10 in US and one study in Canada. The range age of study participants was between 1 and 65 years and the majority of studies (except for one paper; Ashraf et al., 2011), included both genders. Serum 25(OH)D was measured based on enzyme-linked immunosorbent assay (ELISA) in one study (Al-Daghri et al., 2010), gamma counter by radioimmunoassay (RIA) in four studies (Delvin et al., 2010; Nam et al., 2012;

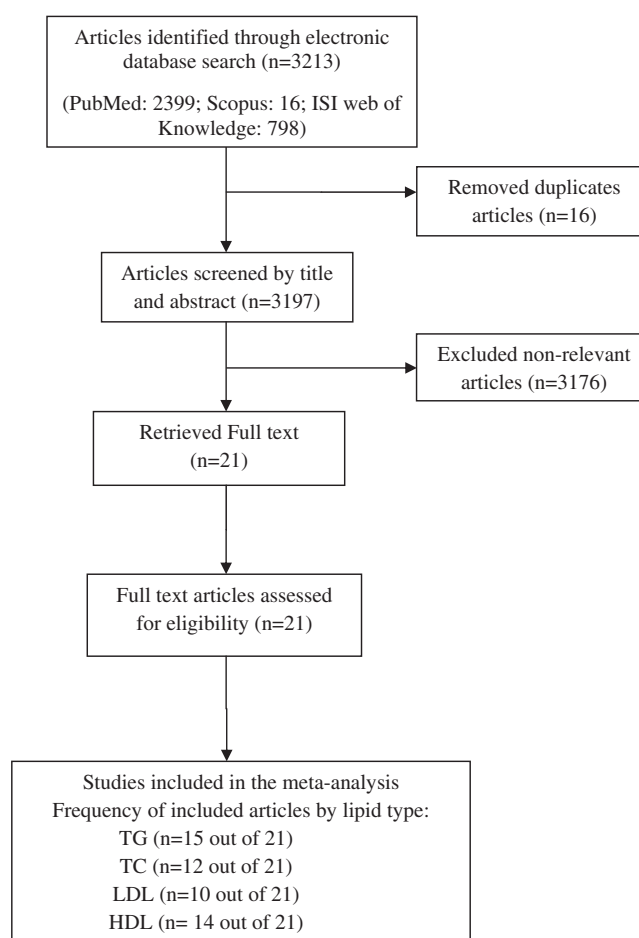
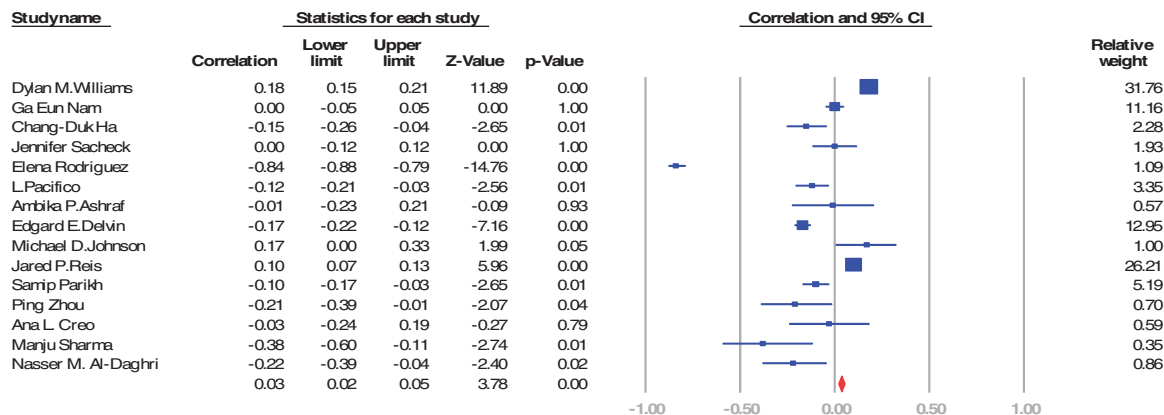


Figure 1. Initial search results regarding vitamin D status and lipid profile in children and adolescents.

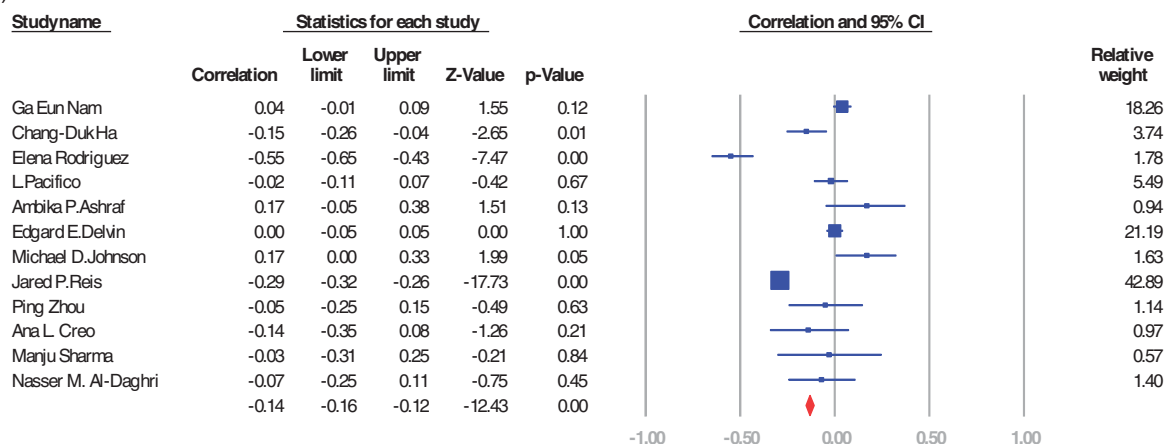
Table 1. Main characteristics of studies included in the systematic review.

Author	Date of publication	Study design	Geographic setting	No. in analysis	Age	Gender	Ethnicity	Adjusted variables for statistical analysis
Kumar et al.	2009	Cross-sectional	US (NHANES)	6036	1–21 years	Boy, girl		Age, gender, race, obesity, PIR, TV, computer use, milk intake, vitamin D supplements
Reis et al.	2009	Cross-sectional	US (NHANES2001–2004)	3528	12–19 years (51.5% boys)	Boy, girl		Age, gender, race, poverty to income ratio, PA, BMI
Delvin et al.	2010	Cross-sectional	Canada	1745	9, 13 and 16 years	Boy, girl	French-Canadian	Age, loge BMI (only in model 2, for girls)
Al-Daghri et al.	2010	Cross-sectional	Riyadh, Saudi Arabia	118	5–17 years	Boy, girl		Not reported
Johnson et al.	2010	Retrospective	Minnesota, Rochester, Mayo clinic	137	2–18 years	Boy, girl		Age, gender, BMI-Zscore, season
Sacheck et al.	2011	Cross-sectional	Boston area	263	9–14 years	Boy, girl		BMI-Zscore
Kumar et al.	2011	Cross-sectional	Pittsburgh, Pennsylvania	237	8–18 years (43% boys)	Boy, girl		Not reported
Rodriguez et al.	2011	Cross-sectional	Madrid, Spain	149	8–13 years (47.7 ± 4.1% boys)	Boy, girl		Age, gender, BMI, PA
Pacifico et al.	2011	Cross-sectional	Rome, Italy	452	16–35 years	Boy, girl	Caucasian	Age, gender, Tanner stage
Brenner et al.	2011	Cross-sectional	Canada	total 1818 (under 6y: omitted)	(49.12% boys)	Boy, girl		Not reported
Ganji et al.	2011	Cross-sectional	US (NHANES)	5867	12–19 years (50.6% boys)	Boy, girl		Not reported
Ashraf et al.	2011	Cross-sectional	Birmingham	80		Girls only	53 African-American, 27 American-Caucasian	Race, BMI
Williams et al.	2011	Cross-sectional	US (NHANES)	3644 (HDL), 1741 (LDL)	12–19 years	Boy, girl		Age, gender, ethnicity, PIR, waist circumference
Zhou et al.	2011	Cross-sectional–Retrospective	Bronx, New York	97 (lipid profile)	6–21 years	Boy, girl	43 African-American, 78 Hispanic, 29 mixed background	Age adjusted data
Williams et al.	2012	Cross-sectional	UK	4274	Mean: 9.9 years	Not reported		Season, age, gender, socio-economic status, waist circumference, PTH, Ca, P
Nam et al.	2012	Cross-sectional	Korea	1504	12–15 years, 16–18 years	Boy, girl		Age, gender, regular physical activity, alcohol, mineral supplements
Parikh et al.	2012	Cross-sectional	Augusta area (Southern US)	701	14–18 years	Boy, girl		Age, gender, race, tanner stage, season, PA, %body fat
Sharma et al.	2012	Cross-sectional	India	50	15–65 years	Men, women		No adjustment
Ha et al.	2013	Cross-sectional	Korea	310	10–12 years	Boy, girl		Age, gender, Tanner stage, body fatness, PA
Lee et al.	2013	Cross-sectional	Korea	1649	9 years	Boy, girl		BMI
Creo et al.	2013	Cross-sectional	Chicago metropolitan area	83	2–6 years	Boy, girl		Not reported

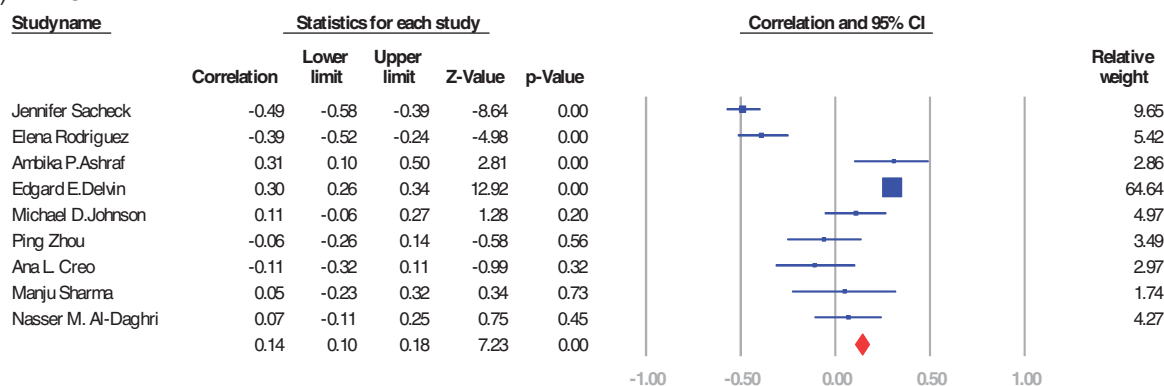
(a) Triglyceride



(b) Total cholesterol



(c) LDL-C



(d) HDL-C

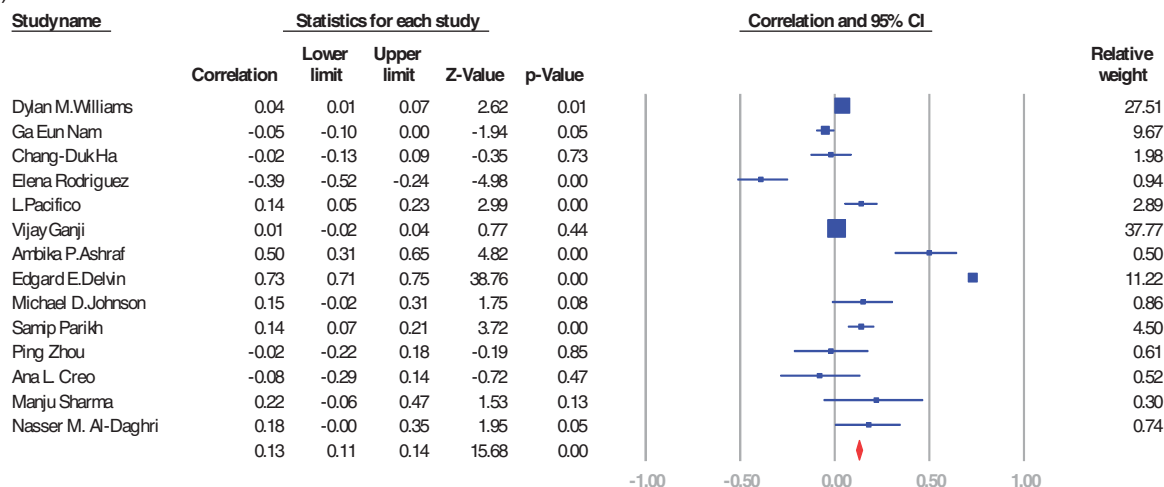


Figure 2. (a-d) a: Triglyceride; b: Total cholesterol; c: LDL-C; d: HDL-C.

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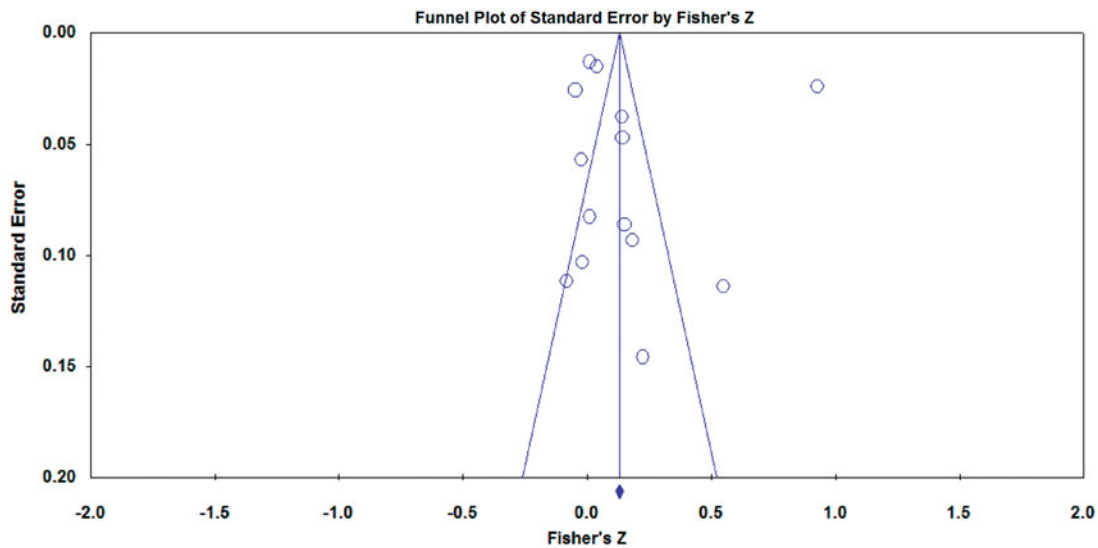


Figure 3. Funnel plot (HDL-C).

Reis et al., 2009; Sharma et al., 2012), direct competitive chemiluminescence immunoassay in five studies (Brenner et al., 2011; Ha et al., 2013; Lee et al., 2013; Rodriguez-Rodriguez et al., 2011; Zhou et al., 2011) high-performance liquid chromatography (HPLC) tandem mass spectrometry in four studies (Ashraf et al., 2011; Creo et al., 2013; Parikh et al., 2012; Williams et al., 2012), competitive binding radioimmunoassay in one study (Sacheck et al., 2011), competitive protein binding assay using vitamin D-binding protein in one study (Kumar et al., 2011), electrochemiluminescence immunoassay ECLIA using an automated clinical chemistry analyzer in one study (Pacifico et al., 2011), Diasorin RIA kit assay in three studies (Ganji et al., 2011; Kumar et al., 2009; Williams et al., 2011), HPLC with ultraviolet quantitation in one study (Johnson et al., 2010).

A meta-analysis of 17 studies, which reported data for 25 394 subjects, was used. Figure 2(a–d) represents the forest plots for blood lipids. Figure 3 shows the funnel plot for HDL-C as a relatively symmetric plot indicating no bias. We found an inverse weak significant association between serum 25(OH)D and TG levels ($r = -0.135$, CI: $-0.243, -0.025$), TC ($r = -0.086$, CI: $-0.0205, 0.035$) and LDL-C ($r = -0.025$, CI: $-0.22, 0.17$). The corresponding figure for HDL-C was direct and significant ($r = 0.156$, CI: $-0.021, 0.324$). No sign of publication bias was detected. In the pooled analysis, we used a random effects model instead of fixed effects model as the heterogeneity between studies was significant ($I^2 = 97.04\%$, $p < 0.001$ for TG; $I^2 = 96.09\%$, $p < 0.001$ for TC; $I^2 = 96.14\%$, $p < 0.001$ for LDL-C; $I^2 = 99\%$, $p < 0.001$ for HDL-C) and we did not conduct sub-group analysis due to the relatively high dispersion between studies.

Discussion

This systematic review and meta-analysis, which, to the best of our knowledge, is the first of its kind, revealed a weak significant association between serum 25(OH)D levels and lipid profiles in children and adolescents. The few existing meta-analysis data have explored the relationships of vitamin D status with type 2 diabetes and metabolic syndrome mostly in adult populations (Parker et al., 2010).

Seventeen studies included more than 25 000 participants. Previous reports have shown conflicting results regarding the association between vitamin D status and lipid profile in the pediatric group (Dolinsky et al., 2013). We found a relatively

weak inverse association between TG and vitamin D status, consistent with the previous results. About 12 of the 15 studies included in the current meta-analysis reported inverse association of TG with increasing serum levels of 25(OH)D, whereas some cohorts did not document such association (Nam et al., 2012; Reis et al., 2009). Only one study reported an inverse non-significant association of TG and 25(OH)D levels among boys, while positive significant association was observed for girls (Ashraf et al., 2011). The discrepancies of these studies might be partly explained by confounders as age and gender. One other explanation might refer to the diet, as increment in fatty fish intake could possibly result in both increased serum vitamin D and decreased serum TG levels (Ashraf et al., 2011).

The vast majority of studies have demonstrated a positive direct association between HDL-C and 25-hydroxy-D levels and one out of 14 reported no relationship (Nam et al., 2012). In accordance with these studies, we observed that cardio-protective levels of HDL-C increase with an increment in serum 25-OH-D levels. Five studies out of ten have reported an inverse association regarding LDL-C levels and vitamin D. However, three other studies showed a non-significant positive association (Nam et al., 2012; Reis et al., 2009; Williams et al., 2012) except for the paper of Ashraf et al. (2011), which reported significant positive association between LDL and vitamin D. This finding is in contrast with recent cross-sectional results showing the protective role of vitamin D against CVD (Major et al., 2007). Although the related mechanisms for the direct association between vitamin D and LDL-C are not clear, several possible explanations have been proposed. According to Zitterman et al. (2009) and Martins et al. (2007), vitamin D might decrease serum TG and it is well known that the clearance of VLDL may lead to increased levels of HDL-C and LDL-C. Furthermore, it is possible that binding of 25-OH-D to LDL-C could result in the reduction of LDL-C clearance (Teramoto et al., 1995). Given the very high prevalence of hypovitaminosis D, even in sunny regions (Kelishadi et al., 2014), interventional programs should be considered as a health priority at individual and public health levels.

Most of the study results presented for the current meta-analysis have found an inverse correlation between serum TC levels and vitamin D status of children and adolescents, however few of them mentioned a non-significant positive association; two studies reported significant positive relations. The confounders as age, gender and some unknown factors might explain these dispersions.

Although our initial aim was to compare the data between gender, age and even for different ethnic subgroups, the results presented in each study were not based on the details to conduct further stratified pooled analyses. These findings might be confounded by heterogeneity, which can be explained partly by multiple dispersions between studies such as study design and the confounders, and variables which adjustments were made for, as well as the techniques for measurement of 25-OH-D, and the way of reporting 25-OH-D.

Conclusion

Based on these cross-sectional data used for meta-analysis where the majority of the study results indicate that serum 25-hydroxy-D is directly associated with serum HDL-C and inversely related to TC, LDL and TG, it is important to mention that higher serum 25-OH-D is related to a more favorable lipid profile in the pediatric age group.

Author contributions

All authors participated actively in the preparation of the manuscript; RK and MB: Search strategy, study selection and drafting of the manuscript, ZF; study selection and data analyses.

Declaration of interest

None to declare. This study was funded by Child Growth and Development Research Center, Isfahan University of Medical Sciences.

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