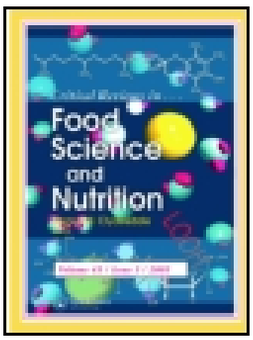

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: M. S. Filgueiras, N. P. Rocha, J. F. Novaes & J. Bressan (2018): Vitamin D status, oxidative stress, and inflammation in children and adolescents: A systematic review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2018.1546671

To link to this article: https://doi.org/10.1080/10408398.2018.1546671

Published online: 30 Dec 2018.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2018.1546671

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REVIEW

Vitamin D status, oxidative stress, and inflammation in children and adolescents: A systematic review

M. S. Filgueiras, N. P. Rocha, J. F. Novaes, and J. Bressan

Department of Nutrition and Health, Federal University of Viçosa, Viçosa, Minas Gerais, Brazil

ABSTRACT

Vitamin D deficiency is considered a global public health problem with high prevalence in children and adolescents. The majority of the studies in the literature have identified a relationship between vitamin D insufficiency/deficiency and obesity, as well as other traditional cardiometabolic risk factors in children and adolescents. Scarce studies address vitamin D status with oxidative stress and inflammation in the young population. The aim of this systematic review was to evaluate the evidence of the association of vitamin D status with oxidative stress and inflammation in children and adolescents. This is a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guideline on reporting systematic reviews. Eight studies were selected for this review. All included studies evaluated inflammatory biomarkers and two out of eight evaluated biomarkers of oxidative stress. The majority of the studies (five out of eight) found association of vitamin D status with biomarkers of oxidative stress and inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), cathepsin S, vascular cell adhesion molecule-1 (VCAM-1), malondialdehyde (MDA), myeloperoxidase, 3-nitrotyrosine, and superoxide dismutase (SOD). Vitamin D status is associated with oxidative stress and inflammation in the majority of the studies with children and adolescents. Thus, the assessment of vitamin D status is important because it is associated with nontraditional cardiometabolic markers in the pediatric population (review registration: PROSPERO CRD42018109307).

KEYWORDS

Vitamin D deficiency; biomarkers; inflammation mediators; antioxidants; calcifediol; child; adolescent

Introduction

Vitamin D is a pro-hormone that is responsible for the metabolism of calcium and phosphorus and is essential for maintaining bone health in childhood and adolescence (Wharton and Bishop 2003; Holick 2006). In addition to the role in bone homeostasis, studies have shown that vitamin D deficiency is associated to the development of infectious, autoimmune, and cardiometabolic diseases (Holick 2004; Borges, Martini, and Rogero 2011; Kelly et al. 2011). Vitamin D is known to control more than 200 genes involved in the regulation of cell proliferation, differentiation, apoptosis, and angiogenesis (DeLuca 2004; Holick 2007; Nagpal, Na, and Rathnachalam 2005).

Vitamin D deficiency is considered a global public health problem (Palacios and Gonzalez 2014) with high prevalence in children and adolescents (Mokhtar et al. 2018; Milagres et al. 2017a; Yu et al. 2013). This can be attributed mainly to decreased sun exposure and insufficient intake of vitamin D rich foods like cold deep-water fish (Bezrati et al. 2016).

25-hydroxy-vitamin D (25(OH)D) is the major circulating form of vitamin D and is used to assess the status of this vitamin (Holick 2007). According to the Institute of Medicine, deficiency is categorized as serum concentrations of 25(OH)D lower than 30 nmol/L or 12 ng/mL, which is insufficient to protect against bone diseases, while sufficiency is categorized as concentrations of 25(OH)D greater than 50 nmol/L or 20 ng/mL, which indicates a lower risk of these diseases in the general population (IOM 2011). However, some studies have shown that higher concentrations of 25(OH)D, 75 nmol/L or 30 ng/mL, are associated with a lower risk of chronic non-communicable diseases and are considered to be optimal or adequate vitamin D status (McDonnell et al. 2016; Gaksch et al. 2017; Calvo and Lamberg-Allardt 2017).

The majority of the studies in the literature have identified a relationship between vitamin D insufficiency/deficiency and obesity, as well as other traditional cardiometabolic risk factors (dyslipidemias, hyperglycemia, insulin resistance, and hypertension) in children and adolescents (Pacifico et al. 2011; Milagres et al. 2017b). However, studies with animals and cells have pointed out that vitamin D has immunomodulatory effects, because immune cells, such as dendritic cells, macrophages, B and T cells express the vitamin D receptor (VDR) (Yin and Agrawal 2014).

Subclinical inflammation and oxidative stress are associated with obesity and its cardiometabolic complications, contributing to the onset of endothelial dysfunction and atherosclerosis (Codoñer-Franch et al. 2011). Oxidative stress is characterized by the decline of antioxidant defenses

CONTACT M. S. Filgueiras mariana.filgueiras@ufv.br Department of Nutrition and Health, Federal University of Viçosa, Viçosa 36570-900, Minas Gerais, Brazil.

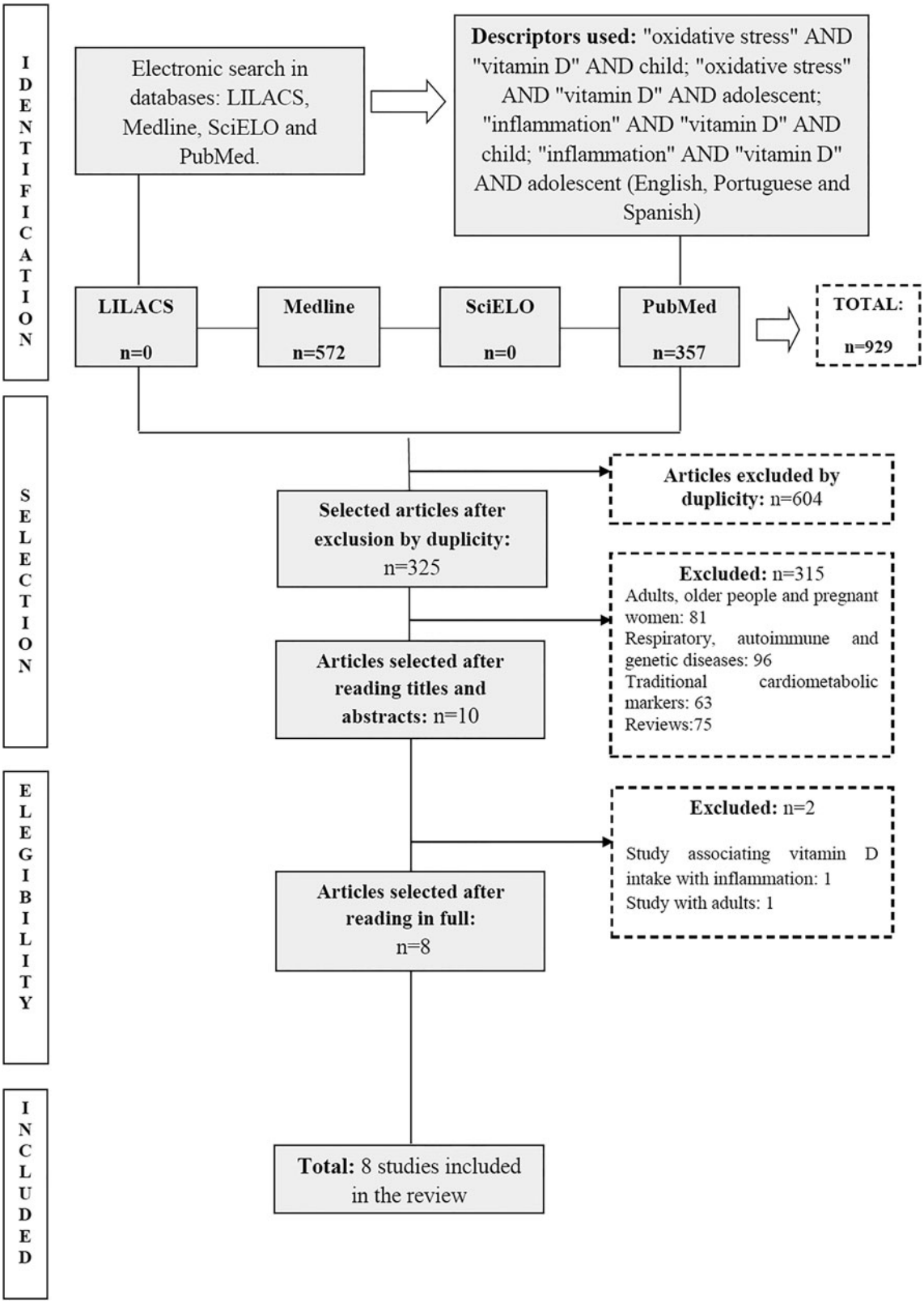

Figure 1. Protocol identifying and selecting eligible studies for the systematic review on vitamin D status, oxidative stress, and inflammation in children and adolescents.

associated with antioxidant enzymes and the increase of reactive oxygen (ROS) and nitrogen (RNS) species (Keaney et al. 2003; Olusi 2002). This oxidative status present in cardiometabolic alterations is associated with the secretion of proinflammatory cytokines, which also trigger oxidative stress (Korda et al. 2008). Although these alterations are more frequent in aging, it is already possible to observe them in young individuals (Gilardini et al. 2011).

Some studies have demonstrated that vitamin D has antioxidant properties, protecting endothelial cells, retinal cone

cells in humans (Uberti et al. 2014; Tohari, Zhou, and Shu 2016), and activating the Nrf2-KEAP1 antioxidant pathway in rats with diabetes (George et al. 2012). However, a large part of studies performed with children and adolescents are about the relationship of oxidative stress with respiratory (Fitzpatrick et al. 2014) and hepatic (Pirgon et al. 2013) diseases, obesity (Codoñer-Franch et al. 2010), and autism (Ghezzo et al. 2013).

So far, we have identified reviews that have examined the relationship between vitamin D and immune diseases in different age groups (Colotta, Jansson, and Bonelli 2017) and oxidative stress in individuals with type 2 diabetes *mellitus* (Berridge 2017). Scarce studies address vitamin D status with oxidative stress and inflammation in the young population. Therefore, the objective of this review was to evaluate the evidence of the association of vitamin D status with oxidative stress and inflammation in children and adolescents.

Methods

Identification and selection of studies

This is a systematic review focused on the research question "What is the evidence of the association of vitamin D status with oxidative stress and inflammation in children and adolescents?" This systematic review was conducted from August to September 2017, based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guideline (Moher et al. 2009) and registered in PROSPERO (registration number: CRD42018109307).

Latin-American and Caribbean System on Health Sciences Information (LILACS), Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (SciELO), and PubMed databases were searched. The following combined descriptors were matched to the Medical Subject Headings (MeSH) index: "oxidative stress" AND "vitamin D" AND child; "oxidative stress" AND "vitamin D" AND adolescent; "inflammation" AND "vitamin D" AND child; "inflammation" AND "vitamin D" AND adolescent, as well as their Portuguese and Spanish equivalents. No geographical and date limits were established.

A protocol was defined to identify and select the studies (Figure 1). The articles were independently screened and selected by two researchers (M.S.F. and N.P.R.). In the case of disagreements, the reviewers jointly reviewed the articles to reach consensus, and a third reviewer assisted when consensus could not be reached. All steps of the systematic review were first performed manually, and later with the software *State of the Art through Systematic Review* (StArt) version 3.0.3 Beta (Research Laboratory in Software Engineering, Federal University of São Carlos, São Carlos, Brazil).

Eligibility criteria

The following eligibility criteria were adopted:

1. inclusion: published observational or interventional studies with children and/or adolescents (aged 2 to 19 years) that evaluated oxidative and/or inflammatory stress biomarkers such as antioxidant enzymes, reactive oxygen (ROS) and nitrogen (RNS) species, cytokines, adipokines, and C-reactive protein (CRP);
2. exclusion: published studies with adults, older people, pregnant women, nursing mothers and infants; animals or cells; children and/or adolescents with respiratory, autoimmune, and genetic diseases, psychomotor and physical disorders, and/or hospitalized; traditional cardiometabolic markers such as cholesterol and fractions, triglycerides, insulin, blood glucose, and blood pressure; studies in duplicate; gray literature; reviews; congress abstracts; books and book chapters; monographs, dissertations, and theses.

Extraction of datum

The information obtained from the articles selected were: author; year of publication; geographic setting; study design; recruitment; sample size; age (year); 25(OH)D assay method and interpretation; outcome variables (oxidative stress and/or inflammation); main statistical method and adjustment variables; vitamin D status; main results; and whether there is association (yes or no).

Quality assessment of studies

We evaluated the quality of the studies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (von Elm et al. 2007).

Each reviewer independently (M.S.F and N.P.R.) scored the overall quality for each study, giving 1 point for each STROBE item covered by the article. After evaluating all the criteria, each study received a score of 0 to 22 from each reviewer. For the final score, an average of the two scores was performed, and the variation of the scores among the reviewers was not higher than 1. The score was transformed in percentage to better evaluate the quality of the articles.

Results

Selection and description of studies included

Both searches, manual and StArt software, identified 929 articles using the combined descriptors. Of these, eight original articles met the eligibility criteria and were included in this review (Figure 1).

Seven studies were cross-sectional and one was a pilot of prospective cohort. Most studies presented recruitment in schools (n = 4) and sample sizes ranged from 25 to 5,867 individuals with ages ranging from 6 to 19 years. All articles included evaluated inflammatory biomarkers, but only two showed oxidative stress variables as outcome (Table 1).

Table 1. Description of the studies that evaluated the association of vitamin D status with oxidative stress and inflammation in children and adolescents.

Author	Year of publication	Geographic setting	Study design	Recruitment	Sample size	Age (year)	Assay method	25(OH) D interpretation	Outcome variables
Petersen et al.	2015	Denmark	Cross-sectional	School (New Nordic Diet – OPUS – School Meal Study)	782	8–11	Chemiluminescent immunoassay (LIAISON® – DiaSorin)	D: <10 ng/mL (<25 nmol/L) I: 10–20 ng/mL (25–50 nmol/L) S: >20 ng/mL (>50 nmol/L)	IL-6, Adiponectin
Singh et al.	2015	United States	Pilot of prospective cohort	Preventive cardiology clinic	25	9–11	LC-MS/MS	D: <20 ng/mL (<50 nmol/L) I: 20–30 ng/mL (50–75 nmol/L) S: >30 ng/mL (>75 nmol/L)	us-CRP
Reyman et al.	2014	Netherlands	Cross-sectional	Pediatric outpatient	96 (64 obese and 32 healthy)	6–16	ECLIA (Elecsys® Vitamin D Assay – Roche)	D: ≤15 ng/mL (≤37.5 nmol/L) I: 15–20 ng/mL (37.5–50 nmol/L) S: ≥20 ng/mL (≥50nmol/L)	us-CRP, IL-18, Cathepsin S, Chemerin, HGF, Leptin, PAI-1, RBP-4, EGF, sVCAM, TNF-R2
Rodríguez-Rodríguez et al.	2014	Spain	Cross-sectional	School	137	9–12	Chemiluminescent immunoassay (LIAISON® - DiaSorin)	D: <20 ng/mL (<50 nmol/L) Adequate: ≥20 ng/mL (≥50 nmol/L);	hs-CRP, IL-6, TNF-α, Adiponectin
Zhang et al.	2014	China	Cross-sectional	School	1,488	7–11	UHPLC-MS/MS	D: <20 ng/mL (<50 nmol/L) I: 20–30 ng/mL (50–75 nmol/L) S: >30 ng/mL (>75 nmol/L)	CRP, IL-6, MDA, SOD
Boucher-Berry et al.	2012	United States	Cross-sectional	School (Reduce Obesity and Diabetes – ROAD study)	106	11–14	DiaSorin radioimmunoassay	NI	IL-6, CRP, TNF-α, Adiponectin
Codoñer-Franch et al.	2012	Spain	Cross-sectional	Pediatric outpatient	66	7–14	ECLIA (Elecsys® Vitamin D Assay – Roche)	I: <20 ng/mL (<50 nmol/L) S: >20 ng/mL (>50 nmol/L)	Adiponectin, Leptin, MDA, Myeloperoxidase, Urinary nitrate, Nitrite + Nitrate, 3-Nitrotyrosine, us-CRP, IL-6, TNF-α, sICAM, sVCAM-1, E-selectin, VEGF
Ganji et al.	2011	United States	Cross-sectional	Population (National Health and Nutrition Examination Survey – NHANES)	5,867	12–19	DiaSorin radioimmunoassay	Tertile 1: 19.2 ng/mL (<48.1 nmol/L) Tertile 2: 19.2–24.6 ng/mL (48.1–66.2 nmol/L) Tertile 3: ≥24.6 ng/mL (≥66.2 nmol/L)	CRP

25(OH)D, 25-hydroxy-vitamin D; CRP, C-reactive protein; D, deficiency; ECLIA, electrochemiluminescence binding assay; EGF, epidermal growth factor; HGF, hepatocyte growth factor; hs-CRP, high-sensitivity C-reactive protein I, insufficiency; IL-6, interleukin-6; IL-18, interleukin-18; LC-MS/MS, liquid chromatography–tandem mass spectrometry; MDA, malondialdehyde; NI, not interpreted; PAI-1, plasminogen activator inhibitor-1; RBP-4, retinol binding protein-4; S, sufficiency; sICAM, soluble intercellular adhesion molecule; SOD, superoxide dismutase; sVCAM, soluble vascular cellular adhesion molecule; sVCAM-1, soluble vascular cellular adhesion molecule-1; TNF-R2, tumor necrosis factor receptor 2; TNF-α, tumor necrosis factor-α; UHPLC-MS/MS, ultra-high-performance liquid chromatography–tandem mass spectrometry; us-CRP, ultra-sensitive C-reactive protein; VEGF, vascular endothelial growth factor.

Assay methods

25(OH)D assay methods varied widely among the studies, being cited: chemiluminescent immunoassay, liquid chromatography–tandem mass spectrometry (LC-MS/MS), electrochemiluminescence binding assay (ECLIA), ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) and radioimmunoassay (Table 1).

Interpretation of 25(OH)D serum concentrations

A similar case was observed for the interpretation of 25(OH)D serum concentrations, which two studies chose not to adopt classification criteria for deficiency, insufficiency and sufficiency (Boucher-Berry et al. 2012; Ganji et al. 2011). Two studies (Singh et al. 2015; Zhang et al. 2014) adopted the classification proposed by Holick (2007), which was recommended by the Institute of Medicine (2011). Two other studies (Reyman et al. 2014; Codoñer-Franch et al. 2012a) followed the classification proposed by Misra et al. (2008). One study (Petersen et al. 2015) used the classification proposed by European Society for Paediatric Gastroenterology, Hepatology and Nutrition (Braegger et al. 2013) (Table 1).

The prevalence of vitamin D deficiency varied from 2.4% to 56.4%, but one study did not evaluate prevalence of deficiency, since serum concentrations of 25(OH)D were categorized as tertiles (Ganji et al. 2011). The study conducted by Boucher-Berry et al. (2012) demonstrated that the prevalence of boys and girls with serum concentrations of 25(OH)D below 20 ng/mL (<50 nmol/L) was 51% and 52%, respectively (Table 2).

Statistical analysis and adjustment variables

Most of the studies adopted as main statistical analysis the multiple linear regression models (n = 5), being adjusted most often by variables such as age, sex, variables related to body adiposity and physical activity. Other studies adopted less robust statistical analyzes, such as linear correlation, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) (Table 2).

Vitamin D status and oxidative stress

Most included studies (n = 5) showed association between 25(OH)D and biomarkers of oxidative stress and/or inflammation (Table 2). Among the studies that verified an association between vitamin D and oxidative stress biomarkers, one cross-sectional study with 1,488 Chinese children aged 7 to 11 years found association of 25(OH)D concentrations with CRP, interleukin-6 (IL-6), malondialdehyde (MDA), and superoxide dismutase (SOD). In the linear regression, 25(OH)D remained associated with SOD concentrations (β: 0.230; $p < 0.001$), after adjusting for sex, age, body mass index (BMI), and body fat percentage (%BF) (Zhang et al. 2014). Another cross-sectional study with 105 Spanish children and adolescents aged 7 to 14 years showed that obese subjects with vitamin D deficiency had higher concentrations of MDA, myeloperoxidase, 3-nitrotyrosine, IL-6, and soluble vascular cell adhesion molecule-1 (sVCAM-1) than subjects with vitamin D sufficiency (Codoñer-Franch et al. 2012a).

Vitamin D status and inflammation

Regarding the inflammatory biomarkers, one study with 96 subjects aged 6 to 16 years in the Netherlands evaluated the association of vitamin D deficiency with a series of inflammatory mediators, and after adjusting for BMI, age, and sex, only the concentrations of cathepsin S (β: −0.341; $p < 0.001$) and sVCAM (β: −0.342; $p < 0.001$) remained inversely associated with 25(OH)D (Reyman et al. 2014). One study with 137 Spanish subjects aged 9 to 12 years showed that 25(OH)D concentrations were inversely associated with IL-6 (β: -0.160 ± 0.068; $p = 0.023$), adjusted for age, physical activity, and %BF (Rodríguez-Rodríguez et al. 2014). Another cross-sectional study showed a significant inverse correlation between 25(OH)D and IL-6 concentrations in Caucasians ($r = -0.45$; $p = 0.047$), in 106 American adolescents aged 11 to 14 years (Boucher-Berry et al. 2012).

However, a one-year prospective cohort pilot study found no association between serum vitamin D and subclinical inflammation, using ultra-sensitive C-reactive protein (us-CRP), in 25 American children and adolescents aged 9 to 11 years (Singh et al. 2015). A cross-sectional study with 782 Danish subjects aged 8 to 11 years found no association between serum concentrations of 25(OH)D and IL-6 (β: 0.01, 95% CI: −0.02; 0.04; $p = 0.49$) and adiponectin (β: 102; 95% CI: −124; 328; $p = 0.38$) (Petersen et al. 2015). A cross-sectional study with NHANES 2001–2006 data, involving 5867 American adolescents aged 12 to 17 years showed no association between CRP concentrations and 25(OH)D concentration tertiles (Ganji et al. 2011).

Quality of the studies

Out of the total score of 22, scores ranged from 16.1 to 18.7 points and percentages ranged from 73% to 85.1% (Table 2). The criteria in which the articles most failed were: to present key elements of study design in abstract and early in the paper; clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; describe any efforts to address potential sources of bias; explain how the study size was arrived at; explain how missing data were addressed; give reasons for nonparticipation at each stage; and indicate number of participants with missing data for each variable of interest.

Discussion

This systematic review, which, to best of our knowledge, is the first of its kind, gathers evidence on the association of

vitamin D status with oxidative stress and inflammation in children and adolescents, as shown in Figure 2. Given that oxidative stress and inflammation are associated with traditional cardiometabolic risk markers in children and adolescents (Codoñer-Franch et al. 2011; Codoñer-Franch et al. 2012b), it is necessary to know more about their relationship with vitamin D. It is noteworthy that original articles addressing this issue are scarce, the existing literature focuses more on vitamin D status associated with traditional cardiometabolic risk factors (Pacifico et al. 2011; Milagres et al. 2017b).

Oxidative stress arises from the imbalance between the production of oxidizing compounds and the performance of the antioxidant defense systems. This, in turn, inhibits and/or reduces the damage caused by the deleterious action of free radicals or non-radical reactive species via antioxidant enzymes such as SOD, catalase, and glutathione peroxidase (enzyme system), or via endogenous antioxidants or diet-derived antioxidants like carotenoids, vitamins C and E, and phytochemicals (non-enzymatic system) (Barbosa et al. 2010).

Besides antioxidant enzymes, it is possible to quantify oxidative stress markers derived from the oxidation of lipids, proteins, and deoxyribonucleic acid (DNA). MDA is an aldehyde derived from the oxidation of fatty acids such as arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). On the other hand, 3-nitrotyrosine is derived from the action of reactive nitrogen oxide species in the oxidation of proteins (Halliwell and Whiteman 2004). Myeloperoxidase has been identified as a new biomarker of oxidative stress because it is an enzyme produced by leukocytes and is related to the modification of cholesterol flow and impairment of vascular relaxation induced by nitric oxide (Anatoliotakis et al. 2013).

Vitamin D is also prominent in modulating the innate immune response to different pathogens in humans and regulating the adaptive immune response in inflammatory and autoimmune diseases (White 2008; Tiosano et al. 2013). In human monocytes, vitamin D inhibits the production of IL-6 and tumor necrosis factor-α (TNF-α) (Zhang et al. 2012), in addition to reducing monocyte chemoattractant protein-1 (MCP-1) expression by inhibiting the activation of nuclear factor-κB (NF-κB) in macrophages (Sanchez-Niño et al. 2012). However, further studies are needed to elucidate the mechanisms of vitamin D in inflammation.

Studies with children and adolescents included in this review found no association between concentrations of 25(OH)D and adipokines. Vitamin D appears to be associated with adipokine concentrations in other population groups (Gannagé-Yared et al. 2009; Ismail et al. 2017), but the mechanisms involved are still unclear. One of the proposed mechanisms is related to the increase in parathormone concentrations and the low concentrations of 25(OH)D, which stimulate lipogenesis, obesity, and insulin resistance, and increases the activity of proinflammatory cytokines such as TNF-α and interleukin-1 (IL-1), associated with adipokine imbalance. Another proposed mechanism is that VDRs present in adipocytes would enable vitamin D to regulate adipokine gene expression in visceral adipose tissue (Mutt et al. 2014). In addition, vitamin D could affect adipokine concentrations via the renin-angiotensin system, in which increased angiotensin production would lead to adipocyte dysfunction and reduced adiponectin production (Vaidya et al. 2011). Finally, vitamin D could stimulate osteocalcin, which increases the adiponectin gene expression in adipocytes (Nimitphong et al. 2009).

CRP is a prototypical marker of inflammation present in high concentrations in individuals with metabolic syndrome (Haffner 2006). In this review, the studies included showed inverse association of 25(OH)D and CRP concentrations, however, mechanisms explaining how vitamin D interferes in the concentrations of CRP are unclear. One possible mechanism is that vitamin D inhibits the synthesis of IL-6 by monocytes, which is the major inducer of CRP in the liver (Zhang et al. 2012). Therefore, experimental studies are needed to clarify this relationship.

The association of 25(OH)D concentrations with cathepsin S and sVCAM has been demonstrated (Reyman et al. 2014). Cathepsin S is a protease that hydrolyzes elastin fibers in the artery wall, promoting vascular inflammation and calcification (Wilkinson et al. 2015), and therefore it has been associated with higher mortality in adults (Jobs et al. 2011). Studies have shown that vitamin D induces the expression of cystatin D, which is a potent inhibitor of cathepsin S (Alvarez-Diaz et al. 2009; Balbin et al. 1994). sVCAM, in its turn, is a cell adhesion molecule expressed by atherosclerotic plaques and is essential in the progression of atherosclerosis. A study with humans has shown that vitamin D is able to reduce the expression of sVCAM in endothelial cells (Stach et al. 2011), reinforcing its anti-inflammatory role.

Each population has different factors influencing the prevalence of vitamin D deficiency, e.g., sun exposure, vitamin D rich foods, supplements, and fortified foods. It is noteworthy that the differences in the assay methods and the interpretation of 25 (OH)D serum concentrations make it difficult to compare the results. The Vitamin D Standardization Program (VDSP) developed protocols in order to standardize measurement procedures of 25(OH)D in health/nutrition surveys for facilitating the comparison among studies and to improve public health practice. In the VDSP, LC-MS/MS is the reference method (Cashman et al. 2013). Regarding the classification criteria, there are different recommendations, but still without a consensus for the pediatric population. In 2016, the Global Consensus Recommendations on Prevention and Management of Nutritional Rickets proposed the following classification: >20 ng/mL (sufficiency), 12–20 ng/mL (insufficiency) and <12 ng/mL (deficiency) (Munns et al. 2016). Since then, the use of this classification has been raised for the general population (Calvo and Lamberg-Allardt 2017). Thus, standardizing measurement methods and cutoff points, especially for children and adolescents, will enable determining the magnitude of vitamin D insufficiency/deficiency.

It is worth noting how the studies recruited the participants to compose the samples The external validity of the studies that recruited in outpatient visits may be impaired,

Table 2. Main statistical analyzes, results and quality assessment of the studies that evaluated the association of vitamin D status with oxidative stress and inflammation in children and adolescents.

Reference	Main statistical method	Adjustment variables	Vitamin D status	Main results	Is there association? (Yes/No)	STROBE score	STROBE (%)
Petersen et al. 2015	Multiple linear regression models	Model 1: sex, age, height, ethnicity, whole-blood EPA + DHA, entered puberty (yes/no) and parental education Model 2: Model 1 + fat mass index Model 3: Model 1 + moderate-to-vigorous physical activity (min/day)	D: 2.4% I: 28.4% S: 69.2%	In all models, there was no association of IL-6 (β: 0.01; 95% CI: −0.02; 0.04; p = 0.49) and adiponectin (β: 102; 95% CI: −124; 328; p = 0.38) with 25(OH)D.	No	18.2	82.8
Singh et al. 2015	ANOVA	NA	D: 1 (4%) I: 17 (68%) S: 7 (28%)	There was no difference in 25(OH)D means among individuals with us-CRP >3 to <10 mg/L (27.7 ± 5.5 ng/mL), 1–3 mg/L (24.0 ± 4.8 ng/mL), and <1 mg/L (28.4 ± 7.1 ng/mL).	No	18.7	85.1
Reyman et al. 2014	Multiple linear regression models	Body mass index, age and gender	Obese: D: 36 (56%) I/S: 28 (44%) Healthy: D: 5 (16%) I/S: 27 (84%)	Cathepsin S (β: −0.341; R^2: 0.141; p < 0.001) and sVCAM (β: −0.342; R^2: 0.273; p < 0.001) remained associated with 25(OH)D in the adjusted multiple linear regression analysis.	Yes	17.0	77.1
Rodríguez-Rodríguez et al. 2014	Multiple linear regression models	Age, physical activity and body fat percentage.	D: 39.4% Adequate: 60,6%	Concentrations of 25(OH)D inversely associated with IL-6 concentrations after adjustment (β: −0.160 ± 0.068; p = 0.023).	Yes	16.1	73.0
Zhang et al. 2014	Multiple linear regression models	Model 1: Sex and age Model 2: Model 1 + body mass index Model 3: Model 1 + percentage of body fat Model 4: Model 1 + body mass index + body fat percentage	D: 839 (56.4%) I: 347 (23.3%) S: 302 (20.3%)	25(OH)D remained associated with SOD in the adjusted multivariate linear regression analysis (β: 0.230; p < 0.001).	Yes	16.6	75.4
Boucher-Berry et al. 2012	Linear correlation	NA	Boys: <20 ng/mL (<50 nmol/L): 51% <30 ng/mL (<75 nmol/L): 88% Girls: <20 ng/mL (<50 nmol/L): 52% <30 ng/mL (<75 nmol/L): 84%	In Caucasian subjects, 25(OH)D correlated inversely with IL-6 concentrations (r = −0.45; p = 0.047).	Yes	16.1	73.1
Codoñer-Franch et al. 2012a	ANCOVA	Sex, age, and Tanner stage.	I: 20 (30%) S: 46 (70%)	Obese individuals with vitamin D deficiency had concentrations of MDA, myeloperoxidase, 3-nitrotyrosine, IL-6, and sVCAM-1 higher than individuals without deficiency.	Yes	16.8	76.2
Ganji et al. 2011	Multiple linear regression models	Age, race-ethnicity, body mass index and poverty-income ratio	UI	There were no differences in CRP concentrations between the tertiles of 25(OH)D concentrations.	No	18.6	84.6

25(OH)D, 25-hydroxy-vitamin D; 95%CI, 95% confidance interval; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CRP, C-reactive protein; D, deficiency; I, insufficiency; IL-6, interleukin-6; MDA, malondialdehyde; NA, not applicable; S, sufficiency; SOD, superoxide dismutase; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SVCAM, soluble vascular cellular adhesion molecule; sVCAM-1, soluble vascular cellular adhesion molecule-1; UI, uninformed; us-CRP, ultra-sensitive C-reactive protein.

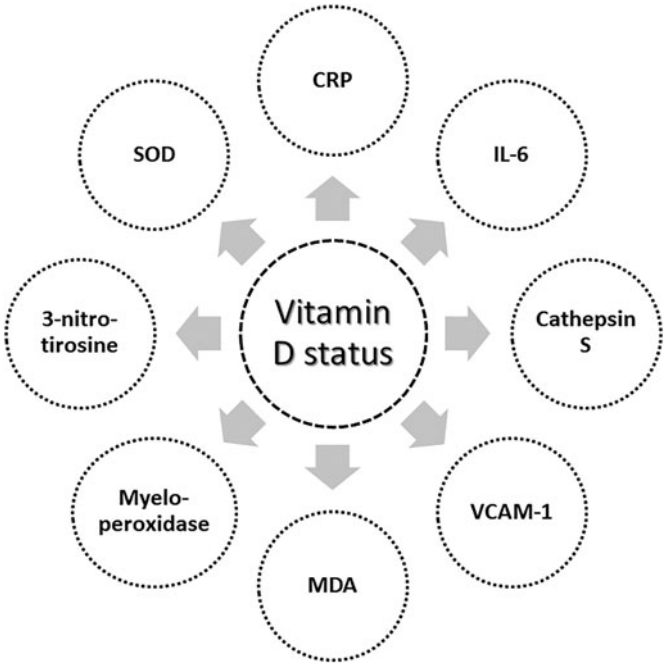

Figure 2. Markers of oxidative stress and inflammation associated with vitamin D status in children and adolescents. CRP, C-reactive protein; IL-6, interleukin-6; VCAM-1, vascular cellular adhesion molecule-1; MDA, malondialdehyde; SOD, superoxide dismutase.

since some studies considered only obese individuals besides the possibility of already presenting some associated comorbidity. However, most of the studies is school-based, making it possible to generalize the results to healthy population.

Considering that different studies have demonstrated possible mechanisms of how adiposity is related to serum vitamin D concentrations (Vimaleswaran et al. 2013; McCarty and Thomas 2003), we can say that the studies that adjusted for possible confounders were careful to include in their models variables such as BMI and body fat percentage.

Regarding the quality of the articles included in this review, it is observed that few described about the sample calculation or study power. Another important point is the absence of description of missing data and bias in the studies, since they may underestimate or overestimate the relationships. Despite the selected studies have not described the possibility of the occurrence of a failure in the internal and external validity, they allow us to raise an association that is poorly investigated, especially in young people. Meanwhile, this indicates the need for longitudinal studies in this approach that better describe sample size calculation, missing data and possible biases.

The strength of this review is a systematic approach based on the PRISMA method, the peer review and the quality assessment of studies based on STROBE method. However, it was not possible to perform meta-analyzes due to statistical limitations. The low number of studies included in this review may be a limitation to assert the association of vitamin D status with oxidative stress and inflammation. However, we have raised the need for further studies with this approach, especially longitudinal studies.

In conclusion, the evidence presented in this review indicates that vitamin D status is associated with oxidative stress and inflammation in children and adolescents. Because of the vitamin D insufficiency/deficiency high prevalence in young subjects and its association with different alterations, we recommend its use it in the screening of nontraditional cardiometabolic risk factors in the pediatric population.

Acknowledgments

We thank Foundation for Research Support of the state of Minas Gerais (FAPEMIG) and Coordination for the Improvement of Higher Education Personnel (CAPES) for granting doctoral scholarships for M.S.F. and N.P.R.

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