ESCOLA BAHIANA DE MEDICINA E SAÚDE PÚBLICA

CURSO BIOMEDICINA

LAÍS SALES DOS SANTOS

NÍVEIS DE VITAMINA D EM CRIANÇAS E ADOLESCENTES COM ASMA – A SUPLEMENTAÇÃO MELHORA OS SINTOMAS? UMA REVISÃO SISTEMÁTICA

SALVADOR – BA

2021

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Trabalho de Conclusão de Curso apresentado à Escola Bahiana de Medicina e Saúde Pública, como parte dos requisitos para obtenção do título de Bacharel em Biomedicina.

Orientador(a): Profª. Drª Cinthia Vila Nova Santana.

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Este Trabalho de Conclusão de Curso foi julgado adequado à obtenção do grau de Bacharel em Biomedicina e aprovada em sua forma final pelo Curso de Biomedicina da Escola Bahiana de Medicina e Saúde Pública.

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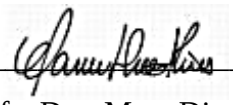

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Dedico este trabalho a Deus, a minha família e todos que fazem parte disto.

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Isaias 41:10

"A big grand gesture, it's not about the actual thing that you do, it's not about what you say, it's about intent. It's about taking the time to tell the person you care about,I see you, I hear you, I know exactly what you need right now,and I'm showing how important that is to me."
- Jack Pearson (This Is Us)

"Palavras são, na minha nada humilde opinião, nossa inesgotável fonte de magia.
Capazes de formar grandes sofrimentos e também de remediá-los."
- Alvo Dumbledore (Harry Potter e as Relíquias da Morte)

RESUMO

O papel imunomodulador da vitamina D vem sendo estudado em diversas patologias do trato respiratório e os estudos da sua atuação na patogênese da asma ainda demonstram resultados divergentes na literatura. Esse trabalho visa revisar sistematicamente a literatura para esclarecer a relação entre a suplementação de vitamina D em crianças e adolescentes asmáticos. Trata-se de uma revisão sistemática cuja pesquisa dos artigos foi realizada nas bases de dados Scielo, Pubmed e Lilacs utilizando os descritores *"vitamin d", "calcitriol", "asthma", "child" e "adolescent"* junto aos operadores boleanos. Determinou-se como critérios de exclusão pacientes que apresentaram outra comorbidade além da asma, artigos que não apresentem dados em crianças e adolescentes, artigos que não apresentem dados correlacionando asma e vitamina D. Dos 506 artigos identificados, sete cumpriram os critérios de inclusão e foram selecionados. Dos estudos incluídos, cinco apresentaram suplementação realizada diariamente, um apresentou dosagem semanal e um apresentou dosagem mensal. Somente um dos estudos apresentou diagnóstico clínico de asma leve e diversos parâmetros foram analisados em cada artigo incluindo score ACT e CACT , IgE , citocinas das vias aéreas, função pulmonar, eosinofilia. Três artigos identificaram um papel para a vitamina D, enquanto que quatro estudos não identificaram a suplementação de vitamina D contribuindo para redução dos sintomas de asma em crianças e adolescentes. Essa heterogeneidade nos resultados disponíveis comprova a necessidade da expansão de novas pesquisas associadas a atuação da suplementação da vitamina D voltada para crianças e adolescentes asmáticos como uma via auxiliadora na terapêutica desta doença.

Palavras-chave: *Vitamin D; Calcitriol; Asthma, Child; Adolescent*

RESUMO EM LÍNGUA ESTRANGEIRA

(ABSTRACT)

The immunomodulatory role of vitamin D has been studied in several pathologies of the respiratory tract and studies of its role in the pathogenesis of asthma still demonstrate divergent results in the literature. This paper aims to systematically review the literature to clarify the relationship between vitamin D supplementation in asthmatic children and adolescents. This is a systematic review whose articles were searched in the Scielo, Pubmed and Lilacs databases using the descriptors “vitamin d”, “calcitriol”, “asthma”, “child” and “adolescent” along with Booleans operators. Exclusion criteria were participants who had a comorbidity other than asthma that may affect serum vitamin D levels, articles that did not present data on children and adolescents, articles that did not present data correlating asthma and vitamin D. Of the 506 articles identified, seven met the inclusion criteria and were selected. Five studies showed daily supplementation of vitamin D, one had weekly supplementation and other had monthly supplementation. Only one of the studies had a clinical diagnosis of mild asthma and several parameters were evaluated in each article including ACT and CACT scores, IgE, airway cytokines, lung function, eosinophilia. Three articles identified a role for vitamin D, however four studies found that vitamin D supplementation did not contribute to the reduction of asthma symptoms in children and adolescents. This heterogeneity in the available results added to the need for expansion of new research associated with the role of vitamin D supplementation in children and adolescents with asthma as an auxiliary route in the treatment of this disease.

Keywords: *Vitamin D; Calcitriol; Asthma, Child; Adolescent*

SUMÁRIO

ARTIGO CIENTÍFICO

NÍVEIS DE VITAMINA D EM CRIANÇAS E ADOLESCENTES COM ASMA – A SUPLEMENTAÇÃO MELHORA OS SINTOMAS? UMA REVISÃO SISTEMÁTICA

VITAMIN D LEVELS IN CHILDREN AND ADOLESCENTS WITH ASTHMA – DOES SUPPLEMENTATION IMPROVE SYMPTOMS? A SYSTEMATIC REVIEW

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1 INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation, and affects more than 339 million people worldwide [1,2]. Considered one of the most frequent respiratory diseases, asthma is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary in time and intensity, and symptoms are accompanied by variable airflow obstruction [3].

A national survey on school health (*PeNSe, Pesquisa Nacional em Saúde Escolar*) carried out in 2012, appoints Brazil as one of the countries with the highest prevalence of asthma in the world and indicates that it is possibly still growing in the population of schoolchildren [4]. About 50-75% of children and adolescents are classified as having mild asthma worldwide, however, 30-40% of all severe exacerbations occur in this group [5,6]. Viral infections stand out as the main trigger for asthma attacks, especially in childhood [7] and this provides an increased risk of developing more severe cases of the disease, as well as a reduction in lung growth and a decline in the maximum potential of lung function [8].

Several studies have identified conflicting relationships regarding the increase of exacerbation of asthma symptoms and hypovitaminosis D [9–15]. In the respiratory system, for example, vitamin D has shown positive results in its immunomodulatory role through antimicrobial and anti-inflammatory mechanisms [16]. Especially in the respiratory system, a deficiency of this vitamin is correlated with an increase of respiratory tract infections and tuberculosis, in addition to a decrease in lung function in asthma [17,18].

Investigations report the prevalence of a reduction in serum vitamin D levels in asthmatics [15,19,20]. However, there is still a divergence in the literature regarding the benefit of vitamin D supplementation in controlling asthma symptoms [14,21]. Thus, this paper aims to systematically review the literature to clarify whether vitamin D supplementation in children and adolescents improves asthma symptoms in this population.

2 METHODS

2.1 STUDY DESIGN

The present work consists of a systematic review of the scientific literature in order to elucidate the relationship between vitamin D supplementation in children and adolescents with asthma and was prepared following the diagram of the *Preferred Report Items for Systematics Reviews and Meta-Analyses* (PRISMA). [22]

To carry out the literature search, the search strategy in each database was based on the investigative question of this review: "Is vitamin D supplementation associated with the improvement of symptoms in children and adolescents with asthma?" which had as support the PICOS strategy *(Patient, Intervention, Comparison, Outcome and Study)* structured in Table 1[23,24].

2.2 DATA COLLECTION

The search was conducted from June to September 2021 using the terms identified in the platform Medical Subject Headings (MeSH) together with the boolean operators "AND" and "OR" in the US databases National Library of Medicine and the National Institutes of Health (PubMed), in Scientific Electronic Library Online (SciELO) and in Latin American and Caribbean Literature in Health Sciences (LILACS). The search strategy according to each database is detailed in Table 2.

2.3 INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria were a) articles in English and Portuguese, b) research carried out in humans, c) original articles being clinical trials or randomized clinical trials. Exclusion criteria were a) participants who had a comorbidity other than asthma that may affect serum vitamin D levels, b) articles that did not present data on children and adolescents, c) articles that did not present data correlating asthma and vitamin D.

2.4 STUDY SELECTION AND ANALYSIS

The located studies were imported into Microsoft Excel 2019 (Microsoft Office 365® Package), duplicates were excluded, and the data were extracted from the included articles. The following variables were collected from the selected articles: country of study, author, year of publication, journal, and impact factor (Table 3); in addition, the number of participants, sex, age, how vitamin D was acquired, dosage of vitamin D used, how vitamin D was collected for analysis, whether there was improvement in asthma symptoms after using vitamin D and control and severity of asthma can be found in Table 4.

After selecting the articles, the risk of bias was assessed using the forms provided by the Joanna Briggs Institute. Studies can be classified according to the answers to the questions as: low risk of bias if 70% or more of the checklist answers were “yes”, medium risk of bias for 50-69% and high risk of bias for 50% or any less (25).

3 RESULTS

506 articles were identified according to the determined search strategy. Of these, 469 were found in the PubMed database, 10 in Scielo and 27 in the LILACS platform. After duplicates evaluation, automation tools and title evaluation, 434 articles were removed. In a second selection, 72 articles were selected for reading evaluation by abstract and of these 60 were excluded by the text for not meeting the inclusion criteria. Twelve articles were evaluated for eligibility and seven were included in this work (Figure 1).

Of the seven eligible studies, two were carried out in the United States of America, two in India, one in Israel, one in Ireland and one in Tokyo (Table 3). We have selected articles published among 2014 and 2021, mostly published in journals with a high impact factor. The articles had a low risk of bias identified through the Joanna Briggs Institute forms, except for Alansari K, et. al[26] who presented medium risk of bias (Table 3).

The sample size of all articles ranged from 36 to 250 individuals resulting in 919 children and adolescents, with a predominance of males, except for Yadav M, et al.[27]. The age of the participants ranged from 2 to 18 years old, and they all had oral supplementation. Alansari K, et al.[26] also opted for intramuscular supplementation to ensure absorption (Table 4).

Of the included studies, five presented daily supplementation with dosages between 400UI and 4000UI, one presented a weekly dosage of 14,000UI [28] and one had a monthly dosage of 60,000UI [27] (Table 4). For the analysis of vitamin D levels, five articles used blood samples and performed the analysis by chemiluminescence and radioimmunoassay methods. In the studies conducted by Forno E, et al.[29] and Yadav M, et al.[27] it was not possible to identify data regarding the collection of vitamin D (Table 4).

Table 4 also shows the classification regarding the control and severity of asthma. Of the seven articles included in this work, only one presented a clinical diagnosis of mild asthma[28]. Three studies classified asthma severity as persistent with high risk of severe exacerbation and moderate to severe asthma [26,27,29]. Five articles showed the classification of asthma control, including controlled, partially controlled and uncontrolled asthma. These parameters were determined according to the ACT scores, CACT scores and GINA guidelines (Table 4).

From the results observed, four articles identified that there was no difference between the participants supplemented with vitamin D vs the placebo group in several parameters, including: severe asthma exacerbation, IgE (immunoglobulin E), airway cytokines, CACT score, ACT and GINA, pulmonary function, eosinophilia[28–31]. However, three studies supported a role for vitamin D in the treatment of asthmatic children, demonstrating a reduction in the number of exacerbations, better asthma control, a reduction in the proportion of emergency visits and steroid requirements, and an increase in PEF (peak expiratory flow) (Table 4). [26,27,32]

4 DISCUSSION

The immunomodulatory role of vitamin D has been highlighted in the treatment of several diseases [33]. In the respiratory system, vitamin D acts in the anti-asthmatic therapy, helping to increase the response to corticosteroids [34,35] in addition to exerting anti-inflammatory [36,37], antimicrobial [38,39] and antiviral [40,41] activity. However, there is still controversy whether vitamin D supplementation improves symptoms in asthmatic individuals [42,43].

In this systematic review, we identified seven articles that analyzed children and adolescents with asthma who were supplemented with vitamin D. In this context, four articles demonstrated that there was no association between vitamin D supplementation and improvement in asthma symptoms when compared to the placebo group[28–31], while three studies showed positive results and attribute the applicability of vitamin D in the treatment of asthmatic individuals [26,27,32].

According to the analysis of the studies, only one articles [27] showed a predominance of females group, while the other six had mainly male in their sample. These data corroborate the literature that identify the highest prevalence of childhood asthma symptoms in the male population [44–46]. However, it goes the opposite way when it is for adolescents, since during puberty, changes in female sex hormones are associated with the pathways of asthma pathogenesis and, therefore, there is an increase in asthma symptoms in the female population[47–49]. Regarding to vitamin D, studies report that in terms of gender difference, lower concentrations of 25OHD are identified in women compared to men[50] and this may be associated due to differences in meal patterns[51] and the use of sunscreen more frequent by women[52]. Besides, the sex hormones differences may be associated with vitamin D synthesis and degradation, considering that it was reported by Harris SS et al., that the total concentrations of 25 OHD are higher in women who take contraceptives containing estrogen[53]

From the selected articles, we identified a diversity of nationalities (United States of America, India, Israel, Ireland and Tokyo) and, consequently, ethnicities. Studies show that the prevalence of asthma varies according to ethnicity[54] and data generated in multiethnic populations showed a higher frequency of symptoms in Afro-descendant populations compared to Caucasian[55–57]. In addition to being associated with asthma, research has identified that lower serum levels of vitamin D are associated with groups of Afro-descendant comprising factors such as adiposity, skin pigmentation, vitamin D binding protein polymorphisms and genetics[58,59].

There is still no consensus regarding the dosage and which supplementation route has the best results in children and adolescents. The American Academy of Pediatrics nutrition committee suggested, in 1963, to a total intake of 400IU (international units) of vitamin D per day [60]. In 1997, the Institute of Medicine in partnership with the National Academy of Sciences Panel for Asthma

recommended a daily intake of 200IU to prevent vitamin D deficiency in infants, children and adolescents [61,62]. Supplementation data among the articles selected for this study are quite heterogeneous, despite that, six studies follow the dosage proposed by the European Food Safety, which identified higher tolerable intake levels of 2000 IU/day for children aged 1 to 10 years old and 4000 IU/day for children from 11 to 17 years old[63].

Alansari K, et al.[26] used oral and intramuscular supplementation and, according to the results, the appropriate therapy was one that also incorporated intramuscular supplementation, promoting improvements in the initial period of 3 months. There are few studies that demonstrate differences in the methodology for supplementation. Gorman, et al. demonstrated that the strategy of administering vitamin D intramuscularly is safe and effective in the ability to increase and maintain serum levels of vitamin D over a period of time in individuals with vitamin D deficiency [64]. However, Jamal A, et. al defends in his research that both oral and intramuscular routes had the same efficacy, without any significant advantage between them for patients with vitamin D deficiency[65].

It is worth to note that our review has some limitations. We identified a methodological heterogeneity to assess the collection of vitamin D. The choice of the most appropriate methodology for measuring and analyzing vitamin D depends, among other factors, on its application and specificity [66]. Of the selected articles, three methods cited were previously compared by a study carried out in a laboratory in Ireland which demonstrated clinically equivalent results [67]. However, the studies conducted by Forno E, et. al [29] and Yadav M, et. al[27] did not identify the way of assessment of the collection of vitamin D and the second represented this as a limitation of the study.

In our work, we aim to identify, among the articles, the control and severity of asthma in the population. Asthma control refers to the extent to which asthma manifestations have been reduced by treatment [68] and according to the GINA guidelines, it must be evaluated through presence of symptoms, need for relief medication, limitation of physical activities and intensity of airflow limitation in the past 4 weeks. According to this, it can be characterized as: controlled, partially controlled and not controlled. Questionnaires currently used for this assessment include the Asthma Control Test (ACT) and the Childhood Asthma Control Test (c-ACT)[6]. The concept of severity, on the other hand, is associated with the intrinsic characteristics of the disease and should be used to refer to the intensity of treatment and categorized as intermittent, mild persistent, moderate persistent and severe persistent, based on symptoms, analgesic use, night awake and peak expiratory flow rate (PEF) or the percentage predicted forced expiratory volume in the first second (FEV1) [68,69]. Although studies are still not concise about a role of the vitamin D in individuals with asthma, investigations report an association of asthma severity and control with vitamin D supplementation,

which there is an improvement in the reduction of lung function, reduction of asthma exacerbations and airway inflammation and consequently increased rate of asthma control.[14,70,71].

Several studies have identified conflicting results in the association of vitamin D supplementation in individuals with asthma. Chinellatto et al. and Brehm et al. conclude from their research that asthmatic children with low vitamin D levels are more likely to have reduced lung function, severe disease exacerbation, and reduced asthma control.[72,73]. Supporting these results, several clinical trials have shown that vitamin D supplementation was associated with improved control of asthma symptoms in children and adolescents. [74–77]. However, other studies indicate the lack of response in improving symptoms in individuals supplemented with vitamin D [78–80], corroborating four of the articles selected in this systematic review. The proportion of studies on this topic was small, therefore, the development of new studies that promote an analysis between serum levels of vitamin D in children and adolescents with asthma is essential to insert vitamin D supplementation as another therapeutic option in the context of asthma in this population.

5 CONCLUSION

The immunomodulatory role of vitamin D has been studied in several pathologies of the respiratory tract, and studies of its role in the pathogenesis of asthma still show divergent results in the literature. This heterogeneity added to the need for expansion of new research associated with the role of vitamin D supplementation for children and adolescents with asthma as a new alternative to improve the treatment of this disease.

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7 APPENDIX

Table 1: PICOS strategy for preparing the investigative question

ACRONYM	COMPONENT	DESCRIPTION
P	*Population* – participants or population.	Children and teenagers with asthma
I	*Intervention* – intervention or exposure.	Vitamin D supplementation
C	*Comparison* – comparison or control.	Placebo (without vitamin D supplementation)
O	*Outcome* – result or outcome.	Observation of the improvement or not of the symptoms
S	*Study* – types of study.	Clinical trials

Table 2: Database search strategy.

Data base	Search strategy
US. National Library of Medicine and National Institutes Health (PUBMED)	*Vitamin D [MeSH] (OR) calcitriol [MeSH] (AND) asthma [MeSH] (AND) child*[MeSH].* *Vitamin D [MeSH] (OR) calcitriol [MeSH] (AND) asthma [MeSH] (AND) adolescent [MeSH].*
Scientific Eletronic Library Online (SciELO)	*Vitamin D [MeSH] (AND) asthma [MeSH] (AND) child*[MeSH].* *Vitamin D [MeSH] (AND) asthma [MeSH] (AND) adolescent [MeSH].*
Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)	*Vitamin D [MeSH] (AND) asthma [MeSH] (AND) child*[MeSH].* *Vitamin D [MeSH] (AND) asthma [MeSH] (AND) adolescent [MeSH].*

Figure 1: Study selection flowchart

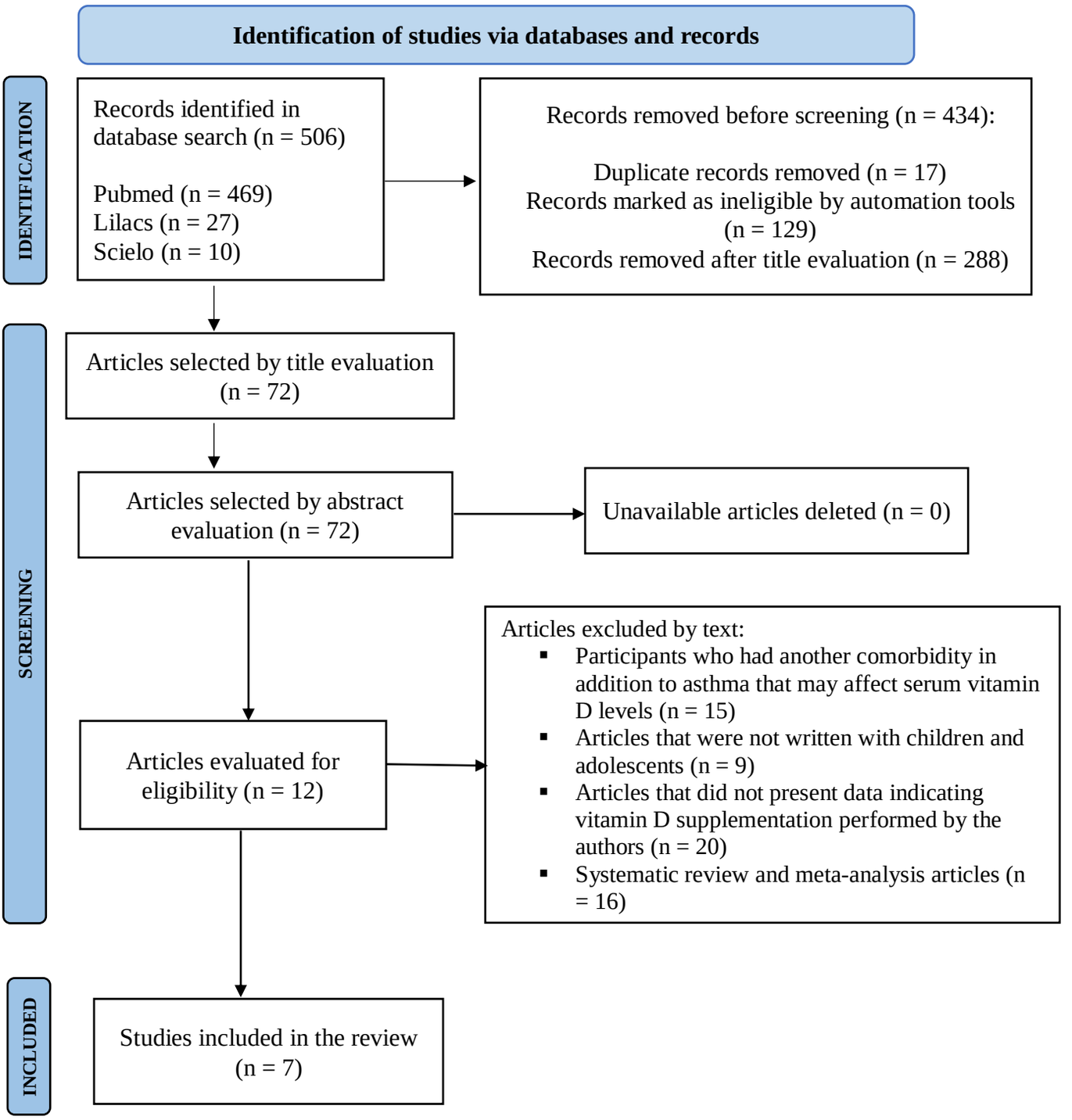

Table 3: Descriptive data of selected articles

Study Countries	*Author*	*Year of Publication*	*Journal*	*Impact Factor*	*Joana Briggs*
EUA	Forno E, et. al	2020	JAMA	45.54	Low risk of bias
Índia	Yadav M, et. al	2014	Indian J Pediatr	1.967	Low risk of bias
Israel	Bar Yoseph R, et. al	2014	Pediatric Pulmonology	2.534	Low risk of bias
Índia	Jat KR, et. al	2021	Pediatric Allergy and Immunology	6.377	Low risk of bias
EUA	Alansari K, et. al	2017	CHEST Journal	9.410	Medium risk of bias
Ireland	Kerley CP, et. al	2016	Pediatric Allergy and Immunology	6.377	Low risk of bias
Tokyo	Tachimoto H, et. al	2016	European Journal of Allergy and Clinical Immunology	14.110	Low risk of bias

Table 4: Sociodemographic characteristics and clinical and laboratory aspects of the studied population

Reference	*Population (N, Age, Sex)*	*Obtaining Vitamin D*	*Vitamin D dosage*	*Vitamin D collection*	*Asthma Control and Severity*	*Results*
Forno E, et. al	N=192 6-16 years old Male	Oral Capsule Treatment (Pharmavite LLC)	4000 IU daily	NI	Subjects with persistent asthma at high risk of severe exacerbation (ACT and C-ACT)	Among children with persistent asthma and low vitamin D levels, vitamin D3 supplementation, compared to placebo, did not significantly improve the time to a severe asthma exacerbation.
Yadav M, et. al	N=82 5-13 years old Female	Oral powder treatment (CADILA)	60,000 IU monthly	NI	Moderate to severe asthma in controlled and uncontrolled patients (GINA)	Patients supplemented with vitamin D had fewer exacerbations and achieved better and earlier asthma control. PEFR increased significantly and emergency visits and the need for steroids was significantly reduced.
Bar Yoseph R, et. al	N=36 6-18 years old Male	Liquid oral treatment (Local pharmacy)	14,000 IU weekly	Blood samples (LIAISON®)	Clinical diagnosis of mild asthma.	There was no difference between the effect of vitamin D and placebo on multiple parameters (MCT, FeNO, hs-CRP, IgE, airway cytokines, eosinophils and PC20-FEV1)
Jat KR, et. al	N=250 4-12 years old Male	Liquid Oral Treatment (Basic Human Healthcare Pvt. Ltd)	1000 IU daily for 9 months	Blood samples (LIAISON®)	Controlled, partially controlled (majority) and uncontrolled asthma (GINA).	Vitamin D supplementation did not contribute to improved asthma control as assessed by the CACT score and the GINA guidelines. There was no difference in lung function parameters.
Alansari K, et. Al	N=231 2-14 years old Male	Oral treatment (NovartisPharma) IM treatment (Biotika)	400 IU (daily oral) and/or 300,000/600,000 IU IM	Blood samples (Architect®)	Moderate to severe asthma. Most controlled according to the ACT score.	During the first 3 months, children who received IM supplementation represented a significantly lower proportion of unplanned visits.

NI: Not identified; UI: International units; IM: intramuscular administration of medications; ACT: Asthma Control Test; CACT: Child Asthma Control Test; MCT: Methacholine challenge test; FeNO: Fractioned exhaled nitric oxide; hs-CRP: high sensitivity C-reactive protein; FEV1: forced expiratory volume in 1 second; PC20-FEV1: provocative concentration of methacholine causing 20% reduction in FEV; FVC: forced vital capacity; IgE: Immunoglobulin E.

Continuation of Table 4

Reference	*Population (N, Age, Sex)*	*Obtaining Vitamin D*	*Vitamin D dosage*	*Vitamin D collection*	*Asthma Control and Severity*	*Results*
Kerley CP, et. Al	N=39 6-16 years old Male	Gel Capsules (Best Formulations Inc)	2000 IU daily	Blood samples (AB SCIEX API 4000)	Atopic asthmatics on anti-asthmatic pharmacotherapy with uncontrolled asthma (GINA)	The study does not support a role for supplemental vitamin D in atopic caucasian children with uncontrolled asthma. A trend towards decreased lung function was observed.
Tachimoto H, et. al	N=89 6-15 years old Male	Oral powder treatment	800 IU daily	Blood samples (radioimmunoassay)	Partially controlled and uncontrolled asthma (GINA)	This study showed significant improvement in levels of asthma control defined by GINA. Short-term, low-dose vitamin D supplementation, in addition to standard treatment, may improve levels of asthma control in school-age Japanese.

NI: Not identified; UI: International units; IM: intramuscular administration of medications; ACT: Asthma Control Test; CACT: Child Asthma Control Test; MCT: Methacholine challenge test; FeNO: Fractioned exhaled nitric oxide; hs-CRP: high sensitivity C-reactive protein; FEV1: forced expiratory volume in 1 second; PC20-FEV1: provocative concentration of methacholine causing 20% reduction in FEV; FVC: forced vital capacity; IgE: Immunoglobulin E.

8 PROPOSTA DE SUBMISSÃO

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Regras para Submissão:

Estrutura do artigo: Os manuscritos principais deverão ser submetidos em arquivo Word (.doc ou .docx). O texto não deve ultrapassar 5.000 palavras, excluindo resumo, referências e ilustrações. O número total de ilustrações não deve ser superior a 8. O número de referências bibliográficas deve se limitar a 80. A sua estrutura deve conter as seguintes partes: Introdução, Métodos, Resultados, Discussão, (Agradecimentos e Contribuição dos Autores somente na title page) e Referências. A seção Métodos deverá conter menção quanto à aprovação do estudo pelo Comitê de Ética em Pesquisa em Seres Humanos, ou pelo Comitê de Ética em Pesquisa em Animais, ligados a Instituição onde o projeto foi desenvolvido. Nessa seção também deve haver descrição da análise estatística empregada, com as respectivas referências bibliográficas. Ainda que a inclusão de subtítulos no manuscrito seja aceitável, o seu uso não deve ser excessivo e deve ficar limitado às sessões Métodos e Resultados.

Resumo: Deve conter informações facilmente compreendidas, sem necessidade de recorrer-se ao texto, não excedendo 250 palavras. Deve ser feito na forma estruturada para os Artigos Originais e Meta-análises com os seguintes subtítulos: Objetivo, Métodos, Resultados e Conclusões. Quando se tratar de Artigos de Revisão e Ensaios Pictóricos, o resumo não deve ser estruturado. Para Comunicações Breves, não deve ser estruturado nem exceder 100 palavras. O resumo deve ser escrito exclusivamente em inglês.

Descritores: Devem ser fornecidos de três a seis termos em inglês, que definam o assunto do trabalho, de acordo com os termos dos Medical Subject Headings (MeSH), disponíveis na homepage http://www.nlm.nih.gov/mesh/MBrowser.html.

Página de identificação: Ela deve conter o título do trabalho, em inglês, o nome de todos os autores e das instituições as quais estão vinculados, endereço completo, inclusive telefone, celular e e-mail do autor correspondente e, se houver, nome do órgão financiador da pesquisa e identificação do protocolo de financiamento. O Open Researcher and Contributor ID (ORCID) de cada autor deverá ser fornecido. Para instruções sobre como obter o identificador ORCID, acesse https://orcid.org/. Devem-se incluir os locais onde o estudo foi realizado. Além disso, as informações sobre a contribuição de cada autor para o trabalho e eventuais agradecimentos devem constar aqui. Primeiro o item agradecimentos e depois, o item contribuição dos autores. Essas informações serão publicadas ao final do manuscrito, antes das referências. A página de identificação deve ser enviada como um arquivo a parte em Word, separado do manuscrito principal.

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que possa ser abreviado e sempre definido na primeira vez em que for citado - por exemplo, proteína C reativa (PCR). Após a definição da abreviatura, o termo completo não deverá ser mais utilizado. Termos com palavras únicas não devem ser abreviados - por exemplo, tuberculose (TB).

Quando os autores mencionarem qualquer substância ou equipamento incomum, deverão incluir o modelo/número do catálogo, o nome da fabricante, a cidade e o país, por exemplo: "... esteira ergométrica (modelo ESD-01; FUNBEC, São Paulo, Brasil)" No caso de produtos provenientes dos EUA e Canadá, o nome do estado ou província também deverá ser citado; por exemplo: "... tTG de fígado de porco da Guiné (T5398; Sigma, St. Louis, MO, EUA)"

Tabelas, quadros e figuras (ilustrações): Tabelas, quadros e figuras devem ser apresentados em preto e branco. As ilustrações devem ser enviadas no seu arquivo digital original; tabelas e quadros em arquivos Microsoft Word e figuras em arquivos JPEG com resolução mínima de 300 dpi. Fotografias de exames, procedimentos cirúrgicos e biópsias nas quais foram utilizadas colorações e técnicas especiais serão consideradas para impressão colorida, sem custo adicional aos autores. As tabelas e figuras devem ser numeradas com algarismos arábicos, de acordo com a ordem de citação no texto.

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