**REVIEW ARTICLE**

# Evaluation of the effect of vitamin D in children with asthma: A systematic review

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## ABSTRACT

Asthma is the most common chronic disease in childhood, with a prevalence of 10 to 30%. The onset of the disease is at the age of 5 and at this time the prevalence is higher in boys than girls (ratio 3:2.5), but during adolescence, the incidence is equal in both sexes. The present study is a systematic review study conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley and with the keywords of Asthma, Children, Childhood, Vitamin D, and airway inflammation and the studies between 2009 and 2020 were reviewed. Out of a total of 627 articles, 17 articles were finally selected based on the inclusion and exclusion criteria for further review; The results of the reviewed studies indicate an association between serum vitamin D levels and the incidence of asthma and asthma attacks, as well as control of the disease, lung function, and consumed dosage of corticosteroids. Although some articles have found no association, in general, vitamin D is effective in reducing inflammation in various parts of the body and strengthening the immune system function, and this affects the lung structures. However, further studies are needed to better understand the role of vitamin D in children with asthma and to explore the relationship between vitamin D and other factors involved in the development and exacerbation of the disease.

**Keywords:** Vitamin D, childhood, Children with asthma, Vitamin deficiency

## INTRODUCTION

Asthma is one of the most common chronic diseases, which leads to a rapid increase in hospitalization rate. Inadequate adherence to treatment may decline the efficacy of prescribed treatment; as a result, it leads to poor expected outcomes[1]. The most important factors that are involved in this disease include recurrent respiratory infections, family history of allergies, severity of the disease, and age. Regular clinical follow-ups, use of inhaled corticosteroids, IgE levels, and saturated oxygen level may reduce the probability of hospitalization during asthma attacks[1]. This disease is a chronic inflammatory disorder of the airways that is associated with reaction and hypersensitivity in the respiratory tract and endangers the patient's health. The most common causes of asthma exacerbation in children are viral respiratory infections, exposure to allergens, and poor asthma control[2]. The diagnosis of asthma in children is based on a pattern of respiratory signs and symptoms. The presence of these factors increases the likelihood of a child developing asthma. These factors include age, sex, severity, and previous history of wheezing, family history, other atopic diseases, and abnormal lung function[1]. Vitamin D is an immune modulator and its receptors are present in immune cells such as macrophages, dendritic cells, monocytes, and active T and B cells. These receptors regulate the transcription of various genes involved in inflammation and modulate the immunity of the respiratory epithelium. Vitamin D suppresses the proinflammatory cytokines interleukin-17 (IL-17) and interleukin-13 (IL-13) and produces anti-inflammatory cytokines such as IL-10. Studies of vitamin D and asthma in children have shown that low levels of 25-hydroxyvitamin D in the mother and umbilical cord blood are associated with an increased risk of wheezing in early childhood(3-5). On the other hand, Gale et al. Showed that high levels of vitamin D during pregnancy increase the risk of eczema in children at 9 months and asthma at 9 years[6]. A study by Bener et al. also found a strong association between vitamin D deficiency and asthma, wheezing, and allergic rhinitis in children[7]. The aim of this study was to provide a systematic review of published research evidence regarding the effect of vitamin D in children with asthma.

**Asthma:** Asthma is a disease characterized by recurrent respiratory attacks and wheezing and varies in severity and frequency from person to person. This condition causes spasms in the bronchi of the lungs and makes it difficult to breathe. Asthma is usually associated with allergic reactions or other forms of severe allergies. This condition is due to inflammation of the airways of the lungs and irritation of nerve endings in the airways. During asthma attacks, the respiratory epithelium becomes swollen, narrowing the airways and reducing the flow of air in and out of the lungs[8]. Patients with recurrent cough, wheezing, shortness of breath, and chest pain are suspected of having asthma. Symptoms that appear as soon as you are exposed to allergens or stimulants, that worsen at night and respond well to the asthma treatment, are signs of asthma. The diagnosis of asthma includes a thorough medical history, physical examination, and objective evaluations of lung function[9].

**Clinical symptoms of asthma:** Clinical symptoms of asthma include wheezing, shortness of breath, chest pain, cough, extensive airway obstruction, premature fatigue, and decreased ability to perform daily activities; Exposure to dust particles, colds, and exercise without warming up could exacerbate asthma attacks[10-13].

**Asthma in children:** Asthma is the most common chronic disease in childhood, with a prevalence of 10 to 30%. Many current pediatric asthma management strategies are based on studies in the adult population with asthma, and there is limited information about asthma in children. The available studies could be divided into two main age groups including

children under 12 years and 12 years and older (adolescents and adults). Although asthma is comparable in adults and adolescents, the disease in adults differs in many ways from asthma in children under 12 years of age. Wheezing and shortness of breath with or without cough are the main symptoms of asthma, but since these respiratory symptoms are common in children, the disease is often misdiagnosed. The relation between cough and asthma is complex and persistent cough is rarely a sign of asthma[14-17]. Also, exacerbation of episodic (intermittent) asthma is the chronic inflammation of the airways. The prevalence of asthma is 7% in France and Germany, 11% in the United States and 15 to 18% in the United Kingdom. Approximately 20% of these patients have severe asthma. The onset of the disease is at the age of 5 and at this time the prevalence is higher in boys than girls (ratio 3: 2.5) but in adolescence, the incidence is equal in both sexes[18] . The most common classes of drugs used in asthma are beta2- adrenergic agonists, corticosteroids, and leukotriene modifiers. Intramuscular triamcinolone is also used for the treatment of severe asthma. Also, Omalizumab is a monoclonal antibody against IgE that has been approved as a new drug in the treatment of patients with IgE-mediated allergic asthma; This medication is used only for patients with a certain range of total IgE levels. There is little evidence of the therapeutic effects of methotrexate as well as macrolide antibiotics in children with asthma, and antifungal drugs are not recommended in these patients. In addition to prescribing medication, non-pharmacological measures may be taken that might improve the patient's quality of life[19].

## MATERIALS AND METHODS

The present study is a systematic review study conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley and with the keywords of Asthma, Children, Childhood, Vitamin D, and airway inflammation. These words were often used separately and in some cases as a combination of two words. Inclusion criteria were full-text articles in the field of vitamin D and the incidence of asthma in children, studies that were conducted after 2008, and articles published in English; Exclusion criteria were articles without full text, the articles were published before 2008, and the studies that were review articles. In the analysis stage, the information collected from the studies included the author (s), year, objective, method of study, and research results. No interpretation was implemented during the data collection and the main phrases of the articles, that were used by the author (s), were used.

## RESULTS

In the first stage, 627 titles were selected. At this stage, all articles were reviewed in terms of duplication of content, title, and, if necessary, abstracts, and finally 75 articles were selected. In the second stage, the full text of the articles was studied and 15 articles were removed due to differences in purpose. Out of the remaining 60 articles, 43 articles were excluded from the study based on the inclusion/exclusion criteria, and finally, full texts of 17 articles published in English on the relationship between vitamin D and asthma in children were included in the final study (figure 1). Studies that had been conducted between 2009 and 2020, were reviewed.

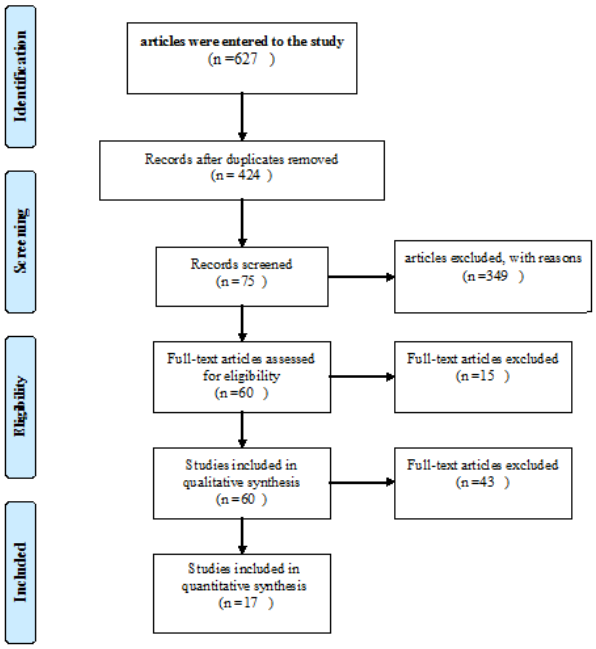


Figure 1. Diagram related to the selection of the reviewed articles

The objectives and results of these 17 studies are listed in Table 1. The results of these studies indicate an association between serum vitamin D levels and the incidence of asthma and asthma attacks, as well as control of the disease, lung function, and consumed dosage of corticosteroids. Thus, the lower levels of vitamin D cause a high risk of asthma and asthma attacks, in which case the patient is forced to use higher doses of steroids and the disease is more difficult to control and manage. However, in some studies, no association was found between serum levels of this vitamin and the incidence of asthma.

Amongst the total of 5,354 children with asthma, from infants to children under 16 years of age, that were studied in these 17 articles, 3,661 children (68.38%) showed a correlation between serum vitamin D levels with asthma incidence and lung function. However, in 71 children with asthma (equivalent to 1.33%), no association was found between this vitamin and inflammation of the respiratory tract. Also, in 700 children (equivalent to 13.08%), it was demonstrated that the relationship between serum levels of vitamin D and asthma is age-dependent so that by reducing the level of this vitamin at a younger age, the possibility of asthma at older ages increases. On the other hand, the results showed that in 922 infants (equivalent to 17.22%) vitamin D levels were inversely related to the risk of lung infection but not to the incidence of asthma.

Table 1- Results related to the relationship between vitamin D and asthma in children

| Author | Title | Number of samples and methods | Results | Conclusion |
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| Brehm et al. (2009)[20] | Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica | Sample number: 616 children 6 to 14 years old<br>Objective: To investigate the relationship between 25-hydroxyvitamin D levels (the main circulating form of vitamin D) and the severity of asthma and allergies. | The results of this study indicate that out of 616 children with asthma, 175 children (28%) had inadequate levels of vitamin D (less than 30 ng/ml). On the other hand, vitamin D levels are significantly and inversely related to total IgE and the number of eosinophils. Also, the logarithm of a unit increase in vitamin D levels was associated with a decrease in the possibility of any hospitalization in the previous year | These results suggest that vitamin D deficiency is relatively common in children with asthma. In these children, decreased vitamin D levels are associated with increased allergy markers and the severity of asthma. |
| Chinellato et al. (2011)[21] | Vitamin D serum levels and markers of asthma control in Italian children | Sample number: 75 children 5 to 11 years old (43 boys and 32 girls)<br>Objective: To investigate the relationship between serum vitamin D levels, pulmonary function and asthma control in children. | The results of this study showed that only 9.4% of these children had sufficient serum levels of D (OH) 25 (at least 30 to 40 ng/ml). There was also a positive and significant correlation between the percentage of forced vital capacity (FVC) and the forced expiratory volume per second (FEV1) with serum D (OH) 25, although this correlation was not statistically significant for FEV1. On the other hand, children with controlled asthma had serum D (OH) 25 levels higher than children with semi-controlled or uncontrolled asthma.<br>A positive correlation was found between D (OH) 25 and childhood asthma control test | Vitamin D deficiency is common in children with asthma living in a Mediterranean country. In these children, low levels of vitamin D are associated with decreased asthma control. |
| Alyasin et al. (2011)[22] | The relationship between serum 25 hydroxy vitamin d levels and asthma in children | Sample number: 50 children with asthma and 50 healthy children as a control group in the ages of 5 to 11 years<br>Objective: To investigate the relationship between 25-hydroxyvitamin D3 level and asthma | Decreased vitamin D levels are associated with a significant increase in the chance of developing asthma. Also, in children with asthma, the level of D (OH) 25 was directly and significantly related to both the predicted FEV and the volume of forced exhalation per second on the forced vital capacity (FEV1/FVC ratio). On the other hand, there was no correlation between vitamin D levels and the number of eosinophils, duration of illness, hospitalization days, or unscheduled visits in the previous year. | These results showed that serum D (OH) 25 level was inversely related to asthma. There is also a direct and significant relationship between vitamin D levels and lung function in children with asthma. |
| Camargo et al. (2011)[23] | Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma | Sample number: 922 infants<br>Objective: To investigate the relationship between 25-hydroxyvitamin D3 levels of cord blood and asthma, wheezing and respiratory infections in children | The mean level of D (OH) 25 in cord blood was 44 nanomoles per liter (range of 29-78). Follow-up was performed at the age of 5 years. On the other hand, D (OH) 25 had inverse relationships with the risk of respiratory infection up to 3 months of age. Also, the level of D (OH) 25 in cord blood was inversely associated with the risk of wheezing at 15 months, 3 years and 5 years of age; But there was no association between vitamin D levels and the incidence of asthma over 5 years. | These results suggest that D (OH) 25 cord blood levels are inversely related to the risk of respiratory infection and wheezing in children but are not associated with asthma. |
| van Oeffelen et al. (2011)[24] | Serum micronutrient concentrations and childhood asthma: the PIAMA birth cohort study | Sample number: 372 children aged 4 years and 328 children aged 8 years.<br>Objective: To investigate the possible relationship between serum magnesium, vitamin D, selenium and zinc concentrations and the prevalence of asthma (severe), atopy and Bronchial hyperresponsiveness (BHR) in childhood. | The results of this study showed that there is an inverse (non-significant) relationship between serum magnesium concentration and the prevalence of asthma. It was also found that serum concentrations of vitamin D measured at age 4 were inversely related to asthma at ages 4-8 and vitamin D measured at age 8 was positively associated with asthma at age 8. | These results suggest that children with high serum magnesium concentrations are less likely to develop asthma, while the association between serum vitamin D concentrations and asthma is age-related. |
| Gupta et al. (2011)[25] | Relationship between serum vitamin D, disease severity, and airway | Sample number: 86 children with a mean age of 11.7 years (36 children with severe | The results of this study showed that the level of D (OH) 25 in children with STRA, moderate asthma, and the | These results suggest that decreased vitamin D levels in children with |

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| | remodeling in children with asthma | therapy-resistant asthma (STRA), 26 children with moderate asthma, and 24 non-asthmatic children as a control group). Out of 36 children with STRA, 22 children were examined for respiratory tract infection.<br>Objective: To investigate the relationship between serum vitamin D, lung function, and pathology in children with STRA | control group were: 28, 42.5, and 56.5 nanomoles per liter, respectively. Also, in all children, there was a positive relationship between D (OH) 25, FEV, FVC, and asthma control test (ACT), while this relationship was inversely formed between the dose of inhaled steroid in the first two groups and the volume (mass) of airway smooth muscle (ASM). In addition, there is an inverse relationship between ASM and ACT. | STRA are associated with increased ASM mass and poorer asthma control and poor lung function. The association between vitamin D, respiratory tract structure, and lung function suggests that vitamin D supplementation may be beneficial in children with STRA. |
| Chinellato et al. (2011) [26] | Serum vitamin D levels and exercise-induced bronchoconstriction in children with asthma | Sample number: 45 children with intermittent asthma<br>Objective: To investigate the association between D (OH) 25 and FEV1, FVC and changes in FEV1 after a standard exercise challenge in children with asthma | The results of this study showed that only 11% of children had adequate serum levels of vitamin D (at least 30-40 ng/ml). There was also a positive correlation between D (OH) 25, FEV1, and FVC. In children with a positive response to the exercise challenge ($\Delta FEV1 \geq 10\%$), serum levels of D (OH) 25 were lower, compared to the children with a negative response to the challenge. | These results suggest that vitamin D deficiency is common in children with asthma. In these children, low levels of vitamin D reduce lung function and increase response to exercise. |
| Bener et al. (2012) [27] | Vitamin D deficiency as a strong predictor of asthma in children | Sample number: 483 children with asthma and 483 healthy children as a control group. All of these children were under 16 years old. Children with serum vitamin D levels of less than 20 nanograms per milliliter were diagnosed as children with vitamin D deficiency.<br>Objective: To measure the serum level of vitamin D in children with asthma and compare them with healthy children | The results of this study showed that serum levels of vitamin D were significantly lower in children with asthma than in non-asthmatic children. 68.1% of all children with asthma were deficient in vitamin D. Children with asthma had moderate to severe vitamin D deficiency compared with the healthy control group. A family history of vitamin D deficiency (35.6%) and asthma (36.4%) were significantly higher in children with asthma. In addition to vitamin D deficiency, people with asthma also have lower levels of phosphorus and magnesium, but higher levels of serum alkaline phosphatase. Most children with asthma were less exposed to sunlight (66.7%) and had less physical activity (71.3%). Vitamin D deficiency was the strongest possible cause of asthma in this population. | These results show that most children with asthma are deficient in vitamin D compared to control children, and a deficiency of this vitamin is one of the main causes of asthma in Qatari children. |
| Wu et al. (2012) [28] | Effect of Vitamin D and inhaled corticosteroid treatment on lung function in children | In this study, children were divided into 3 groups:<br>Group 1: Children with optimal vitamin D levels (more than 30 ng / ml), Group 2: Children with insufficient vitamin D levels (20-30 ng / ml) and Group 3: Children with vitamin D deficiency (less than 20 ng / ml)<br>Objective: To evaluate the effect of vitamin D level on FEV1, response to bronchodilators and methacholine | The results of this study indicate that out of 1024 children studied, 663 children (65%) had adequate levels of vitamin D, 260 (25%) children had inadequate levels of it and 101 children (10%) had a deficiency of this vitamin. Children with vitamin D deficiency are more likely to be older and African-American and have a higher body mass index than children in the other two groups. In the group treated with inhaled corticosteroids, the pro-bronchodilator FEV1 is 140 ml in children with vitamin D deficiency and 330 ml in children with inadequate levels of vitamin D. This amount is 290 ml in children with an optimal amount of vitamin D. | These results suggest that in children with asthma treated with inhaled corticosteroids, vitamin D deficiency is associated with poor lung function. |
| Uysalol et al. (2013) [29] | Childhood asthma and vitamin D deficiency in Turkey: is there cause and effect relationship between them? | Sample number: 85 children with asthma and 85 healthy children aged 2-14 years<br>Objective: To evaluate inadequate levels of vitamin D and its clinical consequences | Vitamin D level in the asthma group was 16.6 ± 8.5 ng/ml and in the control group was 28.2 ± 9.5 ng/ml. It was also found that children with asthma were less exposed to sunlight and had lower levels of vitamin D in their diets. In addition, a significant difference was observed between the two groups in terms of the frequency of respiratory tract infections leading to hospitalization in the emergency department and the number of days of hospitalization. Decreased levels of vitamin D have also been shown to | This study showed an association between D (OH) 25 and childhood asthma. Obviously, this relationship is influenced by various factors other than vitamin D, so more studies should be performed to discover the interaction between all these factors. |

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| | | | increase the severity of asthma and reduce asthma control. | |
| Dogru et al. (2014) [30] | Clinical effects of Vitamin D in children with asthma | Sample number: 121 children with asthma (73 boys (60.8%) and 48 girls (39.2%) with a mean age of 4.4 ± 1.2 years) and 74 healthy children as a control group. Eosinophil count, IgE level, and serum D (OH) 25 levels were measured. Objective: To determine the relationship between clinical parameters of asthma and vitamin D in children. | The results of this study showed that there was no significant difference between the patients and the control group in terms of gender and age. The level of D (OH) 25 in the patient group was 21.49 ± 7.7 ng/ml and in the control group was 23.94 ± 8.97 ng/ml, which demonstrated no statistically significant difference. Children with asthma were divided into three groups in terms of vitamin D status: vitamin D deficiency group, group with insufficient level, and normal group. There was no difference between the groups in terms of the duration of disease, number of hospitalization days, allergen susceptibility, eosinophil count, and serum IgE level, but the severity of asthma and the need for glucocorticoids in the Vitamin D deficiency group was significantly higher. | These results indicate that vitamin D deficiency was common in the study group as well as in the control group. On the other hand, it was found that the clinical severity of the disease, the number of attacks, and the need for glucocorticoids are related to the level of vitamin D. |
| Einisman et al. (2015) [31] | Vitamin D levels and vitamin D receptor gene polymorphisms in asthmatic children: a case-control study | Sample: 75 children with asthma (mean age 9.1 years) and 227 healthy children (mean age 10.3 years) Objective: To compare the level of D (OH) 25 and the frequency of SNPs (FokI, ApaI, TaqI) in Vitamin D receptor (VDR) gene between children with asthma and healthy children. | Adequate, inadequate, and deficient D (OH) 25 levels were 14.9%, 44%, and 41.1%, respectively. The status of adequate levels of D (OH) 25 was similar in patients and healthy children. However, the ratio of adequate levels of D (OH) 25 was significantly different between the patients in stages 2, 3, and 4 of asthma treatment (8.6%, 16.6%, and 43.7%, respectively). All patients in stage 4 (16 of 16) were heterozygous for the C allele (FokI polymorphism in the vitamin D receptor gene); But in stages 2, 3, and the control group, there was a lower level of C allele among patients with asthma (30 of 33, 16 of 24 and 45 of 50, respectively). On the other hand, no significant difference was found in ApaI and TaqI. | These results suggest that there is a possible association between adequate levels of vitamin D and the C allele at the site of the FokI polymorphism, which may play a role in the therapeutic response of children with asthma. Changes in VDR may also affect D (OH) 25 levels. |
| Searing et al. (2010) [32] | Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use | Sample number: 100 children with asthma. In these children, the effects of vitamin D on mitogen-activated protein kinase phosphatase 1 (dexamethasone-induced (DEX)) and IL-10 in PBMCS (peripheral blood mononuclear cells) as well as serum D (OH) 25 were studied. Objective: To investigate the association between vitamin D deficiency and childhood asthma and the association of this vitamin with corticosteroid-dependent anti-inflammatory responses. | The mean serum level of D (OH) 25 was 31 ng/ml. 47% of people had insufficient levels of vitamin D (30 ng / mL) and 17% were deficient in this vitamin (less than 30 ng/mL). The results also showed that there was a significant positive correlation between vitamin D level and FEV1, FVC / FEV1, also, there was a reverse correlation between vitamin D levels and IgE logarithm, the use of oral and inhaled steroids, and the total steroid dose. In addition, the amount of mitogen-activated protein kinase phosphatase 1 and IL-10 mRNA induced by vitamin D plus DEX was significantly higher than that induced by DEX alone. DEX alone is not able to inhibit T cell proliferation. The addition of vitamin D to DEX results in significant suppression of dose-dependent cell proliferation. | Corticosteroid use and exacerbation of airflow restriction are associated with decreased serum levels of vitamin D in patients with asthma. This vitamin also increases glucocorticoid function in the PBMCS of asthma patients and enhances the immunosuppressive function of DEX in vitro. |
| Sharif et al. (2020) [33] | Association of 25-hydroxy vitamin D with asthma and its severity in children: a case-control study | Sample number: 520 children were studied. Children with asthma were considered as the study group (child 260) and children who presented for reasons other than respiratory problems and asthma were considered as the control group (260). Objective: To investigate the relationship between D (OH) 25 levels and asthma and the severity of the disease | The results of this study showed that the mean level of D (OH) 25 in the study group was 25.5 ± 16.62 and in the control group was 31.40 ± 16.76, which showed a statistically significant difference. The level of D (OH) 25 in children with non-severe asthma was 28.05 ± 16.98 and in patients with severe asthma was 21.41 ± 15.20, which indicates that the level of this vitamin is inversely related to the severity of asthma. | The relationship between vitamin D levels and the severity of asthma is inverse. It is recommended to check the amount of this vitamin, especially in cases of severe asthma, and in case of deficiency, appropriate treatment measures should be taken to reduce the severity of the disease. |

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| Arikoglu et al. (2015) [34] | The association of vitamin D, cathelicidin, and vitamin D binding protein with acute asthma attacks in children | Sample number: 67 children (35 children with acute asthma attacks and 32 children with controlled asthma). Objective: To determine the association of vitamin D, vitamin D-binding protein (VDBP), and cathelicidin with acute asthma attacks in children with allergic asthma | The mean serum level of vitamin D in the group of children with asthma was significantly lower than the controlled asthma group. On the other hand, the mean level of cathelicidin in the acute asthma group was significantly higher than children with controlled asthma. There was no difference between the two groups in terms of allergy markers and serum VDBP levels. In addition, body mass index (BMI), duration of sun exposure, and dietary vitamin D levels were shown to independently affect serum vitamin D levels. The results of this study showed that serum vitamin D levels were significantly associated with the risk of asthma attacks. In addition, cathelicidin levels showed a positive and significant relationship with asthma attacks and BMI. | Vitamin D deficiency is directly related to the incidence of asthma attacks independent from cathelicidin deficiency and other factors associated with the severity of chronic asthma. |
| Dabbah et al (2015) [35] | Bronchial Reactivity, Inflammatory and Allergic Parameters, and Vitamin D Levels in Children with Asthma | Sample: 71 non-obese children with asthma who have not received anti-inflammatory therapies. These children underwent spirometry by methacholine challenge test and fractional nitric oxide (FENO) level, serum vitamin D level, total IgE level, blood eosinophil count, and hypersensitivity to C-reactive protein, were assessed in them. Objective: To evaluate the association between vitamin D and asthma and allergy markers in children | 71 children with asthma (25 girls (35%)) with a mean age of 12.5 ± 3.6 were included in this study. The results of this study showed that the mean level of vitamin D was 23 ng / mL, the mean level of IgE was 350 IU / mL, the mean excitatory concentration of methacholine leading to a 20% reduction in FEV1 was 1.1 mg / mL and the mean FENO was 26.5 ppb. No correlation was found between vitamin D levels and response to the methacholine challenge test, FENO, hypersensitivity to C-reactive protein, eosinophil count, IgE level, and the rate of allergic rhinitis or atopic dermatitis. | These results indicate that in the group of children with asthma, no relationship was observed between vitamin D level and the rate of respiratory tract reactions, inflammation of these airways, and allergies. The cause-and-effect relationships between vitamin D, asthma, and allergies need to be further investigated. |
| Munkhbayarlakh et al. (2019) [36] | Vitamin D plasma concentration and vitamin D receptor genetic variants confer risk of asthma: A comparison study of Taiwanese and Mongolian populations | Sample number: A total of 328 Taiwanese children from the Han tribe and 381 Mongolian children were included in the study and their serum vitamin D levels were measured. Genomic DNA was obtained from blood samples of 178 Taiwanese and 90 Mongolians Objective: To investigate the relationship between vitamin D concentration, VDR polymorphism, and asthma in Mongolian and Taiwanese populations living in two different geographical areas. | The results showed that in the Taiwanese population under 14 years of age, the serum level of vitamin D in healthy children and children with asthma was significantly higher than in Mongolian healthy children and children with asthma. In addition, in both the Taiwanese and Mongolian populations, vitamin D levels were significantly lower in children with asthma than in non-asthmatics. The results of this study also showed that the rs2228570 genotype belonging to VDR polymorphism and vitamin D concentration (less than 40 ng / mL) both play a role in increasing asthma susceptibility. | The results of this study suggest a potential role for vitamin D in the prevention and treatment of asthma worldwide. |

## DISCUSSION

The aim of this study was to systematically review the effect of vitamin D levels in children with asthma. Among the total studies on vitamin D levels and asthma and lung function, 17 articles were finally selected for further review. Reviewing the related articles have indicated that adequate levels of vitamin D could reduce the risk of asthma and related attacks, improve lung function, reduce the consumed dose of steroids, and efficiently manage and control the disease in children and inadequate amounts and deficiencies of this vitamin may lead to poor lung function and exacerbation of asthma. Of the 17 articles reviewed in this study, only one study found no association between vitamin D levels and the risk of asthma in infants[23]. A 2011 study by van Oeffelen et al. found that the association between vitamin D levels and asthma was correlated with children's age[24]. Also, in a study conducted by Dabbah et al. In 2015, no association was found between vitamin D levels and inflammation of the airways[35]. Vitamin D is a fat-soluble nutrient that modulates calcium absorption and bone health[37]. Although there are no guidelines for optimal serum levels of D (OH) 25 as the most important indicator of overall vitamin D status, however, D (OH) 25 levels less than 50 L / nmol (20 ng / mL), 75 L / nmol -50 (20-30 ng / mL) and 75-100 l / nmol (30 ng / mL) are considered as deficient, inadequate levels and normal levels of the vitamin, respectively. Also, Serum levels of D (OH) 25 above 150 ng / mL are defined as vitamin D poisoning[38]. The extent of vitamin D deficiency could be attributed to factors such as changes in nutritional status, differences in sun exposure, food enrichment, supplementation, the geographical location of the country, and many other factors in different countries.

Vitamin D deficiency may be inversely related to asthma, since this vitamin is synthesized by sunlight, and children with asthma may spend less time outdoors due to problems of the disease[3]. Possible mechanisms of the effect of vitamin D on the severity of asthma and allergies may include the effects of this vitamin on immune cells, improving function or preventing infections, reducing inflammatory responses, reversing steroid resistance, and affecting the volume and mass of airway smooth muscle [39-43]. Vitamin D deficiency could cause disorders in the structure and function of the lungs and respiratory problems. ASM cells (airway smooth muscle cells) also have an enzymatic mechanism for converting D (OH) to 1,25-dihydroxyvitamin D, which inhibits the proliferation of ASM and suppresses the expression of inflammatory chemokines (family of small cytokines). This process leads to reduced airflow and reduced obstruction of the small airways, which is directly related to lung function and airway regeneration in patients with asthma[44].

## CONCLUSION

In conclusion, the findings of the present study showed that vitamin D deficiency is relatively common in children with asthma and there is a direct and significant relationship between vitamin D levels and pulmonary function in children with asthma. Also, in these children, a decrease in vitamin D levels is associated with an increase in allergy markers and the severity of asthma. Various studies have suggested that sun exposure and periodic vitamin D supplementation may be beneficial in children with asthma.

Although during this systematic review, the effect of vitamin D on asthma and the significant correlation of different levels of vitamin D with the incidence of asthma, the severity of this disease and lung function in children were shown, in order to further understand the role of vitamin D in children with this disease, as well as the discovery of vitamin D interactions with other factors involved in the incidence and exacerbation of the disease, further studies are needed.

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