Annals of Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iann20

Vitamin D supplementation decrease asthma exacerbations in children: a systematic review and meta-analysis of randomized controlled trials

Katherine Fedora, Retno Asih Setyoningrum, Qorri' Aina, Laili Nur Rosyidah, Nur Lailatun Ni'mah & Feelin Fatwa Titiharja

To cite this article: Katherine Fedora, Retno Asih Setyoningrum, Qorri' Aina, Laili Nur Rosyidah, Nur Lailatun Ni'mah & Feelin Fatwa Titiharja (2024) Vitamin D supplementation decrease asthma exacerbations in children: a systematic review and meta-analysis of randomized controlled trials, Annals of Medicine, 56:1, 2400313, DOI: 10.1080/07853890.2024.2400313

To link to this article: https://doi.org/10.1080/07853890.2024.2400313

Published online: 18 Oct 2024.

Elevate Series

ANNALS OF MEDICINE
2024, VOL. 56, NO. 1, 2400313
https://doi.org/10.1080/07853890.2024.2400313

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Vitamin D supplementation decrease asthma exacerbations in children: a systematic review and meta-analysis of randomized controlled trials

Katherine Fedora[a,b], Retno Asih Setyoningrum[a,b], Qorri' Aina[a], Laili Nur Rosyidah[a], Nur Lailatun Ni'mah[c] and Feelin Fatwa Titiharja[d]

[a]Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia; [b]Department of Child Health, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia; [c]Faculty of Medicine, Universitas Islam Malang, Malang, East Java, Indonesia; [d]Faculty of Medicine, Universitas Muhammadiyah Malang, Malang, East Java, Indonesia

ABSTRACT

Background: Observational studies have linked low vitamin D (VD) levels to increased asthma attacks in children. Subsequent meta-analyses of adults and children revealed that VD treatment might benefit asthmatic patients by reducing the incidence of exacerbations. Therefore, this review aims to analyze the effects of VD supplementation in reducing asthma exacerbations in children.

Methods: Published reports from PubMed, Cochrane, and Google Scholar were systematically searched until April 2023. The study protocol was registered in the PROSPERO database CRD42023411796. Randomized controlled trial studies were included in this review. Meta-analysis was performed using Cochrane RevMan 5.1 and presented with 95% confidence intervals (CIs).

Results: Ten relevant studies enrolled 1243 asthmatic children (631 children receiving vitamin D3 supplementation, 612 children receiving placebo) were included in this review. Our pooled analysis found that VD supplementation had a significant effect on lowering the total number of asthma exacerbations (RR 0.62; 95% CI: 0.44, 0.87; $p=0.01$). Subgroup analysis revealed that a daily dose of VD given based on standard daily dose recommendation had a significant improvement on asthma exacerbations [(RR 0.41; 95% CI: 0,18, 0,92; $p=0.03$).

Conclusions: Vitamin D supplementation can lower the occurrence of exacerbations in children with asthma, along with the improvement of FEV1.

ARTICLE HISTORY
Received 9 July 2023
Revised 4 November 2023
Accepted 3 July 2024

KEYWORDS
Vitamin D; supplementation; asthma; exacerbations; children

Introduction

Childhood asthma is the most common chronic condition that affects more than 6 million children in the US [1,2] and is one of the common causes of death in children [3]. More than half of asthmatic children experience minimum one acute attack a year, making it one of the main factors leading to school absenteeism and hospitalization in childhood [4]. Asthma exacerbations is multifactorial, recent observational studies have linked low vitamin D (VD) level to increased risk of asthma exacerbations [5]. VD deficiency was found in 74% of patients with asthma and in 54.5% of healthy children [6]. Low VD levels correlated with increased airway hyper-reactivity, reduced lung function, and reduced response to corticosteroid, thus increase asthma attacks and severity in children [5,6]. These findings could be attributed to VD's immune-modulating and anti-inflammatory properties, which include the induction of regulatory T-cells, suppression of Th2 and Th17 responses, stimulation of IL-10 production, and inhibition of airway smooth muscle hypertrophy and collagen deposition [7–9]. VD also may reduce asthma attacks caused on by viral infections by inhibiting rhinovirus replication in bronchial epithelium, enhancing interferon-mediated antiviral pathways, and increasing production of antimicrobial peptides [10]. Subsequent meta-analyses of adults and children revealed that VD treatment might benefit asthmatic patients by reducing the incidence of exacerbations [1, 11]. Therefore, this review aims to analyze the effects of VD supplementation in reducing asthma exacerbations in children.

CONTACT Retno Asih Setyoningrum retno-a-s@fk.unair.ac.id Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

Methods

Search strategies

This review was carried out in compliance with the Preferred Reporting Items for Systematic Examination and Meta-Analysis (PRISMA) guidelines. The study protocol was registered in the PROSPERO database CRD42023411796. We systematically search published reports from PubMed, Cochrane, and Google Scholar up to April 2023 using medical subject heading (MeSH) and free-text terms: [(((vitamin D) OR (25-hydroxyvitamin D)) OR (25(OH)D)) OR (cholecalciferol)) OR (vitamin D3)] AND [(asthma) OR (bronchial asthma)] AND [(((children) OR (child)) OR (pediatric)) OR (adolescence)]. Type of study included in this review was Randomized Controlled Trials (RCTs) with no language limitation.

Study selection

Two reviewers screened the records independently. Inclusion criteria were as follows: (1) population: children diagnosed with asthma aged 0-18 years old; (2) intervention: vitamin D supplementation, regardless of the drug names, doses, and administration routines, or as an adjunct to other forms of asthma treatment; (3) comparison: either placebo or control group; (4) outcomes: reported in rate of asthma exacerbations and predicted percentage of forced expiratory volume in first second (FEV1%); (5) study design: randomized controlled trials (RCTs).

Data extraction

Data were extracted by two investigators (KF and LNR) independently to a collection form that had been made before. Data collected from studies were: name of the first author, publication year, country of origin, number of participant in intervention and control groups, age range of subjects, dose of vitamin D given as intervention, cumulative dose of vitamin D given, and duration of supplementation. Outcome data extracted were: rate of asthma exacerbations, mean vitamin D levels, and FEV1%. Meta-analysis was performed using Cochrane Revman 5.1 and presented with 95% confidence intervals (CIs).

Outcomes

The primary outcome was the rate of exacerbations. Asthma exacerbation was defined as an increased in symptoms (shortness of breath, cough, wheezing), a progressive decrease in pulmonary function, use of systematic corticosteroid (tablets, suspension, or injection) or increased use of short-acting β2-agonists (SABA) bronchodilator [12]. This review analyzed subgroups of daily dose Vitamin D supplementation based on Vitamin D dosing basic principles that describe the recommended daily dose and upper tolerable daily dose of the patient based on their age. The intervention doses of included studies were classified into two groups: standard-dose and higher-dose, based on the age of subjects and the recommended daily dose [13]. The subgroups of duration of supplementation based on the median distribution. FEV1% and mean vitamin D levels were analyzed as different outcomes. FEV1% was calculated as a change from the baseline.

Quality assessment

Two reviewers (NLN and FFT) independently evaluated the quality of each selected study using the Joanne Briggs Institute (JBI) Critical Appraisal tools, checklist for Randomized Controlled Trials. If a discrepancy was found, senior researchers (RAS) were consulted.

Statistical analysis

Pooled outcomes analyses were assessed using forest plots and presented in 95% confidence intervals. Before identifying significant factors, data were assessed for heterogeneity and potential publication bias. The chi-square and I^2 tests were used to measure study heterogeneity; if p heterogeneity >0.05, and I^2 > 50%, a random-effects model was used. The rate of exacerbations was analyzed using an odd ratio, mean vitamin D level and FEV1% change was evaluated using pooled standardized mean difference (sMD). Data analysis used the Review Manager version 5.1 to analyze the data (Cochrane Collaboration, London, UK). Two authors (KF and QA) conducted statistical analyses independently to avoid methodological errors.

Results

Study selection

Using our search strategy, we observed 677 studies. There were 353 duplicate studies removed. Following a review of the titles and abstracts, 21 potentially relevant studies were identified. After reviewing the full-text, 11 studies were excluded because of the difference of the study design, the insufficient data provided and the different of cut off levels. Finally, we determined 10 studies that met our inclusion criteria. Figure 1 shows a flow chart depicting the study selection process.

This review included ten relevant studies that enrolled 1243 asthmatic children consisting of 631 children receiving vitamin D3 supplementation which then classified to the intervention group, and 612 children receiving placebo which then classified to the control group. The description of each study is shown in Table 1. The duration of supplementation ranges from 3 up to 12 months, with the daily dose given ranging from 150 IU/day up to 4000 IU/day. Eight studies analyzed the occurrence of asthma exacerbations in the intervention and the control group, six studies analyzed the mean vitamin D levels as measured by 25-hydroxyvitamin D in plasma, and four studies evaluated lung function as measured by FEV1.

Study characteristics

The characteristics of the included studies are described in Tables 1 and 2. 10 RCTs were blinded controlled, parallel-group trials that evaluated children and adolescents. Even two studies evaluated children from newborns and preschoolers [6, 14–22]. Included studies were from both developing and developed countries: three studies were conducted in India, two in Poland, and two in Japan, while the other three were conducted in US, Israel, and China. The extracted data about outcome measurements were as follows: the correlations between vitamin D and asthma exacerbations (8 studies), vitamin D levels after intervention (6 studies), and FEV1 (4 studies). The detailed characteristics of included studies were shown in Table 1. Furthermore, the 25(OH) D baseline differed between the studies, with three studies not providing a baseline. Five studies [6, 17, 20–22] enrolled only vitamin D-deficient (VDD) or vitamin D-insufficient participants. The other five did not identify vitamin D deficiency as an inclusion criterion, although many participants were VDD. The most commonly used category levels to characterize serum 25(OH)D deficiency, insufficiency, and sufficiency, respectively, were 20 ng/ml (50 nmol/l), 20-29.9 ng/ml (50-74.9 nmol/l), and 30 ng/ml (75 nmol/l). All included studies were critically appraised using Joanne Briggs

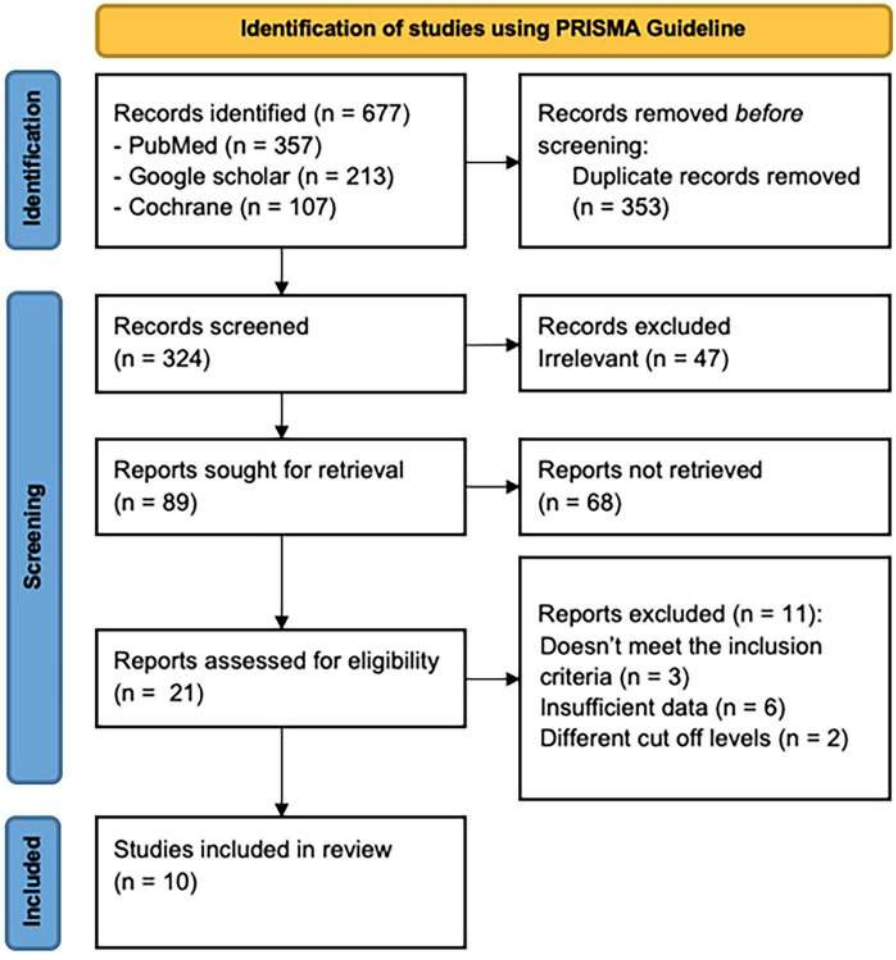

Figure 1. PRISMA flow chart.

Table 1. Details of included studies.

Study (author, year)	Country	Number of samples		Age (years)	Dose	Duration	Cumulative dose	Steroid use	Outcomes measured
		Intervention	Control						
Majak et al. [14]	Poland	18	18	6-12	1000 IU/week	3 months	90000 IU	Oral steroid (prednisone 0.45–0.95 mg/kg)	Vitamin D level, FEV1
Urashima et al. [15]	Japan	167	167	6-15	1200 IU/day	4 months	144000 IU	Not receiving steroid treatment	Asthma exacerbations
Majak et al. [16]	Poland	24	24	6-17	500 IU/day	6 months	90000 IU	Inhaled steroid (budesonide 800 ug/day)	Asthma exacerbations, Vitamin D level, FEV1
Yadav et al. [17]	India	50	50	3-14	2000 IU/day (60000 IU/month)	6 months	360000 IU	Administration route of steroid is not stated	Asthma exacerbations, Asthma control
Bar Yoseph et al. [6]	Israel	19	19	6-18	14000 IU/week	6 weeks	84000 IU	Not receiving steroid treatment	Vitamin D level
Tachimoto et al. [18]	Japan	54	35	6-15	800 IU/day first 2 months	6 months	48000 IU	Not receiving steroid treatment	Asthma exacerbations, GINA, CACT
Kang et al. [19]	China	48	48	0-14	200 IU/day (<6 yo) 400 IU/day (>6 yo)	12 months	73000 – 146000 IU	Inhaled steroid (budesonide)	Asthma exacerbations, ACT, FEV1, FVC, FEV1/FVC
Jat et al. [20]	India	125	125	4-12	1000 IU/day	9 months	270000 IU	Oral and inhaled steroid	Asthma exacerbations Vitamin D level, FEV1, FVC, GINA, CACT
Forno et al. [21]	US	96	96	6-16	4000 IU/day	12 months	1400000 IU	Not receiving steroid treatment	Asthma exacerbations, Vitamin D level
Thakur et al. [22]	India	30	30	6-11	2000IU/day	3 months	180000 IU	Oral steroid	Asthma exacerbations, Vitamin D level, FEV1

Table 2. Baseline characteristics of included studies.

Study (author, year)	Age (Mean ± SD)		25(OH)D (ng/mL) (Mean ± SD)		FEV1% (Mean ± SD)	
	Intervention	Control	Intervention	Control	Intervention	Control
Majak et al. [14]	6 – 12	6 – 12	32.0 ± 3.1	31.3 ± 3.4	95.2 ± 4.8	93.4 ± 3.2
Urashima et al. [15]	10.0 ± 2.2	10.4 ± 2.4	NM	NM	NM	NM
Majak et al. [16]	10.8 ± 3.2	11.1 ± 3.3	36.1 ± 13.9	35.1 ± 16.9	94.4 ± 13	98.7 ± 12
Yadav et al. [17]	9.15 ± 2.4	10.0 ± 1.9	NM	NM	NM	NM
Bar Yoseph et al. [6]	13.5 ± 3.6	12.4 ± 3.6	20.8 ± 6.5	20.0 ± 7.1	NM	NM
Tachimoto et al. [18]	10.0 ± 2.4	9.8 ± 2.2	28.4 ± 2.2	29.2 ± 2.4	87.8 ± 1.8	86.3 ± 1.7
Kang et al. [19]	6.56 ± 1.38	6.48 ± 1.27	NM	NM	NM	NM
Jat et al. [20]	8.2 ± 2.3	7.8 ± 2.2	11.6 ± 4.6	10.8 ± 4.4	92.5 ± 21.7	97.0 ± 17.5
Forno et al. [21]	9.9 ± 2.5	9.7 ± 2.5	22.5 ± 4.6	22.8 ± 4.6	93.9 ± 15.8	90.6 ± 17.3
Thakur et al. [22]	9.0 ± 1.7	8.7 ± 1.6	15.8 ± 8.2	16.5 ± 9.9	75.3 ± 26.5	7.56 ± 15.7

*NM = not measured.

Institute (JBI) Critical Appraisal tools, checklist for Randomized Controlled Trials. Three studies did not clearly report the reasons for subject's discontinuation or dropout [6, 15, 17]. One study did not treat the control and intervention group equally, as the control group only received inhaled budesonide, while the intervention group received inhaled budesonide + salbutamol and VD supplementation [19]. The risk of bias assessment of included studies was shown in Figure 2.

Primary outcome

Effect of vitamin D supplementation on asthma exacerbations

Four out of eight trials included in our meta-analysis reported that VD supplementation had a significant effect on lowering the total number of asthma exacerbations [18, 20–22] (Figure 3). The cumulative pooled analysis showed a significant effect in the reduction of

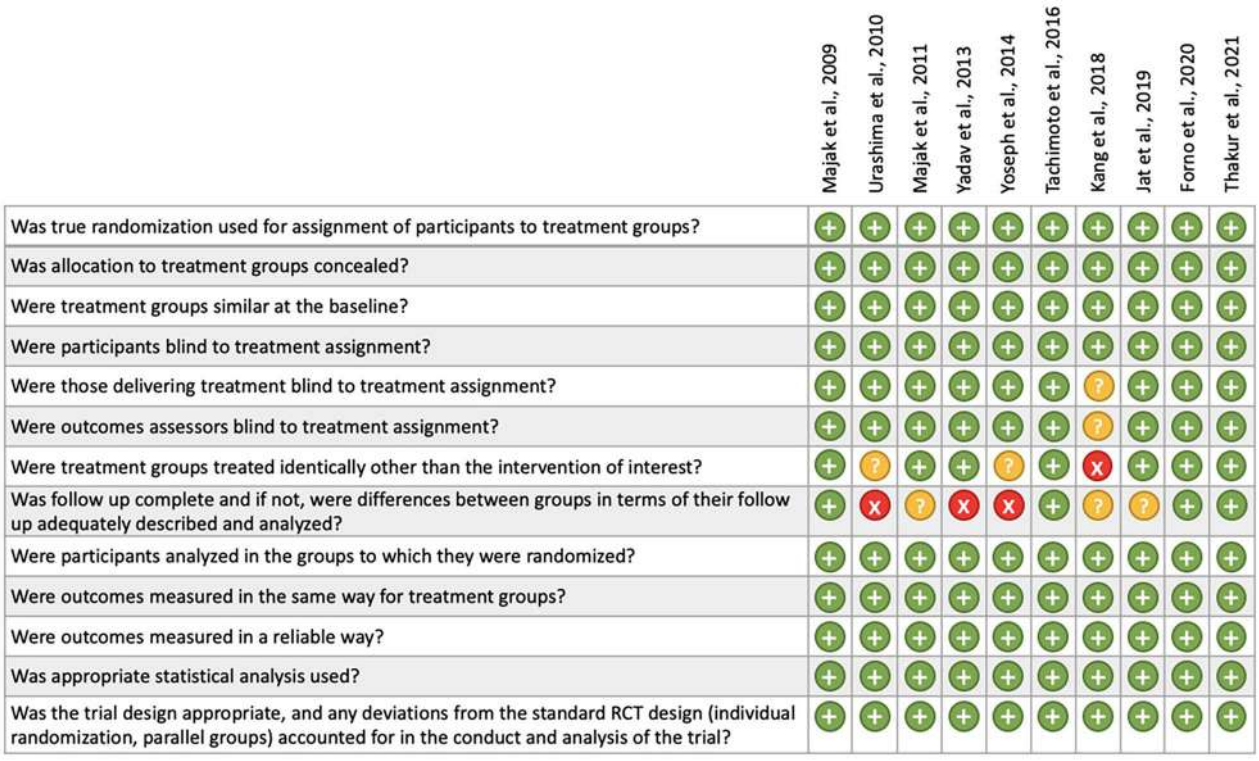

Figure 2. Risk of bias assessment for included studies.

asthma exacerbations in VD supplementation group (RR 0.62; 95% CI: 0.44, 0.87; $p=0.006$) (Figure 4). Five out of eight studies included had a standard daily dose of VD given and showed a statistically significant improvement in asthma exacerbations (RR 0.55; 95% CI: 0,34, 0,89; $p=0.01$) (Figure 5). VD supplementation for <6 months can decrease the occurrence of asthma exacerbations, as seen in Figure 5 (RR 0.51; 95% CI: 0,33, 0,80; $p=0.003$) (Figure 6). VD supplementation with steroid treatment can lower the occurrence of asthma exacerbations compared to children with no steroid treatment (RR 0.54; 95% CI: 0,35, 0,84; $p=0.0025$) (Figure 7).

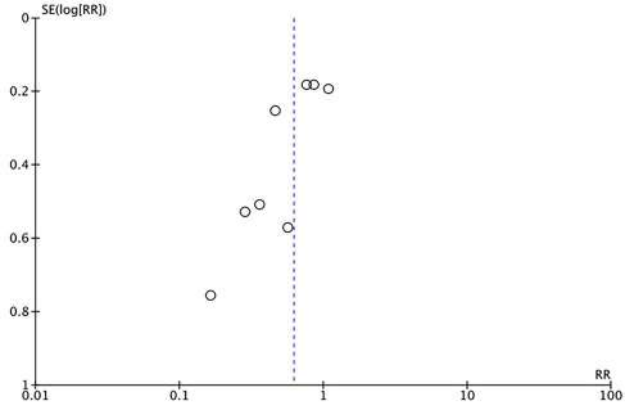

Figure 3. Funnel plot of included studies.

Secondary outcomes

Our study found a significant increase in VD levels in children with VD supplementation (SMD: 1.95; 95% CI: 1,32,2.57 $p=1\times10^{-4}$) (Figure 8). Out of 5 studies included with a VDD or VD insufficient levels participants, 3 of them [6, 21,22] shows an increase in VD levels and with a sufficient VD levels (Figure 8). There was also a significant improvement in predicted percentage of FEV1 levels in children with VD supplementation compared to the placebo group (SMD: −0.23 95% CI: −0,46, −0,01 $p=0.04$) (Figure 9). FEV1% was calculated as a change from the baseline.

Discussion

Our meta-analysis showed that asthma exacerbations were significantly lower in the intervention group compared to the placebo group. This finding is similar to a previous meta-analysis in adults which demonstrated a statistically significant reduction in asthma exacerbations in adults with low VD levels given VD supplementation. However, the aggregated estimate was insignificant among adolescents under 16 [11]. Our findings are also consistent with meta-analysis studies in general asthma populations, which suggest that vitamin D supplementation lowers the asthma exacerbations rate treated with

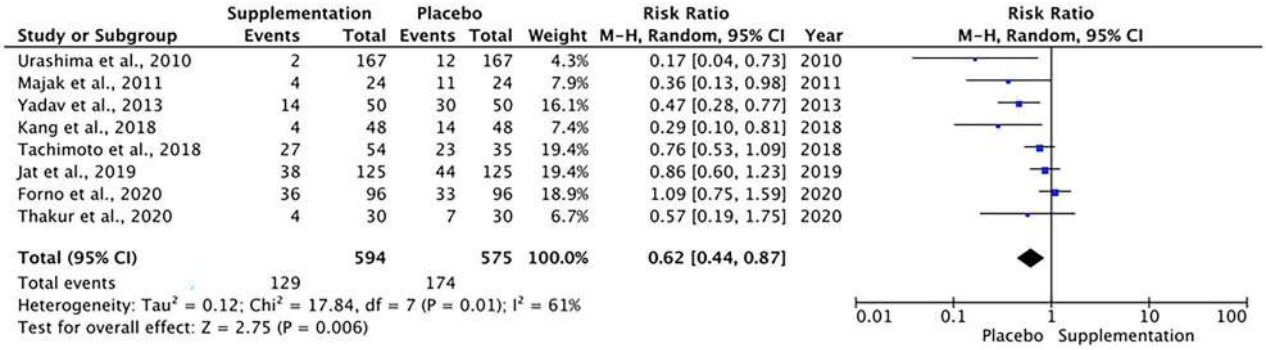

Figure 4. The effect of vitamin D supplementation on exacerbations incidence in children with asthma.

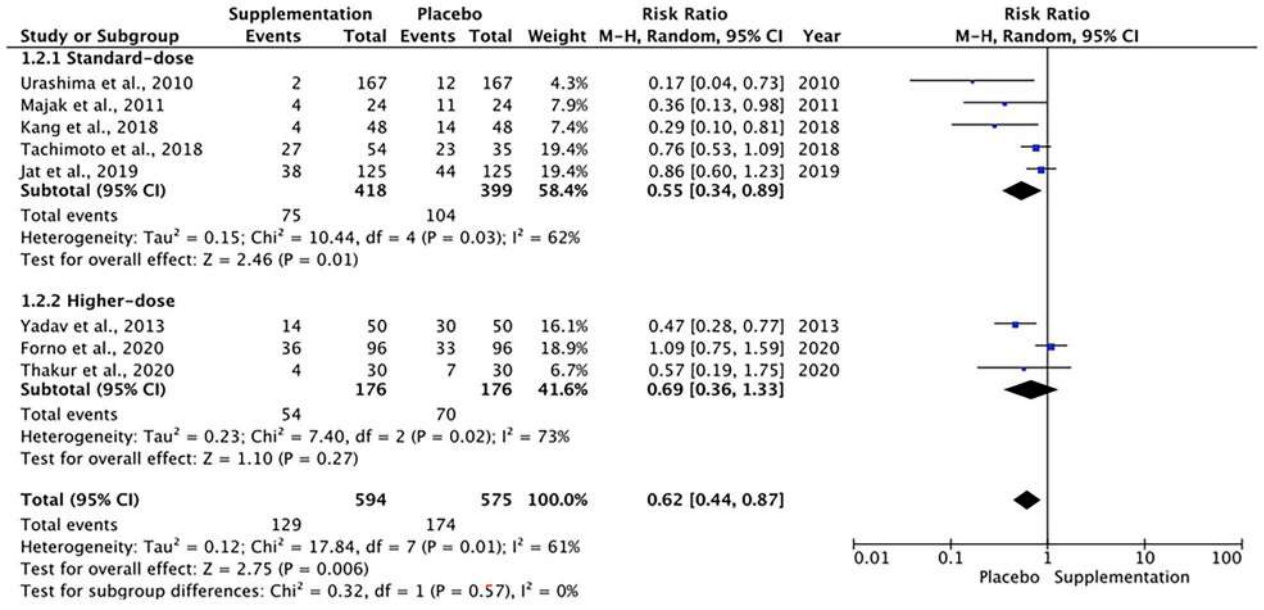

Figure 5. The effect of vitamin D supplementation on asthma exacerbations based on daily dose of vitamin D supplementation.

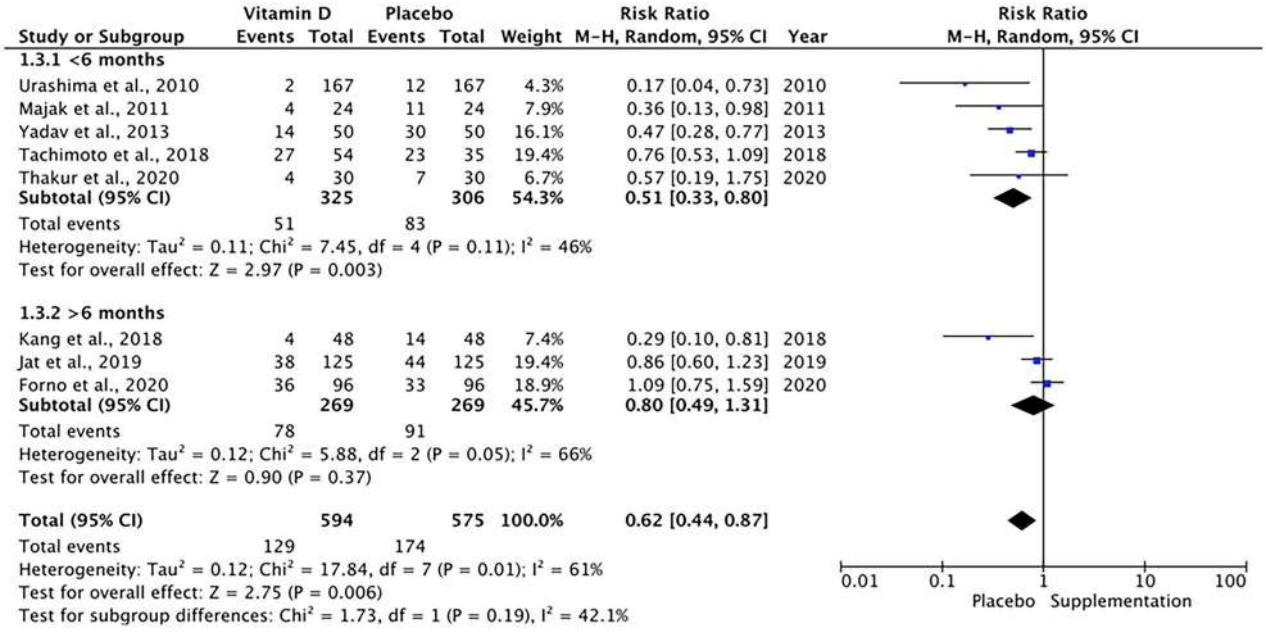

Figure 6. The effect of vitamin D supplementation on asthma exacerbations based on duration of supplementation.

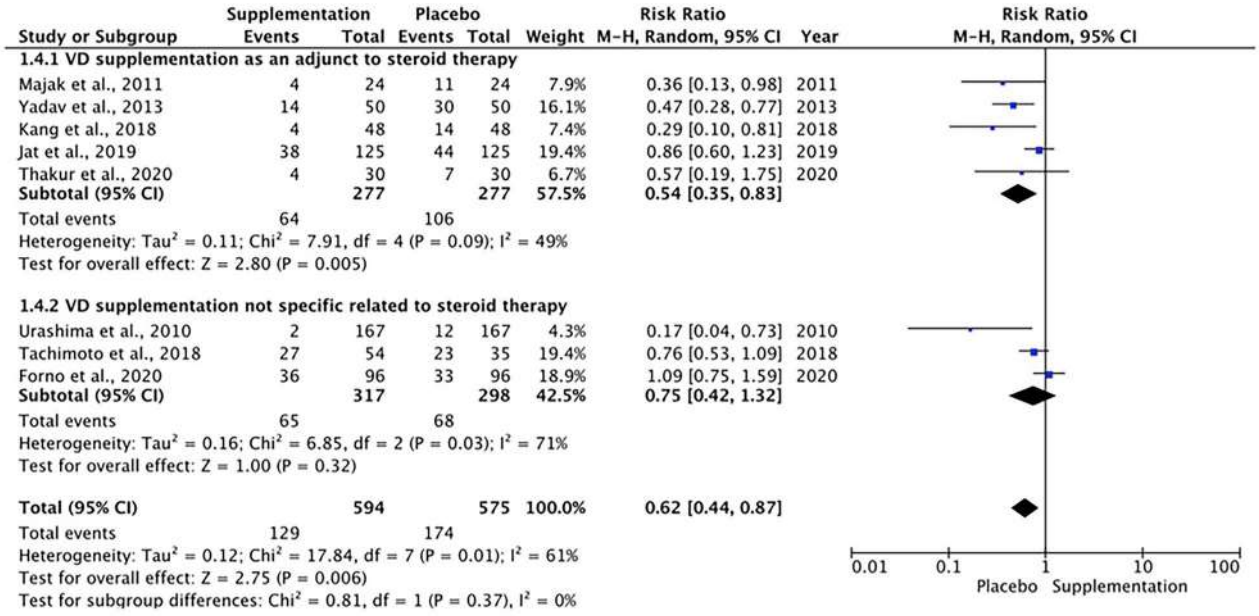

Figure 7. The effect of vitamin D supplementation on asthma exacerbations related to steroid use as a controller medication.

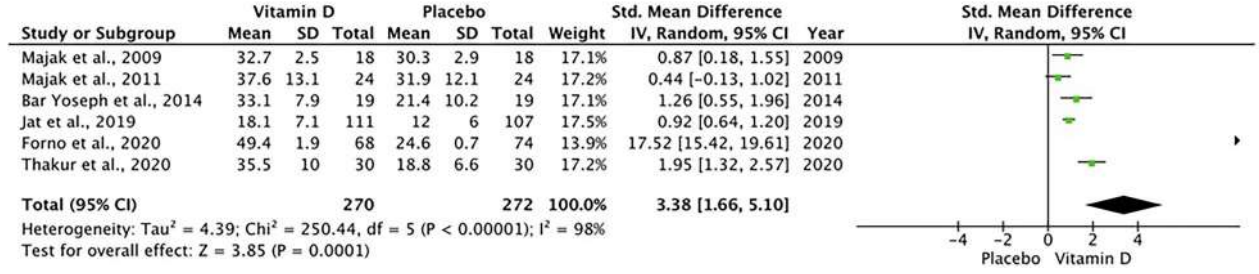

Figure 8. The effect of vitamin D supplementation on vitamin D levels.

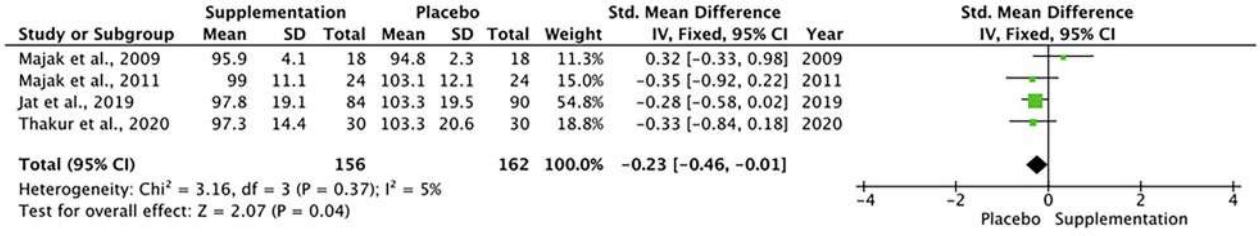

Figure 9. The effect of vitamin D supplementation on FEV1.

systemic corticosteroids, particularly in individuals with vitamin D insufficiency [23,24]. According to the most recent research, vitamin D has significant immunomodulatory effects that inhibit airway inflammation, improve airway hyper-responsiveness, decrease gland secretion, slow bronchial smooth muscle cell growth, improve airway remodeling, boost the body's response to corticosteroids and decrease viral-induced asthma attack [21, 25–27]. Most exacerbations are caused by viral upper respiratory tract infections (URTIs), especially in young children [6]. Vitamin D may attenuate viral-induced asthma attacks by reducing rhinovirus replication in bronchial epithelium, promoting interferon-mediated antiviral pathways and inducing the production of antimicrobial peptides [21].

Several studies have shown the effectiveness of vitamin D supplementation in reducing the incidence of exacerbations in asthma patients [1, 28]. However, none have analyzed the optimal dose and duration of supplementation in children. This review analyzed

subgroups for daily dose based on Vitamin D dosing basic principles [13]. The results of this review revealed that a daily dose of vitamin D in a standard recommended dose is more significant in decreasing exacerbations compared to those higher dose; the optimal duration was seen in subjects receiving supplementation <6 months. Previous clinical trials in patients with atopic dermatitis revealed that a weighted average dose of 1,500–1,600 IU per day for up to three months was associated with clinically significant benefits in reducing disease severity [29].

Standard recommended daily dose VD supplementation fits in with The Endocrine Society's vitamin D supplementation recommendations for children [30]. Higher dose of VD supplementation may not always give a better result because there is an optimal dose for VD supplementation in children. In a study involving the administration of 14,000 IU of vitamin D per week to children aged 13.5 3.6 years, there was no difference between the effects of vitamin D and placebo, even though vitamin D levels in the blood increased significantly [6]. Additionally, there are no specific recommendations regarding the duration of VD supplementation for respiratory health. The supplementation of adults with a high dose of vitamin D monthly for an average duration of 1.1 years, which increased serum 25(OH)D concentration by >50 nmol/L relative to placebo, did not enhance lung function in the study population [31]. One study found that infants with vitamin D deficiency who received ergocalciferol doses greater than 300,000 IU were at a high risk for hypercalcemia [32].

Our pooled analysis found that the mean vitamin D (25(OH)D) levels (four studies) were significantly higher in the intervention group than in the placebo group. This result was similar to the study that Vitamin D supplementation substantially altered serum vitamin D levels in asthmatic children [28]. Vitamin D supplementation may even diminish the lung function of patients [26]. The incidence of adverse events (AEs) was comparable between minors receiving vitamin D and those receiving placebos, so it was generally believed that vitamin D was safe [28].

This review revealed that even though vitamin D may decrease the occurrence of asthma exacerbations generally, the effect is more significant in subjects with steroid treatment compared to no steroid received. Vitamin D is thought to increase the expression of MAPK phosphatase 1 (MKP-1), another anti-inflammatory mechanism, which leads to corticosteroid-induced anti-inflammatory and immunosuppressive effects in peripheral blood mononuclear cells [33,34]. The method for reversing steroid resistance was enhanced by adding vitamin D's ability to decrease fractalkine release [35]. Both corticosteroids and vitamin D are able to individually control the release of inflammatory chemokines in human airway smooth muscle; however, when both are administered together, an additive suppression of this chemokine is produced [36]. Vitamin D and corticosteroids have been shown to synergistically generate a tolerogenic dendritic cell (DC) phenotype that is crucial for immunomodulation and decreased reactivity to self and external antigens (such as allergens) [25]. Oral treatment of vitamin D (calcitriol) also reversed the effects of steroid resistance by activating IL-10-secreting Tregs [37,38]. The effects of VD supplementation were more significant in children than in adult with asthma [33]. It may be because airway remodeling is less common in children than in adults [33, 39,40].

This review also revealed a significant FEV1 improvement in subjects receiving vitamin D supplementation. This finding aligns with previous studies that found a positive correlation between vitamin D and lung function [24, 41]. A 6-week [6] and 15-week [42] Double-Blind Placebo-Controlled Trial study found no correlation between vitamin D supplementation and lung function. However, in an Iranian study conducted before, 8 and 24 weeks after vitamin D administration, FEV1 was significantly improved in the intervention group than the other group after 24 weeks [43]. The various immune modulatory characteristics of vitamin D in different cells were explained [44–46]; nevertheless, it takes time before vitamin D reaches the appropriate concentration and exhibits its effects. Vitamin D can improve lung function by attenuating Th2 and Th17 responses, enhancing IL-10 production, and inhibiting airway smooth muscle hypertrophy and collagen deposition [21].

A notable strength of our systematic review and meta-analysis is the inclusion of only randomized controlled trials (RCTs). RCTs are considered the gold standard in evidence-based medicine for assessing the efficacy of interventions, as they minimize the risk of various biases compared to other study designs. By exclusively including RCTs in our analysis, we have enhanced the internal validity of our findings and provided a robust basis for evaluating the impact of vitamin D supplementation on asthma exacerbations in children. One limitation of our systematic review and meta-analysis is the potential for publication bias. Despite our efforts to include all relevant studies, it is possible that some trials with null or negative results were not published or were difficult to access, leading to an overestimation of the beneficial effects of vitamin D supplementation on asthma exacerbations in children.

Conclusion

In conclusion, the available evidence suggests that vitamin D supplementation decreases the rate of asthma exacerbations in children and improves FEV1, but the effect is dose and duration related. A daily dose of vitamin D based on the standard daily dose recommendation is more significant in decreasing exacerbations compared to those receiving higher dose than the recommendation. The vitamin D supplementation effect was also seen as more significant in patients receiving steroid treatment compared to none. Overall, vitamin D supplementation may be a promising therapy for reducing asthma exacerbations rates in children.

Author contributions

KF and RAS designed the study. QA, LNR, NLN, FFT participated in data collection and literature search. LNR, NLN, FFT designed the keywords and screening all articles. KF, RAS, QA analyzed the results and drafted the manuscript. All authors have agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Katherine Fedora http://orcid.org/0000-0003-0857-1230
Retno Asih Setyoningrum http://orcid.org/0000-0002-4194-6869
Qorri' Aina http://orcid.org/0000-0002-0500-8787
Laili Nur Rosyidah http://orcid.org/0009-0009-6227-6508
Nur Lailatun Ni'mah http://orcid.org/0000-0003-0739-2062
Feelin Fatwa Titiharja http://orcid.org/0000-0002-6296-7191

Data availability statement

Data are publicly available to access.

References

[1] Kumar J, Kumar P, Goyal JP, et al. Vitamin D supplementation in childhood asthma: a systematic review and meta-analysis of randomised controlled trials. ERJ Open Res. 2021;8(1):00662–02021. doi: 10.1183/23120541.00662-2021.
[2] CDC; 2018.
[3] Zhang D, Zheng J. The burden of childhood asthma by age group, 1990-2019: a systematic analysis of global burden of disease 2019 data. Front Pediatr. 2022;10:823399. doi: 10.3389/fped.2022.823399.
[4] Hsu J, Qin X, Beavers SF, et al. Asthma-related school absenteeism, morbidity, and modifiable factors. Am J Prev Med. 2016;51(1):23–32. doi: 10.1016/j.amepre.2015.12.012.
[5] Lizzo JM, Cortes S. Pediatric asthma. In StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. https://europepmc.org/article/NBK/nbk551631
[6] Bar Yoseph R, Livnat G, Schnapp Z, et al. The effect of vitamin D on airway reactivity and inflammation in asthmatic children: a double-blind placebo-controlled trial. Pediatr Pulmonol. 2015;50(8):747–753. doi: 10.1002/ppul.23076.
[7] Norbäck D, Lu C, Wang J, et al. Asthma and rhinitis among Chinese children - indoor and outdoor air pollution and indicators of socioeconomic status (SES). Environ Int. 2018;115:1–8. doi: 10.1016/j.envint.2018.02.023.
[8] Bantz SK, Zhu Z, Zheng T. The role of vitamin D in pediatric asthma. Ann Pediatr Child Health. 2015;3(1):1032.
[9] Jeffery LE, Burke F, Mura M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J Immunol. 2009;183(9):5458–5467. doi: 10.4049/jimmunol.0803217.
[10] Telcian AG, Zdrenghea MT, Edwards MR, et al. Vitamin D increases the antiviral activity of bronchial epithelial cells in vitro. Antiviral Res. 2017;137:93–101. doi: 10.1016/j.antiviral.2016.11.004.
[11] Ogeyingbo OD, Ahmed R, Gyawali M, et al. The relationship between Vitamin D and asthma exacerbations. Cureus. 2021;13(8):e17279. doi: 10.7759/cureus.17279.
[12] Reddel HK, Taylor DR, Bateman ED, et al. An official American thoracic society/european respiratory society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. American Thoracic Society Documents. Am J Respir Crit Care Med. 2009;180(1):59–99. doi: 10.1164/rccm.200801-060ST.
[13] Bleizgys A. Vitamin D dosing: basic principles and a brief algorithm (2021 update). Nutrients. 2021;13(12):4415. doi: 10.3390/nu13124415.
[14] Majak P, Rychlik B, Stelmach I. The effect of oral steroids with and without vitamin D3 on early efficacy of immunotherapy in asthmatic children. Clin Exp Allergy. 2009;39(12):1830–1841. doi: 10.1111/j.1365-2222.2009.03357.x.
[15] Urashima M, Segawa T, Okazaki M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr. 2010;91(5):1255–1260. doi: 10.3945/ajcn.2009.29094.
[16] Majak P, Olszowiec-Chlebna M, Smejda K, et al. Vitamin D supplementation in children may prevent asthma exacerbations triggered by acute respiratory infection. J Allergy Clin Immunol. 2011;127(5):1294–1296. doi: 10.1016/j.jaci.2010.12.016.
[17] Yadav M, Mittal K. Effect of vitamin D supplementation on moderate to severe bronchial asthma. Indian J Pediatr. 2014;81(7):650–654. doi: 10.1007/s12098-013-1268-4.

[18] Tachimoto H, Mezawa H, Segawa T, et al. Improved control of childhood asthma with low-dose, short-term vitamin D supplementation: a randomized, double-blind, placebo-controlled trial. Allergy. 2016;71(7):1001–1009. doi: 10.1111/all.12856.

[19] Kang Q, Zhang X, Liu S, et al. Correlation between the vitamin D levels and asthma attacks in children: evaluation of the effects of combination therapy of atomization inhalation of budesonide, albuterol and vitamin D supplementation on asthmatic patients. Exp Ther Med. 2018;15(1):727–732. doi: 10.3892/etm.2017.5436.

[20] Jat KR, Goel N, Gupta N, et al. Efficacy of vitamin D supplementation in asthmatic children with vitamin D deficiency: a randomized controlled trial (ESDAC trial). Pediatr Allergy Immunol. 2021;32(3):479–488. doi: 10.1111/pai.13415.

[21] Forno E, Bacharier LB, Phipatanakul W, et al. Effect of vitamin D3 supplementation on severe asthma exacerbations in children with asthma and low vitamin D levels: the VDKA randomized clinical trial. JAMA. 2020;324(8):752–760. doi: 10.1001/jama.2020.12384.

[22] Thakur C, Kumar J, Kumar P, et al. Vitamin-D supplementation as an adjunct to standard treatment of asthma in children: a randomized controlled trial (ViDASTA Trial). Pediatr Pulmonol. 2021;56(6):1427–1433. doi: 10.1002/ppul.25287.

[23] Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med. 2017;5(11):881–890. doi: 10.1016/S2213-2600(17)30306-5.

[24] Wang M, Liu M, Wang C, et al. Association between vitamin D status and asthma control: a meta-analysis of randomized trials. Respir Med. 2019;150:85–94. doi: 10.1016/j.rmed.2019.02.016.

[25] Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. Curr Opin Allergy Clin Immunol. 2012;12(2):179–185. doi: 10.1097/ACI.0b013e3283507927.

[26] Britt RD, Thompson MA, Freeman MR, et al. Vitamin D reduces inflammation-induced contractility and remodeling of asthmatic human airway smooth muscle. Ann Am Thorac Soc. 2016;13(Suppl 1):S97–S98. 1 doi: 10.1513/AnnalsATS.201508-540MG.

[27] Ginter E, Simko V. Deficiency of vitamin D and vitamin C in the pathogenesis of bronchial asthma. Bratisl Lek Listy. 2016;117(6):305–307. doi: 10.4149/bll_2016_060.

[28] Hao M, Xu R, Luo N, et al. The effect of vitamin D supplementation in children with asthma: a meta-analysis. Front Pediatr. 2022;10:840617. doi: 10.3389/fped.2022.840617.

[29] Hattangdi-Haridas SR, Lanham-New SA, Wong WHS, et al. Vitamin D deficiency and effects of vitamin D supplementation on disease severity in patients with atopic dermatitis: a systematic review and meta-analysis in adults and children. Nutrients. 2019;11(8):1854. doi: 10.3390/nu11081854.

[30] Holick MF, Binkley NC, Bischoff-Ferrari HA, Endocrine Society., et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–1930. doi: 10.1210/jc.2011-0385.

[31] Sluyter J, Camargo C, Waayer D, et al. Effect of monthly, high-dose, long-term vitamin D on lung function: a randomized controlled trial. Nutrients. 2017;9(12):1353. doi: 10.3390/nu9121353.

[32] Cesur Y, Caksen H, Gündem A, et al. Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. J Pediatr Endocrinol Metab. 2003;16(8):1105–1109. doi: 10.1515/JPEM.2003.16.8.1105.

[33] Augusto AL. Vitamin D and corticosteroids in asthma: synergy, interaction and potential therapeutic effects. Expert Rev Respir Medi. 2013;7(2):101–104. doi: 10.1586/ers.12.85.

[34] Searing DA, Zhang Y, Murphy JR, et al. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. J Allergy Clin Immunol. 2010;125(5):995–1000. doi: 10.1016/j.jaci.2010.03.008.

[35] Sutherland ER, Goleva E, Jackson LP, et al. Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med. 2010;181(7):699–704. doi: 10.1164/rccm.200911-1710OC.

[36] Banerjee A, Damera G, Bhandare R, et al. Vitamin D and glucocorticoids differentially modulate chemokine expression in human airway smooth muscle cells. Br J Pharmacol. 2008;155(1):84–92. doi: 10.1038/bjp.2008.232.

[37] Brehm JM, Schuemann B, Fuhlbrigge AL, Childhood Asthma Management Program Research Group., et al. Serum vitamin D levels and severe asthma exacerbations in the childhood asthma management program study. J Allergy Clin Immunol. 2010;126(1):52–58.e5. doi: 10.1016/j.jaci.2010.03.043.

[38] Liu J, Dong YQ, Yin J, et al. Meta-analysis of vitamin D and lung function in patients with asthma. Respir Res. 2019;20(1):161. doi: 10.1186/s12931-019-1072-4.

[39] Li J, Ye L, She J, et al. Clinical differences between early-and late-oset asthma: a population-bases cross-sectional study. Can Respor J. 2021;2021:8886520.

[40] Liu QH, Kan X, Wang YB, et al. Differences in the clinical characteristics of early- and late-onset asthma in elderly patients. Biomed Res Int. 2020;2020:2940296. doi: 10.1155/2020/2940296.

[41] Kerley CP, Hutchinson K, Cormican L, et al. Vitamin D3 for uncontrolled childhood asthma: a pilot study. Pediatr Allergy Immunol. 2016;27(4):404–412. doi: 10.1111/pai.12547.

[42] Arshi S, Fallahpour M, Nabavi M, et al. The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma. Ann Allergy Asthma Immunol. 2014;113(4):404–409. doi: 10.1016/j.anai.2014.07.005.

[43] Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr. 2001;73(2):288–294. doi: 10.1093/ajcn/73.2.288.

[44] Lange NE, Litonjua A, Hawrylowicz CM, et al. Vitamin D, the immune system and asthma. Expert Rev Clin Immunol. 2009;5(6):693–702. doi: 10.1586/eci.09.53.

[45] Di Rosa M, Malaguarnera M, Nicoletti F, et al. Vitamin D3: a helpful immuno-mod; 2011.

[46] Di Rosa M, Malaguarnera M, Nicoletti F, et al. Vitamin D3: a helpful immuno-modulator. Immunology. 2011;134(2):123–139. doi: 10.1111/j.1365-2567.2011.03482.x.