Abstract

Vitamin D has anti-inflammatory properties by multiple mechanisms. Vitamin D deficiency has been associated with increased inflammation, exacerbations, and overall worse outcomes in pediatric asthma and is seen in asthmatic children with obesity. Also, given the increase in the prevalence of asthma over the last few decades, there has been enormous interest in vitamin D supplementation as a potential therapeutic option. However, recently there have been opposite results studies suggest no strong association between vitamin D levels or vitamin D supplements and childhood asthma. Additionally, recently there have been exciting reports that obesity and vitamin D deficiency has been associated with increased asthma symptoms. Thus, this review will summarize the findings from clinical trials regarding the role of vitamin D in pediatric asthma and analyze the study trend of vitamin D for two decades.

Key words: Vitamin D, Asthma, Clinical trials, Children, Obesity
Key message

- Vitamin D may affect asthma via multiple mechanisms, including lung and optimal immune system functions.

- Many clinical trials have shown the beneficial effect of vitamin D on asthma onset and aggravation. However, definitive clinical trials are lacking, and there have been opposite reports of the beneficial effect of vitamin D in children with asthma.

- There have been exciting reports that obesity and vitamin D deficiency has been associated with increased asthma symptoms in pediatric population.
Introduction

Asthma is a chronic disorder of the conducting airways characterized by reversible airway obstruction and airway inflammation. Pediatric asthma is a significant concern because it increases the number of hospital visits and economic burden more than asthma in adults. In the 2000s, asthma prevalence is increasing globally over a short period due to the impact of environmental risk factors and genetic factors. Previous epidemiological Korean studies reported around 10~14% prevalence of asthma in children.

It is well-known that vitamin D is essential in calcium and bone metabolism and immunomodulation. Vitamin D may affect asthma and allergy risk via multiple mechanisms, and vitamin D deficiency, one of the increasing causes of asthma, has become more severe globally over the last decades. Recent studies in adults and children showed a higher prevalence of low vitamin D levels in asthmatics than in the average population. Also, low vitamin D levels are associated with higher severity of asthma and impaired pulmonary function. Asthmatic patients with vitamin D deficiency have shown increased airway hyper-responsiveness and corticosteroid requirements, and vitamin D might increase the response to glucocorticoids in asthmatic patients. Especially, pregnant maternal vitamin D intake has an inverse association with the risk of recurrent wheezing in childhood in the prospective study. However, although many studies have been conducted in Korea and other countries about the relationship between asthma and vitamin D deficiency or insufficiency, vitamin D deficiency or insufficiency has increased worldwide, especially in adolescents and young adults.

Meanwhile, recent opposite results suggest no strong association between serum vitamin D levels or vitamin D supplements and childhood asthma. Thus, the purpose of the review article
is to summarize the published clinical research to investigate the effects of vitamin D on children with asthma development and symptom aggravation. In this review, we critically reviewed the findings from clinical trials regarding the role of vitamin D in pediatric asthma and analyzed the study trend of vitamin D for two decades.

Study selection and characteristics

PubMed was searched by combining the terms (asthma, pediatric asthma) and (vitamin D, 25-hydroxyvitamin D (25(OH)D)) and duration (from January 2002 to August 2022) to identify studies that reported on research trends in vitamin D and asthma in children. The latest search was performed on August 15, 2022. The search revealed 133 results; after removing duplicates and restrictions aged (> 19 years). 92 records were excluded based on title and abstract screening, 11 relevant studies were subjected to full-text review. Finally, 31 articles were included in this systematic review. According to the article's purpose for vitamin D, a summary of the included articles is outlined in Table 1, Table 2, and Table 3.

1. Effects of vitamin D prevention on asthma onset in childhood

There are several well-established studies on this topic (Table 1). Some birth cohort studies have demonstrated that serum vitamin D level at birth and maternal vitamin D exposure during pregnancy or vitamin D status may affect the incidence of asthma in childhood. In the following, the association between vitamin D and asthma in children will be summarized in two main aspects: serum vitamin D levels before delivery, cord blood, and early infant and supplement studies.
1.1 Vitamin D levels on asthma onset in childhood

In the Hollams EM et al., serum vitamin D was assayed in 989 (6-year-olds) and 1,380 (14-year-olds) from an unselected community birth cohort; 689 subjects were assessed at both ages. Children (particularly males) with inadequate vitamin D are at increased risk of developing atopy, bronchial hyperresponsiveness (BHR), and asthma.

Due to the early onset of childhood asthma, we could hypothesize that maternal exposure during pregnancy and the maternal vitamin D status might play a role in the development of asthma. The 25(OH)D levels were measured mid-gestation and at birth, and airway resistance was measured at 6 years old in offspring to clarify the association of maternal and fetal 25(OH)D levels with lung function and childhood asthma. The maternal levels of 25(OH)D in mid-gestation were not associated with airway resistance in offspring at 6 years old, but low levels of 25(OH)D at birth were associated with higher airway resistance in childhood.

In a Taiwanese birth cohort study, those children aged 0 through 4 years, serum 25(OH)D levels were measured six times in maternal blood (before delivery, cord blood, and at ages 1.5, 3, and 4). Also, specific IgE antibodies against food and inhalant allergens were measured six times in children (at 6 months and 1, 1.5, 2, 3, and 4 years). There was a significant correlation between maternal and cord blood 25(OH)D levels and persistently lower vitamin D serum levels in children born to vitamin D deficient mothers. Vitamin D deficiency in mothers (<20 ng/ml) appeared to be associated with a higher prevalence of allergen sensitization before age 2. Higher maternal 25(OH)D levels were significantly associated with a lower risk of asthma at age 4. Additionally, in the Generation R Study, 4951 mothers and children pairs had patriciated in a population-based prospective cohort and had blood samples for maternal (in mid-
gestation) and umbilical cord (at birth). After additional adjustment for the child's 25(OH)D concentrations at the age of 6 years, only the associations of 25(OH)D concentrations in mid-gestation with forced expiratory volume in 1 s (FEV1) / forced vital capacity (FVC) and forced expiratory flow at 75% (FEF75) at age 10 years have remained.

1.2 Vitamin D supplementation during pregnancy and infancy

The vitamin D intake of the infant or maternal in pregnancy might play a role in the development of asthma in a child (Table 1). In a prospective birth cohort study up to the age of 6 years, prevention through modified vitamin D3 supplementation in infancy could reduce allergic diseases. However, in the Northern Finland Birth Cohort for 31 years, vitamin D supplementation in infancy did not appear to influence the development of asthma or wheezing in children.

There were three randomized controlled trial studies which were ascertaining the role of maternal diet on the risk of asthma development in offspring. In one trial, 180 pregnant women at 27 weeks gestation to either no vitamin D, 800 IU ergocalciferol daily until delivery, or a single oral bolus of 200,000 IU cholecalciferol. Researchers blind to allocation assessed offspring at three years using a questionnaire, impulse oscillometry, and exhaled nitric oxide. However, there was no significant difference in atopy, lung function, or exhaled nitric oxide between supplemented groups and controls. In another trial, 881 mothers and infants received vitamin D (440 women with daily 4000 IU vitamin D plus a prenatal vitamin containing 400 IU vitamin D, and 436 women with placebo plus a prenatal vitamin containing 400 IU vitamin D). The incidence of asthma and recurrent wheezing in their children at age
three years was lower by 6.1%, but this result was insignificant. In the other trial\textsuperscript{20}, mothers and infants had lower or higher doses of vitamin D (400 IU/800 IU in infants and 1000 IU/2000 IU in mothers). Vitamin D supplementation during pregnancy and infancy reduces the proportion of children sensitized to house mites at 18 months, and there were study group differences in the proportion of children with primary care visits described by the doctor as being for asthma.\textsuperscript{20}

To summarize their studies, vitamin D supplementation during maternal pregnancy and infancy may be practical for preventing asthma onset in childhood, but it is still controversial.

\subsection*{2. Effects of vitamin D and asthma severity in pediatric asthma}

Over the last two decades, several research groups have focused on the role of vitamin D in asthma pathogenesis. The following studies have identified a link between vitamin D deficiency and an overall worse outcome of lung function, symptom control, and exacerbation in children with asthma (Table 2).

\subsection*{2.1 Vitamin D levels and pediatric asthma}

In the Brehm JM \textit{et al.} trial,\textsuperscript{7} serum vitamin D was assayed in 616 children with asthma; lower vitamin D levels are associated with increased asthma severity. Also, vitamin D deficiency was higher in asthma than in control; vitamin D sufficiency was lower in asthma than in control.\textsuperscript{21,22} In the asthmatic children, 25(OH)D was positively correlated with FEV\textsubscript{1} and FEV\textsubscript{1}/FVC in the two studies\textsuperscript{21,23}, but there was controversial that asthmatic patients were
a much lower 25(OH)D level compared to healthy controls. In the age, gender, and ethnicity-matched case-control study, 25(OH)D levels were significantly lower, and IgE significantly higher in cases than in controls, with a negative correlation evident. According to the National Health and Nutrition Examination Survey in the USA, from 2001 to 2010, there was a positive correlation between vitamin D insufficiency (<30 ng/ml) and current asthma or wheeze in children (Table 2).

However, in the study of non-obese asthmatic children currently not receiving anti-inflammatory treatment, although the average level of vitamin D was 23 ng/ml, there was no correlation between vitamin D level and airway reactivity and airway inflammation. Furthermore, in a population-based cohort of adults, serum 25(OH)D was positively associated with FEV\(_1\) and FVC and negatively with FeNO; these associations disappeared after adjusting for confounders, including body mass index (BMI). Thus, 25(OH)D levels were not associated with lung function and airway inflammation in non-obese adults.

### 2.2 Vitamin D levels and pediatric asthma exacerbation

Several studies have emphasized a link between vitamin D levels and asthma exacerbation in children. In the analysis of 25(OH)D levels in 36 children with steroid-resistant asthma, 26 with moderate asthma, and 24 healthy controls, 25(OH)D levels were significantly lower in steroid-resistant asthma than either mild asthmatics or controls. Low 25(OH)D was correlated with asthma exacerbation and medication usage. In another study, no significant difference in 25(OH)D levels between 287 asthmatic children and 273 controls, but a lower 25(OH)D correlated with severe asthma exacerbation. Additionally, an analysis of 25(OH)D levels in
preschoolers with asthma and healthy controls showed a significant decrease in asthmatic
children's serum vitamin D levels compared to controls. In the vitamin D sufficient group, the
total number of exacerbations during the previous year was much lower compared to the
vitamin D insufficient group. The number of children with controlled asthma was also higher
in the sufficient group, which suggests a positive correlation between serum vitamin D levels
and asthma control.\textsuperscript{30}

\section*{2.3 Vitamin D supplementation on clinical outcomes in pediatric asthma}

Interestingly, few clinical trials have been conducted to determine the effects of vitamin D
supplementation on clinical outcomes in children with asthma. A concluded double-blind,
randomized, placebo-controlled trial examines whether a 100,000 IU dose of vitamin D
supplementation may rapidly raise serum 25(OH)D levels in preschoolers with asthma. At three
months, all children in the intervention group had serum 25(OH)D levels of \textgreater 30 ng/ml,
compared to only about 50\% in the control group.\textsuperscript{34}

In the Japanese children with asthma study, an assessment of the frequency and severity
of asthma given vitamin D3 supplements (800 IU/day) for two months revealed that asthma
control was improved by vitamin D supplementation.\textsuperscript{32} In a trial with Caucasian children who
received 2000 IU/day of vitamin D for 15 weeks, supplementation significantly decreased the
number of missed school days. However, there were no other advantageous changes in asthma
parameters compared to the placebo group.\textsuperscript{33}

In a double-blind, randomized, placebo-controlled trial,\textsuperscript{34} children with mild asthma, PC20-
FEV1 <16 mg/ml, and vitamin D <30 ng/ml, oral vitamin D group received oral vitamin D
14,000 once weekly. Although there were significant increases in vitamin D blood levels, no difference between the effect of vitamin D and placebo was found.

In another trial\textsuperscript{35} with moderate-to-severe asthma and vitamin D levels $< 25$ ng/mL, children who received vitamin D for 12 months, and loading doses have been used in children. Alansari \textit{et al}\textsuperscript{35} examined the effects of 300,000 or 600,000 IU of vitamin D2 by injection as a loading dose followed by 400 IU of oral vitamin D3 daily versus oral therapy only in 231 children (aged 2-14 years).\textsuperscript{35} Rapid compared to maintenance vitamin D supplementation for children with the lowest levels resulted in short- but not the long-term reduction in asthma exacerbations.\textsuperscript{35}

Additionally, the World Allergy Organization reported in 2016 that based on currently available evidence; they found no support for the hypothesis that vitamin D supplementation reduces the risks of developing allergic diseases, including asthma, in children. The panel suggested not using vitamin D in pregnant women, breastfeeding mothers, or healthy infants to prevent the development of allergic diseases.\textsuperscript{36}

The two recent double-blind, randomized, placebo-controlled trials have supported this recommendation.\textsuperscript{37,38} Among children with persistent asthma and low vitamin D levels, vitamin D3 supplementation, compared with placebo, did not significantly improve the time to a severe asthma exacerbation, and vitamin D supplementation as an adjunct to standard treatment does not improve asthma control in children.\textsuperscript{37,38} However, a recent interventional study with 68 asthmatic children found that asthma severity, FEV1, FVC, and FEV1/FVC indicators were significantly increased after vitamin D supplement.\textsuperscript{39}

In summary, evidence from the highlighted studies has demonstrated an association between
vitamin D supplementation and clinical outcomes of pediatric asthma, but the reports from recent clinical trials have not concluded. More prospective research is needed to clarify if vitamin D supplementation relieved the symptoms associated with asthma.

3. Vitamin D and obesity-related asthma in children

The prevalence of obesity in children has increased significantly since the coronavirus disease 2019 (COVID-19) pandemic because losses of daily routines have been negatively impacted. Adipose tissue may act as an endocrine organ releasing soluble factors, and excess adipose tissue predisposes to an enhanced inflammatory state and may contribute to the pathogenesis and aggravation of asthma. Recent retrospective two cohort studies have analyzed big data over 150,000 subjects. One study was divided into three groups (aged: 2 ~ 6 years, 7 ~ 11 years, and 12 ~ 17 years), and before age 12, females had a higher risk for obesity-related asthma; but after age 12, obese males had a higher asthma risk. Overall, obesity is a major preventable risk factor for pediatric asthma in two studies. Therefore, obesity may contribute substantially to childhood asthma morbidity and healthcare costs.

Recently there have been exciting reports that obesity and vitamin D deficiency has been associated with increased asthma symptoms, and vitamin D supplement could decrease asthma aggravation in children. There are several well-established studies on this topic (Table 3). Epidemiologic studies have reported low levels of serum 25(OH)D in children with difficult to treat asthma irrespective of body weight. According to a nationwide study using National Health and Nutrition Examination Survey (NHANES) data, children with asthma (n=1,192) were likelier to have a higher BMI z-score and a lower serum vitamin D level. Low levels of
serum vitamin D (25(OH)D) have been reported in children who have asthma and in children who are obese, making children who have both asthma and obesity particularly at risk for low vitamin D levels. Also, a population-based cohort found that >10nmol/L 25(OH)D was associated with 0.46% predicted higher FEV₁, 0.46% predicted higher FVC, and 0.24 ppb lower FeNO in obese adults with BMI ≥ 30 kg/m². Thus, higher 25(OH)D levels were associated with better lung function and lower airway inflammation in an obese subject. Turer et al observed that 79% of children who were overweight (BMI 85th–95th percentile for age and gender) and 86% of children with obesity (BMI ≥ 95th percentile) met the criteria for vitamin D insufficiency (serum vitamin D measured as 25(OH)D < 30 ng/ml).

In a study looking at vitamin D levels in 235 children with asthma, only 76 of whom were considered to have obesity, the mean serum 25(OH)D level was 20.6 ng/ml (interquartile range, 13.5–26.0). Children with asthma and low serum 25(OH)D levels are predisposed to worse asthma outcomes. Lautenbacher et al found that vitamin D deficiency was associated with pulmonary function decline among obese children of Hispanic and African American descent but not their healthy weight controls. In another study, Bose et al showed that a relationship between indoor air quality, asthma, and vitamin D levels in obese children in an urban environment. Three-way interaction models demonstrated significantly greater PM₂.₅-associated effects on daytime asthma symptoms only among obese children with low 25-OH D levels. They observed that higher serum 25(OH)D levels appeared to mitigate the effects of increase indoor air pollution.

It is hypothesized that supplementation with vitamin D could be beneficial in this patient population. A Cochrane review has noted that the dose of vitamin D to use in supplementation for asthma (and therefore obesity-related asthma) is still uncertain. A study comparing vitamin
D bioavailability in adults of normal weight versus those with obesity attributed decreased vitamin D levels to deposition of vitamin D in body fat compartments.\textsuperscript{50} However, data on vitamin D pharmacokinetics in children with obesity is lacking. Thus, addressing this critical gap in our understanding of vitamin D pharmacokinetics is an essential first step in investigating the role of vitamin D as a treatment for pediatric obesity-related asthma.

In summary, there is ample evidence that both asthma and obesity are inflammatory conditions, both are associated with decreased serum 25(OH)D levels and that there is the potential for intervention with vitamin D supplementation to decrease the inflammatory properties of both diseases.

Conclusion

Asthma has been currently increasing among children and adolescents in Korea and some other countries, and the socio-economic cost burden of asthma has been increasing. The role of vitamin D in asthma pathogenesis has been a topic of much debate for two decades. The author considered the relationship between asthma in children and vitamin D levels or supplements from a systemic review. Unfortunately, there was no proper protocol (duration and dosage) in the birth cohort and double-blind, randomized, placebo-controlled trial. We should consider that these clinical trials are not without limitations. Thus, future research needs to identify the optimal dose and duration of vitamin D supplement for distinct groups based on gender, ethnicity, age, body mass index, and asthmatic phenotype since all these factors affect absorption and available levels of vitamin D. Also, determine whether these observations reflect long-term effects on immune regulation.


24. Ehlayel MS, Bener A, Sabbah A. Is high prevalence of vitamin D deficiency evidence for


Table 1. Summary of effects of vitamin D prevention on asthma onset in childhood

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollams EM et al. 12</td>
<td>Large unselected cohort study</td>
<td>989 (6-yr-olds) / 1,380 (14-yr-olds) children</td>
<td>Vitamin D levels at age 6 years were significant predictors of subsequent atopy/asthma-associated phenotypes at age 14 years</td>
</tr>
<tr>
<td>2011</td>
<td>Clinical and immunological phenotyping at ages 6 and 14 years</td>
<td>689 subjects were assessed at both ages</td>
<td></td>
</tr>
<tr>
<td>Gazibara T et al. 13</td>
<td>Population-based prospective cohort study during a 6-year serum 25(OH) levels in mid-gestation and at birth</td>
<td>3130 mothers / their children</td>
<td>Low 25(OH)D levels at birth were associated with a higher airway resistance in childhood</td>
</tr>
<tr>
<td>2015</td>
<td>Birth cohort of children aged from 0 to 4 year serum 25(OH)D levels in maternal blood before delivery, cord blood, and at ages 1.5, 3, and 4</td>
<td>A total of 164 mother-child pairs</td>
<td>Low maternal 25(OH)D levels appear not only to be associated with an increase in the prevalence of allergic sensitization but also the risk of asthma in early childhood.</td>
</tr>
<tr>
<td>Chiu CY et al. 14</td>
<td>Birth cohort of children aged from 0 to 4 year serum 25(OH)D levels in maternal blood before delivery, cord blood, and at ages 1.5, 3, and 4</td>
<td>4951 mothers / their children</td>
<td>The associations of 25(OH)D concentrations in mid-gestation with FEV1 /FVC and FEF75 at age 10 years.</td>
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</tr>
<tr>
<td>Mensink-Bout SM et al. 18</td>
<td>Population-based prospective cohort Maternal (mid-gestation) / umbilical cord (birth) blood At age 10 years, lung function, questionnaire, and inhalant allergic sensitization by skin prick tests</td>
<td>4951 mothers / their children</td>
<td>The associations of 25(OH)D concentrations in mid-gestation with FEV1 /FVC and FEF75 at age 10 years.</td>
</tr>
<tr>
<td>2019</td>
<td>The Northern Finland Birth Cohort Vitamin D supplementation during the first year of life Women during pregnancy and their offspring are followed up at ages 1, 14, and 31 years.</td>
<td>Those who attended clinical examination (n= 6,007) were compared with those who were not invited or were invited but did not attend (n= 5,630)</td>
<td>Association between vitamin D supplementation in infancy and an increased risk of atopy and allergic rhinitis later in life, but not asthma</td>
</tr>
<tr>
<td>Hypponen E et al. 17</td>
<td>The Northern Finland Birth Cohort Vitamin D supplementation during the first year of life Women during pregnancy and their offspring are followed up at ages 1, 14, and 31 years.</td>
<td>Those who attended clinical examination (n= 6,007) were compared with those who were not invited or were invited but did not attend (n= 5,630)</td>
<td>Association between vitamin D supplementation in infancy and an increased risk of atopy and allergic rhinitis later in life, but not asthma</td>
</tr>
<tr>
<td>2004</td>
<td>A prospective birth cohort study up to the age of 6 years The relationship between lower or higher vitamin D3 intake and atopic illness later in childhood was assessed.</td>
<td>123 (6-yr-olds) children</td>
<td>Prevention through modified vitamin D3 supplementation in infancy could reduce allergic diseases.</td>
</tr>
</tbody>
</table>
Goldring ST et al. 2013
A randomized controlled trial
Assessed offspring at 3 years
180 pregnant women at 27 weeks gestation
- No vitamin D (n=60)
- Daily 800 IU ergocalciferol (n=60)
- Single 200,000 IU bolus of cholecalciferol (n=60)

Prenatal vitamin D supplementation in late pregnancy was **not** associated with decreased wheezing in offspring at age three years.

Grant CC et al. 2016
A randomized, double-blind, placebo-controlled parallel-group trial
Pregnant women (from 27-week gestation to birth) and their infants (from birth to 6 months)
Woman/infant pairs: placebo/placebo, 1000/400 IU, or 2000/800 IU
A total of 260 mother-child pairs
- Placebo (n=87)
- Lower dose oral vitamin D (n=87)
- Higher dose oral vitamin D (n=86)

Vitamin D supplementation during pregnancy and infancy reduces the proportion of children sensitized to mites at age 18 months.

There were study group differences in the proportion of children with primary care visits described by the doctor as being for asthma

Litonjua AA et al. 1992
A randomized, double-blind, placebo-controlled trial
1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age
2) third trimester maternal 25(OH)D level
881 pregnant women (from 10 to 18 weeks' gestation) at high risk of having children with asthma
- daily 4000 IU vitamin D + prenatal vitamin containing 400 IU vitamin D (n=440)
- placebo + prenatal vitamin containing 400 IU vitamin D (n=436)

The incidence of asthma and recurrent wheezing in their children at age 3 years was lower by 6.1%, but this did **not** meet statistical significance.

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25-hydroxyvitamin D, 25(OH)D; international unit, IU; forced expiratory volume in 1 s, FEV1; forced vital capacity, FVC; FEF75%, forced expiratory flow at 75%
Table 2. Summary of effects of vitamin D and asthma severity in pediatric asthma

<p>| Study            | Design                          | Subjects                          | Description                                                                 |
|------------------|---------------------------------|-----------------------------------|                                                                            |
| Brehm JM et al²⁰  | Cross-sectional study           | 616 children with asthma (aged: 6-14 years) | Lower vitamin D levels are associated with increased markers of allergy and asthma severity. |
| 2009             | Hospitalization/use of anti-inflammatory medications in the previous year     |                                   |                                                                            |
| Alyasin S et al²¹ | Case-control study and cross-sectional study | 50 childhood asthmatics &amp; 50 healthy controls (aged: 6-18 years) | 25(OH)D was significantly lower in asthmatic patients than controls and positively correlated with FEV1 and FEV1/FVC. No correlation with eosinophil counts, asthma duration, number of hospitalization, or unscheduled       |
| 2011             | Serum vitamin D level, pulmonary function test, and eosinophil counts were examined|                                   |                                                                            |
| Chinellato I et al²³ | Case-control study and cross-sectional study | 45 asthmatic &amp; 59 healthy children (aged: 9-11 years) | No significant difference in the 25(OH)D level between the two groups. 25(OH)D positively correlated with FVC and FEV1 but negatively with exercise induced bronchoconstriction. |
| 2011             | Serum vitamin D level, pulmonary function test, and exercise challenge test were examined|                                   |                                                                            |
| Maalmi H et al²² | Case-control and cross-sectional study | 39 children with controlled asthma/30 controls (aged: 6-16 years) | Vitamin D deficiency was higher in asthma compared to control, vitamin D sufficiency was lower in asthma than control. Th1/Th2 ratio and CD25(p) Foxp3(p) T-reg cells were positively related to 25(OH) D level while IL-17 was negatively correlated. |
| 2012             | Vitamin D, Th1, Th2, Th17, Treg, and pulmonary function test | : age- and sex-matched |                                                                            |
| Ehlayel MS et al²⁴ | Case-control study and cross-sectional study | 483 asthma &amp; 483 controls (aged: &lt;15 years) | 25(OH)D levels were significantly lower, and IgE significantly higher in cases than in controls, with a negative correlation evident. Vitamin D deficiency was the strongest predictor of asthma |</p>
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Measures</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Dabbah H et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Cross-sectional study</td>
<td>71 non-obese children with asthma (aged: 6~18 years)</td>
<td>Methacholine challenge test/ FeNO, Serum vitamin D, total IgE, blood eosinophil counts</td>
<td>No correlation was found between vitamin D level and response to the methacholine challenge test, FeNO, IgE levels, eosinophil counts.</td>
</tr>
<tr>
<td>Han YY et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Using data from the National Health and Nutrition Examination Survey from 2001 to 2010</td>
<td>Current asthma or wheeze in 10,860 children (6-17 years)/ 24,115 adults (18-79 years)</td>
<td>Lung function in a subset of participants</td>
<td>Positive correlation between vitamin D insufficiency (&lt;30 ng/ml) and current asthma or current wheeze in children and adults. Children with asthma (n=1,192) were likelier to have a higher BMI z-score and a lower serum vitamin D level.</td>
</tr>
<tr>
<td>Gupta A et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Case-control and cross-sectional study</td>
<td>36 children with steroid resistant asthma, 26 with moderate asthma, and 24 healthy controls (aged: 6~16 years)</td>
<td>25(OH)D, asthma control test, spirometry, corticosteroid use, and exacerbations were assessed, Fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy (severe, therapy-resistant asthma)</td>
<td>25(OH)D levels were significantly lower in steroid resistant asthma than either mild asthmatics or controls and inversely correlated with airway smooth muscle mass, bronchodilator response and IgE but positively correlated with asthma control, FEV1 and FVC. Low 25(OH)D was correlated with asthma exacerbation and medication usage.</td>
</tr>
<tr>
<td>Brehm JM et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Case-control and cross-sectional study</td>
<td>287 asthmatic/ 273 healthy children (aged: 6~14 years).</td>
<td>Serum vitamin D level, pulmonary function test, and specific IgE</td>
<td>No significant difference in 25(OH)D between cases and controls. Lower 25(OH)D correlated with severe asthma exacerbation, atopy, and a lower FEV1/FVC in cases.</td>
</tr>
<tr>
<td>Turkeli A et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Case-control and cross-sectional study</td>
<td>102 pre-school children with asthma/ 102 healthy controls in winter (aged: 1-4 years)</td>
<td></td>
<td>The frequency of vitamin D deficiency and insufficiency was higher in children with asthma, compared to the controls. The frequency of vitamin D deficiency and insufficiency was higher in children with asthma, compared to the controls. In the vitamin D sufficient group, total number of exacerbations during the previous year was much lower compared to the vitamin D insufficient group.</td>
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<tr>
<td>Study Authors</td>
<td>Type of Study</td>
<td>Description</td>
<td>Patients</td>
<td>Results</td>
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<tr>
<td>Yoseph RB et al</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>Methacholine challenge test, skin prick tests, FeNO, and exhaled breath condensate collection</td>
<td>Children with mild asthma, PC20-FEV1 &lt;16 mg/ml, and vitamin D &lt;30 ng/ml for 6 weeks of treatment - oral vitamin D 14,000 in 2 ml units once weekly - placebo (2 ml of olive oil)</td>
<td>No difference could be demonstrated between the effect of vitamin D and placebo.</td>
</tr>
<tr>
<td>Jensen ME et al</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>Serum 25(OH)D: baseline, 10 days, 3/6 months</td>
<td>22 preschool-aged children with asthma -100,000 IU vitamin D3 (intervention)/ placebo (control) - followed by 400 IU vitamin D3 daily for 6 months</td>
<td>Following 100,000 IU vitamin D3, all children reached serum 25OHD ≥75 nmol/L (≥30 ng/ml), compared with half who received placebo</td>
</tr>
<tr>
<td>Tachimoto H et al</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>Childhood asthma control test scores at 2, 6 months.</td>
<td>Japanese schoolchildren with asthma -Vitamin D3 supplements (800 IU/day) with placebo for 2 months</td>
<td>Low-dose, short-term vitamin D supplementation in addition to standard treatment may improve levels of asthma control in schoolchildren</td>
</tr>
<tr>
<td>Kerley CP et al</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>Assessments were completed at baseline and after 15 weeks of supplementation.</td>
<td>Caucasian 51 children from 44 urban (aged: 6–16 years) -Vitamin D supplementation (2000 IU/day)</td>
<td>Vitamin D3 supplementation led to a significant decreased school days missed. There were non-significant, advantageous changes in the placebo group compared with the vitamin D3 group in subjective asthma control and lung function, particularly percentage of predicted FEV1.</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Study Design</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
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<tr>
<td>Alansari K et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Randomized, controlled trial</td>
<td>Children with moderate-to-severe asthma and vitamin D levels &lt; 25 ng/mL for 12 months. (aged: 2–14 years)</td>
<td>Rapid compared to maintenance vitamin D supplementation for children with the lowest levels resulted in short- but not long-term reduction in asthma exacerbations.</td>
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<tr>
<td>Kalmaz RN et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Interventional study</td>
<td>Serum levels of 25(OH)D, asthma severity and pulmonary function tests before and after therapeutic prescription of vitamin D</td>
<td>Therapeutic prescription of vitamin D is very effective in improving the clinical status of asthmatic children.</td>
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<tr>
<td>Forno E et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>400 with low-dose inhaled corticosteroids and serum 25(OH)D levels &lt; 0 ng/mL (aged: 6 ~ 16 years)</td>
<td>Among children with persistent asthma and low vitamin D levels, vitamin D3 supplementation, compared with placebo, did not significantly improve the time to a severe asthma exacerbation. The findings do not support the use of vitamin D3 supplementation to prevent severe asthma exacerbations in this group of patients.</td>
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<tr>
<td>Thakur C et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>60 children with moderate persistent asthma and placebo (n = 30) (aged: 6 ~11 years)</td>
<td>Vitamin D supplementation as an adjunct to standard treatment does not improve asthma control in children.</td>
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</tbody>
</table>
steroids, number of emergency visits, post-
intervention vitamin D levels, and adverse outcomes

25-hydroxyvitamin D, 25(OH)D; international unit, IU; forced expiratory volume in 1 s, FEV1; forced vital capacity, FVC; FEF75%, forced expiratory flow at 75%; fraction of exhaled nitric oxide, FeNO; regulatory T cells, Treg; immunoglobulin E, IgE; provocation dose of methacholine require to induce a 20% drop, PC20
Table 3. Summary of studies concerning vitamin D and obesity-related asthma in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turer CB et al. 2013</td>
<td>Cross-sectional study (the 2003-2006 National Health and Nutrition Examination Survey)</td>
<td>12,292 children (aged: 6 ~ 18 years) - 79% of children with overweight (BMI 85th-95th percentile for age and gender) - 86% of children with obesity (BMI ≥ 95th percentile)</td>
<td>Compared with healthy-weight children, overweight, obese, and severely obese children had significantly greater adjusted odds of vitamin D deficiency. Vitamin D deficiency is highly prevalent in overweight and obese children.</td>
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<tr>
<td>Lautenbacher et al. 2016</td>
<td>Cross-sectional study Pulmonary function test, serum vitamin D and cytokines</td>
<td>72 obese and 71 normal-weight Hispanic and African-American children with asthma recruited at an urban children's hospital (aged: 7 ~ 11 years)</td>
<td>Vitamin D deficiency was associated with pulmonary function deficits among obese children, but not among normal-weight children with asthma, an association that was independent of Th1 and Th2 serum inflammatory measures.</td>
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<tr>
<td>Reinehr T et al. 2018</td>
<td>NIKI cohort Multicenter study between 2013 and 2016</td>
<td>235 children (60% boys, age 9.3±1.7 years) with obesity, ADHD, BA, and AD 3352 children from a healthy population</td>
<td>Vitamin D concentrations were not lower in children with obesity, ADHD, BA, and AD compared to healthy children Vitamin D levels were not linked to the severity of asthma measured as FEV1</td>
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<tr>
<td>Bose S et al. 2019</td>
<td>Longitudinal cohort study Indoor PM2.5, serum 25(OH)D levels and asthma symptoms</td>
<td>120 children with physician-diagnosed asthma (aged: 5~ 12 years)</td>
<td>Among obese urban children with asthma, low vitamin 25(OH)D enhanced adverse respiratory effects associated with indoor PM2.5. 25-OH D was protective against asthma symptoms in high PM2.5 environments</td>
</tr>
</tbody>
</table>

25-hydroxyvitamin D, 25(OH)D; forced expiratory volume in 1 s, FEV1; atopic dermatitis, AD; attention-deficit/hyperactivity disorder, ADHD; body mass index, BMI; particulate matter, PM2.5