



# Prevalence of vitamin D deficiency and its relationship with factors associated with recurrent wheezing

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## INTRODUCTION

Studies in animal models and humans have demonstrated an association of low vitamin D concentrations with atopy and respiratory tract conditions. The mechanism that explains this association is still unclear. It has been suggested that this mechanism is due to the effects of vitamin D status on the regulation of the immune system.<sup>(1)</sup>

The vitamin D receptor is expressed in various cells of the immune system, such as macrophages, monocytes, dendritic cells, and natural killer cells, as well as in B and T lymphocytes. Binding of the active form of vitamin D to its receptor leads to an increase in immunomodulatory activity that maintains the balance between the cellular immune response (Th1) and the humoral response (Th2), in addition to stimulating regulatory T cells.<sup>(2)</sup>

The prevalence of atopic diseases, especially chronic respiratory diseases, such as asthma and recurrent wheezing in childhood, is increasing both in Brazil and worldwide. These diseases represent an important cause of morbidity and mortality in the pediatric age group. They are considered a public health problem because they affect the quality of life of these patients, given

frequent use of the health care system, causing great economic impact.<sup>(3,4)</sup>

Various risk factors are associated with recurrent wheezing and asthma: small airway caliber; decreased lung function at birth; viral respiratory infections; environmental pollution; pets; early daycare attendance; passive smoking; parental history of asthma or atopy; obesity; and socioeconomic factors. In this context, vitamin D plays a prominent role as a risk factor for increased prevalence of allergic diseases.<sup>(5)</sup> Therefore, the objective of the present study was to analyze the prevalence of vitamin D deficiency/insufficiency and its relationship with factors associated with recurrent wheezing and asthma in a population of children with this symptom/disease.

## METHODS

### Study design

This was a cross-sectional study of 124 pediatric patients followed in the Pulmonology Outpatient Clinic of the State Referral Center for Specialized Care, in the

## ABSTRACT

**Objective:** To determine the prevalence of vitamin D deficiency/insufficiency in children 0-18 years of age with recurrent wheezing and/or asthma residing in the microregion of Viçosa, Minas Gerais, Brazil, and treated at a referral center, and to determine its association with major risk factors for wheezing. **Methods:** A cross-sectional study was performed using a semi-structured questionnaire, which was administered by trained interviewers to the legal guardians of the study participants. Data were obtained regarding general characteristics of recurrent wheezing; general sociodemographic, environmental, and biologic factors; and atopy-related factors. The magnitude of the statistical association was assessed by calculating ORs and their corresponding 95% CIs by using multiple logistic regression. **Results:** We included 124 children in the study. The prevalence of vitamin D deficiency/insufficiency in the sample was 57.3%. Vitamin D deficiency/insufficiency was found to be associated with wheezing in the first year of life, personal history of atopic dermatitis, environmental pollution, and vitamin D supplementation until 2 years of age. **Conclusions:** The prevalence of vitamin D deficiency/insufficiency was high in our sample. Vitamin D concentrations were directly associated with vitamin D supplementation until 2 years of age and were inversely associated with wheezing events in the first year of life, personal history of atopic dermatitis, and environmental pollution.

**Keywords:** Vitamin D; Asthma; Respiratory sounds; Minors.

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municipality of Viçosa, Minas Gerais, Brazil, conducted between November 2016 and September 2107. The present study was approved by the Human Research Ethics Committee of the Federal University of Viçosa (Ruling no. 1,713,903).

The State Center for Specialized Care is the only referral facility for pediatric pulmonology in the microregion of Viçosa, serving approximately 20 municipalities. Treatment is provided by an interdisciplinary team, including professionals in the areas of physical therapy, nutrition, psychology, nursing, social work, and medicine, in partnership with the Federal University of Viçosa.

The following inclusion criteria were used to select the present study sample: having recurrent wheezing and/or asthma, being followed in the aforementioned outpatient clinic, and legal guardians providing written informed consent; residing in Viçosa or in the microregion of Viçosa during the data collection period; and being 0 to 18 years of age. The exclusion criteria were as follows: having refused to participate in the study; and having associated diseases (e.g., heart diseases, cystic fibrosis, gastroesophageal reflux disease, pneumonia, pulmonary tuberculosis, bronchopulmonary dysplasia, cerebral palsy, congenital lung malformations, immunodeficiencies, or post-infectious bronchiolitis obliterans). A semi-structured questionnaire, based on the standardized International Study of Asthma and Allergies in Childhood questionnaire and including sociodemographic variables (gender, race, age group, level of maternal education, level of parental education, family income, and daycare or school attendance), was used.<sup>(6)</sup>

During the study period, two peripheral blood samples were collected from each patient (into a tube without anticoagulant for analysis of vitamin D and into an EDTA-containing tube for a complete blood count). Serum 25-hydroxyvitamin D concentrations were measured with a competitive chemiluminescence immunoassay (DiaSorin, Stillwater, MN, USA). The outcome variable, serum vitamin D concentration, was expressed in ng/mL, with deficiency, insufficiency, and sufficiency being defined as values below 20, values between 21 and 29, and values above 30, respectively.<sup>(7)</sup>

### Statistical analysis

In the statistical analysis of variables, absolute and relative frequencies were calculated. In addition, in the analysis of distribution normality, continuous numerical variables were described by their means and standard deviations. Explanatory variables were tested for independence from the outcome variable using the chi-square test, and those showing significant differences at a level less than or equal to 20% ( $p \leq 0.20$ ) were considered for multivariate analysis. Since the vitamin D variable did not meet the linear regression assumptions, we chose to

use logistic regression. To that end, the vitamin D variable was categorized as sufficient or insufficient/deficient. The magnitude of the statistical association between vitamin D concentrations and the other variables was assessed by calculating odds ratios and their corresponding 95% confidence intervals by using multiple logistic regression. We used the Stata statistical software package, version 10 (Stata Corp., College Station, TX, USA).

Given the objectives of the study, the final regression model was selected on the basis of inclusion of all explanatory variables that showed significance ( $p < 0.20$ ) in bivariate analysis. Variables were then selected according to their statistical significance. The equation was evaluated at each step, and the procedure was repeated until all variables remaining in the final equation had a  $p$  value  $\leq 0.05$ , with these variables being responsible for explaining the variance observed in the outcome variable.

## RESULTS

One hundred and twenty-four patients registered at the pediatric pulmonology clinic of the State Center for Specialized Care during the study period participated in the study. We found that most were male and were declared non-White (biracial or Black) and that the mean age was  $5.8 \pm 4.6$  years. Most participants attended daycare or school, and 77 (62.1%) were born by cesarean section. Of the total sample, 97 participants (78.2%) had a monthly family income of  $\leq 2$  times the national minimum wage. Other sociodemographic data are shown in Table 1.

With regard to clinical characteristics, slightly more than half of the children had experienced wheezing in the first year of life as well as in the last four weeks. In the 12 months preceding the interview, 67 (54.0%) visited the emergency room and 37 (29.8%) required hospitalization due to wheezing exacerbation (Table 2).

The prevalence of vitamin D deficiency/insufficiency among the participants was 57.3%. There were no significant race-related differences in vitamin D concentrations. However, we found significantly higher vitamin D concentrations in children in the 0-36-month age group than in those in the 37-72-month age group (Figure 1).

At the time of the interview, 57.1% of the children aged up to 24 months ( $n = 21$ ) were receiving vitamin D supplementation as recommended by the Brazilian Society of Pediatrics.<sup>(8)</sup> However, we found that 50.8% of the study sample did not receive vitamin D supplementation in the first 2 years of life.

In bivariate analysis, the following variables had a  $p$  value  $< 0.20$  for vitamin D status: onset of wheezing before age 1 year; physician-diagnosed asthma; personal history of atopic dermatitis; family history of rhinitis; daycare or school attendance; pets in the household before birth; environmental pollution; oral corticosteroid use during exacerbations;

**Table 1.** Sociodemographic characteristics of the study population (N = 124), Viçosa, Minas Gerais, Brazil, 2016-2017.

Characteristic	n	%
Age group		
< 3 years	31	25.0
3-6 years	47	37.9
> 6 years	46	37.1
Gender		
Female	48	38.7
Male	76	61.3
Race		
White	25	20.2
Non-White	99	79.8
Level of maternal education		
≤ 8 years of schooling	41	33.1
9-11 years of schooling	33	26.6
≥ 12 years of schooling	50	40.3
Level of paternal education		
≤ 8 years of schooling	72	58.1
9-11 years of schooling	21	16.9
≥ 12 years of schooling	30	24.2
No answer	1	0.8
Family income, number of times the national minimum wage		
≤ 1	54	43.5
[1-2]	43	34.7
> 2	27	21.8
Attends daycare or school		
No	28	22.6
Yes	96	77.4

vitamin D supplementation in the first 2 years of life; breastfeeding; and eosinophilia. After multiple logistic regression analysis, the variables that remained associated with vitamin D status were onset of wheezing before age 1 year, personal history of atopic dermatitis, environmental pollution, and vitamin D supplementation in the first 2 years of life (Figure 2).

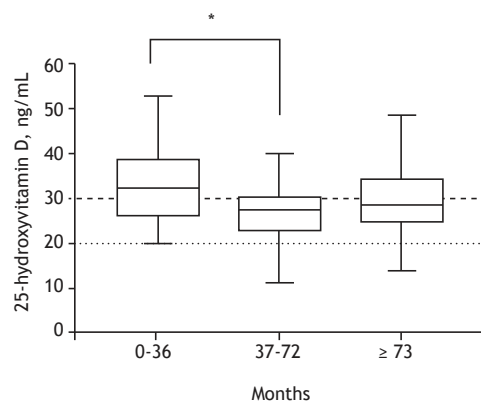
## DISCUSSION

In the present study, the first relevant finding was the high prevalence of vitamin D deficiency/insufficiency (57.3%) in patients with recurrent wheezing and/or asthma registered at our facility. In a systematic review, vitamin D deficiency/insufficiency was observed in 55.2% of the children with asthma, and mean 25-hydroxyvitamin D levels were significantly lower in children with asthma than in those without asthma.<sup>(9)</sup>

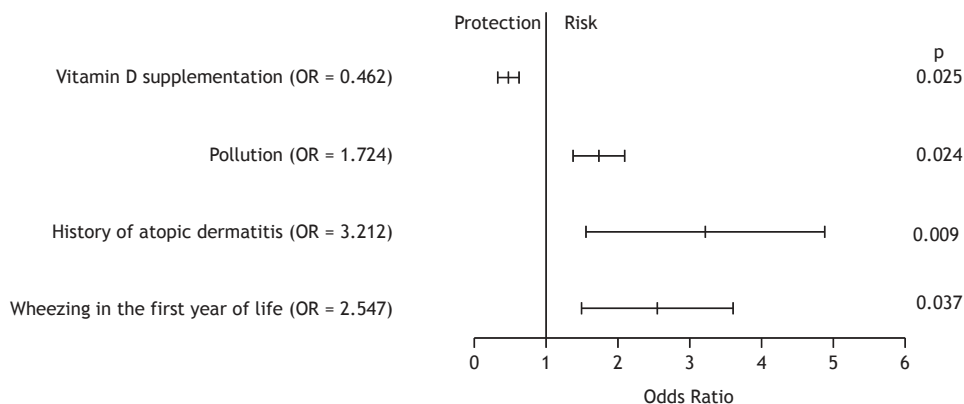
Studies in the literature have increasingly suggested the existence of a relationship between serum vitamin D concentrations and respiratory symptoms, presumably because of the immunomodulatory effects of vitamin D.<sup>(9)</sup> The increased prevalence of vitamin D deficiency/insufficiency in the pediatric population is currently considered a public health problem. Changes in the environmental factors associated with the new urban lifestyles, such as remaining longer indoors, little sun

**Table 2.** Clinical characteristics of the study population (N = 124), Viçosa, Minas Gerais, Brazil, 2016-2017.

Characteristic	n	%
Onset of wheezing before age 12 months		
NO	55	44.4
YES	69	55.6
Wheezing in the last 4 weeks		
NO	54	43.5
YES	70	56.5
Emergency room visits in the last 12 months		
NO	57	46.0
YES	67	54.0
Need for hospitalization		
NO	87	70.2
YES	37	29.8
Diagnosis of pneumonia		
NO	84	67.7
YES	40	32.3
Hospitalization for pneumonia		
NO	92	74.2
YES	32	25.8
Received inhaled corticosteroid treatment		
NO	34	27.4
YES	90	72.6
Currently receiving inhaled corticosteroid treatment		
NO	65	52.4
YES	59	47.6
Received leukotriene receptor antagonist treatment		
NO	113	91.1
YES	8	6.5
I DON'T KNOW	3	0.3
Oral corticosteroid use		
NO	12	9.8
YES	111	90.1
I DON'T KNOW	1	0.1



**Figure 1.** Stratification of serum vitamin D concentrations, as quantified by chemiluminescence, by age group. (...) deficiency threshold; and (---) insufficiency threshold. \*p < 0.04.



**Figure 2.** Independent protective and risk factors for vitamin D deficiency/insufficiency in the study population (N = 124), Viçosa, Minas Gerais, Brazil, 2016-2017.

exposure, and a sedentary lifestyle, may be associated with the increased prevalence of this condition.<sup>(9)</sup>

In the present study, environmental pollution showed an inverse association with serum vitamin D concentrations. It is known that regions that are more polluted, especially those with high ozone levels, which is common in large cities, tend to absorb ultraviolet type B radiation, causing a reduction in the efficacy of sun exposure for producing vitamin D in the skin.<sup>(10)</sup>

A study comparing serum vitamin D concentrations between infants residing in a region with high levels of air pollution in New Delhi, India, and children in a less polluted area found that those residing in highly polluted areas were at an increased risk of developing vitamin D deficiency and rickets.<sup>(10)</sup>

In our study, we also observed that low serum vitamin D concentrations were associated with onset of wheezing before age 1 year and personal history of atopic dermatitis. Viral infections, especially those caused by respiratory syncytial virus and rhinovirus, are known to be the major causes of wheezing in the first years of life.<sup>(11)</sup> Epidemiological data have shown a relationship between vitamin D deficiency and increased susceptibility to acute viral respiratory tract infections.<sup>(12)</sup> A case-control study investigated severity of vitamin D deficiency and its association with recurrent wheezing in children under 3 years of age.<sup>(13)</sup> The authors reported that, for every 10 ng/mL decrease in vitamin D concentration, there was a 7.25% increase in the probability of wheezing. The results support the hypothesis that low serum vitamin D concentrations are associated with respiratory morbidity in infants with recurrent wheezing.<sup>(13)</sup>

Atopic dermatitis is a chronic, relapsing disease of unknown etiology. Its major characteristic is deficiency in skin barrier function due to abnormal lipid metabolism, resulting in drier skin. Another important factor in atopic dermatitis is immune deviation to a Th2 response, leading to greater production of IL-4, IL-13, and IgE. These interleukins can suppress antimicrobial peptide production, causing

a change in the skin microbiota and, consequently, greater susceptibility to skin infections, especially with *Staphylococcus aureus*.<sup>(14)</sup>

Laboratory studies have suggested that vitamin D stimulates expression of antibacterial peptides, such as cathelicidin and filaggrin, strengthening innate immunity and increasing microbicidal capacity against fungi, viruses, and bacteria, especially *S. aureus*, which contributes to persistent skin inflammation. A study of patients with atopic dermatitis found an inverse relationship between serum vitamin D concentrations and the disease. In a meta-analysis, vitamin D was found to play an important role in the improvement of the symptoms of atopic dermatitis.<sup>(15,16)</sup>

There is growing evidence that maternal vitamin D intake during pregnancy has a protective effect against wheezing and atopic dermatitis. In a cohort study of 239 children that aimed to evaluate associations of 25-hydroxyvitamin D concentrations in umbilical cord blood with asthma, wheezing, allergic rhinitis, and atopic dermatitis from birth to age 5 years, an inverse association was found between serum 25-hydroxyvitamin D concentrations and risk of transient early wheezing and atopic dermatitis in the first years of life, suggesting that adequate vitamin D intake and optimal serum vitamin D concentrations reduce the risk of wheezing, especially virus-induced wheezing.<sup>(15,16)</sup>

It was interesting to note in our study that there was a high prevalence of patients who did not receive vitamin D supplementation until 2 years of age, as recommended by the Brazilian Society of Pediatrics.<sup>(7,17)</sup> Vitamin D supplementation for patients with recurrent wheezing and/or asthma remains a controversial issue; however, universal vitamin D supplementation in the first 2 years of life for bone health is well established. Since vitamin D supplementation early in life decreases the risk of vitamin D deficiency, raising awareness of health care professionals and family members about the importance of this public policy strategy is relevant.<sup>(18)</sup>

Although in the present study vitamin D concentrations were not associated with exacerbations, as assessed on the basis of hospitalizations, emergency room visits, and oral corticosteroid use, many studies have indicated such an association.<sup>(19,20)</sup>

Some limitations to the present study should be considered. Because this was a cross-sectional study, it was not possible to establish causal relationships but rather only to report associations. In studies using questionnaires, there is also a recall bias. In an attempt to minimize this bias, we used secondary data collected from the patient medical records at our facility; the medical records are semi-structured, allowing a higher reliability in obtaining data.

One strength of the present study is that the sample size calculation enables the inference of data; in addition, the findings of the present study may motivate further studies, especially in Brazil, to elucidate the true role of vitamin D in the immune system and its relationship with atopic diseases, given that vitamin D deficiency/insufficiency is an environmental factor that can be modified by greater sun exposure and/or vitamin D supplementation.<sup>(9)</sup>

Various studies have demonstrated the high prevalence of vitamin D deficiency/insufficiency and the importance of vitamin D not only for bone health

but also for other immune-mediated diseases, although the pathogenic mechanisms involved have not yet been elucidated.<sup>(21)</sup> The present study demonstrates the prevalence of vitamin D deficiency/insufficiency in pediatric patients with recurrent wheezing and/or asthma treated at a center for specialized care in the municipality of Viçosa, Minas Gerais, Brazil. Vitamin D concentrations were inversely associated with wheezing events in the first year of life, personal history of atopic dermatitis, and environmental pollution. Vitamin D supplementation proved to be a protective factor in the study population. Clinical trials are still needed to clarify the role of serum vitamin D concentrations in childhood wheezing, in asthma, and in other atopic diseases, as well as to determine optimal vitamin D levels to prevent these diseases.

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