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# Vitamin D deficiency in children and adolescents with food allergy: Association with number of allergens, sun exposure and nutritional status

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**Abstract**
Our objective was to describe the serum vitamin D concentrations of children and adolescents with food allergy (FA) and to verify the association between the number of food allergens involved, length of sun exposure, and nutritional status. Through a cross-sectional study, 79 patients with FA, from ages 2 to 15 years, were assessed and followed up in a reference outpatient clinic, in Sao Paulo, Brazil. Clinical and biochemical data were collected for analysis of 25(OH)D, calcium, phosphorus, phosphatase, parathyroid hormone (PTH), and high-sensitivity C-reactive protein (hs-CRP). The cut-off point used for vitamin D deficiency was 25(OH)D ≤ 20 ng/mL. Vitamin D deficiency was detected in 45.6% of patients with a median age of 6.9 years (Interquartile range [IQR] 4.7; 10.2). The median serum 25(OH)D concentration was 21.1 ng/mL (IQR 17.8; 26.0). Multivariate linear regression was performed considering serum vitamin D level as a dependent variable. Allergy to multiple foods (inverse) and length of sun exposure (direct), but not nutritional status, were independently associated with serum 25(OH)D levels (P = 0.034 and P = 0.014, respectively). Patients with cow's milk allergy also showed lower vitamin D concentrations in comparison with other FA (19.1 ng/mL [IQR 16.6; 24.4] vs 22.2 ng/mL [IQR 18.1; 27.1] [P = 0.056]). Vitamin D deficiency affected about half of individuals with FA. Multiple food allergy was associated with lower vitamin D concentrations, reinforcing the importance of monitoring vitamin D status in patients with FA.


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## Introduction

Food allergies are common, and there is an increase in their prevalence, in all age groups around the world.[1] The persistence, multiple foods involved, and the greater severity of food allergy (FA) are also reasons for concern due to their impact on the quality of life and nutritional risk.[2-4]

Vitamin D is a prohormone, involved in skeletal and extra skeletal functions, such as immunomodulatory, tolerogenic, and anti-inflammatory, by reducing the production of proinflammatory cytokines, all linked to the pathogenesis of FA. Vitamin D deficiency is an important public health issue, with increasing prevalence worldwide, even in sunny areas, affecting all age groups.[5,6]

The relationship between vitamin D deficiency and FA has long been established.[7-10] Epidemiological studies suggest that low serum vitamin D concentrations represent a risk factor for FA, although few studies assess its involvement as in established FA.[11-14]

The aim of this study was to describe the serum vitamin D levels of children and adolescents with FA and to verify the association between the number of foods involved, length of sun exposure, and nutritional status.

## Materials and Methods

### Study design

A cross-sectional study was performed to evaluate 79 children and adolescents (2–15 years old) with clinical diagnosis of FA, confirmed or not by oral food challenge test, followed in a reference outpatient clinic, in Sao Paulo, Brazil. The city of Sao Paulo (23°34'S latitude) is crossed by the Tropic of Capricorn with relatively well-defined seasons. Air pollution during winter and cloudiness in summer may reduce cutaneous vitamin D synthesis in subjects.[15]

Children and adolescents who were on systemic corticosteroids and/or vitamin D supplementation at the time of blood collection or in the 3 months preceding and/or presenting chronic diseases of a nonallergic nature, such as celiac disease, cystic fibrosis, and inflammatory bowel diseases, were excluded.

### Ethical aspects

The study was approved by the Research Ethics Committee of UNIFESP, number 3.272.007, and the Free and Informed Consent and Assent forms were applied to the parents and/or guardians of children and adolescents, respectively.

### Collected data

Demographic and clinical data such as age, skin phototype,[16] length of sun exposure, excluded foods, age of first allergic reaction and symptoms, and choice of cow's milk substitute were collected (cow's milk allergy, CMA), and specific IgE levels to food allergens and/or endoscopy and/or Oral Challenge Test were performed.

Weight and height were measured and classified as BMI-for-age z-score (BAZ) and height-for-age (HAZ), respectively, according to World Health Organization.[17] Arm Circumference and triceps and subscapular skinfolds (sum of skinfolds) were measured and classified according to Frisancho.[18] Waist circumference was measured and used to calculate the waist circumference to height ratio (WHT), which was considered as increased when above 0.5.[19,20]

### Laboratory tests

In the spring of 2019, blood samples were collected by peripheral venous puncture according to good clinical laboratory practices, in a room with low light, by a nurse. The samples were centrifuged at 3000 rpm for 10 min. Serum was stored at 4°C and were sent to the Laboratory of Centro Universitário FMABC for analysis of 25(OH)D, PTH (immunometric assays by electrochemiluminescence),[21,22] ionized calcium (colorimetric, calculated), phosphorus (colorimetric),[23] alkaline phosphatase (colorimetric kinetics), and hs-CRP (immunoturbidimetric assay).[24] The Roche kit®, Brazil, with fully automated reading and Cobas 6000 equipment (Roche®) was used for all analyses.

### Statistical analysis

Statistical analysis was performed with the statistical package R (r-project.org). Qualitative variables were compared using Chi-square test or Fisher's Exact test. The quantitative variables were tested using the Shapiro–Wilk test; those with parametric distribution were presented as mean and standard deviation and compared using the Student-t test; those with nonparametric distribution were presented as median, IQR; and were compared using Mann–Whitney or Kruskal Wallis tests. Correlations were performed using Pearson or Spearman tests. The multivariate analysis was performed by Linear Regression (method Enter) adjusted for the variables that showed a statistically significant association with the dependent variable (25[OH]D concentrations), during exploratory analysis. The level of significance adopted was 5%.

## Results

### Clinical and anthropometric characteristics

The general characteristics of the participants of the study are presented below (Table 1). The distribution by age group was as follows: 37 schoolchildren (46.8%), 30 preschoolers (37.9%), and 12 adolescents (15.3%). The predominant skin color was light brown (Type III), observed in 44 individuals (55.7%).

Most families reported sun exposure (72, 91.1%) on mean 5 ± 2.1 days per week and 39.5 ± 28.9 min per day. The mean of school years of the parents was 12 ± 3.9 years.

Regarding the exclusion diet, 45.6% excluded only one food, the most prevalent being egg (20, 55.6%) and milk

**Table 1** Characteristics of children and adolescents with food allergy (N = 79).

| Variable | | Distribution |
|---|---|---|
| Gender | Male | 51 (64.6%)[a] |
| Age | Years | 5.9 (3.9; 9.2)[c] |
| Fitzpatrick Scale | Type-III | 44 (55.7%)[a] |
| Sun exposure | Yes | 72 (91.1%)[a] |
| Sun-exposure length | Minutes/daily | 39.5 ± 28.9[b] |
| Immune mechanism | IgE-mediated | 51 (64.6%)[a] |
| Age of diagnosis | Months | 23.4 ± 27.1[b] |
| Exclusion time | Months | 46 (28.5; 70.5)[c] |
| Number of foods involved | 1 food | 36 (45.6%)[a] |
| | 2 to 3 foods | 30 (37.9%)[a] |
| | 4 or more | 13 (17.7%)[a] |
| Number of foods involved | Egg | 49 (62%)[a] |
| | Milk | 36 (45.6%)[a] |
| | Peanut and chestnut | 22 (27.8%)[a] |
| | Fish and shellfish | 21 (26.6%)[a] |
| | Soybean | 9 (11.4%)[a] |
| | Wheat | 8 (10.1%)[a] |
| | Others* | 28 (35.4%)[a] |
| Clinical manifestation | Cutaneous | 70 (88.6%)[a] |
| | Gastrointestinal | 55 (69.6%)[a] |
| | Respiratory | 38 (48.1%)[a] |
| | Anaphylaxis | 49 (62%)[a] |
| Associated allergic diseases | Rhinitis | 53 (67.1%)[a] |
| | Atopic dermatitis | 44 (55.7%)[a] |
| | Asthma | 22 (27.9%) |
| | None | 11 (13.9%)[a] |
| | 1 or more associated disease(s) | 68 (86.1%) |

[a]Number (percentage): N (%). [b]±Standard deviation. [c]Median (Interquartile range).
*Fruits, vegetables, beef, legumes, and cocoa. IgE: Immunoglobulin E

(11, 30.6%). Multiple foods allergy occurred in 43 individuals (54.4%), most of them being allergic to, in addition to aforementioned, wheat and/or soybean and/or peanuts and/or nuts and/or seafood and/or fish and other foods, such as meat, fruits, vegetables, legumes, and cocoa.

Children and adolescents with CMA (n = 36) used soy-based beverages or formulas (18, 50%), other plant-based industrialized beverages (7, 19.4%), extensively hydrolyzed formula (3, 8.3%), free amino acid formulas (2, 5.6%), and six other homemade beverages, such as juices and teas (6, 16.7%) as alternatives. Breastfeeding was maintained in 8.3% of the subjects (mean age: 2.4 ± 0.1 years).

Regarding the most frequent clinical manifestations, 41 (88.6%) and 55 (49.1%) of the individuals presented cutaneous and gastrointestinal symptoms, respectively. The association with other diseases of allergic nature occurred in 68 children and adolescents (86.1%).

Based on anthropometry, it was observed that 21 (26.6%) were overweight, 13 (17%) increased WHT ratio, and 16 (20.3%) had sum of skinfolds above the 85th percentile, compatible with excess fat. Only two individuals (2.5%) had short HAZ.

### Distribution and associations with serum vitamin D concentrations

The median of serum 25 (OH)D concentrations was 21.1 ng/mL (17.8; 26.3). Vitamin D deficiency, insufficiency, and sufficiency were found in 36 (45.6%), 33 (41.8%), and 10 (12.7%) individuals, respectively.

When comparing the groups with deficiency versus vitamin D insufficiency or sufficiency, it was observed that the median age was higher in the deficient group, compared to the insufficient or sufficient group (6.9 years [4.7; 10.2] vs 5.4 years [2.9; 7.0]; P = 0.009). Regarding pubertal staging, vitamin D deficiency was observed more frequently among pubescent and postpubescent patients (8/10, P = 0.037) compared to prepubescent patients.

Serum vitamin D concentrations according to demographic, clinical, and anthropometric characteristics are described in Table 2. It was observed that patients who had no sun exposure (7/79) had lower serum 25 (OH)D concentrations (18.4 ng/mL [16.6–20.8] vs 22.1 ng/mL [18.1–26.8], P = 0.023). The number of foods involved was also inversely associated with serum concentrations of vitamin D. There was no difference in other characteristics of the allergy.

### Laboratory analysis

Regarding laboratory parameters, it was observed that only one patient had hyperparathyroidism (25[OH]D: 8.7 ng/mL), and four patients had increased CRP (values: 15.3 mg/L; 8.6 mg/L; 6.3 mg/L; 4.8 mg/L). hs-CRP was inversely correlated with serum vitamin D concentrations (r = −0.528, P = 0.000; Table 3).

Using a multivariate linear regression, we observed that age (inverse), number of foods involved (inversely), and length of sun exposure (direct) were independently associated with serum levels of 25(OH)D (dependent variable) (Table 4).

## Discussion

This study showed the vitamin D deficiency in about half of children and adolescents with FA. There was an inverse and independent association of vitamin D concentrations with age and the number of foods involved and a direct association with the length of sun exposure.

In addition to its classical function in bone and calcium metabolism, vitamin D is also involved in immune regulation and allergic diseases. Vitamin D receptors were found in monocytes, dendritic cells, epithelial cells, and lymphocytes T and B.[6,12] Several mechanisms have been postulated for the effects of vitamin D on the innate and adaptive immunity, including reduction of inflammation, food tolerance, and protection of intestinal epithelium integrity. However, the mechanisms by which vitamin D may influence the risk of FA have not yet been fully elucidated.

The serum levels of 25(OH)D are the best indicator of vitamin D status. It reflects the total vitamin D produced cutaneous as well as that obtained through foods and supplements and has a long circulating half-life of 15 days.[25]

**Table 2** Serum 25(OH)D levels according to demographic, clinical and anthropometric characteristics of children and adolescents with food allergy (n = 79).

| Variables | n | Vitamin D (ng/mL) median (interquartile range) | P |
|---|---|---|---|
| Gender | | | 0.235[a] |
| Male | 51 | 20.7 (16.8-24.9) | |
| Female | 28 | 22.7 (10.5-27.2) | |
| Age group | | | 0.001[b] |
| Child | 68 | 22.2 (18.6-27.0) | |
| Adolescent | 11 | 16.5 (13.9-18.9) | |
| Pubertal stage | | | 0.001[a] |
| Prepubescent | 69 | 22.2 (18.5-27) | |
| Pubescent | 10 | 16.7 (16.1-18.7) | |
| Phototype (Fitzpatrick) | | | 0.209[a] |
| II and III | 52 | 22.3 (18.5-26.8) | |
| IV and V | 27 | 19.5 (16.8-24.9) | |
| Sun exposure | | | |
| Yes | 72 | 22.1 (18.1-26.8) | 0.023[a] |
| Limited | 7 | 18.4 (16.6-20.8) | |
| Length of sun exposure | | | 0.151[b] |
| <15 min | 42 | 20.2 (16.9-24.4) | |
| ≥15 min | 37 | 22.6 (18.5-28.6) | |
| Immunological mechanism of FA | | | 0.809[b] |
| IgE mediated | 51 | 20.8 (16.9-26.3) | |
| Non-IgE-mediated and mixed | 28 | 21.5 (18.7-25.1) | |
| Number of food(s) involved in FA | | | 0.039[b] |
| 1 food | 36 | 22.9 (18.6-27.9) | |
| 2 or more foods | 43 | 20.1 (16.0-24.1) | |
| Associated allergic disease | | | 0.136[a] |
| Yes | 68 | 20.8 (17.5-25.6) | |
| No | 11 | 25.3 (19.1-30.6) | |
| Cow's milk allergy (CMA) | | | 0.056[a] |
| Yes | 18 | 19.1 (16.6-24.4) | |
| No | 61 | 22.2 (18.1-27.1) | |
| Cow's milk substitute (n = 36) | | | 0.205[a] |
| Formula or vitamin D fortified beverages | 28 | 25.65 (19.8-30.5) | |
| Homemade and industrialized beverages | 8 | 18.8 (15.2-23.3) | |
| Nutritional status | | | 0.594[b] |
| Normal + thinness | 58 | 20.7 (17.2-26.1) | |
| Overweight + obesity | 21 | 22.2 (18.7-26.7) | |
| Waist-to-height ratio; | | | 0.313[b] |
| Adequate | 46 | 20.2 (18.1-24.4) | |
| Increased | 33 | 22.9 (16.8-27.8) | |

[a]Student's t-test. [b]Mann-Whitney test
FA: Food allergy statistically significant $p<0.05$

Recent epidemiological evidence suggests that both insufficiency and excess of vitamin D may contribute to the acquisition of oral tolerance and the subsequent occurrence of FA in infants. Thus, a U-shaped relationship between vitamin D status and predisposition to FA is described, in which insufficient or excessive vitamin D offers the greatest risk. In recent decades there has been a significant increase in the prevalence of FA and vitamin D deficiency.[26,27]

A randomized controlled trial (RCT) evaluating maternal vitamin D supplementation (800 UI/day) during lactation found increased FA for up to 2 years.[28]

A double-blind and randomized clinical trial conducted in infants with family history for allergic diseases risk with adequate serum vitamin D concentrations at birth, assessing the effects of daily vitamin D supplementation (400 UI) on the incidence of clinically diagnosed allergic diseases or allergen sensitization rates, up to 2.5 years of age, showed no benefits of supplementation.[14]

Similarly, another RCT performed could not find significant differences in a allergic outcomes, including FA, at 1 year between two groups of infants, who were daily supplemented with 400 UI or 1200 UI vitamin D from the age of 2 weeks.[29]

In addition to the participation of vitamin D in reducing the risk for the development of FA, it is worth emphasizing its role in children and adolescents with the disease. Systematic review and meta-analysis did not identify a significant association between vitamin D status and FA. The interpretation of the included studies was limited, considering that the cut-off points adopted to identify deficiency or insufficiency are based on the modulation of calcium metabolism, and that other points still need to be defined regarding the ability of vitamin D to modulate the development and activity of the immune system.[30]

A study conducted with Turkish infants with CMA compared to healthy children have shown no difference in serum levels of 25(OH)D. Vitamin D deficiency was less prevalent than that observed in our study with older children and occurred in 23.2% of infants. Some limitations of the study were not considering the milk substitute used, not assessing inflammatory markers and not mentioning the nutritional status of subjects.[7] On the other hand, a study conducted with infants from Northeastern Brazil, without vitamin D supplementation, has shown a prevalence of 20% deficiency in patients with CMA, higher than that observed in healthy controls. In this group without supplementation, the practice of exclusive or predominant breastfeeding was related to inadequate vitamin D concentrations, and sun exposure did not seem to confer a protective effect.[31]

An article involving 171 Finnish schoolchildren showed a prevalence of vitamin D deficiency (<20 ng/mL) of 16%, much lower than that found in our study. The authors emphasized the importance of public policy strategies in the country, such as the recommendation of vitamin D supplementation and the fortification of food products with vitamin D. In the group of children with a history of CMA, the mean concentrations of 25(OH)D levels were lower than those of children without allergy. Lack of vitamin D supplementation, female gender, non-Caucasian ethnicity, and history of milk allergy were associated with lower vitamin D status.[8]

**Table 3** Laboratory variables related to vitamin D metabolism and to the inflammation of children and adolescents with food allergy (N = 79).

| Variables | Unit | Mean ± SD | Cut-off point in disagreement with reference | Frequency in disagreement with reference n (%) | |
|---|---|---|---|---|---|
| Ionized calcium | mmol/L | 1.1 ± 0.1 | <1.14 ng/mL | 42 | (53.20%) |
| Phosphorus | mg/dL | 5 ± 0.7 | <2.9 mg/dL | 1 | (1.30%) |
| Alkaline phosphatase | U/L | 240.3 ± 71.4 | >335 U/L | 7 | (8.90%) |
| Parathyroid hormone | pg/mL | 25.4 ± 11.4 | >65 pg/mL | 1 | (1.30%) |
| hs-CRP | mg/L | 0.4 ± 2.29 | >5 mg/L | 4 | (5.10%) |

hs-CRP: high-sensitivity C-reactive protein

**Table 4** Multivariate analysis of factors associated with vitamin D levels in children and adolescents with food allergy (n = 79).

| Variable | Beta | 95% CI | | P |
|---|---|---|---|---|
| Age (years) | −0.71 | 0.29 | −2.46 | 0.017 |
| BMI (normal vs overweight + obese) | 1.46 | 1.52 | 0.96 | 0.339 |
| Length of sun exposure (minutes) | 0.05 | 0.02 | 2.33 | 0.023 |
| Number of foods involved (1 vs 2 or more) | −2.85 | 1.34 | −2.13 | 0.037 |
| Time on restriction diet (months) | −0.02 | 0.03 | −0.73 | 0.467 |
| CRP (mg/L) | −0.35 | 0.29 | −1.19 | 0.239 |

CI: confidence interval; BMI: body mass index; CRP: high-sensitivity C-reactive protein; Dependent variable: Vitamin D levels. $R^2 = 0.3181$, F = 5.442. statistically significant $p < 0.05$

More recently, a retrospective American study conducted in a tertiary reference center in the care of allergic diseases, comparing the concentrations of vitamin D of children and adolescents (0–17 years) with FA (n = 147) with those of individuals who had other allergic diseases (n = 87) has shown prevalence of deficiency in up to a quarter of individuals without difference between the groups; the percentage was lower than that observed in our study. Vitamin D concentrations were directly associated with vitamin D supplementation, with breastfeeding, use of cow's milk, infant formula, or plant-based drink, but not with the presence of CMA or other food allergies.[32]

Our study has different characteristics than the aforementioned. It included preschoolers and schoolchildren with FA to a single or to multiple food products, by different immunological mechanisms, with varied clinical manifestations (anaphylaxis in 62%), without drug supplementation of vitamin D and with or without other associated allergic diseases.

The systemic inflammatory response, which can be generated during the allergic process, may be associated with low vitamin D concentrations.[33] We found inverse correlations between the 25(OH)D concentrations and hs-CRP, which may have contributed to the high prevalence of vitamin D deficiency in the analyzed sample. Some factors in addition to FA itself may have led to a chronic inflammatory state in these individuals such as presence of other allergic diseases and overweight in 86% and 26% of the children, respectively. Differently, it is known that the general effect of vitamin D on the innate and adaptive immune system is anti-inflammatory, and thus it is inferred that its deficiency may also contribute to the enhancement of the inflammation.[11]

Other mechanisms of the interface of vitamin D with FA are related to its contribution to the oral tolerance process which include the induction of tolerogenic dendritic cells and regulatory T cells, in addition to the inhibition of the production of IgE in B cells. Active vitamin D may maintain the dendritic cells in an immature stage, which is characterized by a decreased expression of Major Histocompatibility Complex Class II, as well as costimulatory molecules. As a result, the differentiation of naive T cells into Th1 and Th17 decreases, while these immature dendritic upregulate regulatory T and IL-10 cells. Thus, the effect of vitamin D in active form contributes to a tolerogenic response against allergens and prevents the development of an allergic immune response. Perezabad et al. have shown that concentrations of FOXP3 (Fork head box P3), regulatory T lymphocytes, and vitamin D were significantly lower in children with CMA compared to healthy controls.[34] Increased FOXP3 mRNA (messenger ribonucleic acid) expression may predict faster acquisition of tolerance in infants with CMA.[35] In parallel, $1.25(OH)_2D$ increases the expression of proteins such as Claudin 1 and 2, resulting in the formation of tight junctions that increase intestinal barrier function. This decreased epithelial permeability reduces excessive exposure of allergens to the mucosal immune system, thus reducing the risk of developing allergy.[36]

In this sense, assessing 25(OH)D concentrations in allergic children can be very interesting to treat a possible deficiency early, which may contribute to the acquisition of tolerance and enhance the prognosis of FA.[25]

In this study, there was an inverse and independent association of vitamin D concentrations with the number of foods involved and a direct association with the time of sun exposure. To meet the required vitamin D needs, based on sun exposure, it is necessary to consider the best time of day, season, latitude, climate, and the color of the individual's skin. Melanin acts as a barrier in which UVB photons cannot reach the skin's 7-dehydrocholesterol.

The predominant skin color in our study was Type III (light brown) observed in more than half of the assessed children, and the mean daily length of sun exposure referred was 39 min; usually a white person with a fair skin may need 5–15 min for adequate synthesis of vitamin D. The Brazilian Society of Dermatology encourages the population to avoid sun exposure without adequate protection, especially in the period of greatest risk from 10 am to 3 pm. It also reinforces that intentional and unprotected solar exposure should not be considered as a source for vitamin D production or for the prevention of its deficiency, and recommends the use of sunscreens with SPF 30, from 6 months of age.[37] The Brazilian Society of Pediatrics proposes vitamin D drug supplementation up to 24 months of age for rickets prevention in all regions of Brazil; there is no recommendation for other age groups.[38]

Regarding age, a previously cited American study showed a prevalence of vitamin D insufficiency of 83% in older children (over 10 years of age) with FA who did not have cow's milk intake.[31] In this study, we also found an inverse association between vitamin D concentrations and age. These data highlight the importance of careful evaluation of this specific group of older children with FA, who, for having an unvaried diet, end up not receiving more detailed nutritional and lifestyle guidelines. Moreover, they are not part of the groups considered priority for prophylactic vitamin D drug supplementation in the specific FA conduct guides.

Regarding the association of vitamin D concentrations and the number of foods excluded, it is worth remembering that vitamin D is obtained through exposure of the skin to the sun or through the dietary intake of goods such as oily fish, eggs, and liver. While about 80–90% of the required daily dose of vitamin D is received through sun exposure, the remaining 10% is provided through the diet. In the United States and Canada, milk is fortified with vitamin D as are some baked goods, orange juices, cereals, yogurts, and cheeses. In Brazil and in most of the European countries, milk fortification with vitamin D is not mandatory. The high prevalence of egg allergy (62%) in the studied sample, including association with other foods, may have contributed to this finding. The recommended daily vitamin D intake for children and adolescents is of 600 UI,[39] and the amount of vitamin D contained in two eggs is 87 IU. There is no specific vitamin D recommendation in the guidelines for children with FA.

Our study presents some limitations such as the cross-sectional model that does not allow establishing cause and effect relationships, recall bias, and the absence of confirmation of the diagnosis of FA based on the oral food challenge test.

Future longitudinal studies may contribute to a better understanding of the relationship between vitamin D status and FA in children and adolescents.

## Conclusion

The high prevalence of vitamin D deficiency observed in this study, inversely associated with older age and number of allergens involved, even without significant relationship with nutritional status, emphasizes the importance of monitoring the status of this vitamin, especially in multiple food allergies and in older children.

## Conflict of Interest

The authors declare having no potential conflict of interest concerning the research, authorship and/or publication of this article.

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