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Serum 25-hydroxyvitamin D deficiency is associated with atopy, and sex may be an effect modifier of its association with asthma in teenagers from northeast Brazil

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Abstract

Objective: Sufficient vitamin D (25-hydroxyvitamin D [25(OH)D]) serum levels are associated with decreased asthma symptoms. Our aim was to investigate associations between vitamin D and atopy, asthma, asthma severity, and asthma phenotypes in Brazilian teenagers.

Methods: This cross-sectional study involved 942 individuals (11–19 years old) engaged in an asthma cohort. The ISAAC questionnaire was employed to diagnosis asthma and asthma severity. Serum allergen-specific immunoglobulin E (sIgE) was measured by ImmunoCap and serum 25(OH)D was measured by ELISA. We calculated the correlation between sIgE and 25(OH)D. We used multivariate logistic regression analysis to assess associations of interest.

Results: We found that 25(OH)D deficiency was positively associated with atopy (OR 1.45, confidence interval [CI] 1.05–2.00) and high levels of this vitamin negatively correlated with sIgE to *Dermatophagoides pteronyssinus* ($r = -0.11$, $p = 0.019$). The average 25(OH)D serum level was 27.0 ± 9.5 ng/ml; 366 individuals (38.8%) had a sufficient level. There was no association between 25(OH)D and asthma, asthma severity or asthma phenotypes in the population. However, sex was a possible effect modifier of the association between vitamin D and asthma: insufficiency in asthmatic women (86%) was higher than in asthmatic men (42%), and there was an association between insufficient vitamin D levels and greater asthma risk only in women (OR = 3.06, 95% CI 1.16–8.07).

Conclusion: We have shown that vitamin D deficiency was associated with greater risk of atopy in both sexes and vitamin D insufficiency was associated with asthma only in women. There was no association between vitamin D levels and asthma phenotypes or asthma severity.

KEYWORDS

asthma, asthma phenotypes, asthma severity, atopy, epidemiology, IgE, vitamin D

1 | INTRODUCTION

Asthma, a chronic inflammatory disease of the lower airways, affects over 339 million people worldwide.[1] Mortality occurs in about 1% of asthma cases, and it is the fourteenth leading disease in terms of duration and disability.[1,2] This complex disease is triggered by environmental and genetic factors, but its mechanisms are not fully understood.[2] Two classical phenotypes are used to discriminate asthma: atopic and nonatopic.[3] Atopy is an inherited tendency to produce immunoglobulin E (IgE) in response to exposure to allergens, such as mites, pollen, fungi, and food proteins.[4] However, these phenotypes are not sufficient to explain asthma heterogeneity; several immunological mechanisms are involved in asthma immunopathology.[3] In addition, each asthma phenotype is associated with social, demographic, and immunological conditions. In Latin America, nonatopic asthma is more prevalent among children and teenagers, particularly in low-income populations.[5]

Atopy is a risk factor for asthma development. Some conditions may worsen or improve atopy, and as previously demonstrated,[4] poor hygiene and helminthic infections are associated with lower skin reactivity to aeroallergens.[6] A lower vitamin D level has been presented as a risk factor for atopic diseases.[7–12] Vitamin D is the general term for a group of fat-soluble secosteroid metabolites, for which the active form is 1α-25-dihydroxyvitamin D [1,25(OH)D]. The compound 25(OH)D, which is the precursor of 1,25(OH)D, reflects the vitamin D status due to its relatively long half-life (21 days).[13] Guo and collaborators[10] reported higher IgE production (atopy marker) in individuals with insufficient levels of 25(OH)D, and other groups have shown that 1,25(OH)D reduces IgE synthesis by plasma cells.[14]

Vitamin D insufficiency is highly prevalent worldwide.[15] Recently, vitamin D deficiency and/or insufficiency have been associated with asthma.[16,17] Some meta-analyses suggest that a higher vitamin D level correlates with better lung function in people with asthma and a reduction of asthma exacerbation.[17,18] Murine models have shown that vitamin D supplementation blocking tissue remodeling induced by thymic stromal lymphopoietin (TSLP).[19] Immune cells convert 25(OH)D3 into 1,25(OH)D3 by expressing the enzyme cytochrome P450 family 27 subfamily B member 1 (CYP27B1). Vitamin D reduces inflammatory T cell populations (Th1, Th2, and Th17) and induces regulatory T helper (Treg) $FoxP3^+$ cells and the production of interleukin (IL)-10, which downregulates asthma inflammatory reactions.[20] Although evidence has shown vitamin D is a protective factor for asthma and allergic diseases,[21,22] some studies have demonstrated no association[23] or have even described it as a risk factor.[24] Population variation could be an important factor that changes this association.[7]

This study investigates the relationship between serum levels of 25(OH)D with atopy and asthma, asthma morbidity, and asthma phenotypes in a low-income population of a large city in Northeast Brazil. Until now, there have been no reports on the association of vitamin D serum levels with different asthma phenotypes, and there are few reports about the association between vitamin D and atopy and asthma in populations of low-income countries.

2 | MATERIALS AND METHODS

2.1 | Study population

This cross-sectional study used data from the Social Change Asthma and Allergy in Latin America, Brazil (SCAALA) cohort.[5,25,26] Briefly, the original study population was composed of 1445 children, living in 24 deprived areas of Salvador, Northeast Brazil, previously studied to evaluate the impact of a sanitation program on diarrhea occurrence from 1997 to 2003, when the participants were 0–3 years old. The first survey on risk factors for wheezing and atopy was conducted in 2005, the second in 2007, and the third in 2013.[5,26] The data of the present study were obtained from the 2013 survey, when 1,206 individuals, aged 11–19 years, participated in the study. We have used asthma and atopy as outcomes and 25(OH)D serum levels as the principal explanatory variable. There were only 936 individuals in whom 25(OH)D serum levels had been measured and all variables had been studied. The parents or legal guardians—or the participants themselves, when≥18 years—answered the International Study of Asthma and Allergy in Childhood (ISAAC) Portuguese-adapted phase III questionnaire.

2.2 | Definition of atopy and asthma

In a previous study in this population, we found that the prevalence of sIgE for the studied aeroallergens was greater than the skin prick test (SPT), and the frequency of SPT positivity in those without sIgE was very low.[25] For this reason, we defined atopy as the presence of at least one positive test for sIgE≥0.70 kU/L. sIgE was determined by ImmunoCap using Caps to *Blomia tropicalis*, *Dermatophagoides pteronyssinus*, *Blattella germanica*, and *Periplaneta americana* from Phadia (AB, Uppsala, Sweden), the most prevalent allergens detected in this population in the 2005 survey.

In the 2013 survey, asthma was defined as wheezing in the last 12 months plus at least one of the following in the last 12 months: history of asthma, ≥4 wheezing episodes, wheezing with exercise and sleep disorder due to wheezing.[26] All other teenagers were classified as nonasthmatics. The asthma severity definition was based on symptoms, and severe asthma was defined as individuals having at least one of the following symptoms in the last 12 months:≥12 wheezing episodes, wheezing and breathlessness resulting in difficulty in speaking and >1 day of disturbed sleep/week due to asthma. The other cases were considered as mild/moderate asthma.

2.3 | Measuring and classification of 25-hydroxy-vitamin D serum levels

The serum 25(OH)D levels were measured using an inhibition enzyme-linked immunosorbent assay (IDS OCTEIA EIA, IDS), a method recognized by the Vitamin D External Quality Assurance Survey (DEQAS). The lower detection limit was 2 ng/ml. Intra- and

inter-assay coefficients of variation for concentrations between 15.6 and 52.8 ng/ml were <5.9% and <6.6%, respectively.

There is no consensus for vitamin D deficiency and insufficiency categorization; some authors define deficiency as <12 ng/ml and insufficiency as <20 ng/ml,[27] while others define deficiency as <20 ng/ml and insufficiency as <30 ng/ml.[28] We used the following vitamin D classification: (1) deficient (<20 ng/ml), (2) insufficient (≥20 but <30 ng/ml) and (3) sufficient (≥30 ng/ml). To carry out logistic regression analyses, we used dichotomous variables to define 25(OH)D serum levels using two different cut-offs: 20 and 30 ng/ml.[17]

2.4 | Ethical issues

Ethical approval was obtained through the Ethical Committee for Medical Research of the Institute of Public Health of the Federal University of Bahia, Brazil, protocol number 120.616. Written informed consent was obtained from the legal guardian of each individual under 18 years, or the individuals if they were ≥18 years old.

2.5 | Statistical analysis

We used the Mann–Whitney *U* test to determine differences in 25(OH)D serum levels, considering atopy or asthma conditions, and we used Spearman correlation analysis to evaluate the relationship between sIgE and 25(OH)D serum levels. We performed bivariate and multivariate analyses using stepwise logistic regression. *A priori* confounders for the association between principal exposition [25(OH)D] and the study outcomes (atopy and asthma) were sex and age. We included covariables in the final multivariate model if the variable altered the effect estimate by at least 20%. Then, we used the following confounder variables to adjust the multivariate analysis: sex, age, sIgE, total income, contact with dogs, presence of cockroaches, body mass index (BMI) and smokers in the home. We assessed the interaction effect of sex in vitamin D associations using crude odds ratio (OR) and calculated the statistical significance with the Breslow–Day test for OR homogeneity and by the product term to test interaction in multivariate analysis. To analyze the association between 25(OH)D serum levels and asthma phenotypes, we performed multinomial logistic regression as described by Barreto and collaborators.[5]

3 | RESULTS

3.1 | Stratification of the study variable by sex

Table 1 shows that among 936 individuals examined, vitamin D deficiency was present in 195 (20.7%) and insufficiency in 379 (40.5%); 362 (38.7%) had sufficient levels. Four hundred and thirty-five (46.5%) teenagers had sIgE ≥ 0.70 kU/L to least one tested allergen and were considered atopic: 396 (42%) were sensitized to *B. tropicalis*, 320 (34%) to *D. pteronyssinus* and 183 (19.5%) to cockroaches; the remaining 501 (53.5%) were considered nonatopic. Current asthma was reported in 74 (8.6%) individuals, of whom 48 (64.9%) were atopic and 26 (35.1%) were nonatopic. The prevalence of vitamin D insufficiency was higher in females than in males ($p = 0.0001$). Anti-*B. tropicalis* IgE and anti-*D. pteronyssinus* IgE was more prevalent in males ($p = 0.016$ and <0.001, respectively) and 25(OH)D serum levels were higher in males ($p = 0.0001$).

TABLE 1 Prevalence of vitamin D levels, allergen-specific IgE, atopy, and asthma by sex, in 936 teenagers

Variables	Total population		Male		Female		
	N	M ± SD	*N*	M ± SD	*N*	M ± SD	*p*-Value**
25(OH)D serum levels (media ± SD)	936	26.97 ± 9.5	486	28.1 ± 10.11	450	25.73 ± 8.56	<0.001
Variables	***N***	**(%)**	***N***	**(%)**	***N***	**(%)**	***p*-Value**
Vitamin D deficiency	195	20.8	90	19.5	105	23.4	0.076
Vitamin D insufficiency	379	40.5	176	36.1	203	45.2	**<0.001**
Vitamin D sufficiency	362	38.7	221	45.4	141	31.4	**<0.001**
sIgE to Blomia tropicalis	396	42	236	48.2	160	35.4	**<0.001**
sIgE to Dermatophagoides pteronyssinus	320	34	184	37.5	136	30.0	**0.016**
sIgE to cockroaches	183	19.5	106	21.6	77	17.3	0.083
Atopy*	435	46.3	258	52.8	177	39.1	**<0.001**
Total asthma	74	8.6	38	8.4	36	8.8	0.903
Atopic asthma	48	64.9	28	6.2	20	4.9	0.082
Nonatopic asthma	26	35.1	10	2.2	16	3.9	0.082

Note: *Specific IgE ≥0.70 kU/L for one of the tested allergen. **p-value for Chi-squared test. Bold values are statistically significant $p < 0.05$.

TABLE 2 Frequency of the study variables according to atopy and asthma in 942 teenagers

Study variables	Population (942) *n* (%)	Atopy 436 (46.3)* *n* (%)	*p*-Value**	Asthma 74 (7.96) *n* (%)	*p*-Value**
Sex					
Males	487 (52)	258 (53)	**<0.001**	38 (51.35)	0.903
Females	449 (48)	177 (39.4)		36 (48.65)	
Age					
11–14	562 (60)	261 (46.4)	1	53 (71.6)	**0.035**
15–19	374 (40)	174 (46.5)		21 (28.4)	
Atopy					
No	501 (53.5)	–	–	26 (35.13)	**0.001**
Yes	435 (46.5)	–		48 (64.87)	
Mother's education					
≤Primary education	172 (18.4)	74 (43)	0.352	13 (17.57)	0.888
>Primary education	764 (81.6)	361 (47.3)		61 (82.43)	
Total family income					
≤$ 296,00/month	309 (33)	126 (40.8)	**0.015**	26 (35.13)	0.797
>$ 296,00/month	627 (67)	309 (49.3)		48 (64.87)	
Presence of mould at home					
No	293 (31.3)	134 (45.7)	0.778	11 (14.86)	**0.001**
Yes	643 (68.7)	301 (46.8)		63 (85.14)	
Presence of rodents at home					
No	315 (33.8)	138 (43.8)	0.298	23 (31.08)	0.700
Yes	618 (66.2)	294 (47.6)		51 (68.92)	
Contact with cats					
No	626 (67)	294 (47)	0.677	41 (55.4)	**0.019**
Yes	309 (33)	140 (45.3)		33 (44.6)	
Contact with dogs					
No	325 (34.7)	135 (41.1)	**0.028**	16 (21.62.)	**0.015**
Yes	611 (65.3)	300 (49.0)		58 (78.38)	
Presence of cockroaches at home					
No	265 (28.7)	119 (44.9)	0.663	11 (14.86)	**0.005**
Yes	672 (71.3)	314 (46.7)		63 (85.14)	
Presence of smokers at home					
No	788 (84.2)	370 (47)	0.530	56 (75.67)	0.067
Yes	148 (15.8)	65 (43.9)		18 (24.33)	
Body mass index					
Underweight	329	143 (43.5)	0.59	32 (43.24)	**0.007**
Healthy weight	485	233 (48)		25 (33.78)	
Overweight	82	39 (47.6)		12 (16.21)	
Obese	40	20 (50)		5 (6.77)	

TABLE 2 (Continued)

Study variables	Population (942) *n* (%)	Atopy 436 (46.3)* *n* (%)	*p*-Value**	Asthma 74 (7.96) *n* (%)	*p*-Value**
Vitamin D levels					
Sufficiency	741 (79.2)	332 (44.8)	**0.053**	61 (82.43)	0.551
Deficiency (<20 ng/ml)	195 (20.8)	103 (52.8)		13 (17.57)	
Vitamin D levels					
Sufficiency	362 (38.7)	161 (44.5)	0.347	27 (36.48)	0.803
Insufficiency (<30 ng/ml)	574 (61.3)	274 (47.7)		47 (63.52)	

Note: Bold numbers are those statistically significant ($p < 0.05$). *Positive sIgE (≥0.70 kU/ml) for at last one allergen. **p-value for Chi-squared test.

TABLE 3 Bivariate and multivariate logistic analyses of the associations between vitamin D status with atopy among 936 teenagers

Study variables	Population *n* (%)	Atopy *n* (%)	Crude OR (95% confidence interval [CI])	Adjusted OR# (95% CI)*
Vitamin D levels				
Sufficiency	741 (79.2)	332 (44.8)	1	**1**
Deficiency (<20 ng/ml)	195 (20.8)	103 (52.8)	*1.38 (1.00–1.90)*	**1.45 (1.05–2.01)**
Vitamin D levels				
Sufficiency	362 (38.6)	1612 (44.5)	1	1
Insufficiency (<30 ng/ml)	574 (61.3)	274 (47.7)	1.14 (0.88–1.49)	*1.27 (0.96–1.67)*

Note: *Odds ratio adjusted for sex, age, mother's education, contact with dogs, total income and BMI; bold numbers are those statistically significant ($p < 0.05$) and italic numbers are those borderlines. #See odds ratios of adjusted variables in the supplementary material.

3.2 | Descriptive data according to atopy and asthma

Table 2 shows the distribution of the studied variables according to atopy and asthma. Atopy was more prevalent in males ($p < 0.001$), in individuals from families with a higher income ($p = 0.015$), in individuals with contact with dogs ($p = 0.028$) and in individuals with vitamin D deficiency ($p = 0.053$). Asthma was higher in the youngest individuals ($p = 0.035$), in atopic individuals ($p = 0.001$), in individuals living in homes with mold ($p = 0.001$), in the presence of cockroaches at home (0.005), in individual with overweight or obese ($p = 0.007$) and in individuals with contact with cats ($p = 0.019$) and dogs ($p = 0.015$).

3.3 | Vitamin D levels and atopy

Table 3 shows the logistic regression analysis to evaluate the association between 25(OH)D and atopy. Individuals deficient in vitamin D were more atopic than those with sufficient levels in both analyses (crude OR 1.38, 95% confidence interval [CI] 1.00–1.90; adjusted OR 1.45, 95% CI 1.05–2.01). When we used the insufficient levels of vitamin D, the association had a borderline significance only in the adjusted analysis (adjusted OR 1.27, 95% CI 0.96–1.67) (Figure 1).

3.4 | Vitamin D levels and asthma, asthma severity and asthma phenotypes

Among the 936 individuals analyzed, 69 had a history of asthma but did not have current asthma; 3 out of the 936 who did not have the variable "presence of smokers at home" were excluded from the logistic analyses conducted to investigate the association between vitamin D and asthma. In this way, 864 individuals were included in this analysis; of these, 74 were asthmatic (Table 4). There was no significant association between asthma and deficient 25(OH)D serum levels (OR 0.66, 95% CI 0.35–1.26) or insufficient 25(OH)D levels (OR 0.96, 95% CI 0.57–1.62). However, the 25(OH)D levels in the nonasthmatic individuals were slightly higher than those in individuals with asthma (mean = 27.00 ng/ml, standard error [SE] = 0.33 ng/ml and mean = 26.6 ng/ml, SE = 1.08 ng/ml, respectively).

There was no association between vitamin D serum levels and asthma severity (deficiency OR 1.51, 95% CI 0.38–6.03; insufficiency

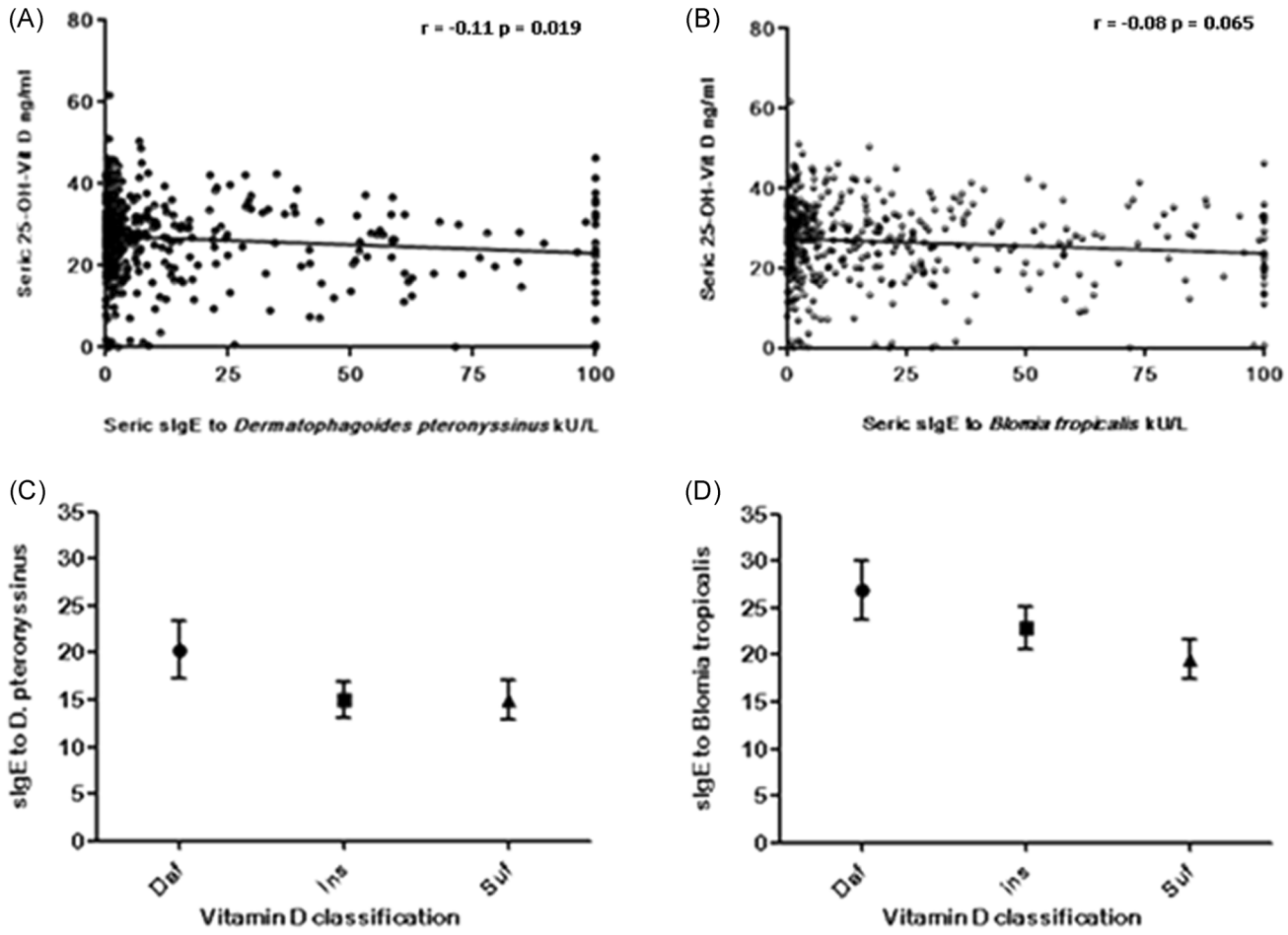

FIGURE 1 Correlation of 25(OH)D serum levels with specific IgE for house dust mite. A and B shows that in atopic individuals, serum levels of vitamin D were negatively correlated with anti-*Dermatophagoides pteronyssinus* IgE ($r = -0.11$, $p = 0.019$) but not with anti-*Blomia tropicalis* IgE ($r = -0.088$, $p = 0.065$). C and D shows specific IgE distribuition for vitamin D classification.

TABLE 4 Bivariate and multivariate logistic analyses of associations between vitamin D levels with asthma in 864 teenagers

	Population	Asthma		
Study variables	***n* (%)**	***n* (%)**	**Crude OR (95% confidence interval [CI])**	**Adjusted OR[#] (95% CI)***
Vitamin D levels				
Sufficiency	683 (79)	61 (8.9)	1	1
Deficiency (<20 ng/ml)	181 (21)	13 (7.2)	0.79 (0.42–1.47)	0.66 (0.35–1.26)
Vitamin D levels				
Sufficiency	332 (38.4)	27 (8.1)	1	1
Insufficiency (<30 ng/ml	532 (61.6)	47 (8.8)	1.10 (0.67–1.80)	0.96 (0.57–1.62)

Note: *Odds ratio adjusted for sex, age, sIgE, total income, contact with dog, presence of cockroaches, any smokers in the house and BMI. #See odds ratios of adjusted variables in the supplementary material.

OR 2.67, 95% CI 0.73–9.73) (Supporting Information: Table S1). Furthermore, there was no association between vitamin D status and asthma phenotypes (Supporting Information: Table S2), considering both nonatopic asthma (deficiency: OR 0.78, 95% CI 0.26–2.35; insufficiency: OR 0.70, 95% CI 0.31–1.59) and atopic asthma, using as a reference the nonatopic nonasthmatic group (deficiency: OR 1.13, 95% CI 0.52–2.35; insufficiency: OR 1.64, 95% CI 0.85–3.16) or using as a reference the atopic nonasthmatic group (OR 0.51, 95% CI 0.17–1.54) to vitamin D deficiency and vitamin D insufficiency (OR 1.32, 95% CI 0.68–2.56).

3.5 | Sex as an effect modifier of the association of vitamin D levels with atopy and asthma

We found a positive and significant association between vitamin D deficiency and atopy in females (OR 1.72, 95% CI 1.11–2.67) but not in males (OR 1.20, 95% CI 0.76–1.90); however, the interaction was not significant ($p = 0.259$, Breslow–Day; $p = 0.257$, product term). We have found a borderline association between vitamin D insufficiency (OR 1.6, 95% CI 0.96–2.22) and atopy in females but not in males (OR 1.11, 95% CI 0.77–1.58); however, the interaction was also not significant ($p = 0.341$, Breslow–Day; $p = 0.314$, product term) (Table 5).

Furthermore, an interaction analysis to investigate the role of sex in the association of vitamin D with asthma (Supporting Information: Table S3) showed significance ($p = 0.004$, Breslow–Day; $p = 0.006$, product term), but the number of asthma cases was low (74). Of the individuals with asthma, 38 were male, of whom 42% had insufficient vitamin D levels. In comparison, in 36 females with asthma, 31 (86.1%) had insufficient vitamin D levels. The low number (5) of females with vitamin D sufficiency may have skewed the statistical analysis, so we chose not to highlight the sex-stratified OR for females (OR 3.06, 95% CI 1.16–8.07) and males (OR 0.56, 95% CI 0.29–1.10). Instead, we present them as supplementary data (Supporting Information: Table S3).

4 | DISCUSSION

The main findings of this study were: (1) 25(OH)D deficiency was associated with atopy in the total population; however, when stratified by sex, the association was significant only for females; (2) higher 25(OH)D serum levels correlated with lower levels of anti-*D. pteronyssinus* IgE; and (3) there was no association between 25(OH)D serum levels with asthma, asthma severity or asthma phenotypes, although we found that sex may be an effect modifier of the association between vitamin D and asthma.

We found that 25(OH)D deficiency was significantly associated with a higher risk of atopy (OR 1.45, 95% CI 1.05–2.01), although this association might be mostly due to the female group, because when we split the population, the association persisted only in the female group. The vitamin D insufficiency was more prevalent in females in this population ($p < 0.001$). In murine models, vitamin deficiency causes deficits in lung functions, and some of these effects are more evident in female.[29] It is suggested that the in situ effect of this hormone is more significant in women, a fact that explains why certain associations between vitamin D and some diseases are found mostly in women. In another study, the authors suggested that the 1,25(OH)2D effect is stronger in females than in males because the concentration required to inhibit 50% of autoreactive T cell proliferation was significantly lower in women than in men.[30]

In addition, there is a biological explanation for vitamin D insufficiency as a risk factor for inflammatory disease being more relevant in women than men. Vitamin D regulates oestradiol and progesterone production; these hormones may induce inflammatory responses.[31,32] Furthermore, in cells from female patients with multiple sclerosis, vitamin D acts more effectively than in men, inducing a significant reduction in the pro-inflammatory cytokines interferon (INF)-γ and IL-17 and increasing the anti-inflammatory cytokine IL-10.[30] The classification of vitamin D levels to different clinical conditions has not yet been defined,[33] and thus deficient and sufficient levels could differ between the sexes. The different actions of vitamin D in males and females found in this and other work deserve further investigation to understand these mechanisms.

25(OH)D levels were inversely correlated with IgE to *D. pteronyssinus*, but not with IgE to *B. tropicalis*. Supporting our finding, other studies have reported that lower vitamin D levels are associated with higher total IgE, higher specific IgE to house dust mite *Dermatophagoides* spp. or atopic manifestation.[8,10–12] We attribute the weaker association between 25(OH)D and anti-*B. tropicalis* IgE to the existence of cross-reactivity of IgE to this mite with helminth species.[34] Given that young individuals in the tropics are frequently infected by these parasites, part of the anti-*B. tropicalis* IgE might be nonspecific IgE induced by helminths, which may not be affected by vitamin D. In addition, other authors have shown that lower 25(OH)D levels are associated with higher total IgE, although it

TABLE 5 Sex effect of on the association of vitamin D with atopy in 936 teenagers

Study variables	Female			Male			$P_{homogeneity}$*
	Total	Atopy		Total	Atopy		
	n (%)	*n* (%)	Crude OR (95% CI)	*n* (%)	*n* (%)	Crude OR (95% CI)	
Vitamin D levels							
Sufficiency	344 (76.6)	125 (36.3)	1	397 (81.6)	207 (52.14)	1	0.259
Deficiency (<20 ng/ml)	105 (23.4)	52 (49.52)	**1.72 (1.11– 2.673)**	90 (18.4)	51 (56.6)	1.20 (0.76– 1.903)	
Vitamin D levels	***n* (%)**	***n* (%)**	**OR (95% CI)**	***n* (%)**	***n* (%)**	**OR (95% CI)**	
Vitamin D levels							
Sufficiency	141 (31.4)	47 (24.9)	1	221 (45.1)	114 (51.58)	1	0.341
Insufficiency (<30 ng/ml)	308 (68.6)	130 (29.5)	*1.6 (0.96–2.22)*	266 (54.9)	144 (54.13)	1.11 (0.77–1.58)	

Note: Bold numbers are those statistically significant ($p < 0.05$). Italic values are significant $p = 0.08$. *$P_{homogeneity}$ by Breslow day test.

remains controversial as to whether 25(OH)D is associated with sIgE.[10] Future studies should investigate biological mechanisms of vitamin D and specific IgE to elucidate these associations.

The explanation behind the effect of vitamin D in atopy has been explored in several studies.[14,35] Vitamin D binds to the vitamin D receptor (VDR) and regulates gene expression of transcription factors such as epsilon germ-line transcription (Ɛ-GLT), a pre-requisite for IgE synthesis. This protein is downregulated in B cells stimulated with 1,25(OH)D.[14] In addition, vitamin D inhibits IgE-mediated mast cell histamine release, cysteinyl leukotriene production and tumor necrosis factor (TNF) and IL-6 production by mast cells.[35] These findings suggest that vitamin D can decrease type I hypersensitivity reactions.

Considering the nonstratified data, we found no association between 25(OH)D serum levels and asthma. Most studies have reported associations with a reduction of asthma symptoms, better biomarkers of asthma severity and lower required corticosteroid doses[16,36] Such work suggests that vitamin D can ameliorate asthma symptoms. A recent meta-analysis has shown that higher vitamin D levels are associated with better asthma control markers in adults and children.[17,18] Furthermore, Jolliffe et al.[37] suggested there is a bidirectional relationship between asthma and vitamin D: perhaps people with asthma have less vitamin D because they perform fewer outdoor activities, or perhaps the effect of vitamin D could not be favorable like the most studies suggest. When we stratified the analysis by sex, we found that sex might act as a modifier for the association between vitamin D insufficiency and asthma in this population. In females with asthma, 25(OH)D insufficiency occurred more frequently than for men, but because the group of women with asthma and sufficient vitamin D levels was small, this could have skewed the statistical analysis, and the finding may be biased.

In our study, some limitations impaired additional discussions. When we suggested the design of this study the project was in progress and it was not possible include information about vitamin D supplementation and solar exposure, information that might make the discussion more robust. We did not find an association between vitamin D and asthma severity and asthma phenotypes. One explanation for these results may be that asthma has a wide spectrum of severity and phenotypes[3]; thus, the small number of individuals with asthma represents a limitation to understand all phenotypes. In addition, the levels of vitamin D required to regulate distinct phenotypes might be different. To study asthma severity, we used only two categories—mild/moderate and severe—because we had no available data related to pulmonary function or the frequency of corticosteroid use.[26]

In conclusion, we have shown that vitamin D sufficiency is associated with reducing specific IgE and there is an association of vitamin D sufficiency with reduced asthma risk in women. The relationship with asthma phenotypes and asthma severity was inconclusive due to the limitations of the study, such as a lack of data on pulmonary function and a small number of asthma cases. These results deserve replication using cohorts with more individuals with asthma. Furthermore, additional initiatives should be undertaken to understand the different vitamin D mechanisms of action in males and females and to investigate the possibility of repositioning vitamin D as a tool for allergy control.

AUTHOR CONTRIBUTIONS

All authors have actively participated in the analysis and approve the version that's been submitted. Neuza M. Alcantara-Neves, Camila A. Figueiredo, Maurício L. Barreto, and Álvaro A. Cruz designed the original work. Alana Alcantara Galvão wrote the first draft. Alana Alcantara Galvão, Emília M. M. de Andrade Belitardo, Flávia de Araújo Sena, Caroline A. Feitosa were involved in data collection. Alana Alcantara Galvão, Emília M. M. de Andrade Belitardo, Flávia de Araújo Sena were involved in laboratorial analysis. Alana Alcantara Galvão, Gustavo N. de Oliveira Costa, Rosemeire L. Fiaccone performed the data analysis. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the author's, Neuza Maria Alcântara Neves and Camila Alexandrina Alcântara Neves, upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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