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Factors associated with allergic rhinitis and combined allergic rhinitis and asthma syndrome (CARAS) in adults undergoing immunotherapy in a tropical country: Is ISAAC-III questionnaire useful in adult populations?

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Abstract

Background: Allergic diseases affect about 10-30% of the population in low- or middle-income tropical countries. Few studies describe the factors associated with allergic diseases in adult patients undergoing immunotherapy in Latin American countries.

Objective: This study aimed to determine the factors associated with allergic rhinitis (AR) and AR in comorbidity with asthma (CARAS) in adults treated with immunotherapy in two allergy referral centers in Bogotá (Colombia).

Material and Methods: Observational, cross-sectional study conducted between January 2018 and January 2019. ISAAC-III and sociodemographic questionnaires were applied to determine the factors associated with AR and CARAS in adults treated with immunotherapy who attended the allergy consult at the Fundación Santa Fe de Bogotá and Unimeq-Orl.

Results: Among 416 adults aged 18-68 years, 71.4% (n = 297) were women. Regarding the sensitization results obtained by skin prick test, the most frequent allergens were house dust mites (64.18%); 49.03% were positive for both *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, while 28.61% were positive for *Blomia tropicalis*. Excluding house dust mites, the most frequent allergens were dog hair (31.01%), cat hair (15.1%), grasses (15.9%), and food (15.9%). The main factor associated with exclusive AR was regular acetaminophen use more than four

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times a year: Prevalence ratio (PR) = 1.77 (95% CI: 1.12-2.25). The main factor associated with CARAS was cesarean delivery PR: 1.44 (95% CI: 1.09-1.78).

Conclusion: The main factor associated with AR was regular acetaminophen use, while that associated with CARAS was cesarean delivery. The ISAAC-III questionnaire can be a useful low-cost tool to assess the factors associated with allergic diseases in adults in tropical countries.

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Introduction

The epidemiology of allergic diseases may be particularly different in tropical countries compared to high-income tempered countries.^{1,2} In sensitized patients, an environmental antigen (allergen) triggers immunoglobulin E-mediated inflammatory reactions.² These environmental allergens may fluctuate among different geographic and socioeconomic conditions that prompt the existence of specific allergens.^{2,4} Current studies suggest that environmental variations induced by industrialization and climate change could partially explain the increase in the prevalence and severity of allergic disease, particularly in tropical countries.⁴ Overall, a high prevalence of allergic diseases has been described in tropical countries due to geographical and environmental characteristics.^{1,4} Allergic rhinitis (AR), asthma, and atopic dermatitis (AD) are the most frequent chronic diseases in childhood, with a worldwide prevalence of 33, 14, and 24%, respectively.⁵⁻⁷ Several epidemiologic studies assessing the prevalence and factors associated with allergic diseases have been performed worldwide such as the International Study of Asthma and Allergies in Childhood phase III (ISAAC-III).^{8,9} The ISAAC-III provides standardized data collection strategies for the epidemiologic research of allergic diseases.⁹

Despite ISAAC-III being initially developed for pediatric populations, a current study applied this self-reported tool together with an objective measure to assess the epidemiology of allergic diseases in an adult population.¹⁰ As self-reported suspicion is not enough for the diagnosis of allergic diseases, objective measures such as specific allergen tests (i.e., skin prick test [SPT]) should be performed.¹¹⁻¹³ The SPT is a low-cost and minimally invasive sensitization test with a high positive predictive value (95-100%) for the diagnosis of IgE-mediated allergic diseases.^{13,14} Moreover, SPT allows the identification of specific allergens that are related to allergic symptoms. The most frequent allergens in tropical countries are house dust mites (*Blomia tropicalis*, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), animal hair (dog, cat, horse, and others), and pollen (cypress, ash, etc).^{1,15} Targeting these allergens that trigger with immunotherapy has proved effective in the control of allergy symptoms, improvement of quality of life, increasing tolerance to allergen exposure, and leading to a reduction in conventional pharmacological treatment.¹⁶ Immunotherapy involves the frequent administration of high doses of standardized extracts of allergens via subcutaneous or sublingual route.¹⁶⁻¹⁸

Colombia is one of the tropical Latin American countries with the highest prevalence of allergic diseases.^{3,19} However, research on the epidemiology, medical, and

sociodemographic factors associated with allergic diseases in adults using standardized methods is scarce.^{3,20} To date, no studies in Latin America assessed the factors associated with allergic diseases confirmed by SPT in patients undergoing specific immunotherapy. This study aimed to describe the medical, sociodemographic, and environmental factors associated with AR and asthma syndrome (CARAS)²¹ in adults aged 18-68 years undergoing specific immunotherapy in two allergy referral centers in Bogotá, Colombia: Fundación Santa Fe de Bogotá (FSFB) and Unidad-Medicoquirúrgica del ORL (UNIMEQ-ORL).

Materials and Methods

Study design

This is an observational, cross-sectional study conducted between January 2019 and January 2020 at the FSFB and UNIMEQ-ORL. The factors associated with AR and CARAS were determined by applying the self-administered ISAAC-III questionnaire in adult patients. All patients had a clinical diagnosis of AR or CARAS, confirmed with SPT, and were undergoing specific immunotherapy. The diagnosis of AR and CARAS and the prescription of immunotherapy were performed by allergists based on the European Academy of Allergy and Clinical Immunology (EAACI) guidelines^{16,22} and who were trained to support the fieldwork of this research. A sociodemographic questionnaire was also applied.

The FSFB and UNIMEQ-ORL are located in the capital city, and both institutions are allergy and immunotherapy referral centers that treat the population of all socioeconomic statuses. For this study, socioeconomic statuses were classified based on the strata classification of the Colombian National Administrative Department of Statistics (DANE) as follows: low-income (strata I and II), middle-income (strata III and IV), and high-income levels (strata V and VI). DANE uses income data, property information, and people's households' residential characteristics to determine this stratification.²³ The study was approved by the Ethics Committee of the Hospital Universitario Fundación Santa Fe de Bogotá (CCEI-10248-2019) according to the Helsinki Declaration. All patients included in this study signed informed consent for participation, and no incentives were offered for study participation.

Study population

The study population should meet the following inclusion criteria according to the EAACI guidelines¹⁶: (a) Patients aged 18-68 years; (b) Positive SPT results (IgE sensitization)

to one or more clinically relevant allergens; (c) Moderate to severe symptoms of the allergic disease that affected their daily activities or sleep and remained despite pharmacotherapy and/or allergen avoidance strategies; (d) Undergoing immunotherapy between 2019 and 2020.

ISAAC-III Questionnaire

The ISAAC-III questionnaire was applied to patients who met the inclusion criteria during the immunotherapy appointments. This questionnaire aims to determine the frequency trends and factors associated with allergic diseases and was priorly adapted and validated in Spanish language.²⁴ The ISAAC-III questionnaire is a low-cost tool to evaluate the frequency of AR, asthma, and AD, as well as their associated factors, with adequate reproducibility and validity.^{8,9,25} Following the ISAAC-III guidelines' recommendations, the prevalence of allergic diseases was defined as follows:

- **AR symptoms:** A positive response to the ISAAC-III question: "In the last 12 months, have you had a problem with sneezing, snoring, or mouth blockage when you did not have a cold/flu?".
- **Asthma symptoms:** "A positive response to: Have you ever had wheezing or whistling in the chest in the last 12 months?".
- **AD symptoms:** "Have you ever had an itching or rash that came and went for at least 6 months or at any time in the last 12 months?".

ISAAC-III questionnaire also assesses the factors associated with allergic diseases in pediatric populations (i.e., acetaminophen use, fast food consumption, exercise, smoking exposure, pet-owning).^{24,26} We applied this Spanish version of the ISAAC-III questionnaire as all these questions were validated prior.²⁴

Statistical analysis

The statistical analysis was performed using Stata16MP. The significance level for the comparisons was priorly established as 5%. In the descriptive analysis, absolute and relative frequencies were calculated for the qualitative variables. Conversely, for the quantitative variables, central tendency measures (average and median) were estimated. For the dispersion measures, standard deviation and interquartile range were calculated along with maximum and minimum values. Height and weight were extracted from the clinical database of the FSFB. The body mass index (BMI) was adjusted by age group and sex according to World Health Organization standards.²⁷ A multivariate analysis based on a logistic regression model was made to identify the variables associated with AR and CARAS. These variables were included in the model considering biological plausibility and statistical associations with a $P < 0.2$. Odds ratio was converted into prevalence ratio (PR).^{28,29} Finally, the diagnosis of the models was performed using linearity and goodness-of-fit tests, assessment of

collinearity, evaluation of deviance residuals, and leverage points.

Results

A total of 416 adults aged 18-68 years were included, of which 71.4% were females. Overall, 65.1% of the population belonged to a middle-income socioeconomic status, and 31.5% of the total population was overweight or obese. Up to 32.7% of the population remained in immunotherapy treatment for at least 6-12 months. The baseline demographic characteristics of the study population are described in Table 1.

Table 1 Baseline demographic and clinical characteristics of the study population.

Variables	n = 416	
	n	%
Sex, Female/Male	297/119	71.4/28.6
Age in years*	33.8 (12.4)	31.6 (22.7-42.3)
Age group		
18-40 years old	296	71.2
41-60 years old	104	25.0
More than 60 years old	16	3.8
Socioeconomic status		
Low-income levels	123	29.6
Middle-income levels	271	65.1
High-income levels	22	5.3
Educational level		
None	7	1.7
Primary education	23	5.5
Secondary education	101	24.3
Technical degree	67	16.1
Higher degree/Education	171	41.1
Other	46	11.1
No data	1	0.2
Mother's educational level		
None	9	2.2
Primary education	107	25.7
Secondary education	115	27.6
Technical education	80	19.2
Higher education	79	19.0
Other	21	5.0
No data	5	1.2
Father's educational level		
None	11	2.6
Primary education	107	25.7
Secondary education	97	23.3
Technical education	69	16.6
Higher education	97	23.3
Other	21	5.0
No data	14	3.4
Weight in kg*	38.6 (11)*	62 (55-70)*
Height in cm*	163 (8.9)*	163 (140-169.5)*
BMI**	23.8 (1.3)	23.5 (21.5-25.9)

(Continues)

Table 1 (Continued)

Variables	n = 416	
	n	%
BMI score classification**		
Underweight	23	5.5
Normal weight	262	63.0
Overweight	104	25.0
Obesity	27	6.5
Exercise frequency per week		
Occasionally or none	167	40.1
1 to 2 times per week	135	32.5
3 or more times per week	113	27.2
No data	1	0.2
Smoking	18	4.3
Parents or siblings with		
Allergic rhinitis	238	57.2
Atopic dermatitis	138	33.2
Current exposure to pets		
Dog	129	31.0
Cat	63	15.1
Frequency of acetaminophen use during the last year		
Never	30	7.2
Less than 4 times per year	156	37.5
More than 4 times per year	230	55.3
Length of immunotherapy		
Less than 6 months	138	33.2
6-18 months	136	32.7
18-36 months	115	27.6
36-48 months	13	3.1
More than 48 months	14	3.4

*Values are expressed in Mean (SD) and Median (p25-p75)
 **WHO categories (BMI: Body Mass Index)

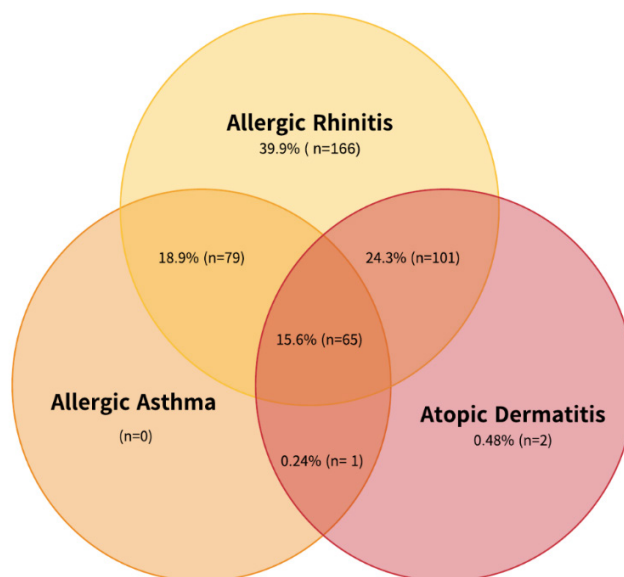
About the SPT sensitization results, the most frequent allergens were house dust mites (64.18%): 49.03% were positive for both *D. pteronyssinus* and *D. farinae*, and 28.61% for *B. tropicalis*. Excluding house dust mites, the most frequent allergens were dog hair (31.01%), cat hair (15.1%), grasses (15.9%), and food (15.9%).

Frequency of allergic diseases

Overall, 39.9% of the population presented with exclusive AR. AR was frequently found in comorbidity with asthma (CARAS: 18.9%) and AD (24.3%). The combination of the three allergic diseases was found in 15.63% of the population. These results are shown in Figure 1 and Table 2.

Factors associated with exclusive AR and CARAS

The factors associated with AR and CARAS were based on a logistic regression model. The PR and 95% confidence intervals for each association are described in Table 3 and Table 4 for AR and CARAS, respectively. The main factor associated with exclusive AR was regular acetaminophen

**Figure 1** Frequency of allergic diseases in the study population.**Table 2** Frequency of allergic diseases in the study population.

Allergic disease	n = 416		
	n	%	CI 95%
Exclusive allergic rhinitis	166	39.9	(35.3-44.7)
Exclusive asthma	0	0	-
Exclusive atopic dermatitis	2	0.48	(0.13-1.74)
Allergic rhinitis in combination with:			
Asthma	79	18.9	(15.5-23.3)
Atopic dermatitis	101	24.3	(20.4-28.6)
Asthma in combination with			
Atopic dermatitis	1	0.24	(0.05-1.3)
Presence of allergic rhinitis, asthma, and atopic dermatitis			
	65	15.63	(12.4-19.4)

use more than four times a year PR:1.77 (95% IC: 1.12-2.25). Meanwhile, the main factor associated with AR in comorbidity with asthma (CARAS) was cesarean delivery PR: 1.44 (95% CI: 1.09-1.48).

Regarding the diagnosis of these regression models, linearity tests and goodness-of-fit tests were carried out and no collinearity problems were found. During the evaluation of deviance residuals and leverage points, no extreme or influential values that could affect the model were found.

Discussion

This study aimed to describe the medical, sociodemographic, and environmental factors associated with AR and CARAS in adults between 18 and 68 years treated with specific immunotherapy in two reference allergy centers from a tropical country. All the patients included in this

Table 3 Logistic regression model of the factors associated with allergic rhinitis.

Variable*	Bivariate analysis		Multivariate analysis	
	PR**	95% IC	PR**	95% CI
Age in years	0.99	(0.98-1.00)	0.99	(0.98-1.00)
Sex				
Male	1.31	(1.01-1.60)	1.18	(0.88-1.50)
Socioeconomic status				
Middle-income levels	1.14	(0.86-1.44)	1.13	(0.83-1.46)
High-income levels	0.99	(0.50-1.63)	0.92	(0.41-1.62)
Cesarean delivery	1.06	(0.78-1.36)	0.98	(0.69-1.31)
Mother's educational level				
Secondary education	1.10	(0.79-1.42)	0.84	(0.54-1.22)
Higher education	1.13	(0.85-1.43)	0.86	(0.55-1.24)
Frequency of acetaminophen use				
Less than 4 times a year	1.62	(0.98-2.16)	1.62	(0.99-2.15)
More than 4 times a year	1.83	(1.19-2.31)	1.77	(1.12-2.25)
Dog ownership at home	1.07	(0.82-1.34)	1.01	(0.74-1.31)
Cat ownership at home	1.04	(0.73-1.38)	1.00	(0.66-1.38)
Fast food consumption				
1-2 times per week	1.21	(0.93-1.50)	1.09	(0.79-1.43)
3 or more times per week	0.75	(0.28-1.48)	0.47	(-1.21)

Bold numbers highlight the significant associated factors with adequate 95% confidence intervals.

*Log-likelihood (only intercept): -262.644; Log-likelihood of the model: -254.741; AIC: 537.482; BIC: 593.079

**PR: Prevalence ratios

Table 4 Logistic regression model of the factors associated with CARAS.

Variable ^(a)	Bivariate analysis		Multivariate analysis	
	PR**	95% IC	PR**	95% CI
Age in years	1.00	(0.99-1.01)	1.01	(0.99-1.02)
Sex				
Male	0.74	(0.52-1.01)	0.86	(0.59-1.18)
Socioeconomic status				
Middle-income levels	0.87	(0.63-1.14)	0.90	(0.63-1.22)
High-income levels	1.21	(0.67-1.77)	1.31	(0.67-1.97)
Cesarean delivery	1.38	(1.03-1.74)	1.44	(1.09-1.78)
Mother's educational level				
Secondary education				
Higher education	0.96	(0.65-1.33)	1.08	(0.72-1.49)
Frequency of acetaminophen use	0.89	(0.61-1.21)	1.00	(0.64-1.40)
Less than 4 times a year	0.53	(0.27-0.94)	0.60	(0.29-1.08)
More than 4 times a year	0.81	(0.46-1.27)	0.86	(0.46-1.39)
Dog ownership at home	0.98	(0.72-1.28)	1.10	(0.81-1.42)
Cat ownership at home	0.80	(0.51-1.17)	0.84	(0.53-1.23)
Fast food consumption				
1-2 times per week	0.81	(0.56-1.10)	0.86	(0.57-1.20)
3 or more times per week	1.18	(0.57-1.89)	1.43	(0.70-2.12)
Overweight or obesity	1.19	(0.89-1.51)	1.07	(0.78-1.39)

Bold numbers highlight the significant associated factors with adequate 95% confidence intervals.

*Log-likelihood (only intercept): -253.048; Log-likelihood of the model: -243.191; AIC: 516.381; BIC: 575.950

**PR: Prevalence Ratios

study were undergoing specific immunotherapy according to EAACI guidelines,¹⁶ and up to 32.7% of them remained in immunotherapy for at least 6-12 months. Therefore, all of the population had a diagnosis of moderate to severe AR symptoms confirmed through clinical diagnosis and an

allergy sensitization assessment. Therefore, our results should be interpreted considering this limitation as the population with mild symptoms of AR may have different associated factors. Few studies have been conducted on the epidemiology of allergic diseases in Latin American

populations, and most of these studies mostly focused on pediatric populations.^{30,31} Further studies in diverse Latin American populations are needed to understand the role of different geographic and environmental characteristics that prompt allergens and allergic diseases.

ISAAC-III questionnaires were initially developed for pediatric populations, and few studies have applied this questionnaire to adult populations, which may be considered a limitation of this study. However, ISAAC-III is a low-cost, internationally standardized tool, and prior studies suggest a high correlation between this tool and the ECRHS (European Community Respiratory Health Survey), which is a European questionnaire to assess respiratory allergies in adult populations.³² However, ECRHS does not assess the presence of AD, which is an important factor priorly associated with respiratory diseases.³² Moreover, the ISAAC strategy granted the improvement and modification of the ISAAC questionnaires including wider evidence about the main factors associated with allergic diseases. Several studies support ISAAC-III's effectiveness and reliability to assess factors associated with allergic disease.^{9,24,25,32} In low- or middle-income countries, there is limited scientific information about the epidemiology of allergic diseases using standardized methodologies, probably due to budget limitations in scientific research.³³⁻³⁵ Therefore, in these Latin American countries, the ISAAC-III tool may be particularly useful to assess the prevalence trends and factors associated with these diseases.

In Colombia, the national prevalence of self-reported allergic diseases in the general population during 2010 was: 32% for AR, 14% for AD, and 12% for asthma.²⁰ Likewise, in our study including moderate to severe atopic population, the frequency of AR was 39.9% and of CARAS was 18.9%. Previously, authors have described the importance of AR in coexistence with asthma, as patients with uncontrolled AR symptoms may have an increased risk of asthma exacerbations.³⁶ Therefore, controlling AR symptoms is particularly important in patients with CARAS. To date, allergen immunotherapy is mainly indicated for the treatment of moderate to severe AR, rather than exclusive asthma symptoms.^{16,22} However, current literature suggests that immunotherapy may improve asthma symptoms, decrease airway hyperresponsiveness, and lead to a reduction in medications.³⁷ Besides, despite that the role of environmental allergens in triggering AD symptoms remains unclear, a current meta-analysis described that allergen immunotherapy can improve AD severity and quality of life.³⁸ Therefore, as up to 15.63% of our study population presented a combination of the three main allergic diseases (AR, asthma, and AD), allergen immunotherapy may induce an immunological remission in these patients.³⁹ Most of these studies have been performed in pediatric populations, and studies including adult populations, particularly in adults exposed to tropical environmental allergens (i.e., *B. tropicalis*), are needed.

The SPT findings in our population are consistent with the previously described distribution of allergens in patients undergoing immunotherapy in tropical and subtropical countries.^{40,41} Prior international studies have reported that the most common mites causing allergy in homes are house dust mites such as *D. farinae*, *D. pteronyssinus*, *Euroglyphus maynei*, and *B. tropicalis*.^{1,40} Up to

28.61% of the population had a positive SPT for *B. tropicalis*, which is particularly high considering that Bogotá city has an oceanic climate with an average temperature of 14.5°C (58°F), average relative humidity of 75%, and a high altitude (2640 m or 8660 ft above sea level).⁴² Previous studies have suggested a higher prevalence of *B. tropicalis* in coastal cities with higher temperatures (over 18-27°C or 65-80°F) and humidity.⁴³⁻⁴⁵ However, over the last decades, an increase in sensitization rates to *B. tropicalis* has been reported.⁴⁶ Current studies suggest that environmental variations induced by climate change and industrialization could partially explain the increase in the prevalence and severity of allergic disease, particularly in tropical countries.⁴ Additional studies assessing the changes in the prevalence of these tropical aeroallergens and the association between this prevalence and the changes in environmental conditions and climate change are needed.

Regarding the factors associated with exclusive AR, AR was most frequent in the population that reported a frequent acetaminophen consumption of more than four times a year (PR: 1.77; 95% CI: 1.12-2.25). Likewise, a current meta-analysis including observational studies by Zeng et al. among 87,0492 patients showed that the regular use of acetaminophen was related to a higher risk of AR symptoms (OR: 1.54; 95% CI: 1.41-1.69).⁴⁷ Furthermore, a study conducted in a Colombian pediatric population described an association between AR and acetaminophen consumption over four times a year (PR: 1.31; 95% CI: 1.03-1.55).¹⁵ Different mechanisms could explain this association: (i) High doses of acetaminophen reduce levels of glutathione, an endogenous antioxidant in lung tissue, and increase pulmonary oxidative stress, causing progression of respiratory diseases⁴⁸; (ii) COX-2 activity and increased prostaglandin E2 production could be stimulated by acetaminophen which promotes allergic pathways⁴⁹; (iii) An IgE-mediated mechanism with acetaminophen as an antigenic agent.⁵⁰⁻⁵² Moreover, several studies suggest that frequent use of acetaminophen may lead to a dose-dependent risk of developing allergic respiratory diseases, worsening lung function, and higher risk of respiratory diseases.⁵¹ However, due to the observational design of most of these studies, no causal relationship could be established, and this association may also reflect reverse causation because patients with a genetic predisposition to allergic diseases could be more prone to febrile syndromes due to respiratory tract infections and thus use acetaminophen more often. Overall, the evidence for this association has been stated in multiple observational studies, but further research is needed to assess this association. On the other hand, the authors highlight that additional medications were not explored in this study (i.e., antihistamines, antibiotics), as these assessments were not included in the original ISAAC-III questionnaire. However, further studies assessing the associations of the most frequently used medications in patients with allergies should be performed, as some observational studies have described these associations.⁵³

On the other hand, CARAS was positively associated with cesarean delivery (PR = 1.44; 95% CI: 1.09 - 1.78). Similarly, a prior meta-analysis of observational studies by Darabi et al. stated that cesarean delivery increased

the risk of childhood asthma (RR; 1.2; 95% CI: 1.15-1.25, $P < 0.0001$).⁵⁴ A systematic review and meta-analysis assessing the pediatric consequences of cesarean section (C-section) revealed that C-section is a risk factor for asthma (pooled OR = 1.23 95% CI 1.14-1.33, $P < 0.00001$).⁵⁵ A current meta-analysis assessing the association between cesarean delivery and childhood asthma also described a higher risk of asthma (OR = 1.26, 95% CI: 1.05-1.5) in children born by C-section.⁵⁶ This association may be explained by different biological mechanisms such as changes in the immunological system development, changes in the infant microbiome, and the mechanical effects on lung growth that may lead to a higher neonatal respiratory morbidity.⁵⁷ Despite the association between asthma and cesarean delivery seeming strong, the association between AR and cesarean delivery still has contradictory evidence.^{57,58} In a study by Richards et al., in a birth cohort of 117,768 children from the United States followed through 6 years of age, cesarean delivery was not associated with AR.⁵⁸ However, Richards et al. reported that in this cohort children of mothers with allergies or asthma who underwent C-section were more likely to develop AR compared to children of mothers without allergies or asthma (AR-RR: 1.56; 95% CI: 1.46-1.67; AD-RR: 1.09; 1.00-1.19; food allergy RR: 1.31; 1.15-1.50; asthma RR: 1.31; 1.20-1.43).⁵⁸ A meta-analysis by Bager et al. assessing the risk of cesarean delivery and risk of allergic diseases reported a higher risk of allergic rhinitis (OR 1.23, 95% CI 1.12-1.35; 7 studies), asthma (OR 1.18, 95% CI 1.05-1.32; 13 studies), and hospitalization for asthma (OR 1.21, 95% CI 1.12-1.31; 7 studies) in patients delivered via C-section.⁵⁹ C-section babies are deprived of the first colonization of the gut with maternal vaginal bacteria and may exhibit a different gut flora compared with neonates born via vaginal delivery.⁵⁹ The gut flora plays an important role in the homeostasis and development of the immune system, and C-sections could interfere with the normal tolerance induction and the homeostasis of the immune system, leading to a higher risk of atopic conditions. However, this meta-analysis highlights that a high heterogeneity was found between the studies due to major differences between the populations and methodology.⁵⁹ Overall, this association may be explained by the relationships among different allergic diseases, but further studies are needed.

Despite no association being found, up to 31.5% of this atopic population were overweight or obese. This association between overweight status and atopy in pediatric populations has been described previously.⁶⁰ Hersoug et al. hypothesized that obesity may decrease immunological tolerance due to changes induced in adipokines, cytokines, and tumor necrosis factor- α secreted by the adipose tissues.⁶¹ However, most of these studies were observational and only included pediatric populations. Further information regarding this interaction is needed to provide adult atopic patients with better care. Finally, this study highlights that the ISAAC-III questionnaire was useful to assess the factors associated with allergic diseases in adult populations, and further studies applying this standardized methodology should be performed.

A major limitation of this study was the observational methodological design that may show associations rather than prove causal relations among the variables.⁶²

Moreover, as previously stated, all populations had a diagnosis of moderate to severe AR symptoms, and the population with mild symptoms of AR may have different associated factors. Among the strengths of the study, the diagnosis of allergic diseases was performed by allergists and confirmed with SPT following the EAACI guidelines.¹⁶ Thus, biases related to heterogeneity in clinical practice were avoided. Moreover, trained medical professionals with broad experience in the ISAAC-III questionnaire performed the data collection, following the ISAAC guidelines.⁹

Conclusion

A high frequency of *B. tropicalis* was found in this adult population aged 18-68 years with moderate to severe symptoms of AR confirmed with positive SPT undergoing immunotherapy. The main factor associated with AR was regular acetaminophen use, while the main factor associated with CARAS was cesarean delivery. These findings were consistent with previous reports in the scientific literature, and overall, the ISAAC-III questionnaire can be a useful low-cost tool to assess the factors associated with allergic diseases in tropical countries. Further studies assessing the factors associated with AR in tropical countries are needed.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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