

Asthma cases in childhood attributed to atopy in tropical area in Brazil

Sergio Souza da Cunha,^{1,2} Mauricio Lima Barreto,¹
Rosemeire Leovigildo Fiaccone,³ Philip J. Cooper,^{4,5}
Neuza Maria Alcantara-Neves,⁶ Silvia de Magalhães Simões,⁷
Álvaro Augusto Cruz,⁷ and Laura Cunha Rodrigues⁸

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ABSTRACT

Objective. *This study aimed to explore the association between asthma and atopy in a cohort of children living in a large urban center in Brazil. Atopy was defined by the presence of allergen-specific IgE in serum or by a positive skin prick test.*

Methods. *In a sample of 1 445 Brazilian children, the association between the prevalence of asthma, skin prick test positivity, and allergen-specific IgE in serum was investigated.*

Results. *The prevalence of asthma was 22.6%. The presence of serum allergen-specific IgE was frequent in asthmatics and nonasthmatics, and the prevalence of asthma increased only with levels of allergen-specific IgE \geq 3.5 kilounits/L. The proportion of asthma attributable to atopy was estimated to be 24.5% when atopy was defined by the presence of allergen-specific IgE. With a given level of specific IgE, no association between skin test reactivity and asthma was observed. Skin prick tests were less sensitive than specific IgE for detection of atopy.*

Conclusions. *Most asthma cases in an urban underprivileged setting in Brazil were not attributable to atopy. This observation has important implications for understanding the risk factors for the asthma epidemic in Latin America.*

Key words Asthma; atopic hypersensitivity; child; Brazil.

¹ Instituto de Saúde Coletiva, Universidade Federal da Bahia, Salvador, Brazil. Send correspondence to: Sergio Souza da Cunha, cunhatmt@hotmail.com

² Departamento de Medicina Social, Universidade Federal de Pernambuco, Recife, Brazil.

³ Departamento de Estatística, Universidade Federal da Bahia, Salvador, Brazil.

⁴ Instituto de Microbiologia, Universidad San Francisco de Quito, Quito, Ecuador.

⁵ Centre for Infection, St. George's University of London, London, United Kingdom.

⁶ Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, Brazil.

⁷ ProAR, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, Brazil.

⁸ London School of Hygiene and Tropical Medicine, London, United Kingdom.

The prevalence of asthma has increased in industrialized countries in recent decades. There is now evidence for a high prevalence of asthma in Latin America that has reached epidemic levels in some urban centers (1, 2). The causes of these temporal trends are not clear but have been attributed to changes in environmental exposures and lifestyle factors such as those associated with the processes of urbanization.

Considering all asthma as a single disease entity is an oversimplification (3). Different asthma phenotypes may predominate in different settings and be as-

sociated with distinct etiological factors and causal mechanisms (4). Of particular interest is that the proportion of asthma cases attributable to atopy has been shown to be highly variable (5); the existing evidence, while scarce, suggests that in Latin American countries most asthma cases in children appear not to be associated with atopy (6–9).

Atopy can be determined by skin test reactivity to environmental allergens or the detection of allergen-specific IgE in serum. The two measures have been used interchangeably to define atopy, even though there is important disagree-

ment between these two measures, particularly in populations in nonindustrialized countries (9–12).

This study explored the relationship between asthma and atopy defined either by the presence of allergen-specific IgE in serum or by skin prick test (SPT) positivity in children living in underprivileged urban settings in northeastern Brazil. The study took advantage of the existence of a cohort study on asthma and allergy in children, and these children were resurveyed.

MATERIALS AND METHODS

Study site

This study was conducted in the city of Salvador, located in the northeastern region of Brazil with more than 2.8 million inhabitants, mostly of mixed African descent, with a high prevalence of symptoms of asthma (defined as wheezing in the last 12 months) in the International Study of Asthma and Allergies in Childhood (ISAAC) surveys: 17% for schoolchildren aged 6–7 years and 25% for those aged 13–14 years (13).

Study design and population

This study was conducted as part of a cohort study on asthma and allergies. The details are described elsewhere (14). Briefly, it comprises a group of 1 445 children living in 24 micro-areas from poor neighborhoods throughout the city. This population was used before in studies to evaluate the impact of a sanitation program on the occurrence of childhood diarrhea (14–17). This study analyzed data on asthma and allergy collected in 2005, when the children were 4–11 years old. Data on helminth infection were available for 1 403 of the 1 445 children: 18.3% were infected with *Ascaris lumbricoides*, 16.3% were infected with *Trichuris trichiura*, and 1% were infected with hookworm. Details on helminth infections and their association with atopy have been described (18), and the association with asthma is described elsewhere (19).

Data collection

A questionnaire, including questions about the core asthma symptoms of the ISAAC questionnaire and translated into

Brazilian Portuguese (20), was applied during household visits by trained interviewers. In a follow-up visit, allergen SPTs were performed on the right forearm of each child with the following extracts (all ALK-Abello, Denmark): *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Blattella germanica* (German cockroach), *Periplaneta americana* (American cockroach), pooled fungi, dog and cat epithelia, and saline and histamine controls. Pollen extracts were not included because pollen allergy is not found in the tropical northeastern region of Brazil. Wheal sizes were read after 15 min. A test was considered positive if the mean of two perpendicular diameters (excluding flare and pseudo-pods) was ≥ 3 mm greater than that of the negative control. The SPT was considered positive if reactivity was present for at least one allergen. Blood samples were collected for measurement of IgE specific to *D. pteronyssinus*, *B. tropicalis*, *B. germanica*, and *P. americana* using the ImmunoCAP assay (Pharmacia, Uppsala, Sweden). The lower detection limit for allergen-specific IgE is 0.35 kilounit (kU)/L. Specific IgE levels were grouped into four categories: < 0.35 kU/L, ≥ 0.35 kU/L to < 0.70 kU/L, ≥ 0.70 kU/L to < 3.5 kU/L, and ≥ 3.5 kU/L. For the purposes of this analysis, atopy was defined by either a positive skin test to at least one allergen or by the presence of at least one detectable allergen-specific IgE. The highest level observed for any specific IgE was used to define a child's allergen-specific IgE level. The analysis was done for the total population studied and separately for those with and without detectable allergen-specific IgE. The questionnaires were applied between June and October 2005, and the laboratory tests were performed between November 2005 and March 2006. Analysis was done with categorical data with cut-offs based on biological grounds rather than using continuous variables because data on IgE and skin tests were highly skewed.

Asthma definition

Children were classified as having asthma if parents reported wheezing in the previous 12 months and at least one of the following: diagnosis of asthma ever, wheezing with exercise in the last 12 months, four or more episodes of wheezing in the last 12 months, and waking up at night because of wheezing in

the last 12 months. These criteria are more specific than wheezing in the last 12 months, the most common criterion used for ISAAC. All other children were classified as nonasthmatic. Details on asthma severity and the association with atopy and other risk factors are described in another manuscript under submission.

Analysis

Association measures using prevalence ratios were done initially with Poisson regression models with a robust estimator specifying micro-areas as a cluster to adjust for the clustering effect. However, only unadjusted results are shown because models with and without adjustment for clustering showed similar results. Parental asthma and sex were used as potential confounders. Age was used as an effect modifier and estimates were done separately for children aged 4–5 years and 6–11 years. Asthma was present in similar proportions in children with and without parents who reported smoking; therefore, this variable was not included in the analysis.

The population attributable fraction (PAF) was estimated as $pd \times [(OR - 1)/OR] \times 100$, where pd is the proportion of total asthma cases arising from the exposure category (21), and the odds ratio (OR) was used instead of a prevalence rate ratio (PRR) (22). Analyses were done using Stata version 8.

Ethical approval

Approval was obtained from the Brazilian National Ethical Committee. Written informed consent was obtained from the legal guardian of each child studied.

RESULTS

Among the 1 445 children, 772 (53.4%) were male and the mean age was 6.8 years (range: 4–11 years). A total of 326 (22.6%) children were asthmatic. The percentage of asthma decreased with age: 37.4% at 4 years (83/222), 23.3% at 5–6 years (137/588), 17.3% at 7–8 years (78/452), and 15.3% at 9–11 years (28/183) ($P < 0.001$).

A total of 1 363 (94.3%) of the 1 445 children had data on specific IgE, which was detectable (≥ 0.35 kU/L) for at least one aeroallergen in 672 (49.3%) of the 1 363 children. The prevalence of asthma

TABLE 1. Association between levels of allergen-specific IgE and prevalence of asthma, Brazil, 2005

Allergen-specific IgE levels (kU/L)	Age group								
	4–5 years old			6–11 years old			Total		
	No. (%) <i>n</i>	Prevalence rate ratio (95% confidence interval) ^a	PAF ^b (%)	No. (%) <i>n</i>	Prevalence rate ratio (95% confidence interval) ^a	PAF ^b (%)	No. (%) <i>n</i>	Prevalence rate ratio (95% confidence interval) ^a	PAF ^b (%)
< 0.35	68 (27.0)/252	1	...	54 (12.6)/430	1	...	122 (17.9)/682	1	...
0.35 to < 0.70	19 (30.2)/63	1.10 (0.71, 1.70)	1.6	17 (17.9)/95	1.31 (0.80, 2.14)	3.0	36 (22.8)/158	1.20 (0.86, 1.66)	2.6
0.70 to < 3.5	23 (26.7)/86	1.00 (0.67, 1.50)	0.0	28 (17.6)/159	1.47 (0.97, 2.27)	7.0	51 (20.8)/245	1.21 (0.90, 1.61)	3.4
≥ 3.5	40 (45.5)/88	1.68 (1.23, 2.28)	14.8	52 (30.4)/171	2.42 (1.73, 3.38)	23.5	92 (35.5)/259	2.01 (1.60, 2.52)	18.6
Total	150 (30.7)/489			151 (17.7)/855			301 (22.4)/1 344		24.5 ^b

Note: kU: kilounits, PAF: population attributable fraction.

^a Based on Poisson regression with robust variance "sandwich" estimator and adjusted for sex and parental asthma and based on Poisson regression adjusted for sex, parental asthma, and age (4–5 years and 6–11 years).

^b Population attributable fraction of asthma attributable to atopy for each category and in the total population comparing those with negative IgE (< 0.35) and positive IgE (≥ 0.35), based on odds ratio rather than prevalence rate ratio. Respective odds ratios for those aged 4–5 years: 1.14, 1.0, 2.25; 5–11 years: 1.37, 1.60, 3.14; all ages: 1.28, 1.25, 2.56; all children: 1.70.

was higher among children with detectable specific IgE against the aero-allergens tested (181/672, 26.9%) than among those without a specific IgE (123/691, 17.8%) (PRR = 1.51; 95% confidence interval [CI] = 1.24, 1.85). The crude association between IgE and asthma was estimated. This association was strongest for those with the highest IgE levels (≥ 3.5 kU/L) (PRR = 1.97; 95% CI = 1.56, 2.46). For those with intermediate IgE levels, no significant increase in PRR was observed (PRR = 1.23; 95% CI = 0.89, 1.71 and PRR = 1.18; 95% CI = 0.89, 1.57 for specific IgE levels 0.35 to < 0.70 kU/L and 0.70 to < 3.50 kU/L, respectively). In Table 1, the adjusted PRRs between IgE and asthma for those aged 4–5 years were 1.10, 1.00, and 1.60, respectively, for IgE levels 0.35 to < 0.70, ≥ 0.70 to < 3.5, and ≥ 3.5, compared with those with IgE < 0.35. In contrast, for those aged 6–11 years, the PRRs were 1.31, 1.47, and 2.47. This result could suggest that the association between atopy and asthma changes with age and is higher among older children. However, to assess whether there was interaction with age (4–5 and 6–11 years), a regression model was run with an interaction term for age, and it was not statistically significant ($P = 0.641$ for likelihood ratio test). Therefore, on statistical grounds, it cannot be assumed that there was a heterogeneity of effect according to age—that is, chance cannot be ruled out as an explanation for the differences in PRRs, but it is worth noting that the study was not planned to assess the hypothesis on heterogeneity of effect.

The prevalence of detectable specific IgE among asthmatics was 59.5% (181/

304) and among nonasthmatics it was 46.4% (491/1 059) ($P < 0.001$); according to age it was 53.9% (41/76) at 4 years, 57.0% (73/128) at 5–6 years, 65.3% (47/72) at 7–8 years, and 71.4% (20/28) at 9–11 years ($P = 0.054$ for trend of odds; data not shown).

The PAF was estimated for each level of allergen-specific IgE and separately for age groups among the 1 344 children with a complete data set (Table 1). The highest value of PAF was among those aged 6–11 years with levels of specific IgE ≥ 3.5 kU/L (23.5%). In those 1 344 children, comparing the prevalence of asthma among those with negative specific IgE (< 0.35 kU/L) with all those with positive IgE, PRR adjusted for sex, parental asthma, and age was 1.50 (95% CI = 1.23, 1.84) with a corresponding OR of 1.70 (95% CI = 1.31, 2.21). There were 179 cases with a positive IgE among a total of 301 cases (59.5%); therefore, the estimate of PAF for positive specific IgE (≥ 3.5 kU/L) in the whole population was 24.5%.

The association between IgE and asthma was also estimated among the 1 344 children with a complete data set, with detectable IgE defined at a higher level: ≥ 0.70 kU/L. The prevalence of asthma was 28.4% among those with IgE ≥ 0.70 kU/L (143/504) and 18.8% (158/840) among those with IgE < 0.70 kU/L. This corresponds to a PRR of 1.51 (95% CI = 1.24, 1.84; adjusted for sex, age, and parental asthma as in Table 1) and an adjusted OR of 1.84 (95% CI = 1.41, 2.41). The corresponding PAF is 21.7%.

SPT was done in 1 388 of 1 445 children (96.1%), of whom 421 (30.3%) had at least one positive skin test result.

There were 1 360 children with data for both IgE and SPT, of whom 670 had detectable IgE. Among the 690 without detectable IgE, only 32 (4.6%) had a positive SPT, while 56.6% (379) of the 670 with detectable specific IgE had a positive SPT. Among the 949 with negative SPT, 291 (30.7%) had detectable specific IgE. The prevalence of asthma in children with detectable allergen-specific IgE in serum was not modified by the SPT reactivity of the individual. The prevalence of asthma was 26.5% in those with negative SPT and 27.6% in those with positive SPT (Table 2 and Figure 1).

In 1 344 children with a complete data set, there were 312 children (22.9%) with detectable IgE for *B. germanica* or *P. americana*, and among those without IgE for these allergens the prevalence of asthma was 19.7% (207/1 051), compared with 31.1% among those with IgE (97/312) (PRR = 1.58; 95% CI = 1.28, 1.93; after adjustment for parental asthma, sex, and age). There were 634 children (46.5%) with IgE for *D. pteronyssinus* or *B. tropicalis*, of whom 176 (27.8%) had asthma, compared with 17.6% (128/729) among those without IgE for these allergens (PRR = 1.57; 95% CI = 1.29, 1.91; after adjustment as above).

DISCUSSION

The main findings of the study were as follows: 1) The prevalence of childhood asthma was high (22.6%) and decreased with age (37% at 4 years versus 15% at 9–11 years). 2) Almost half (49.3%) the study children had detectable allergen-specific IgE levels (≥ 0.35

TABLE 2. Prevalence of asthma by level of allergen-specific IgE and allergen skin prick test (SPT) reactivity in 1 341 children with complete data set (age, sex, IgE, SPT, and parental asthma), Brazil, 2005

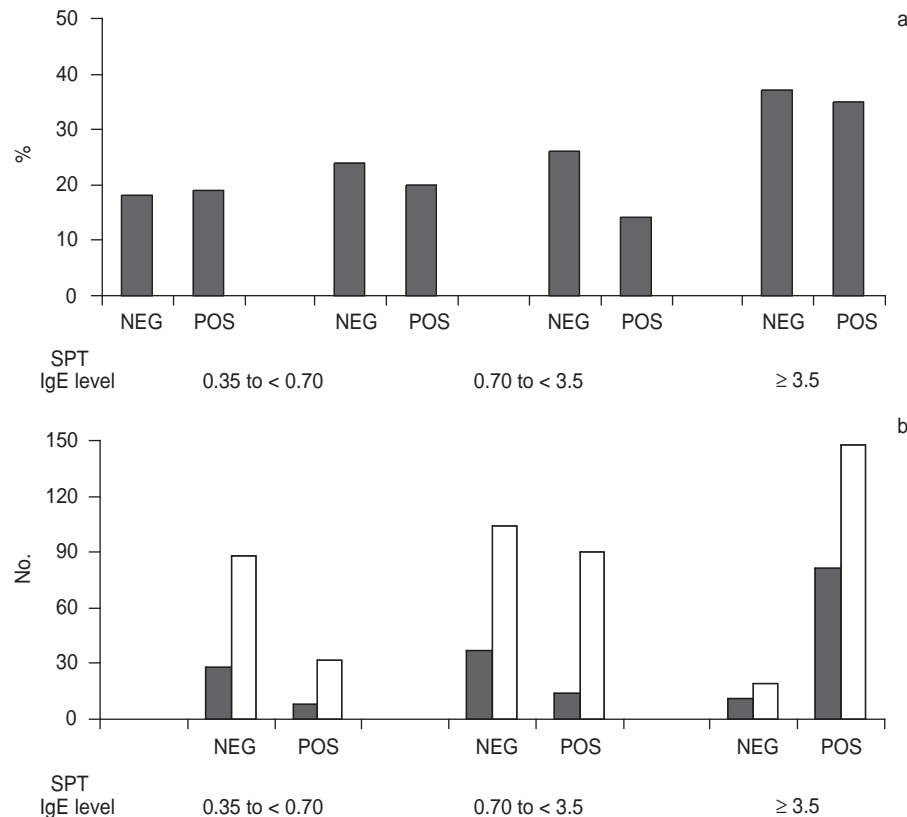
Allergen-specific IgE	SPT	Children with asthma, No. (%) / n according to age group			Prevalence rate ratio (95% CI)		
		4–5 years	6–11 years	Total population	4–5 years ^a	6–11 years ^a	Total population ^b
		No. (%) / n	No. (%) / n	No. (%) / n			
Negative < 0.35 kU/L	Positive	3 (23.1) / 13	3 (15.8) / 19	6 (18.8) / 32	1	1	1
	Negative	65 (27.3) / 238	51 (12.4) / 411	116 (17.9) / 649	0.85 (0.32, 2.21)	1.27 (0.44, 3.67)	1.02 (0.49, 2.10)
Positive ≥ 0.35 kU/L	Positive	43 (34.1) / 126	60 (24.3) / 247	103 (27.6) / 373	1	1	1
	Negative	39 (35.1) / 111	37 (21.0) / 176	76 (26.5) / 287	0.97 (0.68, 1.38)	1.23 (0.86, 1.77)	1.08 (0.84, 1.39)
Total		150 (30.7) / 488	151 (17.7) / 853	301 (22.4) / 1 341			

Note: CI: confidence interval, kU: kilounits.

^a Based on Poisson regression with robust variance “sandwich” estimator and adjusted for sex and parental asthma when separated for age group.

^b Based on Poisson regression with robust variance “sandwich” estimator and adjusted for sex, parental asthma, and age (4–5 years and 6–11 years) for total population.

FIGURE 1. Asthma cases by level of allergen-specific IgE and skin prick test (SPT) reactivity, excluding those with negative IgE and no data on parental asthma, Brazil, 2005



Note: IgE levels are in kilounits/L, and SPT is indicated as negative (NEG) or positive (POS): (a) percentage of asthmatic children in gray; (b) number of children, gray indicates asthmatic children, white indicates nonasthmatic children.

kU/L). 3) The presence of allergen-specific IgE was strongly associated with an increased prevalence of asthma only at high levels (≥ 3.5 kU/L). 4) The PAF of asthma to allergen-specific IgE was 24.5%. 5) For children with the same level of allergen-specific IgE, a positive SPT did not increase the risk of asthma.

The association between atopy and asthma is complex (5, 23); atopy is defined sometimes based on high levels of allergen-specific IgE and sometimes based on allergen skin test positivity. Although these measures are often used interchangeably in epidemiologic studies, they can differ in the same person, par-

ticularly in low- and middle-income countries (24, 25). There are several reasons why a child with a detectable level of allergen-specific IgE can have a negative SPT, including the use of poor-quality allergen extracts for SPTs and the effects of environmental exposures, such as helminth infections, in reducing skin

test reactivity (10, 18) or individual differences in antibody affinities (26).

Helminth infections can potentially induce the production of false-positive allergen-specific IgE in low titers (i.e., 0.35–0.70 kU/L) through immunological cross-reactivity between helminth and aeroallergen-specific IgE (27). There is no evidence for this observation in the current report, however. In this study, specific IgE levels were associated with both SPT and asthma, but, for the same level of specific IgE, the prevalence of asthma was the same in those with positive and with negative SPT. This suggests that the results of SPT in this population do not provide information supplemental to that offered by the level of specific IgE. In this population, and perhaps in similar populations, allergen-specific IgE may be the most useful indicator of the presence of sensitization and therefore atopy in an individual. Levels of specific IgE were also associated with asthma. In this study population, one-third of children with negative SPT had detectable IgE levels and would have been considered nonatopic if specific IgE had not been measured.

The panel of aeroallergens included in this study reflects the most common allergens in the northeastern region of Brazil. The possibility of pollen allergy was not examined in this urban population because, unlike the southern region of the country (28), pollen-associated allergy is not reported in the literature from this tropical region of Brazil (Medline and Lilacs searches) and has not been observed in the authors' clinical practice or in that of other national experts who were canvassed informally.

Atopy as defined by the presence of allergen-specific IgE was very frequent in this study. Atopy is not always accompanied by asthma and the proportion of atopic subjects who develop clinical disease varies. Data from ISAAC Phase II surveys found that a higher fraction of recent wheezing was attributable to atopy (measured by allergen skin test reactivity) in affluent (41%) than in nonaffluent countries (20%) (7). In populations such as the one used in this study where atopy is frequent, not all asthma in atopic children is caused by atopy (25). The fact that nonatopic asthma is more prevalent in this population supports previous work, also in Brazil (6), which demonstrated a higher prevalence of nonatopic

asthma. However, it is worth emphasizing some differences between the two works. In the previous study, the prevalence of atopy was 13%; it was based on a temperate climate (extreme southern Brazil), and the atopy definition was based only on results from SPT and involved children aged 9–12 years. In contrast, in this study atopy was prevalent in 49%, the atopy definition was based on IgE, the study site was located in a tropical area, and younger children from 4 to 8 years old were involved. In this study, when specific IgE levels of asthmatics and nonasthmatics were taken into account, the proportion of asthma cases attributable to the presence of specific IgE was estimated to be no more than 24.5%. The interpretation of a PAF of 24.5% is that, in the absence of atopy, there would be a 24.5% reduction in asthma prevalence in the total population. A higher proportion of children with allergen-specific IgE who are not asthmatics results in a smaller proportion of asthma cases attributable to atopy estimated by the PAF. When it is assumed that allergen-specific IgE is the cause of asthma in children with detectable allergen-specific IgE, the importance of atopy as the sole cause of asthma is likely to be overestimated. This was suggested in previous articles, in which estimates of current wheezing attributable to atopy (PAF) varied from 2.0% to 59.6% (7), as the idea that risk factors other than atopy would play a more relevant role in causing asthma in Latin America (29). This may have led to a distortion of research priorities in the search for causal explanations for the temporal trends of increasing asthma prevalence and detracted from the search for the mechanisms underlying nonatopic asthma and potentially the development of effective prevention and treatment.

The importance of atopy in the asthma epidemic in developing countries may have also been overestimated, for two reasons: inconsistencies between different definitions of atopy (use of either SPT or allergen-specific IgE) and the uncritical assumption that asthma has characteristics similar to those reported in Europe and the United States of America. Asthma with and without atopy may represent distinct phenotypes associated with different environmental and genetic risk factors. As the hygiene hypothesis was proposed to explain temporal trends in atopy

(30), although it remains relevant to populations in which most asthma is atopic, it is unlikely to explain trends in asthma not associated with atopy.

Atopy has been recognized as the strongest risk factor for asthma, and therefore asthma commonly has been considered an atopic disease. However, there is evidence that a large proportion of asthma cases in several settings are not associated with or attributed to atopy. Several studies have found different risk factors for atopic and nonatopic asthma, suggesting different causal pathways. For example, in some studies respiratory infections—especially respiratory syncytial virus (31)—maternal smoking and mold stains (32), and being sedentary (33) were associated with nonatopic but not atopic asthma. This suggests that nonatopic asthma can have a variety of causes related to environmental exposures such as infections. These differences can have important implications with regard to preventive measures. However, there is poor agreement on the definitions of different phenotypes of preschool wheezing disorders (34).

There are two main limitations of this study. First, it is a cross-sectional study and conclusions about causality should be done cautiously, including estimates of PAF that require some assumptions (22). Second, the study site was a tropical and urban area where pollen allergy is not common, and one should be careful in generalizing results to more temperate regions. Given these considerations, the main conclusions are that nonatopic asthma is the most prevalent phenotype of asthma in this population, suggesting that atopy is not causally associated with most asthma cases, the association between specific IgE to common aeroallergens and asthma seems to be independent of skin test reactivity in this population, and the skin test provided no additional information, indicating that specific IgE may be a more accurate measure of atopy than SPT in similar populations.

Clinicians and investigators should be aware that among children from underprivileged settings in low- and middle-income countries who are exposed to helminths and other infectious agents, skin test reactivity may be inhibited by mechanisms that are not completely understood and that require further investigation. Specific IgE may be more sensitive for the identification of atopy.

It is suggested that future studies on risk factors for asthma in nonindustrialized countries, such as in Latin American countries, should define the relative proportion of atopic and nonatopic asthma using allergen-specific IgE, report not only the prevalence of asthma in atopic subjects but also the proportion of

asthma attributable to atopy, and study separately the risk factors for asthma with and without detectable allergen-specific IgE. It is important to explore the factors modulating levels of allergen-specific IgE and SPT reactivity and the factors that affect the association between allergen-specific IgE and SPT reactivity.

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**Asma infantil atribuida a
atopia en la zona tropical
de Brasil****RESUMEN**

Objetivo. Explorar la relación entre el asma y la atopia en una cohorte de niños que viven en un gran centro urbano de Brasil. En este estudio, se considera atopia la detección de IgE sérica específica de algún alérgeno o un resultado positivo a la prueba de punción cutánea.

Métodos. Se estudió la relación entre la prevalencia del asma, el resultado positivo a la prueba de punción cutánea y la detección de IgE sérica específica de algún alérgeno en una muestra de 1 445 niños brasileños.

Resultados. El asma registró una prevalencia de 22,6%. La presencia de IgE séricas específicas de alérgenos fue frecuente tanto en los asmáticos como en los no asmáticos, y la prevalencia del asma fue mayor solo cuando el valor detectado de la IgE específica del alérgeno era $\geq 3,5$ kilounidades/litro. Se calculó que la atopia definida como la detección de IgE específicas de alérgenos es responsable de 24,5% de los casos de asma. No se observó ninguna relación entre la reactividad a la prueba de punción cutánea y el asma en función de los valores de IgE específicas. La prueba de punción cutánea es menos sensible que la detección de IgE específicas en lo que respecta al diagnóstico de atopia.

Conclusiones. La mayoría de los casos de asma que se registran en entornos urbanos desfavorecidos de Brasil no son atribuibles a atopia. Esta observación tiene implicaciones importantes en lo que respecta a la comprensión de los factores de riesgo que predisponen a la epidemia de asma en América Latina.

Palabras clave

Asma; hipersensibilidad inmediata; niño; Brasil.