

## CLINICAL SCIENCE

# Is allergic rhinitis a trivial disease?

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**BACKGROUND:** Asthma and rhinitis often coexist, which potentially increases the disease severity and can negatively impact a patients' quality of life. However, there are few reports based on data obtained from the International Study of Asthma and Allergies in Childhood examining asthma severity in combination with rhinitis-related symptoms.

**OBJECTIVE:** To demonstrate whether current rhinitis and current rhinoconjunctivitis are associated with the development of asthma or its increasing severity in Brazilian adolescents.

**METHODS:** The prevalence of current asthma was correlated with the prevalence of current rhinitis and current rhinoconjunctivitis in adolescents (13 to 14 year olds) from 16 Brazilian centers (based on Spearman's rank correlation index). The influence of current rhinitis and current rhinoconjunctivitis on asthma presentation was also evaluated using the chi-squared test and was expressed as odds ratios with 95% confidence intervals (95%CI).

**RESULTS:** A significant positive correlation was observed between the prevalence of current asthma and current rhinitis ( $r_s=0.82$ ; 95%CI: 0.60–0.93,  $p<0.0001$ ) and between the prevalence of current asthma and current rhinoconjunctivitis ( $r_s=0.75$ ; 95%CI: 0.47–0.89,  $p<0.0001$ ). Current rhinitis was associated with a significantly increased risk of current asthma and of more severe asthma. Similar results were observed for current rhinoconjunctivitis.

**CONCLUSION:** In this epidemiologic study of Brazilian adolescents, the presence of current rhinitis and current rhinoconjunctivitis was associated with a high risk of developing asthma and increased asthma severity. The mutual evaluation of rhinitis and asthma is necessary to establish an adequate treatment plan.

**KEYWORDS:** Epidemiology; Asthma; Rhinitis; Rhinoconjunctivitis; ISAAC.

Solé D, Camelo-Nunes IC, Wandalsen GF, Rosário NA, Sarinho EC, Brazilian ISAAC's Group. Is allergic rhinitis a trivial disease? Clinics. 2011;66(9):1573-1577.

Received for publication on February 11, 2011; First review completed on April 19, 2011; Accepted for publication on May 30, 2011

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## INTRODUCTION

In the last decade, allergic rhinitis (AR) has become prominent among allergic diseases due to its prevalence, negative impact on quality of life, and associated comorbidities.<sup>1,2</sup> Several epidemiological, etiological, anatomical, and therapeutic similarities between asthma and rhinitis have been reported.<sup>1-3</sup> It has been hypothesized that both asthma and AR are manifestations of a single inflammatory process present throughout the airway and that they represent a continuum of disease.<sup>3-5</sup> Brown et al. examined bronchial biopsies from adults with AR and observed an intermediate state of airway inflammation between that seen in healthy individuals and subjects with clinical asthma.<sup>6</sup>

The prevalence of rhinitis and related symptoms found by the International Study of Asthma and Allergies in Childhood (ISAAC) in Phases One (Ph1) and Three (Ph3) was quite high and variable around the world, with a sustained high trend.<sup>7,8</sup> Asthma and rhinitis often coexist, which potentially increases the disease severity and negatively impacts the quality of life.<sup>9</sup>

AR is considered a common condition with a high morbidity, and it is associated with a reduced quality of life due to its coexistence with other diseases, such as chronic sinusitis and asthma.<sup>2,3</sup> AR often precedes the onset of clinical asthma and has been identified as a risk factor for the development of asthma in children<sup>10-14</sup> and adults.<sup>13,15-17</sup>

Several studies have reported a prevalence of AR in asthma patients of 80 to 90%.<sup>1-3,10-12</sup> The concomitance of AR and asthma has been associated with an increase in the healthcare costs associated with asthma<sup>14,18-22</sup> and an impairment in the quality of life.<sup>9,19,23</sup> A retrospective study of asthmatic patients, aged 16 to 55 years, showed that patients with asthma alone had significantly fewer asthma-related visits to general practitioners, lower asthma-related drug costs, and

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fewer hospitalizations due to asthma than patients with rhinitis associated with asthma.<sup>24,25</sup> Similar results have been observed in asthmatic children.<sup>26</sup>

In a previous study of 6,520 children and adolescents enrolled in ISAAC Ph1, we evaluated the effects of rhinitis alone and rhinitis associated with atopic eczema on asthma severity in patients identified as asthmatics (23.2%). A higher prevalence of asthma and severe asthma was observed in children with rhinitis and/or atopic eczema.<sup>27</sup>

To date, few studies using the data from the ISAAC have examined asthma severity in combination with rhinitis-related symptoms. Thus, the aim of this study was to determine whether current rhinitis or current rhinoconjunctivitis are risk factors for the development of asthma or increased asthma severity in Brazilian adolescents.<sup>28</sup>

**METHODS**

The data presented in this epidemiological study were previously published and came from 16 centers in 14 Brazilian cities.<sup>28,29</sup> Adolescents (ADs, 13 to 14 years old) were selected following the ISAAC Ph3 protocol.<sup>30</sup> The cities, states, and regions/areas in which the study took place were Manaus (Amazonas, Northern [N]); Caruaru (Pernambuco [PE], Northeastern [NE]); Aracaju (Sergipe, NE); Feira de Santana (Bahia [BA], NE); Salvador (BA, NE); Vitória da Conquista (BA, NE); Brasília (Distrito Federal, Middle-Western); Nova Iguaçu (Rio de Janeiro, Southeastern [SE]); São Paulo (West and South, São Paulo [SP], SE); Santo André (SP, SE); Curitiba (Paraná, Southern [S]); Itajaí (Santa Catarina, S); Porto Alegre (Rio Grande do Sul [RS], S) and Santa Maria (RS, S). The data from all centers were approved by the ISAAC International Data Center and were considered ISAAC’s official centers (Table 1).

ISAAC’s written questionnaire (WQ), previously translated and validated for the Brazilian culture,<sup>31-33</sup> was completed by 46,770 ADs. The participants were selected from adolescents who attended public and private schools located in the participating cities. Only the asthma and rhinitis core questionnaires were considered in this study.

Information regarding the number of schools and students in each area was obtained from the appropriate Municipal Education Secretary’s official records. The data obtained were transcribed to a database (Epi-Info) supplied by ISAAC’s coordinators. The frequency of affirmative answers to specific questions was analyzed.

ADs were identified as having current asthma if they answered “yes” to the question “Have you had a wheezing episode in the last 12 months?”; as having current rhinitis if they answered “yes” to the question “Have you had nasal problems (sneezing; runny or blocked nose) in the last 12 months without a cold?”; and as having current rhinoconjunctivitis if they answered “yes” to the question “Have you had nasal problems (sneezing; runny or blocked nose) with itchy and watery eyes in the last 12 months?”.<sup>29</sup> ADs were identified as having severe asthma if they answered “yes” to the question “Have you had wheezing severe enough to limit speech in the last 12 months?” or at least two of the following questions: “Have you had more than 12 wheezing episodes in the last 12 months?”, “Have you had wheezing with exercise?”, and “Have you had nocturnal coughing without a cold?” (atypical form of asthma). Asthma diagnosed by a physician was considered a medical diagnosis.<sup>30</sup>

To analyze the correlation between the prevalence of current rhinitis and current rhinoconjunctivitis with current asthma, Spearman’s rank correlation coefficient was used. The influence of current rhinitis and current rhinoconjunctivitis on asthma presentation was analyzed using the chi-square test and is expressed as the odds ratio (OR) with 95% confidence intervals (95%CI). The study was approved by all local ethics committees. In all tests, the level of rejection of the null hypothesis was 5%.

**RESULTS**

The prevalence of current asthma, current rhinitis, and current rhinoconjunctivitis was lower in Nova Iguaçu and higher in Salvador and Vitória da Conquista (Table 1). A significant positive correlation was observed between the

**Table 1 - Prevalence of current asthma, current rhinitis, and current rhinoconjunctivitis in Brazilian adolescents from ISAAC Phase Three centers, based on responses to the ISAAC written questionnaire (determined with Spearman’s correlation coefficient).**

Center	n	Current asthma (%)	Current rhinitis (%)	Current rhinoconjunctivitis (%)
Manaus	3,009	18.1	23.0	12.8
Caruaru	3,026	17.9	25.5	15.4
Aracaju	3,041	18.7	25.6	17.4
Feira de Santana	1,732	21.5	33.0	17.2
Salvador	3,020	24.6	44.2	24.4
Vitória da Conquista	1,679	30.5	39.8	24.4
Brasília	3,009	19.7	29.3	15.4
Nova Iguaçu	3,185	11.8	17.4	8.9
São Paulo West	3,181	21.9	30.1	19.8
São Paulo South	3,161	18.7	27.4	12.2
Santo André	3,232	23.2	28.4	13.8
Curitiba	3,628	18.9	39.2	17.2
Itajaí	2,737	12.3	22.1	12.9
Porto Alegre	3,007	18.2	32.1	15.9
Santa Maria – rural	3,057	15.3	20.6	9.6
Santa Maria – urban	3,066	16.7	24.3	11.4

Spearman’s correlation coefficient:

Current asthma vs. current rhinitis:  $rs=0.82$  (95%CI: 0.60–0.93),  $p<0.0001$ .

Current asthma vs. current rhinoconjunctivitis:  $rs=0.75$  (95%CI: 0.47–0.89),  $p<0.0001$ .

prevalence of current asthma and current rhinitis and between the prevalence of current asthma and current rhinoconjunctivitis (Table 1).

Current rhinitis was associated with a significantly increased risk (odds ratio [OR]) of current asthma in all participating centers, with OR ranging from 2.19 (Curitiba) to 4.36 (Nova Iguaçu) (Table 2). Reports of current rhinitis were also associated with a significant risk of having 12 or more episodes of acute asthma in nine of 16 centers, with OR ranging from 0.68 (Salvador) to 8.03 (São Paulo West) (Table 2). Sleep disturbance was significantly associated with current rhinitis in 13 of 16 centers, with OR ranging from 0.92 (Itajaí) to 4.45 (Nova Iguaçu) (Table 2). Similar results were found for the risk of speech difficulty due to an acute asthma attack, which was observed in nine of 16 centers and ranged from 0.72 (Itajaí) to 5.18 (Nova Iguaçu) (Table 2). The risk of wheezing with exercise in the last year was significantly associated with current rhinitis in all evaluated centers and ranged from 2.38 (Aracaju) to 3.25 (Salvador) (Table 2). The risk of nocturnal cough in the last year was significantly associated with current rhinitis in all centers and ranged from 2.99 (Curitiba) to 4.50 (Nova Iguaçu) (Table 2). The risk of physician-diagnosed asthma was significantly associated with current rhinitis in all centers and ranged from 1.82 (Manaus) to 3.44 (Vitória da Conquista) (Table 2).

Current rhinoconjunctivitis was associated with a significantly increased risk of current asthma in all participating centers that ranged from 2.73 (Curitiba) to 6.04 (Nova Iguaçu) (Table 3). It was also associated with a significant risk of having 12 or more episodes of acute asthma in 10 of 16 participating centers that ranged from 1.31 (Porto Alegre) to 8.85 (São Paulo West) (Table 3). Sleep disturbance was significantly associated with current rhinoconjunctivitis in 13 of 16 participating centers, with OR ranging from 1.27 (Itajaí) to 5.41 (Nova Iguaçu) (Table 3). A similar result was observed in 13 of 16 centers for speech difficulty due to an acute asthma attack, with OR ranging from 1.23 (Itajaí) to 7.18 (Nova Iguaçu) (Table 3). Wheezing caused by exercise in the last year was also significantly associated with current

rhinoconjunctivitis in all participating centers, with OR ranging from 2.77 (Vitória da Conquista) to 4.38 (Itajaí) (Table 3). Nocturnal coughing in the last year was significantly associated with current rhinoconjunctivitis in all centers, with OR ranging from 2.79 (Curitiba) to 5.45 (Nova Iguaçu) (Table 3). Physician-diagnosed asthma was significantly associated with current rhinoconjunctivitis in all centers, with OR ranging from 2.02 (Manaus) to 4.20 (Nova Iguaçu) (Table 3).

## DISCUSSION

In this multicenter study, we evaluated the majority of the Brazilian ADs (46,770 or 80.4%) enrolled in ISAAC Ph3, representing the different regions of Brazil. The mean index of return of the completed WQ was high (approximately 93%).<sup>30</sup> Our study has some limitations arising from its ecological nature. Ecological studies are inherently limited because their analyses are based on a general population rather than individuals. No individual information is available regarding confounding factors that might explain the associations between the studied variable and the outcome. Therefore, such potential confounding factors can be neither examined nor controlled for in the analysis. Nevertheless, such studies can provide useful information about the potential impact of a disease or drug on a population. Another point to consider is the validity of self-reported information (such as the responses to the ISAAC WQ) in studies using questionnaires; the possibility of inaccuracy and bias must be considered.<sup>31</sup> However, the ISAAC has strengths that improve its reliability; these strengths include its sample size, comprehensiveness, and high response rates; its inclusion of hitherto unstudied populations; and its use of an identical, standardized, simple and validated questionnaire based on asthma and rhinitis symptoms.<sup>31</sup>

The prevalence of current asthma is assumed to be high in patients with current AR.<sup>1-3</sup> In this study, we observed a mean prevalence of current asthma in AD with current rhinitis of 33.0% and a mean prevalence of current asthma in AD with current rhinoconjunctivitis of 40.9%. Differences in

**Table 2 - Odds ratio (OR) and 95% confidence interval (95% CI) for wheezing-related symptoms in Brazilian adolescents with current rhinitis from ISAAC Phase Three centers.**

Center	Wheezing last year OR (95%CI)	>12 wheezing episodes last year OR (95%CI)	Sleep disturb. last year OR (95%CI)	Speech problems last year OR (95%CI)	Asthma ever OR (95%CI)	Wheezing with exercise last year OR (95%CI)	Nocturnal coughing last year OR (95%CI)
Manaus	4.18 (3.43-5.09)*	2.41 (1.02-5.69)*	1.58 (1.12-2.21)*	2.37 (1.57-3.55)*	1.82 (1.49-2.22)*	2.92 (2.40-3.54)*	3.56 (2.98-4.26)*
Caruaru	3.30 (2.72-4.01)*	1.06 (0.46-2.44)	1.44 (1.03-2.02)*	1.37 (0.89-2.11)	2.45 (2.03-2.97)*	3.12 (2.56-3.80)*	3.05 (2.57-3.61)*
Aracaju	3.03 (2.50-3.70)*	1.61 (0.59-4.39)	0.99 (0.71-1.37)	0.83 (0.56-1.23)	2.56 (2.08-3.14)*	2.38 (1.93-2.83)*	3.07 (2.60-3.64)*
Feira Santana	3.67 (2.90-4.66)*	6.93 (1.58-30.5)*	1.81 (1.19-2.74)*	1.35 (0.81-2.24)	2.08 (1.53-2.82)*	2.94 (2.40-3.65)*	3.46 (2.80-4.28)*
Salvador	3.80 (3.18-4.53)*	0.68 (0.33-1.44)	1.71 (1.23-2.37)*	1.57 (1.03-2.40)*	2.47 (2.00-3.06)*	3.25 (2.78-3.80)*	3.24 (2.77-3.80)*
Vitória Conquista	3.47 (2.80-4.30)*	2.90 (0.82-10.32)	1.71 (1.19-2.45)*	1.75 (1.11-2.75)*	3.44 (2.55-4.63)*	3.16 (2.57-3.88)*	3.13 (2.55-3.85)*
Brasília	3.67 (3.05-4.43)*	3.96 (1.12-14.1)*	1.85 (1.33-2.57)*	1.59 (1.01-2.52)	2.42 (1.97-2.97)*	2.77 (2.31-3.33)*	4.25 (3.60-5.02)*
Nova Iguaçu	4.36 (3.44-5.52)*	2.35 (0.80-6.90)	4.45 (3.31-5.99)*	5.18 (3.46-7.75)*	2.97 (2.22-3.98)*	3.00 (2.40-3.70)*	4.50 (3.70-5.49)*
São Paulo West	3.75 (3.14-4.46)*	8.03 (2.95-21.8)*	3.36 (2.75-4.12)*	4.27 (3.11-5.84)*	2.77 (2.16-3.54)*	3.18 (2.65-3.81)*	3.49 (2.98-4.09)*
São Paulo South	2.91 (2.42-3.51)*	1.69 (0.71-4.02)*	1.56 (1.12-2.18)*	1.70 (1.02-2.85)	2.50 (1.97-3.14)*	2.40 (1.98-2.90)*	3.37 (2.82-3.97)*
Santo André	3.32 (2.80-3.94)*	2.62 (1.08-6.40)*	1.61 (1.21-2.16)*	1.59 (1.03-2.45)*	2.28 (1.78-2.91)*	2.53 (2.10-3.05)*	3.30 (2.81-3.87)*
Curitiba	2.19 (1.85-2.59)*	1.68 (0.71-3.99)	1.93 (1.41-2.66)*	2.24 (1.45-3.47)*	2.40 (1.91-3.02)*	2.52 (2.13-2.98)*	2.99 (2.59-3.44)*
Itajaí	3.94 (3.11-4.99)*	1.83 (0.92-3.64)	0.92 (0.60-1.42)	0.72 (0.39-1.35)	3.25 (2.54-4.17)*	3.16 (2.56-3.90)*	3.86 (3.20-4.67)*
Porto Alegre	3.65 (3.02-4.43)*	1.70 (1.04-2.76)*	1.93 (1.37-2.73)*	1.19 (0.77-1.85)	2.40 (2.00-2.87)*	2.88 (2.41-3.44)*	3.31 (2.82-3.89)*
Santa Maria	3.74 (3.03-4.62)*	2.76 (1.30-5.86)*	1.15 (0.79-1.66)	2.20 (1.35-3.59)*	2.61 (2.12-3.22)*	2.78 (2.29-3.37)*	3.83 (3.22-4.55)*
Santa Maria - rural	3.59 (2.94-4.38)*	2.07 (1.16-3.71)*	1.82 (1.28-2.58)*	1.82 (1.12-3.00)*	2.92 (2.30-3.71)*	2.72 (2.23-3.33)*	3.95 (3.29-4.74)*

I \*p<0.05.

**Table 3** - Odds ratio (OR) and 95% confidence interval (95% CI) for wheezing-related symptoms in Brazilian adolescents from ISAAC Phase Three centers with current rhinoconjunctivitis.

Center	Wheezing last year OR (95%CI)	>12 wheezing episodes last year OR (95%CI)	Sleep disturb. last year OR (95%CI)	Speech problems last year OR (95%CI)	Asthma ever OR (95%CI)	Wheezing from exercise last year OR (95%CI)	Nocturnal coughing last year OR (95%CI)
Manaus	4.63 (3.68–5.83)*	2.57 (1.15–5.76)*	1.57 (1.09–2.27)*	3.06 (2.03–4.61)*	2.02 (1.60–2.57)*	3.38 (2.69–4.25)*	4.08 (3.22–5.17)*
Caruaru	3.21 (2.58–4.00)*	1.48 (0.63–3.50)	1.38 (0.96–1.98)	2.57 (1.66–3.99)*	2.44 (1.96–3.03)*	3.24 (2.60–4.04)*	3.20 (2.60–3.92)*
Aracaju	2.93 (2.37–3.61)*	2.15 (0.80–5.84)	1.61 (1.13–2.29)*	1.33 (0.89–2.01)	2.50 (2.00–3.12)*	3.24 (2.63–3.98)*	3.98 (3.25–4.86)*
Feira Santana	3.73 (2.85–4.87)*	2.19 (0.87–5.55)	1.52 (0.99–2.33)	1.35 (0.81–2.24)	2.18 (1.54–3.08)*	3.13 (2.42–4.04)*	3.96 (3.05–5.13)*
Salvador	3.40 (2.84–4.07)*	1.33 (0.64–2.77)	1.87 (1.39–2.52)*	1.65 (1.14–2.38)*	2.21 (1.80–2.75)*	2.93 (2.47–3.48)*	3.12 (2.63–3.71)*
Vitória Conquista	3.18 (2.52–4.01)*	4.67 (1.48–14.69)*	2.88 (2.00–4.16)*	2.10 (1.38–3.22)*	2.83 (2.11–3.80)*	2.77 (2.20–3.48)*	2.92 (2.32–3.67)*
Brasília	4.11 (3.32–5.08)*	4.56 (1.56–13.33)*	1.84 (1.30–2.60)*	2.75 (1.74–4.33)*	2.60 (2.05–3.29)*	3.30 (2.67–4.09)*	3.77 (3.05–4.65)*
Nova Iguaçu	6.04 (4.58–7.97)*	3.68 (1.16–11.6)*	5.41 (3.88–7.54)*	7.18 (4.71–10.90)*	4.20 (3.00–5.80)*	4.00 (3.00–5.25)*	5.45 (4.15–7.17)*
São Paulo West	3.62 (2.99–4.37)*	8.85 (3.59–21.8)*	3.80 (3.07–4.68)*	5.47 (4.02–7.44)*	2.79 (2.15–3.60)*	3.27 (2.69–3.97)*	3.73 (3.11–4.47)*
São Paulo South	4.17 (3.32–5.23)*	1.49 (0.61–3.61)*	2.09 (1.45–3.01)*	2.31 (1.38–3.89)*	2.94 (2.23–3.87)*	3.23 (2.55–4.08)*	4.83 (3.85–6.05)*
Santo André	3.70 (3.00–4.56)*	3.17 (1.40–7.20)*	2.04 (1.48–2.82)*	2.21 (1.42–3.42)*	2.88 (2.18–3.80)*	3.21 (2.57–4.00)*	3.93 (3.20–4.84)*
Curitiba	2.73 (2.25–3.31)*	2.32 (1.02–5.24)*	1.74 (1.25–2.42)*	1.72 (1.13–2.61)*	2.72 (2.13–3.48)*	2.95 (2.44–3.57)*	2.79 (2.34–3.33)*
Itajaí	4.71 (3.62–6.12)*	2.37 (1.20–4.70)*	1.27 (0.81–2.01)	1.23 (0.65–2.32)	3.91 (2.97–5.14)*	4.38 (3.44–5.57)*	3.83 (3.05–4.82)*
Porto Alegre	4.18 (3.37–5.18)*	1.31 (0.82–2.10)	1.65 (1.16–2.34)*	1.61 (1.04–2.49)*	2.71 (2.19–3.35)*	3.80 (3.09–4.70)*	4.19 (3.42–5.15)*
Santa Maria	4.32 (3.33–5.60)*	1.96 (0.93–4.15)	1.43 (0.93–2.20)*	2.16 (1.30–3.62)*	3.18 (2.47–4.10)*	3.72 (2.94–4.72)*	3.93 (3.12–4.95)*
Santa Maria - rural	5.26 (4.14–6.68)*	3.34 (1.88–5.94)*	2.14 (1.45–3.17)*	3.03 (1.85–4.95)*	2.94 (2.20–3.97)*	3.19 (2.47–4.11)*	3.58 (2.80–4.60)*

\*p<0.05.

the definition of current asthma, current rhinitis or current rhinoconjunctivitis could explain the differences between study findings.

In this study, we used definitions used by ISAAC coordinators and in studies worldwide.<sup>8,9,30,35</sup> The differences in sensitivity and specificity for diagnosing asthma and rhinitis via a written questionnaire could also have affected the results. Despite these differences, as previously reported, this study found a significant correlation between the prevalence of current asthma and current rhinitis (rs=0.82; 95%CI: 0.60–0.93) and current asthma and current rhinoconjunctivitis (rs=0.75; 95%CI: 0.47–0.89), demonstrating that these diseases are correlated in the studied population.

The association between an asthma diagnosis and current rhinitis or current rhinoconjunctivitis ranged from 1.82 to 3.44 and from 2.02 to 4.20, respectively, which reinforces the association between asthma and AR.

Rhinitis in asthmatic patients is a risk factor for severe asthma and poorly controlled asthma. In a recent prospective study, severely asthmatic patients who were followed for one year had a 12.6 times greater risk of having uncontrolled asthma, a 3.8 times greater risk of having more visits to the emergency room, a 2.9 times lower risk of a 10% improvement in airway obstruction, and a 2.9 times lower risk of a 50% reduction in the emergency room visits if they had moderate/severe allergic rhinitis.<sup>25</sup>

In a previous study, we identified rhinitis as a risk factor for severe asthma in children and adolescents enrolled in ISAAC Ph1.<sup>27</sup> The prevalence of severe asthma was 1.6 times higher in children with asthma and rhinitis living in the southern area of the city of São Paulo; this prevalence is lower than the prevalence in the same area in the present study.

Regarding asthma severity, the ISAAC protocol defined severe asthmatics as those children who had wheezing severe enough to limit speech in the last 12 months or had awoken in the night due to wheezing in the last 12 months.<sup>25,35</sup> As defined using sleep disturbance, speech difficulty, or both sleep disturbance and speech difficulty, a significantly higher risk of severe asthma was observed in AD with current rhinitis in 13, 9,

and 7 of 16 centers, respectively. Current rhinoconjunctivitis was a significant risk factor for speech difficulty and for sleep disturbance in 13 of 16 centers. In 12 of 16 centers, the risk was significantly higher for ADs who had both conditions. The ISAAC protocol indicates that the combination of nasal and ocular symptoms make this question more specific for the diagnosis of AR and lessen the chance of bias.<sup>36</sup>

Because asthma is a heterogeneous disease with various clinical presentations, we analyzed other indications of severe asthma, such as having had more than 12 wheezing episodes in the last 12 months. A significantly higher risk of having more than 12 wheezing episodes in the last year was associated with current rhinitis in nine of 16 centers and was associated with current rhinoconjunctivitis in ten of 16 centers. Other criteria included wheezing with exercise and coughing during the night without having a cold. Both were significantly associated with rhinitis and rhinoconjunctivitis in all centers participating in this study.

Although wheezing with exercise and nocturnal cough without a cold are atypical asthma presentations, both were significantly associated with current rhinitis and current rhinoconjunctivitis.

In a program for asthma and AR control, Brandão et al. observed that a low education level, chronic rhinitis, and more severe asthma were risk factors for hospitalizations<sup>38</sup> and emergency room visits due to increased asthma severity.<sup>37</sup> Treatment for rhinitis was associated with a reduction in asthma severity.

In conclusion, this epidemiologic study of Brazilian adolescents revealed that both current rhinitis and current rhinoconjunctivitis were associated with a high risk of developing asthma and with more severe asthma. The evaluation of both rhinitis and asthma is necessary for the development of an adequate treatment plan.

## APPENDIX

The **Brazilian ISAAC's Group** comprises: Maria Socorro Cardoso (Federal University of Amazon, Manaus); Almerinda R Silva (Federal

University of Pernambuco, Caruaru); Jackeline Motta and Ricardo Gurgel (Federal University of Sergipe, Aracaju); Leda Solano de Freitas (Federal University of Bahia, Salvador); Wellington Borges (Hospital de Base do Distrito Federal, Brasília); Fábio Kuschnir and Antônio José Ledo Alves da Cunha (Federal University of Rio de Janeiro, Nova Iguaçu); Antônio C Pastorino and Cristina Miuki A Jacob (State University of São Paulo, São Paulo); Karyn Chacon de Mello (Federal University of São Paulo, São Paulo); Cássia Gonzalez and Neusa F Wandalsen (ABC Foundation School of Medicine, Santo André); Carlos Riedi (Federal University of Paraná, Curitiba); Cláudia Benhardt (Federal University of Santa Catarina, Itajaí); Gilberto B Fischer (Medical Federal Foundation of Rio Grande do Sul, Porto Alegre); Vitor E. Cassol (Federal University of Rio Grande do Sul, Santa Maria, Brazil).

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