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Risk factors for atopic eczema in Colombia, a tropical country

Factores de riesgo de eccema atópico en Colombia, un país tropical

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Abstract

Objective: This study aimed to estimate the prevalence of atopic eczema (AE) in children/adolescents and adults and variables associated with risk factors.

Methods: We used data from a cross-sectional, population-based study performed in six cities of Colombia during 2009–2010. A nested case-control study was used to determine AE-associated risk factors.

Results: In adults, AE was mainly associated with a family history of AE (adjusted OR [aOR] 4.66, 95%IC:3.18 to 6.82) and Allergic Rhinitis (AR) (aOR 2.21, 95%CI: 1.61 to 3.03). We also found a dose-dependent positive association between acetaminophen use and AE, being more assertive at once per week (aOR 2.12, 95%CI: 1.47 to 3.06) than once per month (aOR 1.82, 95%CI: 1.28 to 2.59). Female gender (aOR 1.49, 95%CI: 1.15 to 1.93), smoking (aOR 1.60, 95%CI: 1.19 to 2.14), and cats at home (aOR 1.57, 95%CI: 1.06 to 2.31), were positively associated with AE. In contrast, meat (aOR 0.45, 95%CI: 0.27 to 0.74), and seafood consumption (aOR 0.71, 95%CI: 0.56 to 0.91) were negatively associated. In children/adolescents, family history of AR (aOR 2.97, 95%CI: 1.79 to 4.93) and acetaminophen consumption once per week (aOR 4.00, 95%CI: 1.39 to 11.50) were associated with AE.

Conclusions: The most critical risk factors for AE were a family history of atopy and acetaminophen exposure, supporting an essential contribution of both genetic and environmental factors in disease presentation.

Keywords: Atopic eczema; Risk factors; Allergic rhinitis; Acetaminophen.

Resumen

Objetivo: Estimar la prevalencia del eccema atópico (EA) en niños, adolescentes y adultos, así como las variables asociadas con factores de riesgo.

Métodos: Se utilizaron datos de un estudio transversal de base poblacional realizado en seis ciudades de Colombia entre 2009 y 2010. Se empleó un estudio de casos y controles anidado para determinar los factores de riesgo asociados al EA.

Resultados: En adultos, el eccema atópico se asoció principalmente con antecedentes familiares de EA (OR ajustada [ORa] 4,66; IC95%: 3,18 a 6,82) y rinitis alérgica (RA) (ORa 2,21; IC95%: 1,61 a 3,03). También se observó una asociación positiva dosis-dependiente entre el uso de paracetamol y la asertividad, siendo esta más frecuente con un uso semanal (ORa 2,12; IC95%: 1,47 a 3,06) que con un uso mensual (ORa 1,82; IC95%: 1,28 a 2,59). El sexo femenino (ORa 1,49; IC95%: 1,15 a 1,93), el tabaquismo (ORa 1,60; IC95%: 1,19 a 2,14) y la presencia de gatos en

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el hogar (ORa 1,57; IC del 95%: 1,06 a 2,31) se asociaron positivamente con la asertividad. En contraste, el consumo de carne (ORa 0,45; IC95%: 0,27 a 0,74) y de mariscos (ORa 0,71; IC95%: 0,56 a 0,91) se asoció negativamente. En niños y adolescentes, los antecedentes familiares de rinitis alérgica (ORa 2,97; IC95%: 1,79 a 4,93) y el consumo de paracetamol una vez por semana (ORa 4,00; IC95%: 1,39 a 11,50) se asociaron con dermatitis atópica.

Conclusiones: Los factores de riesgo más importantes para la dermatitis atópica fueron los antecedentes familiares de atopia y la exposición al paracetamol, lo que respalda la contribución esencial tanto de factores genéticos como ambientales en la manifestación de la enfermedad.

Palabras clave: Eccema atópico; Factores de riesgo; Rinitis alérgica; Acetaminofén.

INTRODUCTION

Atopic eczema (AE) is an increasingly common disease affecting children and adults.[1] AE impairs quality of life (QoL) and increases psychological distress.[2,3] Among skin disorders, this disease caused the highest number of disability-adjusted life years (DALYs) among skin and subcutaneous diseases.[4,5] Recent epidemiological surveys show higher prevalence rates than in previous decades in several countries, especially those from the Tropics.[6] The Tropics have certain particularities that can impact natural history and risk/protective factors for allergies.[7] One of the most important is the perennial exposure to allergens such as house dust mites (HDM). Helminth infections and microbiota composition can potentially modify allergic responses, even to common allergens. Additionally, urban centers in tropical regions share risk factors like air pollution and distinctive dietary habits.[7]

The International Study of Asthma and Allergies in Childhood (ISAAC) has provided meaningful information about the state of allergic diseases (asthma, rhinitis, and AE) worldwide, including in tropical countries.[8] Although Colombia was part of the third phase of this project, the study focused only on the child/adolescent population, and there is still a need for further information about AE in adults. In 2010, we performed a cross-sectional study in six of the major cities in Colombia, using the ISAAC questionnaire on subjects from 5 to 59 years old.[9] In our first analysis, we estimated the prevalence of AE in children/adolescents and adults at 19 and 11%, respectively. In this paper, we conducted a sub-analysis of this database and evaluated possible associated factors for AE by age: children/adolescents and adults.

METHODS

Study design

We conducted a nested case-control study, a cross-sectional, population-based study performed in six Colombian cities (Bogotá, Bucaramanga, Cali, Barranquilla, Medellín, and San Andrés) between 2009 and 2010. The research design has been published previously.[9] A total weighted sample of 5978 subjects was used to represent the actual population size in all six cities. Due to the definitions of case and control that we used for the nested case-control study; 3996 subjects were included. The Clinical Research Ethics Committee approved the protocol at Fundación Cardioinfantil, Colombia (IORG0006438).

Questionnaire and definitions of cases and controls

The questionnaire used questions developed and validated by The International Study of Asthma and Allergy in Childhood (ISAAC).[10] The ISAAC questionnaire for AE has demonstrated high specificity (>90%) but moderate to low sensitivity (20–70%), depending on region and study population. The following items were added from the current Spanish environmental questionnaire of the ISAAC III study[11] as the frequency of eating or drinking selected foods, frequency of exercising, combustible material for cooking, socio-economic status, frequency of acetaminophen consumption, mother's educational attainment, and frequency of public transportation. A self-administered questionnaire was given to adolescents (13 to 17 years old) and adults. Parents of children (5 to 12 years old) were interviewed at home. Answers from the cross-sectional survey were used to define cases and controls. A "case" was defined as a subject who reported atopic eczema symptoms by responding "yes" to two of the following questions: "In the past year, have you had itchy skin rashes that come and go for a minimum period of six months? "*Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes*" were subjects who never had been diagnosed with either asthma, allergic rhinitis, or atopic eczema by a physician, answered "*no*" to the questions mentioned above, as well as answered "*no*" to the questions about the diagnosis of allergic rhinitis and asthma. Field supervisors conducted daily form reviews and random back-checks, and the staff involved in data collection were trained following the ISAAC guidelines.

Sample size

To calculate the sample size, we used the adjusted Odds ratio reported in the literature for the relationship between AE and family history of allergy (AE, AR, or Asthma) of 1.85 (12), which is like other reports in adults and children/adolescent.[13,14] A prevalence of the factors for the exposure groups of 15.4%, a significance level of 5%, and a power of 80%, given the following formula.[15,16]

$$n \geq n_1[1 + \sqrt{1 + \left[\frac{2(r+1)}{n_1 \cdot r \cdot (p_2 - p1)}\right]}$$

Where r = case-control ratio, p_2 and p_1 = frequencies of the groups to be compared, and n_1 is defined as:

$$n_1 = \left(\frac{\left[Z_{\frac{\alpha}{2}}\sqrt{(r+1)p_1q_1} + Z_{1-\beta}\sqrt{(r+1)p_2q_2}\right]^2}{r(p_1 - p_2)^2}\right)$$

With an exposed/unexposed ratio equal to 1 (r = 1), the sample size with the largest number of individuals is 290 cases and 290 controls. However, for our study, we

used all patients who fulfilled the criteria of case or control (**Figure 1**) to obtain a larger sample to account for other associated factors.

Data management/Statistical analysis

As the objective was to compare cases and controls to identify possible factors associated with AE, we performed a bivariate analysis to evaluate the possible association with a broad range of explanatory variables that might be associated with AE. The variable selection plan for the analyses was: *1)* Variables with a p-value <0.15 in the bivariate analysis were kept for the weighted multivariable logistic regression model;[17] *2)* For any variable, the category of response with the lowest prevalence of AE was chosen as the reference category; *3)* sex and age (continuously) as biological variables were included as control variables in the multivariable model; *4)* hierarchical backward elimination approach was carried out; *5)* interaction terms of having a cesarean delivery with socioeconomic status (SES) and age and socio-economic status (SES) were explored. The selection of variables was guided considering the biological plausibility of the covariates in relation to AE, together with a literature review on potential effect modifiers/mediators and by the inclusion of variables that in the bivariate analyses had a p-value < 0.15 in the association tests. To avoid collinearity issues, we evaluated the variance inflation factor (VIF) in the final models, considering VIF > 10 as indicative of strong multicollinearity. To address potential instability and collinearity, we also assessed interaction terms deemed plausible based on the reviewed evidence.

We performed weighted logistic regression models separately for each sub-population in the study. To assess the statistical significance of interaction terms, we compared the full model that included all interaction terms and the model without these interaction terms using a single Chunk test.[18] Variables were not statistically significant during the backward elimination procedure and were not confused, nor were control variables eliminated from the multivariable model. All the analyses are presented as weighted statistics using the Taylor series linearization method for variance estimation[19] using Stata Statistical Software for Windows, release 12 (Stata Corp., College Station, TX, USA). Two subpopulation analyses are presented: one for children/adolescents (participants aged 1-17) and the second one for adults (participants aged 18 to 59) as crude and adjusted odds ratios (OR) as well as 95% confidence intervals (CI).

RESULTS

Out of the 5,978 subjects in the cross-sectional survey, 887 and 3,109 were identified as cases and controls, respectively (**Figure 1**). Of the 1,982 subjects left, 286 correspond to missing data, and 1,696 were excluded based on the definition of case and controls. The mean age in the subpopulation of children/adolescents was 7.9 (Standard Deviation (SD): 4.3). The mean age in the adult population was 37.7 (SD: 12.7). In the adult population, the proportion of control was almost five times the proportion of cases; meanwhile, in children, it was nearly double. Most children/adolescents, as well as most adults, had health care insurance. The most frequent SES for cases and controls in both populations were low and middle status, also following the distribution of the Colombian census and projections for 2009.[9]

In the bivariate analysis (**Table 1**), women had higher odds for AE symptoms than men (OR 1.61, 95%CI: 1.28 to 2.03), and after adjustment (**Table 2**), this was confirmed as a risk factor (aOR 1.49, 95%CI: 1.15 to 1.93). A family

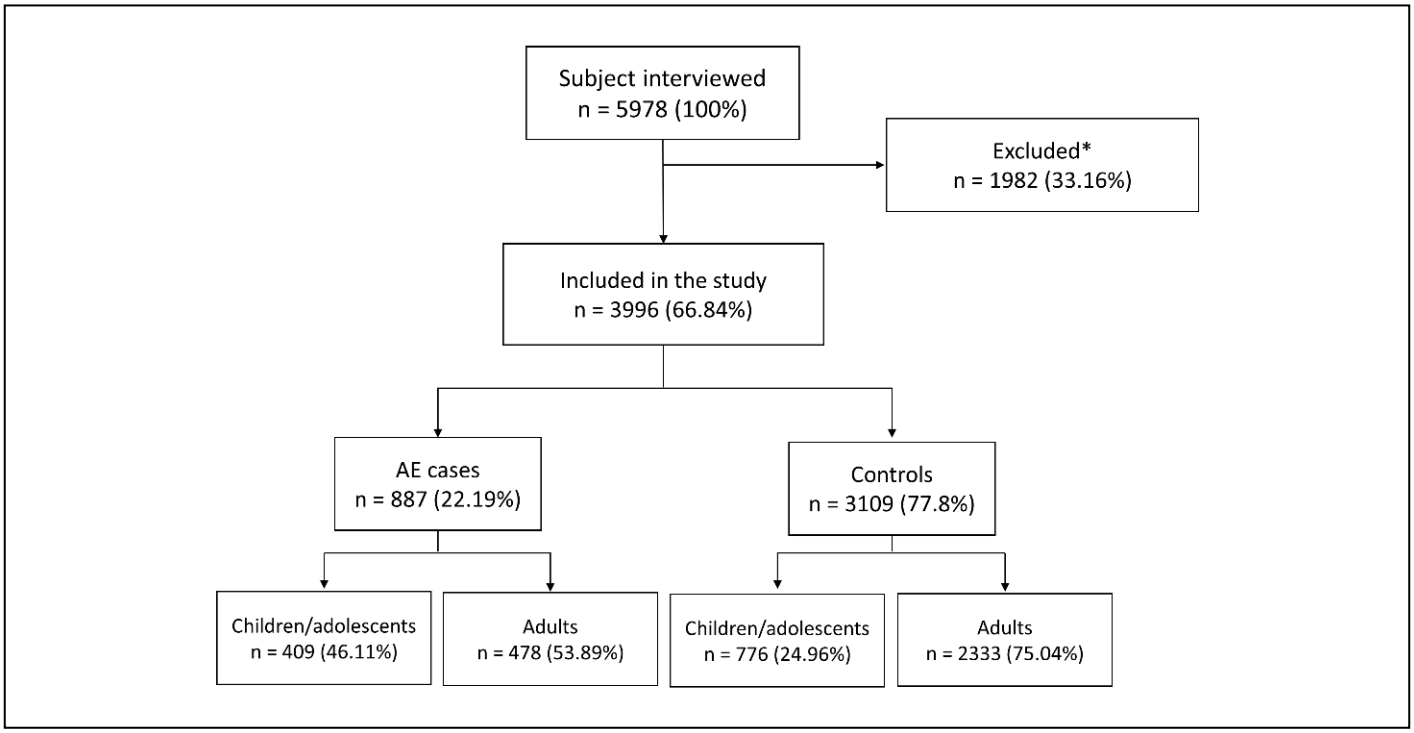

Figure 1. Flow chart of the study. Children/adolescents (1 – 17 years old); adults (16 – 59 years old).

*Exclusion reasons are presented in the body text.

Table 1. Weighted percentages by age and gender of children/adolescent´s characteristics and OR of the association between possible related factors and AE.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Gender							
Male	570	48.67	37.93 - 59.54	47.80	41.34 - 54.34	1.00	
Female	615	51.33	40.46 - 62.07	52.20	45.67 - 58.66	0.97	0.58 - 1.61
Age							
< 5 years	321	22.70	17.5 - 28.91	29.38	25.78 - 33.25	1.00	
5 - 11 years	589	52.99	42.31 - 63.41	51.84	45.67 - 57.95	1.32	0.82 - 2.13
12 - 17 years	275	24.31	16.25 - 34.7	18.79	13.03 - 26.31	1.67	0.87 - 3.23
Educational attainment							
No education/ Elementary school	877	75.01	64.29 - 83.34	81.73	73.91 - 87.6	1.00	
High school	235	24.99	16.66 - 35.71	18.27	12.4 - 26.09	1.49	0.75 - 2.97
Mother´s educational attainment							
No education/ Elementary school	210	21.28	13.91 - 31.13	16.37	11.76 - 22.32	1.00	
High school	593	50.14	38.98 - 61.29	52.08	45.53 - 58.56	0.74	0.37 - 1.48
Technician/ University/Postgrad	360	28.58	20.01 - 39.04	31.55	26.09 - 37.58	0.70	0.34 - 1.42
Shared rooms							
Yes	833	65.75	54.88 - 75.18	73.58	67.57 - 78.83	0.69	0.4 - 1.19
No	350	34.25	24.82 - 45.12	26.42	21.17 - 32.43	1.00	
Combustible material used for cooking							
Electricity	61	3.89	1.94 - 7.64	2.02	1.213 - 3.341	1.00	
Natural gas/gas cylinder/other	1120	96.11	92.36 - 98.06	97.98	96.66 - 98.79	0.51	0.21 - 1.23

...continuation table 1.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Animals living in the same house							
Yes	471	46.71	35.68 - 58.06	36.52	30.47 - 43.03	1.52	0.90 - 2.59
No	714	53.29	41.94 - 64.32	63.48	56.97 - 69.53	1.00	
Dogs							
Yes	336	33.03	22.27 – 45.92	25.46	20.07 – 31.72	1.44	0.77 - 2.70
No	849	66.97	54.08 – 77.73	74.54	68.28 – 79.93	1.00	
Cats							
Yes	99	8.06	4.99 – 12.76	6.22	4.24 – 9.04	1.32	0.69 - 2.54
No	1086	91.94	87.24 – 95.01	93.78	90.96 – 95.76	1.00	
Rodents							
Yes	14	0.79	0.19 – 3.21	0.82	0.34 – 1.95	0.96	0.18 - 5.15
No	1171	99.21	96.79 - 99.66	99.18	98.05 - 99.66	1.00	
Birds							
Yes	185	17.35	11.05 – 26.19	12.99	9.45 – 17.60	1.41	0.74 - 2.66
No	1000	82.65	73.81 – 88.95	87.01	82.40 – 90.55	1.00	
Other animals							
Yes	8	0.61	0.15 – 2.43	0.97	0.20 – 4.55	0.62	0.07 - 5.21
No	1177	99.39	97.57 – 99.85	99.03	95.45 – 99.80	1.00	
Fishes							
Yes	12	2.04	0.57 – 7.07	1.42	0.59 – 3.36	1.45	0.30 - 6.94
No	1173	97.96	92.93 – 99.43	98.58	96.64 – 99.41	1.00	

...continuation table 1.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Turtles							
Yes	10	0.33	0.08 – 1.36	0.49	0.20 – 1.20	0.67	0.12 – 3.64
No	1175	99.67	98.64 - 99.92	99.51	98.80 – 99.80	1.00	
Smoke							
Yes	16	5.20	1.719 - 14.69	3.10	0.9122 - 10	1.72	0.32 - 9.31
No	1169	94.80	85.31 - 98.28	96.90	90 - 99.09	1.00	
Passive smoke							
Yes	342	42.48	31.22 - 54.58	29.05	23.41 - 35.42	1.80	1.02 - 3.18
No	842	57.52	45.42 - 68.78	70.95	64.58 - 76.59	1.00	
Asthma in parents or siblings							
Yes	228	21.31	11.62 - 35.8	13.73	10.2 - 18.22	1.70	0.77 - 3.78
No	927	78.69	64.2 - 88.38	86.27	81.78 - 89.8	1.00	
AR in parents or siblings							
Yes	308	34.00	24.71 - 44.72	15.90	12.1 - 20.61	2.72	1.57 - 4.73
No	828	66.00	55.28 - 75.29	84.10	79.39 - 87.9	1.00	
AE in parents or siblings							
Yes	140	17.33	11.79 - 24.74	10.82	7.14 - 16.09	1.73	0.91 - 3.28
No	985	82.67	75.26 - 88.21	89.18	83.91 - 92.86	1.00	
Cesarean delivery							
Yes	400	33.03	22.37 - 45.78	29.57	24.27 - 35.47	1.18	0.64 - 2.14
No	765	66.97	54.22 - 77.63	70.43	64.53 - 75.73	1.00	

...continuation table 1.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Health care insurance							
Yes	1115	94.80	89.08 - 97.6	95.59	92.53 - 97.43	0.84	0.32 - 2.24
No	53	5.20	2.4 - 10.92	4.41	2.573 - 7.469	1.00	
Type of health care insurance							
Contributive/ Special	780	77.50	69.69 - 83.76	66.83	60.15 - 72.9	1.71	1.04 - 2.81
Subsidized	331	22.50	16.24 - 30.31	33.17	27.1 - 39.85	1.00	
Average hours of television per day							
≤ 2 hours	464	30.23	22.53 - 39.23	40.63	34.36 - 47.22	1.00	
> 2 hours	719	69.77	60.77 - 77.47	59.37	52.78 - 65.64	1.58	0.98 - 2.55
Average acetaminophen consumption							
At least once per week	154	10.36	5.191 - 19.59	15.12	11.04 - 20.36	3.37	1.21 - 9.38
At least once per month	198	29.45	19.09 - 42.48	12.74	8.729 - 18.23	1.80	0.74 - 4.4
At least four time per year	322	29.54	21.13 - 39.6	23.89	19.03 - 29.55	1.03	0.42 - 2.53
At least once per year	387	25.31	17.6 - 34.96	35.74	29.69 - 42.28	0.62	0.23 - 1.66
Never	124	5.35	3.2 - 8.82	12.51	9.036 - 17.05	1.00	
Eating habits in the last 12 months							
Meat							
Occasionally or never	44	4.14	1.688 - 9.81	7.30	3.972 - 13.02	1.00	
One or two times per week	1141	95.86	90.19 - 98.31	92.70	86.98 - 96.03	1.82	0.59 - 5.61

...continuation table 1.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Seafood							
Occasionally or never	823	66.31	55.31 - 75.78	74.69	68.6 - 79.95	1.00	
One or two times per week	361	33.69	24.22 - 44.69	25.31	20.05 - 31.4	1.50	0.86 - 2.61
Fruits							
Occasionally or never	107	5.16	3.12 - 8.44	9.89	6.016 - 15.82	1.00	
One or two times per week	1078	94.84	91.56 - 96.89	90.12	84.18 - 93.98	2.02	0.95 - 4.28
Vegetable							
Occasionally or never	198	15.47	9.786 - 23.57	17.01	12.34 - 22.98	1.00	
One or two times per week	987	84.53	76.43 - 90.21	82.99	77.02 - 87.66	1.12	0.59 - 2.13
Beans							
Occasionally or never	85	6.15	3.191 - 11.52	7.77	4.735 - 12.5	1.00	
One or two times per week	1100	93.85	88.48 - 96.81	92.23	87.5 - 95.26	1.29	0.54 - 3.06
Cereal							
Occasionally or never	69	7.64	3.705 - 15.09	4.71	2.445 - 8.883	1.00	
One or two times per week	1116	92.36	84.91 - 96.29	95.29	91.12 - 97.55	0.60	0.21 - 1.66
Pasta							
Occasionally or never	145	12.11	7.75 - 18.44	14.64	10.19 - 20.57	1.00	
One or two times per week	1039	87.89	81.56 - 92.25	85.36	79.43 - 89.81	1.24	0.65 - 2.37

...continuation table 1.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Rice							
Occasionally or never	15	0.71	0.2321 - 2.149	1.78	0.3599 - 8.334	1.00	
One or two times per week	1170	99.29	97.85 - 99.77	98.22	91.67 - 99.64	2.54	0.36 - 18.07
Butter							
Occasionally or never	551	44.21	33.2 - 55.82	46.68	40.39 - 53.08	1.00	
One or two times per week	634	55.79	44.18 - 66.8	53.32	46.92 - 59.61	1.10	0.65 - 1.88
Margarine							
Occasionally or never	877	75.36	66.35 - 82.59	72.51	65.4 - 78.63	1.00	
One or two times per week	308	24.64	17.41 - 33.65	27.49	21.37 - 34.6	0.86	0.5 - 1.5
Nuts and peanuts							
Occasionally or never	902	71.41	60.16 - 80.51	74.71	67.71 - 80.63	1.00	
One or two times per week	283	28.59	19.49 - 39.84	25.29	19.37 - 32.29	1.18	0.64 - 2.18
Potato							
Occasionally or never	58	2.36	1.246 - 4.419	4.30	2.131 - 8.489	1.00	
One or two times per week	1126	97.64	95.58 - 98.75	95.70	91.51 - 97.87	1.86	0.7 - 4.92
Milk							
Occasionally or never	102	10.16	5.31 - 18.58	7.55	4.801 - 11.68	1.00	
One or two times per week	1082	89.84	81.42 - 94.69	92.45	88.32 - 95.2	0.72	0.31 - 1.69

...continuation table 1.

Variable	n	Cases[a]		Controls[b]		Crude OR	95% CI
		%	95% CI	%	95% CI		
Eggs in the last 12 months							
Occasionally or never	65	3.48	1.607 - 7.35	5.65	3.185 - 9.822	1.00	
One or two times per week	1116	96.52	92.65 - 98.39	94.35	90.18 - 96.81	1.66	0.62 - 4.48
Hamburger/hot dogs or other fast food							
Occasionally or never	879	73.23	62.94 - 81.51	80.23	74.24 - 85.11	1.00	
One or two times per week	306	26.77	18.49 - 37.06	19.77	14.89 - 25.76	1.48	0.82 - 2.67
Frequency of public transportation passing through the street where subjects lived (n= 1172)							
Never	700	66.70	56.84 - 75.29	62.95	56.36 - 69.10	1.00	
Occasionally	184	13.58	8.045 - 22.01	13.05	9.23 - 18.12	0.98	0.47 - 2.04
Frequently	288	19.72	13.85 - 27.28	24.00	18.64 - 30.34	0.78	0.45 - 1.35
Socioeconomic status							
1 and 2 (low)	706	58.21	47.65 - 68.06	65.79	59.49 - 71.58	1.00	
3 and 4 (middle)	460	39.01	29.56 - 49.37	32.51	26.85 - 38.73	1.36	0.82 - 2.26
5 and 6 (high)	19	2.78	0.8733 - 8.47	1.70	0.57 – 5.00	1.85	0.36 - 9.52

[a] Affirmative answer to question 34: symptoms in the last year.
[b] Control: People who have not had any symptoms of disease (asthma, AR, AE) in the last year and people who have never had medical diagnosis of any of the diseases (asthma, AR, AE).

Table 2. Adults' significant associated factors with AE symptoms after multivariate analysis.

Variable	Cases (n = 478)	Controls (n = 2333)	Bivariate analysis		Multivariate analysis	
			Crude OR	95% CI	Adjusted OR	95% CI
Gender						
Male	128 (39.04)	888 (50.82)	1.00		1.00	
Female	350 (60.96)	1445 (49.18)	1.61	1.28 - 2.03	**1.49**	**1.15 - 1.93**
Educational attainment						
No education/ Elementary school	113 (22.95)	599 (25.86)	1.00		1.00	
High school	203 (43.42)	1162 (48.89)	1.00	0.76 - 1.31	0.96	0.70 - 1.31
Technician/University/ Postgrad	155 (33.64)	555 (25.25)	1.50	1.12 - 2.01	**1.49**	**1.06 - 2.10**
Animals living in the same house						
Cats						
Yes	54 (24.86)	187 (17.36)	1.57	1.07 - 2.31	**1.57**	**1.06 - 2.31**
No	167 (75.14)	855 (82.64)	1.00		1.00	
Smoke						
Yes	97 (25.44)	390 (19.67)	1.39	1.07 - 1.82	**1.60**	**1.19 - 2.14**
No	381 (74.56)	1943 (80.33)	1.00		1.00	
Asthma in parents or siblings						
Yes	103 (20.69)	329 (13.46)	1.68	1.28 - 2.20	1.28	0.94 – 1.75
No	373 (79.31)	1990 (86.54)	1.00		1.00	
AR in parents or siblings						
Yes	121 (25.8)	224 (9.232)	3.42	2.60 - 4.49	**2.21**	**1.61 - 3.03**
No	355 (74.2)	2091 (90.77)	1.00		1.00	

...continuation table 2.

Variable	Cases (n = 478)	Controls (n = 2333)	Bivariate analysis		Multivariate analysis	
			Crude OR	95% CI	Adjusted OR	95% CI
Atopic eczema in parents or siblings						
Yes	85 (19.09)	86 (3.721)	6.11	4.32 - 8.62	**4.66**	**3.18 - 6.82**
No	388 (80.91)	2232 (96.28)	1.00		1.00	
Average acetaminophen consumption						
At least once per week	72 (17.58)	539 (25.84)	2.30	1.64 - 3.22	**2.12**	**1.47 - 3.06**
At least once per month	145 (27.7)	461 (17.72)	1.88	1.35 - 2.62	1.82	1.28 - 2.59
At least four time per year	154 (30.64)	607 (23.92)	1.10	0.76 - 1.60	1.20	0.81 - 1.78
At least once per year	81 (17.1)	508 (22.77)	1.05	0.63 - 1.77	1.06	0.60 - 1.87
Never	26 (6.989)	213 (9.742)	1.00		1.00	
Eating habits in the last 12 months		888 (50.82)				
Meat						
Occasionally or never	27 (6.09)	71 (3.035)	1.00		1.00	
One or two times per week	451 (93.91)	2262 (96.96)	0.48	0.29 - 0.79	**0.45**	**0.27 - 0.74**
Seafood						
Occasionally or never	291 (65.89)	1274 (57.61)	1.00		1.00	
One or two times per week	187 (34.11)	1059 (42.39)	0.70	0.56 - 0.88	**0.71**	**0.56 - 0.91**
Frequency of public transportation passing through the street where subjects lived						
Never	377 (78.81)	1724 (75.06)	1.00		1.00	
Occasionally	34 (7.155)	313 (13.09)	0.52	0.35 - 0.78	**0.56**	**0.36 - 0.88**
Frequently	67 (14.03)	295 (11.85)	1.13	0.82 - 1.54	1.21	0.85 - 1.71

history of asthma, AR, and AE was found to be associated with AE symptoms in adults (OR 1.68, 95%CI: 1.28 to 2.20; OR 3.42, 95%CI: 2.60 to 4.49; and OR 6.11, 95%CI: 4.32 to 8.62, respectively), but after adjustment only AR (aOR 2.21, 95%CI: 1.61 to 3.03) and AE (aOR 4.66, 95%CI: 3.18 to 6.82) reached significance. Adults who reported educational attainment at Technician/University/Postgrad level had higher odds of reporting AE symptoms than adults who reported no education or elementary education (aOR 1.49, 95%CI: 1.06 to 2.10). Adults who reported having a cat at home had higher odds of reporting AE symptoms (aOR 1.57, 95%CI: 1.06 to 2.31). Active smoking and passive exposure to cigarette smoke were also associated with an increased risk for AE (OR 1.39, 95%CI: 1.07 to 1.82 and OR 1.30 95%CI: 1.02 to 1.67, respectively). After adjustment, only active smoking remained a risk factor for AE (aOR 1.60, 95%CI: 1.19 to 2.14). Contrary to expectations, adults who reported occasional frequency of public transportation passing through the street where they lived had lower odds for AE symptoms (aOR 0.56, 95%CI: 0.36 to 0.88) compared to those who reported no having public transportation passing through the street where they lived. Almost half of the entire adult population consumes acetaminophen once or more per month (43.4%). Its consumption was associated with disease presentation in a dose-dependent manner, being stronger at once per week (aOR 2.12, 95%CI: 1.47 to 3.06) than once per month aOR: 1.82, 95%CI: 1.28 to 2.59). Regarding eating habits, adults consuming meat and seafood at least once per week in the last 12 months before the survey date had lower odds (aOR 0.45, 95%CI: 0.27 to 0.74, and aOR 0.71, 95%CI: 0.56 to 0.91, respectively) in comparison with those reporting occasional consumption or never.

DISCUSSION

The present study is the first to evaluate potential factors associated with AE in a large sample of children/adolescents and adults in Colombia, a tropical country. The most essential AE risk factors in the adult population were a positive AE and AR family history. Adult women also presented a greater risk of AE. In children/adolescents, only the family history of AR was positively associated with this disease. Among the environmental factors in the adult population, we found acetaminophen consumption, smoking, and cats at home as risk factors; and meat and seafood eating as protective factors for AE. In the child/adolescent group, only acetaminophen consumption was found as a risk factor for AE. It is worth noting that these environmental factors also have been reported in temperate countries.[1,12]

A family history of atopy (i.e., asthma, AR, or AE) has shown a consistently high and significantly positive association with AE in numerous global studies.[12,20] Related to the family history of AE, it appears that a maternal history of AE seems to have stronger effects than a paternal history of AE;[21-23] meanwhile, when asthma, AR, and AE were considered together, they appeared to contribute similarly to child/adolescent AE.[14,24,25] Our study also showed a strong hereditary component in presenting AE in children/adolescents and adults. Although only the family history of AR was associated with AE in children/adolescents, this may be because we did not analyze separately maternal and paternal history of atopy. Our investigation also showed that AE is more common among adult women, a common observation in previous studies from temperate countries.[12,20,26] Like a study done in the tropics, this association was found in the urban population, but not in the rural setting,[27] possibly because of other risk/protective factors in those settings.[28]

The mechanisms underlying sex differences in AE presentation may be related to the effect of female hormones (i.e., estrogen and progesterone) on the immune system or directly upon the skin.[29] These hormones enhance type 2 responses and IL-17A production which synergistically may have a deleterious effect on the skin permeability barrier.[30] Likewise, women are more responsive to pruritogens and have more histamine receptors.[29]

Acetaminophen consumption was the most important risk factor for children/adolescents and adults. We found a dose-dependent association between acetaminophen use and adult AE, with a 1.82-fold and 2.12-fold increased risk associated with use at once per month and once per week, respectively. This has been found throughout different regions of the world, including tropical countries.[3,31-33] Reverse causation and recall bias have been suggested as possible explanations for this association.[31] However, other types of studies recently published support a causal relationship between acetaminophen and AE. A 5-year follow-up birth cohort study from Ethiopia found that acetaminophen use in the first 3 years of life is associated with an increased incidence between ages 3 and 5.[34] The highest risk was observed in the group reporting persistent use in the first three years of life, with more than a 3-fold increased risk of new-onset AE. Additionally, the authors from the ISAAC phase three study, in a re-analysis of their data, conducted two sets of multilevel logistic regression analyses in children and adolescents, using individual-level exposure data and school-level average exposure.[35] This analysis evaluated the average reported exposure (i.e., the prevalence) at the school level rather than the reported individual exposure to assess whether associations seen for these multiple variables at the individual level could be due to bias from reverse causation. In this manner, they showed that acetaminophen consumption at the school level remains a strong risk factor for both groups of age evaluated, providing evidence against this bias.[35]

Biological explanations for the association between acetaminophen and AE have been proposed. Acetaminophen decreases the amount of reduced glutathione available, leading to a reduction of glutathione-dependent enzymes.[36-38] Consequently, there is a lack of capacity to withstand oxidative stress, which may enhance the inflammatory response after an allergic or non-allergic stimulus. Likewise, glutathione depletion in antigen-presenting cells could result in type 2 immune response polarization.[39,40] Both mechanisms might drive the development and worsening of pre-existing allergies, including AE. Prior studies suggest a dose-dependent risk of developing allergic respiratory diseases as it leads to worsening lung function, and higher risk of respiratory diseases.[35,37-39] Nevertheless, considering

that most of these studies have an observational design of most of these studies, no causal relationship can be established, and this association may also be explained by reverse causation as patients with genetic predisposition to allergic diseases can be more likely to develop to febrile syndromes and thus use more acetaminophen.[38-40] Overall, further research is needed to assess this association.

In children, several studies have shown contradictory results about exposure to cats and AE presentation.[41] Our data showed that having a cat at home was not associated with AE in children/adolescents, but it was a risk factor for adult AE. This association, in adults, has not been extensively evaluated, but different studies have shown that sensitization to cat allergens is associated with persistent and severe AE.[42,43] Although we did not evaluate the sensitization rate in this population, studies conducted in tropical countries have found a high rate of sensitization to cat allergens, around 20 percent, in AE patients.[44] Also, a previous study completed in Colombia showed that AE patients present a high rate of polysensitization, including HDM, fungus, dogs, birds, and cockroaches, and when those patients were also sensitized to cat allergens the risk of severe and persistent AE increased.[45]

The westernization of dietary patterns has been suggested as a cause of the increase of allergic diseases over the world, including AE.[46-48] In this study, adults who ate meat and seafood one or two times per week in the past year were less likely to report AE symptoms. To our knowledge, there are no studies from tropical countries reporting this association. A previous study in children from Latin American countries showed that a more frequent intake of fruits was a protective factor for AE, while fast food was a risk factor for AE,[49] but there was no association with seafood and meat. Studies from other regions of the world have suggested meat and processed food consumption as a risk factor for AE.[48,50] However, in these studies, the authors analyzed meat and processed food as a single variable, which could lead to bias because processed food alone has been reported as a decisive risk factor for AE.[51] Seafood consumption, especially fish, suggests a diet rich in long-chain omega-3 fatty acids, which has been associated with a lower risk for AE or reduced disease severity.[52] Moreover, these environmental associations are biologically plausible. Higher fish/seafood intake supplies long-chain omega-3 fatty acids that generate specialized pro-resolving mediators and may dampen type-2/Th17 skin inflammation,[52] whereas processed/instant foods can favor pro-inflammatory pathways and gut–skin dysbiosis.[48,50,51] However, we must consider that participants could avoid food consumption due to food allergies, as our questionnaire did not evaluate this. Around 2% of adults in the general population have food allergies,[53] and adult atopic dermatitis patients show higher sensitization to foods than healthy individuals.[54] Therefore, we cannot conclude about the role of food allergy as an explanation for avoiding selected foods.

In adults, we found a positive association between active smoking and AE. This association has been confirmed by several studies,[55] but in tropical countries has not been thoroughly evaluated. It is well known that cigarette smoke has different harmful effects on the immune system,[56] but the direct effect on the skin is unclear.[57] Some studies have suggested that exposure to cigarette smoke, through the production of reactive oxygen species, might damage keratinocytes leading to impaired skin barrier function.[58,59]

We found differences in potential risk factors for AE between children/adolescents and adults. Several of the risk factors reported previously throughout the world for children/adolescents, such as active or passive smoking, were not significantly associated with our study.[55,60] These results may be due to the broad age assessed for children/adolescents. Interestingly, in our study, occasional exposure to bus traffic near the residence was associated with a lower risk of atopic dermatitis, contrasting with previous findings in the same population for asthma and allergic rhinitis. This discrepancy may reflect differences in how pollutants affect target organs: while the respiratory mucosa is directly exposed to inhaled air, the skin may require more intense or sustained exposure to trigger inflammation.[55] Unmeasured factors such as urban design or mitigation practices in areas with occasional traffic might also contribute. Additionally, the discrete categorization of exposure could have introduced statistical artifacts. Further studies are needed to confirm this finding and assess its biological plausibility.

For our study, we used an internationally validated questionnaire, the ISAAC questionnaire. However, the questionnaire and the methodology entail several limitations. First, in validation studies of similar questionnaires for children, good sensitivity but low specificity has been reported[61]. Second, we used different methods to collect data, which may influence the exposure to risk factors of the different age groups. Third, the questionnaire has not been validated for people under six years old and older than 14 years old. However, several studies around the world have used this questionnaire to evaluate the prevalence and risk factors of AE in those groups of age.[14,62] Additionally, a study conducted in Bangladesh, in children/adolescents and adults, showed a good agreement of the ISAAC questionnaire with the UK criteria, widely used criteria to screen for AE.[62] On the other hand, as AE status was ascertained using the ISAAC questionnaire rather than clinical examination, outcome misclassification is possible. Given the questionnaire's typically high specificity and moderate sensitivity, any non-differential misclassification would be expected to underestimate prevalence and bias associations toward the null.

In Colombia, as well as in other tropical countries, other causes of pruritus and injuries are common, which can hinder the diagnosis of AE. For example, scabies, a skin infestation caused by the mite *Sarcoptes scabiei,* is characterized by intense itching and superficial burrows; miliaria, common in hot and humid conditions, is a skin disease marked by small and itchy rashes which are especially common in children and infants.[63] Papular urticaria, a hypersensitivity reaction to insect bites, it is also prevalent in Latin American countries.[64-66] Since we did not use clinical validation of the results, this could lead to diagnostic misclassification, and it could be considered a study limitation.

Overall, our findings should be interpreted considering the geographic heterogeneity within Colombia. The Caribbean/insular setting is characterized by warm, humid climate, higher rates of helminthic infections, and perennial mite exposure has been linked to higher AE symptom prevalence in regional studies.[64-67] In this scenario, *Blomia tropicalis* is particularly relevant, unlike temperate settings where aeroallergen exposure is more seasonal. On the other hand, in the Andean cities (Bogotá, Medellín, Cali, Bucaramanga), higher altitude does not necessarily translate into lower mite exposure, as sensitization and detectable mite allergens have been reported even above 2,500 meters. These factors, together with differences in urbanization, socioeconomic conditions, health-care access, and air pollution, help explain the heterogeneity in AE prevalence observed among Colombian cities, which is similar across Latin America.[64-67] Finally, our study sampled six large urban centers, and findings are therefore generalizable to urban populations. Differences in diagnostic practices, health-care access, aeroallergen and irritant exposures, and the prevalence of competing dermatoses may yield different AE prevalence and risk-factor patterns in rural areas. Future research should include rural populations and incorporate clinical confirmation.

Another limitation is the cross-sectional design of the study; in this sense, the independent variables should be taken as association instead of causality. On the other hand, our results are only generalizable to urban areas of Colombia since we did not include rural settings. A recent study in Colombia showed a higher prevalence of AE for children/adolescents in rural zones than in urban cities, but it was not possible to assess the associated factors due to the small sample size of children with AE.[67] In that sense, it is still necessary to further evaluate the risk/protective factors for AE in the rural population. In summary, we found different factors associated with AE presentation that have been observed in temperate regions. We found that family history of atopy and acetaminophen consumption are the most significant risk factors for AE in children/adolescents and adults.

CONCLUSIONS

Our results support the contribution of both genetic and environmental factors to AE presentation and encourage further evaluation of these associated factors.

DECLARATIONS

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability

No datasets were generated or analyzed during the current study.

Human and animal rights and informed

Consent This article does not contain any studies with human, or animal subjects performed by any of the authors.

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