Risk factors for atopic and non-atopic asthma in a rural area of Ecuador

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ABSTRACT

Background Asthma has emerged as an important public health problem of urban populations in Latin America. Epidemiological data suggest that a minority of asthma cases in Latin America may be associated with allergic sensitisation and that other mechanisms causing asthma have been overlooked. The aim of the present study was to investigate risk factors for atopic and non-atopic asthma in school-age children.

Methods A cross-sectional study was conducted among 3960 children aged 6—16 years living in Afro-Ecuadorian rural communities in Esmeraldas province in Ecuador. Allergic diseases and risk factors were assessed by questionnaire and allergic sensitisation by allergen skin prick reactivity.

Results A total of 390 (10.5%) children had wheeze within the previous 12 months, of whom 14.4% had at least one positive skin test. The population-attributable fraction for recent wheeze associated with atopy was 2.4%. Heavy *Trichuris trichiura* infections were strongly inversely associated with atopic wheeze. Non-atopic wheeze was positively associated with maternal allergic symptoms and sedentarism (watching television (>3 h/day)) but inversely associated with age and birth order.

Conclusions The present study showed a predominance of non-atopic compared with atopic wheeze among schoolchildren living in a poor rural region of tropical Latin America. Distinct risk factors were associated with the two wheeze phenotypes and may indicate different causal mechanisms. Future preventive strategies in such populations may need to be targeted at the causes of non-atopic wheeze.

INTRODUCTION

An estimated 300 million people have asthma worldwide, and the prevalence has increased over recent decades among children living in industrialised countries,[1] and may also be increasing in developing countries where such increases may be linked to environmental changes associated with urbanisation and the acquisition of a 'modern' lifestyle.[1 2] The multicentre ISAAC (International Study of Asthma and Allergies in Childhood) phase III study estimated an annual increase in prevalence of current wheeze of 0.32% among adolescents aged 13—14 years between the 15 study centres in nine Latin American countries.[3]

Atopy is a consistent risk factor for asthma from many epidemiological studies. The proportion of asthma attributable to atopy in children has been estimated to be 38%, but there is considerable variation between studies (25—63%).[4] The ISAAC phase II study showed that the population fraction of asthma attributable to atopy differed greatly between countries according to economic development, being 40.7% in study centres from 'affluent' countries and 20.3% in centres from 'non-affluent' countries.[5]

A non-atopic phenotype is the most common presentation of childhood asthma in Latin American populations.[5—7] ISAAC phase II study centres in Latin America reported that only 11% of asthma was attributable to atopy.[5] These data suggest that a minority of asthma cases in Latin America may be associated with allergic sensitisation.[4]

Epidemiological studies in Europe have shown distinct patterns of risk factors for atopic and non-atopic asthma in children and adolescents[8—11]: atopic asthma was positively associated with other allergic symptoms[8] and asthma in siblings,[8] but was inversely associated with household pets[9]; non-atopic asthma was positively associated with recurrent chest infections at 2 years,[8] other early-life infections such as otitis media and croup,[10] household damp[9] or mould,[11] maternal smoking,[9 11] breast feeding for <3 months[9] and pet exposures during the first year of life.[10] Both atopic and non-atopic asthma were associated with a family history of asthma,[8—11] male sex[8 9 11] and a higher body mass index.[10] A recent study of children from a poor urban community in Southern Brazil suggested that bronchiolitis before the age of 2 years and *Ascaris lumbricoides* infection were risk factors for non-atopic asthma.[7]

Different patterns of risk factors for atopic and non-atopic asthma may indicate distinct phenotypes with different underlying causal mechanisms. The identification of such factors may provide novel information on potential causal mechanisms and future public health strategies that could be appropriately targeted for asthma prevention. The aim of the present study was to investigate risk factors for atopic and non-atopic asthma in school-age children living in a rural area of tropical Ecuador.

METHODS

Study area and population

The study was conducted among schoolchildren attending rural schools in Afro-Ecuadorian communities in the Districts of Eloy Alfaro and San Lorenzo, in Esmeraldas province in northeastern Ecuador. The characteristics of the study area and population have been described in detail elsewhere.[12]

Study design

A cross-sectional study was conducted among children aged 6—16 years to estimate the frequency of atopy and allergic diseases and identify

associated risk factors in rural populations. A convenience sample of 58 communities within the two study districts was selected. Annually updated censuses were used to identify children of school age in each community. The study was conducted in small communities (<250 pupils in community schools) with similar economic activities (ie, agriculture, hunting and logging). The mean community cluster size was 68.3 (range 15–230) children.

Data collection

Questionnaire

Data collection was performed between March 2005 and May 2007. The questionnaire was modified from the ISAAC phase II questionnaire translated into Spanish and has been extensively field tested. The questionnaire collected information about allergic diseases and risk factors as described elsewhere.[12] The questionnaire was administered to the parent or guardian in the presence of the child.

Allergen skin prick testing

Allergic sensitisation was measured by skin prick testing with seven allergen extracts (Greer Laboratories, Lenoir, North Carolina, USA): *Dermatophagoides pteronyssinus/farinae* mix, American cockroach (*Periplaneta americana*), *Alternaria tenuis*, cat, dog, '9 southern grass mix' and 'New stock fungi mix', positive histamine and negative saline controls. A positive reaction was defined as a mean wheal diameter at least 3 mm greater than the saline control 15 min after pricking the allergen onto the the volar side of the forearm using ALK lancets (ALK, Hungerford, UK).

Stool examinations

Single stool samples were collected and analysed for geohelminth eggs and larvae using the modified Kato Katz (quantification of *A lumbricoides* and *Trichuris trichiura*) and formol–ether concentration (detection of all geohelminths including hookworm and *Strongyloides stercoralis*) methods.[13] Infection intensities were expressed as eggs per gram (epg) of faeces.

Statistical analysis

Atopy was defined by the presence of at least one positive allergen skin test. The presence of recent wheeze was defined by reported wheezing during the previous 12 months. Recent wheeze was classified as atopic and non-atopic by the results of allergen skin tests.

Random effect logistic regression models were used to identify risk factors for recent wheeze and atopy allowing for two-level data structure (ie, individual and community levels). Variables with $p<0.20$ in univariate analyses were included in multivariate models. ORs and 95% CIs were calculated for each variable. Polytomous logistic regression that allows a single comparison group for more than one mutually exclusive outcome was used to predict independent risk factors for atopic and non-atopic asthma. Associations between risk factors and non-atopic or atopic asthma were compared with all children without asthma or atopy. We used a two-step approach in which the unadjusted association with the two outcomes for each variable was assessed. Variables associated with at least one of two outcomes with $p<0.20$ were retained in the models. Estimates of effect were calculated using ORs and 95% CIs with adjustment for clustering. Population-attributable fractions (PAFs) were calculated by: $PAF=P_{ew} \times (OR-1)/OR$ where P_{ew} is the prevalence of allergen skin test reactivity among children with recent wheeze. All statistical analyses were done using STATA, version 10.

Ethics

The study protocol was approved by the ethics committee of the Hospital Pedro Vicente Maldonado, Ecuador. Written informed consent was obtained from the parent of each child and signed minor assent from the child. The parent or guardian of each

Table 1 Characteristics of the study population of school-age children

Variables	n	%
Demographic and socioeconomic		
Age, years		
6–9	1531/3960	38.7
10–13	1386/3960	35.0
14–16	1043/3960	26.3
Sex		
Male	1905/3960	48.1
Female	2055/3960	51.9
Family income		
>US$150	732/3901	18.8
≤US$150	3169/3901	81.2
Maternal education level		
Complete secondary or higher	309/3853	8.0
Complete primary or incomplete secondary	1330/3853	34.5
Illiterate or incomplete primary	2214/3853	57.5
Household electric appliances		
None	700/3959	17.7
1–2	2164/3959	54.7
3–4	1095/3959	27.6
Allergic symptoms		
Asthma		
Wheeze ever	1249/3847	32.5
Wheeze in past year	406/3858	10.5
Wheeze attacks in past year		
1–3 attacks	311/3871	8.0
4–12 attacks	69/3871	1.8
≥12 attacks	27/3871	0.7
Woken by wheeze in past year	316/3346	9.4
Wheeze limiting speech in past year	146/3857	3.8
Wheeze during or after exercise in past year	224/3860	5.8
Rhinitis		
Rhinitis ever	480/3907	12.3
Rhinitis in past year without colds	346/3907	8.9
Rhinitis in past year with itchy eyes	246/3895	6.3
Eczema		
Eczema ever	330/3912	8.4
Itchy rash affecting flexures in past year	191/3912	4.9
Woken at night by itchy rash in past year	83/3881	2.1
Skin prick reaction ≥3 mm		
Any allergen	477/3821	12.5
House dust mite	252/3821	6.6
Mixed grass	73/3821	1.9
Cockroach	167/3821	4.4
Fungus	18/3821	0.5
Cat	15/3821	0.4
Dog	67/3821	1.8
Alternaria	8/3692	0.2
Geohelminth infections		
Any helminth	2851/3804	74.9
Ascaris lumbricoides	2013/3804	52.9
Trichuris trichiura	2178/3804	57.3
Hookworm	350/3804	9.2
Strongyloides stercoralis	16/3804	0.4

child was provided with a copy of all laboratory results, and all children with intestinal helminth infections were offered appropriate treatment.

RESULTS

A total of 3960 children participated in the study of which 3858 (97.4%) provided complete information on wheeze symptoms and 3821 (96.5%) underwent allergen skin testing. The number of children with complete data for both variables was 3726 (94.1%). We evaluated ~92% of school-age children resident in each community using updated censuses.

General characteristics of the study population are shown in table 1. A monthly income <US$150 represents one minimum wage. The prevalence of infection with any geohelminth parasite was 74.9% and the prevalence of *A lumbricoides*, *T trichiura*, hookworm and *S stercoralis* was 52.9%, 57.3%, 9.2% and 0.4%, respectively. The prevalence of skin test reactivity to any allergen was 12.5%. The prevalence of wheeze in the previous 12 months was 10.5%. None of the children with wheeze symptoms was taking regular asthma medications. The prevalence of rhinitis with itchy eyes within the previous 12 months and eczema (itchy flexural rash) was 6.3% and 4.9%, respectively. Of 390 children with recent wheeze, 14.4% (56) had allergen skin test reactivity while 85.6% (334) did not. The PAFs for recent wheeze, allergic rhinitis and eczema associated with atopy were 2.4%, 0% and 5.6%, respectively.

Table 2 Risk factors for allergen skin test reactivity

Risk factor	Total n=3.821	Skin test reactivity n=477	Univariate OR (95% CI)	Multivariate OR (95% CI)	p Value
Sex					
Female	1855	189 (10.2%)	1.0		
Male	1966	288 (14.6%)	1.48 (1.21 to 1.81)		
Age, years					
6–9	1491	130 (8.7%)	1.0*		
10–12	1340	186 (13.9%)	1.76 (1.38 to 2.24)		
13–16	990	161 (16.3%)	2.06 (1.60 to 2.66)		
Gas for cooking (3)†					
No	220	39 (17.7%)	1.0	1.0	
Yes	3598	438 (12.2%)	0.69 (0.47 to 1.02)	0.70 (0.47 to 1.04)	0.075
Consumption of river water					
No	1094	93 (8.5%)	1.0	1.0	
Yes	2727	384 (14.1%)	1.40 (1.02 to 1.93)	**1.40 (1.01 to 1.95)**	0.043
Birth order (1)†					
1st–3rd	2087	236 (11.3%)	1.0	1.0	
≥4th	1733	241 (13.9%)	1.24 (1.02 to 1.51)	1.20 (0.97 to 1.48)	0.090
Attending day care (117)†					
No	1973	262 (13.3%)	1.0	1.0	
<1 year old	462	45 (9.7%)	0.67 (0.46 to 0.97)	0.72 (0.50 to 1.05)	
≥1 year old	1269	154 (12.1%)	0.80 (0.64 to 1.01)	0.85 (0.67 to 1.07)	0.164
Contact with animals in farms at least once a week (5)†					
No	2625	290 (11.0%)	1.0	1.0	
Yes	1191	186 (15.6%)	1.38 (1.11 to 1.72)	**1.27 (1.01 to 1.59)**	0.042
Mother smoked in pregnancy (66)†					
No	3305	397 (12.0%)	1.0	1.0	
Yes	450	74 (16.4%)	1.35 (1.02 to 1.80)	1.24 (0.92 to 1.68)	0.163
Any helminth infection (103)†					
No	932	160 (17.2%)	1.0	1.0	
Yes	2786	309 (11.1%)	0.69 (0.54 to 0.87)	**0.69 (0.54 to 0.87)**	0.002
A lumbricoides infection (103)†					
No	1724	247 (14.1%)	1.0	1.0	
Yes	1971	222 (11.3%)	0.84 (0.68 to 1.05)	0.96 (0.76 to 1.20)	0.713
T trichiura infection (103)†					
No	1590	265 (16.7%)	1.0	1.0	
Yes	2128	204 (9.6%)	0.64 (0.51 to 0.80)	**0.64 (0.50 to 0.81)**	<0.001
Intensity of *A lumbricoides* infection, median (103)†					
Negative	2135	307 (14.4)	1.0*	1.0	
≤4620 epg	791	82 (10.4%)	0.78 (0.59 to 1.03)	0.82 (0.61 to 1.09)	
>4620 epg	792	80 (10.1%)	0.68 (0.51 to 0.91)	0.81 (0.60 to 1.10)	0.237
Intensity of *T trichiura* infection, median (103)†					
Negative	1759	290 (16.5%)	1.0*	1.0†	
≤490 epg	1030	112 (10.9%)	0.70 (0.54 to 0.89)	0.68 (0.52 to 0.88)	
>490 epg	929	67 (7.2%)	0.47 (0.34 to 0.64)	**0.49 (0.36 to 0.68)**	<0.001

Factors showing statistical significance in univariate analysis ($p<0.20$) are shown. Multivariate ORs and 95% CIs were calculated from random effect logistic regression model and adjusted for age and sex.
Models were made separately for: (1) any helminth; (2) prevalence of *Ascaris* and *Trichuris* infection; (3) intensity of *Ascaris* and *Trichuris* infection.
epg, eggs per gram.
*Test for trend, $p<0.001$.
†Numbers of missing values are given in parentheses.

Table 3 Risk factors associated with wheeze in the last 12 months

Risk factor	Total n=3.858	Wheeze n=406	Univariate OR (95% CI)	Multivariate OR (95% CI)	p Value
Sex					
Female	1852	199 (10.7%)	1.0		
Male	2006	207 (10.3%)	0.96 (0.78 to 1.18)		
Age (years)					
6–9	1496	199 (13.3%)	1.0		
10–12	1355	136 (10.0%)	0.73 (0.58 to 0.92)		
13–16	1007	71 (7.0%)	0.50 (0.37 to 0.66)*		
Maternal education level (83)†					
Complete secondary or higher	300	43 (14.3%)	1.0	1.0	
Complete primary or incomplete secondary	1308	116 (9.7%)	0.63 (0.43 to 0.92)	0.66 (0.43 to 1.02)	
Illiterate or incomplete primary	2167	207 (10.7%)	0.71 (0.50 to 1.02)	0.81 (0.52 to 1.24)	0.112
Family income (49)†					
>US$150	718	91 (12.7%)	1.0	1.0	
≤US$150	3091	311 (10.1%)	0.78 (0.60 to 1.01)	0.82 (0.61 to 1.10)	0.194
House construction (15)†					
Cane	392	46 (11.7%)	1.0	1.0	
Mixed (wood/cane)	247	16 (6.5%)	0.51 (0.28 to 0.93)	0.53 (0.28 to 1.02)	
Wood	1984	204 (10.3%)	0.82 (0.57 to 1.16)	0.78 (0.53 to 1.13)	
Mixed (wood/cement)	662	70 (10.6%)	0.86 (0.57 to 1.29)	0.81 (0.51 to 1.28)	
Brick/block/cement	558	70 (12.5%)	1.04 (0.69 to 1.57)	1.06 (0.67 to 1.67)	0.134
Gas for cooking (3)†					
No	234	32 (13.7%)	1.0	1.0	
Yes	3621	374 (10.3%)	0.70 (0.47 to 1.04)	0.73 (0.45 to 1.17)	0.171
Wood for cooking (4)†					
No	2925	323 (11.0%)	1.0	1.0	
Yes	929	82 (8.8%)	0.82 (0.62 to 1.08)	0.81 (0.58 to 1.12)	0.201
Consumption of river water					
No	1111	141 (12.7%)	1.0	1.0	
Yes	2747	265 (9.6%)	0.76 (0.59 to 0.97)	0.84 (0.65 to 1.09)	0.193
Excreta disposal (2)†					
Toilet or latrine	2411	231 (9.6%)	1.0	1.0	
Open field	1445	174 (12.0%)	1.23 (0.98 to 1.55)	**1.31 (1.02 to 1.68)**	0.034
Birth order (1)†					
1st–3rd	2096	249 (11.9%)	1.0	1.0	
≥4th	1761	156 (8.9%)	0.72 (0.58 to 0.89)	**0.70 (0.55 to 0.89)**	0.004
Attending day care (97)†					
No	2000	215 (10.7%)	1.0	1.0	
<1 year old	467	38 (8.1%)	0.71 (0.49 to 1.03)	0.80 (0.55 to 1.18)	
≥1 year old	1294	145 (11.2%)	1.05 (0.83 to 1.32)	1.11 (0.87 to 1.42)	0.254
Chicken outside house (3)†					
No	524	46 (8.8%)	1.0	1.0	
Yes	3331	359 (10.8%)	1.28 (0.91 to 1.78)	1.24 (0.86 to 1.77)	0.244
Cat inside house ever (6)†					
No	2174	205 (9.4%)	1.0	1.0	
Yes	1678	198 (11.8%)	1.23 (0.99 to 1.53)	1.26 (1.00 to 1.59)	0.051
Breast feeding (20)†					
No	69	12 (17.4%)	1.0	1.0	
Yes	3769	392 (10.4%)	0.55 (0.29 to 1.03)	0.55 (0.27 to 1.14)	0.111
Frequency of exercise (16)†					
Daily	2874	285 (9.9%)	1.0	1.0	
3 times a week	474	55 (11.6%)	1.18 (0.87 to 1.61)	1.18 (0.84 to 1.66)	
Once a week or less	494	63 (12.7%)	1.35 (1.00 to 1.81)	1.19 (0.85 to 1.68)	0.432
Maternal allergic diseases (93)†					
No	2307	160 (6.9%)	1.0	1.0	
Yes	1458	237 (16.3%)	2.59 (2.09 to 3.21)	**2.90 (2.30 to 3.67)**	<0.001
A lumbricoides infection (148)†					
No	1741	166 (9.5%)	1.0	1.0	
Yes	1969	222 (11.3%)	1.19 (0.96 to 1.49)	1.21 (0.96 to 1.54)	0.105
SPT for any allergen (132)†					
No	3261	334 (10.2%)	1.0	1.0	
Yes	465	56 (12.0%)	1.24 (0.91 to 1.69)	1.33 (0.95 to 1.86)	0.098

Continued

Table 3 Continued

Risk factor	Total n = 3.858	Wheeze n = 406	Univariate OR (95% CI)	Multivariate OR (95% CI)	p Value
SPT for house dust mite (132)†					
No	3480	357 (10.3%)	1.0	1.0	
Yes	246	33 (13.4%)	1.39 (0.94 to 2.04)	**1.59 (1.03 to 2.44)**	0.035
SPT for American cockroach (132)†					
No	3563	368 (10.3%)	1.0	1.0	
Yes	163	22 (13.5%)	1.39 (0.87 to 2.22)	1.16 (0.67 to 1.99)	0.590

Factors showing statistical significance in univariate analysis ($p<0.20$) are shown. Multivariate ORs and 95% CIs were calculated from random effect logistic regression model and adjusted for age and sex.
Models were made separately for skin test reactivity: (1) any allergen; (2) house dust mite; (3) American cockroach.
SPT, skin prick test.
*Test for trend, $p<0.001$.
†Numbers of missing values are given in parentheses.

Risk factors for allergen skin test reactivity

The prevalence of allergen skin test reactivity increased with age (test for trend, $p<0.001$) and was greater in males than females (table 2). Data for factors excluded from multivariate analyses (ie, univariate $p>0.20$) are provided in supplementary table 5 online. In multivariate analyses, consumption of river water (adjusted OR 1.40, 95% CI 1.01 to 1.95) and contact with animals in farms (adjusted OR 1.27, 95% CI 1.01 to 1.59) were independently associated with an increased risk of skin test reactivity. There was evidence for statistically significant inverse associations between allergen skin test reactivity and any geohelminth infection (adjusted OR 0.69, 95% CI 0.54 to 0.87) and *T trichiura* infection (adjusted OR 0.64, 95% CI 0.50 to 0.81). The prevalence of skin test reactivity declined with increasing intensities of infection with *T trichiura* (≤490 epg; adjusted OR 0.68, 95% CI 0.52 to 0.88; >490 epg: adjusted OR 0.49, 95% CI 0.36 to 0.68) (test for trend, $p<0.001$).

Risk factors for recent wheeze

Risk factors for recent wheeze included in the multivariate model are shown in table 3. Excluded factors (ie, univariate $p>0.20$) are shown in supplementary table 6 online. The prevalence of recent wheeze declined with age (test for trend, $p<0.001$). Multivariate analyses adjusting for age and sex showed that maternal history of allergic symptoms (adjusted OR 2.90, 95% CI 2.30 to 3.67) and use of an open field for excreta disposal (adjusted OR 1.31, 95% CI 1.02 to 1.68) were risk factors for recent wheeze, while birth order was inversely associated with recent wheeze (adjusted OR for ≥4th vs <3rd, 0.70, 95% CI 0.55 to 0.89). Although the majority of those with asthma were non-atopic, sensitisation to house dust mite was a risk factor for asthma (adjusted OR 1.59, 95% CI 1.03 to 2.44).

Risk factors for atopic and non-atopic asthma

Stratification of wheeze by allergen skin test reactivity showed distinct risk factors for atopic and non-atopic wheeze (table 4). Atopic wheeze was positively associated with male gender (adjusted OR 2.73, 95% CI 1.44 to 5.16) and inversely associated with intensity of *T trichiura* infection (>490 epg vs ≤490 epg: adjusted OR 0.24, 95% CI 0.09 to 0.63). For non-atopic wheeze, watching TV for >3 h per day (adjusted OR 1.51, 95% CI 1.06 to 2.16) and maternal allergic diseases (adjusted OR 3.24, 95% CI 2.42 to 4.32) were significant risk factors. The prevalence of non-atopic wheeze decreased with age (adjusted OR for ≥13 years old vs <13 years old, 0.39, 95% CI 0.25 to 0.62) and was inversely associated with birth order (adjusted OR 0.71, 95% CI 0.57 to 0.88).

A comparison of the effects for risk factors associated with atopic and non-atopic wheeze showed significant differences for sex (males with greater risk of atopic wheeze, $p=0.004$), age (decline in prevalence with increasing age for non-atopic wheeze, $p=0.019$), presence of a cat inside the house (associated with increased risk of atopic but decreased risk of non-atopic wheeze, $p=0.011$) and intensity of *T trichiura* infection (associated with decreased risk of atopic wheeze and no association for non-atopic wheeze, $p=0.010$).

DISCUSSION

Non-atopic asthma in childhood has been shown to be far more common than atopic asthma in non-affluent countries including in Latin America.[5] The present cross-sectional study identified risk factors for atopic and non-atopic asthma in school-age children living in small communities in a poor rural area of tropical Latin America. Only a small proportion of children with asthma (14.4%) in our study population had evidence of allergen skin test reactivity. The population fraction of asthma attributable to atopy was extremely low (2.4%)—much lower than previous estimates for industrialised countries of 38%[4] to 40.7%.[5] However, such a low PAF was perhaps not unexpected—the ISAAC phase II study showed values of PAF <10% in four of the 12 study centres from non-affluent countries.[5] Because the value of PAF is influenced by the prevalence of allergen skin test reactivity among wheezers and the association between skin test reactivity and wheeze, factors reducing these parameters will reduce the PAFs. Such factors are likely to include those reducing atopy or the process of T helper 2 (Th2) polarisation such as those associated with microbial and infectious exposures, and, in our own population, chronic helminth infections that can induce potent immune regulation.[2 14]

Previous studies in Latin America have shown a varying role for atopy in asthma.[6 7 15] Pereira *et al* studied 10-year-old children in a non-affluent community in Southern Brazil, and showed that the majority of wheeze and active asthma at the age of 10 years was non-atopic.[7] In a deprived urban area of Peru, recent asthma or respiratory symptoms were not associated with atopy in children aged 8–10 years.[6] In contrast, the study by Rona *et al* [15] in adults showed a high prevalence of recent wheeze in Brazil (19.4%) and Chile (27.4%), and the attributable fraction of sensitisation on asthma was high for both countries (54% for Brazil and 44% for Chile). However, 50% of Brazilian adults were sensitised, as were 22% of Chileans. One possible explanation for the difference between these studies is the age of the study population—the association between asthma and atopy may increase with age. Further, atopic asthma may be more persistent and likely to continue into adulthood.[16] Another factor that may be important is socioeconomic level—the populations studied in Brazil and Chile were relatively wealthy and the fraction of wheeze attributable to atopic sensitisation may increase with economic development.[5]

Table 4 Risk factors for atopic and non-atopic wheeze

Risk factors	Healthy n = 2.927 n (%)	Children with wheeze				
		Skin test reactivity n = 56		Non-skin test reactivity n = 334		
		n (%)	OR (95% CI)	n (%)	OR (95% CI)	p Value*
Demographic and socieconomic factors						
Sex						
Female	1449 (88.3)	18 (1.1)	1.0	174 (10.6)	1.0	
Male	1478 (88.2)	38 (2.3)	**2.73 (1.44 to 5.16)**	160 (9.5)	0.91 (0.71 to 1.16)	0.004
Age, years						
6—9	1153 (85.6)	18 (1.3)	1.0	176 (13.1)	1.0	
10—12	1022 (88.9)	23 (2.0)	1.34 (0.70 to 2.57)	105 (9.1)	**0.56 (0.42 to 0.74)**	0.019
13—16	752 (91.7)	15 (1.8)	0.95 (0.40 to 2.28)	53 (6.5)	**0.39 (0.25 to 0.62)**	0.082
Family income						
>US$150 dollars	520 (85.5)	9 (1.5)	1.0	79 (13.0)	1.0	
≤US$150	2367 (88.8)	47 (1.8)	1.29 (0.71 to 2.36)	251 (9.4)	0.78 (0.60 to 1.01)	0.112
Maternal education level						
Complete secondary or higher	220 (83.6)	7 (2.7)	1.0	36 (13.7)	1.0	
Complete primary or incomplete secondary	1044 (89.3)	16 (1.4)	0.33 (0.09 to 1.23)	104 (9.3)	0.75 (0.47 to 1.18)	0.256
Illiterate or incomplete primary	1635 (87.9)	33 (1.8)	0.53 (0.11 to 2.65)	191 (10.3)	0.80 (0.49 to 1.30)	0.626
Environmental factors						
Charcoal for cooking						
No	2685 (88.2)	47 (1.5)	1.0	314 (10.3)	1.0	
Yes	235 (89.0)	9 (3.4)	2.22 (0.74 to 6.61)	20 (7.6)	0.79 (0.46 to 1.35)	0.068
River water						
No	852 (86.4)	12 (1.2)	1.0	122 (12.4)	1.0	
Yes	2075 (89.0)	44 (1.9)	1.22 (0.61 to 2.46)	212 (9.1)	0.80 (0.55 to 1.16)	0.263
Excreta disposal						
Toilet or latrine	1835 (89.2)	34 (1.6)	1.0	189 (9.2)	1.0	
Open field	1091 (86.8)	22 (1.7)	1.16 (0.57 to 2.38)	144 (11.5)	1.31 (0.94 to 1.83)	0.752
Cat inside house presently						
No	1905 (88.4)	32 (1.5)	1.0	219 (10.1)	1.0	
Yes	1020 (88.1)	24 (2.1)	1.50 (0.86 to 2.63)	114 (9.8)	0.76 (0.56 to 1.02)	0.011
Cat inside house ever						
No	1656 (89.3)	28 (1.5)	1.0	171 (9.2)	1.0	
Yes	1.269 (87.1)	28 (1.9)	1.45 (0.85 to 2.46)	160 (11.0)	1.25 (0.94 to 1.66)	0.631
Pig around house presently						
No	1457 (87.5)	27 (1.6)	1.0	181 (10.9)	1.0	
Yes	1466 (89.0)	29 (1.8)	1.22 (0.71 to 2.12)	152 (9.2)	0.87 (0.65 to 1.17)	0.281
Contact with animals on farms						
No	2041 (88.4)	33 (1.4)	1.0	235 (10.2)	1.0	
Yes	883 (87.9)	23 (2.3)	1.04 (0.60 to 1.81)	98 (9.8)	1.01 (0.74 to 1.39)	0.925
Maternal- and family-related factors						
Birth order						
1st—3rd	1597 (86.9)	33 (1.8)	1.0	207 (11.3)	1.0	
≥4th	1330 (89.9)	23 (1.6)	0.61 (0.29 to 1.28)	126 (8.5)	**0.71 (0.57 to 0.88)**	0.703
Day care						
No	1490 (88.0)	32 (1.9)	1.0	172 (10.1)	1.0	
<1 year old	383 (91.0)	4 (0.9)	0.66 (0.20 to 2.19)	34 (8.1)	0.81 (0.55 to 1.19)	0.731
≥1 year old	979 (87.4)	18 (1.6)	1.04 (0.52 to 2.09)	123 (11.0)	1.08 (0.85 to 1.38)	0.911
Mother smokes presently						
No	2488 (88.4)	44 (1.6)	1.0	283 (10.0)	1.0	
Yes	413 (87.3)	12 (2.5)	1.10 (0.39 to 3.12)	48 (10.2)	1.46 (0.83 to 2.56)	0.648
Mother smoked in pregnancy						
No	2555 (88.3)	44 (1.5)	1.0	295 (10.2)	1.0	
Yes	333 (87.6)	11 (2.9)	2.18 (0.63 to 7.48)	36 (9.5)	0.94 (0.53 to 1.67)	0.195
Maternal allergic diseases						
No	1842 (92.4)	29 (1.5)	1.0	122 (6.1)	1.0	
Yes	1016 (81.6)	24 (1.9)	1.64 (0.78 to 3.42)	206 (16.5)	**3.24 (2.42 to 4.32)**	0.055
Sedentarism						
Frequency of watching television						
Never or sometimes	809 (89.2)	17 (1.9)	1.0	81 (8.9)	1.0	
1—3 h/day	1653 (88.3)	32 (1.7)	0.97 (0.56 to 1.65)	188 (10.0)	1.20 (0.85 to 1.68)	0.421
>3 h/day	459 (86.5)	7 (1.3)	0.86 (0.32 to 2.30)	65 (12.2)	**1.51 (1.06 to 2.16)**	0.294

Continued

Table 4 Continued

Risk factors	Healthy n = 2.927 n (%)	Children with wheeze				
		Skin test reactivity n = 56		Non-skin test reactivity n = 334		
		n (%)	OR (95% CI)	n (%)	OR (95% CI)	p Value*
Frequency of exercise						
Daily	2209 (89.0)	42 (1.7)	1.0	232 (9.3)	1.0	
3 times a week	349 (86.8)	7 (1.7)	0.94 (0.40 to 2.20)	46 (11.5)	1.23 (0.82 to 1.83)	0.562
Once a week or less	363 (85.8)	5 (1.2)	0.95 (0.36 to 2.48)	55 (13.0)	1.32 (0.81 to 2.14)	0.471
Geohelminth infections						
Intensity of *T trichiura*, median						
Negative	1301 (88.3)	36 (2.5)	1.0	136 (9.2)	1.0	
≤490 epg	803 (88.2)	14 (1.5)	0.49 (0.24 to 1.01)	93 (10.3)	1.00 (0.74 to 1.35)	0.072
>490 epg	746 (88.5)	5 (0.6)	**0.24 (0.09 to 0.63)**	92 (10.9)	1.00 (0.70 to 1.43)	0.010

Only the factors which had a significant effect ($p<0.20$) in the univariate analysis for at least one of two outcomes are shown.
The OR and 95% CIs were calculated using a polytomous logistic regression model.
epg, eggs per gram.
*p Value for the test comparing the ORs for atopic and non-atopic wheeze.

The observation of associations between different risk factors and atopic and non-atopic asthma suggests that they may be distinct asthma phenotypes. Male sex was positively associated with atopic wheeze while heavy *T trichiura* infection was strongly inversely associated with atopic wheeze; the prevalence of non-atopic wheeze declined with age and it was positively associated with maternal allergic diseases and watching television (>3 h/day) but inversely associated with birth order. Asthma is a heterogeneous disease with different clinical phenotypes. Longitudinal studies have provided evidence for three wheeze phenotypes in childhood[16]: (1) transient wheeze that is associated with impairment of lung function in early life and lower respiratory tract illnesses and may resolve by 6 years of age; (2) non-atopic wheezing occurring in the first 3 years of life that is associated with lower respiratory tract illnesses, may persist beyond 6 years and is not associated with atopy; and (3) atopic wheezing that starts before 6 years, may persist into adulthood, is strongly associated with atopy and has a more severe clinical course.

The hygiene hypothesis has tried to explain temporal trends in allergy prevalence in industrialised countries in the context of improvements in hygiene and reduced exposure to childhood infectious diseases. Our data provide some support for this hypothesis: variables related to hygiene (eg, low educational level, low income, consumption of river water, birth order, breast feeding and *T trichiura* infection) were negatively associated with recent wheeze, but only birth order and *T trichiura* infections were statistically significant. Birth order was also inversely associated with symptoms of eczema and rhinitis in this population (data not shown). A systematic review of the association between allergic disease and sibling effect (birth order, number of siblings, number of older siblings and family size) showed inverse associations for sibling effect with asthma/wheezing in 21 of 31 studies, with hay fever in 17 of 17 studies, and with eczema in nine of 11 studies.[17]

Asthma symptoms were inversely associated with hookworm infection but positively associated with the presence of *A lumbricoides* infection in a meta-analysis of cross-sectional studies,[18] and immunoglobulin E (IgE) sensitisation to *A lumbricoides* has been identified as a risk factor for wheeze in several studies.[19 20] There are very limited data on the association between intestinal helminth infections and atopic and non-atopic asthma. Pereira *et al*[7] provided data to suggest that *A lumbricoides* was an important risk factor for non-atopic asthma in a deprived community in Southern Brazil with a low prevalence of infection. Several previous studies from different geographic regions have shown inverse associations between allergen skin test reactivity and infections with the helminths *A lumbricoides*,[21–23] *T trichiura*[22–24] and *Schistosoma mansoni*.[14 25] In the present study *T trichiura* infections were inversely associated with both allergen skin test reactivity and atopic asthma, with evidence of a greater effect at higher parasite burdens. The apparent protective effect of *T trichiura* against atopic asthma may be mediated by reduced atopy. It is not clear how a purely enteric pathogen like *T trichiura* may have effects at distant tissues sites (ie, the skin and lung). Experimental infections of mice with *Heligmosomoides polygyrus*, an intestinal helminth that does not migrate through the lungs, are associated with a suppression of allergen-induced airway eosinophilia[26 27] and bronchial hyper-reactivity[26] induced by allergen sensitisation, an effect that appears to be mediated by $CD4^+CD25^+$ T cells.[27]

Time spent watching television is an indicator of sedentarism. A recent report provided evidence that duration of TV viewing was associated with the development of asthma in later childhood.[28] Our study demonstrated that watching television for >3 h per day was a risk factor only for non-atopic asthma. Some cross-sectional studies have reported a positive association between low physical activity and asthma,[29–31] and this may be related to complex effects of sedentarism on respiratory physiology.[32]

The principal methodological limitation with our study was its cross-sectional design and the potential for information and recall bias using questionnaire data. We selected a convenience sample that was likely to be representative of Afro-Ecuadorian children of school age living in small rural communities in the study districts. Because the sample was not random we cannot exclude biases affecting generalisability of our findings to other study populations. Atopy and geohelminth prevalence and intensity were both objectively measured. Another limitation was the relatively small number of children with atopy, limiting the power to detect associations with potential risk factors. Risk factors that showed either positive (OR ≥1.3) or negative (OR ≤0.7) associations with atopic wheeze and might have shown statistical significance with a larger sample size and more precise estimate of effect were: (1) protective factors—lower maternal educational level, fourth or more in birth order, day care during the first year of life and low infection intensity with *T trichiura* (compared with no infection); and (2) risk factors—charcoal for cooking, household cat, maternal smoking during pregnancy and maternal history of allergic diseases.

In conclusion, the present study shows a predominance of non-atopic compared with atopic wheeze among schoolchildren

living in a poor rural tropical region of Latin America. Further, there was evidence for different risk factors being associated with the two wheeze phenotypes that may suggest possible different causal mechanisms, and, therefore, has important implications for future preventive strategies.

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