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The effect of single and multiple infections on atopy and wheezing in children

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Abstract

Background—The current epidemic of asthma and atopy has been explained by alterations in immune responses related to reduction in childhood infections. However, the findings of epidemiologic studies investigating the association between infection with atopy and asthma have been inconsistent.

Objective—We sought to investigate the effect of single or multiple infections (pathogen burden) on atopy and wheeze in urban children from Latin America.

Methods—Specific IgE against aeroallergens (sIgE) and skin prick test (SPT) reactivity for the most common local allergens were measured in 1128 children aged 4 to 11 years. Data on wheezing and potential confounders were collected by questionnaire. Infections by 8 pathogens were assessed by using serology and stool examination. Associations of wheeze and atopic outcomes with single and multiple infections were analyzed by means of logistic regression.

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Results—Negative results for *Toxoplasma gondii* were associated with a higher prevalence of sIgE (≥0.70 kU/L), whereas negative results for *Ascaris lumbricoides*, *T gondii*, herpes simplex virus, and EBV were associated with a higher prevalence of SPT reactivity. Children with 3 or fewer infection markers had a higher prevalence of sIgE and SPT reactivity compared with those with 4 or more infection markers. However, isolated infections or pathogen burden were not associated with the prevalence of atopic or nonatopic wheeze.

Conclusion—The findings provide support for the idea that the hygiene hypothesis is operating in an urban Latin American context, but its expression is thus far restricted to the atopic status of patients and not the perceived asthma symptoms.

Keywords

Atopy; infections; pathogen exposure; allergen-specific IgE; skin prick test; wheezing illnesses; asthma

Asthma is among the most common chronic diseases worldwide, causing high morbidity and avoidable premature deaths. Asthma is a heterogeneous condition and is the final presentation of different etiologies and pathways that are associated with diverse and complex genetic backgrounds.1 Atopy is considered an important risk factor for asthma in developed societies.2 The International Study of Asthma and Allergies in Childhood Phase II study showed that a higher fraction of recent wheeze was attributable to atopy in affluent (41%) compared with nonaffluent (20%) countries.3 Therefore by far the majority of asthma observed in Latin America is likely to be nonatopic.4,5

The prevalence of both asthma and atopy has increased over recent decades, being most marked in developed countries but also in urban populations in developing countries.6 The causes of this increase are poorly understood, but temporal changes in environmental exposures, such as pollution,7 diet,8 and allergen exposure,9 have been implicated. However, a widely accepted explanation is the hygiene hypothesis, which is based on epidemiologic observations suggesting that populations living in conditions of improved hygiene have reduced exposure to childhood infections, leading to reduced priming of T_H1 or immune-regulatory responses that might protect against T_H2-induced allergic reactions.10 Such reactions are orchestrated by T_H2 cells11 that produce the cytokines IL-4, IL-5, IL-13, and IL-9, leading to an accumulation of inflammatory cells in tissues, such as the airways, and causing mucous production, bronchial constriction, and airways hyperreactivity.

There is a large body of evidence from experimental animal models and epidemiologic studies of human populations supporting a potentially protective role of exposures to a wide variety of pathogens against atopy and asthma.12–17 In developed countries associations between atopy or asthma and infections by viruses (hepatitis A,15 EBV,18 herpes simplex virus,19 and herpes zoster20), protozoa *(Toxoplasma gondii)*,21 and bacteria *(Helicobacter pylori)*22 have been explored, but results have not been consistent.23 In developing countries the studies have focused on the role of intestinal helminths (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms), which cause chronic infections, but the findings have been heterogeneous.24 Such conflicting data could be explained by factors such as age at infection and duration and intensity of infections.17 However, 2 recent systematic reviews

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and meta-analysis25,26 have shown that although *T trichiura* has no effect on asthma occurrence, *A lumbricoides* was associated with an increase, and hookworm was associated with a strong decrease in asthma.25 Regarding atopy, a protective effect was observed for infections with any of the 3 helminths.26

The mechanisms by which microorganisms and helminths might regulate allergic diseases have been extensively studied.17,27,28 The hygiene hypothesis, which originally emphasized the role of T_H1 cells in regulating T_H2 responses, has been modified to emphasize a role of regulatory T cells in the regulation of both T_H1- and T_H2-induced inflammatory responses through mechanisms that include the production of regulatory cytokines, such as IL-10 and TGF-β,28 and the expression of regulatory factors, such as the transcription factor forkhead box protein 3 and glucocorticoid-induced TNF receptor.29 Regulatory natural killer and B cells might also participate in this immune regulation.30,31 This so-called immune-regulatory network has been extensively studied in helminth-infected hosts, in whom chronic infections are associated with the tight regulation of allergic-type responses that allow parasites to survive but also protect the host against potentially damaging immune pathology.17,32 Similarly, this regulatory network might have a role during the development of chronic infections by pathogens that induce T_H1 immune responses. As for helminths, such immune regulation might allow pathogens to persist by attenuating chronic inflammation.33

It is a common feature, especially in less hygienic environments, for subjects to have cumulative courses of childhood viral, bacterial, or helminth infections. Although most studies have investigated the association between atopy or asthma and 1 or a few infections, a few studies, all conducted in developed countries, have investigated the association with the burden of infections accumulated over the life course,23,34–38 but no helminth infections were investigated in these studies because they rarely infect human subjects in these countries. In the present study we investigated the effect of current intestinal helminth (*A lumbricoides* and *T trichiura*) infections and markers of protozoal *(T gondii)*, bacterial *(H pylori)*, and viral (herpes simplex, herpes zoster, EBV, and hepatitis A) infections on atopy and wheezing in a cohort of children living in underprivileged neighborhoods of a large Latin American city.

Methods

Study population and data collection

The study was conducted in the city of Salvador, Northeastern Brazil, with a population of 2.8 million. The methods of this study have been reported elsewhere.39 Briefly, the entire study population consisted of 1445 children, part of a series of cohorts originally set up to study the effect of a city-wide sanitation program on child health during the period 1996 to 2004.39 The children were resurveyed in 2005 when they were aged 4 to 11 years, and new data were collected, including information on wheezing and risk factors for wheezing and allergic diseases, by using a Portuguese-adapted International Study of Asthma and Allergies in Childhood Phase II questionnaire.40 The study design was cross-sectional and nested within a cohort.

Skin prick tests (SPTs) were done with 7 common aeroallergens, the presence of serum specific IgE against aeroallergens (sIgE) was measured for 4 allergens (*Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Periplaneta americana*, and *Blattella germanica*), serum IgG levels were measured against 6 relevant pathogens, and fecal examination was done to detect intestinal helminth infections. Pulmonary clinical manifestations were classified as follows:

1. wheezing in the last 12 months (current wheeze);
2. wheezing in the last 12 months and at least 1 of the following:
   - **A.** asthma diagnosis,
   - **B.** wheezing with exercise in the last 12 months,
   - **C.** 4 or more episodes of wheezing in the last 12 months, or
   - **D.** waking up at night because of wheezing in the last 12 months (current wheeze plus symptoms); and
3. asthma ever in life.

All other children were classified as current nonwheezers. Because the prevalence of sIgE for each of the studied allergens was greater than SPT reactivity and the frequency of positive SPT responses among those without sIgE was very low (fungi, 0.5%; dog epithelium, 1.1%; and cat epithelium, 0.9%), atopy was defined as the presence of at least 1 serum antiaeroallergen IgE level of 0.70 kU/L or greater, irrespective of SPT results. Atopic and nonatopic wheezing was defined as symptoms of wheezing in the presence or absence, respectively, of a serum IgE level of 0.70 kU/L or greater for any of the tested aeroallergens.

Laboratory measurements

SPTs were performed on the right forearm of children with extracts of *D pteronyssinus*, *B tropicalis*, *B germanica*, *P americana*, dog and cat epithelia, and a fungi mix (*Aspergillus amstelodami*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terrus*, *Penicillium brevicompactum*, *Penicillium expansum*, *Penicillium notatum, Penicillium roqueforti*, *Cladosporium fulvum*, and *Cladosporium herbarum*; ALK-Abelló, São Paulo, Brazil). The extracts were pricked onto the skin with a disposable lancet (ALK-lancet, ALK-Abelló). The negative and positive controls were saline and histamine at 10 mg/mL, respectively. Readings were done after 15 minutes. Results were considered positive if the mean diameter of the wheal was equal to or greater than 3 mm after subtraction of the negative control.

Blood was collected and sera were frozen at −20°C until use. sIgE for *D pteronyssinus*, *B tropicalis*, *B germanica*, and *Pamericana* in serum was measured with the Pharmacia ImmunoCAP System IgE FEIA (Pharmacia, Uppsala, Sweden), according to the manufacturer's instructions. Results of sIgE measurement were considered positive in a child if levels of 0.70 kU/L or greater were detected for at least one of the 4 tested allergens.

Exposure to *T gondii* and *H pylori*, herpes simplex virus, varicella zoster virus, and EBV was determined by means of measurement of specific serum IgG levels with commercially available immunoassays (Diamedix, Miami, Fla). Anti–hepatitis A virus serum IgG was

detected with kits from ADALTIS (Toronto, Ontario, Canada). Seropositive test results were defined as recommended by the manufacturers.

For detection of intestinal helminths, 2 fecal samples were collected 2 days apart and analyzed by using a sedimentation method41 and the Kato-Katz thick-smear technique42 to determine the presence and numbers of helminth eggs *(T trichiura*, *A lumbricoides*, hookworms, and *Schistosoma mansoni)*. Because only a few children were infected with *S mansoni* and hookworms, these parasites were not considered further in the present analysis.

Definition of infection, pathogen burden, and selection of pathogens

Infection (or pathogen exposure) was defined by the presence of positive serologic test results for IgG to 6 pathogens (*T gondii*, *H pylori*, EBV, and hepatitis A, herpes simplex, herpes zoster viruses) and the presence of intestinal helminth eggs in stool samples (*A lumbricoides* and *T trichiura*). In addition to analyzing pathogen burden based on the number of infections, we used a threshold of 3 or fewer infections to distinguish light from heavy infection, as used by Janson et al.23 These pathogens were selected because they cause chronic infection and have been reported to be associated with decreased prevalence of atopy or clinical manifestations of allergies15,18–21,43,44 or have been shown to decrease allergen-specific IgE levels and lung inflammation in experimental animal models.12,13

Ethical considerations

Ethical approval was provided by the Ethical Committee of the Instituto de Saúde Coletiva, Universidade Federal da Bahia and by the Brazilian National Ethical Committee. Written informed consent forms detailing all procedures to be carried out on the children were signed by a parent or the legal guardian of each child.

Statistical analyses

Initially, we assessed the association between the presence and burden of markers of current or past infections as exposures and sIgE and SPT results to allergens and current wheeze, current wheeze plus symptoms, and asthma ever as outcomes. We repeated the analysis for current wheeze and current wheeze plus symptoms separately for atopic and nonatopic status, but we did not include asthma ever in this analysis because we only have current atopic status and this is unlikely to correspond to atopic status at the time of the asthma diagnosis. Potential confounders for these associations were as follows: maternal educational level, household connection to the municipal sewage system, frequency of changing bed linen, number of siblings, presence of a cat or dog in the house, parental smoking, presence of mold or dampness on the walls of the house (by inspection), and whether the child had attended day care. The effect of markers of infection was analyzed one by one or in 2 aggregated approaches: aggregated into 4 levels (0-1, 2, 3, or 4-8 markers) or into light burden (0-3 markers) and heavy burden (4-8 markers). Variables that remained statistically significant by using a stepwise process remained in the final multivariate logistic regression model.45 Because wheezing in early childhood is frequently associated with respiratory tract infections and might not to be associated with markers of chronic infection,46–49 we repeated the analysis using the same exposures and outcomes but stratifying by

age group (4-5, 6-7, and 8-11 years). The univariate and multivariate logistic regression analyses were done with SPSS software, version 16 (SPSS, Inc, Chicago, Ill).

Results

Among 1445 eligible children, the prevalence of current wheezing symptoms was 22.6%, an sIgE level of 0.70 kU/L or greater in serum for at least 1 allergen was present in 37.7%, and a positive SPT response for at least 1 allergen (≥3 mm) was found in 30.3%. The present analysis is based on 1182 of the 1445 eligible children for whom complete data were available. No statistically significant differences were seen in the studied risk factors and outcomes between those children excluded and included in the analysis (data not shown). Frequencies of the confounding variables considered in the multiple logistic regression analyses were as follows: male sex, 53.6%; age, mean of 7.2 years (age frequencies: 4-5 years, 26.3%; 6-7 years, 40.9%; and 8-11 years, 32.8%); and maternal education (21.9% had primary education, 47.2% had incomplete secondary education, and 30.9% had complete secondary or higher-level education). The presence of an sIgE level of 0.70 kU/L or greater to at least 1 allergen was found in 448 (37.9%) children, SPT reactivity for at least 1 allergen was found in 359 (30.4%) children, atopic wheezing was found in 125 (10.5%) children, and nonatopic wheezing was found in 138 (11.6%) children.

Tables I and II show the prevalence of each of the 8 past or present studied infections. The associations adjusted for confounders between each infection and the 5 outcomes (presence of sIgE level ≥0.70 kU/L and SPT reactivity for ≥1 allergen, current wheeze with and without other asthma symptoms, and asthma ever in life) are shown. Compared with seropositive children, those seronegative for *T gondii* had a higher prevalence of sIgE (adjusted odds ratio [OR], 1.48; 95% CI, 1.07-2.05). Similarly, a positive SPT response was significantly associated with negative serology for *T gondii* (adjusted OR, 1.60; 95% CI, 1.13-2.28), herpes simplex virus (adjusted OR, 1.48; 95% CI, 1.15-1.91), EBV (adjusted OR, 1.63; 95% CI, 1.12-1.91), and the presence of *A lumbricoides* eggs in stool (adjusted OR, 1.60; 95% CI, 1.10-2.33). Current wheeze with or without other asthma symptoms and asthma ever in life were not significantly associated with markers of any of the studied past or present infections isolated. Tables E1 to E3, presenting a more detailed analysis stratified by age group, can be found in this article's Online Repository at www.jacionline.org.

Tables III and IV show the associations between burden of infection and the studied outcomes (positive sIgE level or SPT response, current wheeze or current wheeze with symptoms, and asthma ever in life) in children stratified by age group, by number of markers of infection (0-1, 2, 3, or 4-8), or by using a cutoff of light (0-3) or heavy (4-8) burden of infection. In children 4 to 6 years old, no statistically significant association was found between burden of infection and any of the studied outcomes.

Children 6 to 7 years old with 3 markers of infection had less asthma ever than children with 4 to 8 markers of infection (OR, 0.26; 95% CI, 0.07-0.96) or with 0 to 1 and 2 markers of infection, and the prevalence of a positive SPT response was higher in children with a light than a high infection burden (OR, 1.64; 95% CI, 1.02-2.65). In the 7- to 11-year age group, having 0 to 1, 2, or 3 infections was positively associated with SPT reactivity compared with

having 4 to 8 infections in a dose-dependent manner (ORs of 1.83 [95% CI, 1.03-3.23], 2.62 [95% CI, 1.45-4.74], and 2.70 [95% CI, 1.30-5.56], respectively). Children with a light burden of infection had a higher prevalence of positive SPT responses than children with a heavy burden of infection (OR, 2.24; 95% CI, 1.38-3.64). For sIgE only, lightly infected children had more positive responses than heavily infected children (OR, 1.59; 95% CI, 1.01-2.50).

Also in Table III, for all age groups, children with decreasing numbers of markers of infection had an increasing prevalence of positive sIgE and SPT results. For both sIgE and SPT result, this was significant only for the comparison between children with 0 to 1 markers and 4 to 8 markers (ORs of 1.45 [95% CI, 1.01-2.06] and 1.80 [95% CI, 1.22-2.66], respectively) and for the comparison between those with a light and those with a heavy burden of infection (ORs of 1.34 [95% CI, 1.02-1.76] and 1.70 [95% CI, 1.26-2.29], respectively).

In Tables V and VI we show the association of infection burden with the atopic and nonatopic phenotypes of the respiratory clinical manifestations studied in children stratified or not by age. In children younger than 6 years, having 3 infections was negatively associated with current wheeze compared with having 4 to 8 infections (OR, 0.29; 95% CI, 0.08-0.98).

Discussion

We investigated the effects of markers of 8 different infections, either individually or aggregated, on the prevalence of atopy (sIgE results) and wheeze and asthma among underprivileged children in an urban center in Latin America. The absence of markers of 4 infections (*H simplex*, EBV, *T gondii*, and *A lumbricoides*) increased the prevalence of positive SPT responses, but only 1 *(T gondii)* increased the prevalence of positive sIgE levels. None appeared to affect the prevalence of wheezing or asthma. Children with a light burden of infection showed an increased prevalence of positive SPT and sIgE results compared with those with a heavy infection burden; this was stronger in terms of SPT than IgE responses. The negative association between markers of infection and markers of atopy was stronger in the oldest age group. Burden of infection was not associated with current wheeze (neither atopic nor nonatopic), current wheeze plus symptoms (neither atopic nor nonatopic), or asthma ever. The fact that the effect of burden of infection on SPT and sIgE results is more marked in older children is consistent with a longer duration of infection having a stronger downmodulating effect on allergic inflammatory reactions.17,28

As far as we are aware, this is the first study to investigate the association between atopy and wheezing and a large range of different pathogens outside of Europe and the United States. This is of particular interest to proponents of the hygiene hypothesis given the high prevalence of asthma symptoms in Latin American populations50 in spite of relatively unhygienic environments.4,51

Studies from developed countries have provided evidence for strong inverse associations between increasing burden of infection and the prevalence of positive SPT and sIgE results,

allergic asthma, or rhinitis.23,34–38 For instance, Janson et al23 compared 3 countries with different living conditions in Europe and found that those with fewer infections (generally in more affluent populations) had a higher prevalence of atopy and allergic symptoms.

An inverse association between infections, particularly of helminth origin, and positive SPT responses has been reported in nonaffluent populations from Latin America and Africa.26 In the population of the current study, an association was described between *T trichiura* infection in early childhood and a reduced prevalence of positive SPT responses in later childhood, even in the absence of *T trichiura* infection at the time of skin testing in later childhood.44 However, the study of helminth infections in isolation only provides a partial picture of the infections that might be involved in the downregulation of SPT reactivity. The relatively weaker effect of helminths in reducing the prevalence of positive sIgE results compared with positive SPT responses could be attributed to possible cross-reactivity between homologous allergens shared between helminths (and perhaps also ectoparasitic infections, such as scabies, that are present in the population) and aeroallergens.51–55 This phenomenon could attenuate the apparent downregulatory effects induced by other nonhelminth pathogens.

On reflection, the lack of association between burden of infection and wheeze found in our study is not so surprising given that 75% of the wheeze in this population is not attributable to atopy.5,51 The lack of association between burden of infection and atopic wheeze in the presence of an effect of SPT and especially sIgE results requires explanation. We can envisage at least 3 lines of argument. First, much of our asthma, although apparently associated with atopy, might be mediated through nonatopic mechanisms, resulting in the high prevalence of atopy in nonasthmatic subjects.5 Second and third are the cross-reactivity between helminth allergens and aeroallergens52–55 and the lack of power, although our sample size was large.

Our study does have important strengths. To our knowledge, it is the first study to investigate the associations between multiple pathogen exposures in childhood and atopy and wheezing in a developing country context, and importantly, we were able to study the effects of helminth infections in the context of other relevant nonhelminth pathogens that cause chronic infections in our study population.

A limitation of this study is the cross-sectional design that limits our ability to infer the presence of chronic infections using serology (for bacterial, protozoal, and viral infections). Although our study was nested within a cohort, we were unable to analyze prospectively the effects of pathogen exposures on study outcomes. A positive test result cannot distinguish present from past resolved infections, despite its widespread use in epidemiologic studies.15,19,21,23,34,36

In summary, our results are consistent with multiple pathogen exposures, particularly to chronic infections, leading to a more robust immune regulation and less atopy. The observed reduction in the prevalence of atopy, mostly through effects on SPT reactivity and less markedly on sIgE results, provides support for the idea that the hygiene hypothesis is operating in this urban Latin American context, but its expression is thus far restricted to the

allergic status of subjects and not on the perceived asthma symptoms. Further population-based research, including long-term birth cohorts, are necessary to clarify the reasons for the lack of association between infections and atopic asthma and to monitor the long-term consequence on asthma occurrence of the environmental changes ongoing in Latin America.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

OR	Odds ratio
sIgE	Specific IgE against aeroallergens
SPT	Skin prick test

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Clinical implications: The study provides support for a role of childhood exposures to pathogens in reducing the prevalence of atopy, but not wheezing, in an urban population of children in Latin America.

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Table I

Associations between the prevalence of chronic infections with positive sIgE results, skin reactivity (positive SPT responses) to aeroallergens in children from 4 to 11 years old (n = 1182)

	No. of positive sIgE results (≥0.70 kU/L)*		No. of positive SPT responses*	
Infections	**No. (%)**	**OR (95% CI)†**	**No. (%)**	**OR (95% CI)†**
T gondii				
Yes (n = 217 [18.4%])	67 (30.9)	**1**	50 (23.0)	**1**
No (n = 965 [81.6%])	381 (39.5)	**1.48 (1.07-2.05)**	309 (32.0)	**1.60 (1.13-2.28)**
H pylori				
Yes (n = 328 [27.7%])	122 (37.2)	1	95 (29.0)	1
No (n = 854 [72.3%])	326 (38.2)	1.06 (0.81-1.39)	264 (30.9)	1.12 (0.84-1.49)
Hepatitis A virus				
Yes (n = 196 [16.6%])	73 (37.2)	1	59 (30.1)	1
No (n = 986 [83.4%])	375 (38.0)	1.03 (0.75-1.43)	300 (30.4)	1.01 (0.71-1.41)
Herpes zoster virus				
Yes (n = 536 [45.3%])	200 (37.3)	1	160 (29.9)	1
No (n = 646 [54.7%])	248 (38.4)	1.05 (0.83-1.34)	199 (30.8)	1.07 (0.83-1.38)
Herpes simplex virus				
Yes (n = 644 [54.5%])	232 (36.0)	1	171 (26.6)	**1**
No (n = 538 [45.5%])	216 (40.1)	1.16 (0.91-1.48)	188 (34.9)	**1.48 (1.15-1.91)**
EBV				
Yes (n = 1046 [88.5%])	386 (36.9)	1	304 (29.1)	**1**
No (n = 136 [11.5%])	62 (45.6)	1.42 (0.99-2.05)	55 (40.4)	**1.63 (1.12-1.91)**
A lumbricoides				
Yes (n = 190 [16.1%])	73 (38.4)	1	43 (22.6)	**1**
No (n = 992 [83.9%])	375 (37.8)	0.99 (0.71-1.38)	316 (31.9)	**1.60 (1.10-2.33)**
T trichiura				
Yes (n = 128 [10.8%])	44 (34.4)	1	31 (24.2)	1
No (n = 1054 [89.2%])	404 (38.3)	1.28 (0.86-1.90)	328 (31.1)	1.43 (0.92-2.20)

Boldface numbers are statistically significant.

*Positive sIgE and SPT results for at least 1 tested allergen.

†Adjusted for sex, age, maternal education, and parental asthma.

Table II

Associations between the prevalence of chronic infections and current wheeze, current wheeze plus symptoms, and asthma ever in life in children from 4 to 11 years old (n = 1182)

	Current wheeze		Current wheeze plus symptoms		Asthma ever in life	
Infections	**No. (%)**	**OR (95% CI)***	**No. (%)**	**OR (95% CI)***	**No. (%)**	**OR (95% CI)***
T gondii						
Yes (n = 217 [18.4%])	69 (31.8)	1	53 (24.4)	1	19 (8.8)	1
No (n = 965 [81.6%])	275 (28.5)	0.75 (0.54-1.05)	210 (21.8)	0.76 (0.53-1.10)	61 (6.3)	0.59 (0.33-1.04)
H pylori						
Yes (n = 328 [27.7%])	85 (25.9)	1	60 (18.3)	1	13 (4)	1
No (n = 854 [72.3%])	259 (30.3)	1.14 (0.85-1.53)	203 (23.8)	1.28 (0.92-1.79)	67 (7.8)	2.03 (1.09-3.79)
Hepatitis A virus						
Yes (n = 196 [16.6%])	54 (27.6)	1	41 (20.9)	1	17 (8.7)	1
No (n = 986 [83.4%])	290 (29.4)	1.04 (0.72-1.48)	222 (22.5)	1.05 (0.71-1.55)	63 (6.4)	0.59 (0.33-1.07)
Herpes zoster virus						
Yes (n = 536 [45.3%])	155 (28.9)	1	118 (22.0)	1	36 (6.7)	1
No (n = 646 [54.7%])	189 (29.3)	0.88 (0.68-1.15)	145 (22.4)	0.89 (0.67-1.19)	44 (6.8)	0.98 (0.61-1.58)
Herpes simplex virus						
Yes (n = 644 [54.5%])	184 (28.6)		134 (20.8)	1	43 (6.7)	1
No (n = 538 [45.5%])	160 (29.7)	0.96 (0.74-1.26)	129 (24.0)	1.10 (0.83-1.47)	37 (6.9)	0.89 (0.55-1.43)
EBV						
Yes (n = 1046 [88.5%])	296 (28.3)	1	229 (21.9)	1	68 (6.5)	
No (n = 136 [11.5%])	48 (35.3)	1.43 (0.97-2.12)	34 (25.0)	1.24 (0.81-1.91)	12 (8.8)	1.33 (0.68-2.59)
A lumbricoides						
Yes (n = 190 [16.1%])	68 (35.8)	1	49 (25.8)	1	12 (6.3)	1
No (n = 992 [83.9%])	276 (27.8)	0.72 (0.51-1.02)	214 (21.6)	0.87 (0.59-1.28)	68 (6.8)	1.10 (0.56-2.15)
T trichiura						
Yes (n = 128 [10.8%])	39 (30.5)	1	196 (23.2)	1	8 (6.2)	1
No (n = 1054 [89.2%])	305 (28.9)	0.92 (0.61-1.41)	233 (22.1)	0.96 (0.60-1.51)	72 (6.8)	0.96 (0.44-2.12)

*Adjusted for sex, age, maternal education, and parental asthma.

Table III

Associations between burden of infection with detectable (≥0.70 kU/L) sIgE levels in serum, positive SPT responses to aeroallergens in children from 4 to 11 years old, stratified by age

	Positive sIgE results (≥0.70 kU/L)*		Positive SPT response*	
Markers of infections (no. and burden)	**No. (%)**	**OR (95% CI)†**	**No. (%)**	**OR (95% CI)†**
4-5 y (n = 311)				
4-8 (n = 62 [19.9%])	21 (33.9)	1	18 (29.0)	1
3 (n = 70 [22.5%])	26 (37.1)	1.26 (0.70-2.61)	17 (24.3)	0.80 (0.37-1.76)
2 (n = 96 [30.9%])	40 (41.7)	1.51 (0.76-2.99)	30 (31.3)	1.15 (0.56-2.34)
0-1 (n = 83 [26.7%])	29 (34.9)	1.30 (0.62-2.70)	24 (28.9)	1.11 (0.52-2.38)
Heavy (4-8; n = 62 [19.9%])	21 (33.9)	1	18 (29.0)	1
Light (0-3; n = 249 [80.1%])	95 (38.1)	1.36 (0.74-2.51)	71 (28.5)	1.02 (0.54-1.93)
6-7 y (n = 483)				
4-8 (n = 135 [28.0%])	48 (35.6)	1	29 (21.5)	**1**
3 (n = 123 [25.5%])	47 (38.2)	1.09 (0.65-1.84)	39 (31.7)	1.61 (0.92-2.84)
2 (n = 129 [26.7%])	47 (36.4)	1.08 (0.64-1.81)	42 (32.6)	1.62 (0.92-2.85)
0-1 (n = 96 [19.9%])	43 (44.8)	1.41 (0.81-2.44)	33 (34.4)	1.72 (0.94-3.13)
Heavy (4-8; n = 135 [27.9%])	48 (35.6)	1	29 (21.5)	1
Light (0-3; n = 348 [72.1%])	137 (39.4)	1.16 (0.76-1.78)	114 (32.8)	**1.64 (1.02-2.65)**
7-11 y (n = 388)				
4-8 (n = 139 [35.8%])	44 (31.7)	**1**	31 (22.3)	**1**
3 (n = 110 [28.4%])	43 (39.1)	1.46 (0.86-2.50)	37 (33.6)	**1.83 (1.03-3.23)**
2 (n = 92 [23.7%])	39 (42.4)	1.60 (0.93-2.88)	39 (42.4)	**2.62 (1.45-4.74)**
0-1 (n = 47 [12.1%])	21 (44.7)	1.84 (0.91-3.73)	20 (42.6)	**2.70 (1.30-5.56)**
Heavy (4-8; n = 139 [35.8%])	44 (31.7)	1	31 (22.3)	1
Light (0-3; n = 249 [64.2%])	103 (41.4)	**1.59 (1.01-2.50)**	96 (38.6)	**2.24 (1.38-3.64)**
4-11 y (n = 1182)				
4-8 (n = 336 [28.4%])	113 (33.6)	1	78 (23.2)	**1**
3 (n = 303 [25.6%])	116 (38.3)	1.07 (0.75-1.53)	93 (30.7)	0.97 (0.68-1.40)
2 (n = 317 [26.8%])	126 (39.8)	1.14 (0.79-1.63)	111 (35)	1.20 (0.82-1.74)
0-1 (n = 226 [19.1%])	93 (41.2)	**1.45 (1.01-2.08)**	77 (34.1)	**1.80 (1.22-2.66)**
Heavy (4-8; (n = 336 [28.4%])	113 (33.6)	1	78 (23.2)	1
Light (0-3; n = 846 [71.6%])	335 (39.6)	**1.34 (1.02-1.76)**	281 (33.2)	**1.70 (1.26-2.29)**

Boldface numbers are statistically significant.

*Positive sIgE and SPT results for at least 1 tested allergen.

†Adjusted for sex, age, maternal education, and parental asthma.

Table IV

Associations between burden of infection and current wheeze, current wheeze plus symptoms, and asthma ever in life in children from 4 to 11 years old, stratified by age (n = 1182)

Markers of infections (no. and burden)	Current wheeze		Current wheeze plus symptoms		Asthma ever in life	
	No. (%)	OR (95% CI)*	No. (%)	OR (95% CI)*	No. (%)	OR (95% CI)*
4-5 y (n = 311)						
4-8 (n = 62 [19.9%])	23 (37.1)	1	30 (48.4)	1	6 (9.7)	1
3 (n = 70 [22.5%])	22 (31.4)	0.83 (0.40-1.75)	25 (35.7)	0.58 (0.28-1.19)	4 (5.7)	0.49 (0.12-1.93)
2 (n = 96 [30.9%])	38 (39.6)	1.25 (0.63-2.47)	49 (51.0)	1.15 (0.59-2.22)	7 (7.3)	0.68 (0.21-2.26)
0-1 (n = 83 [26.7%])	26 (31.3)	0.92 (0.44-1.93)	31 (37.3)	0.65 (0.32-1.32)	8 (9.6)	0.87 (0.25-3.03)
Heavy (4-8; n = 62 [19.9%])	23 (37.1)	1	30 (48.4)	1	6 (9.7)	1
Light (0-3; n = 249 [80.1%])	86 (34.5)	1.01 (0.55-1.86)	105 (42.2)	0.80 (0.45-1.43)	19 (7.6)	0.67 (0.24-1.90)
6-7 y (n = 483)						
4-8 (n = 135 [28.0%])	24 (17.8)	1	37 (27.4)	1	12 (8.9)	1
3 (n = 123 [25.5%])	25 (20.3)	1.27 (0.68-2.40)	34 (27.6)	1.04 (0.60-1.81)	3 (2.4)	**0.26 (0.07-0.96)**
2 (n = 129 [26.7%])	28 (21.7)	1.28 (0.68-2.38)	35 (27.1)	0.96 (0.55-1.68)	13 (10.1)	0.95 (0.39-2.29)
0-1 (n = 96 [19.9%])	24 (25.0)	1.58 (0.82-3.06)	30 (31.3)	1.17 (0.65-2.11)	8 (8.3)	0.90 (0.33-2.45)
Heavy (4-8; n = 135 [27.9%])	24 (17.8)	1	37 (27.4)	1	12 (8.9)	1
Light (0-3; n = 348 [72.1%])	77 (22.1)	1.35 (0.80-2.28)	99 (28.5)	1.04 (0.66-1.64)	24 (6.9)	0.68 (0.32-1.49)
7-11 y (n = 388)						
4-8 (n = 139 [35.8%])	20 (14.4)	1	29 (20.9)	1	8 (5.8)	1
3 (n = 110 [28.4%])	16 (14.5)	1.11 (0.54-2.28)	22 (20.0)	1.04 (0.55-1.97)	3 (2.7)	0.45 (0.11-1.76)
2 (n = 92 [23.7%])	10 (10.9)	0.88 (0.38-2.03)	12 (13.0)	0.71 (0.33-1.50)	4 (4.3)	0.74 (0.21-2.61)
0-1 (n = 47 [12.1%])	7 (14.9)	1.28 (0.49-3.37)	10 (21.3)	1.31 (0.56-3.06)	4 (8.5)	1.44 (0.39-5.29)
Heavy (4-8; n = 139 [35.8%])	20 (14.4)	1	29 (20.9)	1	8 (5.8)	1
Light (0-3; n = 249 [64.2%])	33 (13.3)	1.06 (0.57-1.96)	44 (17.7)	0.96 (0.56-1.65)	11 (4.4)	0.72 (0.27-1.91)
4-11 y (n = 1182)						
4-8 (n = 336 [28.4%])	67 (19.9)	1	96 (28.6)	1	26 (7.7)	1
3 (n = 303 [25.6%])	63 (20.8)	1.07 (0.72-1.59)	81 (26.7)	0.89 (0.62-1.28)	10 (3.3)	0.38 (0.17-0.81)
2 (n = 317 [26.8%])	76 (24.0)	1.18 (0.79-1.74)	96 (30.3)	0.97 (0.68-1.39)	24 (7.6)	0.84 (0.45-1.54)
0-1 (n = 226 [19.1%])	57 (25.2)	1.20 (0.78-1.85)	71 (31.4)	0.96 (0.65-1.43)	20 (8.9)	0.93 (0.48-1.80)
Heavy (4-8; (n = 336 [28.4%])	67 (19.9)	1	96 (28.6)	1	26 (7.7)	1
Light (0-3; n = 846 [71.6%])	196 (23.2)	1.14 (0.82-1.59)	248 (29.3)	0.94 (0.70-1.27)	54 (6.4)	0.69 (0.41-1.15)

*Adjusted for sex, age, maternal education, and parental asthma.

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Table V

Associations between burden of infection and atopic or nonatopic current wheeze in children from 4 to 11 years old stratified by age (n = 1182)

	Current wheeze			
	Nonatopic *		Atopic †	
Markers of infection (no. and burden)	No. (%)	OR (95% CI) ‡	No. (%)	OR (95% CI) ‡
4-5 y (n = 311)				
4-8 (n = 62 [19.9%])	18 (29.3)	1	12 (19.3)	1
3 (n = 70 [22.5%])	17 (24.3)	0.85 (0.35-2.07)	8 (11.4)	**0.29 (0.08-0.98)**
2 (n = 96 [30.9%])	24 (25.0)	1.08 (0.46-2.50)	25 (26.0)	1.11 (0.37-3.33)
0-1 (n = 83 [26.7%])	19 (22.4)	0.80 (0.33-1.97)	12 (14.5)	0.42 (0.13-1.39)
Heavy (4-8; n = 62 [19.9%])	18 (29.0)	1	12 (19.4)	1
Light (0-3; n = 249 [80.1%])	60 (24.1)	0.91 (0.44-1.91)	45 (18.1)	0.58 (0.22-1.58)
6-7 y (n = 483)				
4-8 (n = 135 [28.0%])	21 (15.6)	1	16 (11.8)	1
3 (n = 123 [25.5%])	16 (13.0)	0.91 (0.43-1.93)	18 (14.6)	1.19 (0.51-2.79)
2 (n = 129 [26.7%])	21 (16.3)	1.10 (0.54-2.24)	14 (10.9)	0.80 (0.33-1.94)
0-1 (n = 96 [19.9%])	15 (15.6)	1.34 (0.61-2.98)	15 (15.6)	0.92 (0.38-2.24)
Heavy (4-8; n = 135 [27.9%])	21 (15.6)	1	16 (11.9)	1
Light (0-3; n = 348 [72.1%])	52 (14.9)	1.08 (0.60-1.97)	47 (13.5)	0.97 (0.47-1.97)
7-11 y (n = 388)				
4-8 (n = 139 [35.8%])	18 (13.0)	1	11 (7.9)	1
3 (n = 110 [28.4%])	8 (7.3)	0.62 (0.24-1.56)	14 (12.7)	1.57 (0.61-4.06)
2 (n = 92 [23.7%])	4 (4.4)	0.44 (0.14-1.40)	8 (8.7)	0.93 (0.32-2.67)
0-1 (n = 47 [12.1%])	4 (8.5)	0.97 (0.28-3.33)	6 (12.8)	1.49 (0.45-4.99)
Heavy (4-8; n = 139 [35.8%])	18 (13.0)	1	11 (7.9)	1
Light (0-3; n = 249 [64.2%])	16 (6.4)	0.61 (0.28-1.30)	28 (11.2)	1.29 (0.56-2.97)
4-11 y (n = 1182)				
4-8 (n = 336 [28.4%])	57 (17.0)	1	39 (11.6)	1
3 (n = 303 [25.6%])	41 (13.5)	1.80 (0.50-1.28)	40 (13.2)	0.95 (0.55-1.67)
2 (n = 317 [26.8%])	49 (15.5)	0.88 (0.55-1.40)	47 (14.8)	1.02 (0.59-1.76)
0-1 (n = 226 [19.1%])	38 (16.8)	0.98 (0.58-1.64)	33 (14.6)	0.86 (0.47-1.57)
Heavy (4-8; n = 336 [28.4%])	57 (17.0)	1	39 (11.6)	1
Light (0-3; n = 846 [71.6%])	128 (15.3)	0.87 (0.59-1.29)	120 (14.2)	0.95 (0.60-1.52)

Boldface numbers are statistically significant.

* Nonatopic nonwheezer as reference.

† Atopic nonwheezer as reference.

‡ Adjusted for sex, age, maternal education, and parental asthma.

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Table VI

Associations between burden of infection and atopic or nonatopic current wheeze plus symptoms in children from 4 to 11 years old, stratified by age (n = 1182)

	Current wheeze plus symptoms			
	Nonatopic*		Atopicy†	
Markers of infection (no. and burden)	No. (%)	OR (95% CI)‡	No. (%)	OR (95% CI)‡
4-5 y (n 5 311)				
4-8 (n = 62 [19.9%])	13 (21.0)	1	10 (16.1)	1
3 (n = 70 [22.5%])	14 (20.0)	1.19 (0.46-3.07)	8 (11.4)	0.45 (0.13-1.52)
2 (n = 96 [30.9%])	17 (17.7)	1.17 (0.47-2.89)	21 (21.9)	1.17 (0.39-3.47)
0-1 (n = 83 [26.7%])	16 (19.3)	1.24 (0.48-3.22)	10 (12.1)	0.53 (0.16-1.78)
Heavy (4-8; n = 62 [19.9%])	13 (21.0)	1	10 (16.1)	1
Light (0-3; n = 249 [80.1%])	47 (18.9)	1.19 (0.54-2.63)	39 (15.7)	0.73 (0.27-1.95)
6-7 y (n = 483)				
4-8 (n = 135 [28.0%])	16 (11.9)	1	8 (5.9)	1
3 (n = 123 [25.5%])	11 (8.9)	0.86 (0.37-2.01)	14 (11.4)	2.12 (0.78-5.76)
2 (n = 129 [26.7%])	16 (12.4)	1.13 (0.52-2.49)	12 (9.3)	1.63 (0.58-4.55)
0-1 (n = 96 [19.9%])	13 (13.5)	1.69 (0.72-3.97)	11 (11.5)	1.51 (0.53-4.31)
Heavy (4-8; n = 135 [27.9%])	16 (11.9)	1	8 (5.9)	1
Light (0-3; n = 348 [72.1%])	40 (11.5)	1.14 (0.59-2.22)	37 (10.6)	1.76 (0.74-4.18)
7-11 y (n = 388)				
4-8 (n = 139 [35.8%])	12 (8.6)	1	8 (5.7)	1
3 (n = 110 [28.4%])	6 (5.5)	0.71 (0.25-2.04)	10 (9.1)	1.49 (0.51-4.31)
2 (n = 92 [23.7%])	2 (2.2)	0.32 (0.07-1.52)	8 (8.7)	1.42 (0.46-4.37)
0-1 (n = 47 [12.1%])	2 (4.3)	0.72 (0.14-3.55)	5 (10.6)	1.71 (0.46-6.33)
Heavy (4-8; n = 139 [35.8%])	12 (8.6)	1	8 (5.8)	1
Light (0-3; n = 249 [64.2%])	10 (4.0)	0.57 (0.23-1.42)	23 (9.2)	1.50 (0.59-3.77)
4-11 y (n = 1182)				
4-8 (n = 336 [28.4%])	41 (12.2)	1	26 (7.7)	1
3 (n = 303 [25.6%])	31 (10.2)	0.90 (0.53-1.53)	32 (10.6)	1.26 (0.69-2.32)
2 (n = 317 [26.8%])	35 (11.0)	0.91 (0.54-1.53)	41 (12.9)	1.50 (0.83-2.71)
0-1 (n = 226 [19.1%])	31 (13.7)	1.21 (0.69-2.13)	26 (11.5)	1.11 (0.57-2.16)
Heavy (4-8; n = 336 [28.4%])	41 (12.2)	1	26 (7.7)	1
Light (0-3; n = 846 [71.6%])	97 (11.5)	0.98 (0.63-1.49)	99 (11.7)	1.31 (0.78-2.19)

*Nonatopic nonwheezer as reference.

†Atopic nonwheezer as reference.

‡Adjusted for sex, age, maternal education, and parental asthma.