ERJ Express. Published on March 1, 2007 as doi: 10.1183/09031936.00127606

Non-atopic asthma is associated with helminth infections and bronchiolitis in poor children

Short title: Non-atopic asthma in children

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Abstract

Asthma is common in urban centers in Latin America, but atopic asthma may not be the main phenotype among children. Helminth infections are highly prevalent in poor populations and we hypothesized that they attenuate allergic asthma, while other factors are related to the expression of a non-atopic wheeze/asthma phenotype.

A total of 1982 children aged 10.1 (0.76) years (SD) from Southern Brazil completed asthma questionnaires and 1011 were evaluated for intestinal parasites and atopy with skin-prick tests (SPTs).

Wheeze in the previous 12 months was reported by 25.6% and 9.3% had current asthma; 13% were SPT-positive and 19.1% were positive for any helminthes. Most children with either wheeze or asthma were SPT-negative; however, severe wheeze was more prevalent amongst the atopic minority. Helminth infections were inversely associated with positive SPTs. Bronchiolitis before the age of two was the major independent risk factor for asthma at age 10; high-load Ascaris infection, family history of asthma, and positive SPTs were also asthma risk factors.

Most asthma and wheeze are of thenon-atopic phenotype suggesting that some helminthes may exert an attenuating effect on the expression of the atopic portion of the disease while viral bronchiolitis predisposes more specifically to recurrent airway symptoms.

Word count = 200

Keywords: wheeze, allergy, non-atopic asthma, intestinal parasites, helminthes, bronchiolitis

Introduction

The increased burden and prevalence of wheeze and asthma in the past decades are well documented, especially among children living in affluent societies. [1] Asthma in school-age children from developed countries is commonly associated with an atopic phenotype; including bronchial hyper-responsiveness (BHR), peripheral blood eosinophilia, increased allergen-specific IgE levels, and positive allergen skin-prick tests (SPTs). [2,3] The International Study onAsthma and Allergies in Children (ISAAC) has demonstrated that asthma and asthma-related symptoms are highly prevalent among many of the less privileged communities in this region. [4] These data are seemingly at odds with the so-called "hygiene hypothesis" and suggest that the relationship between asthma and the atopic phenotype is less clear in children from developing countries. Data from Africa show that the association of asthma with atopy is stronger in children living in urban than in rural settings. [5]

Parasitic infections are common amongst disadvantaged populations in Africa and Latin America. Recent data from these areas have shown an inverse association between helminth infections and allergy (defined by SPT) and probably an attenuation of asthma-related symptoms. [6,7] A series of studies in rural Ecuador have shown that asthma is not common in a highly parasitized population and that helminth infections are inversely related to allergen skin test reactivity.[8] This raises the question of which environmental factors may be responsible for the high prevalence of asthma and asthma-related symptoms in non-affluent populations in Latin America.[9]

In the present study we evaluated a population of school-age children from a poor urban community in Southern Brazil where helminth infections are common. We determined the impact of parasite load and other environmental exposures on asthma and asthma-related symptoms at age 10 years. We hypothesized that asthma and asthma-related symptoms were common among these children living in a "pro-inflammatory" urban environment and that helminth infections would attenuate the role of atopy in driving asthma in these children.

Methods

As part of the ISAAC Phase II study a sample of 2058 schoolchildren aged between 9 and 13 years were randomly chosen from a total of 3049 children enrolled in the 4th and 5th middle-school levels from the public system of a small town, Uruguaiana, in the extreme South of Brazil. Parents were interviewed at home by trained research interviewers and completed the basic questionnaire of the ISAAC-Phase II protocol plus some extra questions. The main issues under investigation were personal and familial risk factors for asthma, as well as environmental and lifestyle variables. Our main outcome variables were current wheeze ("wheeze in the past 12 months") and active asthma ("wheeze in past 12 months" plus "asthma ever"). Severe asthma was defined as four or more acute attacks in the previous 12 months. Children were classified as having had "bronchiolitis" when mothers or caretakers answered positive for the question: "Was your child admitted to a hospital or seen in an emergency room with bronchiolitis before the age of two years?" Variables such as "born before term" (i.e. "Was your child born before term?"), normal birth weight ($\geq$ 2,500g), maternal smoking (current and during pregnancy), number of siblings, humidity in the home, current maternal smoking (not a quantitative variable), and exclusive breast-feeding for at least 6 months were defined as in the ISAAC-phase II core protocol.[10] Living in a poor neighborhood, a marker of living standard, was classified by the response "the family lived in a suburban area with few parks and gardens".

A random sample of these children (n=1200) was selected to provide stool samples for the determination of intestinal parasitic infections. Three stool samples were collected from the children on different days by home visits, with specimens rapidly transported to and processed in the lab. Each stool sample was analyzed using three methods: a) Ritchie [11] to detect helminth ova and protozoan cysts and oocysts; b) Baerman for identification of *Strongyloides stercoralis* larva;[12] and c) Kato-Katz for quantitative evaluation of helminth ova.[13] A subject was considered infected if positive in any of the tests for specific parasites. High quantitative counts based on the Kato-Katz were defined as those egg counts falling into the upper tertile of the distribution (which

corresponded to ≥ 100 eggs/g) for any helminth or for specific *Ascaris lumbricoides* (Ascaris) infections (called "high-load")

The same sub-sample of children was also skin tested using relevant aeroallergens (*D. pteronisinus*, *D. farinae*, cat dander, mix of grasses, mix of trees, and *Alternaria alternata*, plus positive and negative controls) according the protocol [10,14] used in the ISAAC-Phase II study (ALK®, Spain). All SPTs were performed in the schools by a single trained researcher. A subject was defined as atopic according to the ISAAC protocol, i.e. a mean wheal diameter ≥ 3 mm (minus the negative control) for at least one allergen.

Statistical analyses

Univariate and multivariate logistic regression models were used to calculate adjusted and unadjusted odds ratio and 95% confidence intervals [OR (95%CI)] for the main outcome variables (current wheeze, active asthma, and SPTs). Risk factors known to be associated with wheeze and asthma, and those significantly associated with these outcomes in the bivariate analyses were included in the multivariate models; which were always adjusted for age and for gender. Analyses were performed using SPSS for Windows (version 12.0, SPSS Inc., Chicago, IL, USA).

The study was approved by the Human Ethics Committee of the Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (PUCRS), Brazil.

Results

The city of Uruguaiana has a population of about 130,000 inhabitants; its major economic activity relates to agriculture with a small part of the population working in the fields and most in service-related jobs in town. Most of the population is not served by a sewage system and there are high rates of unemployment and under-employment.

Questionnaires were completed for 96.3% (1982/2058) of the ISAAC Phase II sample of children. SPTs were completed in all but one of the target sub-sample of 1200 and three stool samples were collected from 87.8% (1054/1200). A total of 1011 subjects had complete data for parasite analysis, SPTs, and ISAAC-phase II questionnaires. This sub-sample was broadly representative of the entire cohort with no statistical differences between the two samples except that there were fewer mothers with at least 8 years of formal education and fewer families living in a poor neighborhood in the sub-group (Table 1). Mean age at the time of the survey was 10.1 (0.76) years (SD) for both the complete cohort and for the sub-sample with a range of 8.2 to 13.3 years. The results presented here will be restricted to the 1011 children with complete data.

Demographic data

Children were breastfed for at least 6 months and one tenth of the population was born before term. Approximately one third of mothers smoked either during their children's first year of life or at the time of the year 10 survey; 22% smoked during pregnancy. Mothers were schooled for a mean of 6.6 ($\pm$2.9) years, with most reporting less than 8 years of formal education (Table 1). Children had, on average, 2.7 (SD=2.0) siblings, with a third of the subjects being single children. More than 90% lived in a poor neighborhood and half of the households were reported as being humid.

Wheeze in the previous 12 months was present in a quarter of the children and 9.2% were reported to have active asthma (Table 1). Severe asthma was reported in 6.9%, 5.8% had acute exacerbations severe enough to limit speech and 17.3% had wheeze after exercising. Hospital admission or emergency room attendance for bronchiolitis before the age of two was reported for 6.3% of the children (Table 1). Maternal and paternal history of asthma was positive for less than 10% of the children.

Thirteen percent of the children were atopic; the most prevalent sensitization was to *D. pteronisinus* (11.2%), followed by *D. farinae* (6.6%). Very few (3.6%) were SPT-

positive for the other four tested allergens (cat dander, *Alternaria*, grass, and tree mixes).

Table 1. Demographic characteristics of the ISAAC Phase II questionnaire-only sample (N=1982), and the sub-sample of children with completed questionnaires, stool samples for parasitological tests, and skin-prick tests (N=1011)*

	N=1982	*N=1011*
	n (%)	n (%)
Male gender	993 (50.1)	495 (49.0)
Birth weight ≥ 2500	1,736 (90.4)	865 (88.6)
Born before term	189 (9.9)	93 (9.6)
Breast feeding ≥ 6 months	1705 (86.0)	852 (84.7)
Current maternal smoking	624 (31.5)	322 (31.9)
≥ 8y of maternal schooling	481 (24.3)	195 (19.3)*
≥ 1 Sibling	1373 (69.3)	730 (72.2)
Humid household	893 (45.1)	474 (46.9)
Poor neighborhood	1777 (99.7)	956 (94.7)*
Maternal asthma	149 (7.5)	78 (7.7)
Paternal asthma	108 (5.5)	58 (5.8)
Wheeze past 12 months	510 (25.6)	273 (27.0)
Active asthma	184 (9.3)	93 (9.2)
Atopy	N.A.	131 (13.0)
Bronchiolitis < 2 y.o.	136 (6.9)	63 (6.3)
Severe asthma (≥ 4 attacks)	130 (6.6)	70 (6.9)

*$p \leq 0.01$ - Denominators for the variables may differ slightly due to missing values

Infection with intestinal parasites

Almost 20% of the children were infected by helminthes, with *Giardia lamblia*, and *Ascaris lumbricoides* being the most common parasite recovered in the stool samples (Table 2). Approximately 10% of children were infected with multiple parasites; e.g., 5.4% of the Ascaris infected children were also infected by *Giardia*.

Table 2. Frequencies of different species of intestinal parasites found in fecal samples. Results are for any positive identification of parasites in any of three stool samples examined with 3 different laboratory techniques (see methods).

	n (%)
No Helminthes	853 (80.9)
Any positive helminth	201 (19.1)
Ascaris lumbricoides	130 (12.3)
Trichiurus trichiura	57 (5.4)
Hyminolepis nana	27 (2.6)
Enterobius vermicularis	12 (1.1)
Taenia solium	8 (0.8)
Strongiloides stercoralis	3 (0.3)
Entamoeba hystolitica	74 (7.0)
Giardia lamblia	105 (10.0)
Higher-load helminths (≥100eggs/g)	70 (6.6)
Higher-load Ascaris (≥ 100eggs/g)	58 (5.5)

Associations with wheeze and asthma

The vast majority (79%, 216/273) of the children with current wheeze were not atopic with only 57 having any positive SPT. Similarly the majority of those with active asthma were non-atopic (70%, 65/93). However, atopic children with current asthma were more likely to have more severe disease (odds ratio [OR]=2.6, 95% confidence interval [CI]= 1.04-6.4) than non-atopic asthmatics. Similar findings were also observed for SPT-positive current wheeze. Despite the fact that the majority of asthmatics were not atopic, being atopic was a significant risk factor for both current wheeze (OR= 2.4, 95% CI= 1.6-3.5) and for active asthma [3.4 (2.1-5.5)] in the total study group.

Most children (24/25, 96.0%) with high-load of helminths and wheezing at age 10 were SPT-negative. Children with high-load of Ascaris, or high-load (any) helminth when compared to those with both lower load and no helminths were more likely to have wheeze or active asthma at age 10 (Table 3). Non-atopic wheezers were almost four times more likely (OR=3.9, 95% CI= 1.3-11.3) to have helminth infections (49/216, 22.7%) than atopic wheezers (4/57, 7%).This risk was even greater for non-atopic wheezers with higher-load helminths and higher-load Ascaris infections.

Children with bronchiolitis seen in hospital before age two were at a high risk for wheezing later in life and were 12 times more likely to have active asthma at age 10 (Table 3). There was a synergistic interaction between bronchiolitis before the age of 2y and helminth infection at 10 y, increasing the risk for active asthma at age 10 more than 40 fold (OR=42.7, 95% CI= 11.4-160.5). Children with bronchiolitis in early life were not more likely to be SPT-positive when compared to those who did not have bronchiolitis.

Children living in humid households were significantly more likely to have current wheeze and active asthma. Maternal smoking was also a risk factor for both current wheeze and active asthma (Table 3). Paternal asthma was significantly associated with

wheeze (OR=5.0, 95% CI= 2.9-8.6) and asthma (OR=5.2, 95% CI= 2.9-9.5) as was maternal asthma (Table 3).

Table 3. Bivariate analyses of various risk factors and the main outcome variables of Wheeze ("wheeze in the previous 12 months"), and Asthma ("wheeze in the previous 12 months" and "asthma ever") at age 10 years; The number positive for the risk factor is shown together with the proportion of having the outcome and the odds ratio (OR) and 95% Confidence Intervals (95% C.I.).

Variables	**Number positive (total in analysis)**	**Wheeze**		**A**
		N (%)	**OR (95% CI)**	**N (%)**
Maternal schooling ≥ 8y	195 (1011)	43/195 (22.1)	0.7 (0.5-1.4)	11/195 (5.5)
Born before term	93 (970)	30/93 (32.3)	1.3 (0.8-2.1)	8/93 (8.6)
maternal smoking	322 (1009)	104/322 (32.3)	1.5 (1.1-2.0)**	38/322 (11.8)
Humid household	474 (1011)	158/474 (33.3)	1.8 (1.4-2.4)***	62/474 (13.1)
Maternal asthma	78 (1007)	42/78 (53.8)	3.5 (2.2-5.6)***	25/78 (32.1)
Poor neighborhood	956 (1009)	253/956 (26.5)	0.6(0.3-1.05)	84/956 (8.8)
Bronchiolitis ≤ 2y	159 (1007)	95/159 (59.7)	5.6 (4.0-8.0)***	56/159 (35.2)
Any helminthes	195 (1011)	53/195 (27.2)	1.0 (0.7-1.4)	20/195 (10.3)
Higher-load helminthes	68 (1011)	25/68 (36.8)	1.6 (1.0-2.7)	10/68 (14.7)
Higher-load Ascaris	56 (1011)	22/56 (39.3)	1.8 (1.0-3.0)*	9/56 (16.1)

* $p \leq 0.05$ **$p \leq 0.01$ ***$p \leq 0.001$

Risk Factors for atopy

The minority of children with better educated mothers (> 8 years of schooling) were more likely to be atopic (OR=1.8, 95% CI= 1.2-2.7) than those with less maternal schooling. Other risk factors for positive SPT on bivariate analyses were current wheeze (OR=2.4, 95% CI= 1.6-3.5), and active asthma (OR=3.4, 95% CI= 2.1-5.5); while infection with any parasite (OR=0.6, 95% CI= 0.4-0.9) or with any helminth (OR=0.4, 95% CI= 0.2-0.8), and a higher infective load (helminth) (OR=0.3, 95% CI= 0.09-0.94) were protective. A similar trend was seen for higher-load Ascaris (OR=0.4, 95% CI= 0.1-1.2) and for living in a poor neighborhood (OR=0.7, 95% CI= 0.3-1.5), but these did

not reach significance. Atopic children had significantly fewer siblings (on average) [mean 2.35 (SD=1.70) vs. 2.90 (2.17), p<0.01] when compared to the non-atopic.

Multivariate Logistic Regression Analyses

After adjusting for are and gender, the strongest independent risk factor for active asthma and current wheeze was bronchiolitis before the age of 2y (Table 4). A maternal or paternal history of asthma, living in a humid house, positive SPT and a high Ascaris load (or high load any helminth) were all risk factors for active asthma (Table 4). More years of maternal schooling and having two or more siblings were protective against active asthma. The risk factors for current wheeze at age 10 were similar to those for active asthma (Table 4); however, high Ascaris load was of borderline significance (p=0.06) with wheeze at age 10 and more than 8 years of maternal schooling was borderline and inversely associated with wheeze (p=0.06).

When a multivariate analysis was run selecting for those who were positive for any helminthes, children with a history of bronchiolitis were shown to be at an even greater risk for active asthma at age 10 years (OR=68.7, 95% CI= 10.0-470.0), p<0.001].

Table 4. Multivariate logistic regression analyses. Risk factors associated with wheeze in the previous 12 months and with active asthma, adjusted for age, and for gender. Total number of subjects included in the two multivariate logistic regression analyses was 954.

	Wheeze in previous 12m OR (95% C.I.)	*Active Asthma OR (95% C.I.)*
Maternal Hx Asthma	3.1 (1.8-5.3)***	5.6 (2.8-11.1)***
Paternal Hx Asthma	3.9 (2.1-7.3)***	3.6 (1.6-7.9)***
Bronchiolitis < 2y	5.4 (2.9-9.9)***	18.1 (9.1-36.0)***
Any positive skin test	2.7 (1.8-4.1)***	6.3 (3.4-11.8)***
Humid household	1.5 (1.1-2.1)**	2.2 (1.3-3.8)**
Maternal smoking	1.2 (0.9-1.7)	1.1 (0.6-2.0)
Born before term	1.4 (0.8-2.3)	0.7 (0.3-1.8)
Years of maternal schooling	0.98 (0.92-1.0)	0.9 (0.8-0.9)*
≥ 2 Siblings	1.1 (0.8-1.5)	0.5 (0.3-0.9)*

Higher-load Ascaris (≥100eggs/g)	1.8 (0.98-3.4)	2.4 (1.0-6.1)*

* p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

Risks for non-atopic wheeze

Despite the majority of children with wheeze being non-atopic, atopy was a strong risk factor for current wheeze, active asthma and severe wheeze. To investigate whether non-atopic asthma may be a different phenotype with different risk factors, the analyses were re-run on the non-atopic population. The association of Ascaris with both current wheeze and active asthma was stronger for the non-atopic phenotype (OR= 11.6, 95% CI= 1.5-86.3) and (OR=7.4, 95% CI= 0.96-59.4) than in the general population.The results of multivariate analyses in 829 subjects are shown in Table 5. The small number of atopic subjects in our study does not allow for a proper analysis of risk factors among this group. In general, the risk factors for current wheeze and active asthma are similar in the non-atopic and total populations, with the risks due to bronchiolitis <2y and higher-load Ascaris being greater in the non-atopics.

Table 5. Multivariate logistic regression analyses for non-atopic children. Risk factors associated with wheeze in the previous 12 months and with active asthma, adjusted for age, and for gender. Total number of subjects included in these analyses was 829.

	Wheeze in previous 12m OR (95% C.I.)	*Active Asthma OR (95% C.I.)*
Maternal Hx Asthma	2.8 (1.6-5.0)***	5.4 (2.5-11.7)***
Paternal Hx Asthma	3.9 (2.1-7.5)***	3.3 (1.4-7.6)***
Bronchiolitis < 2y	4.7 (2.5-8.9)***	14.5 (7.0-30.0)***
Humid household	1.5 (1.1-2.1)**	2.7 (1.4-5.2)**
Maternal smoking	1.2 (0.8-1.7)	1.0 (0.5-1.8)
Born before term	1.3 (0.8-2.3)	0.6 (0.2-1.7)
Maternal schooling ≥ 8y	0.7 (0.4-1.1)	0.3 (0.1-0.9)*
≥ 2 Siblings	1.1 (0.7-1.5)	0.6 (0.3-1.05)
Higher-load Ascaris (≥100eggs/g)	2.0 (1.1-3.8)*	3.1 (1.1-6.6)*

* p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

Discussion

In this cross-sectional study we aimed to identify risk factors associated with current wheeze and with active asthma in 10 year old children from a non-affluent community in Southern Brazil. The major finding from this study is that most wheeze and asthma in these children was not related to atopy. Helminth infection, especially with a higher infective load, increased the risk of wheeze and active asthma as did attending a hospital for acute bronchiolitis in the first 2 years of life. Furthermore, in this population non-atopic asthma was associated with an attenuated form of disease, with less severe or frequent exacerbations when compared to atopic asthmatics.

Some authors [15-17] have suggested that the role of atopy in childhood asthma has been over-estimated, even in Western countries. The fact that wheeze and asthma-like symptoms are frequently associated with atopy does not imply that these two phenomena are related in the individual child. Longitudinal studies following children from birth [18] and school-age children to adulthood [19,20] have convincingly shown that distinct wheezing phenotypes exist in children. The interaction between genetic susceptibilities and early life environmental exposures play a key role in determining the distribution of these wheeze phenotypes in different populations. This is particularly important in relation to early life infections, especially those due to respiratory viruses, and their profound impact on the recurrence of wheezing in the first decade of life.[21,22]

Pearce and coworkers have raised the issue that the role of non-atopic asthma has been under-estimated in many population studies. [17] The recently published data from the Isle of Wight birth cohort study shows that at age 10 years the prevalence for atopic and non-atopic wheeze was similar, but that atopic wheezing was more frequently associated with a diagnosis of asthma and with treatment for asthma while non-atopic wheeze was more closely associated with recurrent chest infections before age 2 years. [15] In the present study the vast majority of wheeze and active asthma at age 10 years was non-atopic. However, our population was infected by helminths, which was not the situation in the Isle of Wight study nor in those studies reviewed by Pearce et al [17]. When interpreting our findings one has also to take into account the potential impact of

the helminth infections on skin prick-testing to aeroallergens. Helminth infections and parasite load have been associated with negative SPT to aeroallergens in a number of studies [5,8,23] Brazilian researchers, studying a population chronically infected with *Schistosoma mansoni* have reported a suppressive effect on SPT and reduced severity of asthma symptoms. [7]

Despite the inverse association of helminth infections and positive SPT tests to aeroallergens, we found that a higher load of Ascaris was a risk factor for asthma and asthma-related symptoms at age 10, independent of other common risk factors. This was particularly true when considering non-atopic children in isolation. A similar association has been observed in a large rural population in China. [24] The respiratory effects of Ascaris on the airways may be related to its passage through the lungs as part of its life cycle and to its high allergenicity.[25] The clinical symptoms may be associated with Loëffler-like syndrome, through either local effects of larval tissue migration, airway reactivity or bronchospasm, infectious bacterial complications from parasitic migration and aspiration, or even more rarely, chronic eosinophilic pneumonia. [26] Helminths may suppress atopic inflammation in the airways, while at the same time increasing the risk of non-atopic wheeze, possibly via the mechanism outlined above. However, in the absence of serum IgE data we can only speculate on the true effect of helminth infection on atopy.

It is important to take into account that we arbitrarily defined a high-Ascaris or high-helminth load as being values in the upper tertile of the distribution. This corresponded to an infective load of $\geq$ 100 eggs/g, which suggests a significant but far from "heavy" infection. Other studies, mainly from rural environments, report a much higher burden of infection than we found in this rather urbanized community of Southern Brazil. A protective effect by helminth infection on asthma and allergies may be related to either infective load or frequency of infection rather than just to the presence of helminths. In many African studies a protective effect has been shown with hookworm, whereas in areas where Ascaris is the most prevalent species a protective effect may not be found. [6] These differences have been elegantly discussed in the recent meta-analysis by

Leonardi-Bee and colleagues. However longitudinal studies will be needed to adequately investigate whether these apparent helminth-related differences are real and why they occur.

An important risk factor for asthma reported in many studies is wheezing due to early life respiratory viral infections, [21,27] a variable that is generally not considered in previous "parasite" studies. In the present study bronchiolitis in early life was the strongest risk factor for asthma at age 10. Children with hospital admission or Emergency Room visits for bronchiolitis before age two were 17 times more likely to have active asthma, independently of other risk factors. Even more impressive was the finding that subjects with bronchiolitis who were also infected by helminthes at age 10 were at a much greater risk for active asthma. This finding may suggest that this combined exposure (assuming that children infected by Ascaris at age 10 have most likely been exposed to these agents since early in life) exerts a major effect on asthma among this mostly non-atopic population through either common or related mechanisms. Due to the cross-sectional nature of the study bronchiolitis was defined by the specific question answered by mothers. Recall bias or misclassification may play a role here. While we have no data on the agent(s) responsible for bronchiolitis in our children, we have recently demonstrated that in a population with similar social background RSV and Rhinovirus were the most common agents associated with wheeze during infancy. [28]

In this study SES was defined by a loose variable ("living in poor neighborhoods") as defined in the original ISAAC phase II protocol. There was a strong correlation between level of maternal education and place of living (either in a poor or in a better area of town) with an R=0.93. Although we have no data on healthcare utilization there is reason to believe that being infected by helminths is related to not having access to medications (which these children on and off receive) since the major risk factor for these infections is poor hygiene (i.e. lack of good sanitation structure). This is in fact the picture in the city where very few houses have proper sewage and garbage disposal systems in place.

The findings related to the protective factors for asthma and allergies in the proposed "hygiene hypothesis" must be interpreted with caution in low socio-economic environments such as the one described in this study. It seems reasonable to assume that some environmental factors do exert "protective" effects by blocking the expression of allergy in populations where atopic asthma is highly prevalent and in fact, environmental factors such as a higher number of siblings and greater maternal education were protective against atopy in the present study. However, the most potent environmental exposure reducing the risk of atopy here was infection with intestinal parasites.

In conclusion, our study shows that asthma and asthma-related symptoms are highly prevalent in this Brazilian community where the majority of the population is of low socio-economic status. The most prevalent wheeze phenotype in this population was non-atopic. Even though family history of asthma and positive skin tests are significant risk factors for wheezing at age 10 years, the strongest risk factor for persistence of wheeze at this age was bronchiolitis in early life. Our data show that helminth infections can induce airway-related symptoms and attenuate atopic disease simultaneously.

Acknowledgments

We acknowledge the support of the “Rudolph and Clothilde Ebehardt Stiftung”, Ulm, Germany with a grant; and ALK-Spain for the donation of the allergens used in the skin prick-testing. We also thank Professor Carlos Graeff Teixeira, for the helpful contribution with methods and analysis of the parasitological testing.

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