ORIGINAL ARTICLE

Effect of Early-Life Geohelminth Infections on the Development of Wheezing at 5 Years of Age

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Abstract

Rationale: Exposures to geohelminths during gestation or early childhood may reduce risk of wheezing illness/asthma and atopy during childhood in tropical regions.

Objectives: To investigate the effect of maternal and early childhood geohelminths on development of wheeze/asthma and atopy during the first 5 years of life.

Methods: A cohort of 2,404 neonates was followed to 5 years of age in a rural district in coastal Ecuador. Data on wheeze were collected by questionnaire and atopy was measured by allergen skin prick test reactivity to 10 allergens at 5 years. Stool samples from mothers and children were examined for geohelminths by microscopy.

Measurements and Main Results: A total of 2,090 (86.9%) children were evaluated at 5 years. Geohelminths were observed in 45.5% of mothers and in 34.1% of children by 3 years. Wheeze and asthma were reported for 12.6% and 5.7% of children, respectively, whereas 14.0% had skin test reactivity at 5 years. Maternal geohelminths were associated with an increased risk of wheeze (adjusted odds ratio, 1.41; 95% confidence interval, 1.06–1.88), whereas childhood geohelminths over the first 3 years of life were associated with reduced risk of wheeze (adjusted odds ratio, 0.70; 95% confidence interval, 0.52–0.96) and asthma (adjusted odds ratio, 0.60; 95% confidence interval, 0.38–0.94) but not skin prick test reactivity. The effects on wheeze/asthma were greatest with later age of first infection, were observed only in skin test–negative children, but were not associated with parasite burden or specific geohelminths.

Conclusions: Although maternal exposures to geohelminths may increase childhood wheeze, childhood geohelminths during the first 3 years may provide protection through a nonallergic mechanism. Registered as an observational study (ISRCTN41239086).

Keywords: geohelminths; atopy; wheeze; asthma; childhood

Asthma is the commonest chronic disease of childhood in industrialized countries, is estimated to affect more than 300 million worldwide (1), and has emerged as an important public health problem in many nonindustrialized regions (1, 2).

Increases in asthma prevalence, such as observed in urban regions of Latin America (2, 3), may be explained by environmental changes leading to a decreased incidence of infectious diseases and reduction in diversity of environmental microbiota (4). Such changes have followed improvements in public services including sewage, clean water, and access to vaccines and antiinfective drugs. A consequence of improved environmental hygiene and anthelmintic drug provision has been a decline in the prevalence of geohelminth parasites, common infections of poverty infecting more than 1 billion worldwide (5).

Helminth infections including geohelminths have potent effects on the human immune response, particularly T-helper cell type 2 responses that are critical for parasite killing and elimination (6). Chronic geohelminth infections are

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At a Glance Commentary

Scientific Knowledge on the Subject: Geohelminths have been suggested to protect against the development of atopy and asthma in childhood, but evidence for a causal link is limited by a lack of longitudinal studies from birth.

What This Study Adds to the Field: This study explored the effects of maternal geohelminths and the acquisition of geohelminth infections by the child during the first 3 years of life on the development of atopy and wheeze at 5 years of age. The study, the first adequately powered longitudinal study of childhood geohelminths to be done in an endemic region, showed that although children of mothers infected with geohelminths had more wheeze, childhood infections to 3 years of age reduced the risk of wheeze but no strong effects were seen on atopy. However, geohelminth effects were independent of parasite species and infection intensity. Although our data indicate a complex relationship between geohelminths and wheeze/asthma, the issue of causality remains inconclusive and there remains a need for further studies in endemic populations to explore possible causal mechanisms.

associated with the modulation of antiparasite T-helper cell type 2 responses (6). It has been suggested that the modulation of allergy by geohelminths, particularly in early life, may protect against the development of atopy and asthma (6, 7) and could explain the apparently low prevalence of allergic diseases in the rural tropics where such parasites are common.

Data from experimental animal models of allergy provide compelling evidence that helminths can mediate protection against allergy (8) but data from human populations are less clear (9). Although cross-sectional studies tend to show inverse associations between geohelminths and allergen skin prick test reactivity (SPT) (10), the relationship with allergic symptoms and asthma is uncertain (11–14) and may depend on age at first exposure, the intensity of infection, and species of infecting parasites (6, 15). Randomized intervention studies of the effects of anthelmintic treatment on atopy in schoolchildren have shown inconsistent effects on atopy (16–19) but no effects on asthma (17–19). However, helminth-mediated suppression of allergy may not be alterable by anthelmintic treatments given at school-age and early-life exposures may be key for protection (20).

To test the hypothesis that early exposures to geohelminths, either *in utero* through an infected mother or early childhood, reduce atopy and asthma development in later childhood, we followed an Ecuadorean birth cohort in an area of high geohelminth endemicity. We have reported previously our findings on effects of maternal geohelminths on allergic outcomes at 3 years (21) and report here our observations on the effects of maternal and early childhood geohelminths on wheeze/asthma and SPT at 5 years. Some of the results of these studies have been previously reported in the form of an abstract (22).

Methods

Study Design, Setting, and Participants

A prospective study from birth was done in the District of Quininde in Esmeraldas Province, Ecuador, as described (23). Inclusion criteria to enter the cohort were: *1*) healthy baby aged less than 2 weeks, *2*) maternal stool sample from the mother, *3*) mother of at least 17 years, *4*) family resident in District of Quininde for at least 2 years, and *5*) accessible household. Exclusions were a negative response to any of these criteria. The District serves a population of approximately 150,000 with limited access to basic services. The economy in the District is based on agricultural activities, primarily African palm oil. Neonates were recruited in Hospital "Padre Alberto Buffoni," the public hospital that serves the District between November 2005 and December 2009. Follow-up evaluations to collect data on geohelminths and/or study outcomes were done at 13, 24, 36, and 60 months.

Questionnaires

A questionnaire was used to collect data on sociodemographic factors, family history of allergy, and home environment by interview of the child's mother around the time of birth of the child. Questionnaires were repeated at 60 months to collect data on the allergic symptoms.

Measurement of Geohelminth Infections

Stool samples to detect geohelminth infections were collected from mothers during the third trimester or immediately following birth of the child, and in children at 13, 24, and 36 months of age. Samples were examined using a combination of methods, including saline mounts, modified Kato-Katz, formol-ether concentration, and carbon-coproculture methods (24). A positive sample was defined by the presence of at least one egg or larva from any of the four detection methods. *Ascaris lumbricoides* and *Trichuris trichiura* infection intensities were expressed as eggs per gram of feces using results of Kato-Katz.

Measurement of Wheeze and Asthma

Wheeze was defined as any episode of parentally reported wheeze during the previous 12 months and any wheeze as any episode of wheeze during the first 5 years of life. Asthma was defined as parentally reported wheeze during the previous 12 months plus one or both of parentally reported wheeze up to 3 years and a doctor diagnosis of asthma.

Allergen Skin Prick Test Reactivity

Allergic sensitization was measured using SPTs with 10 allergen extracts (Greer Laboratories): house dust mites (*Dermatophagoides pteronyssinus/Dermatophagoides farinae* mix), American cockroach (*Periplaneta americana*), *Alternaria tenuis*, cat, dog, grass pollen (nine southern grass mix), fungi (new stock fungi mix), egg, milk, and peanut, with positive histamine and negative saline controls. A positive reaction was defined as a mean wheal diameter at least 3-mm greater than that elicited by the saline control 15 minutes after pricking the allergen onto the volar side of the forearm with ALK-Abello lancets (ALK-Abello). Positive SPT was defined as a positive reaction to any of the allergens tested.

Statistical Analysis

We estimated that at least 1,725 children would be followed up at 5 years of age, considering that approximately 50% of mothers would be infected with geohelminths and that 35% of children would have at least one documented geohelminth infection during early childhood giving the study greater than 80% power and a significance level of 0.05 to detect a difference in asthma prevalence of at least 6% (23). The primary analysis was the associations between maternal geohelminth infections and childhood geohelminths to 13, 24, or 36 months and the presence of wheeze, asthma, and SPT at 5 years of age. Secondary analyses addressed the effects of geohelminth species and infection intensities in mothers and children on the development of outcomes including subgroups of SPT to mite and perennial allergens. Univariable and multivariable logistic regression were used to estimate associations between geohelminths and study outcomes. Potential confounders considered in the analyses are shown in Table 1. Urban-rural residence was defined by geographic boundaries. A socioeconomic status index was created using principal components analysis of seven socioeconomic variables as described (21). Potential confounders in univariable analyses with P less than 0.20 were kept in the final models using the same set of confounders to adjust all models. All statistical analyses were done using Stata 11 (StataCorp).

Ethical Considerations

The protocol was approved by the ethics committees of the Hospital Pedro Vicente Maldonado and Universidad San Francisco de Quito, Ecuador. The study is registered as an observational study (ISRCTN41239086). Informed written consent was obtained from the child's mother. Anthelmintic treatment (single dose of 400-mg albendazole) was provided to mothers with geohelminth infections after delivery. Children with positive stools for geohelminths were treated with single doses of anthelmintic drugs as recommended by the Ecuadorean Ministry of Public Health (25).

Results

Cohort Participants

A total of 4,712 newborns were evaluated of which 2,404 were recruited. Analyses at 5 years of age were done using data from 2,090 (86.9%) children for whom complete data were available (Figure 1). Children included in the analysis had older and more educated mothers and lived in wealthier households (*see* Table E1 in the online supplement) compared with those not included. Maternal infections with malaria, HIV, and other helminths were infrequent ($<$0.5%).

Frequencies of Exposures and Outcomes

Geohelminth infections were observed in 45.5% of mothers during pregnancy and in 11.7%, 24.2%, and 34.1% of children to 13, 24, and 36 months of age, respectively. Prevalence of maternal infections with individual parasites was *A. lumbricoides* (27.4%), *T. trichiura* (28.4%), and hookworm (5.7%). Among children, most infections were with *A. lumbricoides*: to 13 months (*A. lumbricoides* 9.1%; *T. trichiura* 3.0%), to 24 months (*A. lumbricoides* 18.0%; *T. trichiura* 10.5%), and to 36 months (*A. lumbricoides* 25.9%; *T. trichiura* 16.7%). Infections with other helminth parasites were infrequent: hookworm (0.6%), *Strongyloides stercoralis* (0.6%), and *Hymenolepis* spp. (1.5%) at 36 months. Infection intensities were greatest at 36 months of age; geometric mean intensities among infected children were 2,009 eggs per gram for *A. lumbricoides* and 256 eggs per gram for *T. trichiura*. The prevalence of wheeze or asthma at 5 years of age was 12.6% and 5.7%, respectively. At least one episode of wheeze during the first 5 years of life was reported for 33.4% of children, whereas 5.4% had wheeze reported for two or more observation times (i.e., 13, 24, 36, and 60 mo). The prevalence of SPT at 5 years was 14.0%: *D. pteronyssinus*/*D. farinae* (8.2%), cockroach (4.3%), mixed fungi (0.6%), dog (1.1%), cat (0.3%), mixed grasses (1.5%), peanut (0.6%), milk (0.4%), and egg (0.4%). Prevalence of SPT to perennial allergens was 11.2%.

Determinants of Wheeze, Asthma, and SPT

The distributions of demographic and confounding factors for wheeze, asthma, and SPT at 5 years of age are shown in Table 1. Univariable associations between exposures or potential confounders and outcomes are shown in Table 1 and adjusted analyses in Table 2. In adjusted analyses, maternal geohelminths were significantly associated with increased risk of wheeze at 5 years (adjusted odds ratio [OR], 1.41) but not asthma or SPT. In univariable analyses, childhood geohelminths acquired during the first 36 months of life were not associated with study outcomes (Table 1), but after adjustment for confounders, significant inverse associations were observed for childhood infections acquired during the first 36 months of life and wheeze (OR, 0.70) or asthma (OR, 0.60) (Table 2). Maternal geohelminths, with which childhood geohelminths were strongly associated (OR, 2.8; 95% confidence interval [CI], 2.3–3.4), were a strong negative confounder; the childhood geohelminth effect was seen only after controlling for this variable. Childhood geohelminths to 13 or 24 months of age were not associated with outcomes (*see* Figure E1). Maternal or childhood geohelminth infections were not significantly associated with any wheeze episode reported during the first 5 years of life (maternal: adjusted OR, 1.22; 95% CI, 1.00–1.49) (childhood to 36 months: adjusted OR, 1.04; 95% CI, 0.84–1.28). With respect to other risk factors in the adjusted analysis (Table 2), pneumonia during the first 13 months was associated with wheeze (OR, 2.32); asthma was associated with having a younger mother ($\geq$30 yr vs. $\leq$20 yr; OR, 0.38), maternal allergy (OR, 2.61), infant pneumonia (OR, 4.71), but was less frequent among children with more educated mothers; and SPT was associated with rural residence (OR, 1.81).

When we explored possible associations of maternal and childhood geohelminths with SPT to house dust mite allergens, the dominant allergens in the population, and to perennial allergens, we observed a significant inverse association between childhood geohelminths and SPT to perennial allergens (OR, 0.70; 95% CI, 051–0.98; $P = 0.035$). This effect was present even for infections acquired during the first 13 months (OR, 0.60; 95% CI, 0.36–1.01; $P = 0.054$).

Effects of Individual Geohelminth Parasites and Parasite Burdens on Wheeze/Asthma and SPT

We explored the effects of different geohelminth parasites and infection intensities on study outcomes. Univariable and adjusted analyses are shown in Tables

Table 1. Frequencies of Maternal and Childhood Geohelminth Infections to 36 Months of Age and Potential Confounders and Associations with Wheeze, Asthma, and SPT Reactivity to Any Allergen at 5 Years of Age

Variable	Overall n (%)	Wheeze %	Wheeze OR (95% CI)	Wheeze P Value	Asthma %	Asthma OR (95% CI)	Asthma P Value	SPT %	SPT OR (95% CI)	SPT P Value
Any maternal geohelminth*										
No	1,140 (54.5)	10.7	**1**		5.1	1		13.7	1	
Yes	950 (45.5)	14.8	**1.47 (1.13–1.90)**	0.004	6.4	1.30 (0.90–1.89)	0.162	14.4	1.06 (0.83–1.36)	0.629
Any childhood geohelminths†										
No	1,377 (65.9)	13.3	1		6.2	1		14.9	1	
Yes	713 (34.1)	11.4	0.84 (0.63–1.11)	0.209	4.6	0.74 (0.49–1.11)	0.148	12.3	0.80 (0.62–1.05)	0.113
Maternal age, yr										
⩽20	546 (26.1)	11.5	1		5.6	1		13.7	1	
21–29	1,005 (48.1)	14.1	1.26 (0.92–1.74)	0.140	6.9	1.24 (0.80–1.92)	0.331	14.0	1.02 (0.76–1.30)	0.873
⩾30	539 (25.8)	10.9	0.94 (0.65–1.37)	0.757	3.3	0.57 (0.32–1.04)	0.067	14.3	1.05 (0.74–1.470	0.794
Maternal ethnicity										
Afro-Ecuadorean	540 (25.8)	14.7	1		6.6	1		15.0	1	
Non–Afro-Ecuadorean	1,550 (74.2)	11.8	0.78 (0.59–1.03)	0.079	5.3	0.80 (0.53–1.18)	0.251	13.7	0.90 (0.68–1.18)	0.446
Maternal educational level										
Illiterate	308 (14.8)	15.1	1		7.1	1		11.4	1	
Complete primary	1,221 (58.4)	12.3	0.79 (0.55–1.12)	0.181	5.1	0.71 (0.43–1.17)	0.179	15.2	1.39 (0.95–2.05)	0.092
Complete secondary	561 (26.8)	11.9	0.76 (0.51–1.23)	0.172	6.0	0.84 (0.48–1.47)	0.541	13.0	1.17 (0.76–1.79)	0.481
Area of residence										
Urban	1,473 (70.5)	13.0	1		6.3	1		12.2	1	
Rural	617 (29.5)	11.6	0.88 (0.66–1.17)	0.379	4.0	**0.63 (0.40–0.98)**	0.039	18.3	**1.61 (1.25–2.08)**	<0.001
Sex										
M	1,063 (50.9)	12.1	1		5.9	1		13.9	1	
F	1,027 (49.1)	13.1	1.09 (0.84–1.41)	0.515	5.4	0.92 (0.63–1.33)	0.651	14.1	1.02 (0.97–1.30)	0.897
Socioeconomic status‡										
1	672 (32.1)	12.0	1		4.3	1		13.1	1	
2	704 (33.6)	12.7	1.07 (0.78–1.48)	0.665	5.8	1.37 (0.84–2.23)	0.205	15.1	1.18 (0.87–1.60)	0.296
3	714 (34.3)	13.0	1.10 (0.80–1.51)	0.558	6.8	1.62 (1.00–2.60)	0.052	13.9	1.07 (0.78–1.45)	0.675
Birth order										
1st	522 (25.0)	11.6	1		5.5	1		15.9	1	
2nd–4th	1,161 (55.4)	13.2	1.16 (0.85–1.59)	0.354	5.9	1.08 (0.69–1.69)	0.738	13.5	0.83 (0.62–1.10)	0.197
⩾5th	407 (19.6)	12.1	1.05 (0.71–1.57)	0.802	5.1	0.92 (0.52–1.64)	0.777	13.0	0.79 (0.55–1.15)	0.219
Maternal allergy										
No	1,997 (95.3)	12.4	1		5.4	1		14.0	1	
Yes	98 (4.7)	16.3	1.37 (0.79–2.39)	0.260	12.2	**2.46 (1.30–4.64)**	0.005	14.3	1.03 (0.58–1.83)	0.928
Household overcrowding§										
⩽3	1,180 (56.5)	11.7	1		5.1	1		14.2	1	
>3	910 (43.5)	13.8	1.21 (0.93–1.57)	0.148	6.3	1.25 (0.87–1.82)	0.230	13.9	0.97 (0.76–1.25)	0.841
Pets inside house										
No	1,561 (74.2)	12.4	1		5.2	1		13.8	1	
Yes	539 (25.8)	13.1	1.07 (0.80–1.43)	0.656	6.8	1.33 (0.89–1.98)	0.165	14.7	1.07 (0.81–1.42)	0.621
Large farm animals‖										
No	1,414 (67.7)	11.8	1		5.7	1		13.6	1	
Yes	676 (32.3)	14.3	1.25 (0.96–1.64)	0.103	5.5	0.95 (0.63–1.41)	0.785	14.9	1.18 (0.86–1.45)	0.402
Pneumonia to 13 mo										
No	1.919 (95.4)	12.0	1		5.1	1		14.7	1	
Yes	92 (4.6)	23.7	**2.30 (1.40–3.78)**	0.001	18.3	**4.26 (2.42–7.49)**	<0.001	7.61	0.48 (0.22–1.04)	0.064

Definition of abbreviations: CI = confidence interval; OR = odds ratio; SPT = skin prick test.

SPT reactivity to any of 10 allergens. OR and 95% CI were estimated using logistic regression. Bold indicates $P < 0.05$. In maternal ethnicity, non–Afro-Ecuadorean represents 1,544 mestizo/six indigenous. Numbers of missing values (brackets) were: maternal allergy (13) and child geohelminth infections (27).

*Other helminths: *S. stercoralis*, 4.0%; *Hymenolepis* spp., 0.5%.

†Other helminths: hookworm, 0.6%; *S. stercoralis*, 0.6%; *Hymenolepis* spp., 1.5%.

‡Socioeconomic status represents tertiles of *z*-scores obtained using a factor analysis with 1 representing the lowest and 3 the highest socioeconomic status.

§Household overcrowding is defined as the number of people living in the household per sleeping room.

‖Any of cows, pigs, mules, donkeys, and horses.

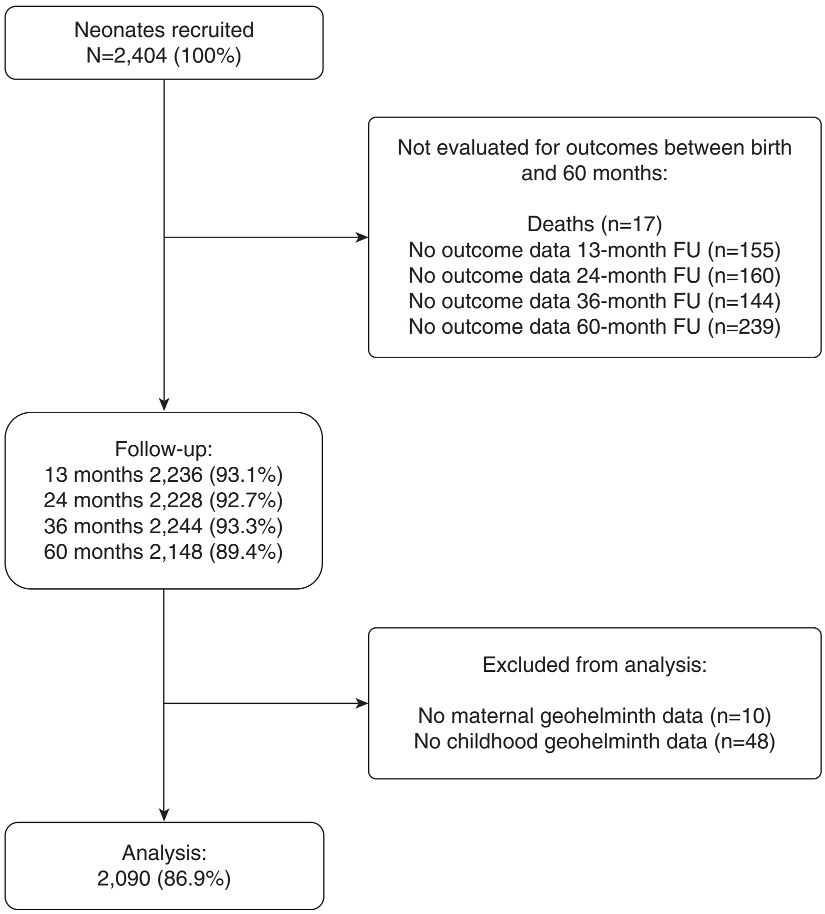

Figure 1. Participant flow through follow-up to 5 years of age and those included in and excluded from the analysis. FU = follow-up.

E2 and E3, respectively. No significant associations were observed between individual maternal geohelminth parasites and study outcomes. There was evidence for an increased risk of wheeze (OR, 1.44) in children whose mothers had light infection intensities with *A. lumbricoides* (*see* Table E3). Neither geohelminth species in children to 36 months nor parasite burdens at 36 months were significantly associated with study outcomes.

Effects of Infection Chronicity and Age of First Infection on Wheeze/Asthma and SPT

Chronic exposures to geohelminth infections were evaluated using two surrogate measures; as repeated infections in childhood (i.e., 0, 1, or ⩾2 documented childhood infections with *Ascaris* and or *Trichuris* during the first 36 mo of life) or in a four-group analysis as combinations of maternal and childhood geohelminth infections (mother−/child−, mother−/child+, mother+/child−, and mother+/child+). Repeated childhood infections had no significant effects on outcomes (data not shown). In the four-group adjusted analysis, maternal geohelminths in the absence of childhood infections were associated with an increased risk of wheeze (OR, 1.51; 95% CI, 1.08–2.10; $P = 0.016$) and trends of increased risk for asthma (OR, 1.27; 95% CI, 0.79–2.03) and SPT (OR, 1.36; 95% CI, 0.99–1.87) were observed while the presence of childhood infections tended to attenuate such maternal effects (data not shown). The protective effect of childhood geohelminths against wheeze was strongest among children who acquired their first infection later in childhood (all adjusted analyses): first infection in first year versus never infected (OR, 0.86; 95% CI, 0.57–1.31); second versus never (OR, 0.68; 95% CI, 0.44–1.06); and third versus never (OR, 0.55; 95% CI, 0.33–0.93). A similar pattern was observed for asthma (third vs. never: OR, 0.51; 95% CI, 0.24–1.09). However, for SPT strongest effects were observed for first infections acquired during the first year of life (first vs. never: OR, 0.66; 95% CI, 0.42–1.04).

Associations between Geohelminths and Asthma/Wheeze in Children with and without Atopy

SPT reactivity was associated with wheeze (adjusted OR, 1.97; 95% CI, 1.41–2.70) and asthma (adjusted OR, 1.97; 95% CI, 1.22–2.98). We explored the associations between maternal and childhood geohelminth infections to 36 months among children with and without atopy. Univariable and adjusted analyses children with and without atopy are shown in Table E4 and Table 3, respectively. In adjusted analyses, maternal helminths were positively (OR, 1.60) and childhood geohelminths negatively (OR, 0.60) associated with wheeze in children without atopy but no significant associations were seen for children with atopy. Childhood geohelminths were also inversely associated with asthma (OR, 0.52) among children without atopy.

Discussion

There is an unresolved debate about whether geohelminth infections protect against allergy and asthma in populations where these parasites are endemic. Such protection has important consequences for future risk of allergic diseases in populations where these infections are endemic but where improvements in hygiene and widespread use of anthelmintic drugs are expected to reduce parasite prevalence substantially. The effects of geohelminth infections on allergy, in common with other protective environmental exposures, such as pets and farming, are considered to be greatest when occurring in early life (20, 26). Here, we analyzed data from a birth cohort done in a rural district of tropical Ecuador with a high prevalence of geohelminth parasites, mainly *A. lumbricoides* and *T. trichiura*. Our data show that exposures to maternal infections and infections acquired during the first 3 years have contrasting effects on wheeze/asthma at 5 years. Exposures during the first 3 years, particularly when acquired for the first time at 3 years, seemed to provide protection against wheeze/asthma, whereas maternal

Table 2. Adjusted Analyses for Associations between Maternal and Childhood Geohelminth Infections to 36 Months of Age or Potential Confounders and Associations with Wheeze, Asthma, and SPT Reactivity to Any Allergen at 5 Years of Age

	Wheeze		Asthma		SPT	
Variable	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Any maternal geohelminth						
No	1		1		1	
Yes	**1.41 (1.06–1.88)**	0.017	1.28 (0.85–1.94)	0.238	1.17 (0.89–1.53)	0.262
Any childhood geohelminths						
No	1		1		1	
Yes	**0.70 (0.51–0.95)**	0.021	**0.60 (0.38–0.95)**	0.029	0.79 (0.59–1.06)	0.120
Maternal age, yr						
⩽20	1		1		1	
21–29	1.16 (0.82–1.68)	0.431	0.86 (0.52–1.45)	0.577	1.25 (0.88–1.78)	0.218
⩾30	0.86 (0.53–1.40)	0.547	**0.38 (0.18–0.79)**	0.010	1.37 (0.87–2.17)	0.172
Maternal ethnicity						
Afro-Ecuadorean	1		1		1	
Non–Afro-Ecuadorean	0.76 (0.56–1.03)	0.074	0.80 (0.52–1.24)	0.321	0.80 (0.59–1.07)	0.136
Maternal educational level						
Illiterate	1		1		1	
Complete primary	0.78 (0.52–1.16)	0.223	**0.55 (0.31–0.97)**	0.039	1.40 (0.92–2.13)	0.121
Complete secondary	0.72 (0.44–1.19)	0.200	0.57 (0.29–1.15)	0.118	1.15 (0.69–1.91)	0.601
Area of residence						
Urban	1		1		1	
Rural	0.84 (0.60–1.16)	0.286	0.66 (0.40–1.09)	0.106	**1.81 (1.35–2.43)**	<0.001
Sex						
M	1		1		1	
F	1.14 (0.87–1.49)	0.349	0.97 (0.66–1.43)	0.874	1.01 (0.78–1.30)	0.941
Socioeconomic status*						
1	1		1		1	
2	1.18 (0.84–1.66)	0.336	1.53 (0.92–2.56)	0.104	1.31 (0.95–1.80)	0.101
3	1.20 (0.83–1.74)	0.339	1.64 (0.94–2.84)	0.081	1.23 (0.86–1.76)	0.249
Birth order						
1st	1		1		1	
2nd–4th	1.15 (0.78–1.69)	0.487	1.43 (0.82–2.49)	0.206	0.72 (0.50–1.02)	0.068
⩾5th	0.92 (0.52–1.64)	0.779	1.46 (0.64–3.32)	0.372	0.62 (0.36–1.07)	0.086
Maternal allergy						
No	1		1		1	
Yes	1.37 (0.78–2.43)	0.273	**2.61 (1.33–5.12)**	0.005	1.00 (0.55–1.82)	0.992
Household overcrowding†						
⩽3	1		1		1	
>3	1.21 (0.90–1.62)	0.212	1.24 (0.81–1.90)	0.331	1.10 (0.83–1.46)	0.505
Pets inside house						
No	1		1		1	
Yes	1.01 (0.74–1.37)	0.974	1.26 (0.82–1.93)	0.300	1.06 (0.79–1.41)	0.715
Large farm animals‡						
No	1		1		1	
Yes	1.29 (0.96–1.73)	0.093	1.00 (0.65–1.54)	0.990	0.97 (0.73–1.29)	0.822
Pneumonia to 13 mo						
No	1		1		1	
Yes	**2.32 (1.39–3.87)**	0.001	**4.71 (2.60–8.54)**	<0.001	0.46 (0.21–1.02)	0.055

Definition of abbreviations: CI = confidence interval; OR = odds ratio; SPT = skin prick test.
SPT reactivity to any of 10 allergens. OR and 95% CI were estimated using logistic regression and adjusted for all variables. Bold indicates $P < 0.05$.
*Socioeconomic status represents tertiles of *z*-scores obtained using a factor analysis with 1 representing the lowest and 3 the highest socioeconomic status.
†Household overcrowding is defined as the number of people living in the household per sleeping room.
‡Any of cows, pigs, mules, donkeys, and horses.

infections were associated with an increased risk of wheeze, an effect that was attenuated by childhood infections.

Few prospective studies have examined the effects of geohelminths on allergy in early childhood and, to our knowledge, none have been able to address adequately effects on wheeze and asthma. Previous studies include: *1*) a birth cohort in Ethiopia where the prevalence of geohelminths (<4%) was considered to be too low to explore effects on wheeze and eczema to 5 years (27); *2*) an observational analysis within a randomized-controlled trial of anthelmintic treatment during pregnancy that showed that maternal and childhood hookworm and childhood *T. trichiura* were associated with a reduced risk of eczema to 5 years (28); *3*) a prospective study in Brazil that showed that *T. trichiura* infections, particularly at high parasite burdens,

Table 3. Adjusted Analyses for Associations between Geohelminth Infections to 36 Months and Asthma/Wheeze at 5 Years in Children with and without Atopy

Variable	SPT− (*n* = 1,797)				SPT+ (*n* = 293)			
	N	*n* (%)	OR (95% CI)	*P* Value	*N*	*n* (%)	OR (95% CI)	*P* Value
Wheeze								
Maternal geohelminths								
No	984	92 (9.4)	1	0.005	156	30 (19.2)	1	0.396
Yes	813	113 (13.9)	**1.60 (1.16–2.20)**		137	29 (21.2)	0.75 (0.38–1.47)	
Childhood geohelminths								
No	1,172	145 (12.4)	1	0.005	205	38 (18.5)	1	
Yes	625	60 (9.6)	**0.60 (0.43–0.86)**		88	21 (23.9)	1.38 (0.70–2.71)	0.351
Asthma								
Maternal geohelminths								
No	984	44 (4.5)	1	0.369	156	13 (8.3)	1	0.292
Yes	813	47 (5.8)	1.24 (0.78–1.98)		137	14 (10.2)	1.68 (0.64–4.41)	
Childhood geohelminths								
No	1,172	67 (5.7)	1	0.014	205	18 (8.8)	1	0.620
Yes	625	24 (3.8)	**0.52 (0.31–0.87)**		88	9 (10.2)	1.27 (0.49–3.28)	

Definition of abbreviations: CI = confidence interval; OR = odds ratio; SPT = skin prick test; SPT− = no allergen skin prick test reactivity; SPT+ = allergen skin test reactivity to any of 10 allergens.
OR and 95% CI were estimated using logistic regression and adjusted for maternal age, ethnicity, and educational status; area of residence; sex; socioeconomic status; birth order; maternal allergy; household overcrowding; pets inside the house; contact with large farm animals; and pneumonia to 13 months. Bold indicates $P < 0.05$.

during the first 5 years of life were associated with a reduced risk of SPT in later childhood (29); and *4*) a previous analysis of this Ecuadorean cohort to 3 years that showed no significant effects of maternal infections on allergic outcomes (21).

None of our observed effects were explained by specific geohelminth species or parasite burdens. However, relatively few mothers had heavy parasite burdens with *A. lumbricoides* (5.0%) and *T. trichiura* (4.0%) limiting the power of this analysis to show effects at high parasite burdens. Similarly, few children at 3 years of age had heavy infection intensities (≤5.0%) with either parasite. The use of adult infection intensity categories for small children may not be appropriate given that even small parasite burdens might be expected to have comparatively greater effects on growth and the maturing immune response. However, categorization of intensities using the geometric mean as cutoff (29) did not affect the results. Repeated treatments for positive stool samples in this study and anthelmintic treatments obtained from other sources are likely to have affected the parasite burdens acquired by 3 years of age and blunted any atopy or wheeze modulating effect of chronic infections.

Previous studies have shown differing effects of *A. lumbricoides* infections on wheeze/asthma depending on age of study population and prevalence. A study of 1 to 4 year olds in Ethiopia with a high prevalence of geohelminths showed an inverse association of wheeze with *A. lumbricoides* (12). However, in older individuals, *A. lumbricoides* infection or *Ascaris* sensitization was associated with asthma (11, 15, 30) or bronchial hyperresponsiveness (30, 31), an effect generally observed in areas of low prevalence (11, 14, 30). Both effects were largely independent of SPT (11, 12, 31) with stronger effects in those without atopy (32). Hookworm infection, which has been associated inversely with asthma symptoms in previous studies (15), was of low prevalence (5.7%) in study mothers, limiting our ability to infer hookworm-specific effects. *T. trichiura* infection has also been associated with increased asthma (33), although most studies showed no effect (13, 23, 31, 32, 34).

So how can we interpret our findings in the context of these studies? As for the previous Ethiopian study of young children (12), childhood infections with geohelminths over the first 3 years in this study were associated with a reduced risk of wheeze. It is not clear why such an effect only emerged at 3 years and is inconsistent with a conceptual model of early critical exposures (7). All documented geohelminth infections in children were treated and these repeated and abbreviated infections acquired before 3 years may have had less impact on the host immune response than those detected later. The dominant protective effect of childhood geohelminths against wheeze was in children without atopy, the dominant phenotype in nonaffluent countries (14, 34, 35). Mechanisms by which environmental exposures reduce nonatopic asthma may include hyporesponsiveness to migratory larvae, contributing to the development of more robust antiinflammatory mechanisms in the lungs and a reduction in bronchial hyperresponsiveness (14). Geohelminths have been associated with the induction of immune hyporesponsiveness, an effect mediated by the increased expression of inhibitory CTLA-4 on $CD4^+$ T cells (36).

In contrast, we observed a greater risk of wheeze/asthma among children of infected mothers. We have shown previously in this cohort that maternal ascariasis is associated with increased immune responsiveness to *Ascaris* antigens in newborns (37). Thus, not only may *A. lumbricoides* infections in older children and adults increase wheeze/asthma (11, 14, 30, 31), but this effect may be transmitted from mother to child through *in utero* sensitization to *Ascaris* antigens. Contrasting effects of geohelminths on wheeze/asthma in younger versus older subjects may depend on history of geohelminth exposures and type of inflammatory lung response. Earlier infections may modulate antiparasite inflammatory responses in highly endemic populations (7) allowing protective effects against wheeze/asthma to appear. Protective immunity to helminth parasites is age-dependent and nonsterile in endemic populations (38). With continued exposures and immune maturation (e.g., around school age), more effective antiparasite (38, 39) but heightened inflammatory responses may emerge. Such responses when transmitted by infected mothers to their infants may be downregulated when early geohelminth exposures are sufficient.

Suppression of the antiparasite response in early childhood is unlikely to occur in populations with a low prevalence and older age of first infection. This, however, does not explain the lack of parasite-specific effects on wheeze/asthma. Effects on wheeze are most consistent and biologically plausible for *A. lumbricoides* given that *T. trichiura* is restricted to the intestinal lumen. Lack of parasite-specific effects could be explained by differential therapeutic efficacy of the anthelmintic used, albendazole, which is highly efficacious against *A. lumbricoides* (i.e., cure rates of >95%) but of limited efficacy against *T. trichiura* (<50%) (40). Such differential efficacy may have obscured parasite-specific effects. Certainly, these observations require replication in other studies.

Strengths of the study were the prospective design and high rates of follow-up as was the use of standardized instruments and study procedures to measure exposures and outcomes. Outcomes and geohelminth exposures were measured using standardized methods by experienced staff, all blind to exposure and outcome data, respectively. Detailed information on potential confounding factors were collected and controlled for, where appropriate, although we cannot exclude residual confounding by unknown or unmeasured factors. Potential limitations were: *1*) use of maternal questionnaires to measure wheeze and asthma outcomes at 5 years could have led to misclassification, *2*) the study had limited power for analysis of subgroup effects, and *3*) lack of longitudinal data for geohelminths among mothers limits our ability to infer longevity of infection.

In conclusion, we report the effects of maternal and childhood infections with geohelminths on the development of SPT and wheeze/asthma by 5 years of age in a birth cohort from rural Ecuador. Maternal and childhood infections to 3 years had contrasting effects on the risk of wheeze/asthma with maternal geohelminths increasing but childhood infections decreasing the risk, but only among children without atopy. Further follow-up of the cohort will clarify whether such effects are transient or longer lasting. ■

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