

Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics

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Background: Childhood infections might protect against the expression of atopy. Geohelminths are among the most prevalent infections of childhood and might contribute to the low prevalence of allergic disease reported from rural areas of the tropics.

Objective: We sought to establish whether geohelminth infections protect against atopy and to explore whether this protection is dependent on infection chronicity.

Methods: The risk of atopy (measured by means of allergen skin test reactivity) associated with active geohelminth infections (measured by means of the presence of eggs in stool samples) or with chronic geohelminth infections (measured by means of high levels [≥ 3564 IU/mL] of total serum IgE or the presence of detectable anti-*Ascaris lumbricoides* IgG4 antibodies) was investigated in an analytic cross-sectional study conducted among school-age children attending rural schools in Pichincha Province in Ecuador.

Results: A total of 2865 children aged 5 to 19 years from 55 schools was examined. Active infection with any geohelminth and infections with *A. lumbricoides* or *Ancylostoma duodenale* were associated with significant protective effects against allergen skin test reactivity. Children with the highest levels of total IgE or with anti-*A. lumbricoides* IgG4 antibodies were protected against skin test reactivity also, and the protective effects of high IgE or anti-*A. lumbricoides* IgG4 and or active geohelminth infections were statistically independent.

Conclusion: Active infections with geohelminth parasites and the presence of serologic markers of chronic infections (high levels of total serum IgE or anti-*A. lumbricoides* IgG4) are independent protective factors against allergen skin test reactivity among school-age children living in an endemic region of the rural tropics. (J Allergy Clin Immunol 2003;111:995-1000.)

Key words: Geohelminths, intestinal helminths, atopy, total IgE, anti-*Ascaris lumbricoides* IgG4, tropics, Ecuador

Abbreviation used

OR: Odds ratio

The prevalence of atopy and allergic diseases is greater in industrialized countries^{1,2} compared with that seen in nonindustrialized countries. In Africa the prevalence of atopy is greater among populations with lifestyles that are more urban and presumably more industrialized.³ Environmental factors might be important determinants of these large differences in the expression of atopy and include differences in infectious disease exposures.⁴

Several infectious agents, including measles and hepatitis A, have been associated with a protective role against allergic disease.⁵ Geohelminths are probably the most prevalent and persistent of all childhood infections in many regions of the tropics and are estimated to infect approximately one third of the human population. *Ascaris lumbricoides* (ascariasis), *Trichuris trichiura* (trichuriasis), and *Ancylostoma duodenale* (hookworm) are the most prevalent geohelminth infections.⁶ Previous studies have shown a negative relationship between geohelminth infection and allergen skin test reactivity^{7,8} and recent wheezing.⁹ There are no large published studies investigating the protective effects of geohelminth infections on atopy conducted among school-age children living in endemic areas.

To investigate the hypothesis that children infected with geohelminth parasites are protected against the development of atopy, we conducted an analytic cross-sectional study among school-age children attending schools in a rural region of Ecuador. Because the postulated suppression of atopy by geohelminth infection is likely to be mediated through immunologic mechanisms, we hypothesized that antiallergic suppressive mechanisms are likely to develop after chronic or repeated geohelminth infections and would only be observed among children with chronic infections. To examine the protective effects of geohelminth infections, we sought to do the following: (1) to compare the prevalence of atopy in children with and without active geohelminth infections; (2) to investigate the association of atopy with 2 putative markers of chronic geohelminth infection (total serum IgE or anti-*A. lumbricoides* IgG4 antibodies); and (3) to

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test whether chronic geohelminth infection is a necessary precondition for the effect of active geohelminth infection on atopy or whether the effects of active and chronic geohelminth infections are independent.

METHODS

Study population

The study area covered schools (for children aged 5-19 years) in the Districts of Pedro Vicente Maldonado, Puerto Quito, and Los Bancos in Pichincha Province. The area is a subtropical-tropical rain forest at altitudes of 200 to 1100 meters above sea level. All 55 schools included in the study served rural communities that ranged in size from approximately 100 to 3000 individuals. All children attending the schools were eligible to participate. Informed verbal consent was obtained from the parent or guardian of each child. The study was approved by the ethical committees of the National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md; St George's Hospital Medical School, London, United Kingdom; and the foundation Salud y Desarrollo Andino (SALUDESA), Quito, Ecuador.

Study design

Parents of study children were questioned about the presence of allergic symptoms and recent anthelmintic treatment by using a questionnaire modified from the International Study of Asthma and Allergies in Childhood phase I studies.² Children were examined by means of allergen skin prick testing, examination of stool samples for geohelminth infection, and analysis of blood for measurement of levels of total IgE and anti-*A lumbricoides* IgG4. Skin prick testing was used to determine atopic status. Seven allergens and 2 control agents were used for skin testing. The specific allergens used were selected on the basis of the results of a previous unpublished survey. The allergens and control agents included glycerol and saline control (Greer Laboratories Inc), *Dermatophagoides pteronyssinus* (ALK-Abello, Denmark), *Dermatophagoides farinae* (ALK), grass pollen mix (9 Southern grass mix, Greer), tree pollen mix (11 North American tree mix, Greer), American cockroach (Greer), *Alternaria tenuis* (Greer), cat (Greer), and histamine control (10 g/L, ALK). Allergens were scratched onto the volar side of the forearm of each child with ALK plastic bifurcated lancets according to the manufacturer's instructions. After 15 minutes, wheal sizes were recorded by measuring the 2 perpendicular diameters of reactions at each scratch site, excluding pseudopods; reactions were positive if the size (mean of the 2 perpendicular readings) was at least 3 mm greater than that produced by the saline control. Fresh stool samples were collected and examined by means of the modified Kato Katz method, as previously described.¹⁰ One slide per person was read, the numbers of helminth eggs were counted, and the number of helminth eggs per gram of feces was calculated. All samples were generally examined within 1 hour. For measurement of levels of total IgE, Immulon 4 plates (Dynatech, Chantilly, Va) were coated with monoclonal anti-human IgE (E5 clone; ATCC, Springfield, Va) and were incubated overnight at 4°C. After coating the wells with blocking buffer (0.005% Tween and 5% BSA in PBS) for 2 hours, the plates were washed, and diluted plasma samples (diluted 1:100) and standards (IgE standard; Immulite, Los Angeles, Calif) were added to the plates. After incubating the plates overnight at 4°C, the detection antibody was added (alkaline phosphatase-conjugated polyclonal goat anti-human IgE; Kirkegaard Perry Inc, Gaithersburg, Md). Plates were developed with *p*-nitrophenyl phosphate in sodium carbonate buffer and read with a microplate reader, and results were expressed as international units per milliliter. Further serum dilutions were used if the results exceeded the evaluable range of the assay. The measured range for IgE levels was 12 to

31,250 IU/mL. Measurement of *A lumbricoides*-specific IgG4 was performed as described previously,¹¹ and antibody levels were expressed as arbitrary units.

Statistical analysis

Atopy was defined as a positive reaction to any of the 7 allergens tested, and active geohelminth infection was defined by the presence of geohelminth ova in stool samples. Chronic infection was defined on the basis of total serum IgE levels of at least 3564 IU/mL or detectable anti-*A lumbricoides* IgG4 antibodies. High levels of total serum IgE and the presence of parasite-specific IgG4 antibodies are typical features of chronic helminth infections.¹²⁻¹⁵ Because ascariasis was the dominant geohelminth infection in the study area and because there is significant immunologic cross-reactivity between antigens of different geohelminth species,¹⁵ we considered that anti-*A lumbricoides* IgG4 responses would be a useful marker for the antiparasite IgG4 response. All estimates of risk were calculated by using conditional logistic regression with matching by school. The effects of geohelminths and total IgE levels were examined in univariate analyses and also in multivariate analyses in which the effects of age and sex and other relevant variables were controlled. An odds ratio (OR) of less than 1 indicates a protective effect, whereas an OR of greater than 1 indicates increased risk. The effects of infection intensity for infections with *A lumbricoides* and *T trichiura* on the risk of atopy were examined by using categories of infection intensity that were multiples of 70 (the sensitivity of the parasite detection method used). Infection intensities with *A duodenale* were not examined because the prevalence of *A duodenale* was low (2.8%) and the range of intensities were narrow (0-5325 eggs per gram). Dose-response relationships between geohelminth parasite burden and risk of skin test reactivity were examined by using χ^2 tests for trend.

For assessment of total IgE and *A lumbricoides*-specific IgG4 antibodies, plasma from a subsample of 1483 (51.8%) children from 42 schools was analyzed. Analyses of the effect of total IgE on the risk of allergen skin test reactivity initially used total IgE expressed as an ordinal categorical variable (quintile). This was recoded as a binary categorical variable (upper quintile vs the rest) because the risk of allergen skin test reactivity in the first 4 quintiles was the same but was lower (43% reduction in risk) in the upper quintile. In the analysis presented here, the high IgE stratum included individuals with total IgE levels of greater than or equal to 3564 IU/mL (geometric mean, 8698 IU/mL), whereas the low IgE stratum had a geometric mean concentration of 733 IU/mL. Because *A lumbricoides*-specific IgG4 was detected in only 48% of subjects, this variable was analyzed as a binary categorical variable (presence vs absence of antibody). To examine the dependence of the protective effects of active infection on the presence of chronic infection, we divided the data from the subsample of 1483 children into 4 strata according to the presence and absence of active and chronic infections. These strata were as follows: (1) no geohelminth infection (ova negative and low IgE level or ova negative and absence of anti-*A lumbricoides* IgG4); (2) no active infection but serologic evidence of chronic infection (ova negative and high IgE level or ova negative and presence of anti-*A lumbricoides* IgG4); (3) new active infection (ova positive and low IgE level or ova positive and absence of anti-*A lumbricoides* IgG4); and (4) chronic active infection (ova positive and high IgE level or ova positive and presence of anti-*A lumbricoides* IgG4). A 4-way analysis was performed in which the risk of atopy associated with each geohelminth infection stratum was calculated by comparison with the no geohelminth infection stratum as baseline, and the presence of statistical interactions between total IgE or anti-*A lumbricoides* IgG4 and active geohelminth infections on the risk of atopy were assessed. In addition, we used a hierarchic approach to investigate whether the variables

of IgE or anti-*A lumbricoides* IgG4 levels were intermediate factors in the biologic pathway between geohelminth infection and skin test reactivity or whether the variables were independent risk factors. In this approach controlling for an intermediate factor in the biologic pathway would be expected to decrease the estimate of effect for skin test reactivity toward unity. The risk of skin test reactivity associated with active geohelminth infection was examined by means of the addition of the 2 serologic variables, separately and together, to the conditional logistic regression models for the risk of skin test reactivity associated with geohelminth infections. All statistical analyses were performed by using Stata 7 software. Statistical significance is inferred by a *P* value of less than .05.

RESULTS

Stool and skin test examinations were performed on samples from 2865 (88.2%) subjects of a total eligible school population of 3249 attending 55 schools. The main reason for nonparticipation was failure to provide a stool sample (366 [95.3%] of 384 nonparticipants). There were only slight differences in the mean age (10.3 vs 10.6 years), sex distribution (boys 46.9% vs girls 52.5%), prevalence of recent anthelmintic treatment (63.4% vs 63.6%), and prevalence of atopy (21.9% vs 22.4%) between those who participated in the study and those who were eligible but did not participate. The prevalences of allergic symptoms over the previous 12 months in the study group were as follows: wheezing, 2.6%; eczema, 4.0%; and rhinitis, 4.1%. The prevalences of infection with *A lumbricoides*, *T trichiura*, and *A duodenale* were 54.5%, 46.4%, and 2.8%, respectively, and the prevalence of infection with any of the 3 geohelminths was 68.6%. The prevalences of atopy to the allergens tested were as follows: *D pteronyssinus*, 9.2%; *D farinae*, 6.0%; grass mix, 2.8%; tree mix, 2.3%; cockroach, 11.3%; *Alternaria*, 0.9%; and cat, 1.6%. Positive skin test reactions to any allergen were observed in 627 (21.9%) subjects. There were wide ranges in the prevalence of allergen skin test reactivity (0%-80%) and geohelminth infection (22.2%-100%) among schools, and a weak negative correlation ($r = -0.22$, $P = .1$) was observed between the prevalence of infection with any geohelminth and the prevalence of skin test reactivity at the level of the schools.

Age, sex, and the receipt of anthelmintic treatment within the previous 6 months were not risk factors for allergen skin test reactivity in the study group. In univariate analyses, there was evidence for statistically significant protective effects against allergen skin test reactivity for each of the 3 geohelminth parasites and for any of the 3 geohelminth parasites (Table I). High levels of IgE and the presence of anti-*A lumbricoides* IgG4 antibodies were protective against allergen skin test reactivity (Table II) in the sample of 1483 subjects analyzed for these serologic parameters.

The effect on allergen skin test reactivity of having any geohelminth infection and of having infections with *A lumbricoides* or *A duodenale* remained significantly protective in multivariate analyses (Table I). A statistically significant dose-response relationship was observed between the intensity of geohelminth infection and the

risk of skin test reactivity (Table I) for infections with *A lumbricoides* or *T trichiura*. The effects of geohelminth infections were also significant against the specific allergens (house dust mite [*D pteronyssinus* and *D farinae* combined]: OR, 0.66; 95% CI, 0.509-0.86; $P = .002$; cockroach: OR, 0.59; 95% CI, 0.46-0.76; $P < .001$), and these remained significant in the multivariate analyses (house dust mite: adjusted OR, 0.65; 95% CI, 0.50-0.85; $P = .002$; cockroach: adjusted OR, 0.59; 95% CI, 0.46-0.76; $P < .001$).

There was evidence of a strong protective effect of high IgE levels against skin test reactivity to any allergen (OR, 0.63; 95% CI, 0.43-0.92; $P = .02$) in multivariate analyses that controlled for age and sex. Similarly, the risk of skin test reactivity was reduced among children with *A lumbricoides*-specific IgG4 antibodies (OR, 0.71; 95% CI, 0.54-0.93; $P = .01$) after controlling for age and sex.

Analyses that examined the dependence of the protective effects of active infection on the presence of chronic infection indicated no evidence of statistically significant interactions ($P > .5$) between the serologic parameters of chronic infection and active geohelminth infection on the risk of atopy. Four-way analyses showed that the protective effect of new active infections (ova positive and low IgE level or ova positive and absent anti-*A lumbricoides* IgG4) were of a similar magnitude to that of chronic nonactive (ova negative and high IgE level or ova negative and present anti-*A lumbricoides* IgG4) infections, although only the former effects were statistically significant. The strongest protective effects were observed in children with chronic active infections (ova positive and high IgE level or ova positive and present anti-*A lumbricoides* IgG4; Table III). The magnitude of the protective effects associated with high total IgE and anti-*A lumbricoides* IgG4 (ie, chronic nonactive and chronic active infections) were similar (Table III). In the hierarchic analyses controlling for total levels of IgE (age- and sex-adjusted OR for any geohelminth infection of 0.65 [95% CI, 0.49-0.87, $P = .004$] vs age-, sex-, and total IgE-adjusted OR for any geohelminth infection of 0.67 [95% CI, 0.50-0.90; $P = .007$]) and *A lumbricoides*-specific IgG4 (age- and sex-adjusted OR for any geohelminth infection of 0.65 [95% CI, 0.49-0.87; $P = .004$] vs age-, sex-, and anti-*A lumbricoides* IgG4-adjusted OR for any geohelminth infection of 0.66 [95% CI, 0.49-0.88; $P = .005$]) had very little effect on the OR for risk of skin test reactivity for any of the parameters of geohelminth infection (data not shown). Similarly, controlling for the different parameters of geohelminth infection had little effect on the estimates of effect for the antibody parameters (adjusted ORs for IgE were 0.66 for all analyses and ranged from 0.63 to 0.75 for anti-*A lumbricoides* IgG4). These results indicate that the effect of geohelminth infections was independent of the effects of either antibody parameter and that neither of the 2 serologic parameters is on the biologic pathway between geohelminth infection and skin test reactivity. Models that included both antibody parameters indicated colinearity between them.

TABLE I. Univariate and multivariate analyses of the association between skin test reactivity (atopy) and age, sex, recent anthelmintic treatment, and geohelminth infection prevalence and intensity*

Factor	Nonatopic (n = 2238)	Atopic (n = 627)	Univariate		Multivariate	
			OR (95% CI)	P value	OR (95% CI)	P value
Age (y)						
5-9	879 (76.7%)	267 (23.3%)	1.00			
10-14	1272 (78.9%)	340 (21.1%)	0.97 (0.72-1.05)	.14		
15-19	87 (81.3%)	20 (18.7%)	0.86 (0.50-1.49)	.60		
Sex						
Male	1040 (77.4%)	304 (22.6%)				
Female	1198 (78.8%)	323 (21.2%)	1.00 (0.83-1.21)	.98		
Recent anthelmintic treatment†						
No	796 (78.6%)	217 (21.4%)				
Yes	1358 (77.3%)	399 (22.7%)	0.91 (0.74-1.12)	.39		
<i>A lumbricoides</i>						
Negative	964 (73.9%)	340 (26.1%)				
Positive	1274 (81.6%)	287 (18.4%)	0.68 (0.56-0.83)	<.001	0.74 (0.60-0.91)	.005
Intensity (epg)‡						
0	964 (73.9%)	340 (26.1%)	1.00	.007‡	1.00	.01‡
70-700	250 (83.1%)	51 (16.9%)	0.54 (0.39-0.75)	<.001	0.58 (0.41-0.81)	.001
701-7000	344 (78.7%)	93 (21.3%)	0.81 (0.62-1.07)	.13	0.88 (0.66-1.16)	.37
7001-70,000	566 (81.1%)	132 (18.9%)	0.73 (0.57-0.93)	.01	0.84 (0.64-1.09)	.19
>70,000	114 (91.2%)	11 (8.8%)	0.32 (0.17-0.62)	.001	0.42 (0.21-0.82)	.01
<i>T trichiura</i>						
Negative	1151 (74.9%)	385 (25.1%)				
Positive	1087 (81.8%)	242 (18.2%)	0.73 (0.60-0.89)	.002	0.82 (0.67-1.01)	.07
Intensity (epg)						
0	1151 (74.9%)	385 (25.1%)	1.00	.007‡	1.00	.03‡
70-700	709 (79.5%)	183 (20.5%)	0.81 (0.60-1.00)	.05	0.88 (0.71-1.10)	.31
>700	378 (86.5%)	59 (13.5%)	0.53 (0.38-0.74)	<.001	0.63 (0.44-0.90)	.01
<i>A duodenale</i>						
Negative	2167 (77.8%)	619 (22.2%)				
Positive	71 (89.8%)	8 (10.1%)	0.33 (0.16-0.72)	.005	0.39 (0.18-0.85)	.02
Any geohelminth						
Negative	677 (71.6%)	269 (28.4%)				
Positive	1561 (81.3%)	358 (18.7%)	0.64 (0.52-0.78)	<.001	0.64 (0.52-0.78)	<.001

epg, Eggs per gram.

*Shown are matched univariate and multivariate ORs with 95% CIs. Multivariate ORs are adjusted for age, sex, and other geohelminth infections (presence or intensity, where appropriate).

†Recent anthelmintic treatment (ie, treatment within the previous 6 months).

‡ χ^2 Test for trend.

DISCUSSION

The results of our cross-sectional study indicate that current infections with geohelminths are protective against allergen skin test reactivity. To our knowledge, this is the first large study to show a protective effect among school-age children living in an endemic rural area. A strong protective effect was observed for the presence of any of the 3 locally endemic geohelminth parasites (*A lumbricoides*, *T trichiura*, and *A duodenale*) after controlling for the effects of age, sex, recent anthelmintic treatment, and schools. There was evidence of a nonlinear relationship between parasite burden with *A lumbricoides* and *T trichiura* and risk of skin test reactivity, but greater protection was seen at the highest parasite burdens.

The major potential confounder is geography, which is likely to have been associated with exposure to both geohelminth parasites and aeroallergens, as indicated by the interschool differences in the prevalence of geohelminths

and sensitization to aeroallergens and the negative correlation between the prevalence of geohelminth infection and allergen skin test reactivity at the school level. Analysis was based on children being matched by school to control for geography. We considered that school would reflect more accurately the shared environment of small rural communities in which exposure to geohelminths and aeroallergens is likely to be more homogeneous and should permit the statistical control of factors that determine such exposures in a relatively efficient manner. We were not able to control for other factors that might have confounded the relationship between geohelminth infection and skin test reactivity. Such factors might include socioeconomic status, other infectious agents (including enteric infections), diet, and antibiotic use. Uncontrolled confounding by these factors cannot be discounted. A limitation of the study is misclassification of exposure. Nondifferential misclassification might have affected the estimate of effect for current geohelminth infections: infection status was defined on the

TABLE II. Skin test reactivity (atopy) by IgE level and presence of anti-*A lumbricoides* IgG4 antibodies in a subsample of 1483 school-age children*†

Factor	Nonatopic (n = 1151)	Atopic (n = 332)	OR (95% CI)	P value
Quintiles of IgE (IU/mL)				
1: 162 (12-355)	227 (76.7%)	69 (23.3%)	1.00	.170‡
2: 566 (364-888)	228 (77.3%)	67 (22.7%)	0.94 (0.64-1.40)	.78
3: 1269 (893-1810)	223 (74.8%)	75 (25.2%)	1.08 (0.73-1.60)	.69
4: 2469 (1811-3561)	220 (74.1%)	77 (25.9%)	1.05 (0.71-1.56)	.81
5: 8698 (3564-31,250)	253 (85.2%)	44 (14.8%)	0.57 (0.41-1.02)	.06
IgE (IU/mL)				
Low: 733 (12-3561)	898 (75.7%)	288 (24.3%)		
High: 8698 (3564-31,250)	253 (85.2%)	44 (14.8%)	0.63 (0.43-0.92)	.02
Anti- <i>A lumbricoides</i> IgG4				
Negative	560 (72.6%)	211 (27.4%)		
Positive	591 (83.0%)	121 (17.0%)	0.68 (0.52-0.90)	.007

*Shown are matched univariate ORs with 95% CIs.

†Values of IgE show geometric means and ranges (in parentheses).

‡ χ^2 Test for trend.

TABLE III. Four-way analysis of skin test reactivity (atopy) by active geohelminth infection level (ova positive vs ova negative) and chronic infection level (high vs low IgE levels or presence vs absence of anti-*A lumbricoides* IgG4) in a subsample of 1483 school-age children*

Factor	Nonatopic (n = 1151)	Atopic (n = 332)	Univariate		Multivariate	
			OR (95% CI)	P value	OR (95% CI)	P value
IgE						
1: Ova negative/low	280 (69.3%)	124 (30.7%)	1		1	
2: Ova negative/high	41 (83.7%)	8 (16.3%)	0.49 (0.22-1.12)	.09	0.49 (0.22-1.09)	.08
3: Ova positive/low	618 (79.0%)	164 (21.0%)	0.65 (0.49-0.91)	.005	0.65 (0.48-0.88)	.005
4: Ova positive/high	212 (85.5%)	36 (14.5%)	0.47 (0.29-0.75)	.002	0.47 (0.29-0.76)	.002
Anti- <i>A lumbricoides</i> IgG4						
1: Ova negative/absent	213 (68.1%)	100 (32.0%)	1		1	
2: Ova negative/present	108 (77.1%)	32 (22.9%)	0.74 (0.46-1.19)	.21	0.72 (0.45-1.18)	.20
3: Ova positive/absent	347 (75.8%)	111 (24.2%)	0.69 (0.49-0.97)	.04	0.68 (0.48-0.96)	.03
4: Ova positive/present	483 (84.4%)	89 (15.6%)	0.48 (0.33-0.70)	<.001	0.49 (0.33-0.70)	<.001

Strata 1, No geohelminth infection; strata 2, no active infection but serologic evidence of chronic infection; strata 3, new active infection; strata 4, chronic active infection.

*Shown are matched univariate and multivariate (adjusted for age and sex) ORs with 95% CIs.

basis of a single stool sample, and the presence of low-level infections cannot be excluded.

The geohelminth infections *A lumbricoides*, *T trichiura*, and *A duodenale*, unlike many other infectious agents, do not replicate within the host, and adult parasites survive for periods of 1 to 7 years depending on parasite species. The presence of infection in a cross-sectional study with sampling at a single time point might indicate either a new active infection or a chronic active infection through repeated reinfections or a single long-lasting infection. The absence of infection might indicate no infection and presumably no exposure or no infection because of recent anthelmintic treatment or parasite expulsion by other causes. In the latter case a child might have serologic evidence of chronic infection but no active infection at the time of sampling. Because there is no easy way of identifying chronic infection, we used 2 serologic parameters as surrogate markers for chronic infection: high total IgE levels might reflect either parasitism or atopy, but anti-*A lumbricoides* IgG4 is likely to relate only to parasite infection.

We were able to demonstrate a negative association between very high levels of total IgE and skin test reactivity. Helminth parasites are the most powerful known inducers of IgE production and are associated with very high circulating levels.¹⁴ There are 2 possible explanations for our observation of a protective effect of high levels of total IgE against atopy: (1) the production of large amounts of polyclonal IgE in helminthiasis might modulate immediate hypersensitivity reactions by means of saturation of high-affinity Fc ϵ RI receptors on mast cells and basophils^{7,16,17} by IgE of multiple specificities, and (2) high levels of total IgE might be a marker for other immunologic factors that mediate protection against atopy. Such immunologic factors that mediate protection against atopy include anti-inflammatory cytokines, such as IL-10, which has been associated with a protective effect of *Schistosoma haematobium* infection against atopy to house dust mites.¹⁸ The observation that protective effects of similar magnitudes were observed for the presence of *A lumbricoides*-specific IgG4 would support the latter explanation. Statistical colin-

earity between high levels of total IgE and the presence of *A lumbricoides*-specific IgG4 might indicate that the protective effects associated with each serologic parameter could occur through the same biologic pathway.

We used the data to test the hypothesis that the protective effects of active infection are dependent on the presence of high total IgE or anti-*A lumbricoides* IgG4 antibodies that were used as markers of chronic infection with geohelminths. We considered that the protective effects of active geohelminth infections against allergen skin test reactivity could be explained by immune adaptations that follow chronic infections with geohelminths. Contrary to our hypothesis, the study findings indicate that active and chronic geohelminth infections have independent protective effects: there was no evidence for statistical interactions between active and chronic infections on the risk of atopy and no evidence that the serologic parameters of chronic infections lie on the biologic pathway between active geohelminth infection and atopy. The conceptual model of geohelminths being protective against atopy (rather than vice versa) is likely to be valid because a previous study has demonstrated an increase in the prevalence of atopy after long-term anthelmintic treatment of geohelminth-infected children.¹⁹

The magnitude of the protective effects against atopy were similar for children with serologic evidence of chronic infection but without active infections as for children without evidence of chronic infection but with active infections, irrespective of the serologic parameter used to identify chronic infection. The strongest protective effects were observed in children with evidence of both chronic and active infections, but the statistical independence of the 2 forms of infection in hierarchic analyses might indicate that the protective effects of active and chronic geohelminth infections occur through different biologic pathways. The use of 2 different serologic parameters as markers of chronic infection that showed similar estimates of effect in the various analyses is supportive of our analytic approach and our study findings.

In conclusion, our data suggest that active infections with geohelminth parasites are associated with a strong protective effect against skin test reactivity to environmental allergens and that the magnitude of this effect is partly dependent on parasite burden. The consistency between the findings of a protective effect at the individual and school levels is supportive. We have provided evidence that high levels of total IgE or the presence of anti-*A lumbricoides* IgG4 antibodies, both of which represent serologic markers for chronic infections with geohelminth parasites, were protective also against allergen skin test reactivity, and the protective effects of active and chronic infections appeared to be statistically independent. Although atopy and allergic disease are not important public health problems in rural areas of the tropics at present, epidemiologic studies are required now to investigate potential protective exposures that might permit the design of interventions to prevent the large increases in allergic disease that are expected in the future. Future studies are required to determine whether the suppressive effects of geohelminth infections are reversible by means of

anthelmintic treatment and to identify the mechanisms of protection associated with active and chronic infections.

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