

Effects of maternal geohelminth infections on allergy in early childhood



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Background: Maternal geohelminth infections during pregnancy may protect against allergy development in childhood.

Objective: We sought to investigate the effect of maternal geohelminths on the development of eczema, wheeze, and atopy during the first 3 years of life.

Methods: A cohort of 2404 neonates was followed to 3 years of age in a rural district in coastal Ecuador. Data on wheeze and eczema were collected by means of questionnaire and physical examination at 13, 24, and 36 months of age. Atopy was measured based on skin prick test (SPT) reactivity to 9 allergens at 36 months. Maternal stool samples were examined for geohelminths by microscopy. Data on potential confounders was collected after birth by questionnaire.

Results: Geohelminths were observed in 45.9% of mothers. Eczema and wheeze were reported for 17.7% and 25.9%, respectively, of 2069 (86.1%) children with complete follow-up to 3 years, and allergen SPT reactivity to any allergen was present in 17.2% and to house dust mite in 8.7%. Maternal geohelminth infections were not significantly associated with eczema (adjusted odds ratio [OR], 1.26; 95% CI, 0.98-1.61), wheeze (adjusted OR, 1.02; 95% CI, 0.82-1.27), and SPT reactivity to any allergen (adjusted OR, 0.79; 95% CI, 0.61-1.01). In subgroup analyses maternal geohelminths were associated with a significantly reduced risk of SPT reactivity to mite and other perennial allergens, and maternal ascariasis was associated with an increased risk of eczema and reduced risk of SPT reactivity to all allergens.

Conclusion: Our data do not support a protective effect of maternal infections with geohelminth parasites during

pregnancy against the development of eczema and wheeze in early childhood, although there was evidence in subgroup analyses for a reduction in SPT reactivity to house dust mites and perennial allergens. (*J Allergy Clin Immunol* 2016;137:899-906.)

Key words: Geohelminths, maternal infections, atopy, wheeze, eczema, early childhood

Allergic diseases, such as asthma and eczema, have emerged as major health problems in many developing countries, particularly in urban Latin America.¹ The causes of such temporal increases are likely to be explained by environmental changes.^{1,2}

The hygiene hypothesis has explained the increasing prevalence of allergic diseases in the context of decreasing exposures to common infectious diseases of childhood³ and a decreased diversity of microbial exposures in the environment.⁴ Among potentially protective infections, there has been considerable interest in the role of geohelminth parasites (eg, *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm), which are extremely common chronic infections of childhood in developing countries, where an estimated 2 billion humans are infected. The relationship between geohelminth infections and allergy is complex.⁵ Although infections are generally associated with a reduced prevalence of allergen skin prick test (SPT) reactivity,⁶ their effects on allergic diseases are less clear.⁷ Treatment studies of geohelminths in schoolchildren have not shown effects on the prevalence of allergic diseases⁸⁻¹⁰ or consistent increases in allergen SPT reactivity prevalence⁸⁻¹¹ after anthelmintic treatment. It has been suggested that *in utero* and early-life exposures might be important for mediating protection.¹² Other environmental exposures that have been associated with protection against allergy, such as farming, have stronger effects when exposure occurs *in utero* and in early childhood.¹³⁻¹⁵

We recruited a birth cohort in an area of Ecuador with a high maternal prevalence of geohelminth infections to test the hypothesis that *in utero* exposures to geohelminth parasites through having an infected mother protect against the development of eczema, wheeze, and atopy during the first 3 years of life.

METHODS

Study design and setting

A prospective study from birth was done in the rural District of Quininde, Esmeraldas Province, Ecuador, as described in detail elsewhere.¹⁶ The district serves a population of approximately 150,000 with an economy based on agricultural activities, primarily African palm oil, and limited access to basic services.

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Abbreviations used

epg: Eggs per gram
HDM: House dust mite
OR: Odds ratio
SPT: Skin prick test

Study participants

Neonates were recruited in the public hospital, Hospital "Padre Alberto Buffini," which serves the district, between November 2005 and December 2009. Eligibility criteria were as follows: (1) healthy baby aged less than 14 days; (2) collection of stool sample from the mother; (3) mother aged 17 years or more; (4) family resident in the District of Quinde for at least 2 years with plans to stay for at least 3 more years; and (5) accessible household.

Questionnaires

Children were followed up to 3 years of age. Data on demographic and socioeconomic factors, household characteristics, maternal obstetric history, family history of chronic illnesses, and relevant environmental exposures within and outside the household were collected using an interview-led questionnaire from the child's mother after the child's birth. Questionnaires were done annually at 13, 24, and 36 months to collect data on the development of eczema and wheezing and other relevant information.

Measurement of maternal infections with geohelminth infections

Stool samples to measure geohelminth infections were collected from mothers during the third trimester or immediately after the child's birth and in children at 13 and 24 months of age. Samples were examined using a combination of methods, including saline mounts, the Kato-Katz method, formol-ether concentration, and carbon coproculture methods.¹⁷ A positive sample was defined by the presence of at least 1 egg or larva from any of the 4 detection methods. *A lumbricoides* and *T trichiura* infection intensities were expressed as eggs per gram (epg) of feces using results from the Kato-Katz method.¹⁸

Measurement of eczema and wheeze

Data were collected using periodic questionnaires and examinations for visible signs of flexural dermatitis with a standardized photographic protocol.¹⁸ Eczema was defined using the United Kingdom refinement of the Hanifin and Rajka diagnostic criteria.¹⁸ Children were considered to have eczema if the mother reported the child to have had an itchy skin condition during the previous 12 months plus at least 3 of the following: (1) involvement of skin creases and cheeks; (2) history of allergic disease in siblings or parents; (3) history of generally dry skin; and (4) visible flexural dermatitis, including that affecting the cheeks, forehead and outer limbs. Recent wheeze was defined as any episode of reported wheeze during the previous 12 months.

Allergen SPT reactivity

Allergic sensitization was measured at 36 months using SPTs with 9 allergen extracts (Greer Laboratories, Lenoir, NC): house dust mites (HDMs; *Dermatophagoides pteronyssinus*/*Dermatophagoides farinae* mix), American cockroach (*Periplaneta americana*), cat, dog, grass pollen (9 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 of at least 2 mm greater than that elicited by the saline control 15 minutes after pricking the allergen onto the volar side of the forearm with ALK-Abelló lancets (ALK-Abelló, Hungerford, United Kingdom). A positive SPT response was defined as a positive reaction to any of the allergens tested. All testing was done by trained physicians (M.E.C. and M.V.).

Statistical analysis

We estimated that with 1840 children followed up at 3 years of age and approximately 50% of mothers infected with geohelminths, we would have greater than 95% power to detect a difference of at least 5% between groups for outcomes with 10% or greater prevalence, considering a *P* value of less than .05. The primary analysis was the association between maternal geohelminths and eczema, wheeze, and atopy. Secondary analyses addressed associations between maternal geohelminth species and study outcomes, including mite atopy. Bivariate logistic regression analyses were done to estimate associations between maternal geohelminth infections or potential confounders and outcomes. Multivariate logistic regression was used to estimate associations between maternal geohelminth infections and outcomes. Potential confounders considered in the analyses are shown in Table I. A socioeconomic status index was created by using principal components analysis of 7 socioeconomic variables, as previously described.¹⁹ Child geohelminth infections were defined as any infection during the first 2 years of life. Potential confounders in any of the bivariate analyses with a *P* value of less than .20 were kept in the final models using the same set of confounders to adjust all models. All statistical analyses were done with Stata 11 software (StataCorp, College Station, Tex).

Ethical considerations

The protocol was approved by the ethics committees of the Hospital Pedro Vicente Maldonado, Universidad San Francisco de Quito, and Pontificia Universidad Católica del 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 of albendazole) was provided to mothers with geohelminth infections after delivery. Children with positive stool results for geohelminths were treated with a single dose of 400 mg of albendazole if aged 2 years or greater and with pyrantel pamoate (11 mg/kg) if aged less than 2 years, according to Ecuadorian Ministry of Public Health recommendations.^{20,21}

RESULTS**Cohort participants**

Follow-up information for the 2404 neonates recruited is provided in Fig 1. Follow-up was greater than 90% at each of the annual follow-ups during the first 3 years of life in the cohort, and complete data for all 3 observation times (ie, 13, 24, and 36 months) were available for 2069 (86.1%) children. Maternal infections with malaria, HIV, and other helminths were of low prevalence (<0.5%) in the study population.

Frequencies of exposures and outcomes

Geohelminth infections were detected in 45.9% of mothers as follows: *A lumbricoides* (27.5%), *T trichiura* (28.9%), hookworm (5.6%), and *Strongyloides stercoralis* (3.9%). The only other helminth parasite observed was the cestode *Hymenolepis nana* (0.5%). The proportions of mothers by infection intensity category were as follows: *A lumbricoides* light (<5000 epg) at 17.1% and moderate/heavy (>5000 epg) at 5.1% and *T trichiura* light (<1000 epg) at 22.0% and moderate/heavy (>1000 epg) at 4.2%. The prevalence of eczema at 13, 24, and 36 months was 12.6%, 4.7%, and 3.4%, respectively, with 17.7% of children having eczema at least once. Only 2.5% had episodes of eczema documented for 2 or more visits. The prevalence of reported wheeze at 13, 24, and 36 months was 16.1%, 8.0%, and 8.5%, respectively, and 25.9% had at least 1 reported episode. Allergen SPT reactivity was present in 17.2% of children at 3 years of age: *D pteronyssinus*/*D farinae* (8.7%), cockroach (2.9%), mixed

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