Effect of early life geohelminth infections on the development of wheezing at 5 years of age

Philip J Cooper1-3, Martha E Chico2, Maritza G Vaca2, Carlos A Sandoval2, Sofia Loor2, Leila Amorim5, Laura C Rodrigues6, Mauricio L Barreto5, David P Strachan4.

1Facultad de Ciencias Medicas, de la Salud y la Vida, Universidad Internacional del Ecuador, Quito, Ecuador; 2Laboratorio de Investigaciones FEPIS, Quininde, Esmeraldas Province, Ecuador; Institutes of 3Infection and Immunity and 4Population Health Research, St. George’s University of London, London, UK; 5Instituto de Saude Coletiva, Universidade Federal da Bahia, Salvador, Brazil; 6Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK.

**Correspondence**:

Dr. Philip J. Cooper

Institute of Infection and Immunity,

St George’s University of London,

Cranmer Terrace,

London SW17 ORE.

e-mail: pcooper@sgul.ac.uk

tel: (44) 208 725 55372.

**Author contributions:** Conception and design, PJC, LCR, MLB, DPS; Data collection, MEC, MGV, CAS, SL; Data analysis, PJC, LA; Drafted manuscript, PJC; All authors contributed to the writing and editing of the manuscript

..

**Funding source**: Wellcome Trust grant 088862/Z/09/Z

**Running title**: Geohelminths and childhood wheeze in Ecuador

**Descriptor:** Asthma - Epidemiology (Pediatric): Risk Factors

**Word count (body):** 3499

**Word count (abstract):** 250

**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 while 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. While 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.

**Online Data Supplement**: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

**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**: Cohort of 2,404 neonates followed to 5 years of age in rural District in coastal Ecuador. Data on wheeze collected by questionnaire and atopy measured by allergen skin prick test reactivity to 9 allergens at 5 years. Stool samples from mothers and children examined for geohelminths by microscopy.

**Measurements and Main Results:** 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, while 14.0% had skin test reactivity at 5 years. Maternal geohelminths were associated with an increased risk of wheeze (adjusted OR 1.41, 95% CI 1.06-1.88) while childhood geohelminths over the first 3 years of life were associated with reduced risk of wheeze (adjusted OR 0.70, 95% CI 0.52-0.96) and asthma (adjusted OR 0.60, 95% CI 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:** While maternal exposures to geohelminths may increase childhood wheeze, childhood geohelminths during the first 3 years may provide protection through a non-allergic mechanism.

**Key words**: geohelminths, atopy, wheeze, asthma, childhood, tropics

**Introduction**

Asthma is the commonest chronic disease of childhood in industrialized countries, is estimated to affect over 300 millions worldwide[1], and has emerged as an important public health problem in many non-industrialized regions[1,2].

Increases in asthma prevalence, such as observed in urban regions of Latin America[2,3], are 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 anti-infective 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 Th2 responses that are critical for parasite killing and elimination[6]. Chronic geohelminth infections are associated with the modulation of anti-parasite Th2 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]. While 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 Ecuadorian 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 these 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 <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 4) 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 socio-demographic 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 of a combination of methods, including saline mounts, modified Kato-Katz method, 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. *A. lumbricoides* and *T. trichiura* infection intensities were expressed as eggs per gram (epg) of faeces 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 9 allergen extracts (Greer laboratories, Lenoir, North Carolina, USA): house dust mites (HDMs; *Dermatophagoides pteronyssinus/Dermatophagoides farinae* mix), American cockroach (*Periplaneta americana*), *Alternaria tenuis*, 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 at least 3 mm greater than that elicited by the saline control 15 min after pricking the allergen onto the volar side of the forearm with ALK-Abello lancets (ALK-Abello, Hungerford, UK). 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 >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 or 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 sub-groups of SPT to mite and perennial allergens. Univariable and multivariable logistic regression were used to estimate associations between geohelminths and potential confounders study outcomes. Potential confounders to be considered in the analyses are shown in Table 1. Urban-rural residence was defined by geographic boundaries. A socio-economic status (SES) index was created using principal components analysis of 7 socio-economic variables as described[21]. Potential confounders in univariable analyses with P<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, College Station, Tex).

*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 Ecuadorian 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 (Table E1, online supplement) compared to 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 gramme (epg) for *A. lumbricoides* and 256 epg 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, while 5.4% had wheeze reported for two or more observation times (i.e. 13, 24, 36, and 60 months). 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% 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 (Figure E1). Maternal or childhood geohelminth infections were not significantly associated with any wheeze episode reported during the first 5 years of life (maternal, adj. OR 1.22, 95% CI 1.00-1.49; childhood to 36 months, adj. OR 1.04, 95% CI 0.84-1.28). With respect to other risk factors 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 (≥30 years vs. ≤20 years; OR 0.38), maternal allergy (OR 2.61), infant pneumonia (OR 4.71), but was less frequent in 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 (HDM) 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, 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 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* (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 months 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: for wheeze; first infection in 1st year vs. never infected, OR 0.86, 95% CI 0.57-1.31; 2nd vs. never, OR 0.68, 95% CI 0.44-1.06; 3rd vs. never, OR 0.55, 95% CI 0.33-0.93). A similar pattern was observed for asthma (3rd 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 (1st vs. never, OR 0.66, 95% CI 0.42-1.04).

*Associations between geohelminths and asthma/wheeze in atopics and non-atopics*.

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 atopic and non-atopic children. Univariable and adjusted analyses for atopic and non-atopic children are shown in Tables E4 and 3, respectively. In adjusted analyses, maternal helminths were positively (OR 1.60) and childhood geohelminths negatively (OR 0.60) associated with wheeze in non-atopic children but no significant associations were seen for atopic children. Childhood geohelminths were also inversely associated with asthma (OR 0.52) among non-atopic children.

**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 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 three 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, appeared to provide protection against wheeze/asthma, while maternal 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[23]; 2) an observational analysis within a randomized-controlled trial of anthelmintic treatment during pregnancy 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 showed that *T. trichiura* infections, particularly at high parasite burdens, 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 Ecuadorian cohort to 3 years 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 cut-off[29] did not affect the results. Repeated treatments for positive stool samples in this study as well as 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 population and prevalence. A study of 1-4 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 hyper-responsiveness[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 non-atopics[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 non-atopic children, the dominant phenotype in non-affluent countries[14,34,35]. Mechanisms by which environmental exposures reduce non-atopic asthma may include hyporesponsiveness to migratory larvae, contributing to the development of more robust anti-inflammatory 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 anti-parasite inflammatory responses in highly endemic populations[7] allowing protective effects against wheeze/asthma to appear. Protective immunity to helminth parasites is age-dependent and non-sterile in endemic populations[38]. With continued exposures and immune maturation (e.g. around school age), more effective anti-parasite[38,39] but heightened inflammatory responses may emerge. Such responses when ‘transmitted’ by infected mothers to their infants may be down-regulated when early geohelminth exposures are sufficient. Suppression of the anti-parasite 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 was collected and controlled for, where appropriate, although we cannot exclude residual confounding by unknown or unmeasured factors. Potential limitations were: i) Use of maternal questionnaires to measure wheeze and asthma outcomes at 5 years could have led to misclassification; ii) the study had limited power for analysis of sub-group effects; and iii) 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 non-atopic children. Further follow-up of the cohort will clarify whether such effects are transient or longer lasting.

**Acknowledgements**

We thank the ECUAVIDA study team for their dedicated work and the cohort mothers and children for their enthusiastic participation. We acknowledge also the support of the Director/s and staff of the Hospital “Padre Alberto Buffoni” in Quinindé, Esmeraldas Province. The study forms part of the SCAALA (Social Changes, Asthma and Allergies in Latin America) programme of research.

**References**

1. Global asthma report 2014. <http://www.globalasthmareport.org/burden/burden.php> (accessed 30/8/16)

2. Eder W, Ege MJ, von Mutius E. [The asthma epidemic.](http://www.ncbi.nlm.nih.gov/pubmed/17124020) N Engl J Med 2006; 355:2226-35

3. Cooper PJ, Rodrigues LC, Cruz AA, Barreto M. The asthma epidemic in Latin America: a public heath challenge and research opportunities. Allergy 2009; 64: 5-17.

4. [Liu AH](http://www.ncbi.nlm.nih.gov/pubmed/?term=Liu%20AH%5BAuthor%5D&cauthor=true&cauthor_uid=26449798). Revisiting the hygiene hypothesis for allergy and asthma. J Allergy Clin Immunol. 2015 Oct;136(4):860-5. doi: 10.1016/j.jaci.2015.08.012

5. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. [Global numbers of infection and disease burden of soil transmitted helminth infections in 2010.](http://www.ncbi.nlm.nih.gov/pubmed/24447578) Parasit Vectors. 2014 Jan 21;7:37.

6. [Wammes LJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Wammes%20LJ%5BAuthor%5D&cauthor=true&cauthor_uid=24981042), [Mpairwe H](http://www.ncbi.nlm.nih.gov/pubmed?term=Mpairwe%20H%5BAuthor%5D&cauthor=true&cauthor_uid=24981042), [Elliott AM](http://www.ncbi.nlm.nih.gov/pubmed?term=Elliott%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=24981042), [Yazdanbakhsh M](http://www.ncbi.nlm.nih.gov/pubmed?term=Yazdanbakhsh%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24981042). Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. Lancet Infect Dis 2014; pii:S1473-3099

7. [Cooper PJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Cooper%20PJ%5BAuthor%5D&cauthor=true&cauthor_uid=17204485), [Barreto ML](http://www.ncbi.nlm.nih.gov/pubmed/?term=Barreto%20ML%5BAuthor%5D&cauthor=true&cauthor_uid=17204485), [Rodrigues LC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Rodrigues%20LC%5BAuthor%5D&cauthor=true&cauthor_uid=17204485). Human allergy and geohelminth infections: a review of the literature and a proposed conceptual model to guide the investigation of possible causal associations. Br Med Bull. 2006;79-80:203-18.

8. Maizels RM. [Parasitic helminth infections and the control of human allergic and autoimmune disorders.](http://www.ncbi.nlm.nih.gov/pubmed/27172808) Clin Microbiol Infect. 2016;22:481-6.

9. [Santiago HC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Santiago%20HC%5BAuthor%5D&cauthor=true&cauthor_uid=27573628), [Nutman TB](http://www.ncbi.nlm.nih.gov/pubmed/?term=Nutman%20TB%5BAuthor%5D&cauthor=true&cauthor_uid=27573628). Human Helminths and Allergic Disease: The Hygiene Hypothesis and Beyond. Am J Trop Med Hyg. 2016; pii: 16-0348.

10. [Feary J](http://www.ncbi.nlm.nih.gov/pubmed?term=Feary%20J%5BAuthor%5D&cauthor=true&cauthor_uid=21087217), [Britton J](http://www.ncbi.nlm.nih.gov/pubmed?term=Britton%20J%5BAuthor%5D&cauthor=true&cauthor_uid=21087217), [Leonardi-Bee J](http://www.ncbi.nlm.nih.gov/pubmed?term=Leonardi-Bee%20J%5BAuthor%5D&cauthor=true&cauthor_uid=21087217). Atopy and current intestinal parasite infection: a systematic review and meta-analysis. Allergy 2011; 66:569-78.

11. Palmer LJ, Celedón JC, Weiss ST, Wang B, Fang Z, Xu X. [Ascaris lumbricoides infection is associated with increased risk of childhood asthma and atopy in rural China.](https://www.ncbi.nlm.nih.gov/pubmed/12045121) Am J Respir Crit Care Med. 2002 Jun 1;165(11):1489-93.

12. Dagoye D, Bekele Z, Woldemichael K, Nida H, Yimam M, Hall A, et al. [Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia.](https://www.ncbi.nlm.nih.gov/pubmed/12738598) Am J Respir Crit Care Med 2003;167:1369-73.

13. Cooper PJ, Chico ME, Bland M, Griffin GE, Nutman TB. [Allergic symptoms, atopy, and geohelminth infections in a rural area of Ecuador.](https://www.ncbi.nlm.nih.gov/pubmed/12714349) Am J Respir Crit Care Med 2003 ;168:313-7.

14. da Silva ER, Sly PD, de Pereira MU, Pinto LA, Jones MH, Pitrez PM, Stein RT. [Intestinal helminth infestation is associated with increased bronchial responsiveness in children.](https://www.ncbi.nlm.nih.gov/pubmed/18484663) Pediatr Pulmonol 2008;43:662-5.

15. Leonardi-Bee J, Pritchard D, Britton J, and the Parasites in Asthma Collaboration. Asthma and current intestinal parasite infection: a systematic review of comparative epidemiological studies. Am J Respir Crit Care Med 2006; 174:514-523.

16. van den Biggelaar AH, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, et al. [Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren.](http://www.ncbi.nlm.nih.gov/pubmed/14976607) J Infect Dis 2004; 189:892-900.

17. Flohr C, Tuyen LN, Quinnell RJ, Lewis S, Minh TT, Campbell J, et al. [Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam.](http://www.ncbi.nlm.nih.gov/pubmed/19758373) Clin Exp Allergy 2010; 40:131-42.

18. Cooper PJ, Chico ME, Vaca MG, Moncayo AL, Bland JM, Mafla E, et al. Impact of bimonthly treatment of geohelminth-infected children with albendazole on atopy prevalence: a cluster-randomized trial. Lancet 2006; 367:1598-603.

19. Wiria AE, Hamid F, Wammes LJ, Kaisar MM, May L, Prasetyani MA, et al. [The effect of three-monthly albendazole treatment on malarial parasitemia and allergy: a household-based cluster-randomized, double-blind, placebo-controlled trial.](http://www.ncbi.nlm.nih.gov/pubmed/23526959) PLoS One 2013; 8:e57899.

20. [Wlasiuk G](http://www.ncbi.nlm.nih.gov/pubmed?term=Wlasiuk%20G%5BAuthor%5D&cauthor=true&cauthor_uid=22892709)1, [Vercelli D](http://www.ncbi.nlm.nih.gov/pubmed?term=Vercelli%20D%5BAuthor%5D&cauthor=true&cauthor_uid=22892709). The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. Curr Opin Allergy Clin Immunol 2012; 12:461-6.

21. Cooper PJ, Chico ME, Amorim LD, Sandoval C, Vaca M, Strina A, et al. [Effects of maternal geohelminth infections on allergy in early childhood.](http://www.ncbi.nlm.nih.gov/pubmed/26395817) J Allergy Clin Immunol. 2016;137:899-906.

22. Cooper PJ, Chico M, Vaca M, Sandoval C, Loor S, Rodrigues LC, et al. Effects of early life exposures to geohelminths on atopy and wheeze in children. Presented at the 65th American Society of Tropical Medicine and Hygiene Annual Meeting. Abstract number 5248, November 14-17th Atlanta, USA.

23. Cooper PJ, Chico ME, Guadalupe I, Sandoval CA, Mitre E, Platts-Mills TA, et al. [Impact of early life exposures to geohelminth infections on the development of vaccine immunity, allergic sensitization, and allergic inflammatory diseases in children living in tropical Ecuador: the ECUAVIDA birth cohort study.](http://www.ncbi.nlm.nih.gov/pubmed/21714922) BMC Infect Dis. 2011;11:184.

24. World Health Organization. Diagnostic Techniques for Intestinal Parasitic Infections (IPI) applicable to primary health care (PHC) services. WHO: Geneva, 1985.

25. Calvopiña M. Terapéutica antiparasitaria. Ministerio de Salud Pública del Ecuador, Ecuador, 2nd Edition, 1997.

26. Schaub B, Vercelli D. [Environmental protection from allergic diseases: From humans to mice and back.](https://www.ncbi.nlm.nih.gov/pubmed/26210896) Curr Opin Immunol. 2015 Oct;36:88-93.

27. Amberbir A, Medhin G, Alem A, Britton J, Davey G, Venn A. [The role of acetaminophen and geohelminth infection on the incidence of wheeze and eczema: a longitudinal birth-cohort study.](http://www.ncbi.nlm.nih.gov/pubmed/20935107) Am J Respir Crit Care Med 2011; 183:165-70.

28. Mpairwe H, Ndibazza J, Webb EL, Nampijja M, Muhangi L, Apule B, et al. [Maternal hookworm modifies risk factors for childhood eczema: results from a birth cohort in Uganda.](https://www.ncbi.nlm.nih.gov/pubmed/25171741) Pediatr Allergy Immunol 2014;25:481-8.

29. Rodrigues LC, Newcombe PJ, Cunha SS, Alcantara-Neves NM, Genser B, Cruz AA, et al. Early infections with intestinal helminths reduce the risk of atopy later in childhood. Clin Exp Allergy 2008; 38:1769-77.

30. Hunninghake GM, Soto-Quiros ME, Avila L, Ly NP, Liang C, Sylvia JS, et al. [Sensitization to Ascaris lumbricoides and severity of childhood asthma in Costa Rica.](https://www.ncbi.nlm.nih.gov/pubmed/17336615) J Allergy Clin Immunol 2007;119:654-61.

31. [Calvert J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Calvert%20J%5BAuthor%5D&cauthor=true&cauthor_uid=19962746), [Burney P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Burney%20P%5BAuthor%5D&cauthor=true&cauthor_uid=19962746). Ascaris, atopy, and exercise-induced bronchoconstriction in rural and urban South African children. J Allergy Clin Immunol  2010;125:100-5.

32. Pereira MU, Sly PD, Pitrez PM, Jones MH, Escouto D, Dias AC, et al. [Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children.](https://www.ncbi.nlm.nih.gov/pubmed/17331964) Eur Respir J 2007;29:1154-60

33. Alcântara-Neves NM, Badaró SJ, dos Santos MC, Pontes-de-Carvalho L, Barreto ML. [The presence of serum anti-Ascaris lumbricoides IgE antibodies and of Trichuris trichiura infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children.](https://www.ncbi.nlm.nih.gov/pubmed/20731833) Respir Res 2010;11:114.

34. Cooper PJ, Vaca M, Rodriguez A, Chico ME, Santos DN, Rodrigues LC, Barreto ML. [Hygiene, atopy and wheeze-eczema-rhinitis symptoms in schoolchildren from urban and rural Ecuador.](https://www.ncbi.nlm.nih.gov/pubmed/24105783) Thorax 2014;69:232-9.

35. Weinmayr G, Weiland SK, Björkstén B, Brunekreef B, Büchele G, Cookson WO, et al. [Atopic sensitization and the international variation of asthma symptom prevalence in children.](https://www.ncbi.nlm.nih.gov/pubmed/17575099) Am J Respir Crit Care Med 2007;176:565-74.

36. Wammes LJ, Hamid F, Wiria AE, May L, Kaisar MM, Prasetyani-Gieseler MA, et al. [Community deworming alleviates geohelminth-induced immune hyporesponsiveness.](https://www.ncbi.nlm.nih.gov/pubmed/27791067) Proc Natl Acad Sci U S A 2016;113:12526-12531.

37. Guadalupe I, Mitre E, Benitez S, Chico ME, Nutman TB, Cooper PJ. [Evidence for in utero sensitization to Ascaris lumbricoides in newborns of mothers with ascariasis.](https://www.ncbi.nlm.nih.gov/pubmed/19426111) J Infect Dis 2009;199:1846-50.

38. Woolhouse ME, Taylor P, Matanhire D, Chandiwana SK. [Acquired immunity and epidemiology of Schistosoma haematobium.](https://www.ncbi.nlm.nih.gov/pubmed/1905786) Nature 1991;351:757-9.

39. Turner JD, Faulkner H, Kamgno J, Cormont F, Van Snick J, Else KJ, et al. [Th2 cytokines are associated with reduced worm burdens in a human intestinal helminth infection.](https://www.ncbi.nlm.nih.gov/pubmed/14639550) J Infect Dis 2003;188:1768-75.

40. Vercruysse J, Behnke JM, Albonico M, Ame SM, Angebault C, Bethony JM, et al. [Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic.](https://www.ncbi.nlm.nih.gov/pubmed/21468309) PLoS Negl Trop Dis 2011;5:e948.

**Figure legends**

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

Table 1. Frequencies of maternal and childhood geohelminth infections to 36 months of age and potential confounders and associations with asthma, wheeze, and allergen skin test (SPT) reactivity to any allergen at 5 years of age.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Overall | Wheeze  | Asthma | SPT  |
| n (%) | % | OR (95% CI) | P value | % | OR (95% CI) | P value | % | OR (95% CI) | P value |
| Any maternal geohelminthNoYes | 1,140 (54.5)950 (45.5) | 10.714.8 | **1****1.47 (1.13-1.90)** | 0.004 | 5.16.4 | 11.30 (0.90-1.89) | 0.162 | 13.714.4 | 11.06 (0.83-1.36) | 0.629 |
| Any childhood geohelminthsNoYes | 1,377 (65.9)713 (34.1) | 13.311.4 | 10.84 (0.63-1.11) | 0.209 | 6.24.6 | 10.74 (0.49-1.11) | 0.148 | 14.912.3 | 10.80 (0.62-1.05) | 0.113 |
| Maternal age (yrs)≤2021-29≥30 | 546 (26.1)1,005 (48.1)539 (25.8) | 11.514.110.9 | 11.26 (0.92-1.74)0.94 (0.65-1.37) | 0.1400.757 | 5.66.93.3 | 11.24 (0.80-1.92)0.57 (0.32-1.04) | 0.3310.067 | 13.714.014.3 | 11.02 (0.76-1.30)1.05 (0.74-1.470 | 0.8730.794 |
| Maternal ethnicityAfro-EcuadorianNon-Afro-Ecuadorian | 540 (25.8)1,550 (74.2) | 14.711.8 | 10.78 (0.59-1.03) | 0.079 | 6.65.3 | 10.80 (0.53-1.18) | 0.251 | 15.013.7 | 10.90 (0.68-1.18) | 0.446 |
| Maternal educational levelIlliterateComplete primaryComplete Secondary | 308 (14.8)1,221 (58.4)561 (26.8) | 15.112.311.9 | 10.79 (0.55-1.12)0.76 (0.51-1.23) | 0.1810.172 | 7.15.16.0 | 10.71 (0.43-1.17)0.84 (0.48-1.47) | 0.1790.541 | 11.415.213.0 | 11.39 (0.95-2.05)1.17 (0.76-1.79) | 0.0920.481 |
| Area of residenceUrbanRural | 1,473 (70.5)617 (29.5) | 13.011.6 | 10.88 (0.66-1.17) | 0.379 | 6.34.0 | 1**0.63 (0.40-0.98)** | 0.039 | 12.218.3 | 1**1.61 (1.25-2.08)** | <0.001 |
| SexMaleFemale | 1,063 (50.9)1,027 (49.1) | 12.113.1 | 11.09 (0.84-1.41) | 0.515 | 5.95.4 | 10.92 (0.63-1.33) | 0.651 | 13.914.1 | 11.02 (0.97-1.30) | 0.897 |
| Socioeconomic status§123 | 672 (32.1)704 (33.6)714 (34.3) | 12.012.713.0 | 11.07 (0.78-1.48)1.10 (0.80-1.51) | 0.6650.558 | 4.35.86.8 | 11.37 (0.84-2.23)1.62 (1.00-2.60) | 0.2050.052 | 13.115.113.9 | 11.18 (0.87-1.60)1.07 (0.78-1.45) | 0.2960.675 |
| Birth order1st2nd-4th≥5th  | 522 (25.0)1,161 (55.4)407 (19.6) | 11.613.212.1 | 11.16 (0.85-1.59)1.05 (0.71-1.57) | 0.3540.802 | 5.55.95.1 | 11.08 (0.69-1.69)0.92 (0.52-1.64) | 0.7380.777 | 15.913.513.0 | 10.83 (0.62-1.10)0.79 (0.55-1.15) | 0.1970.219 |
| Maternal allergyNo Yes | 1,997 (95.3)98 (4.7) | 12.416.3 | 11.37 (0.79-2.39) | 0.260 | 5.412.2 | 1**2.46 (1.30-4.64)** | 0.005 | 14.014.3 | 11.03 (0.58-1.83) | 0.928 |
| Household overcrowding¶≤3>3 | 1,180 (56.5)910 (43.5) | 11.713.8 | 11.21 (0.93-1.57) | 0.148 | 5.16.3 | 11.25 (0.87-1.82) | 0.230 | 14.213.9 | 10.97 (0.76-1.25) | 0.841 |
| Pets inside houseNoYes | 1,561 (74.2)539 (25.8) | 12.413.1 | 11.07 (0.80-1.43) | 0.656 | 5.26.8 | 11.33 (0.89-1.98) | 0.165 | 13.814.7 | 11.07 (0.81-1.42) | 0.621 |
| Large farm animals‡NoYes | 1,414 (67.7)676 (32.3) | 11.814.3 | 11.25 (0.96-1.64) | 0.103 | 5.75.5 | 10.95 (0.63-1.41) | 0.785 | 13.614.9 | 11.18 (0.86-1.45) | 0.402 |
| Pneumonia to 13 monthsNoYes | 1.919 (95.4)92 (4.6) | 12.023.7 | 1**2.30 (1.40-3.78)** | 0.001 | 5.118.3 | 1**4.26 (2.42-7.49)** | <0.001 | 14.77.61 | 10.48 (0.22-1.04) | 0.064 |

SPT – allergen skin prick test reactivity to any of 10 allergens. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using logistic regression. P<0.05 are shown in bold.. Ethnicity ‘other’ represents: 1,518 Mestizo/6 Indigenous. Numbers of missing values (brackets) were: maternal allergy (13) and child geohelminth infections (27). §Socioeconomic status (SES) represents tertiles of z scores obtained using a factor analysis with 1 representing the lowest and 3 the highest SES. ¶ Household overcrowding is defined as the number of people living in the household per sleeping room. ‡ Any of cows, pigs, mules, donkeys, and horses. Other helminths: mother (*S. stercoralis*, 4.0%; *Hymenolepis* spp., 0.5%); child (hookworm, 0.6%; *S. stercoralis*, 0.6%; *Hymenolepis* spp., 1.5%).

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 allergen skin test (SPT) reactivity to any allergen at 5 years of age.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Wheeze  | Asthma  | SPT  |
| OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Any maternal geohelminthNoYes | 1**1.41 (1.06-1.88)** | 0.017 | 11.28 (0.85-1.94) | 0.238 | 11.17 (0.89-1.53) | 0.262 |
| Any childhood geohelminthsNoYes | 1**0.70 (0.51-0.95)** | 0.021 | 1**0.60 (0.38-0.95)** | 0.029 | 10.79 (0.59-1.06) | 0.120 |
| Maternal age (yrs)≤2021-29≥30 | 11.16 (0.82-1.68)0.86 (0.53-1.40) | 0.4310.547 | 10.86 (0.52-1.45)**0.38 (0.18-0.79)** | 0.577**0.010** | 11.25 (0.88-1.78)1.37 (0.87-2.17) | 0.2180.172 |
| Maternal ethnicityAfro-EcuadorianNon-Afro-Ecuadorian | 10.76 (0.56-1.03) | 0.074 | 10.80 (0.52-1.24) | 0.321 | 10.80 (0.59-1.07) | 0.136 |
| Maternal educational levelIlliterateComplete primaryComplete Secondary | 10.78 (0.52-1.16)0.72 (0.44-1.19) | 0.2230.200 | 1**0.55 (0.31-0.97)**0.57 (0.29-1.15) | 0.0390.118 | 11.40 (0.92-2.13)1.15 (0.69-1.91) | 0.1210.601 |
| Area of residenceUrbanRural | 10.84 (0.60-1.16) | 0.286 | 10.66 (0.40-1.09) | 0.106 | 1**1.81 (1.35-2.43)** | <0.001 |
| SexMaleFemale | 11.14 (0.87-1.49) | 0.349 | 10.97 (0.66-1.43) | 0.874 | 11.01 (0.78-1.30) | 0.941 |
| Socioeconomic status§123 | 11.18 (0.84-1.66)1.20 (0.83-1.74) | 0.3360.339 | 11.53 (0.92-2.56)1.64 (0.94-2.84) | 0.1040.081 | 11.31 (0.95-1.80)1.23 (0.86-1.76) | 0.1010.249 |
| Birth order1st2nd-4th≥5th  | 11.15 (0.78-1.69)0.92 (0.52-1.64) | 0.4870.779 | 11.43 (0.82-2.49)1.46 (0.64-3.32) | 0.2060.372 | 10.72 (0.50-1.02)0.62 (0.36-1.07) | 0.0680.086 |
| Maternal allergyNo Yes | 11.37 (0.78-2.43) | 0.273 | 1**2.61 (1.33-5.12)** | 0.005 | 11.00 (0.55-1.82) | 0.992 |
| Household overcrowding¶≤3>3 | 11.21 (0.90-1.62) | 0.212 | 11.24 (0.81-1.90) | 0.331 | 11.10 (0.83-1.46) | 0.505 |
| Pets inside houseNoYes | 11.01 (0.74-1.37) | 0.974 | 11.26 (0.82-1.93) | 0.300 | 11.06 (0.79-1.41) | 0.715 |
| Large farm animals‡NoYes | 11.29 (0.96-1.73) | 0.093 | 11.00 (0.65-1.54) | 0.990 | 10.97 (0.73-1.29) | 0.822 |
| Pneumonia to 13 monthsNoYes | 1**2.32 (1.39-3.87)** | 0.001 | 1**4.71 (2.60-8.54)** | <0.001 | 10.46 (0.21-1.02) | 0.055 |

SPT – allergen skin prick test reactivity to any of 10 allergens. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using logistic regression and adjusted for all variables. P<0.05 are shown in bold. §Socioeconomic status (SES) represents tertiles of z scores obtained using a factor analysis with 1 representing the lowest and 3 the highest SES.

¶Household overcrowding is defined as the number of people living in the household per sleeping room. ‡ Any of cows, pigs, mules, donkeys, and horses

Table 3. Adjusted analyses for associations between geohelminth infections to 36 months and asthma/wheeze at 5 years in atopics versus non-atopics.

|  |  |  |
| --- | --- | --- |
| Variable | SPT- (n=1797) | SPT+ (n=293) |
| N | n (%) | OR (95% CI) | P value | N | n (%) | OR (95% CI) | P value |
| WheezeMaternal geohelminthsNo YesChildhood geohelminths\*NoYes | 9848131172625 | 92 (9.4)113 (13.9)145 (12.4)60 (9.6) | 1**1.60 (1.16-2.20)**1**0.60 (0.43-0.86)** | 0.0050.005 | 15613720588 | 30 (19.2)29 (21.2)38 (18.5)21 (23.9) | 10.75 (0.38-1.47)11.38 (0.70-2.71) | 0.3960.351 |
| AsthmaMaternal geohelminthsNoYesChildhood geohelminths\*NoYes | 9848131172 625 | 44 (4.5)47 (5.8)67 (5.7)24 (3.8) | 11.24 (0.78-1.98)1**0.52 (0.31-0.87)** | 0.3690.014 | 15613720588 | 13 (8.3)14 (10.2)18 (8.8)9 (10.2) | 11.68 (0.64-4.41)11.27 (0.49-3.28) | 0.2920.620 |

SPT- : no allergen skin prick test reactivity; SPT+ : allergen skin test reactivity to any of 10 allergens. Odds ratios (OR) and 95% confidence intervals (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, P<0.05 are shown in bold.