INTRODUCTION

Over the past 20 years we have conducted a programme of research in Ecuador exploring how helminths may affect the development of allergy among children. Our research followed observations made in Africa and a highly influential series of studies published during the 1990s by Lynch and colleagues in Venezuela. The Venezuelan studies and others that followed elsewhere showed variable but measurable effects of soil-transmitted helminth (STH) or geohelminth infections on allergen skin test reactivity and asthma symptoms, and were done in the context of a growing interest in the hygiene hypothesis and potential protective effects against allergy of childhood infections.

In this review, we present an overview of the findings of epidemiological and immunological studies done in Ecuador to understand better the effects of STH parasites on allergy during childhood. We will present current evidence for effects of STH parasites on atopy and allergic symptoms, focussing largely on the findings of studies done in Ecuador, and referring where relevant to the wide body of research that has been done elsewhere in Latin America and other endemic regions for STH parasites. The review will show that evidence for a protective effect of STH parasites against allergy in children remains fragmentary and inconsistent and that, while STH parasites do modulate the host anti-parasite immune response, there is limited evidence that they play a critical role in modulating the host inflammatory responses that may lead to allergic diseases in humans (Figure 1).
regions among populations living in poverty and inadequate sanitation. STH infections have been associated with significant disability and mortality, particularly in children. The World Health Assembly (WHA) in 2001 endorsed a strategy for the control of these parasites through periodic treatments of schoolchildren with anthelmintic drugs. In line with this resolution, WHO, national governments and donor organisations have prioritised the control of STH infections through periodic treatments with anthelmintic drugs to school-age children. Subsequently, recommendations for preventive chemotherapy have been expanded to include other high-risk groups, namely pre-school children and women of childbearing age.

The prevalence of STH infections is likely to have declined significantly in many low and middle-income countries (LMICs) over the past 10-20 years through reductions in extreme poverty, access to improved sanitation and increasing coverage rates for preventive chemotherapy for high-risk groups. Nevertheless, regions of high STH prevalence are likely to persist among populations that continue to suffer high levels of poverty and which are geographically isolated. A recent national survey of STH prevalence in Ecuador that studied a representative sample of schoolchildren estimated a national prevalence of 28%, considerably lower than previous estimates, reflecting substantial progress over the previous 10 years in achieving the millennium development goals. However, the Amazon region of Ecuador continued to have high prevalence rates (59%) reflecting the relative isolation of this population that continues to suffer high levels of poverty.

3 | ALLERGY

Asthma and eczema, considered to be caused by inflammatory mechanisms, are among the commonest of all chronic diseases of childhood in industrialized countries. Asthma alone is estimated to affect more than 300 millions worldwide and has emerged as an important public health problem in many non-industrialized regions, particularly in growing cities and among urbanizing populations.

Temporal trends of increasing allergic disease prevalence are thought to be explained by a changing living environment, perhaps related to a decline in the incidence of childhood infectious diseases and reduction in the diversity of environmental microbiota. Rural residence has consistently been shown to be protective against allergy but it is not clear which rural exposures may mediate this protection. Numerous studies in traditional farming settings in Europe have shown farming to be strongly protective against atopy and allergic diseases, particularly if farming exposures occur in early life. In such settings, protection appears to be partly dependent on exposures to a diverse range of microorganisms in the environment. Protection against allergy is thought to be strongest when protective exposures occur during early life while the immune system is still developing and may allow the developing immune response to develop a greater capacity to regulate inflammation. Such exposures are likely to be multiple, are likely to vary according the environment in which a child is raised and may include helminths.

4 | STH PARASITES AND ALLERGY

The apparently low prevalence of allergy in the rural tropics may be explained partly by endemic helminth infections. In order to survive for periods of years in their mammalian hosts, helminth parasites have developed immune mechanisms that modulate the inflammatory responses that the host has evolved to kill them. Such inflammatory responses include key elements of Th2-mediated allergic inflammation (e.g., IgE, mast cells, eosinophils, Th2 cells, etc). Helminths may suppress not only these killing and expulsion mechanisms but also shared inflammatory pathways that lead to atopy and allergic diseases. A protective role for STH and other helminth parasites against allergy has been incorporated into an extended hygiene hypothesis that attributes protection against allergy not only to early childhood infections (e.g., bacteria and viruses) but also parasites and a more diverse host microbiota. The specific effects of STH parasites may depend on age of first exposure, intensity of
infection and species of infecting parasite. We will now consider the findings of epidemiological studies done in Ecuador examining the effects of STH parasites on atopy and allergic diseases.

5  |  EFFECTS OF STH PARASITES ON ALLERGY IN ECUADOR

5.1  |  STH and atopy

We have repeatedly observed, in a series of cross-sectional studies in tropical and sub-tropical regions of the Ecuadorian Provinces of Esmeraldas and Pichincha, an inverse association between the microscopic presence of STH parasites in stool samples and atopy measured using skin test reactivity to environmental allergens. These studies were done in schoolchildren with high prevalence rates for STH (~70%), where the dominant parasites were A. lumbricoides and T. trichiura, and where the background prevalence of SPT was variable (~10% in Esmeraldas vs ~20% in Pichincha). The findings are summarized in Table 1. These studies showed inverse associations between STH infections and SPT with odds ratios of ~0.7 and independent effects of both A. lumbricoides and or T. trichiura on SPT with evidence for greater inverse effects at higher parasite burdens for both parasites (Table 1). Further, the presence of anti-Ascaris IgG4 antibodies, used as a marker for chronic STH infection, was inversely associated with SPT.

Based on these findings, we hypothesized that STH were actively suppressing SPT and that this suppression might be reversed by curative chemotherapy. To test this hypothesis, we did a cluster-randomized study in which schoolchildren living in endemic communities were randomized to receive albendazole given every 2 months for a year vs no treatment. A placebo was not used because of difficulties in blinding mothers to treatment allocation. The study showed no effect on atopy after 12 months of periodic anthelmintic treatment. The study had several limitations: (a) a period of exposure occurs in utero and in early childhood. In the case of STH infections, early exposures could occur through trans-placental passage of parasite antigens from the mother to foetus in utero, through breast milk in the infant or through early childhood exposures to STH parasites in the home. Such early exposures could cause immunological sensitization or tolerization to parasite antigens leading to down-regulation of host anti-parasite responses and reduced allergy through immunological cross-reactivity between parasite and environmental allergens or bystander suppression. Certainly, antigen-specific T cell responses to Ascaris antigens are measurable in newborns of infected mothers indicating in utero sensitization. To explore the potential role of early-life exposures to STH parasites on the development of allergy, we followed a birth cohort, the ECUAVIDA cohort, in a rural District in Esmeraldas Province. We measured the presence of STH infections in mothers and their children during the first 5 years of life and monitored the effects of these early exposures on the development of SPT. Analyses of the cohort to date have shown no significant effects on SPT overall. However sub-group analyses showed a reduced prevalence of SPT to mite or perennial allergens among 3-year-old children who had infected mothers and among 5-year-old children who had STH infections during the first 3 years of life. Differential effects of parasite
| Study                        | Design/population                     | Sample                                      | Geohelminths                  | Outcomes                                      | Findings                                                                 |
|------------------------------|---------------------------------------|---------------------------------------------|-------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------|
| Cooper et al, 2016<sup>26</sup> | Cross-sectional, Pichincha             | Schoolchildren, 5-19 y, n = 2865            | Active STH; anti-Ascaris IgG4; total IgE | Prevalence: any 69%; Al 55%; TT 46%; Hk 3%                      | Inverse associations with active (any STH OR 0.64, Al 0.74 and Hk 0.64) and chronic (high total IgE; and presence of anti-Ascaris IgG4) infections. Dose-response for Al and TT |
| Cooper et al, 2003<sup>27</sup> | Cross-sectional, Pichincha & Esmeraldas | Schoolchildren, 5-18 y, n = 4433            | STH prev: any 63%; Al 50%; TT 44%; Hk 2% | Prevalence: any 70%; Al 52%; TT 52%; Hk 8%                      | Inverse association with active STH (any OR 0.62; Al 0.65 and Hk 0.67). Dose-response for Al and Tt. STH effect independent of household crowding and SES |
| Cooper et al, 2004<sup>28</sup> | Cross-sectional, Pichincha             | Schoolchildren, 7-17 y, n = 1002             | STH prev: any 72%; Al 56%; TT 56%; Hk 15% | Prevalence: any 20%; Dp 9%; Df 6%; cock 12%                     | Inverse association with SPT (any OR 0.65; Al OR 0.65; Tt OR 0.67). Dose-response for Al and Tt. Long-term MDA associated with higher prevalence of SPT (OR 2.1) |
| Cooper et al, 2006<sup>29</sup> | Cluster-randomized trial with bi-monthly albendazole for 12 mo, Pichincha | Schoolchildren, 7-17 y, n = 2373 in 68 schools | STH prev: any 72%; Al 56%; TT 56%; Hk 15% | Prevalence: any 25%, hdm 10%, cock 17%                          | Inverse association at baseline (any 0.78). No effect of treatment on atopy |
| Endara et al, 2010<sup>34</sup> | Cross-sectional, Comparison of communities receiving ivermectin MDA for 15-17 y vs non-MDA communities Esmeraldas | Rural schoolchildren, 6-16 y, n = 3901 | STH prev: any 63 vs 86%, Al 49 vs 57%, Tt 31 vs 82%, Hk 15 vs 4% | Prevalence: any 17 vs 9%, hdm 8 vs 5%, cock 4 vs 3%             | Inverse association with active STH (any OR 0.71; Tt OR 0.72). Dose-response for Tt. Long-term MDA associated with higher prevalence of SPT (OR 2.1) |
| Moncayo et al, 2013<sup>35</sup> | Case-control, Esmeraldas               | Rural schoolchildren, 7-19 y, n = 376        | STH prev: any 72%; Al 47%; Tt 58%; Hk 8%; Anti-Ascaris IgE 65% | Presence of anti-Ascaris IgE (P inter = 0.02) but not active STH attenuated association between sIgE and SPT |
| Cooper et al, 2014<sup>30</sup> | Cross-sectional, Esmeraldas            | Rural and urban schoolchildren, 5-16 y, n = 6821 | Rural prev: any 69%, Al 42%, Tt 54%, Hk 6%; Urban: any 43%, Al 20%, Tt 35%, Hk 5% | Prevalence: any 46%, Al 28%, Tt 29%, Hk 6%                      | Inverse association with SPT (Al OR 0.73; Tt, OR 0.71). No interactions by urban vs rural |
| Cooper et al, 2016<sup>26</sup> | Prospective, Esmeraldas                | Rural birth cohort to 3 y, n = 2069 (of 2404 recruited) | Maternal prev: any 46%, Al 28%, Tt 29%, Hk 6% | Prevalence: any 46%, Al 27%, Tt 28%, Hk 6%                      | No overall effect of maternal STH on child SPT (any allergen) at 3 y. Inverse association with hdm (OR 0.61). Maternal ascariasis associated with reduced SPT (any OR 0.70, hdm 0.48) |
| Cooper et al, 2018<sup>40</sup> | Prospective, Esmeraldas                | Rural birth cohort to 5 y, n = 2090 (of 2404 recruited) | Maternal prev: any 46%, Al 28%, Tt 29%, Hk 6% | Prevalence: any 14%; hdm 8%, cock 4%                             | Overall, neither maternal nor childhood STH associated with SPT. Childhood STH inversely associated with SPT to perennial allergens (OR 0.70) |

SPT, allergen skin prick test reactivity; sIgE, presence of any allergen-specific IgE (≥0.7 kU/L); anti-Ascaris IgE, presence of specific IgE to Ascaris (≥0.7 kU/L); years; MDA, mass drug administration or given at community level; Al, *A. lumbricoides*; Tt, *T. trichiura*; Hk, hookworm; prev., prevalence; Dp, *Dermatophagoidespteronyssinus*; Df, *Dermatophagoidesfarinae*; hdm, house dust mite; cock, cockroach (*Periplaneta americana*); OR, Odds Ratio; P inter., P value for interaction.

<sup>a</sup>SPT positivity defined by wheal size ≥2 mm above negative control.

<sup>b</sup>SPT positivity defined by wheal size ≥3 mm above negative control.
species or by parasite burden were not seen. Ongoing analyses of
the cohort at 8 years of age are trying to discern the significance of
these sub-group findings over the longer term.

If we are to ignore the findings of sub-group analyses within the
birth cohort which require replication, it would seem overall that, in
Ecuadorian populations where we have repeatedly observed inverse
associations between STH and SPT, that early-life exposures to STH
or short-term anthelmintic treatments at school age do not affect
SPT prevalence while longer term treatments might, although the
latter observation comes with the caveat of potential biases in the
study design. Thus, the strength of evidence for an effect of STH
SPT prevalence while longer term treatments at school age do not affect
associations between STH and SPT, that early-life exposures to STH
and asthma, an effect that was only seen among non-atopic chil-
dren. These observed effects were not associated with specific
parasites. STH parasitisms or were affected by parasite burden although burdens
were low in young children.

How might these contradictory findings be explained? We have
shown previously in the same cohort that maternal ascariasis is asso-
ciated with increased immune responsiveness to Ascaris antigens
in newborns. A. lumbricoides infections have been shown to in-
crease the risk of wheeze/asthma in older children and adults
and this effect may be "transmitted" from mother to child through in
utero sensitization to Ascaris antigens. Contrasting effects of STH on
wheeze/asthma in younger vs older subjects may depend on history
of STH exposures and type of inflammatory lung response. Earlier
infections may modulate anti-parasite inflammatory responses in
highly endemic populations allowing protective effects against
wheeze/asthma to appear. Protective immunity to helminth para-
sites is age-dependent and non-sterile in endemic populations.

With continued exposures and immune maturation (eg, around
school age), more effective anti-parasite but heightened inflam-
matory responses may emerge. Such responses when "transmitted"
by infected mothers to their infants may be down-regulated when
early STH 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.

Epidemiological studies generally have detected STH parasitisms
by microscopic examination of single stool samples, an approach
that has poor sensitivity among individuals with light infections.
An alternative is to measure the presence of parasite-specific an-
tibodies that indicate past STH exposures, may also indicate cur-
rent infections, and may be a particularly useful infection marker
in populations that have received recent anthelmintic treatments.
It has been suggested that measurement of anti-Ascaris IgE is a
useful marker for exposure to STH including A. lumbricoides in
areas of low prevalence where many more people tend to have
this marker compared to those with detectable intestinal infec-
tions. However, the presence of anti-Ascaris IgE indicates also
allergic sensitization to Ascaris and, hence, is probably a measure
for atopy or the capacity to respond to parasite allergens with an
IgE response. Numerous studies have measured the associations
between anti-Ascaris IgE and asthma symptoms, generally show-
ing strong positive associations with wheeze, asthma and bron-
chial hyper-reactivity. In cross-sectional studies in Ecuador,
we have observed strong associations between anti-Ascaris IgE
and wheeze symptoms among schoolchildren living in rural and
urban areas of Esmeralda's Province. Among rural schoolchil-
dren, the presence of anti-Ascaris IgE explained approximately
50% of wheeze symptoms and 30% of wheeze and asthma in the
City of Esmeraldas. In the case of the latter, only 4% had pos-
tive stool samples for STH while 49% had anti-Ascaris IgE. The
presence of anti-Ascaris IgE was associated with IgE sensitization
to aeroallergens, an effect that might be mediated by a higher
degree of atopy among wheezy/asthmatic children exposed to
ascariasis or by a direct effect on airways reactivity caused by
inflammation consequent to the host response to the presence
of Ascaris larvae migrating through the lungs. Alternatively,
| Study                  | Design/population                      | Sample                                | Exposures/Intervention                  | Outcomes                                      | Findings                                                                 |
|------------------------|----------------------------------------|----------------------------------------|----------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------|
| Cooper et al, 2003³⁷   | Cross-sectional, Pichincha & Esmeraldas | Schoolchildren, 5-18 y, n = 4433        | Prev: any (63.4%); AL (49.7%); TT (43.8%); Hk (2.3%) | Wheeze 2%, rhinitis 4%; eczema 4%             | No significant associations with allergic symptoms                        |
| Cooper et al, 2006³⁸   | Cluster-randomized trial; bi-monthly albenzazole vs no treatment; Pichincha | Schoolchildren, 7-17 y, n = 2373 in 68 schools | Bi-monthly albendazole vs no treatment over 12 mo. Prev: any 72%; AL 56%; Tt 56%; Hk 15% | Wheeze 3%, rhinitis 3%, eczema 4% | No effect of treatment wheeze, rhinitis and eczema after 12 mo |
| Moncayo et al, 2010³⁹ | Cross-sectional, Esmeraldas            | Rural schoolchildren, 6-16 y, n = 3960 | Prev: any 75%; Al 53%; Tt 57%; Hk 9%     | Wheeze 11%, rhinitis 6%, eczema 5%             | No inverse associations with wheeze, rhinitis and eczema. High parasite burden with Tt inversely associated with atopic wheeze (high Tt vs negative, OR 0.24) |
| Endara et al, 2010³⁴  | Cross-sectional, Esmeraldas            | Rural schoolchildren, 6-16 y, n = 3901 | Comparison of communities receiving ivermectin MDA for 15-17 y vs non-MDA communities. Prev: any 63 vs 86%, Al 49 vs 57%, Tt 31 vs 82%, Hk 15 vs 4% | MDA vs non-MDA: wheeze 10 vs 11%; rhinitis 6 vs 7%; eczema 7 vs 3% | No significant associations with allergic symptoms. Long-term MDA associated with higher prevalence of eczema (OR 2.24) but not wheeze or rhinitis. No effect of MDA on association between SPT and allergic symptoms |
| Moncayo et al, 2013³⁵ | Case-control, Esmeraldas               | Rural schoolchildren, 7-19 y, n = 376   | Prev: any 72%; Al 47%; Tt 58%; Hk 8%     | Cases wheeze vs control non-wheeze             | Active STH not associated with wheeze although inverse association between Tt and atopic wheeze (OR 0.47). Anti-Ascaris IgE associated with atopic (OR 6.98) and non-atopic (OR 2.67) wheeze |
| Cooper et al, 2014³⁰  | Cross-sectional, Esmeraldas            | Rural and urban schoolchildren, 5-16 y, n = 6821 | Rural prev: any 69%; Al 42%; TT 54%; Hk 6%. Urban: any 43%, Al 20%; Tt 35%, Hk 5% | Rural: Wheeze 10%, rhinitis 6%, eczema 5%. Urban: Wheeze 9%, rhinitis 8%, eczema 6% | Overall no associations with wheeze, rhinitis and eczema. Wheeze associated with Tt (urban OR 1.40 vs rural OR 0.95, P inter = 0.04); rhinitis associated with Al (urban OR 0.62 vs rural OR 1.09, P = 0.03); Eczema associated with Hk (urban OR 0.50 vs rural OR 1.76, P = 0.01) |
| Endara et al, 2015³³   | Case-control, Esmeraldas               | Rural and urban schoolchildren, 7-19 y, n = 600 | Rural prev: any 73%; Al 47%; Tt 58%. Urban prev: 41%, Al 17%, Tt 32% | Cases wheeze vs control non-wheeze             | No associations with active infections. Presence anti-Ascaris IgE associated with wheeze (urban OR 3.33, rural OR 2.76). PAF% for anti-Ascaris IgE: rural 50% vs urban 35%. Associations between anti-hdm IgE and wheeze attenuated by geohelminth infection markers |
| Ardura et al, 2015³⁴   | Case-control, Esmeraldas               | Urban, children, 5-15 y, n = 179        | Prev: any 4%; Al 2%, Tt 2% Anti-Ascaris IgE 49% | Acute asthma cases vs non-asthma controls     | Association between asthma and anti-Ascaris IgE (OR 2.24). PAF% for anti-Ascaris IgE 31% |
| Cooper et al, 2016³⁶   | Prospective, Esmeraldas                | Rural birth cohort to 3 y, n = 2069 follow-up | Maternal prev: any 46%, Al 28%, Tt 29%, Hk 6% | Any during first 3 y: wheeze, 26%; eczema 18% | No effect of maternal STH on childhood wheeze and eczema to 3 y |
| Cooper et al, 2018³⁷   | Prospective, Esmeraldas                | Rural birth cohort to 5 y, n = 2090 (of 2404 recruited) | Maternal prev: any 46%, Al 27%, Tt 28%, Hk 6%. Childhood prev. to 3 y: any 34%, Al 26%, Tt 17%, Hk 1% | Wheeze 13%, asthma 6% | Maternal STH associated with increased wheeze (OR 1.41). Childhood STH associated with reduced wheeze (OR 0.70) and asthma (OR 0.60). Effects greatest with later age of infection in children and seen only in non-atopics. Effects not associated with specific parasites or infection intensities |

Anti-Ascaris IgE, presence of specific IgE to Ascaris (≥0.7 kU/L); y, years; MDA, mass drug administration or given at community level; Al, A. lumbricoides; Tt, T. trichiura, Hk, hookworm; prev., prevalence; hdm, house dust mite; OR, Odds Ratio; P inter, P value for interaction.
the association between anti-Ascaris IgE and wheeze could be explained by cross-reactivity between IgE epitopes of parasites and aeroallergens. Mite atopy appeared to explain a greater proportion of wheeze in urban compared to rural schoolchildren and in a population of asthmatics with a low prevalence of STH, the association between anti-Ascaris IgE and acute asthma disappeared after controlling for mite IgE. This is in contrast to a previous rural study that showed that controlling for mite IgE did not affect the association between anti-Ascaris IgE and wheeze. Rural wheeze, much of which was explained by anti-Ascaris IgE (and not mite IgE), was a mild self-limiting illness not requiring maintenance therapy while that in the urban population was more severe, required maintenance therapy more frequently, and was more strongly associated with mite atopy. These data may indicate, therefore, that endemic exposures to ascariasis attenuate asthma severity and that urban populations with a lower prevalence of STH parasites and stronger mite atopy, may suffer more severe disease.

Soil-transmitted helminths parasites might affect the expression and severity of wheeze asthma through the attenuation of the association with atopy. There is evidence from other regions, that STH parasites may weaken the association between atopy and allergic symptoms. In case-control studies done among rural and urban schoolchildren in Esmeraldas Province, we showed that mite atopy (measured by IgE) was more strongly associated with recent wheeze in urban compared to rural children and that the association between atopy and wheeze was attenuated by markers of STH infection.

Overall, data from a series of cross-sectional studies conducted in Ecuador have not shown consistent effects of STH on allergic diseases. However, 3 observations from these studies are of particular interest: (a) the role of anti-Ascaris IgE as an important risk factor for a mild wheezing illness in rural populations where STH are endemic; (b) the role of STH infections in attenuating the associations between atopy and wheeze; and (c) the potential role of maternal and childhood STH infections in modulating risk of wheezing illness by school age.

7 IMMUNOLOGICAL MECHANISMS MEDIATING STH EFFECT ON HOST INFLAMMATORY RESPONSE

Our observations to date of effects of STH parasites on atopy and allergic diseases in Ecuador indicate a complex relationship. The inverse association between STH parasites and SPT has been interpreted to suggest an active suppressive mechanism but our observations indicate, that if real, this relationship may take many years of living in a parasite-free or less endemic environment to be reversed. Observations from Europe indicate that emergence of atopy, once a protective farming-related exposure has been removed, may occur over a period of years and is largely independent of age.

Findings of studies investigating immunological mechanisms are summarized in Table 3. Although STH parasites induce strong Th2 response in humans, the intensity of the response seems to be modulated by concurrent STH infections and increases following effective treatment. Th2-mediated inflammatory responses are required to kill and expel parasites and the ability of the parasites to modulate the severity of these responses has clear implications for parasite survival. The mechanisms by which STH parasites modulate host inflammatory responses are uncertain. The anti-inflammatory cytokine, IL-10, has a powerful immune modulatory role in tissue helminth infections such as filarial and schistosome parasites, but its role during STH infections is less clear.

The suppression of SPT associated with STH parasites may be explained by a reduction in the responsiveness of cells that bear the high-affinity receptor for IgE (ie, mast cells and basophils) to activation signals including cross-linking of specific IgE. An effect of this suppression is the marked disassociation between the presence of specific IgE and SPT to specific allergens that has been reported in numerous STH endemic populations including in Ecuador. Explanations for the disassociation include immunological suppression through immune mediators such as IL-10 and the presence of IgE of low biological activity directed against cross-reactive protein and carbohydrate structures in STH parasites. We have explored potential mechanisms by which STH infections might suppress SPT and were unable to identify a role for parasite-induced IL-10 in suppressing SPT or the disassociation between specific IgE and skin test reactivity to specific allergens, reported previously for schistosomiasis. It has been suggested that high levels of polyclonal IgE may modulate immediate hypersensitivity reactions by "saturation" of high-affinity IgE receptors (IgE-FcRI) on mast cells—we have observed a reduced prevalence of SPT among children with high levels of polyclonal IgE (ie, >3561 IU/mL). However, we observed a similar inverse association with SPT for the presence of anti-Ascaris IgG4. Both total IgE and anti-Ascaris IgG4 are likely to be associated with chronic STH infections and may be markers for other immunological factors associated with chronic infections that mediate protection against SPT. Further, it has been shown that polyclonal IgE levels during helminth infections are rarely high enough to inhibit allergen-specific IgE-FcRI binding and to suppress allergen-induced degranulation of mast cells and basophils. We were able to show that basophil reactivity to IgE-dependent (anti-IgE) and IgE-independent (ionomycin) stimuli increased rapidly following treatment of STH parasites. However, we were unable to detect specific effects of long-term anthelmintic treatment on basophil or Th2 responses to aeroallergens. A study in Indonesia provided evidence that STH parasites may suppress cellular hypersensitiveness through increased expression of inhibitory CTLA-4 on CD4+ T cells although it is not clear if this mechanism could affect immediate hypersensitivity responses.

Helminths parasites are not alone in being associated inversely with atopy. Infections with several childhood infections have been associated with a similar inverse association. These include a variety of bacterial, viral and parasitic infections as well as a variety
| Study | Design/population | Sample | Exposures/intervention | Outcomes | Findings |
|-------|-------------------|--------|------------------------|----------|----------|
| Cooper et al, 2006<sup>46</sup> | Case-control, Manabi | Teens & adults, 13-66 y, rural, (n = 113) | Ascaris-infected cases vs uninfected “non-endemic” controls. STH cases: any 100%, AL 100%, Tt 71% | PBMC cytokine responses by ELISA & ELISPOT to Ascaris adult and larval antigens | Infected had greater lymphocyte proliferation, frequencies of PBMCs expressing IL-4 and IL-5 and IL-5 protein production indicative of a highly polarized Th2 response to parasite antigen. No differences for IFN-γ and IL-10 |
| Cooper et al, 2004<sup>45</sup> | Cross-sectional, Pichincha | Schoolchildren, 5-17 y, rural, (n = 132) | Sample stratified into 4 groups by SPT status and Ascaris infection. Population of high prevalence of Al and Tt (ie, >50%) | PBMC cytokine responses by ELISPOT and PBL histamine release to Ascaris adult and larval antigens | Elevated histamine release and IL-4 and IL-5 expression to larval antigens in SPT+ children, particularly among uninfected |
| Cooper et al, 2008<sup>46</sup> | Case-control, Pichincha | Schoolchildren, 7-13 y, rural, (n = 80) | SPT+ cases vs SPT- controls. STH cases: any 43%, AL 23%, Tt 33%, Hk 3%; controls any 30%, AL 15%, Tt 25%, Hk 3% | PBL cultures with parasite antigen or aeroallergen for IL-10 protein and frequencies of IL-10+ T cells | No association between SPT+ and Ascaris-induced IL-10 and frequencies of IL-10+ T cells. Immune parameters did not affect association between of hdm-specific IgE and SPT |
| Cooper et al, 2008<sup>52</sup> | Cross-sectional analysis nested within prospective, Pichincha | Schoolchildren, mean age 9 y, rural, (n = 214) | Either treated with albendazole every 2 mo for 12 mo or no treatment. Baseline STH: any 75%, Al 57%, Tt 57%, Hk 7% | Whole blood collected at 12 mo. PBL cultures with parasite antigen or aeroallergen for histamine release (HR) and cytokines | Treatment associated with greater IL-5 and IL-13 protein to parasite antigens and SEB in treated children and reduction in IL-10 protein to Ascaris. No effect on HR and aeroallergen-specific responses |
| Guadalupe et al, 2009<sup>38</sup> | Case-control, Esmeraldas | Mothers and newborns, rural, (n = 28) | Newborn of infected mothers vs newborn of uninfected mother controls. STH infected mothers: any 100%, Al 100%, Tt 79%, Hk 29% | Cord blood frequencies of CD4+ T cells positive for IFN-γ or IL-4 from PBL cultures stimulated with Ascaris antigens | Higher frequencies of IL-4+ and IFN-γ+ CD4+ T cells in cord blood of newborns from infected mothers |
| Teran et al, 2011<sup>31</sup> | Cross-sectional, Esmeraldas | Children, 6 mo-5 y, (n = 240) | STH, urban at 4-5 y: any 43%, Al 23%, Tt 37%; rural, any 54%, Al21%, Tt 54% | PBL cytokine responses to SEB and TLR agonists. Frequencies of Tregs | Area of residence but not STH infections in children at 6-9 mo had significant effects on outcomes. Age-dependent down-regulation of IL-10 |
| Reina Ortiz et al, 2011<sup>76</sup> | Cross-sectional, Esmeraldas | Schoolchildren, 7-12 y, rural (n = 60) | Children classified as uninfected, light- and chronically-infected. STH chronic: Any 100%, Al 100%, Tt 100% | PBMCs cultured in medium alone and gene expression on unstimulated PBLs | Chronic STH associated with greater production of cytokine protein incl. IL-5 and IL-10. Evidence of differential gene regulation: chronic infections greater expression of homeostatic genes (eg, IDO) |
| Larson et al, 2012<sup>55</sup> | Prospective, Esmeraldas | Schoolchildren, 8-12 y, rural (n = 22) | STH prev.: any 100%, Al 100%, Tt 100% | Whole blood histamine release to anti-IgE before vs 14 d after treatment | Basophil activation by anti-IgE increased post-treatment |
| Cooper et al, 2015<sup>77</sup> | Cross-sectional, Esmeraldas | Schoolchildren, 6-19 y, urban and rural n = 440 | STH prev.: urban, any 21%, Al 10%, Tt 17%; Rural, any 74%, Al50%, Tt 62% | PBL cytokine responses to medium alone (homeostasis), Ascaris, hdm, and SEB | Urban children more likely to produce IL-10 to multiple stimuli. SEB-induced IL-10 partly explained by STH in urban but not rural schoolchildren |
| Figueiredo et al, 2016<sup>78</sup> | Cross-sectional, Esmeraldas | Schoolchildren, 6-19 y, urban and rural n = 310 | STH prev. (any 51%) and other poor hygiene exposures | Innate and adaptive cytokines by PBLs stimulated with media alone and SEB (maximal stimulation) | Cytokine response phenotypes defined by latent class analysis. Phenotypes: innate—low vs high; adaptive— low vs modified Th2. STH associated with regulated phenotypes |

PBMC, peripheral blood mononuclear cells; PBL, peripheral blood leukocytes; SEB, Staphylococcus enterotoxin B; SPT+/− allergen skin prick test positive/negative; Tregs, regulatory T cells; anti-Ascaris IgE, presence of specific IgE to Ascaris (≥0.7 kU/L); y, years; mo, months; IDO, indoleamine oxidase; MDA, mass drug administration or given at community level; Al, A. lumbricoides; Tt, T. trichiura; Hk, hookworm; prev., prevalence; hdm, house dust mite; OR, Odds Ratio.
of exposures associated with poverty and poor hygiene such as household hygiene,72 exposure to farm animals,59,73 and household overcrowding.28 Thus, the helminth effect on SPT might not be mediated by STH but by exposures with which they are associated or the effect might be one for which STH are sufficient but not necessary. As mentioned above, it appears unlikely that STH-specific IL-10 has a key role in modulatory effects of STH on non-parasite inflammatory responses such as that measured by SPT.

Soil-transmitted helminths infections have been associated with a stronger regulation of the immune response that can be measured in vitro either at homeostasis (ie, that measured in unstimulated cultures of peripheral blood leukocytes [PBLs]) or upon maximal stimulation (ie, after mitogen stimulation of PBLs). For example, STH infections have been associated with greater levels of homeostatic IL-10 and expression of homeostatic genes that may contribute to a more robust regulation of inflammatory responses in a non-specific manner in the context of a wide array of poor hygiene exposures with similar effects.75,77-80 The immune systems of children living in poor environments in LMICs are likely to be exposed to a wide variety of infectious disease insults. For example, we have observed that young children up to 5 years of age in rural and marginal urban areas of Ecuador show a rapid development of the memory T cell response and down-regulation of innate inflammatory responses and anti-inflammatory responses measured by IL-10.81 Studies including those using unbiased clustering methods to define phenotypes of host immune response indicate that STH infections are associated with more regulated immune phenotypes and that such immune phenotypes are associated with a lower risk of atopy.72 These phenotypes do not appear to be explained solely by the presence of STH parasites but by multiple poor hygiene and poverty-related exposures within a child’s living environment.72,75

8 | CONCLUSION

There is an unresolved debate on whether STH parasites protect against allergy and allergic diseases including asthma, potentially of great importance in populations where improvements in hygiene and widespread use of anthelmintic drugs are expected to reduce the prevalence of STH prevalence dramatically over the coming years. We have reviewed a series of epidemiological and immunological studies done in Ecuador of the effects of endemic STH parasites on the development of allergic diseases and the allergic inflammatory response. Data from cross-sectional studies of schoolchildren in regions that are highly endemic for the STH parasites, A. lumbricoides and T. trichiura, have consistently shown inverse associations between the presence of these STH parasites and a reduced risk of allergen skin prick test (SPT) reactivity. However, a prospective study from birth and a randomized intervention study in which schoolchildren were dewormed were unable to show a measurable effect of STH parasite infections on the development or presence of SPT, respectively. Similarly, the presence of STH infections did not appear to affect the risk of allergic symptoms although they did attenuate the association of allergic symptoms with atopy, and allergic sensitization to Ascaris appeared to explain a significant proportion of mild wheezing illness observed in rural populations. Findings from a birth cohort did, however, indicate that the acquisition of STH infections in early childhood might reduce the risk of wheezing illness in later childhood, but it remains uncertain if such protective effects persist beyond early childhood. Analyses of the effects of STH infections on host immune and inflammatory responses show that these parasites do modulate the host anti-parasite immune response and are likely to contribute to tighter regulation of the inflammatory response but in the context of a wide variety of other environmental exposures. Overall, these data indicate that potentially protective effects of STH parasites against wheeze may be present in early childhood in endemic regions of rural Ecuador, but such effects may not persist beyond school age at which time the development of allergic sensitization to Ascaris may contribute to a mild but self-limiting asthmatic illness.

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REFERENCES

1. Masters S, Barrett-Connor E. Parasites and asthma–predictive or protective? Epidemiol Rev. 1985;7:49-58.
2. Lynch NR, Medouze L, Di Prisco-Fuenmayor MC, Verde O, Lopez RI, Malave C. Incidence of atopic disease in a tropical environment: partial independence from intestinal helminthiasis. J Allergy Clin Immunol. 1984;73:229.
3. Lynch NR, Hagel I, Perez M, Di Prisco MC, Alvarez N, Rojas E. Bronchoconstriction in helminthic infection. Int Arch Allergy Immunol. 1992;98:77.
4. Hagel I, Lynch NR, Perez M, Di Prisco MC, Lopez R, Rojs E. Modulation of the allergic reactivity of slum children by helminthic infection. Parasite Immunol. 1993;15:311.
5. Hagel I, Lynch NR, Perez M, Di Prisco MC, Lopez R, Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol. 1993;92:404.
6. Weiss ST. Parasites and asthma/allergy: what is the relationship? J Allergy Clin Immunol. 2000;105:205-210.
7. Leonardi-Bee J, Pritchard D, Britton J, 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.
8. Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. Allergy. 2011;66:569-578.
9. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299:1259-1260.
10. Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521-1532.
11. World health Assembly. Schistosomiasis and soil-transmitted helminths. http://www.who.int/neglected_diseases/mediacentre/WHA_54.19_Eng.pdf. Accessed September 28, 2018.
12. Reaching girls and women of reproductive age with deworming. Report of the WHO Advisory Group on deworming in girls and women of reproductive age. WHO/CDS/NTD/PCT/2018.01.

13. WHO. Preventive chemotherapy to control soil transmitted helminth infections in at risk population groups http://apps.who.int/iris/bitstream/handle/10665/258983/9789241550116-eng.pdf;jsessionid=D4A432F038DCCDBAA4CDAA88C275A2D385?sequence=1. Accessed September 28, 2018.

14. Moncayo AL, Lovato R, Cooper PJ. Soil-transmitted helminth infections and nutritional status in Ecuador: findings from a national survey and implications for control strategies. BMJ Open. 2018;8:e021319.

15. Romero-Sandoval N, Ortiz-Rico C, Sánchez-Pérez HJ, et al. Soil transmitted helminthiasis in indigenous groups. A community cross sectional study in the Amazonian southern border region of Ecuador. BMJ Open. 2017;7:e013626.

16. Global asthma report; 2014. http://www.globalasthmareport.org/ burden/burden.php. Accessed May 31, 2018.

17. Cooper PJ, Rodrigues LC, Barreto ML. Influence of poverty and infection on asthma in Latin America. Curr Opin Allergy Clin Immunol. 2012;12:171-178.

18. Rodriguez A, Brickley E, Rodrigues LC, Normansell R, Barreto ML, Cooper PJ. Urbanisation and asthma in low and middle-income countries: systematic Review of the urban-rural differences in asthma prevalence. Thorax. 2011;66:1043-1050.

19. Rook GA. Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. Proc Natl Acad Sci USA. 2013;110:18360-18367.

20. Wong GW, Chow CM. Childhood asthma epidemiology: insights from comparative studies of rural and urban populations. Pediatr Pulmonol. 2008;43:107-116.

21. Grabenhenrich L, Keil T. How much of the farming effect is environmental? J Allergy Clin Immunol. 2011;128:780-781.

22. Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med. 2011;364:701-709.

23. Douwes J, Cheng S, Travier N, et al. Farm exposure in utero may protect against asthma, hay fever and eczema. Eur Respir J. 2008;32:603-611.

24. Wlasik G, Vercelli D. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. Curr Opin Allergy Clin Immunol. 2012;12:461-466.

25. Zaph C, Cooper PJ, Harris NL. Mucosal immune responses following intestinal nematode infection. Parasite Immunol. 2014;36:439-452.

26. Cooper PJ, Chico ME, Amorim LD, et al. Effects of maternal geohelminth infections on allergy in early childhood. J Allergy Clin Immunol. 2016;137:899-906.

27. Cooper PJ, Chico ME, Bland M, Griffin GE, Nutman TB. Allergic symptoms, atopy, and geohelminth infections in a rural area of Ecuador. Am J Respir Crit Care Med. 2003;168:313-317.

28. Cooper PJ, Chico ME, Rodrigues LC, et al. Risk factors for atopy among school-age children in a rural region of the Tropics. Clin Exp Allergy. 2004;34:845-852.

29. Cooper PJ, Chico ME, Vaca MG, et al. Impact of bimonthly treatment of geohelminth-infected children with albendazole on atopy prevalence: a cluster-randomized trial. Lancet. 2006;367:1598-1603.

30. Cooper PJ, Vaca M, Rodriguez A, et al. Hygiene, atopy and wheeze-eczema-rhinitis symptoms in schoolchildren from urban and rural Ecuador. Thorax. 2014;69:232-239.

31. van den Biggelaar AH, Rodrigues LC, van Ree R, et al. Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese school children. J Infect Dis. 2004;189:892-900.

32. Flohr C, Tuyen LN, Quinell RJ, et al. Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. Clin Exp Allergy. 2010;40:131-142.

33. Wiria AE, Hamid F, Wamnes LJ, et al. The effect of three-monthly albendazole treatment on malarial parasitemia and allergy: a household-based cluster-randomized, double-blind, placebo-controlled trial. PLoS ONE. 2013;8:e57899.

34. Endara P, Vaca M, Chico ME, et al. Long-term periodic anthelminthic treatments are associated with increased allergen skin reactivity and eczema prevalence. Clin Exp Allergy. 2010;40:1669-1677.

35. Vieira JC, Cooper PJ, Lovato R, et al. Impact of long-term treatment with ivermectin for onchocerciasis in Ecuador: potential for elimination of infection. BMC Med. 2007;5:9.

36. Rodrigues LC, Newcombe PJ, Cunha SS, et al. Early infections with intestinal helminths reduce the risk of atopy later in childhood. Clin Exp Allergy. 2008;38:1769-1777.

37. Cooper PJ, Barreto M, Rodrigues LC. Human allergy and intestinal helminth infections: a review of the literature and discussion of a conceptual model to investigate the possible causal association. Br Med Bull. 2006;79–80:203-318.

38. 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. J Infect Dis. 2009;199:1846-1850.

39. Cooper PJ, Chico ME, Plattas-Mills TAE, Rodrigues LC, Strachan DP, Barreto ML. Cohort profile: The Ecuador Atopy Study. J Clin Immunol. 2015;44:1517-1527.

40. Cooper PJ, Chico ME, Vaca MG, et al. Effect of early life geohelminth infections on the development of wheezing at 5 years of age. Am J Respir Crit Care Med. 2018;197:364-372.

41. Moncayo AL, Vaca M, Oviedo G, et al. Risk factors for atopic and non-atopic asthma in a rural area of Ecuador. Thorax. 2010;65:409-416.

42. da Silva ER, Sly PD, de Pereira MU, et al. Intestinal helminth infestation is associated with increased bronchial responsiveness in children. Pediatr Pulmonol. 2008;43:662-665.

43. 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. Am J Respir Crit Care Med. 2002;165(11):1489-1493.

44. Calvert J, Burney P, Ascaris, atopy, and exercise-induced bronchoconstriction in rural and urban South African children. J Allergy Clin Immunol. 2010;125:100-105.

45. Woolhouse ME, Taylor P, Matanhire D, Chandiwana SK. Acquired immunity and epidemiology of Schistosoma haematobium. Nature. 1991;351:775-779.

46. Turner JD, Faulkner H, Kamgno J, et al. Th2 cytokines are associated with reduced worm burdens in a human intestinal helminth infection. J Infect Dis. 2003;188:1768-1775.

47. Fincham JE, Markus MB, van der Merwe L, Adams VJ, van Stuijvenberg ME, Dhansay MA. Ascaris, co-infection and allergy: the importance of analysis based on immunological variables rather than egg excretion. Trans R Soc Trop Med Hyg. 2007;101(7):680-682.

48. Cooper PJ. Interactions of parasites with allergy. Curr Opin Allergy Clin Immunol. 2009;9:29-37.

49. Hunninghake GM, Soto-Quiros ME, Avila L, et al. Sensitization to Ascaris lumbricoides and severity of childhood asthma in Costa Rica. J Allergy Clin Immunol. 2007;119:654-661.

50. Buenoza E, Zakzuk J, Mercado D, Alvarez A, Caraballo L. The IgE response to Ascaris molecular components is associated with clinical indicators of asthma severity. World Allergy Organ J. 2015;8[1]:8.

51. Ahumada V, García E, Dennis R, et al. IgE responses to Ascaris and mite tropomyosins are risk factors for asthma. Clin Exp Allergy. 2015;45(7):1189-1200.

52. Hagel I, Cabrera M, Hurtado MA, et al. Infection by Ascaris lumbricoides and bronchial hyper reactivity: an outstanding association in Venezuelan school children from endemic areas. Acta Trop. 2007;103(3):231-241.
53. Endara P, Vaca M, Platt-Mills TA, et al. Effect of urban vs. rural residence on the association between atopy and wheeze in Latin America: findings from a case-control analysis. Clin Exp Allergy. 2015;45:438-447.

54. Ardura-García C, Vaca M, Oviedo G, et al. Risk factors for acute asthma in tropical America: a case-control study in the City of Esmeraldas, Ecuador. Pediatr Allergy Immunol. 2015;26:423-430.

55. Moncayo AM, Vaca M, Oviedo G, et al. Effects of geo-helminth infection and age on the associations between allergen-specific IgE, skin test reactivity and wheeze: a case-control study. Clin Exp Allergy. 2013;43:60-72.

56. Santiago HC, Nutman TB. Human helminths and allergic disease: the hygiene hypothesis and beyond. Am J Trop Med Hyg. 2016;95:746-753.

57. Scrivener S, Yemaneberhan H, Zebenigus M, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. Lancet. 2001;358:1493-1499.

58. Amarasekera M, Gunawardena NK, de Silva NR, Douglass JA, O’Hehir RE, Weerasinghe A. Impact of helminth infection on childhood allergic diseases in an area in transition from high to low infection burden. Asia Pac Allergy. 2012;2:122-128.

59. Sozańska B, Blaszczzyk M, Pearce N, Cullinan P. Atopy and allergic respiratory disease in rural Poland before and after accession to the European Union. J Allergy Clin Immunol. 2014;133:1347-1353.

60. Cooper PJ, Chico ME, Sandoval C, et al. Human infection with Ascaris lumbricoides is associated with a polarized cytokine response. J Infect Dis. 2000;182:1207-1213.

61. Cooper PJ, Chico ME, Sandoval C, Nutman TB. Atopic phenotype is an important determinant of IgE-mediated inflammation and Th2 cytokine expression to Ascaris antigens in children exposed to Ascariasis. J Infect Dis. 2004;190:1338-1346.

62. Cooper PJ, Moncayo AL, Guadalupe I, et al. Repeated albendazole treatments enhance Th2 responses to Ascaris lumbricoides but not aeroallergens in children from rural communities in the Tropics. J Infect Dis. 2008;198:1237-1242.

63. Babu S, Nutman TB. Immunology of lymphatic filariasis. Parasite Immunol. 2014;36:338-346.

64. van den Biggelaar AH, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. Lancet. 2000;356:1723-1727.

65. Hamid F, Versteeg SA, Wiria AE, et al. Molecular diagnostics and lack of clinical allergy in helmint-endemic areas in Indonesia. J Allergy Clin Immunol. 2017;140:1196-1199.

66. Cooper PJ, Mitre E, Moncayo AL, Chico ME, Vaca M, Nutman TB. Ascaris lumbricoides-induced interleukin-10 is not associated with atopy in school children in a rural area of the tropics. J Infect Dis. 2008;197:1333-1340.

67. Mitre E, Norwood S, Nutman TB. Saturation of immunoglobulin E (IgE) binding sites by polyclonal IgE does not explain the protective effect of helmint infections against atopy. Infect Immun. 2005;73:4106-4111.

68. Larson D, Cooper PJ, Hubner MC, et al. Helminth infection is associated with decreased basophil responsiveness in humans. J Allergy Clin Immunol. 2012;130:270-272.

69. Wammes LJ, Hamid F, Wiria AE, et al. Community deworming alleviates geo-helminth-induced immune hypersensitiveness. Proc Natl Acad Sci USA. 2016;113:12526-12531.

70. Alcantara-Neves NM, Veiga RV, Datoll VCC, et al. The effect of single and multiple infections on atopy and wheeze in children. J Allergy Clin Immunol. 2012;129:359-367.

71. Janson C, Asbjornsdottir H, Birgisdottir A, et al. The effect of infectious burden on the prevalence of atopy and respiratory allergies in Iceland, Estonia, and Sweden. J Allergy Clin Immunol. 2007;120:673-679.

72. Figueiredo CA, Amorim L, Cooper PJ, Matos S, Rodrigues LC, Barreto ML. Environment, immune phenotypes, atopy and asthma: new evidence shaping our understanding of the hygiene hypothesis. J Allergy Clin Immunol. 2013;131:1064-1068.

73. Lampi J, Canoy D, Jarvis D, et al. Farming environment and prevalence of atopy at age 31: prospective birth cohort study in Finland. Clin Exp Allergy. 2011;41:987-993.

74. Reina MO, Schreiber F, Benitez S, et al. Gene and microRNA expression and cytokine production associated with chronic ascariasis in children in the rural tropics. PLoS Negl Trop Dis. 2011;5:e1157.

75. Figueiredo CA, Alcantara-Neves N, Amorim LD, et al. Evidence for suppressive phenomena of IL-10 on Th1/Th2 cytokine bias: the effect of environment. Clin Immunol. 2011;139:57-64.

76. Turner JD, Jackson JA, Faulkner H, et al. Intensity of intestinal infection with multiple worm species is related to regulatory cytokine output and immune hypersensitiveness. J Infect Dis. 2008;197(8):1204-1212.

77. Cooper PJ, Amorim LD, Figueiredo CA, et al. Effects of environment on human cytokine responses during childhood in the tropics: role of urban versus rural residence. World Allergy Organ J. 2015;8:22.

78. Figueiredo CA, Amorim LD, Vaca M, et al. Effects of poor hygiene on cytokine phenotypes in children in the tropics. World Allergy Organ J. 2016;9:34.

79. Figueiredo CA, Barreto ML, Rodrigues LC, et al. Chronic intestinal helminth infections are associated with immune hypersensitiveness and induction of a regulatory network. Infect Immun. 2010;78:3160-3167.

80. Alcântara-Neves NM, Britto GdeSG, Veiga RV, et al. Effects of helmint co-infections on atopy, asthma and cytokine production in children living in a poor urban area in Latin America. BMC Res Notes. 2014;7:817.

81. Teran R, Vaca M, Erazo S, et al. Immune system development during early childhood in tropical Latin America: evidence for the age-dependent downregulation of the innate immune response. Clin Immunol. 2011;138:299-310.

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