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REVIEW

Do helminth parasites protect against atopy and allergic disease?

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Summary

Allergic diseases are rare in areas with high helminth parasite exposure and common where helminth exposure is lacking or significantly reduced, such as urban areas of developing countries and industrialized nations. Studies suggest that helminths induce a systemic immuno-modulatory network, including regulatory T cells and anti-inflammatory IL-10, which might play a key role in the protection against the allergic phenotype. Here, we review the current cross-sectional, birth cohort, and intervention study evidence for a protective effect of helminth infection on allergy. There is increasing evidence for a causal relationship between helminth infection and reduced skin prick test responsiveness to allergens. Cross-sectional studies have shown a consistent negative relationship, and these results have been confirmed in several, although not all, intervention studies. The immunological basis for this protective effect is less clear. Recent studies do not support the mast-cell IgE saturation hypothesis, but suggest that protection is associated with IL-10 production. As for allergic disease, cross-sectional studies support a negative relationship between clinical asthma and infection with some helminth species, particularly hookworm, but more studies are required to draw conclusions for eczema and rhinitis. In addition, none of the few intervention studies to date have demonstrated an increase in clinical allergy after helminth treatment, and further studies are needed. Furthermore, we are only beginning to understand the host genetic factors that are potentially involved. A genetically predetermined T-helper type 2 cell-dominated cytokine milieu reduces parasite burden and may enhance host survival in an environment where helminth parasites are prevalent. Lack of parasite exposure in such hosts might lead to hypersensitivity to seemingly minor environmental allergen stimuli. Large birth cohort studies in helminth-endemic areas that use epidemiological, genetic, and immunological tools are required to further examine how helminth parasites affect the development of atopy and allergic disease. Intervention studies with hookworm in parasite-naïve allergic individuals are currently ongoing in the United Kingdom to test the above hypotheses further.

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Introduction

About one in five children in industrialized countries suffer from asthma, allergic rhinitis (AR), or eczema, the so-called 'allergic diseases' [1]. A positive family history is a strong risk factor for allergic disease susceptibility. However, genetic factors cannot explain the marked increase in allergic disease prevalence that has occurred in many economically developed countries over recent decades, the urban–rural prevalence gradient in less developed countries, the strong social class gradient in disease risk [2–4], or that migrants tend to acquire the allergy risk of their host population [5–7]. Epidemiological research has therefore focused on identifying the possible environmental factors that are associated with increased allergy risk, with a particular emphasis on investigating lifestyle differences and other exposures that might be responsible. Helminth infections are one of the factors identified in this context.

World-wide, more than two billion people are chronically infected with soil-transmitted helminths (STH): schistosomiasis, *Ascaris lumbricoides*, the hookworms (*Ancylostoma duodenale* and *Necator americanus*), and *Trichuris trichiura* [8]. Poor sanitation and hygiene are the main factors that predispose to all four infections. While *Ascaris* and *Trichuris* are transmitted fecal-orally, hookworm larvae and schistosomal cercariae enter the host via the skin. All these infections, with the exception

of *Trichuris*, have a systemic phase in the lifecycle, which requires the parasite to survive in the bloodstream and selected internal organs of the host. Another potentially important group of helminth parasites with regard to allergic diseases are filarial nematodes, principally *Wuchereria bancrofti, Brugia malayi,* and *Onchocerca volvulus*, and around 150 million people are thought to be infected world-wide [9]. Filarial infections are characterized by long-lived, tissue-dwelling adult worms, with transmission by blood-feeding insects. In endemic areas without existing de-worming campaigns, people are commonly chronically infected with multiple helminth species.

Immune responses in helminth infections and allergy share many important features, such as a T-helper type 2 (Th2)-dominated cytokine milieu, associated with an up-regulation of IL-4-, IL-5-, and IL-13-mediated IgE and mast cell production as well as eosinophilia (Fig. 1). Such Th2 responses are generally protective against parasitic infection, although IgE-driven acute sequelae of helminth infection, for example eosinophilic pneumonitis associated with ascariasis, are occasional disease complications [10, 11]. Indeed, it is generally considered that Th2 responses evolved to control extra-cellular parasites. Because this Th-2-mediated immunity is also central to the pathogenesis of allergic disease, it may be that susceptibility to allergic disease in developed countries represents the manifestation of a phenotype with particularly strong Th2-driven responses, which originally conveyed a higher chance of survival in an environment

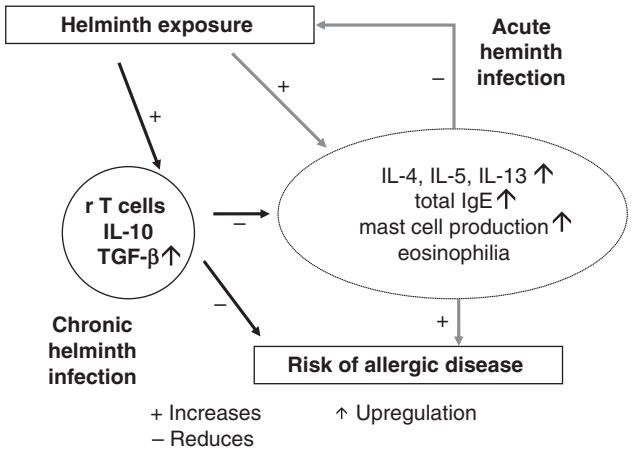

Fig. 1. Helminth infections and allergic diseases are strong inducers of Th2 responses. The up-regulation of IL-4, IL-5, IL-13, total IgE and eosinophilia are part of the host immune response against the parasite and are hallmarks of acute helminth infections as well as allergic disease. However, helminth infections tend to be long-lived and largely asymptomatic. There is evidence to suggest that helminth infections are sustained through a parasite-induced immuno-modulatory network, in particular activation of regulatory T cells and systemically elevated levels of IL-10 and possibly TGF-β. This, in turn, may have a down-regulatory effect on the risk of developing allergic disease. r T cells, regulatory T cells.

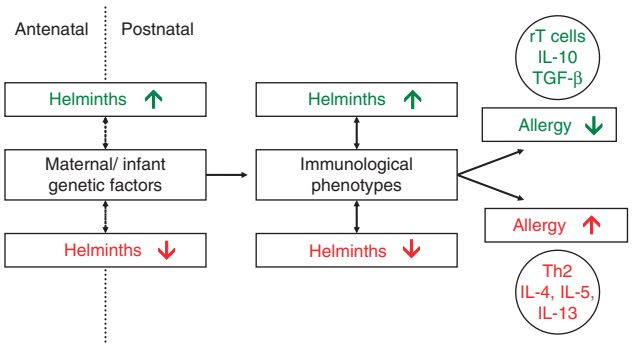

Fig. 2. Helminth exposure in endemic areas (green) occurs already *in utero* and continues post-natally. It is very likely that host genetic factors through interaction with helminth parasites determine the regulatory T cell-dominated immunological phenotype that is thought to underlie the observed decrease in allergy risk. In areas where helminth exposure is significantly reduced or absent (red), a Th2-dominated cytokine milieu continues to evolve and leads to an increased risk in atopy and clinical allergy. r T cells, regulatory T cells; Th2, type 2 T helper cells.

where parasitic infestations were endemic. In the absence of endoparasite and other infective stimuli, however, it is possible that the immune system does not develop immune tolerance post-natally, and this may consequently lead to a pre-disposition to allergic disease ([12]; Fig. 2).

While IgE-mediated host responses are associated with helminth infections, parasites have developed methods to modulate the host immune system, presumably to permit and prolong survival within the host [11]. Despite the immunological similarities between host responses to endoparasitic infections and to external allergens, helminth-infected individuals appear to be protected from mast cell degranulation and inflammatory responses in affected tissues, and it has been suggested that this is due to a protective immuno-modulatory network generated by parasite-induced T cells and their cytokines, including IL-10, ultimately leading to prevention of allergic tissue inflammation [11, 13, 14].

In this paper, we review recent studies of the interaction between helminth infection and allergic disease, concentrating on community-based studies in humans. Papers on the current epidemiological, immunological, and genetic evidence for a protective effect of helminthic infections on atopy and allergies were identified through searches of MedLine, EMBASE, Web of Science, and Biosis Reviews from their inception to the end of July 2008.

Perinatal exposure to parasite antigens

Fetal exposure to helminth antigens can occur *in utero* through maternal infection [15]. For instance, cord blood lymphocytes from babies born to helminth-infected mothers have been found to produce parasite antigen-specific IgE [16, 17]. Another source of helminth antigen exposure of the neonate may be through breastmilk as

well as early post-natal infection, although the latter is probably less important in children who are not yet able to walk. It has also been suggested from work on lymphatic filariasis that such early exposure may lead to lasting immune tolerance to parasite antigens and may prevent children from developing tissue inflammation in response to acute infection and re-infection, and that this may be particularly advantageous in highly endemic areas [15, 18–20]. Thus, perinatal exposure to high levels of parasite antigen may prove sufficient to induce long-term immune system hyporesponsiveness, and through the cross-reactivity between parasite antigens and environmental allergens, such as house dust mites (HDMs) and cockroach, this may also confer protection against atopy and allergic disease ([21]; Fig. 2).

Helminths and skin sensitization to environmental allergens (atopy)

Following the suggestion that frequent and heavy helminth infection might protect against allergic skin sensitization based on observations made among Venezuelan children [22], there have been a number of cross-sectional studies of the relationship between atopy and helminth infection, summarized in Table 1. Protective effects on skin prick test (SPT) responses have been consistently

Table 1. Cross-sectional studies on the link between helminths and skin prick test positivity (atopy)

Type of helminth infection (author, country, year)	Number of participants	Age	Odds ratio (95% CI)	Effect direction
Any helminth				
Cooper et al., Ecuador, 2003 [25]	4433	5–18	0.62 (0.50–0.76)	↓
Cooper et al., Ecuador, 2003 [26]	2865	5–19	0.64 (0.52–0.78)	↓
Cooper et al., Ecuador, 2004 [27]	1002	7–17	0.65 (0.47–0.91)	↓
Davey et al., Ethiopia, 2005 [28]	7649	5–70+	0.75 (0.58–0.97)	↓
Flohr et al., Vietnam, 2006 [29]	1742	6–18	0.70 (0.50–0.99)	↓
Nyan et al., The Gambia, 2001 [30]	429	15–34	0.30 (0.11–0.80)	↓
Hookworm				
Cooper et al., Ecuador, 2003 [25]	4433	5–18	0.67 (0.33–1.37)	NS
Cooper et al., Ecuador, 2003 [26]	2865	5–19	0.39 (0.18–0.85)	↓
Dagoye et al., Ethiopia, 2003 [24]	7155	1–4	1.20 (0.70–1.70) Dp	NS
			1.30 (0.80–2.20) Cock	NS
Davey et al., Ethiopia, 2005 [28]	7649	5–70+	0.74 (0.55–0.99)	↓
Flohr et al., Vietnam, 2006 [29]	1742	6–18	0.61 (0.39–0.96)	↓
Grove & Forbes, Papua New Guinea, 1975 [31]	50 atopics 139 non-atopics	All ages	0.24 (0.11–0.51)*	↓
Scrivener et al., Ethiopia, 2001 [32]	403	14–60+	1.70 (0.88–3.27)**	NS
Ascaris				
Cooper et al., Ecuador, 2003 [25]	4433	5–18	0.65 (0.54–0.78)	↓
Cooper et al., Ecuador, 2003 [26]	2865	5–19	0.74 (0.60–0.91)	↓
Dagoye et al., Ethiopia, 2003 [24]	7155	1–4	1.10 (0.70–2.00) Dp	NS
			1.00 (0.70–1.40) Cock	NS
Flohr et al., Vietnam, 2006 [29]	1742	6–18	0.28 (0.10–0.78)	↓
Obihara et al., South Africa, 2006 [33]	359	6–14	0.57 (0.23–1.40)	NS
Palmer et al., China, 2002 [23]	1896	8–18	Increased no of pos SPTs	↑
Scrivener et al., Ethiopia, 2001 [32]	403	14–60+	1.52 (0.81–2.87)**	NS
Trichuris				
Cooper et al., Ecuador, 2003 [25]	4433	5–18	0.69 (0.56–0.86)	↓
Cooper et al., Ecuador, 2003 [26]	2865	5–19	0.82 (0.67–1.01)	Borderline ↓
Dagoye et al., Ethiopia, 2003 [24]	7155	1–4	1.40 (0.90–2.20) Dp	NS
			1.70 (1.10–2.40) Cock	↑
Scrivener et al., Ethiopia, 2001 [32]	403	14–60+	1.10 (0.56–2.16)**	NS
Schistosomiasis				
Araujo et al., Brazil, 2000 [34]	42 cases 133 controls	6–40	0.14 (0.03–0.63)	↓
van den Biggelaar et al., Gabon, 2000 [35]	520	5–14	0.32 (0.16–0.63)	↓

*Calculated from raw data as protective effect of >2000 epg.

**Calculated from raw data.

↓, negative association between helminths and atopy; ↑, positive association between helminths and atopy; NS, non-significant; SPT, skin prick test; CI, confidence interval.

shown for all helminths investigated, including *A. lumbricoides*, *T. trichiura*, hookworm, and *Schistosoma*, although the effect sizes have been varied and have not always been statistically significant. Although the number of studies is small, schistosome infection appears to have the strongest protective effect. In contrast, in the case of *Trichuris* and *Ascaris* infection, one study for each parasite has found a significant increase (rather than decrease) in atopy risk [23, 24]. To our knowledge, there have been no published studies on the relationship between filarial infection and atopy.

Helminths and clinical allergic disease

While the majority of studies point towards an inverse relationship between SPT positivity and helminth infection, the picture is less clear for clinical allergic disease, namely asthma, eczema, and hayfever.

Hayfever

In 1976, a British researcher reported having been completely symptom free from hitherto treatment-resistant hayfever, while he remained experimentally infected with *N. americanus* [36]. However, few have studied the association between hayfever and helminths since. Lynch et al. looked at urban–rural prevalence differences of allergic disease and helminth infection among 811 Venezuelan children. AR was significantly more common in the urban population while *A. lumbricoides* was equally prevalent among both urban and rural participants [37], suggesting that other exposures were responsible for urban–rural prevalence differences in rhinitis. Equally, a large cross-sectional questionnaire-based survey conducted in a paediatric population in rural Ecuador found no significant association between rhino-conjunctivitis symptoms and *A. lumbricoides* infection (adjusted odds ratio (OR) = 1.00, 0.55–1.79 [27]), nor did a population-based cross-sectional survey in Cape Town, South Africa (OR = 1.04, 0.22–4.82 [33]). However, a study conducted among 3,107 primary schoolchildren in Taipei, Taiwan, suggested that *Enterobius vermicularis* may be protective against physician-diagnosed rhinitis (adjusted OR = 0.61, 0.45–0.84 [38]).

Eczema

There is evidence from observational studies that eczema is common in populations with a low parasite burden [12, 39–42]. However, cross-sectional studies have not provided strong evidence for an effect of helminth infection on eczema, with both negative and positive associations reported. In 2005, Schäfer et al. [43] showed an independent inverse association between *A. lumbricoides* and questionnaire-diagnosed eczema in a population-based study of 4169 East German children (adjusted OR = 0.45, 0.33–0.60). This effect was even more pronounced in children with increased specific IgE levels to aeroallergens (adjusted OR = 0.31, 0.18–0.56), suggesting that helminth infection may be causing a dissociation between sensitization and eczema phenotype. The latter has also been observed in other developing country settings [44]. Further supporting evidence for an inverse relationship between eczema and helminth infection comes from a small birth cohort study among 103 mother–infant pairs in Uganda, where cumulative eczema risk was decreased by 74% until age 15 months among children whose mothers were infected with helminths (predominantly hookworm) during the last trimester of pregnancy (adjusted OR = 0.26, 0.08–0.83 [45]).

In contrast, a nested case–control study among 732 Ethiopian children age 1–5 indicated a significant positive association between flexural eczema and the presence of 'any parasite infection', with this effect predominantly caused by *Trichuris*, but not *Ascaris* or hookworm (adjusted OR *Trichuris* = 1.61, 1.14–2.26 [46]). Finally, no significant association was seen with *Ascaris* or *Trichuris* infection in a cross-sectional survey among 4433 Ecuadorian schoolchildren (adjusted OR = 0.85, 0.50–1.46 [25]), nor with *E. vermicularis* infection among 3107 Taiwanese primary schoolchildren [38].

Asthma/wheeze

Herrick [47] was the first to recognize that helminths can trigger asthma attacks. Following his work in the early 20th century, little attention was paid to the potential links between endoparasitic infestations and asthma until the early 1970s. Reports that asthma was commonly caused by endoparasites were, however, not confirmed [48, 49]. Two previous reviews of the literature suggested that further evidence was needed to either support or disprove the hypothesis that parasites protect against asthma [50, 51]. A more recent systematic review and meta-analysis of 30 cross-sectional studies found that an inverse relationship between asthma and geohelminths was seen for hookworm infection (predominantly *N. americanus*; pooled OR = 0.50, 0.28–0.90), and that this effect was infection intensity related (OR for the highest tertile of infection intensity = 0.34, 0.19–0.62). However, *A. lumbricoides* appeared to increase asthma risk (pooled OR = 1.34, 1.05–1.71), while *T. trichiura* had no significant effect (pooled OR = 1.19, 0.98–1.43; Fig. 3, [52]). In addition, one small population-based case–control study from Brazil has suggested that asthmatics infected with *Schistosoma mansoni* have a milder course of disease than non-infected individuals, marked by lower symptom frequency and reduced use of asthma medication. However, there was no difference in objective pulmonary function measurements between infected and non-infected asthmatics [53].

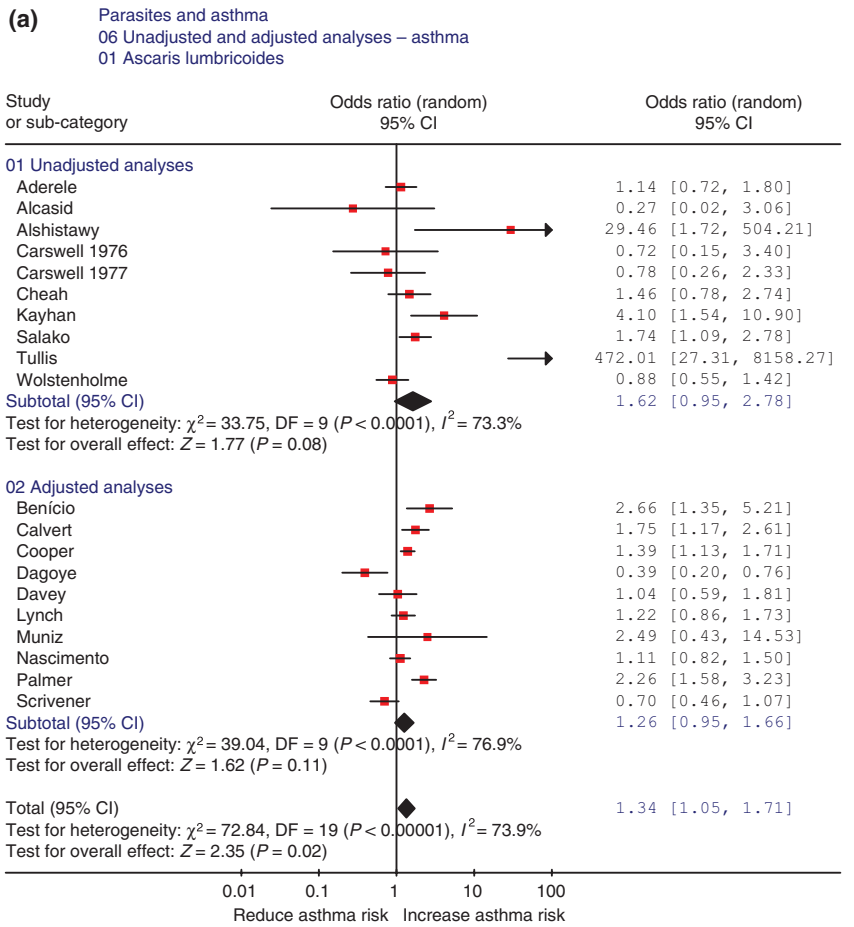

Fig. 3. Relationship between *Ascaris lumbricoides* (a), hookworm (b), and *Trichuris trichiura* (c) infection and asthma in cross-sectional studies, using meta-analysis. Results are presented as odds ratios for individual studies (squares) and in pooled analysis (rhomboids), using random effect models. Reproduced with permission from the *Am J Respir Crit Care Med* [52].

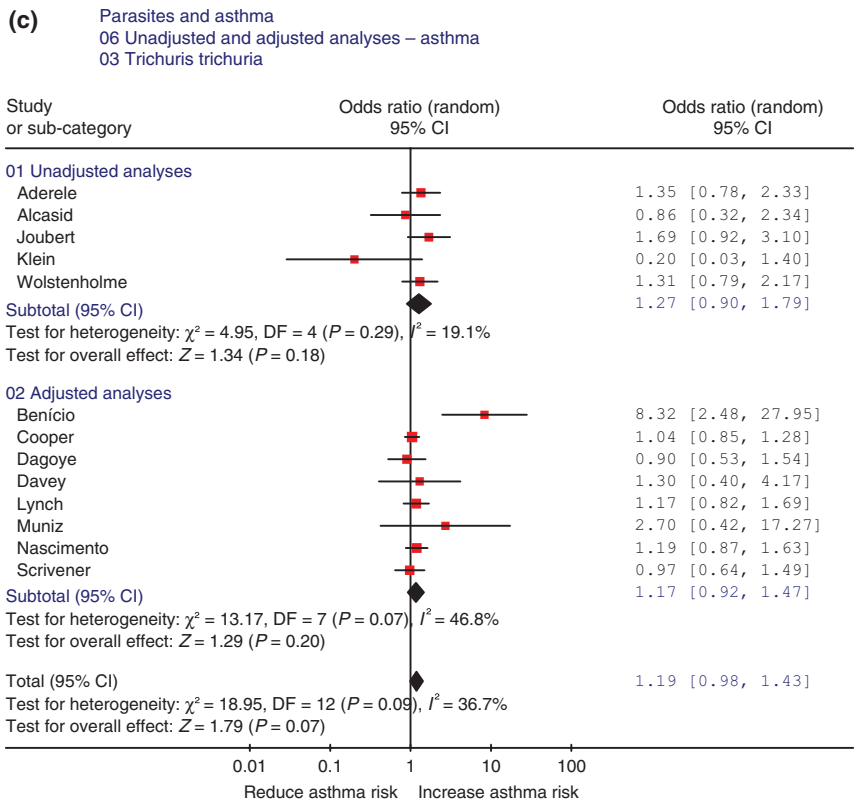

Fig. 3. Continued.

Evidence from intervention studies

Despite mounting cross-sectional evidence that STHs are associated with protection against SPT positivity to aeroallergens, asthma, and potentially eczema, this observation does not prove causality. Confounding by other exposures remains a clear possibility, as does reverse causation arising from higher levels of protection from helminth infection among allergic individuals. To address these possibilities, evidence is required on the effects of either parasite infection in previously unexposed allergic individuals, or of the effect of parasite eradication on allergic disease prevalence in helminth-infected populations. In the latter group, two studies in children, one an observational study built into a helminth eradication programme in 375 Venezuelan children [54], the other a single blind trial of 317 children in Gabon [55], have reported evidence of a significant increase in allergic skin sensitization following anti-helminthic therapy, consistent with the hypothesis that helminth parasites protect against atopy. We have also recently completed an individually randomized placebo-controlled trial among 1566 Vietnamese schoolchildren and shown a significantly higher risk of allergic sensitization in the anti-helminthic treatment compared with the placebo group after 12 months (adjusted OR = 1.31, 1.02–1.67), and this effect was particularly strong in children infected with both *Ascaris* and hookworm at baseline (adjusted OR = 4.90, 1.48–16.19 [56]). However, no effect of de-worming treatment on atopy was shown in a cluster randomized trial of helminth therapy in 2372 Ecuadorian children [57].

There is no evidence to date for an increase in clinical asthma after anti-helminthic treatment, as neither our study in Vietnam nor the Ecuadorian study found a significant effect [56, 57]. However, a randomized placebo-controlled study in Uganda among 103 mother–infant pairs found that administration of albendazole to pregnant mothers was associated with an increased cumulative eczema risk in infants until age 15 months in univariate analysis [45]. This effect did not reach statistical significance after adjustment for potential confounders (adjusted RR = 2.40, 0.77–7.48), possibly due to small participant numbers and resulting low statistical power. In contrast, clinical *improvement* of established asthma following de-worming was reported in a small study among 89 Venezuelan adults and children with asthma. In the same individuals, a reduction in positive SPT responses and specific IgE levels to HDM was also seen [58].

As far as we are aware, there are to date no published studies of the effects of parasite infection in previously uninfected individuals with allergies. J. B., in collaboration with Prof. David Pritchard (University of Nottingham), has recently initiated studies of hookworm (*N. americanus*) as

a potential therapeutic agent for allergic disease [59]. A safety study of the effect of hookworm infection on airway responsiveness in individuals with AR has been conducted (http://clinicaltrials.gov/ct2/show/NCT00232518; paper submitted for publication), and an intervention trial in asthmatics is currently being completed (http://clinicaltrials.gov/ct2/show/NCT00469989).

The immuno-epidemiology of allergy and atopy in helminth-infected populations

For at least some helminth species, the epidemiological evidence reviewed above suggests that parasite infection is associated with lowered SPT responses to allergen and lowered risk of clinical asthma. Several immunological mechanisms have been suggested to explain the potential anti-allergy effects of helminths (reviewed by [13, 60–62]). Up-regulated Th2 responses in helminth-infected individuals may interfere with anti-allergen effector pathways either directly via antibody-mediated interactions at the mast cell surface (the IgE saturation hypothesis). Alternatively, the induction of an anti-inflammatory network mediated by dendritic cell and regulatory T cells may suppress immune responses to both helminth and non-helminth antigens. These mechanisms are not mutually exclusive, as key anti-inflammatory molecules such as IL-10 also affect antibody production. There may also be direct effects of parasite products, for instance mast cell degranulation is inhibited by the filarial parasite product ES-62 [63]. Here, we concentrate on evidence from recent human field studies and propose that convincing evidence for a role of immune responses in mediating the protective effects of helminth infection on allergic disease and atopy requires that the immune response meets the following criteria: firstly, it should be negatively associated with allergy in parasitized populations, not only in cross-sectional analysis but also longitudinally after treatment. Secondly, the immune response should be up-regulated in helminth infection, and decrease after helminth treatment.

Mast cell immunoglobulin E receptor saturation hypothesis

The IgE saturation hypothesis was the earliest suggested mechanism to potentially explain a protective effect of helminth parasites on allergic disease [64, 65]. It was based on the observation that helminth infections stimulate polyclonal total IgE production, often to a much greater level than seen in unparasitized individuals with either asthma or eczema, suggesting that high levels of polyclonal IgE could saturate IgE receptors on the mast cell surface, preventing binding of allergen-specific IgE and mast cell degranulation. In addition, total IgE levels typically decrease after anti-helminthic treatment [54, 55, 58]. Further supporting evidence also came from *in vitro* studies, which suggested that inhibition of mast cell histamine release was possible in the presence of high total IgE levels [65]. This hypothesis predicts that total IgE levels or the ratio of total : allergen-specific IgE are critical for helminth-mediated protective effects on allergic disease phenotypes.

Two recent studies in humans have tested the IgE saturation hypothesis, demonstrating that basophils from hookworm or filarial patients with high levels of polyclonal IgE retain the ability to release histamine in response to parasite antigens *in vitro* [66, 67]. Moreover, in filarial patients there was no change in histamine release over a wide range of natural ratios of polyclonal to specific IgE, from 14 : 1 to 388 : 1, likely related to the IgE-driven increased FcεRI expression on basophils. However, higher ratios of $>500:1$ did block histamine release *in vitro*. The authors suggest that such ratios are unlikely to be seen in human helminth infections, and further studies of total : anti-allergen IgE ratios would be useful to confirm this.

Human field studies that have measured total IgE levels and their relation to SPT positivity and/or clinical allergy have also not shown a convincing inverse relationship (Table 2). It is possible that these results are confounded by variation in the ratio of total : allergen-specific IgE, and few studies have measured this ratio. The effects of helminth infection on specific (anti-allergen) IgE are apparently variable, as intervention studies have shown no change [55, 56], an increase [54], or a decrease [58] in specific IgE after anti-helminthic treatment. It has also been suggested that effects vary with the intensity of infection, with low-intensity infection stimulating specific IgE and thus SPT responses and suppression only seen in high-intensity infection [37]. However, an inverse relationship between helminth infection and atopy has been shown in low-intensity infection areas as well [29].

In summary, both the immuno-epidemiological and the experimental evidence suggests that the IgE saturation hypothesis is unlikely to explain reduced SPT responses in helminth-infected populations, except perhaps in a very small number of individuals [66, 67, 79]. However, further studies of basophil responses to *non-helminth* allergens, and of total : specific IgE ratios in other helminth infections, such as *Ascaris* infection, would be useful. Other potential antibody-mediated mechanisms have been proposed, such as the production of low-affinity anti-allergen IgE, or blocking by anti-allergen IgG4, but both have so far received little attention [13, 80].

Anti-inflammatory regulatory network

Human and murine studies have revealed that helminth infection induces a complex immuno-regulatory network. This includes dendritic cells, natural regulatory T cells,

Table 2. Evidence for a protective effect of helminth-induced immune responses on atopy and allergy

Prediction	Total IgE	IL-10
Association with atopy	*Negative (high IgE, low atopy risk)*	*Negative (high IL-10, low atopy risk)*
	Cooper et al. 2003 [26]	Flohr et al. 2007 (hookworm-induced IL-10) [56]
	Hagel et al. 1993 [68]	Van den Biggelaar et al. 2000 (schistosome-induced IL-10) [35]
	Van den Biggelaar et al. 2001 [69]	
	No association	*No association*
	Lynch et al. 1987 [70]	Cooper et al. 2008 (*Ascaris*-induced IL-10, allergen-induced IL-10) [71]
	Scrivener et al. 2001 [32]	
	Van den Biggelaar et al. 2004 [55]	
	Positive (high IgE, high atopy risk)	*Positive (high IL-10, high atopy risk)*
	Flohr et al. 2007 [56]	No studies.
	Grove et al. 1974 [72]	
	Lynch et al. 1987 [70]	
	Nyan et al. 2001 [30]	
Association with allergy		
Asthma/wheeze	*Negative (high IgE, low asthma risk)*	*Negative (high IL-10, low asthma risk)*
	Warrell et al. 1975 [73]	No studies.
	No association	*No association*
	Carswell et al. 1977 [74]	No studies.
	Medeiros et al. 2003 [53]	
	Scrivener et al. 2001 [32]	
	Selassie et al. 2000 [75]	
	Positive (high IgE, high asthma risk)	*Positive (high IL-10, high asthma risk)*
	Alshishtawy et al. 1991 [76]	No studies.
	Palmer et al. 2002 [23]	
	Macfarlane et al. 1979 [77]	
Eczema	No studies.	No studies.
Hayfever	No studies.	No studies.
Intervention studies		
Decrease after helminth treatment	*Yes*	*Yes*
	Van den Biggelaar et al. 2004 [55]	Araujo et al. 2004 (house dust mite-induced IL-10) [78]
	Lynch et al. 1993 [54]	
	Lynch et al. 1997 [58]	
	No	*No*
	Flohr et al. 2007 (non-significant reduction) [56]	Flohr et al. 2007 (non-significant reduction hookworm-induced IL-10) [56]
	Not measured	*Not measured*
	Araujo et al. 2004 [78]	Lynch et al. 1993 [54]
		Lynch et al. 1997 [58]
		Van den Biggelaar et al. 2004 [55]

inducible regulatory T cells (Tr1 cells), and alternated activated macrophages [81]. There are a number of potential immunosuppressive mechanisms associated with these subsets, but production of the anti-inflammatory cytokines TGF-β and especially IL-10 is thought to play a key role. A number of murine studies have demonstrated helminth-induced down-regulation of allergic responses, with evidence for both IL-10-dependent and non-IL-10-dependent mechanisms [82–86]. However, it should be noted that parasite-induced exacerbation of allergic tissue inflammation has also been observed in some murine models [62, 82].

Human field studies of asthma and helminths have focused on one potential immunosuppressive marker, IL-10. Up-regulation of IL-10 production in helminth infection has been shown for filarial and schistosome infections [87–90]. However, evidence for up-regulated IL-10 production in hookworm [91–93] and *Ascaris* [71, 94–97] infection is less consistent, although a significant decline in IL-10 production after treatment of hookworm infections has been seen [93]. Two studies have shown a negative relationship between anti-parasite IL-10 production and SPT responses in hookworm and schistosome infection in cross-sectional analysis ([35, 56]; Table 2). The hookworm study also assessed cytokine levels after anti-helminthic therapy with a non-significant decline in IL-10 [56]. In addition, a case–control study among helminth-infected and non-infected

asthmatics demonstrated a positive association between schistosome infection status and HDM-induced IL-10 [78]. In this study, IL-10 levels also declined following anti-helminthic therapy. However, a recent detailed study in an Ecuadorian population infected with *Ascaris* and *Trichuris* found no association between SPT responses and either anti-*Ascaris* or anti-allergen IL-10 production, and also no association with numbers of IL-10-positive T cells, including $CD4^+CD25^+$ subsets [71]. IL-10 may have a direct role in suppressing mast cell responses in helminth infection, as IL-10 suppression of mast cell histamine release has been seen *in vitro* [98]. An indirect role for IL-10 via the up-regulation of potentially blocking IgG4 responses has also been suggested [13]. Alternatively, IL-10 may be acting as a marker for the immuno-regulatory response, or the relationship may be confounded by non-immunological factors [71]. Given the range of immuno-regulatory cells and mechanisms potentially involved, including IL-10 independent mechanisms [86, 99], there is a clear need for further longitudinal studies that measure not only SPT positivity in relation to IL-10 but also clinical allergy as well as other suppressive cytokines, such as TGF-β, and regulatory T cell subsets.

Does atopy protect against helminth infection? Reverse causation and host genetics

An alternative explanation for a negative association between helminths and atopy is that atopic individuals have a greater resistance to helminth infection. Indeed, this was the interpretation of the first study to show such a negative association [31]. The immunological bias in atopic individuals may lead to stronger anti-parasite immune responses and thus lower parasite burdens. Evidence for stronger anti-parasite immune responses in atopics comes from a recent study by Cooper et al. [100] in which atopic children had stronger Th2 responses to *Ascaris* than non-atopics, with higher frequencies of IL-4- and IL-5-expressing peripheral blood mononuclear cells and greater basophil histamine release in response to *Ascaris* antigen. These responses are potentially protective against helminth infection. However, anti-parasite IgE, which has also been associated with protection, is not consistently higher in atopics [32, 33, 56, 71].

Why might atopics be protected against parasites? Both atopy and helminth burden are known to have a significant host genetic component [101, 102], and it has been hypothesized that both phenotypes are under common genetic control. This would provide an evolutionary explanation for genetic predisposition to atopy and allergy, as such individuals would be protected against helminth infection, and a functional explanation for the negative association between asthma and helminth burden. It has also been suggested that geographical variation in selective pressures for an up-regulation of Th2 responses may underlie some ethnic differences in allergy risk [103]. There is some indirect evidence that the same genes control atopy and helminth infection from work in different populations [104]. For instance, the Th2 gene cluster on chromosome 5q31–33 has been linked to control of both asthma and schistosome phenotypes [105, 106]. Several association studies have demonstrated that risk alleles or haplotypes at asthma loci are associated with low worm burden. In particular, the study of *STAT6* haplotypes in British asthmatics and Chinese with *Ascaris* infection has revealed that haplotypes associated with allergic phenotypes in the United Kingdom are associated with low *Ascaris* burden in China [107]. Similarly, the *IL13-1055T* allele has been associated with both low schistosome burden in Mali and an increased asthma risk in Europe [108, 109], and the *ADRB2* Gly16 allele has been associated with low *Ascaris* burden in Venezuela and more severe asthma [110, 111]. Helminth-mediated immunomodulation may also be affected by host genetics, as IL-10 polymorphisms have been associated with SPT positivity and IL-10 production in children in Gabon [112].

These results are intriguing, although several caveats should be borne in mind. Very few genetic association studies have been performed for helminth infection, and associations require confirmation in independent populations. The loci investigated in helminth infection have been strongly biased towards loci known to be important in asthma. In contrast, loci identified from whole-genome scans for *Ascaris* and *Trichuris* infection, where loci are not selected *a priori*, did not contain genes known to be important in asthma [113, 114]. What is now required are genetic studies of allergic disease and helminth infection in the *same* population. In particular, pedigree-based genetic epidemiology studies have the potential to determine whether there is a positive genetic correlation between atopy, clinical allergy, and resistance to helminth infection across individuals, reflecting common genetic control. Interestingly, a Venezuelan founder population with a genetic predisposition to asthma had lower *Ascaris* burdens than similar areas in Venezuela, although confounding effects cannot be ruled out [42].

Are all worms equal?

The studies of interactions between helminths, allergy, and immune responses reviewed above show variable results, with both positive and negative associations reported. A possible explanation for this heterogeneity is variation between studies in the species of helminth, the age when infections were acquired, and the intensity of infection. Helminths are often implicitly treated as a homogeneous group, because they share a pronounced up-regulation of IgE responses, but important inter-species differences exist. In particular, the degree of

immunosuppression induced by different species is likely to vary, with long-lived, tissue-dwelling parasites such as filarial worms and schistosomes expected to induce stronger immuno-regulatory responses than lumen-dwelling gastrointestinal parasites [81]. It has also been suggested that parasites with a lung-migratory stage, such as hookworm, *Ascaris,* and schistosomes, may be more effective at suppressing allergic inflammation in the lungs [32, 62]. There is some evidence from human field studies for species differences in effects on allergy, although in most studies polyparasitism is common. The strongest associations between infection and atopy or asthma are seen for schistosome and hookworm infection, and there is evidence for a role of IL-10 in both infections. In contrast, *Ascaris* infection does not appear to protect against asthma, despite a lung-migratory stage, nor elicit a strong IL-10 response. Allergic reactions to parasite antigens are also more common in *Ascaris* infection. Furthermore, the degree of parasite-induced host immuno-suppression is likely to be positively associated with worm burden, as indicated by a lower atopy and asthma risk with higher helminth egg counts [26, 29, 32], and polyparasitism [29, 56].

Conclusions

There is epidemiological evidence from a number of cross-sectional and intervention studies to suggest a direct immuno-modulatory effect of helminth infection on SPT responses for hookworm, *Ascaris*, and schistosomes. To date, there have been no human studies with filarial worms and this warrants further research. There is also cross-sectional evidence to suggest a protective effect of hookworm, but an exacerbatory effect of *Ascaris* infection, on asthma. However, two recent intervention studies have not demonstrated changes in asthma prevalence after helminth treatment. Thus, it is not possible to rule out that the cross-sectional associations with asthma result from confounding or reverse causation (e.g. host genetics). Cross-sectional studies on eczema and rhinitis are few in number and inconsistent. While the mast cell saturation hypothesis appears not to be important, there is limited evidence that helminth effects on atopy may be mediated by parasite-induced anti-inflammatory IL-10. However, further detailed immunological studies are needed, and the precise mechanisms whereby intestinal or systemic helminths prevent mast-cell degranulation in the skin remain to be determined. It is likely that the perinatal environment plays an important role in the priming of the infant's immune system. Large intervention and birth cohort studies that combine epidemiological, genetic, and immunological tools are required to shed further light on the intricate relationship between helminth infection and allergy. Of particular interest are gene–environment interactions and regulatory T cell subsets and their cytokines as well as allergen-specific IgG4. It is hoped that such research, together with the currently ongoing intervention studies involving the voluntary infection of allergic individuals with helminth parasites, will ultimately lead to the development of parasite-derived drugs not only for the treatment but also for the prevention of allergic diseases.

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