

Atopy and current intestinal parasite infection: a systematic review and meta-analysis

J. Feary, J. Britton & J. Leonardi-Bee

Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK

To cite this article: Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. *Allergy* 2010; DOI: 10.1111/j.1398-9995.2010.02512.x

Keywords

allergen skin sensitization; atopy; helminth; IgE; parasite.

Correspondence

Johanna Feary, Division of Epidemiology and Public Health, University of Nottingham, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK.

Tel.: +44 115 8231388

Fax: +44 115 8231337

E-mail: jofeary@doctors.org.uk

Accepted for publication 22 October 2010

DOI:10.1111/j.1398-9995.2010.02512.x

Edited by: Hans-Uwe Simon

Abstract

Background: The rate of increase in prevalence of allergic disease in some countries implies environmental exposures may be important etiological factors. Our aim was to undertake a systematic review and meta-analysis of epidemiological studies to quantify the association between current intestinal parasite infection and the presence of atopy and to determine whether this relation is species specific.

Methods: We searched MEDLINE, EMBASE, LILACS and CAB Abstracts (to March 2009); reviews; and reference lists from publications. No language restrictions were applied. We included studies that measured current parasite infection using direct fecal microscopy and defined atopy as allergen skin sensitization or presence of specific IgE. We estimated pooled odds ratios (OR) and 95% confidence intervals (95% CI) using data extracted from published papers using random-effects model.

Results: Twenty-one studies met our inclusion criteria. Current parasite infection was associated with a reduced risk of allergen skin sensitization OR 0.69 (95% CI 0.60–0.79; $P < 0.01$). When we restricted our analyses to current geohelminth infection, the size of effect remained similar OR 0.68 (95% CI 0.60–0.76; $P < 0.01$). In species-specific analysis, a consistent protective effect was found for infection with *Ascaris lumbricoides*, *Tricuris trichuria*, hookworm and *Schistosomiasis*. There were insufficient data to pool results for atopy defined by the presence of specific IgE.

Conclusion: Intestinal parasite infection appears to protect against allergic sensitization. Work should continue to identify the mechanisms of this effect and means of harnessing these to reduce the global burden of allergic disease.

Allergic disease is one of the most common causes of chronic morbidity in childhood in developed countries (1) and has increased rapidly in prevalence in low- and middle-income countries over the last 30 years (2). Allergy occurs as a result of a complex interaction between genetic and environmental exposures (3), with the rate of change in prevalence over recent decades indicating that environmental factors have played a particularly important role. Many environmental factors have been identified as being associated with asthma, eczema, and atopy (4–8), one of which is parasite infection. In a previous systematic review and meta-analysis, we reported that current hookworm infection halved the risk of asthma (9). However, the effect of parasite infection on the occurrence of atopy has not, to date, been subject to a similar systematic study.

We therefore now report a systematic review and meta-analysis of the epidemiologic literature relating to the relation between parasite infection and allergic skin sensitization to

common allergens, specifically to cockroach and dust mite, and allergen-specific IgE. As in the study of asthma, we have also sought to determine whether this relation is species specific (9).

Methods

Systematic review methods

A comprehensive literature search in MEDLINE/PUBMED (1966 to March 2009), EMBASE (1980 to March 2009), LILACS (1982 to March 2009), and CAB Abstracts (January 2000–March 2009) was performed according to standard guidelines (10) to identify all epidemiological studies, with no restrictions on language, using the search strategy detailed in the Data S1. Studies were included if they met the following criteria: (i) design was a comparative epidemiological study (cross-sectional, cohort, case-control) or presented baseline

data from a randomized controlled trial; (ii) atopy was described using current allergen skin sensitization or specific IgE; (iii) direct fecal microscopy was used to measure current parasite infection. Studies were initially selected on the basis of their titles, and the abstracts, and then if appropriate, full texts were obtained for those potentially fulfilling our inclusion criteria. To identify any additional papers, we checked the reference lists of published reviews and papers for which the full text was obtained. Selection of eligible papers and data extraction were independently performed by two authors (JF and JL-B) and cross-checked, with discrepancies decided by consensus opinion. Studies by the same research groups were checked for replicated data to ensure they were not included more than once. Included studies were scored for methodological quality using the Newcastle-Ottawa Quality Assessment Scale (11) with a score of 7 or more chosen (from a maximum of 7 for cross-sectional studies (unable to score for selection/definition of controls) and 9 for case-control studies) *a priori* to indicate a high standard for comparative observational studies. We used only the baseline data from the randomized controlled trial and therefore, for the purposes of quality assessment and during the statistical analyses, these data were considered to be cross-sectional. The systematic review was carried out in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (12).

Statistical analysis

Data were analyzed to yield effect estimates using unadjusted odds ratios (OR) from extracted data from the papers, or in preference, and if available, using adjusted ORs. Where exposure was expressed based on the burden of infection, the highest exposure category was compared with those without infection. Where possible, the individual effect estimates from the studies were combined using a random study effects model (13) to estimate the pooled OR with 95% confidence intervals (CI) to allow for heterogeneity between the estimates of effect. Heterogeneity between study estimates was anticipated because of inherent biases in the studies and was assessed using established methods (14) with any differences explored using subgroup analyses. Publication bias was assessed using a funnel plot (15) where adequate numbers of studies were included in the meta-analyses. Data were analyzed using Review Manager 5 (Cochrane Collaboration).

For our primary analysis of current infection with any parasite and sensitization to at least one allergen, we performed subgroup analyses according to study methodological quality, study design, wheal size used to define atopy, study population (i.e. children, adults or both), and geographic area where the studies were undertaken. We also performed subgroup analyses to look at current infection with different groups of parasites and individual parasite species. In addition, we explored whether it was possible to estimate pooled effects according to burden of infection. To allow appropriate comparison between studies, the following three groupings of intestinal parasite infection were used: (i) geohelminths (including *Trichuris trichiura*, *Ascaris lumbricoides*, hook-

worm, *Enterobius vermicularis*, *Toxocara canis* and *T. cati* and *Strongyloides stercoralis*); (ii) helminths (all geohelminths plus *schistosomiasis* species) and (iii) any intestinal parasite infection. While our main measure of outcome was skin sensitization to at least one allergen, several studies reported separate results for specific skin sensitization to cockroach and dust mite and we therefore report these effects individually as secondary outcomes.

Results

Overview of the included studies

Our search strategy, using skin sensitization to define atopy, initially identified 1273 studies published between 1966 and March 2009. The full texts of 225 papers were obtained, and of these, 21 met our inclusion criteria, including one that was unpublished data but identified to us by the authors (Obeng et al., unpublished data). The most common reasons for excluding papers were that appropriate data were not presented or that a different definition of atopy had been used, such as history of allergic disease (Fig. 1). Sixteen of the included studies used a cross-sectional design (16–30) (Obeng et al., unpublished data), four used case-control designs (31–34), and the remaining study was a randomized controlled trial from which we used the baseline data (35). No studies using a cohort design were found.

The majority of the studies were undertaken in school-age children from 5 to 19 years with one in infants aged 1–4 years (32). Five were performed in both adults and children (16, 17, 22, 27, 33) and two in adults alone (24, 34). The total number of individuals included in all 21 included studies was 28 818.

Eleven studies presented data using 'any parasite infection' as an exposure (18–22, 24, 26, 28, 30, 35) (Obeng et al., unpublished data), and these were used for our primary analysis; the remaining 10 studies had results only for species-specific infection (16, 17, 23, 25, 27, 29, 31–34). A positive skin sensitization test was defined in one study as a saline-adjusted wheal of ≥ 2 mm (32) and in another as ≥ 1 mm (31); all other included studies used adjusted wheal sizes of ≥ 3 mm (16, 18–30, 33–35) (Obeng et al., unpublished data) or ≥ 4 mm (17). Six studies presented results for sensitization to cockroach and mite separately (22, 23, 27, 32, 34) (Obeng et al., unpublished data). One study assessed rural and urban populations independently (34).

Methodological quality of studies and publication bias

Using the Newcastle-Ottawa score and the *a priori* chosen cut of seven to indicate higher methodological quality, 16 of the 21 included studies were of higher quality and five were judged to be of lower quality because of an inadequate definition of their control population, a failure to adjust for age or other factors, or omission of non-response rate. In total, 16 of the included studies presented their data after adjusting their analyses for confounders. The median overall score was 7 (range 3–9) (Table 1), confirming that the quality was generally high

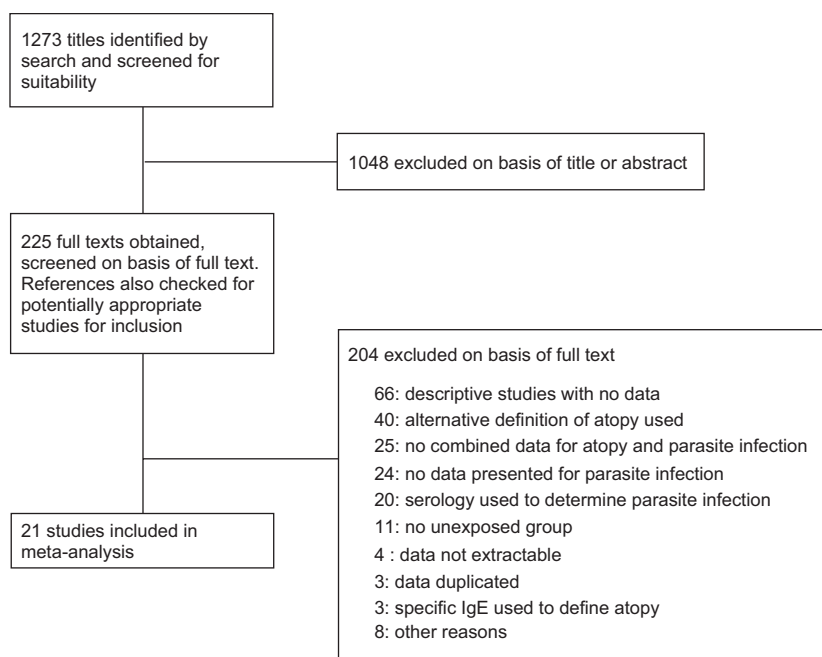


Figure 1 Flow diagram of included and excluded studies for skin sensitization.

using this particular scoring system (11). Funnel plots did not suggest evidence of publication bias (See Figures S1 and S2).

Effects of current intestinal parasite infection on atopy

The pooled analysis of estimates from the 11 studies using any combination of intestinal parasite infection (18–22, 24, 26, 28, 30, 35) (Obeng et al., unpublished data) demonstrated a reduction in the risk of atopy in individuals with any current intestinal parasite infection with an OR of 0.69 (95% CI 0.60–0.79; $P < 0.01$). Moderate levels of heterogeneity were observed across these studies ($I^2 = 45\%$). Although significant for an effect on sensitization to any allergen, no significant effect was seen for specific sensitization to mite or cockroach (Figs 2 and Table S1).

Subgroup analysis indicated that there were no significant differences in the results according to the methodological quality of the study (higher quality studies; OR 0.67, 95% CI 0.59–0.75; $P < 0.01$) or study design (cross-sectional studies; OR 0.67, 95% CI 0.57–0.78; $P < 0.01$), and the magnitude of the effect was very similar for studies using adjusted and unadjusted data. All of the studies included in the subgroup analysis used a wheal size of ≥ 3 mm to define a positive skin sensitization test. Limiting studies to the eight studies of just children made little difference to the results (OR 0.70, 95% CI 0.61–0.80; $P < 0.01$). Restriction of the analyses by geographic area to the seven studies conducted in Central or South America found similar effects (OR 0.68, 95% CI 0.60–0.75; $P < 0.01$) (Table S2). When the analysis was restricted to those studies of current geohelminth infection, the effect was similar (OR 0.68, 95% CI 0.60–0.76; $P < 0.01$) (Table S1).

Three papers provided information on egg counts and while pooled effects of burden of infection could not be determined because of the format of the data presented, there was a suggestion from two of these studies that sensitization to any allergen was related to intensity of infection (19, 28).

Effects of current infection with individual parasite species on atopy

Fifteen of the 21 studies provided species-specific data on parasite infection. We analyzed the individual effects of four helminth species that were present in at least 1% of the study populations.

Ascaris lumbricoides

Fifteen studies described the relation between *A. lumbricoides* infection and the risk of current atopy (19–23, 25–28, 30–34) (Obeng et al., unpublished data). A pooled analysis of nine studies demonstrated a statistically significant reduction in the odds of atopy to at least one allergen in individuals with current *A. lumbricoides* infection (OR 0.69, 95% CI 0.59–0.80; $P < 0.01$) with little heterogeneity between the studies ($I^2 = 30\%$) (19–21, 25, 26, 28, 30, 31, 33). In contrast to this general effect on allergen sensitization, there were no statistically significant effects in four studies on specific sensitization to cockroach [OR 0.90, 95% CI 0.75–1.08; $P = 0.25$ ($I^2 = 0\%$)] (22, 23, 32) (Obeng et al., unpublished data) or in six studies to mite [OR 1.03, 95% CI 0.73–1.46; $P = 0.86$ ($I^2 = 47\%$)] (22, 23, 27, 32, 34) (Obeng et al., unpublished data) (Figs 3 and Table S1).

Table 1 Studies included in meta-analysis

Author, year	Study design	Number in study	Age in years mean (SD) or range	Parasite	Country	Methodologic quality score*
Araujo (2000) (16)	XS	175	U: 20.2 (11.9) I: 18.0 (9.7)†	<i>Schistosoma mansoni</i>	Brazil	5
Araujo (2004) (17)	XS	43	6–40	<i>S. mansoni</i>	Brazil	3
Bahceciler (2007) (18)	XS	997	4–12	Any parasite‡	Turkey	5
Calvert (2005) (31)	CC	743	8–13	<i>Ascaris lumbricoides</i>	South Africa	9
Cooper (2003a) (19)	XS	2865	5–18	Any geohelminth <i>A. lumbricoides</i> Hookworm <i>Tricuris tricuris</i>	Ecuador	7
Cooper (2003b) (20)	XS	3681	5–19	Any geohelminth <i>A. lumbricoides</i> Hookworm <i>T. tricuris</i>	Ecuador	7
Cooper (2004) (21)	XS	987	7–17	Any geohelminth <i>A. lumbricoides</i> <i>T. tricuris</i>	Ecuador	7
Cooper (2006) (35)	RCT	2331	C: 9.8 (2.1) V: 9.6 (2.0)†	Any geohelminth	Ecuador	7
Dagoye (2003) (32)	CC	563	1–4	<i>A. lumbricoides</i> Hookworm <i>T. tricuris</i>	Ethiopia	9
Davey (2005) (22)	XS	7508	5–95	Any geohelminth <i>A. lumbricoides</i> Hookworm	Ethiopia	7
Flohr (2006) (23)	XS	1601	6–18	<i>A. lumbricoides</i> Hookworm	Vietnam	7
Joubert (1979) (33)	CC	109	12–44	<i>A. lumbricoides</i>	South Africa	4
Nyan (2001) (24)	XS	429	≥15	Any geohelminth	Gambia	7
Obeng (unpublished data)	XS	2019	5–16	Any geohelminth <i>A. lumbricoides</i> Hookworm <i>T. tricuris</i> <i>Schistosomiasis</i>	Ghana	7
Obihara (2006) (25)	XS	359	6–14	<i>A. lumbricoides</i>	South Africa	7
Peireira (2007) (26)	XS	1011	9–13	Any helminth <i>A. lumbricoides</i>	Brazil	5
Ponte (2006) (27)	XS	113	12–30	<i>A. lumbricoides</i>	Brazil	4
Rodrigues (2008) (28)	XS	1055	4–12	Any geohelminth <i>A. lumbricoides</i> Hookworm <i>T. tricuris</i>	Brazil	5
Scrivener (2001) (34)	CC	403	≥16	<i>A. lumbricoides</i> Hookworm <i>T. tricuris</i> <i>Schistosomiasis</i>	Ethiopia	9
Van den Biggelaar (2000) (29)	XS	513	5–14	<i>Schistosoma haematobium</i>	Gabon	4
Wördemann (2008) (30)	XS	1313	4–14	Any geohelminth <i>A. lumbricoides</i> Hookworm <i>T. tricuris</i> <i>Enterobius vermicularis</i>	Cuba	7

XS, cross-sectional; CC, case-control; RCT, randomized controlled trial.

*Based on Newcastle-Ottawa Quality Assessment Scale from a maximum score of 7 for cross-sectional studies and 9 for case-control studies; baseline data were used for the RCT and assessed as per cross-sectional data.

†Means (standard deviation) presented separately for uninfected (U), infected (I), control (C) and intervention (V) groups.

‡*E. vermicularis* 23.3% (using perianal tape), *Blastocystis hominis* 22.4%, *Giardia intestinalis* 13%, *Entamoeba coli* 2.2%, *Entamoeba histolytica* 1.7% (other parasites contribute <1%).

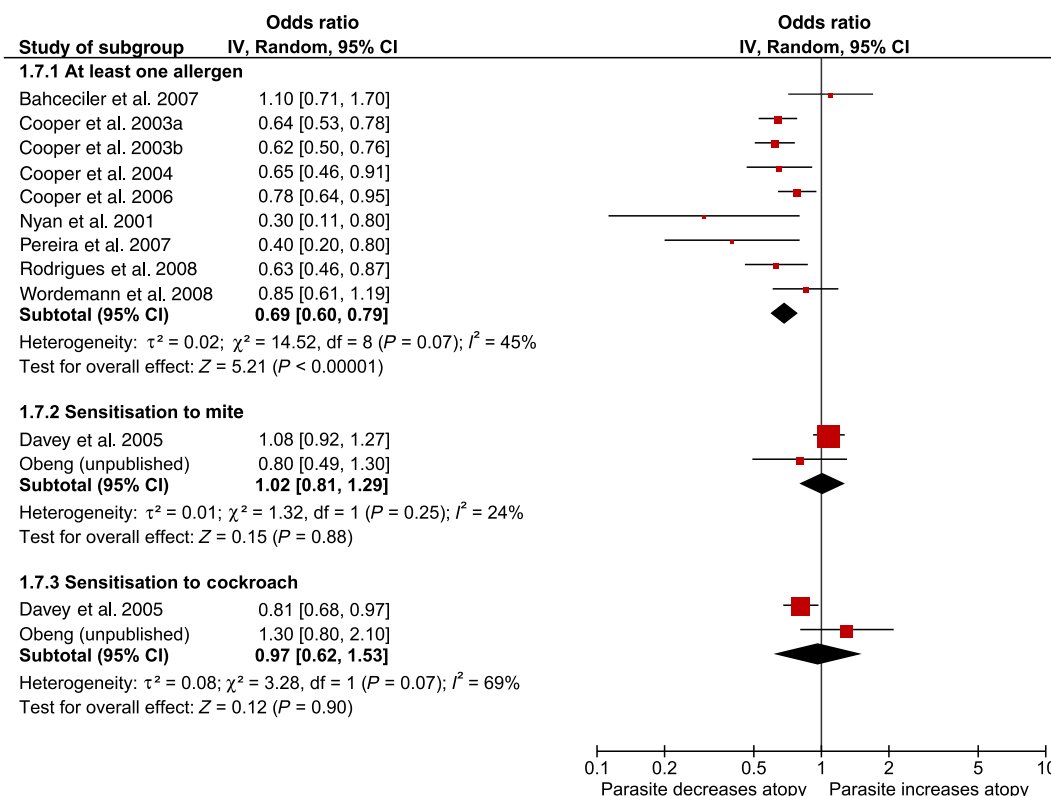


Figure 2 Atopy and any parasite.

Hookworm (*Necator americanus* and *Ancylostoma duodenale*). Nine studies reported the association between hookworm infection and the risk of current atopy (19, 20, 22, 23, 28, 30, 32, 34) (Obeng et al., unpublished data). Pooled data from four homogeneous studies ($I^2 = 14\%$) indicated that current infection with hookworm was associated with a reduction in skin sensitization to at least one allergen, though not to the point of statistical significance (OR 0.68, 95% CI 0.46–1.01; $P = 0.06$) (19, 20, 28, 30). The pooled effects of hookworm infection on sensitization to cockroach in four of these studies were not significant [OR 0.81, 95% CI 0.62–1.08; $P = 0.15$ ($I^2 = 52\%$)] (22, 23, 32) (Obeng et al., unpublished data) nor in the five studies of sensitization to mite [OR 0.94, 95% CI 0.65–1.36; $P = 0.73$ ($I^2 = 62\%$)] (22, 23, 32, 34) (Obeng et al., unpublished data) (Figs 4 and Table S1).

Trichuris trichuria

Eight studies looked at the effects of *Trichuris trichuria* infection with the risk of current atopy (19–21, 28, 30, 32, 34) (Obeng et al., unpublished data). Pooled effects of five homogenous studies reporting current *T. trichuria* infection showed a significant reduction in atopy to at least one allergen [OR 0.75, 95% CI 0.65–0.86; $P < 0.01$ ($I^2 = 7\%$)] (19–21, 28, 30). In contrast, two studies of sensitization to cockroach found infection was associated with a significant increase in current atopy [OR 1.86, 95% CI 1.24–2.80; $P = 0.003$ ($I^2 = 13\%$)] (32) (Obeng et al., unpublished

data); and three studies of sensitization to mite found infection was nonsignificantly associated with a increase in atopy [OR 1.72, 95% CI 0.90–3.29; $P = 0.10$ ($I^2 = 47\%$)] (32, 34) (Obeng et al., unpublished data) (Figs 5 and Table S1).

Other individual parasite species

Pooled results from the three studies of *Schistosomiasis* species (16, 17, 29) found current infection was associated with a statistically significant reduction in the odds of current atopy (OR 0.12, 95% CI 0.03–0.57; $P = 0.007$); however, the results from these studies were heterogeneous ($I^2 = 69\%$) and all three studies were scored as having lower methodological quality (Figs 6 and Table S1). No effect on the risk of current atopy was seen with *E. vermicularis* (18, 30), *Giardia intestinalis* (18), or *Blastocystis hominis* (18).

Studies using specific IgE to define atopy status

Seven studies were identified from the systematic review that defined atopy as a positive specific IgE to mite or other aero-allergens (16, 17, 27, 29, 31, 36, 37). Extraction of data was not possible in four studies owing to the format of the data (27, 29), because no uninfected individuals had specific IgE testing performed (16) or because no data were presented (31), although the authors of this last paper did comment that they had found no significant association between *A. lumbricoides* infection and specific IgE.

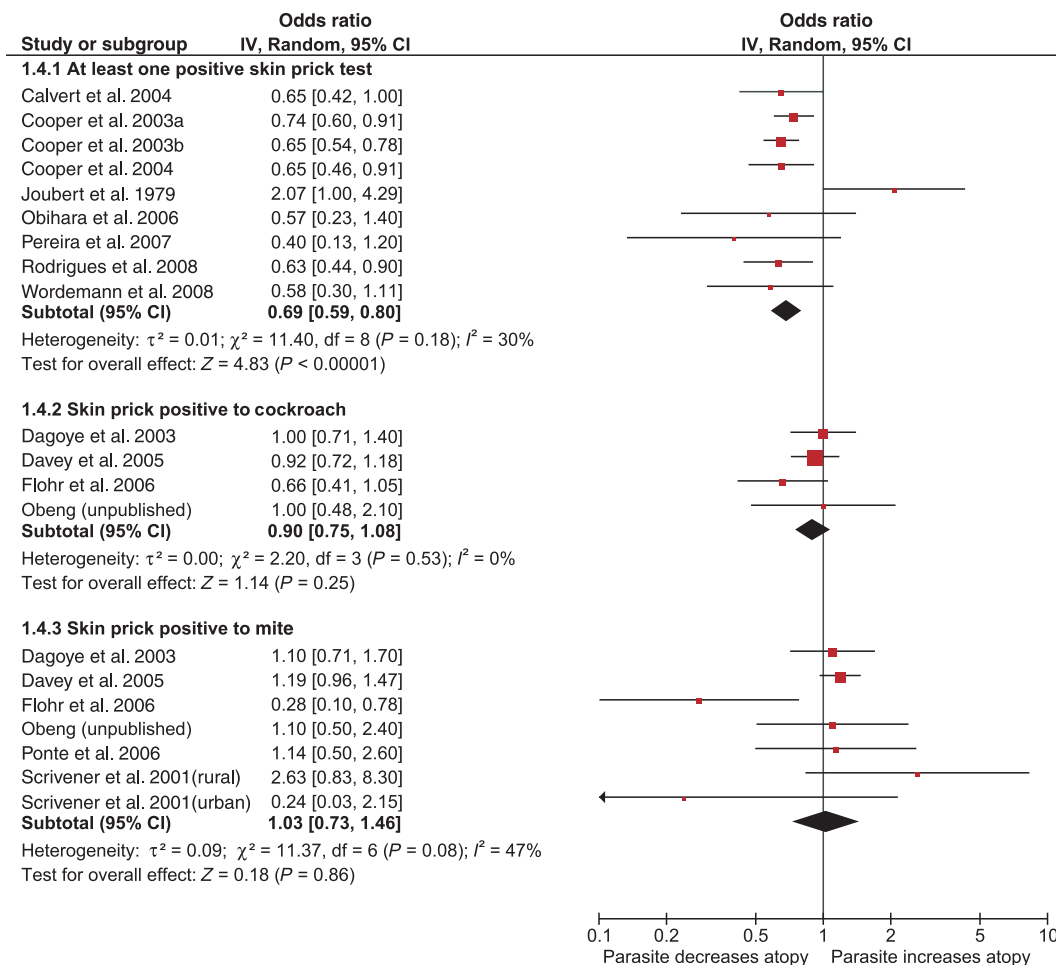


Figure 3 Atopy and *Ascaris lumbricoides*.

The three remaining studies reported inconsistent findings in the relation between infection and presence of specific IgE. One study found geohelminth infection (with the combination of *A. lumbricoides* and *T. tricurria*) to be associated with a statistically significant increase in the likelihood of having raised specific IgE (> 1.0 IU/ml) to mite (OR 1.94, 95% CI 1.20–3.15; $P < 0.01$) (37). In contrast, another study reported no significant association in multivariate analyses between specific IgE to mite and infection with either *A. lumbricoides* (OR 1.74, 95% CI 0.55–5.51) or *T. tricurria* (OR 2.70, 95% CI 0.95–7.67) (36). Finally, a study of *Schistosomiasis* found current infection to be associated with a significant reduction in presence of aeroallergen-specific IgE (OR 0.24, 95% CI 0.09–0.60; $P < 0.01$) (17).

Discussion

Main findings

This systematic review and meta-analysis of the epidemiologic literature demonstrates strong evidence that current intestinal parasite infection, in particular geohelminth infection, is

associated with a reduced prevalence of allergic skin sensitization to at least one allergen. A similar pattern was seen for the individual species although this was only statistically significant for the effects of *A. lumbricoides* and *T. tricurria*. There was no evidence that intestinal parasite infection was associated with an increase in risk of skin sensitization to cockroach or mite, with the exception of *T. tricurria* that was associated with a significant increase in risk of skin sensitization to cockroach.

Strengths and limitations

We are confident that our literature search was comprehensive and, so far as we are aware, identified all potentially suitable studies in this area. In addition, our funnel plot did not suggest that our results would have been significantly affected by publication bias. We found a surprisingly low degree of heterogeneity between some of the studies that may be attributable to the majority of studies being published by a small selection of research groups. The methodological quality of the studies included in this review was, with few exceptions,

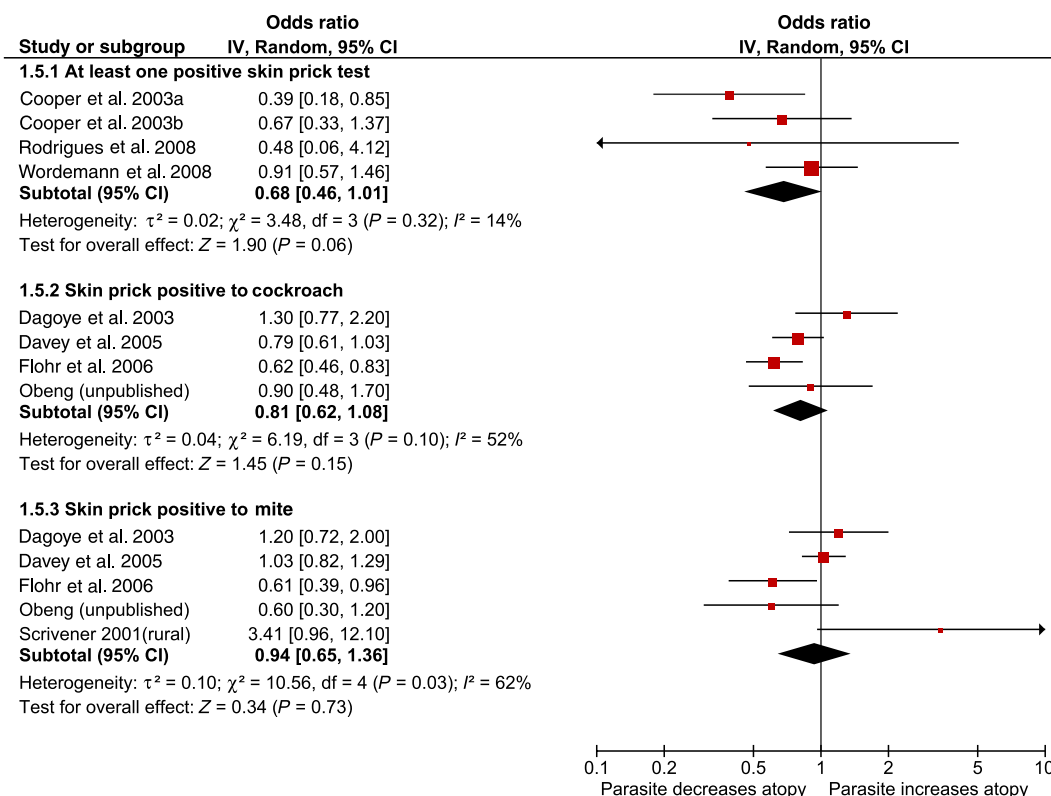
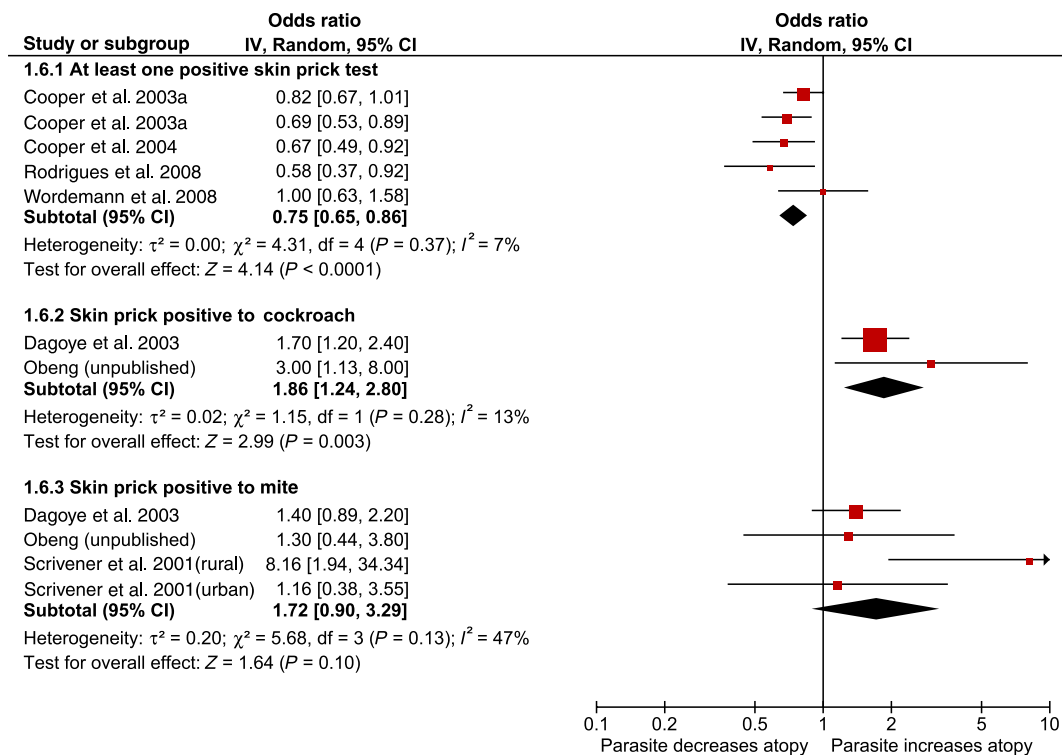
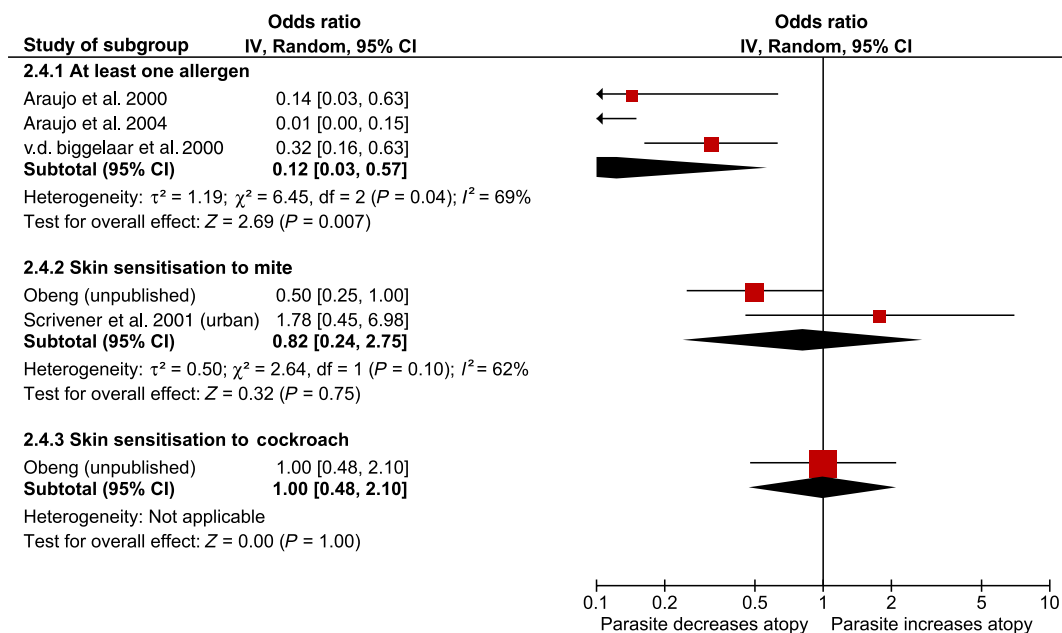


Figure 4 Atopy and Hookworm species.

very good. The MOOSE guidelines recommend assessing the impact of key components of study design (such as case-control, cohort and cross-sectional) using subgroup or sensitivity analysis (12); however, we were unable to do this fully as most of our studies were cross-sectional in design. Therefore, we explored the impact of quality on the findings using subgroup analyses as recommended by the MOOSE guidelines: the majority of studies were scored as being of high quality and the results varied little when lower scoring studies were removed. However, the use of such scoring systems within meta-analyses is controversial because the findings from analyses may not be reliably associated with quality (38). The majority of studies were published within the past 10 years. As 19 of the 21 included studies were carried out in Central or South America or Africa, [the remaining two studies were from Vietnam (23) and Turkey (18)], our findings are particularly applicable to those regions of the world; though, there are no grounds to suggest that the findings will not be generalizable elsewhere where similar environmental conditions exist. While our primary analysis was for infection with any parasite, the majority of parasites were, in fact, geohelminths, and it may be that other parasite infections will demonstrate a different relationship with atopy but further studies are needed before any conclusions can be drawn. To maximize the validity of our results, we used a definition of current infection ascertained by direct fecal microscopy, rather than a reported history of infection or by serological testing,

neither of which differentiates between past and current infection. We defined our outcomes using skin sensitization, a relatively simple and cheap test and unlikely to be subjected to measurement bias (compared with a subjective history of atopic disease) and increased validity by using sensitization to different allergens. Minimal numbers of studies used parasite-specific IgE data and looked at different exposures, so we were not able to analyze these results as pooled data; however, results did not show any particular pattern or trend. The main limitation of the meta-analysis was that we were unable to account for the effects of age, gender, or socioeconomic status in a number of studies that presented unadjusted estimates of effect. However, less than half of the studies included in the meta-analysis did not adjust for confounding factors and low levels of heterogeneity were generally detected between the studies, indicating that the findings were similar. For our primary outcome, the size of effect was similar for unadjusted and adjusted data. However, age could be of particular importance in this respect as different intestinal parasites are acquired at different ages throughout childhood, most commonly, either after weaning or as infants become mobile. Our subgroup analysis of studies of just children did not suggest the size of effect varied significantly between adults and children, but skin sensitization to allergens increases with age and is rare before the age of 5 years, so the study of infants aged < 5 years of age may be misrepresentative.

Figure 5 Atopy and *Tricuris trichuria*.Figure 6 Atopy and *Schistosomiasis*.

Possible explanations for observed results

The variation in effect estimates observed between species is likely to reflect, in part, the relatively small number of avail-

able species-specific studies and also genuine differences of effect on allergy between species. Previous research has suggested that the protective effect of intestinal parasites on asthma may arise from a host systemic phase in the parasite

life cycle (34) but the present study suggests that this may be less relevant for allergic sensitization. It is of note that none of the parasites were associated with an increase in the odds of atopy to at least one allergen; though, *Tricuris trichuria* infection was associated with an increased risk of specific sensitization to cockroach. Several authors presented results separately for sensitization to cockroach and mite. Interestingly, Flohr et al. were the only authors to find both *A. lumbricoides* and hookworm infection to be significantly associated with a reduction in atopy to mite and cockroach (23), which may reflect geographic variation as this was the only study performed in Asia. With these few exceptions, no association was found between mite and cockroach and skin sensitization, suggesting that other allergens are responsible for the reduced risk of atopy.

We have previously reported that in the relation between current intestinal parasite infection and asthma, hookworm was associated with a 50% reduction in wheeze, in contrast to *A. lumbricoides* that was associated with an increase in wheeze (34). This is surprising in the context of the results from this current study on atopy and raises questions about the relation between parasite infection and different allergic diseases, and indeed on the relation between allergic sensitization and clinical symptoms. While atopy is a strong risk factor for allergic disease in developed countries, studies have shown that it appears to be less closely related or not at all in developing countries (20, 39).

Conclusions

This study thus provides evidence that parasite infections protect against allergy. A clearer understanding of the etiology of allergic disease and the relation between environment and host is important for many reasons. Allergy is already a common cause of chronic disease in childhood in economi-

cally developed countries. The prevalence of allergic disease is increasing, particularly in low- and middle-income countries, placing a huge burden on already stretched health services. An increase in comprehension of the mechanisms underlying development of allergic disease may help direct future therapeutic advancements, which are at present limited to treatments with undesirable side-effects. Parasite infection is endemic in large parts of the world, and while eradication is acknowledged to be an important aspect of ensuring public health, there is a chance that this may in fact lead to an increase in allergic disease. It is for this reason that characterization of the relation between the two is especially important.

Funding

This study did not receive any external funding support.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Funnel plot for any current geohelminth infection and sensitization to at least one allergen.

Figure S2. Funnel plot for current *Ascaris* infection and sensitization to at least one allergen.

Table S1. Summary of results for all analyses.

Table S2. Summary of results for subgroup analyses for infection with any parasite and sensitization to at least one allergen.

Data S1. Search strategy.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

References

- Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;**1**:69–75.
- Weinberg EG. Urbanization and childhood asthma: an African perspective. *J Allergy Clin Immunol* 2000;**105**:224–231.
- von Mutius E. Environmental factors influencing the development and progression of pediatric asthma. *J Allergy Clin Immunol* 2002;**109**:S525–S532.
- Barreto ML, Cunha SS, Alcantara-Neves N, Carvalho LP, Cruz AA, Stein RT et al. Risk factors and immunological pathways for asthma and other allergic diseases in children: background and methodology of a longitudinal study in a large urban center in Northeastern Brazil (Salvador-SCAALA study). *BMC Pulm Med* 2006;**6**:15.
- Cooper PJ. Interactions between helminth parasites and allergy. *Curr Opin Allergy Clin Immunol* 2009;**9**:29–37.
- Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;**358**:1129–1133.
- Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;**181**:E181–E190.
- Venn AJ, Yemaneberhan H, Bekele Z, Lewis SA, Parry E, Britton J. Increased risk of allergy associated with the use of kerosene fuel in the home. *Am J Respir Crit Care Med* 2001;**164**:1660–1664.
- Leonardi-Bee J, Pritchard D, Britton J. Asthma and current intestinal parasite infection: systematic review and meta-analysis. *Am J Respir Crit Care Med* 2006;**174**:514–523.
- Deeks J, Glanville J, Sheldon T. Undertaking Systematic Reviews of Effectiveness: CRD Guidelines for Those Carrying Out or Commissioning Reviews, 4th edn. ed. Centre for Reviews and Dissemination York, UK: York Publishing Services, 1996.
- Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. Newcastle-Ottawa scale (NOS) for assessing the quality of non randomised studies in meta-analysis. [Cited 2 April 2010]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm2009.
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–2012.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558.

15. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–634.
16. Araujo MI, Lopes AA, Medeiros M, Cruz AA, Sousa-Atta L, Sole D et al. Inverse association between skin response to aeroallergens and *Schistosoma mansoni* infection. *Int Arch Allergy Immunol* 2000;**123**:145–148.
17. Araujo MI, Hoppe B, Medeiros M Jr, Alcantara L, Almeida MC, Schrieffer A et al. Impaired T helper 2 response to aeroallergen in helminth-infected patients with asthma. *J Infect Dis* 2004;**190**:1797–1803.
18. Bahceciler NN, Ozdemir C, Kucukosmanoglu E, Arkan C, Over U, Karavelioglu S et al. Association between previous enterobiasis and current wheezing: evaluation of 1018 children. *Allergy Asthma Proc* 2007;**28**:174–182.
19. Cooper PJ, Chico ME, Rodrigues LC, Ordóñez M, Strachan D, Griffin GE et al. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol* 2003;**111**:995–1000.
20. 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.
21. Cooper PJ, Chico ME, Rodrigues LC, Strachan DP, Anderson HR, Rodriguez EA et al. Risk factors for atopy among school children in a rural area of Latin America. *Clin Exp Allergy* 2004;**34**:845–852.
22. Davey G, Venn A, Belete H, Berhane Y, Britton J. Wheeze, allergic sensitization and geohelminth infection in Butajira, Ethiopia. *Clin Exp Allergy* 2005;**35**:301–307.
23. Flohr C, Tuyen LN, Lewis S, Quinnell R, Minh TT, Liem HT et al. Poor sanitation and helminth infection protect against skin sensitization in Vietnamese children: a cross-sectional study. *J Allergy Clin Immunol* 2006;**118**:1305–1311.
24. Nyan OA, Walraven GE, Banya WA, Milligan P, Van Der SM, Ceesay SM et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. *Clin Exp Allergy* 2001;**31**:1672–1678.
25. Obihara CC, Beyers N, Gie RP, Hoekstra MO, Fincham JE, Marais BJ et al. Respiratory atopic disease, Ascaris-immunoglobulin E and tuberculin testing in urban South African children. *Clin Exp Allergy* 2006;**36**:640–648.
26. Pereira MU, Sly PD, Pitrez PM, Jones MH, Escouto D, Dias AC et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. *Eur Respir J* 2007;**29**:1154–1160.
27. Ponte EV, Lima F, Araujo MI, Oliveira RR, Cardoso LS, Cruz AA. Skin test reactivity and Der p-induced interleukin 10 production in patients with asthma or rhinitis infected with *Ascaris*. *Ann Allergy Asthma Immunol* 2006;**96**:713–718.
28. Rodrigues LC, Newcombe PJ, Cunha SS, Alcantara-Neves NM, Genser B, Cruz AA et al. Early infection with *Trichuris trichiura* and allergen skin test reactivity in later childhood. *Clin Exp Allergy* 2008;**38**:1769–1777.
29. van den Biggelaar AH, van RR, Rodrigues LC, Lell B, Deelder AM, Kremsner PG et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000;**356**:1723–1727.
30. Wordemann M, Diaz RJ, Heredia LM, Collado Madurga AM, Ruiz EA, Prado RC et al. Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. *Trop Med Int Health* 2008;**13**:180–186.
31. Calvert J, Burney P. Effect of body mass on exercise-induced bronchospasm and atopy in African children. *J Allergy Clin Immunol* 2005;**116**:773–779.
32. Dagoye D, Bekele Z, Woldemichael K, Nida H, Yimam M, Hall A et al. Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. *Am J Respir Crit Care Med* 2003;**167**:1369–1373.
33. Joubert JR, de Klerk HC, Malan C. Ascaris lumbricoides and allergic asthma: a new perspective. *S Afr Med J* 1979;**56**:599–602.
34. Scrivener S, Yemaneberhan H, Zebenigus M, Tilahun D, Girma S, Ali S 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.
35. Cooper PJ, Chico ME, Vaca MG, Moncayo AL, Bland JM, Mafía E et al. Effect of albendazole treatments on the prevalence of atopy in children living in communities endemic for geohelminth parasites: a cluster-randomised trial. *Lancet* 2006;**367**:1598–1603.
36. Moneo I, Puente S, Subirats M, Ruiz A, Lozano M, Gonzalez-Munoz M. Histamine liberation and specific IgE against *Dermatophagoides pteronyssinus* in parasitized patients. [Spanish]. *Allergol Immunopathol* 1994;**22**:46–51.
37. van den Biggelaar AH, Lopuhaa C, van RR, van der Zee JS, Jans J, Hoek A et al. The prevalence of parasite infestation and house dust mite sensitization in Gabonese schoolchildren. *Int Arch Allergy Immunol* 2001;**126**:231–238.
38. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282**:1054–1060.
39. von HL, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy* 2005;**60**:283–292.

ONLINE DATA SUPPLEMENT

ATOPY AND CURRENT INTESTINAL PARASITE INFECTION:

A SYSTEMATIC REVIEW AND META-ANALYSIS

Johanna Feary, John Britton, Jo Leonardi-Bee

Search Strategy

Incidence or exp mortality or follow up studies.mp or prognos.tw or prognosis.tw or predict.tw
or Exp cohort studies or exp risk or (odds and ratio).tw or (relative and risk).tw or (case and
control) or (Systematic adj review.tw) or (data adj synthesis).tw or *(published adj studies).ab
or meta analysis/ or meta analysis.ti or comment.pt or letter.pt or editorial.pt or (data adj
extraction).ab

AND

(Pteronyssinus.mp or skin test.mp or RAST.mp or house dust.mp or feather.mp or cotton
flock.mp or skin reaction.mp or antigen.mp or dermatophagoides,.mp or mold.mp or skin
prick.mp or mite.mp or skin test.mp)

AND

(Parasite infection.mp or helminth infection.mp or parasites or helminths or ascaris.mp or
tricuris.mp or enterobius.mp or hookworm.mp or necator.mp)

NOT

(HIV .mp or AIDS.mp or wounds.mp or TB.mp or leprosy.mp or transplant.mp or cancer.mp
or virus.mp or arthritis.mp or coeliac.mp or hepatitis,mp)

LIMIT TO HUMAN

Table E1: Summary of results for all analyses

Parasite	Atopy	Total number of trials	Effect Size (95% CI)	I^2 , %	P Value for I^2	P Value for association
Any parasite	≥1 allergen	9	0.69 (0.60, 0.79)	45%	p=0.07	p<0.01
	cockroach	2	0.97 (0.62, 1.53)	69%	p=0.07	p=0.90
	mite	2	1.02 (0.81, 1.29)	24%	p=0.25	p=0.88
Any geohelminth	≥1 allergen	7	0.68 (0.60, 0.76)	21%	p<0.01	p<0.01
	cockroach	2	0.97 (0.62, 1.53)	69%	p=0.07	p=0.90
	mite	2	1.02 (0.81, 1.29)	24%	p=0.25	p=0.88
<i>Ascaris</i>	≥1 allergen	9	0.69 (0.59, 0.80)	30	p<0.01	p<0.01
	cockroach	4	0.90 (0.75, 1.08)	0	p=0.25	p=0.25
	mite	6	1.03 (0.73, 1.46)	47	P=0.86	p=0.86
<i>Hookworm</i>	≥1 allergen	4	0.68 (0.46, 1.01)	14	p=0.06	p=0.06
	cockroach	4	0.81 (0.62, 1.08)	52	p=0.15	p=0.15
	mite	5	0.94 (0.65, 1.36)	62	p=0.73	p=0.73
<i>Tricuris</i>	≥1 allergen	5	0.75 (0.65, 0.86)	7	p<0.01	p<0.01
	cockroach	2	1.86 (1.24, 2.80)	13	p=0.003	p=0.003
	mite	3	1.72 (0.90, 3.29)	47	p=0.10	p=0.10
<i>Schistosomiasis</i>	≥1 allergen	3	0.12 (0.03, 0.57)	69	p=0.007	p=0.007

Table E2: Summary of results for subgroup analyses for infection with any parasite and sensitisation to at least one allergen.

	Total number of trials	Effect Size (95% CI)	I^2 , %	P Value for I^2	P Value for association
All studies	9	0.69 (0.60, 0.79)	45%	p=0.07	p<0.01
Quality Score ≥7	8	0.67 (0.59, 0.75)	29%	p=0.20	p<0.01
Quality Score <7	1	1.10 (0.71, 1.70)	n/a	n/a	p=0.67
Adjusted data	6	0.68 (0.60, 0.78)	33%	p=0.19	p<0.01
Crude data	3	0.68 (0.41, 1.13)	72%	p=0.03	p=0.14
Skin wheal ≥3mm	9	0.69 (0.60, 0.79)	45%	p=0.07	p<0.01
Skin wheal <3mm	0				
Children only	8	0.70 (0.61, 0.80)	41%	p=0.11	p<0.01
Adults only	1	0.30 [0.11, 0.80]	n/a	n/a	p=0.02
Adults and children	0				
South/central America	7	0.68 (0.60, 0.75)	17%	p=0.30	p<0.01
Africa	1	0.30 [0.11, 0.80]	n/a	n/a	p=0.02
Europe/Asia	1	1.10 (0.71, 1.70)	n/a	n/a	p=0.67
Cross-sectional study	8	0.67 (0.57, 0.78)	44%	p=0.09	p<0.01
Randomized controlled trial	1	0.78 (0.64, 0.95)	n/a	n/a	p=0.01
Case-control study	0				

Funnel plots

Figure E1: Funnel plot for any current geohelminth infection and sensitization to at least one allergen

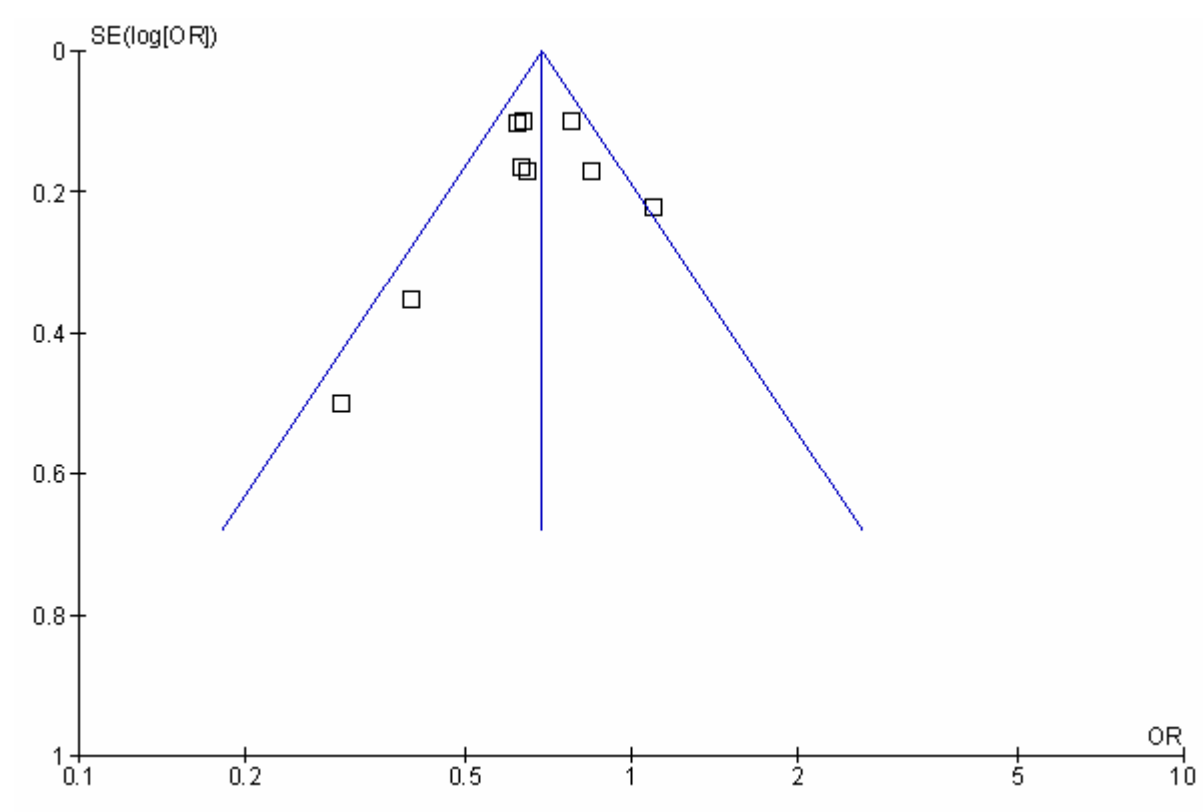


Figure E2: Funnel plot for current *Ascaris* infection and sensitization to at least one allergen

