

Asthma and Current Intestinal Parasite Infection

Systematic Review and Meta-Analysis

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Rationale: Epidemiologic studies suggest that intestinal parasite infections may protect against asthma.

Objectives: A systematic review and meta-analysis of epidemiologic studies to determine whether total or species-specific current parasite infection is associated with a reduced risk of asthma or wheeze.

Methods: We searched MEDLINE, EMBASE, and CINAHL (up to January 2006); reviews; and reference lists from publications, with no language restrictions. We included studies that reported asthma or wheeze as an outcome measure and ascertained parasite infection by fecal examination. We estimated pooled odds ratios (OR) and 95% confidence intervals (CI) using data extracted from published papers, or where available, original data provided by authors, using random effect models.

Measurements and Main Results: Thirty-three studies met the inclusion criteria. Infection with any parasite was associated with a small, nonsignificant increase in asthma risk (OR, 1.24; 95% CI, 0.98–1.57; 29 studies). In species-specific analysis, *Ascaris lumbricoides* was associated with significantly increased odds of asthma (OR, 1.34; 95% CI, 1.05–1.71; 20 studies), while hookworm infection was associated with a significantly strong reduction (OR, 0.50; 95% CI, 0.28–0.90; 9 studies) that was directly and significantly related to infection intensity ($p < 0.001$; OR for highest tertile of infection, 0.34; 95% CI, 0.19–0.62). Other species had no significant effects on asthma. Infection effects on wheeze were derived from smaller numbers, but revealed a broadly similar pattern of results.

Conclusions: Parasite infections do not in general protect against asthma, but infection with hookworm may reduce the risk of this disease.

Keywords: asthma; meta-analysis; parasites; systematic review

Asthma is one of the most common chronic diseases of developed countries, but is relatively rare in the developing world, especially in rural subsistence communities (1–3). Infection with intestinal parasites has been postulated as an important factor that could produce these geographic differences in prevalence (4–7) through various mechanisms that may suppress or inhibit the immune processes leading to the asthma and other allergic diseases (8–10).

Although a review of the epidemiologic evidence in 1985 concluded that the data “neither refute nor support the theory that parasite infection protects against asthma” (11), the relation between parasite infections and asthma risk has continued to attract interest (1, 12–19). A further potentially relevant observation from some of our own work in Ethiopia (13, 20) that is consistent with earlier findings on *Schistosoma* infection in

Gabon (15) is that protection against asthma may be greater with parasite species that have a host systemic phase in their life cycle, and may also be related to the intensity of infection (13).

We have therefore reviewed and performed a meta-analysis of the epidemiologic literature to determine whether, in pooled data from the published literature to date, parasite infection is associated with a reduced risk of asthma or wheeze, and whether there are any significant species-specific or intensity related effects.

The preliminary results from this study have been previously reported in the form of an abstract (21).

METHODS

Systematic Review Methods

A comprehensive literature search in MEDLINE (1966 to January 2006), EMBASE (1980 to January 2006), and CINAHL (1982 to January 2006) was performed according to standard guidelines (22) to identify all epidemiologic studies with no restrictions on language. We also searched published reviews, reference lists from identified publications, and abstracts from major conference proceedings.

Studies were included if they fulfilled the following criteria: (1) the design was a comparative epidemiologic study; (2) asthma or wheeze was listed as an outcome; (3) current parasite infection was measured by direct fecal microscopy. Studies that met the inclusion criteria were scored for methodologic quality using the Newcastle-Ottawa Quality Assessment Scale (23). A score of 7 or more was chosen *a priori* to indicate high methodologic quality. We attempted to contact at least one author from each identified study to invite them to share original study data.

Additional detail on the methods used for the systematic review is provided in an online data supplement.

Statistical Analysis

Data were analyzed to yield effect estimates either using unadjusted (crude) odds ratios (OR) from extracted data from the publications, or where possible, using age- and sex-adjusted OR from the original data. Wherever possible, the individual effect estimates from the studies were combined using a random study effects model (24) to calculate pooled OR with 95% confidence intervals (CI) because the effect estimates were expected to be heterogeneous due to inherent biases in the studies.

Heterogeneity between study estimates was assessed using established methods (25). To explore reasons for heterogeneity between the studies, subgroup analyses were used to assess the differences between developed and developing countries, timing of when the studies were published (before 1980 or from 1980 onwards), the definitions of asthma used within the studies (clinician assessed, self reported, exercise-induced bronchoconstriction/spasm), and the effect of species-specific parasite associations with asthma or wheeze for parasites infecting 1% or more of the available study population.

To assess the effect of a dose-response relationship between intensity of species-specific parasite infection and asthma, we analyzed original data from studies that recorded intensity of infection in eggs per gram of feces. Original data were also used to explore the possibility that the effect of parasite infections on asthma would be different for infection at early versus later age (dichotomized into above or below 2 yr). Publication bias was assessed using a funnel plot and Egger's Asymmetry test (26). Data were analyzed using STATA, version 8.0 (Stata Corporation, College Station, TX) and SAS for Windows, version 8

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(SAS Institute, Inc., Cary, NC). *p* values less than 0.05 were considered statistically significant. Additional detail on the methods for statistical analysis is provided in the online supplement. The work was performed in accordance with the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines (27).

RESULTS

Overview of the Included Studies

Our search identified 57 studies that assessed the association between parasites and asthma or wheeze published between 1966 and January 2006, including one published only in abstract form (28) and one unpublished study (Muniz PT, de Castro TG, de Araújo TS, Nunes NB, Santiago FS, Elefant GR, Nunes MdS, Hoffmann EHE, Ferreira MU, and Cardoso MA. Saúde e nutrição infantil na Amazônia Ocidental Brasileira: inquérito de base populacional em dois municípios acreanos. Unpublished manuscript, 2004) (Figure 1). Thirty-three of the 57 studies met our inclusion criteria. Three of the eligible studies were excluded because they either did not present outcomes in a form appropriate for use in meta-analysis (14, 29) or presented parasite infection as a geometric mean of egg count for individuals with and without asthma (30) (Figure 1). A total of 29 studies (7, 13, 18–20, 28, 31–52, and Muniz *et al.*) were available for analysis of asthma as an outcome, and 7 for analysis of wheeze (13, 18–20, 34, 53, and Muniz *et al.*). The studies included 25,753 individuals (Table 1). Methods of defining or measuring asthma or wheeze varied substantially between the studies, but the most widely used method was based on a clinical diagnosis of asthma (7, 31–33, 35, 37–40, 42, 43, 45–49, 52). Some surveys used questionnaire ascertainment of a self-reported (or for children, parent-reported) diagnosis of asthma (13, 18–20, 34, 36, 41, 44, and Muniz *et al.*), and three studies used a measure of exercise-induced bronchoconstriction (28, 50, 51). Several case-control studies used clinically defined asthma cases drawn from hospital patient populations.

Of the 30 studies included in the meta-analyses, 5 included only adults (13, 33, 39, 41, 43), 14 only children (18–20, 28, 31,

35–37, 42, 44, 46, 50, 51, and Muniz *et al.*), and 11 studies included both adults and children (7, 32, 34, 38, 40, 45, 47–49, 52, 53). Thirty-nine percent of the individuals included in the studies were currently infected with parasites.

We were able to establish contact with investigators from 20 of the original 57 identified studies, including 13 of the studies included in the present analysis (Table 1), and nine of these provided original data to enable adjusted analyses to be performed (13, 18–20, 34, 42, 44, 46, and Muniz *et al.*). The original data from most of the remaining studies had been discarded.

Methodologic Quality of Studies and Publication Bias

The methodologic quality of the 30 included studies in the meta-analyses as judged by the Newcastle-Ottawa scale score is presented in Table 1. The median overall score was 6 (range 3 to 9), indicating that generally the methodologic quality was moderately good. The Newcastle-Ottawa scores for the studies published in the last 25 yr were significantly higher than those published before 1980 (median 8 vs. 5.5, Mann Whitney U test, $p = 0.02$). Using the *a priori* chosen cut of 7 to indicate high methodologic quality, we judged 13 of the studies to be of high quality; and the remaining 17 to be of lower quality primarily due to either a less clearly defined asthma definition, unclear description of individuals without asthma, or lack of adjusted analyses. Fourteen of the studies used reference participants identified from a representative population-based survey. There was no evidence of publication bias from Egger's asymmetry test (asthma as outcome, $p = 0.296$, 29 studies) or identified from the funnel plot (*see* Figure E1 in the online supplement).

Effects of Current Infection with Any Parasite on Asthma

A pooled analysis of estimates from the 29 studies with a measure of asthma as an outcome demonstrated a small, nonsignificant increase in the relative odds of asthma in individuals currently infected with any parasite, by an OR of 1.24 (95% CI, 0.98–1.57; $p = 0.07$; Figure 2). The effects were similar between the adjusted (OR, 1.21; 95% CI, 0.90–1.64; 10 studies) and unadjusted (OR, 1.29; 95% CI, 0.87–1.92; 19 studies) analyses. High levels of heterogeneity (I^2) were seen across all of these analyses; (unadjusted $I^2 = 77\%$, adjusted $I^2 = 81\%$, and combined $I^2 = 78\%$). The results were also consistent when the studies were categorized by methodologic quality (high quality: OR, 1.11; 95% CI, 0.80–1.53; lower quality: OR, 1.40; 95% CI, 0.97–2.02).

In a subgroup analysis of studies that were performed in developed countries, high levels of heterogeneity remained between studies ($I^2 = 68\%$, 5 studies) however this was attributed to the study by Tullis (49), which was extremely unusual in that it found that over 95% of asthma cases recruited from a Canadian sanatorium were infected with parasites. These findings are so atypical of the other evidence that they suggest a local outbreak of parasite infection at the sanatorium may have been responsible. Excluding this study from the analyses significantly reduced heterogeneity ($I^2 = 1\%$, 4 studies). In the developing countries, the results from studies published before 1980 were less heterogeneous ($I^2 = 53\%$, 11 studies) than those published in the last 25 yr ($I^2 = 83\%$, 14 studies).

In a subgroup analysis based on the method of ascertainment of asthma, cases of clinician-diagnosed asthma were significantly more likely to be infected (OR, 1.47; 95% CI, 1.02–2.12; 17 studies). Consistent pooled results were seen in studies that used self-reported ascertainment (OR, 1.24) and exercise-induced bronchoconstriction ascertainment (OR, 1.42). High levels of heterogeneity were seen among studies that used clinician-diagnosed ($I^2 = 79\%$, 17 studies) or self-reported ($I^2 = 72\%$,

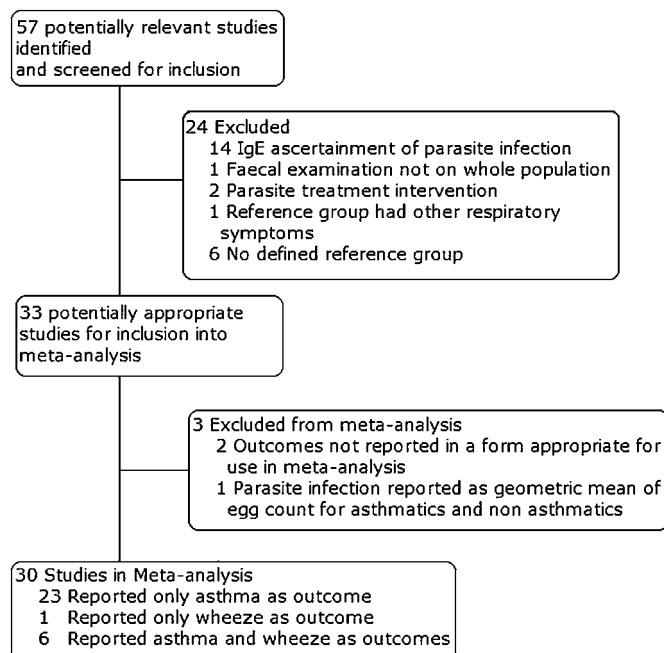


Figure 1. Flow diagram of included and excluded studies.

TABLE 1. STUDIES INCLUDED IN THE REVIEW

Author of Study	Individuals with Asthma (n)	Individuals without Asthma (n)	Species of Parasite	Location	Contacted Author	Methodologic Quality Score [‡]
Aderale (31)	228	116	<i>Ascaris lumbricoides</i> , <i>Trichuris trichuria</i> , hookworm, <i>Strongyloides stercoralis</i>	Nigeria	No	4
Alcasid (32)	131	73	<i>A. lumbricoides</i> , <i>Enterobius vermicularis</i> , <i>T. trichuria</i>	New York	No	5
Alshishtawy (33)	68	37	<i>A. lumbricoides</i> , <i>E. vermicularis</i>	Egypt	Yes	6
Benício (19)	148	984	<i>A. lumbricoides</i> , <i>T. trichuria</i>	Brazil	Yes	8
Calvert (28)	383	390	<i>A. lumbricoides</i>	South Africa	Yes	9
Carswell (50)	7	97	<i>A. lumbricoides</i> , hookworm, <i>E. vermicularis</i>	Tanzania	No	7
Carswell (51)	14	175	<i>A. lumbricoides</i> , hookworm, <i>E. vermicularis</i>	Tanzania	No	7
Cheah (52)	108	300	<i>A. lumbricoides</i> , hookworm	Singapore	No	6
Cooper (18)	403	3,650	<i>A. lumbricoides</i> , <i>T. trichuria</i>	Ecuador	Yes	8
Dagoye (20)	65	1,305	<i>A. lumbricoides</i> , hookworm, <i>T. trichuria</i>	Ethiopia	Yes	8
Davey (34)	99	6,501	<i>A. lumbricoides</i> , hookworm, <i>T. trichuria</i>	Ethiopia	Yes	8
de Almeida (35)	47	16	Combined <i>E. vermicularis</i> and <i>A. lumbricoides</i>	Portugal	No	6
Huang (36)	429	2,678	<i>E. vermicularis</i>	Taipei	No	9
Jarrett (37)	24	21	<i>E. vermicularis</i>	Glasgow	No	6
Joubert (38)	123	71	<i>A. lumbricoides</i>	Western Cape	No	6
Kayhan (39)	50	50	<i>A. lumbricoides</i>	Turkey	No	4
Klein (40)	17	10	<i>T. trichuria</i>	Puerto Rico	No	3
Yeseeman (41)	19	244	<i>S. stercoralis</i>	New York	No	3
Lynch (42)	290	250	<i>A. lumbricoides</i>	Coche Island	Yes	7
Macfarlane (43)	31	30	Any species	Nigeria	Yes	6
Muniz*	40	500	<i>A. lumbricoides</i> , <i>T. trichuria</i>	Brazil	Yes	9
Nascimento Silva (44)	443	299	<i>A. lumbricoides</i> , <i>T. trichuria</i> , <i>E. vermicularis</i>	Brazil	Yes	6
Obtulowicz (45)	287	57	Any species	Poland	No	5
Palmer (46)	468	1592	<i>A. lumbricoides</i>	China	Yes	9
Perdomo de Ponce† (53)	27	31	<i>A. lumbricoides</i> , hookworm, <i>T. trichuria</i>	Venezuela	No	8
Salako (47)	250	100	<i>A. lumbricoides</i> , hookworm	Nigeria	No	5
Scrivener (13)	26	377	<i>A. lumbricoides</i> , hookworm, <i>T. trichuria</i> , <i>E. vermicularis</i>	Ethiopia	Yes	8
Tullis (48)	201	20	<i>A. lumbricoides</i> , hookworm	Canada	No	6
Warrell (7)	36	415	Any species	Nigeria	No	4
Wolstenholme (49)	85	817	<i>A. lumbricoides</i> , <i>T. trichuria</i>	Maldives	Yes	5

* Unpublished study.

† Measured only wheeze as outcome.

‡ Methodologic quality of the studies are based on the Newcastle-Ottawa Quality Assessment Scale.

9 studies) definitions of asthma; however, considerably less heterogeneity was seen for studies that used exercise-induced bronchoconstriction/spasm ($I^2 = 16\%$, 3 studies).

Effects of Infection with Individual Parasite Species on Asthma

Twenty-six of the 29 studies provided species-specific data on parasite infection. We analyzed effects of five intestinal parasite

species that were present in at least 1% of the study populations, comprising *Ascaris lumbricoides*, hookworm (predominately *Necator americanus*), *Trichuris trichuria*, *Enterobius vermicularis*, and *Strongyloides stercoralis*. The studies providing data on these species and the results of pooled analyses are presented in Figure 3. Two of the 29 studies also provided data on infection with *Schistosoma mansoni* (13, 33).

Review: Parasites and asthma
 Comparison: 06 Unadjusted and adjusted analyses - asthma
 Outcome: 04 Any parasite infection

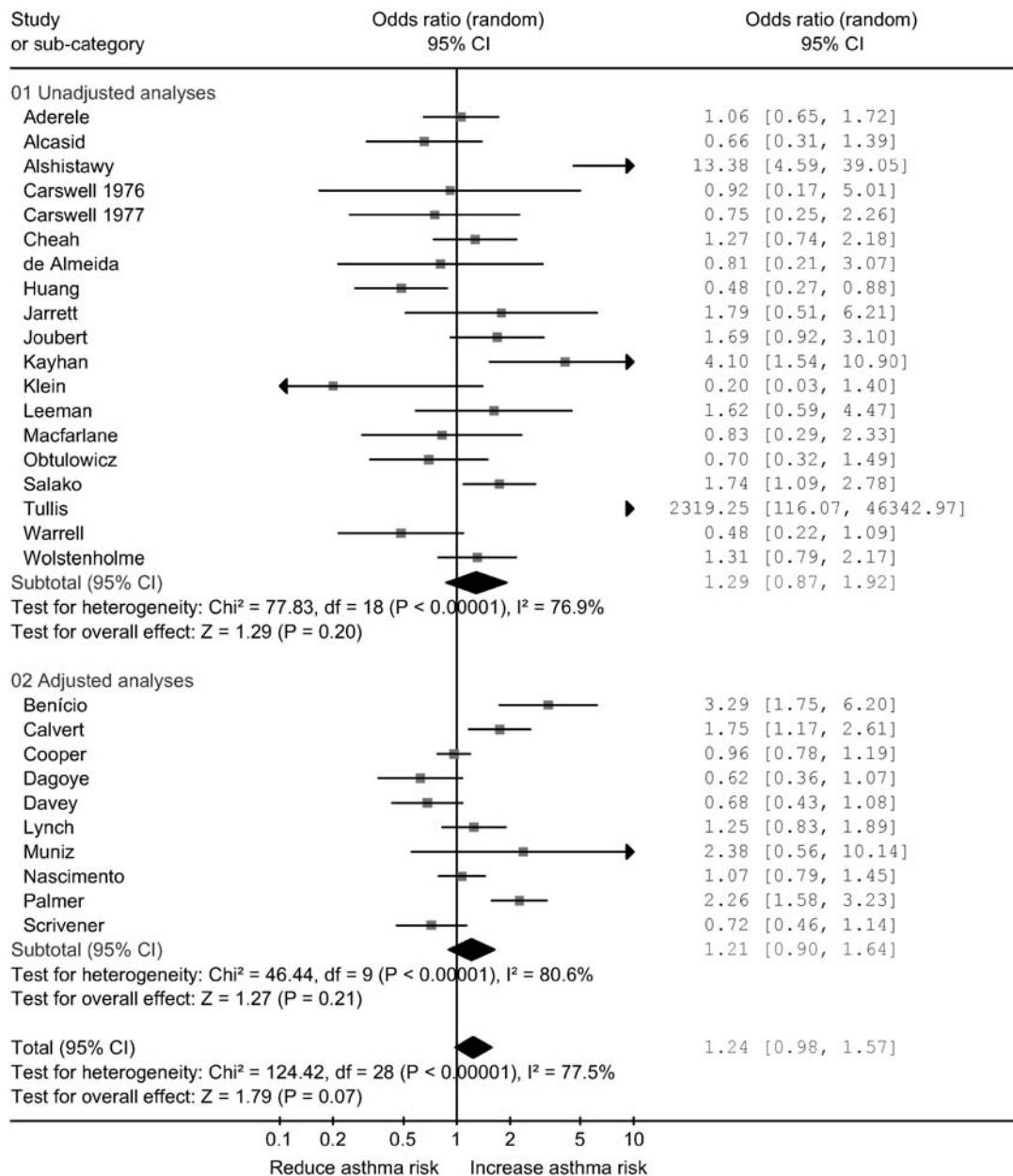


Figure 2. Relationship between any current intestinal parasite infection and asthma using a meta-analysis of comparative epidemiologic studies. Data are presented as odds ratios (OR) for any parasite infection between individuals with asthma and individuals without asthma and are pooled using random effect models. Squares represent OR and horizontal lines denote 95% confidence intervals (CI). Size of the data markers corresponds to the weight of the study in the meta-analysis.

Current infection with *A. lumbricoides* was associated with a significant increase in the risk of asthma (OR, 1.34; 95% CI, 1.05–1.71; $p = 0.02$; 20 studies; Figure 3A), whereas current infection with hookworm was associated with significant reduction in risk (OR, 0.50; 95% CI, 0.28–0.90; $p = 0.02$; 9 studies; Figure 3B). Infection with *T. trichuria*, *E. vermicularis*, or *S. stercoralis* was not associated with significant effects on asthma risk (Figures 3C–3E). The pooled estimate for current infection with *S. mansoni* indicated a numerically high but nonsignificant increase in asthma risk (OR, 2.77; 95% CI, 0.54–14.28; 2 studies). High levels of heterogeneity among study findings were seen for *A. lumbricoides* and hookworm (74 and 67%, respectively); however, little heterogeneity was seen among the studies for *T. trichuria*, *E. vermicularis*, or *S. stercoralis*.

Effects of Current Infection on Wheeze

The seven studies that used wheeze as an outcome measure comprised 14,156 individuals (13, 18–20, 29, 35, 54). No significant pooled effects were seen between any current intestinal parasite infection and wheeze (OR, 0.87; 95% CI, 0.69–1.10; 7 studies; see Figure E2). Species-specific data in adequate numbers for analysis were available from these studies for *A. lumbricoides*, hookworm and *T. trichuria* (see Figures E3–E5). Pooled analysis from these studies indicated that none of these individual infections had a statistically significant effect on the risk of wheeze, the OR for *A. lumbricoides* infection being 1.04 (95% CI, 0.68–1.59; 7 studies); for *T. trichuria* 1.30 (95% CI, 0.86–1.95; 7 studies); and for hookworm 0.62 (95% CI, 0.24–1.60; 3 studies).

Effects of Infection Intensity

Five studies provided sufficient data to explore the effects of parasite infection intensity of *A. lumbricoides*, *T. trichuria*, and hookworm (13, 18, 20, 34, 42). Analysis of effects on asthma and wheeze across three tertiles of infection intensity revealed no marked effect of *T. trichuria*, nonsignificant reductions in risk at higher levels of infection with *A. lumbricoides*, and significant dose-related reductions in risk of both asthma and wheeze with hookworm infection (Table 2). The risk of asthma in the highest tertile of hookworm infection was reduced by approximately two-thirds (OR, 0.34; 95% CI, 0.19–0.62).

Interactions with Age

There was no evidence of age by species-specific interaction for the relation between *A. lumbricoides* and asthma (interaction $p = 0.38$) or wheeze (interaction $p = 0.30$), or for hookworm and

wheeze (interaction $p = 0.60$). There were no cases of concurrent hookworm infection and asthma at less than 2 yr of age.

DISCUSSION

Parasite infections are very common, particularly in the developing world, and systematic eradication programs are being introduced in many areas. Although eradication is undoubtedly beneficial to many aspects of individual and public health, the hypothesis that parasite infections may protect against allergic disease raises the possibility that eradication may increase asthma and other manifestations of allergy. For this reason, and also because any protective effect is likely to provide important insights into pathogenesis and possible therapeutic opportunities in allergic disease, it is important to establish as clearly as possible whether parasite infections and asthma are indeed related. This

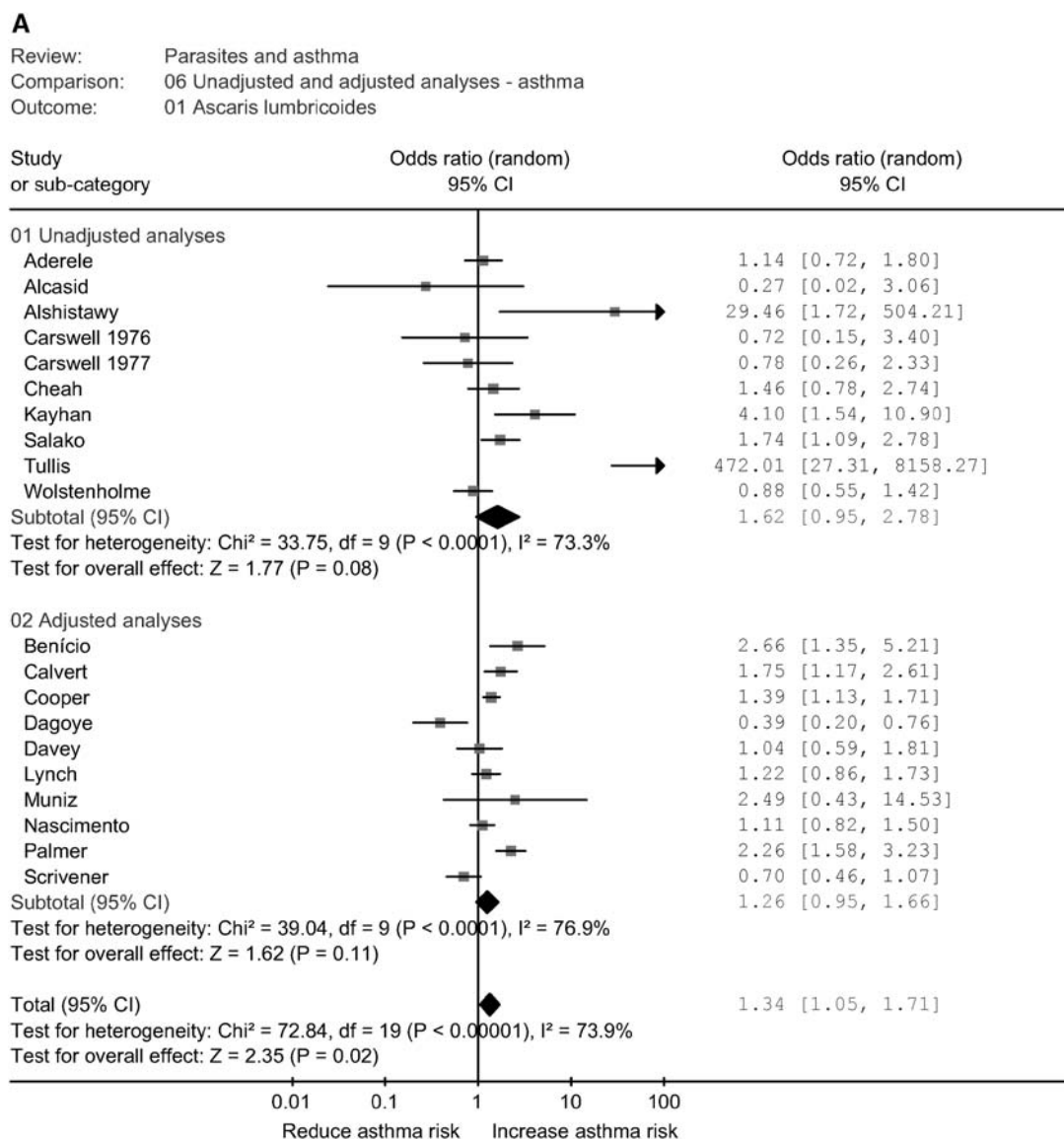


Figure 3. (A) Relationship between *Ascaris lumbricoides* infection and asthma using a meta-analysis of comparative epidemiologic studies. (Data are presented as OR for *A. lumbricoides* infection between individuals with asthma and individuals without asthma and are pooled using random effect models.) (B) Relationship between hookworm infection and asthma using a meta-analysis of comparative epidemiologic studies. (Data are presented as OR for hookworm infection between individuals with asthma and individuals without asthma and are pooled using random effect models.) (C) Relationship between *Trichuris trichuria* infection and asthma using a meta-analysis of comparative epidemiologic studies. (Data are presented as OR for *T. trichuria* infection between individuals with asthma and individuals without asthma and are pooled using random effect models.) (D) Relationship between *Enterobius vermicularis* infection and asthma using a meta-analysis of comparative epidemiologic studies. (Data are presented as OR for *E. vermicularis* infection between individuals with asthma and individuals without asthma and are pooled using random effect

models.) (E) Relationship between *Strongyloides stercoralis* infection and asthma using a meta-analysis of comparative epidemiologic studies. (Data are presented as OR for *S. stercoralis* infection between individuals with asthma and individuals without asthma and are pooled using random effect models.) Squares represent OR and horizontal lines denote 95% CI. Size of the data markers corresponds to the weight of the study in the meta-analysis.

B

Review: Parasites and asthma
 Comparison: 06 Unadjusted and adjusted analyses - asthma
 Outcome: 02 Hookworm

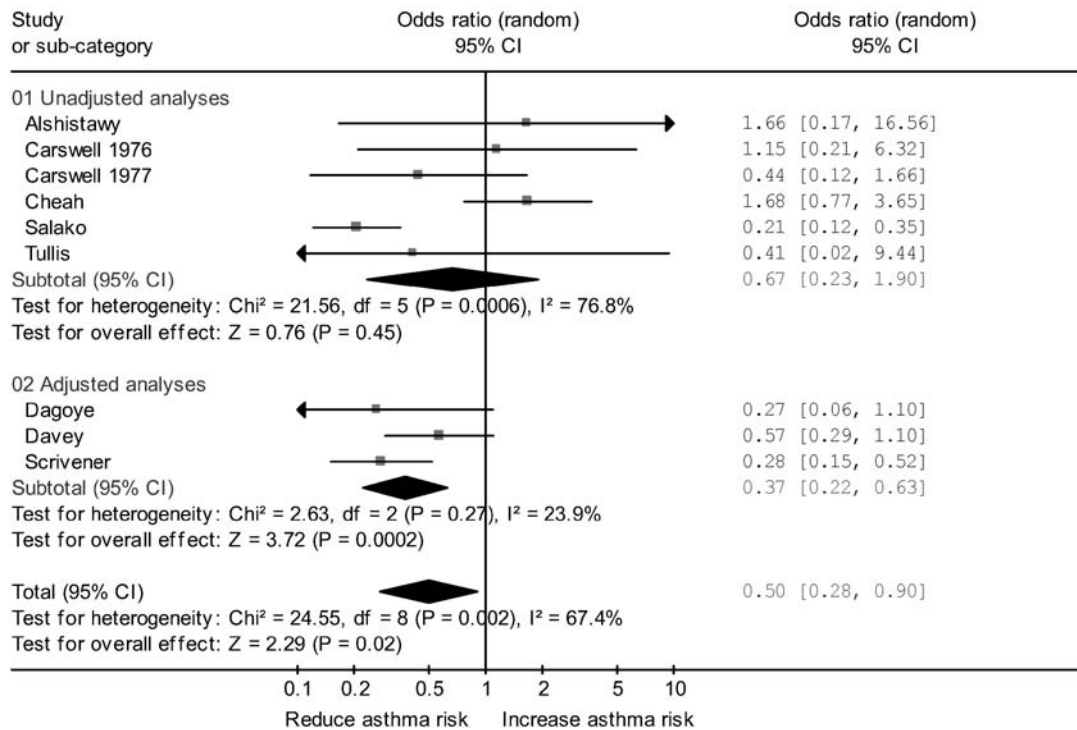
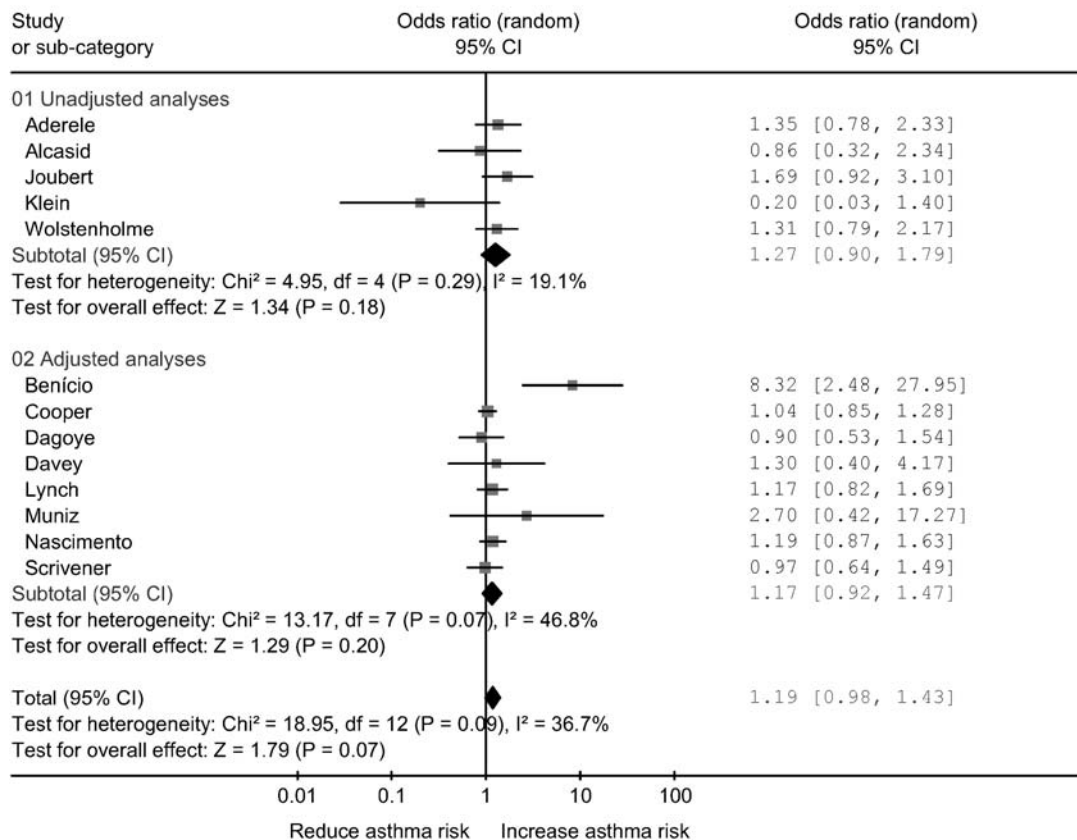


Figure 3. (Continued)

C

Review: Parasites and asthma
 Comparison: 06 Unadjusted and adjusted analyses - asthma
 Outcome: 03 Trichuris trichuria



D

Review: Parasites and asthma
 Comparison: 06 Unadjusted and adjusted analyses - asthma
 Outcome: 05 *Enterobius vermicularis*

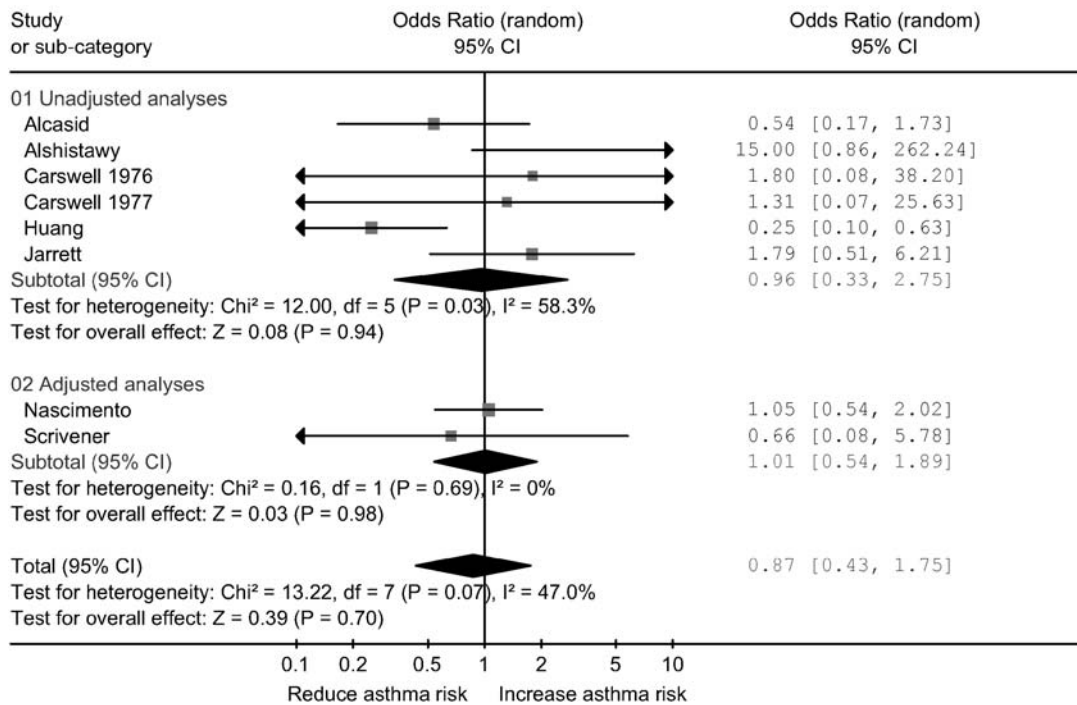
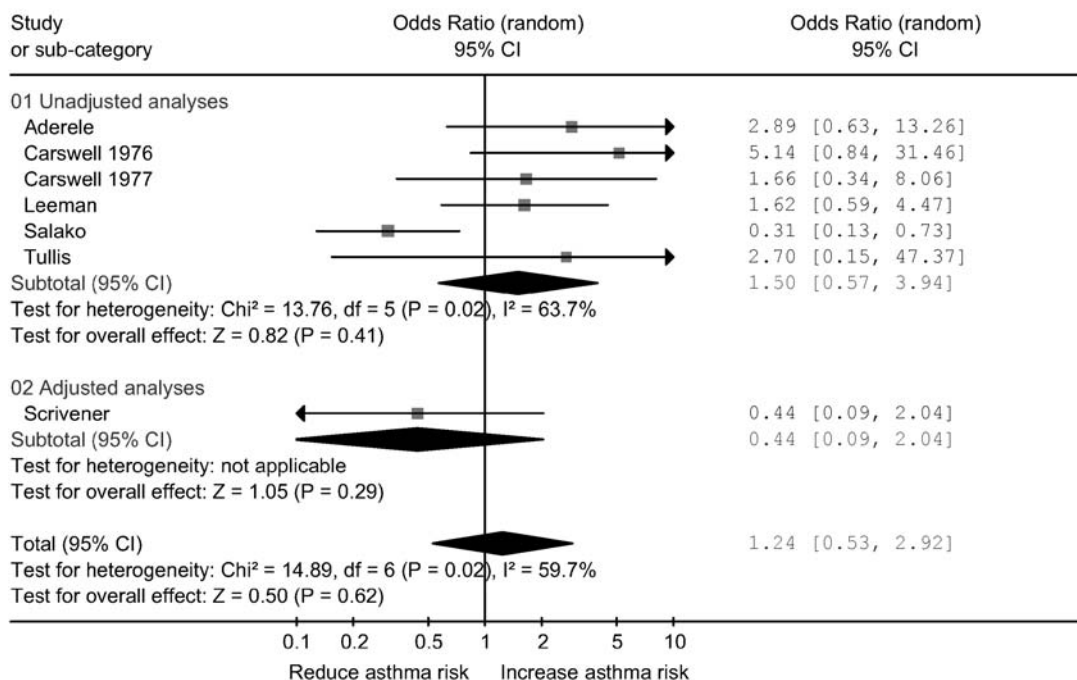


Figure 3. (Continued)

E

Review: Parasites and asthma
 Comparison: 06 Unadjusted and adjusted analyses - asthma
 Outcome: 06 *Strongyloides stercoralis*



systematic review and meta-analysis indicates that any relation between intestinal parasite infection and asthma risk is likely to be species specific, and for hookworm, intensity related. Within the overall finding of no significant effect of infection on asthma,

there were two opposing effects of individual species, with *A. lumbricoides* being associated with an increased risk, and hookworm (predominantly *N. americanus* in these studies) a more marked decrease. The other intestinal parasite species we were

TABLE 2. CURRENT LOAD OF PARASITE AND ODDS OF ASTHMA OR WHEEZE FOR SPECIES-SPECIFIC EFFECTS

Parasite	Range (eggs/g)	Asthma		Wheeze	
		Adjusted OR (95% CI)*	p Value†	Adjusted OR (95% CI)*	p Value†
<i>Ascaris lumbricoides</i>					
No eggs		1.00		1.00	
Tertile 1	1–8	1.00 (0.66, 1.51)	0.15	0.70 (0.53, 0.94)	0.09
Tertile 2	9–45	0.73 (0.50, 1.08)		1.01 (0.77, 1.32)	
Tertile 3	46–52,732	0.85 (0.66, 1.12)		0.75 (0.54, 1.06)	
<i>Trichuris trichuria</i>					
No eggs		1.00		1.00	
Tertile 1	1–56	1.09 (0.86, 1.39)	0.76	1.03 (0.79, 1.35)	0.61
Tertile 2	57–283	1.00 (0.79, 1.25)		0.99 (0.70, 1.41)	
Tertile 3	284–14,290	1.03 (0.82, 1.30)		0.85 (0.56, 1.31)	
Hookworm					
No eggs		1.00		1.00	
Tertile 1	1–3	0.43 (0.19, 0.94)	< 0.001	0.84 (0.62, 1.15)	< 0.01
Tertile 2	4–6	0.35 (0.14, 0.87)		0.88 (0.64, 1.20)	
Tertile 3	7–1,458	0.34 (0.19, 0.62)		0.63 (0.44, 0.90)	

Definition of abbreviations: CI = confidence interval; OR = the odds ratio for asthma or wheeze for tertile of parasite egg count as compared with no eggs (reference category).

* Adjusted for age and sex as fixed effects, and study as a random effect.

† For groups as ordered categories using *F* test.

able to study individually (*T. trichuria*, *E. vermicularis*, and *S. stercoralis*) had no clear effect.

The methodologic quality of studies included in this review, particularly those reported more recently, was generally good. We are also confident that our literature search, combined with the results of contacting investigators from most of the research groups known to be engaged in this area, identified the great majority of potentially suitable studies. Our funnel plot analysis indicates that publication bias is unlikely to have had a marked effect on our findings. We maximized the validity of our exposure measure by restricting analysis to studies using direct fecal examination for eggs or parasites, because measures based on serologic tests do not distinguish current from past infection. Most studies available to us used asthma as an endpoint, which was defined in several ways. Although asthma is an outcome measure potentially susceptible to both diagnostic and ascertainment bias, the fact that our findings were qualitatively broadly similar for the relatively small number of studies using self-reported wheeze as an outcome suggests that these biases are unlikely to be a major influence on our findings.

We were able to obtain original data from several investigators, allowing us to control for sex and the potential confounding effect of age, but the data from many studies (particularly the older ones) were unavailable. However, the data available to us did not allow us to adjust for some other potentially important confounders or sources of heterogeneity, particularly socioeconomic status and urban/rural residence (13). Because only two of the included studies provided parasite-specific IgE data, we were unable to explore these effects in asthma any further.

Our analysis of species-specific effects was performed to test the hypothesis arising in part from previous work (13, 20) that any protective effect was more likely to arise from intestinal parasites such as *A. lumbricoides* and hookworm, which include a host systemic phase in their lifestyle. The evidence, however, indicated that these parasites were associated with different effects on asthma risk, being greater for *A. lumbricoides* and lesser for hookworm. If our findings in relation to these species are in fact correct, the reason for this discrepancy is unclear but may relate to the relatively high allergenicity of *A. lumbricoides* (54), which unlike hookworm, is a recognized cause of tropical pulmo-

nary eosinophilia. The different effects may also arise from species-specific differences in the immune polarization and other potentially antiallergic effects that have been suggested as the mechanism by which parasite infection might protect against allergic disease (10). It is true that the atopic state seems to confer an element of resistance to worm infections. We have previously shown that high levels of IgE and eosinophilia result in reduced worm fecundity and postchemotherapy reinfection rates (55). However, this does not detract from the hypothesis that hookworms may have evolved to survive by suppressing the allergic state, and hence have an effect on atopic disease. The relative timing of allergen exposure in relation to parasite infection is important as parasites have a documented ability to potentiate responses to allergen, and can even convert nonallergenic proteins into allergens during concomitant infection. Another possibility is that the effect is dependent on age at infection, because children tend to develop *A. lumbricoides* infection in the first years of life, whereas hookworm infection is acquired after children become old enough to be mobile and independent (56). We found no evidence in support of this in the age interactions we explored, but this remains a possible explanation. Our finding for *A. lumbricoides* is supported, however, by the results of a study of the effects of parasite eradication in asthma, in which treatment actually improved asthma control in participants from a population with predominant *A. lumbricoides* infection (57).

Parasites have a built-in antiinflammatory defense, and there is increasing evidence that these defense mechanisms include effects on regulatory T cells (for reviews, see References 10 and 58), of which there are three populations, some secreting antiinflammatory cytokines such as transforming growth factor- β and interleukin-10, and others that seem to depend on contact with activated T cells to survive. There is mounting evidence that this population of cells is expanded during parasite infection, but the pathologic impact of this expansion is not yet clear.

An alternative explanation is that the associations we have observed arise from reverse causation, and that, in particular, allergic individuals are less likely to acquire hookworm infection. The cross-sectional nature of the data available to us precludes any further insight into this possibility. Overall, however, our study indicates that different species of parasite infection may

have important effects on the pathogenesis of asthma, and that in particular, the potential individual or public health benefits of hookworm infection merit further investigation.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript.

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Asthma and Current Intestinal Parasite Infection: Systematic Review and Meta-Analysis

Jo Leonardi-Bee, David Pritchard, John Britton

Online Data Supplement

Additional Information on Methods

Search strategy

For the electronic searches, we combined these search terms with 10 terms for asthma and wheeze (lung, airflow, airways, bronch\$, respirat\$, asthma [MeSH], wheeze, wheezing, whistling, spasm), and with 9 terms for parasite infection (parasite [MeSH], helminths [MeSH], parasite infection, *Ascaris*, *Trichuris*, hookworm, *Necator*, *Schistosoma*, *Enterobius*). We also attempted to contact at least one author from the identified studies to find out whether they knew of any relevant published or unpublished studies which were not yet identified.

Inclusion and exclusion criteria

Two authors (JL-B & JB) reviewed the titles and abstracts identified from the searches and included studies based on the inclusion criteria. Males and females of all ages and from any population were included. We included all working definitions of asthma or wheeze used in the studies, including self- or parent-reported diagnosed asthma or wheeze ever or in the past year, asthma reported as a diagnosis in clinical notes or by clinical examination, or asthma defined by measured exercise-induced bronchoconstriction. We excluded studies which did not use faecal examination to assess current parasite infection, did not measure current parasite infection in the whole population of the study, or involved a parasite treatment intervention.

Data extraction

Data relating to study design, methods, asthma status and definition, wheeze status and definition, characteristics of reference group, presence of any parasite infection, presence of species-specific parasite infection, and parasite infection intensity in eggs/g of faeces, location of study, age and sex of the study populations were extracted into a standardised database by the authors. Raw data and missing data were obtained from the authors of the original studies, where possible.

Assessment of methodological quality

The scores of the Newcastle-Ottawa quality assessment scale are based on three broad categories relating to the selection of the study groups (4 points); the comparability of the groups (2 points); and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively (3 points). The scores can range from 0 to 9, where higher scores indicate better methodological quality.

Statistical analysis

To assess the effect of a dose-response relationship between intensity of species-specific parasite infection and asthma, we analysed original data from studies which recorded intensity of infection in eggs per gram of faeces. Tertiles of infection intensity were constructed based on the pooled original data across the studies and analysed using logistic regression models adjusted for age and sex as fixed effects, and study as a random effect. The dose-response relationship was assessed using the F test assuming ordered tertiles.

Original data were also used to explore the possibility that the effect of parasite infections on asthma would be different for infection at early versus later age. Logistic regression models adjusted for age, sex and species-specific parasite infection as fixed effects, and study as a random effect were used, with an interaction term between age (dichotomised into above or below two years) and absence or presence of parasite infection.

Checklist for MOOSE guidelines

Reporting of background should include

- | | |
|--|-----|
| 1. Problem definition | Yes |
| 2. Hypothesis statement | Yes |
| 3. Description of study outcome(s) | Yes |
| 4. Type of exposure or intervention used | Yes |
| 5. Study population | Yes |

Reporting of search strategy should include

- | | |
|--|-----|
| 6. Qualification of searchers | No |
| 7. Search strategy and period | Yes |
| 8. Contacting authors | Yes |
| 9. Databases and registries searched | Yes |
| 10. Search software used, explosion effects | Yes |
| 11. Use of hand searching | Yes |
| 12. List citations included and excluded and reasons | Yes |
| 13. Foreign languages | Yes |
| 14. Abstracts and unpublished data | Yes |
| 15. Contact with authors | Yes |

Reporting of methods should include

- | | |
|--|-----|
| 16. Relevance or appropriateness of identified studies | Yes |
| 17. Rationale for selecting and coding of data | Yes |

18. How were data classified and coded	Yes
19. Confounding & assessment of comparability between groups	Yes
20. Assessment of study quality	Yes
21. Assessment of heterogeneity	Yes
22. Description of statistical methods	Yes
23. Tables and Figures	Yes

Reporting of results should include

24. Graphic for primary outcome with individual studies	Yes
25. Table for descriptive information for each study	Yes
26. Results for sensitivity/subgroup analyses	Yes
27. Indication of statistical uncertainty of findings	Yes

Reporting of discussion should include

28. Quantitative assessment of bias	Yes
29. Justification for exclusion of certain studies	Yes
30. Assessment of quality of included studies	Yes

Reporting of conclusions should include

31. Consideration of alternative explanations for results	Yes
32. Generalisability of results	Yes
33. Guidelines for future research	Yes
34. Disclosure of funding source	Yes

Figure Legends in the online data supplement

Figure E1 – Funnel plot for any current intestinal parasite infection against asthma.

(Plot shows the standard error of the odds ratio versus odds ratio for each study (random effect model). Vertical dotted lines indicate pooled effect estimate; dashed lines, 95% confidence intervals; and dots, individual studies.)

Figure E2 – Relationship between any current intestinal parasite infection and wheeze using a meta-analysis of comparative epidemiological studies (Data are presented as odds ratios for any parasite infection between wheeze as compared to non-wheeze and are pooled using random effect models. Squares represent odds ratios and horizontal lines denote 95% confidence intervals (CI). Size of the data markers corresponds to the weight of the study in the meta-analysis.)

Figure E3 – Relationship of current *Ascaris lumbricoides* infection and wheeze using a meta-analysis of comparative epidemiological studies. (Data are presented as odds ratios for *Ascaris lumbricoides* infection between wheeze as compared to non-wheeze and are pooled using random effect models. Squares represent odds ratios and horizontal lines denote 95% confidence intervals (CI). Size of the data markers corresponds to the weight of the study in the meta-analysis.)

Figure E4 – Relationship of current *Trichuris trichuria* infection and wheeze using a meta-analysis of comparative epidemiological studies. (Data are presented as odds ratios for *Trichuris trichuria* infection between wheeze as compared to non-

wheeze and are pooled using random effect models. Squares represent odds ratios and horizontal lines denote 95% confidence intervals (CI). Size of the data markers corresponds to the weight of the study in the meta-analysis.)

Figure E5 – Relationship of current hookworm infection and wheeze using a meta-analysis of comparative epidemiological studies. (Data are presented as odds ratios for hookworm infection between wheeze as compared to non-wheeze and are pooled using random effect models. Squares represent odds ratios and horizontal lines denote 95% confidence intervals (CI). Size of the data markers corresponds to the weight of the study in the meta-analysis.)

Figure E1

Review: Parasites and asthma
Comparison: 10 Funnel plot analysis
Outcome: 01 Unadjusted and adjusted analyses - stool samples

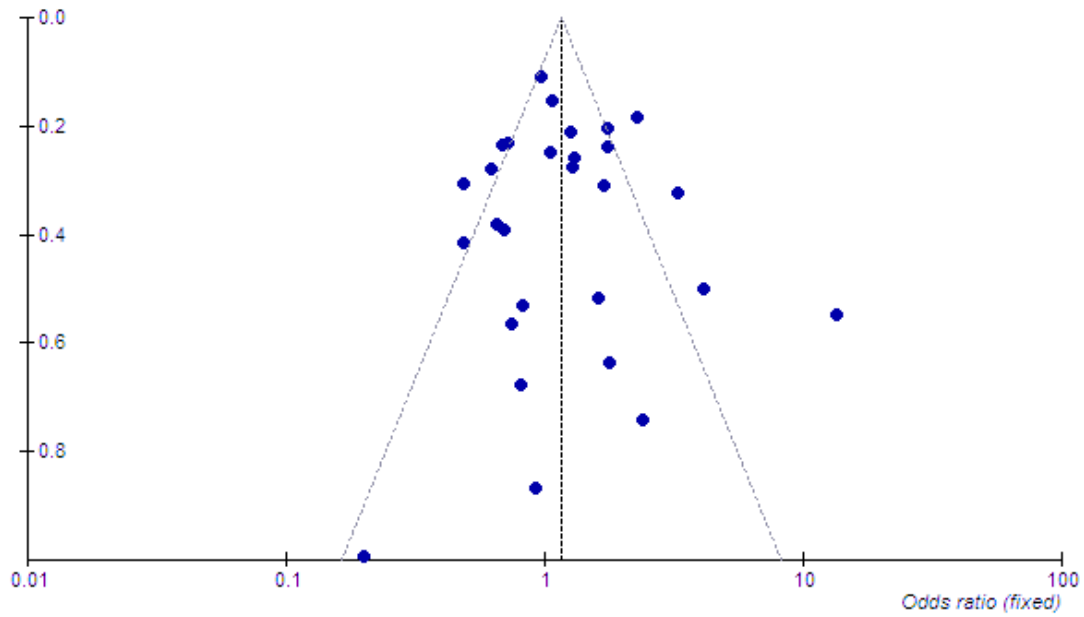


Figure E2

Review: Parasites and asthma
 Comparison: 08 Unadjusted and adjusted analyses - wheeze
 Outcome: 01 Wheeze and any parasite infection

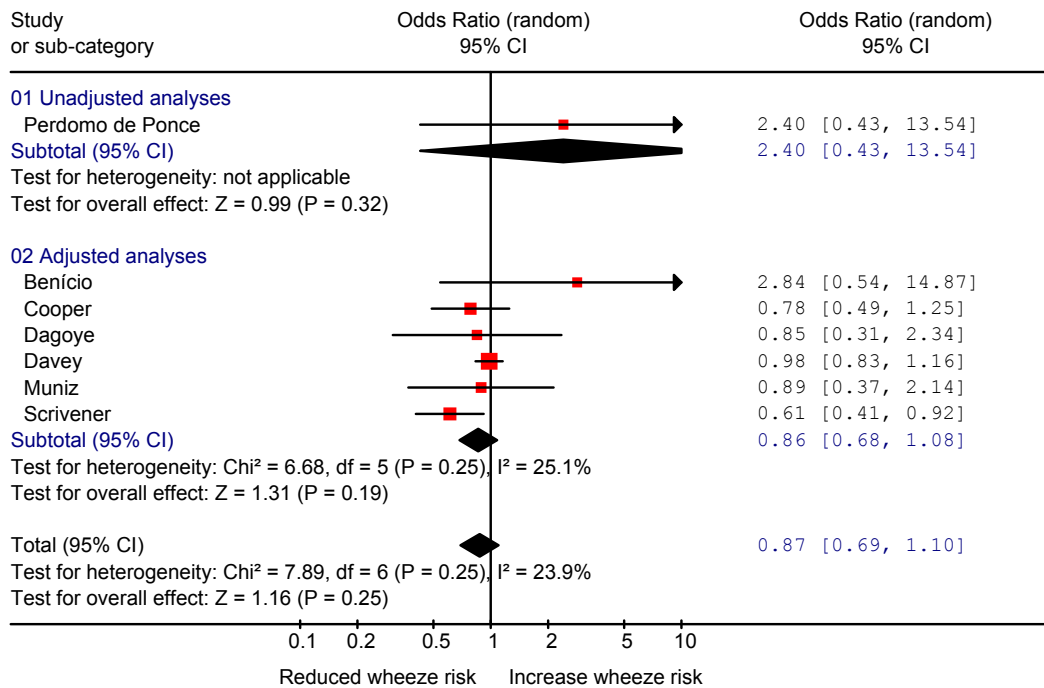


Figure E3

Review: Parasites and asthma
 Comparison: 08 Unadjusted and adjusted analyses - wheeze
 Outcome: 02 Ascaris lumbricoides

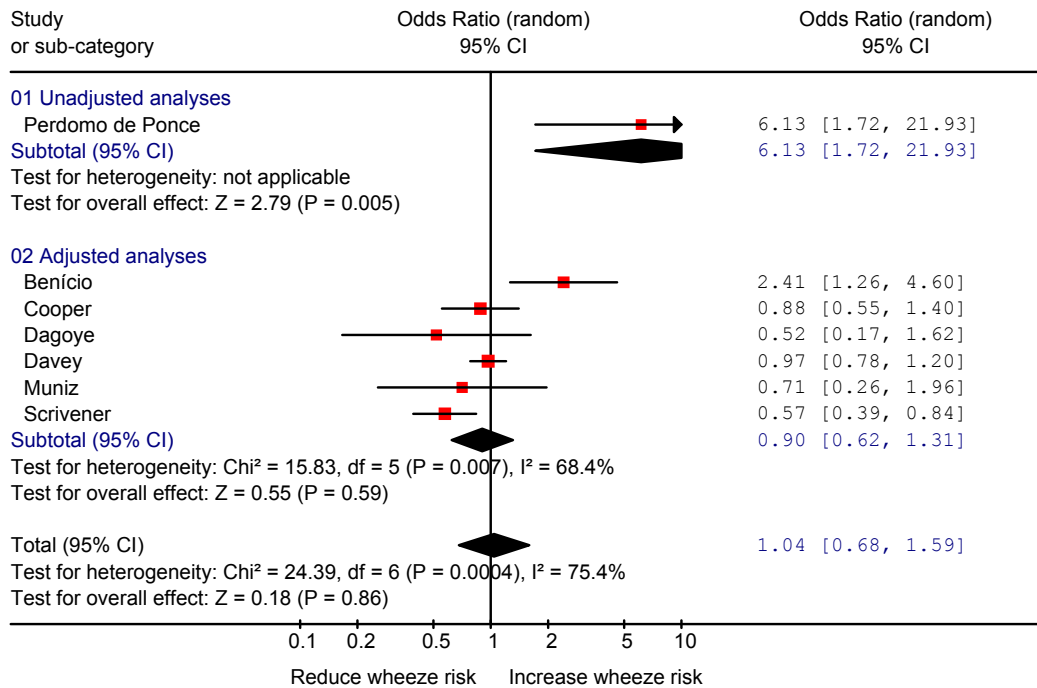


Figure E4

Review: Parasites and asthma
 Comparison: 08 Unadjusted and adjusted analyses - wheeze
 Outcome: 03 Trichuris trichuria

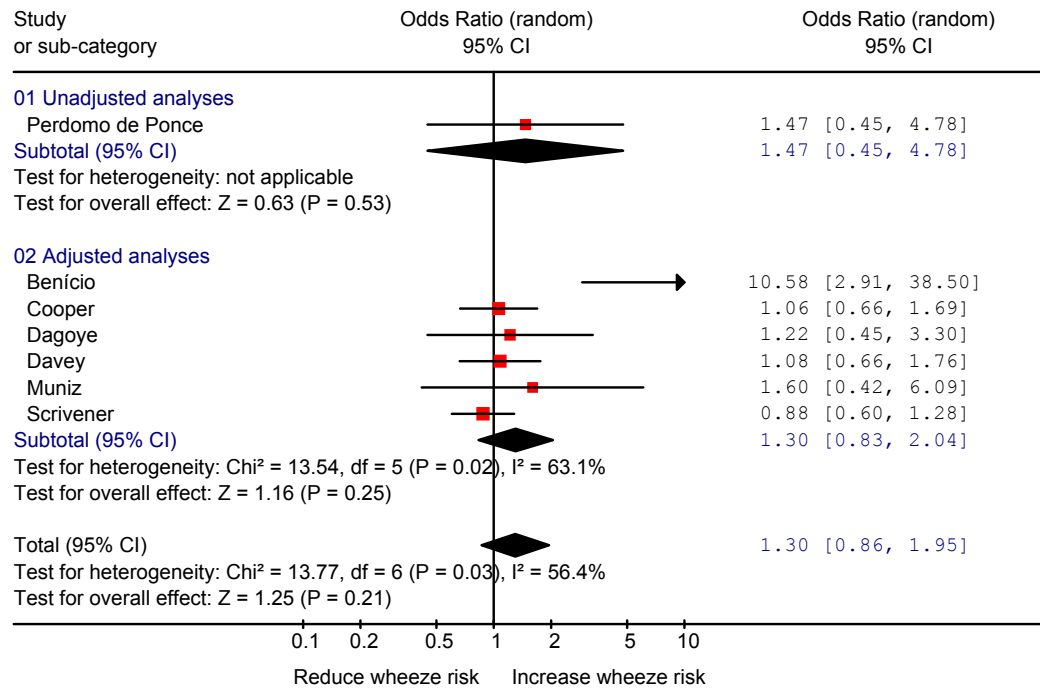


Figure E5

Review: Parasites and asthma
 Comparison: 08 Unadjusted and adjusted analyses - wheeze
 Outcome: 04 Hookworm

