Helminth infections and allergic diseases: Systematic review and meta-analysis of the global literature

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Background: There is considerable research interest in the role of helminth infections in the development of allergic diseases. However, findings from previous studies are mixed. Existing systematic reviews of these studies are outdated. We performed a systematic review of the global literature on the association between helminth infections and development and clinical outcomes of allergic diseases.

Methods: We searched Cochrane Library, MEDLINE, EMBASE, ISI Web of Science, PubMed, Global Index Medicus, Scielo, KoreaMed, Google Scholar, and Lilacs for studies published up to January 2020. We included observational epidemiological studies (cohort, case-control, and cross-sectional studies) of children and adults reporting associations between helminth infections and asthma, allergic rhinitis, eczema, and atopy. We performed random-effects meta-analysis to summarize the effect estimates.

Results: We included 80 studies with 99,967 participants. In the meta-analyses, we did not observe an overall association between helminth infections and allergic diseases. There was, however, evidence that *Ascaris lumbricoides* infections were associated with an increased risk of bronchial hyperreactivity in children (risk ratio, 1.41; 95% CI, 1.17-1.70; $I^2 = 50$; P for $I^2 = .09$), and were associated with an increased risk of atopy among helminth-infected adults (risk ratio, 1.37; 95% CI, 1.18-1.61; $I^2 = 52$; P for $I^2 = .02$). We found no study that addressed the association between helminth infection and clinical outcomes of allergic diseases. The overall strength of the underlying evidence was low to moderate.

Conclusions: Helminth infections may increase the risk of bronchial hyperreactivity in children and atopy in adults. Well-designed longitudinal cohorts may help clarify potential causal associations between chronic helminth infections and allergic diseases. (J Allergy Clin Immunol 2022;149:2139-52.)

Key words: *Helminths, asthma, allergic disease, atopy, risk factor*

Helminth parasites are estimated to infect more than 2 billion people[1] worldwide and include nematode (roundworms), cestode (tapeworms), and trematode (flukes) groups capable of parasitizing various niches within the host, including the intestine, tissues, and intravascular spaces.[2] The most prevalent infections are caused by intestinal nematodes, including *Ascaris lumbricoides* and *Trichuris trichiura*, and hookworms (*Necator americanus* and *Ancylostoma duodenale*).[3] The prevalence of intestinal helminths vary by geographic regions, depending on climate and sanitation, and particularly affect poor regions of sub-Saharan Africa, Latin America, China, and Eastern Asia.[4-7]

Allergic diseases, such as asthma, allergic rhinitis, and atopic eczema, affect hundreds of millions of people worldwide.[8-10] Among environmental factors considered to influence the emergence of allergic diseases are childhood infections, including helminths.[11,12] Helminth parasites are potent modulators of host inflammatory responses, particularly T2 responses that mediate allergic inflammation, and chronic helminth infections may reduce the prevalence of allergic diseases.[11-13] The findings of epidemiological studies focusing on the relationship between helminth infections and risk of allergic diseases, however, have been mixed.[13-20]

There are 2 previous systematic reviews summarizing the evidence of studies investigating the relationship between intestinal helminth infection and allergic diseases: (1) an analysis of the relationship between intestinal helminths and asthma or wheeze including 33 studies up to 2006 concluding that helminths did not protect against asthma overall, but that hookworm reduced and *A lumbricoides* increased the risk of asthma symptoms[21]; and an analysis of the relationship between intestinal helminths and atopy (measured by allergen skin prick test [SPT] reactivity) including 21 studies up to 2009 and concluded that intestinal helminths may protect against atopy.[22] In addition, 3 more recent meta-analyses have addressed the association between infections with the zoonotic tissue-invasive parasite *Toxocara* spp, detected by the presence of specific IgG antibodies, and allergy and

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Abbreviations used
BHR: Bronchial hyperreactivity
ISAAC: International Study of Asthma and Allergies in Childhood
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR: Risk ratio
SPT: Skin prick test

showed that *Toxocara* spp seropositivity was associated with an increased risk of asthma[23] and urticaria[24] but not atopy or eczema.[24]

Previous systematic reviews and meta-analyses of the relationship between helminth infection and allergy do not cover literature published in the last decade, with the exception of *Toxocara* spp for which such analyses are up to date.[23-25] Furthermore, published analyses only cover a limited spectrum of atopic and allergic diseases, namely asthma and atopy, leaving important gaps in the literature with respect to eczema and rhinitis and the range of helminth parasites. The current systematic review aimed to identify, critically appraise, and synthesize evidence from observational studies investigating the associations between specific helminth parasites and the risk of asthma, rhinitis, eczema, and atopy. Literature on *Toxocara* spp was not included given recent systematic reviews.[23-25]

METHODS

A protocol for this study was developed, registered with PROSPERO (registration no. CRD42020167249), and published before the systematic review was undertaken.[26] This review is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews[27] and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for meta-analysis of observational epidemiological studies.[28]

Eligibility criteria for study selection

Participants and study types. We included all studies, irrespective of age, describing relationships between helminth infection and respiratory allergic diseases, eczema, rhinitis, and/or atopy. Observational designs, including cohort, case-control, and cross-sectional studies, were included. Discussion papers, nonresearch letters, editorials, randomized controlled trials, clinical case studies and case-series, and animal studies were excluded.

Exposure. Studies of any type of helminth infection, including *Enterobius vermicularis*, *A lumbricoides*, *T trichiura*, hookworm (*A duodenale and N americanus*), *Strongyloides stercoralis*, *Hymenolepsis spp* (*Hymenolepis nana and Hymenolepis diminuta*), and *Schistosoma spp* (*Schistosoma mansoni and Schistosoma haematobium*), were included. Studies of *Toxocara* spp were excluded.

Study outcomes. The primary outcomes were the incidence or prevalence of allergic diseases. Among the included studies we found available information on asthma or wheezing (defined by either doctor-diagnosed or wheeze in the past 12 months using ISAAC [International Study of Asthma and Allergies in Childhood] definition[29] or other comparable definitions), on rhinitis (doctor-diagnosed or as defined in ISAAC or other comparable definitions), on eczema (flexural dermatitis diagnosed by doctor or as defined in ISAAC or other comparable definitions), on atopy (assessed using allergen-specific IgE or allergen SPTs), and on bronchial hyperreactivity (BHR; assessed by exercise, bronchodilator reversibility, or challenge with methacholine, histamine, or hypertonic saline). Most studies used ISAAC definitions for wheeze/asthma, rhinitis, and eczema. As secondary outcomes, we searched clinical outcomes of respiratory allergic diseases, including exacerbations, hospitalizations, severity according to clinical/symptom evaluation (using any type of validated scale or questionnaire), and health-related quality of life (using any type of validated scale or questionnaire).

Search strategy

We developed a comprehensive search strategy for retrieving published and unpublished studies on the topic (see Appendix E1 in this article's Online Repository at www.jacionline.org). We searched the Cochrane Library, MEDLINE, EMBASE, ISI Web of Science, PubMed, Global Index Medicus, Scielo, KoreaMed, Google Scholar, and Lilacs. Search dates were from January 1970 to January 2020. The references in all eligible studies were reviewed to identify additional studies. No language restrictions were imposed in the searches, and translations were made where necessary.

Selection process

Studies retrieved from the databases were exported to the online reference management software Rayyan (available at rayyan.qcri.org). Two reviewers (M.A. and T.M.) independently selected the articles according to the defined criteria and applied the following screening stages: cleaning of duplicated articles, selection of articles according to eligibility criteria and by reading title and abstract, and selection of articles according to full-text reading. All disagreements were resolved through discussion or arbitrated by a third review author (L.T.-B.).

Reasons for excluding articles during the full-text screening were noted and indicated in PRISMA diagram (Fig 1).[27]

Data collection process

Two authors (M.A. and T.M.) extracted data from included articles on a Microsoft Excel spreadsheet, tailored to the current systematic review. We also collected indirect data from figures and charts, adapting their interpretation by consensus, and contacted authors of original articles for further information and data where necessary. Any disagreement in data collection was resolved through discussion or arbitrated by a third review author (L.T.-B.).

Type of data collected

We collected the following information from all included studies: study design, number of participants and their characteristics (namely, wheezing due to early-life respiratory viral infections, early childhood respiratory infections, personal and family history of allergies, household smoking), country of study, year of publication, profiles of helminth infection (presence, load, duration of infection, types of parasites, monoinfection or coinfection, recent or past treatments, frequency of infection), geographical differences; estimates (odds ratio, 95% CIs, mean and SD) of the association between helminth infection and the study outcomes, as well as the technical aspects of determination/operational definition of helminth infection. One author (T.M.) inserted data into Review Manager Software (RevMan) (available at http://community.cochrane.org), and data were double-checked for correct entry by a second author (M.A.).

Quality assessment

Two authors (M.A. and T.M.) appraised the quality of included studies using the Critical Appraisal Skills Programme quality assessment tool.[30] We evaluated different components of each study, including appropriateness of study design, potential for selection bias, measurement of exposures and outcomes, and generalizability of the study findings. For each study, the grading of each individual component and the global study rating assigned categories of risk of bias: low, moderate, and high. All disagreements not settled by discussion were resolved by a third reviewer (L.T.-B.).

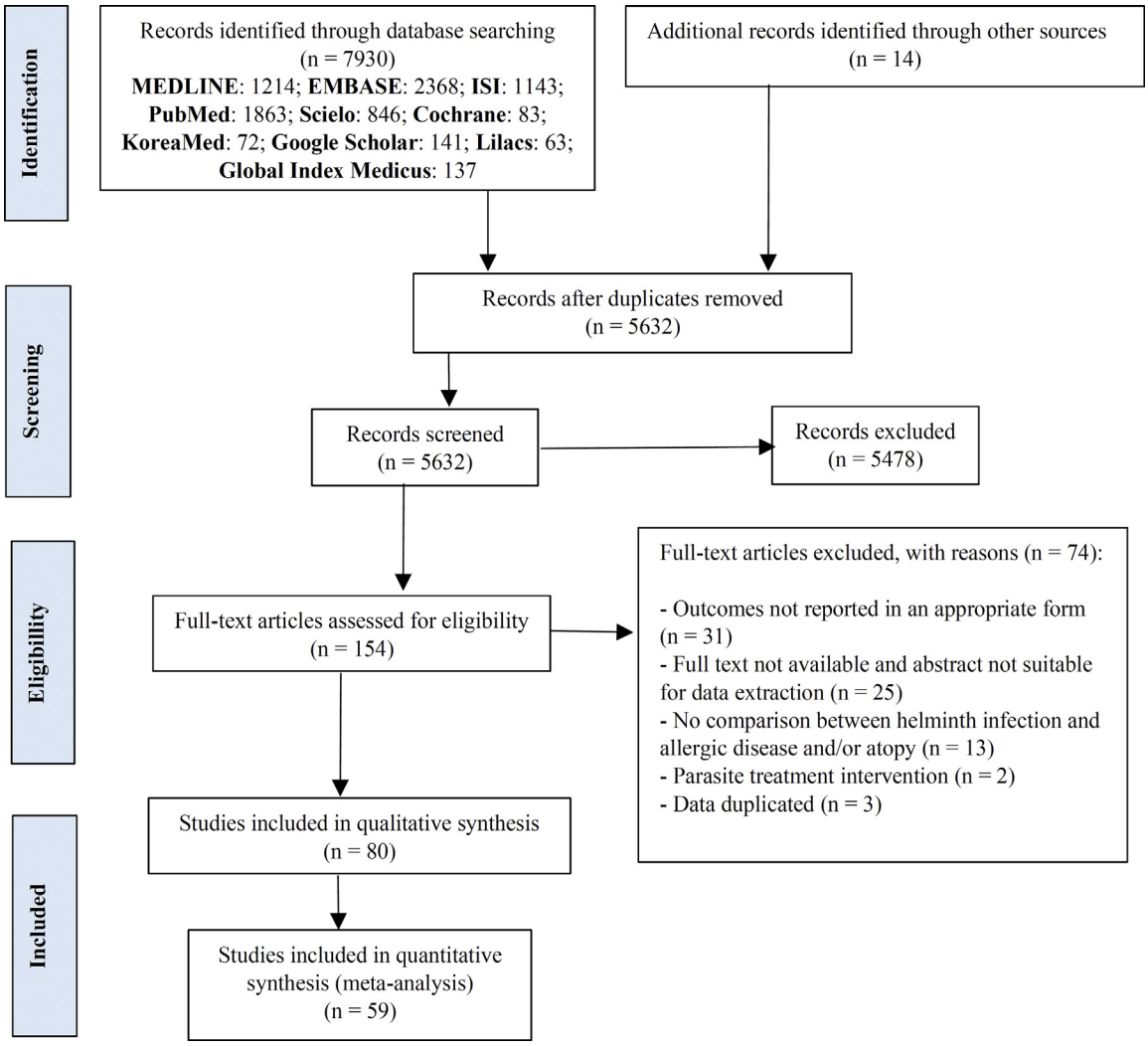

FIG 1. Flow diagram on search and article inclusion, according to PRISMA statement.[27]

Data synthesis

We performed both narrative and quantitative synthesis of the generated evidence. Quantitative synthesis involved meta-analysis to summarize numerical estimates from included studies. Meta-analysis was performed using random effects in which effect estimates from studies judged to be sufficiently homogeneous (by clinical, methodological, and statistical criteria) were pooled. We used Mantel-Haenzsel risk ratios (RRs) in the meta-analysis for dichotomous data, accompanied by their respective 95% CI. Meta-analysis results are presented graphically in forest plots. Heterogeneity between effect sizes of included studies was assessed by visual inspection of forest plots and by using the chi-square test for heterogeneity (with a P value of <.1), and inconsistency between studies was given using the percentage of the variability in effect estimates that is due to heterogeneity rather than chance (I^2). In the meta-analysis, estimates from studies not presented as RRs were converted to RRs using the recently proposed formulas provided by VanderWeele and Ding.[31] Data for continuous outcomes were not available. Sensitivity analyses were performed to assess the impact of specific studies on the pooled meta-analysis results, and subgroup analyses were also performed according to variables of interest. For such purposes, the following variables were considered: helminth species, risk of bias assessment, study size, study year, country income level (defined as high vs low, and according to The World Bank classification, available at: https://datahelpdesk.worldbank.org), geographical region, participants' age, study design, detection methods used for geohelminths (stratified into low, moderate, and high sensitivity) and whether techniques were based on detection of active infections using stool samples or using serological methods (eg, measurement of parasite-specific IgG or IgE), and type of method used for atopy classification (measurement of specific IgE vs allergen SPT reactivity). In addition, geohelminth endemicity was defined on the basis of prevalence into low (<20%), moderate (20%-40%), and high (>40%).

RESULTS

Description of studies

We obtained 7930 articles (Fig 1) from which, after elimination of duplicates, 5632 remained. Of these, 5478 were excluded after reading title and/or abstract. Thus, we obtained 154 studies from which, after reading the full text, 74 were excluded, as shown in Fig 1.

Of the 80 eligible studies,[11,13-15,17,19,32-105] 46 (57.5%) were cross-sectional, 25 (31.3%) were case-control, and 9 (11.2%) were cohort studies. A total of 99,967 individuals were studied, and most (n = 47 [58.8%]) were children, followed by studies in children and adults (n = 25 [31.3%]). Regional distribution of the studies indicated that 33 (41.3%) studies were carried out in South America, 21 (26.2%) in Africa, 16 (20.0%) in Asia, and 10 (12.5%) in Europe.

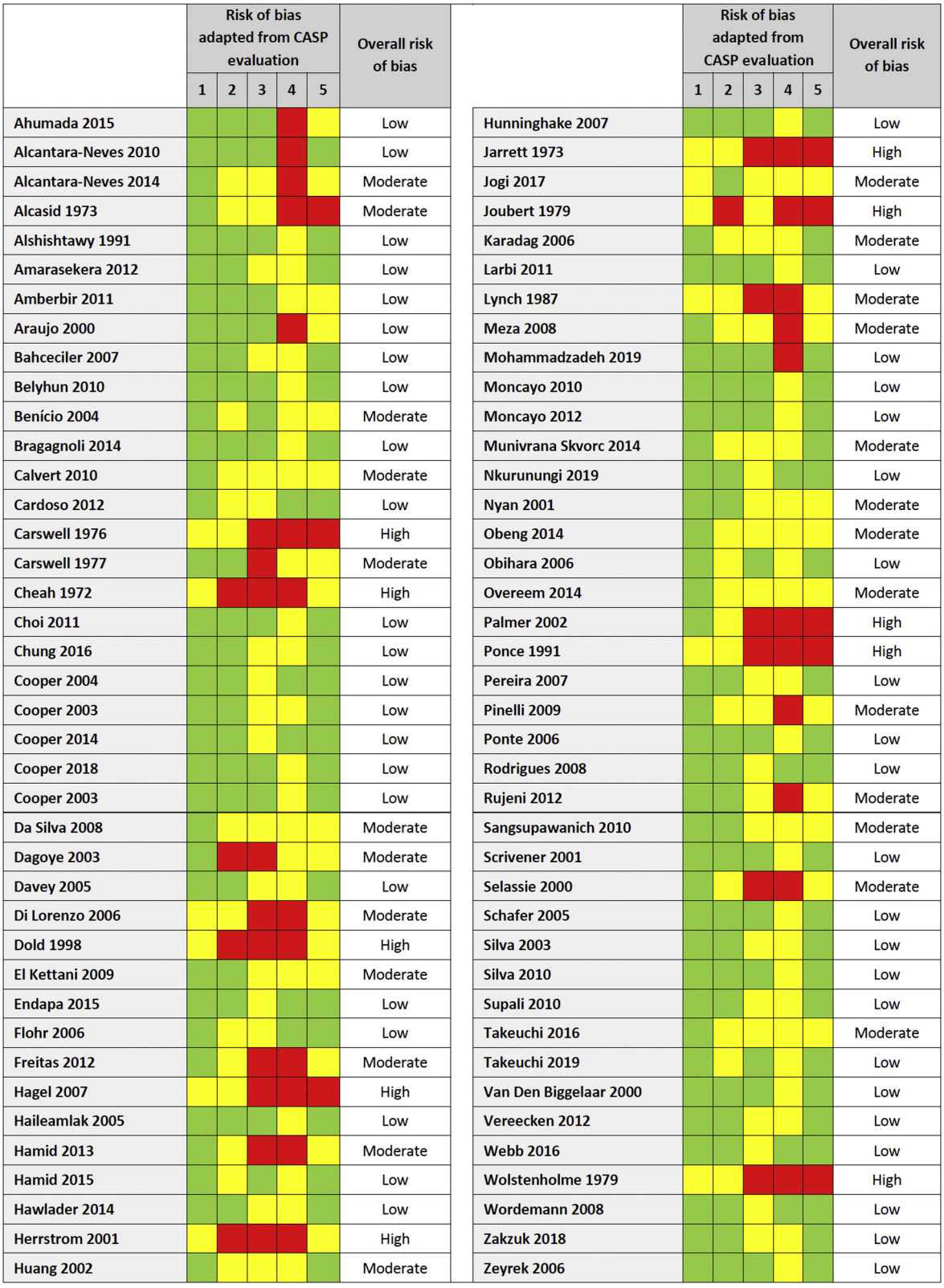

FIG 2. Risk of bias assessment in included studies according to CASP tool.[30] (1) appropriateness of study; (2) design; (3) potential for selection bias; (4) measurement of exposures and outcomes; (5) generalizability of the study findings. *CASP*, Critical Appraisal Skills Programme.

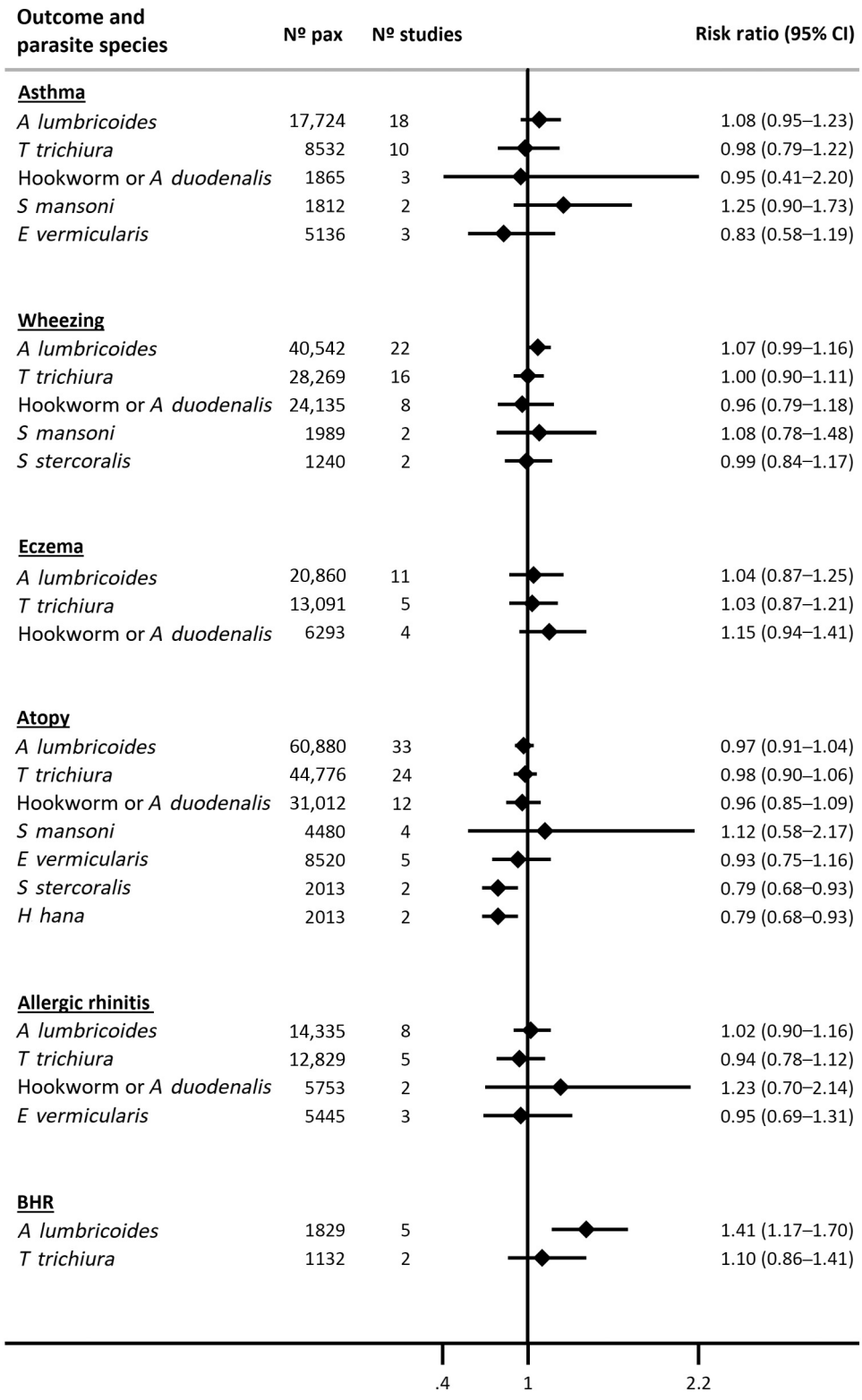

FIG 3. Forest plot of results for the risk of allergy outcomes, according to the infection with specific helminth species.

For helminth detection, 19 (23.8%) studies used a single stool sample, 16 (20.0%) used 2 to 3 stool samples, although most (32 [40.0%]) did not define the number of samples analyzed. Three (3.8%) studies used the perianal tape test (to detect *E vermicularis*), and 7 (8.8%) used serum.

Regarding measurement of infection, more than half the studies (42 [52.5%]) used microscopy, 9 (11.2%) used serology (detection of specific IgG or IgE antibodies in sera), and 20 (25.0%) used both measurements. Four (5.0%) studies used molecular detection methods (real-time PCR) for detection of hookworm.

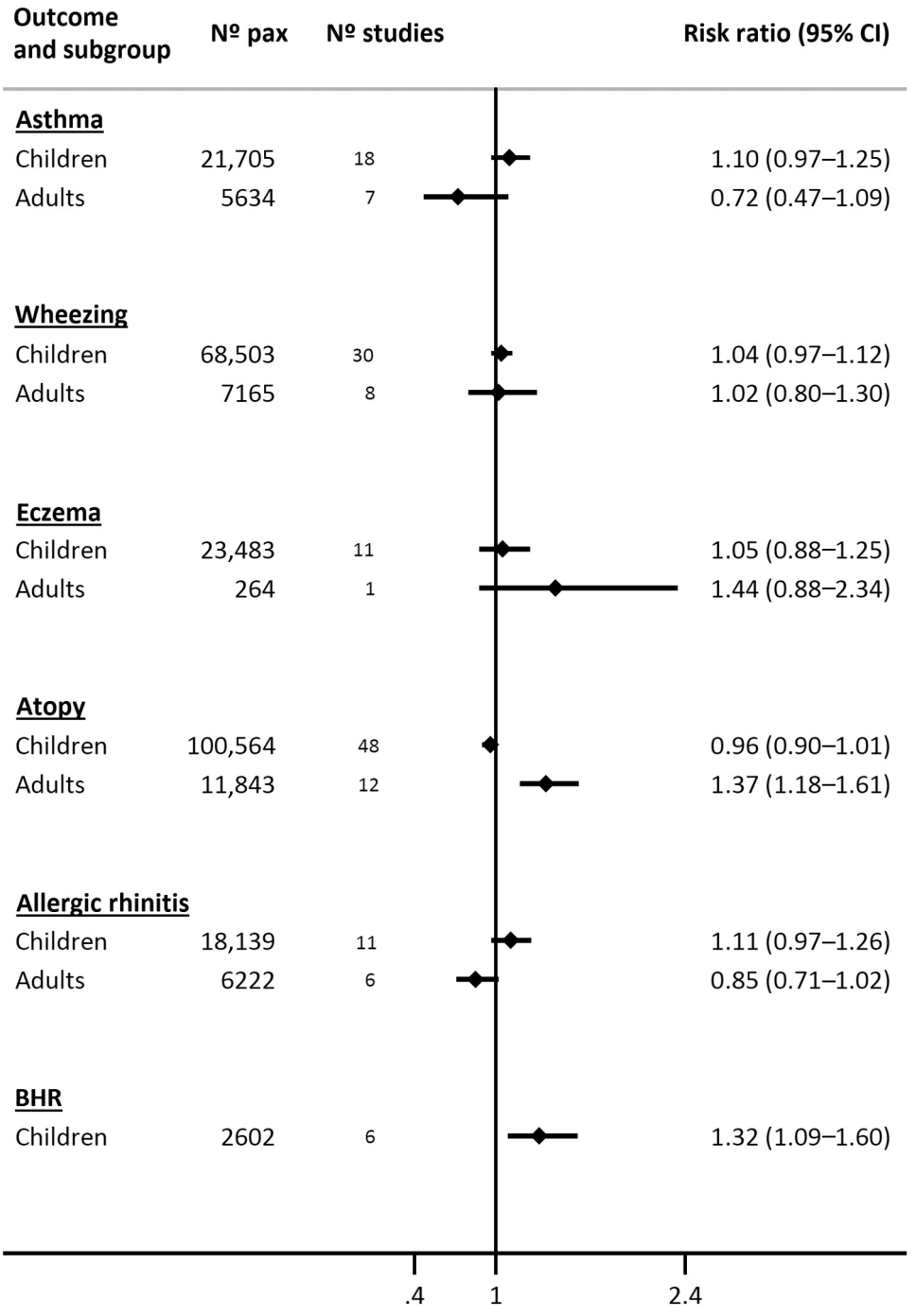

FIG 4. Forest plot of results for the risk of allergy outcomes, according to participants' age (children and adults).

Most studies, 24 (30.0%), studied only 1 species of helminth, 22 (27.5%) studied 2 species, 16 (20.0%) 3 species, and 13 (16.3%) studied between 4 and 6 species.

Forty-five studies (56.3%) used ISAAC definitions for asthma, rhinitis, and eczema, 33 (41.3%) used only the SPT to measure atopy, and 19 (23.8%) used both SPT and serological detection of allergen-specific IgE.

Most studies (57.0%) considered several allergic diseases such as asthma, wheezing, rhinitis, and eczema, associated or not with atopy, as primary outcomes, whereas the primary outcome reported was atopy in 53 studies, asthma in 40, wheezing in 28, rhinitis in 19, and eczema in 17. A few studies (6; 7.5%) measured BHR.

As secondary outcomes, we searched estimates of association between helminth infection and clinical outcomes of allergic respiratory diseases such as exacerbations, hospitalizations, and severity. Six studies (7.6%) evaluated associations between *Ascaris* or hookworm infections and clinical disease outcomes for asthma, wheeze, or eczema (severity, exacerbations, and hospitalizations): findings showed no significant effects except

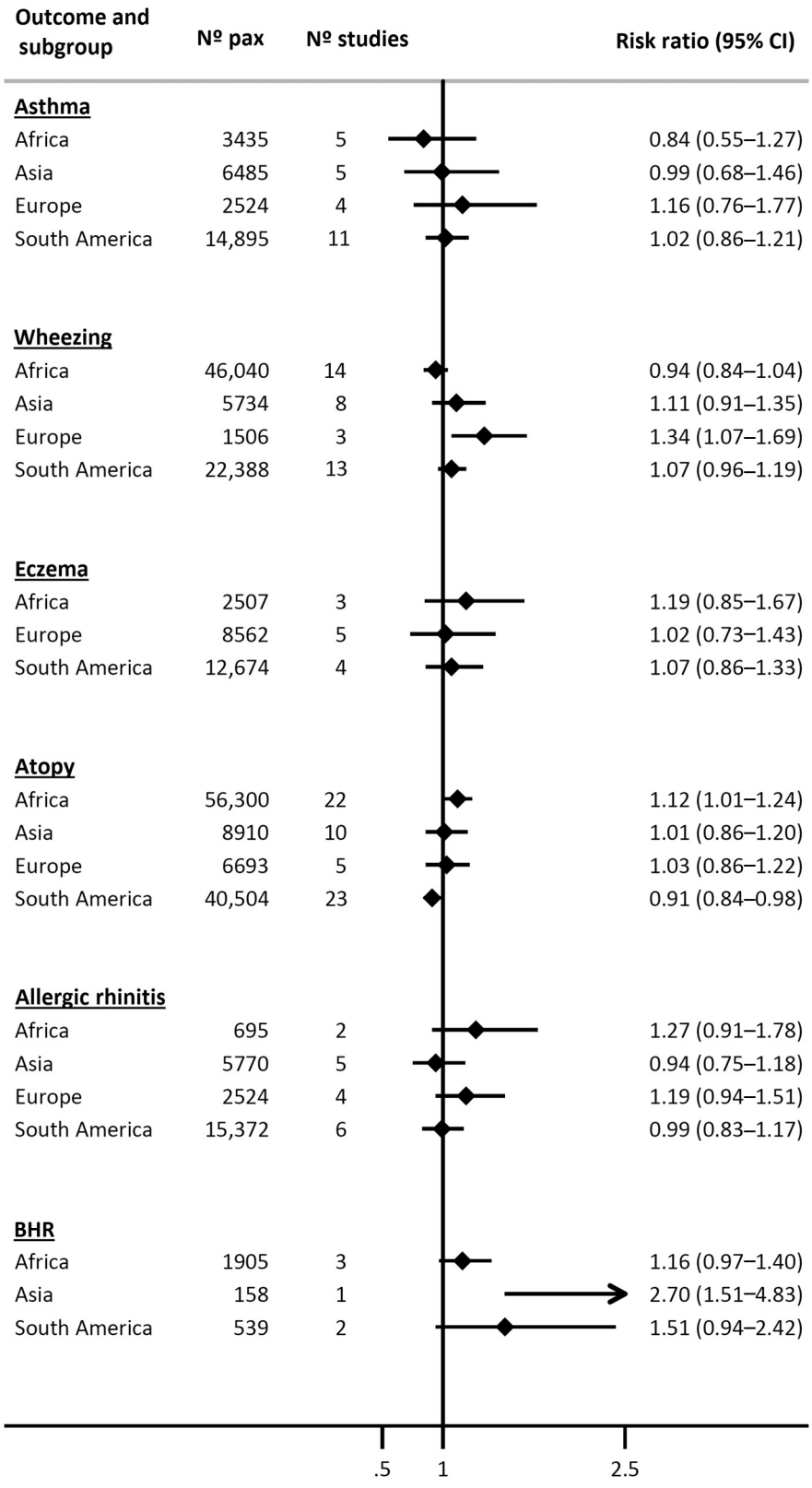

FIG 5. Forest plot of results for the risk of allergy outcomes, according to world regions.

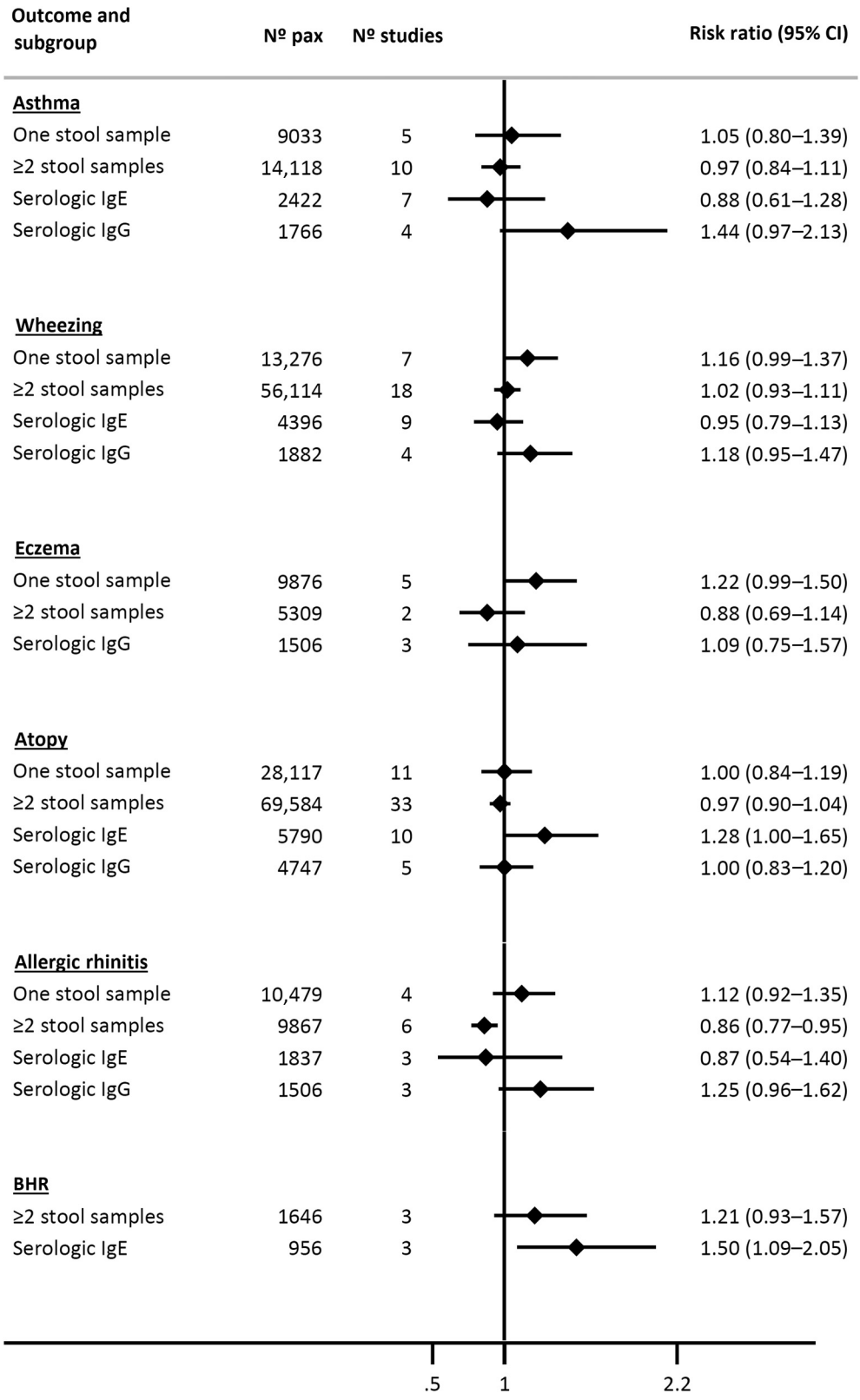

FIG 6. Forest plot of results for the risk of allergy outcomes, according to the method used for Helminth detection.

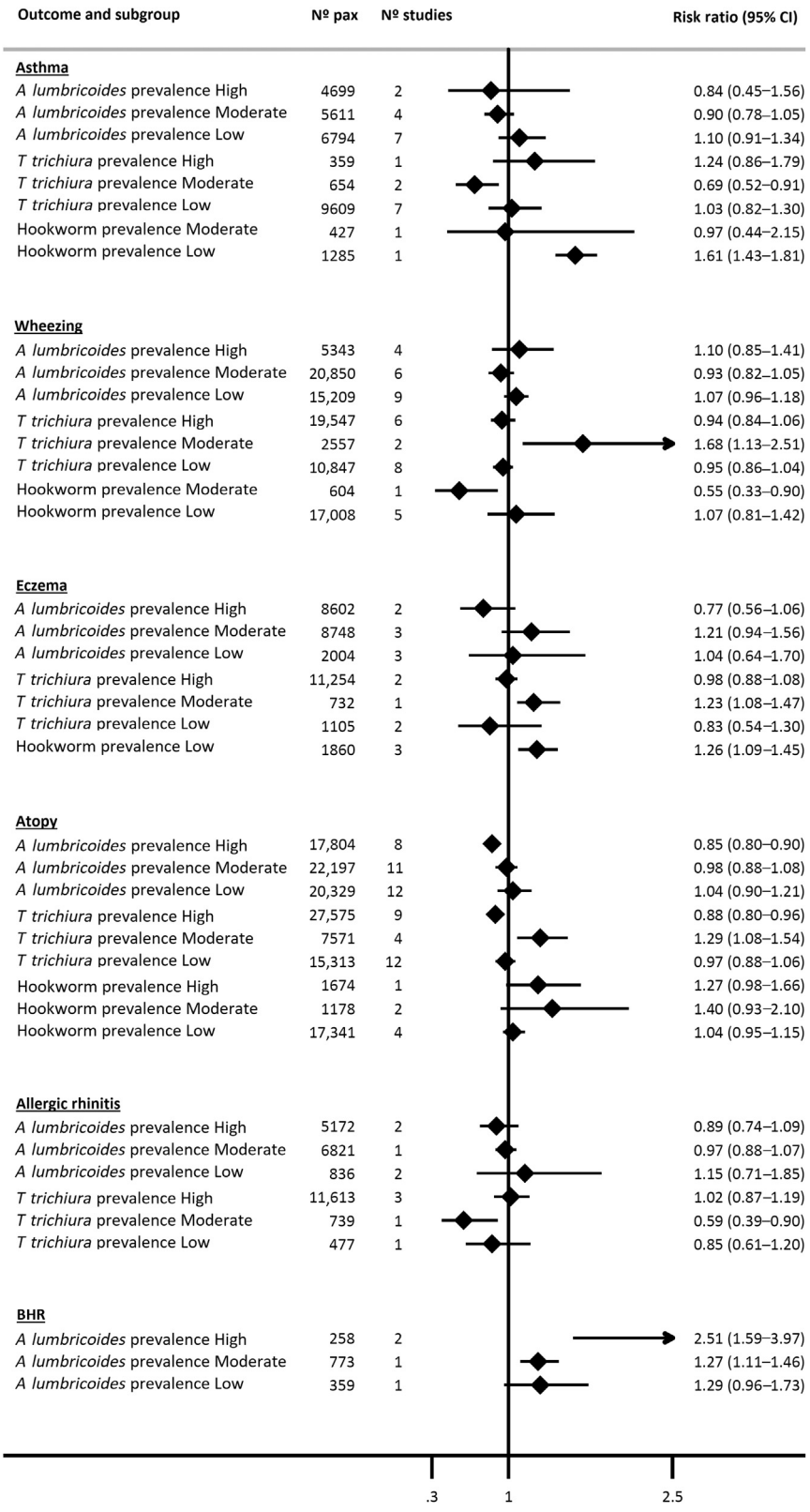

FIG 7. Forest plot of results for the risk of allergy outcomes, according to helminth-endemic prevalence.

for 1 study, which showed an increased risk of allergic disease. However, we did not find sufficient studies reporting accurate data on these results that might be pooled in this meta-analysis. Detailed information for all selected studies is available in Appendix E4 in this article's Online Repository at www.jacionline.org.

Risk of bias in included studies

Two reviewers (M.A. and T.M.) independently evaluated the risk of bias of the included studies, reaching consensus in all evaluations (Fig 2). Most studies were considered to be of low and moderate risk of bias, and many had reasonably generalizable findings. Among 80 studies included in quality assessment, 45 (56.3%) had a global low risk of bias, 25 (31.3%) moderate, and 10 (12.4%) high risk of bias. The dimension found to have the highest risk of bias concerned measurement of exposures and outcomes, where only 9 (11.3%) studies showed good quality (evaluation provided in Appendix E2 in this article's Online Repository at www.jacionline.org).

Helminths and risk of asthma and allergic diseases

Among the 80 selected studies, 47 (58.8%) studies were performed in children and/or adolescents and only 5 studies (6.3%) mainly included adults. The most frequently studied helminth species was *A lumbricoides* (N = 68 [85.0%]), and the frequencies of reported outcomes were atopy (N = 53; 66.3% studies), asthma (N = 40; 50.0% studies), wheezing (N = 28; 35.0% studies), rhinitis (N = 19; 23.8% studies), eczema (N = 17; 21.2% studies), and BHR (N = 6; 7.5%).

Fifty-nine studies were eligible for data extraction, reporting data from 84,453 participants, and allowing inclusion in meta-analyses of the associations between helminths and the risk of allergic diseases. Detailed information on meta-analyses for each main outcome is provided in Appendix E3 in this article's Online Repository at www.jacionline.org.

We did not observe statistically significant associations between infections with specific helminth species and the risk of asthma, wheeze, eczema, and allergic rhinitis (Fig 3). However, *A lumbricoides* infections were associated with an increased risk of BHR (RR, 1.41; 95% CI, 1.17-1.70), and infections with *S stercoralis* and *H nana* were associated with a decreased risk of atopy (RR, 0.79; 95% CI, 0.68-0.93), although the latter was based on just 2 studies.

After stratifying studies by those conducted in children or adults (Fig 4), we observed a significant association between *A lumbricoides* exposure and the development of BHR (RR, 1.32; 95% CI, 1.09-1.60; $I^2 = 50$) in children and a greater risk of atopy in adults (RR, 1.37; 95% CI, 1.18-1.61).

Analysis of findings by geographic region (Fig 5) showed that serologic detection of helminth infections was associated with an increased risk of wheeze in Europe (RR, 1.34; 95% CI, 1.07-1.69) but not in other geographic regions. Helminth infections were associated with a small increased risk of atopy in Africa (RR, 1.12; 95% CI, 1.01-1.24) but a small decreased risk in South America (RR, 0.91; 95% CI, 0.84-0.98); and increased risk of BHR in all regions, although this reached statistical significance only in Asia in a single study (RR, 2.70; 95% CI, 1.51-4.83).

Studies were also stratified by diagnostic method to detect helminth infection (Fig 6). No significant associations were observed for allergic symptoms. However, there was evidence of a positive association between the presence of specific IgE antibodies (generally to *A lumbricoides*) and atopy (RR, 1.28; 95% CI, 1.00-1.65) and BHR (RR, 1.50; 95% CI, 1.09-2.05). A lower risk of allergic rhinitis was observed in studies examining 2 or more stool samples for detection of helminth infections (RR, 0.86; 95% CI, 0.77-0.95).

To explore the effect of helminth endemicity on the risk of allergic outcomes, we stratified studies by prevalence of infection for the most common geohelminths (*A lumbricoides*, *T trichiura*, and hookworm) into low-, moderate-, and high- prevalence populations. Significant associations were observed, although generally the findings were based on few studies (Fig 7) showing high heterogeneity indices, and findings were generally inconsistent with no clear pattern according to changes in endemicity. Where data from more studies were available, there was evidence of a decreased risk of atopy with infection to *A lumbricoides* (RR, 0.85; 95% CI, 0.80-0.90) or *T trichiura* (RR, 0.88; 95% CI, 0.80-0.96) and atopy in high-prevalence areas. However, in moderate-prevalence settings, there was an increased risk of atopy with infection to *T trichiura* infection (RR, 1.29; 95% CI, 1.08-1.54). Despite data from few studies, there was a consistently increased risk of BHR associated with *A lumbricoides* infections, irrespective of parasite prevalence (Fig 7).

Additional sensitivity analysis revealed no significant changes in the risk estimates regarding study sample sizes or design type, risk of bias assessment, and countries' income level.

We could not evaluate the effect of helminths on the expression of clinical outcomes and disease severity in patients with already-established allergic diseases because of insufficient data.

DISCUSSION

Summary of key findings

Our comprehensive systematic review included all studies published so far on the association between helminth infections and risk of atopy and allergic diseases in children and adults from all world regions. Polyparasitic helminth infections were reported in most studies, although *A lumbricoides* was the most frequently detected helminth parasite. Our results showed a slightly increased risk of BHR associated with *A lumbricoides* infection in children and an increased risk of atopy associated with helminth infections in adults. Although more than half of the included studies had a low risk of bias in their global quality rating, there was evidence of significant heterogeneity between them with respect to the specific components of the studies, limiting the strength of evidence. There were limited data on the association between helminth infections and disease severity or worsening or other clinical outcomes among patients with already-established allergic diseases.[106]

Strengths and limitations of the review

Our systematic review is reported according to PRISMA recommendations,[27] which makes the review process structurally robust. Our search was comprehensive because we used the most relevant databases without any restrictions in time, region, or language. To complement the databases searches, we also searched other secondary sources, including the gray literature, which provided important complementary sources. Through

snowballing, we identified additional eligible studies from previous systematic reviews, thus ensuring the completeness of our literature search.

Although there is no universally accepted definition for allergic outcomes, most studies included in this meta-analysis used well-recognized epidemiological definitions for allergic diseases derived from ISAAC and Global INitiative for Asthma, which likely make our findings more robust. The helminths included in this analysis include a systemic helminth infection (*Schistosoma* spp) and those living in the intestinal tract during the adult stage of the parasite life cycle. The latter group includes those with purely enteric life cycles (ie, *T trichiura* and *E vermicularis*) and those with a systemic phase of larval migration (ie, *A lumbricoides*, hookworm, and *S stercoralis*). Helminth infections can induce various T2 effector and regulatory responses, the presence and role of which may vary between helminths and life cycle stages and according to factors such as duration (ie, chronicity) and intensity of infection and presence of coinfections. Given that most studies were cross-sectional and there was lack of availability of disaggregated date, we were unable to infer effects of infection chronicity and intensity, respectively, 2 factors that could modify the associations observed in our meta-analyses. The proportion of infections that are chronic and high-intensity would increase with increasing prevalence, hence, our stratified analysis by parasite prevalence.

To assess quality of evidence, we used the Critical Appraisal Skills Programme scale,[30] and our analysis showed that several of the studies had moderate to high risk of bias with respect to specific components of the studies. Furthermore, most studies were cross-sectional in design, making it impossible to establish causal relationship between helminth infection and the study outcomes. These considerations limit the confidence of our findings because true comparisons between the studies are limited and temporality between helminth infections and allergic diseases/atopy cannot be determined. There is a lack of longitudinal cohort studies that would help clarify potential causal associations.

Comparison with previous studies

Results of epidemiological studies that evaluated the relationship between helminth infection and risk of allergic diseases, carried out in many regions worldwide, have shown conflicting findings.[13-15,19] Only 2 previous systematic reviews have summarized the evidence of the relationship between helminth infections and allergic diseases. The first, published in 2006, found no overall association between helminth infections and reported symptoms of asthma, did show a reduced risk of symptoms associated with hookworm, but showed an increased risk with *A lumbricoides*.[21] The authors addressed only asthma and wheeze as the main outcomes and evaluated exposure to helminths using microscopy only. The second, published in 2011, showed a decreased risk of allergen SPT reactivity associated with helminths,[22] and evaluated exposure to helminths using microscopy only. These previous works failed to include a broader spectrum of allergic phenotypes or conditions (eg, BHR and eczema, respectively) and did not evaluate relevant subgroup patterns, regarding age, continental region, helminth detection methods, and helminth endemicity.

Thus, our systematic review gives an up-to-date and more comprehensive insight into the question of role of helminth infection in the development of allergic diseases. Our review covered studies published during the last 50 years worldwide and considered the effects of age, geography, parasite species, and prevalence (used as a marker for endemicity) on the main allergic outcomes for which data are available. The studies included in this review, especially the most recent ones, were in general, methodologically sound, using comparable and reasonably standardized methodologies for measurement of helminths and allergic outcomes: allergic diseases symptoms using the definitions of ISAAC,[107] and Global INitiative for Asthma[108]; atopy by allergen skin prick testing or presence of specific IgE; and geohelminth infections by examination of feces with qualitative and quantitative (mainly Kato-Katz) methods. Previous studies have shown different associations depending on the type of helminth and allergic disease measured[17,42,74,83,93] and with respect to recent versus past infections.[104] Some studies evaluated the intensity of parasitic load[11,13,35,78,85,88,105] and the severity of allergic diseases,[68,75,90,95] but their results were not sufficient to globally assess these effects on associations in this analysis.

One study evaluated the association between allergic disease, namely asthma and rhinitis, and antihelmintic treatment, as a secondary outcome, and found that such treatment was associated with a reduced risk of recent asthma but not rhinitis symptoms.[83]

Overall, it was not possible to assess sociodemographic data to control confounding factors, such as sex and age, socioeconomic level, and urban or rural residence, because there were few studies reporting enough disaggregated data to permit such analyses.[51,58,61-63,73,79,84,88] However, some confounding factors, such as coinfections, were already analyzed in the risk estimates of the included studies, which may attenuate such bias. In this context, coinfections such as tuberculosis[50,59] showed no significant associations with allergy, and malaria, in the presence of sensitization to cockroach[59] and eczema,[15] was related to an increased risk of atopy and allergic disease.

Interpretation and implications of the findings

Because of the cross-sectional design of most included studies, and their inherent risk of bias, it is hard to establish confident and solid evidence regarding most of the outcomes we analyzed. Overall, there is no evidence that helminth infection may significantly increase or decrease the risk of asthma, wheezing, or eczema, although there might be a slight trend in adults toward an increased risk of atopy, but with low strength of evidence. The most pronounced statistical association that we found involved the risk of BHR in children infected with *A lumbricoides*, and this may be considered in future studies and clinical guidelines for preventive measures. This association may be due to the inflammatory response to the pulmonary stage of the life cycle of *Ascaris*, which may trigger BHR particularly with heavy parasite burdens. This inflammatory process in the airways may involve sensitization to *Ascaris* with production of specific IgE antibodies against this helminth, contributing to T2-type inflammation[100,109] and could be exacerbated through immunologic cross-reactivity between helminth and aeroallergen-derived molecules such as tropomyosins.[110,111] In any case, the association between *Ascaris* infection and BHR may, to some extent, change according to sociodemographic context of the exposed populations, or even according to time-related factors that might change susceptibility over time, parameters that we were unable to address. This highlights the need for more longitudinal cohorts addressing

effects of timing of initial exposures, duration of infections, and parasite-specific and intensity effects, on the development of allergic outcomes.

Conclusions

There is no strong evidence for an effect of helminth infections on the risk of asthma, wheezing, and eczema. There was some evidence that childhood infections with *A lumbricoides* might increase the risk of BHR, and helminth infections in adults might increase the risk of atopy. Robust longitudinal cohorts are required to address the effects of helminths on the development of atopy and allergic diseases.

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Clinical implications: This comprehensive synthesis of the global literature indicates that although helminth infections may play a role in the development of BHR in children, it may increase the risk of atopy in adults. Evidence is lacking on the impact of helminth infection on clinical outcomes in patients with already-established allergy or asthma.

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