

Toxocara spp. infection and risk of childhood asthma: A systematic review and meta-analysis



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ABSTRACT

Asthma is one of the most common chronic respiratory disease worldwide, with a negative impact on quality of life and socio-economic status of patients. There are some evidences to suggest that *Toxocara* infection is a neglected risk factor for childhood asthma. We performed a systematic review and meta-analysis to further understanding of this relationship. Five databases include PubMed, Science Direct, Scopus, Web of Science (ISI), and Google scholar were searched (up to October 2017) to identify the relevant studies. We used random-effects meta-analysis model to estimate the pooled odds ratio (OR) and 95% confidence intervals (CI). Heterogeneity was assessed with the Q-test and I^2 statistic. A total of 17 studies including 11 studies with case-control design (1139 patients and 1023 controls) and six studies with cross-sectional design (a total of 5469 participants, 872 asthmatics, and 4597 non-asthmatics children) met the eligibility criteria. An increased risk for asthma was observed in children with *Toxocara* infection seropositivity (OR, 1.91; 95% CI, 1.47–2.47). In sub-group analysis, the pooled ORs were (OR, 2.13; 95% CI, 1.43–3.15) and (OR, 1.73; 95% CI, 1.23–2.44) for case-control and cross-sectional studies, respectively. Moreover, considering to specific IgE seropositivity, a pooled OR of 2.36 (95% CI, 0.93–5.98) was observed. In conclusion, this meta-analysis revealed that children infected with *Toxocara* spp. are more likely to have asthma compared to non-infected children. More studies (especially longitudinal studies) are needed to further investigate the impact of *Toxocara* spp. infection on the onset or development of asthma.

1. Introduction

Asthma is one of the most common chronic respiratory disease affecting both children and adults. Childhood asthma is responsible for substantial worldwide burden of disease, societal costs, and mortality in countries throughout the world (Subbarao et al., 2009). In spite of significant reduction in rates of deaths resulting from the asthma, its prevalence continues to increase in both developed (2%–21%) and developing countries (0.2%–7.5%) (Beasley et al., 2015; Subbarao et al., 2009; To et al., 2012). A comprehensive range of risk factors including both genetic (e.g. family history, polymorphisms in chromosomal regions and disturb in gene expression) and environmental factors (e.g. parental smoking, maternal smoking during pregnancy,

indoor and outdoor allergens, chemical irritants in the workplace and air pollution) are associated with the development of childhood asthma (Beasley et al., 2015; Kumar and Ghosh, 2009; Martinez and Vercelli, 2013). Moreover, it is well demonstrated that infectious agents especially viral and bacterial pathogens are likely to be important contributory factors in the onset and severity of childhood asthma (Thomas et al., 2014).

Nematode helminth infections have a worldwide distribution and their related infections are associated with suppression of allergic effectors in hosts, a potential mechanism for parasite killing (Pfefferle and Renz, 2014). These inhibitory effects on allergic inflammation and also inverse geographical distribution with asthma suggested that helminth infections may have an inhibitory effect on the development of

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asthma and other allergic diseases (Cooper, 2009). In contrast to other soil-transmitted helminths, *Toxocara* spp. infection could trigger the inception of allergic diseases such as asthma (Cooper, 2008; Pinelli, 2006).

Human toxocariasis is one of the most prevalent zoonotic diseases caused by *Toxocara canis* and *Toxocara cati*, intestinal ascarid nematodes of dogs and cats, respectively. The seroprevalence of human toxocariasis ranges from 0.6% (in Canada) to 86% (in Nigeria) in both developed and developing countries (Ma et al., 2017). The main risk factors for *Toxocara* infection among humans are intake of embryonated eggs from contaminated soil, water, raw or unwashed vegetables and consumption of raw or semi-cooked meat from paratenic hosts (Rostami et al., 2016; Macpherson, 2013; Maleki et al., 2018). The clinical manifestations of human toxocariasis are associated with migration of larvae via the bloodstream to the liver, brain, eyes and lungs (Macpherson, 2013). In last two decades, a growing body of epidemiological and experimental studies have specified a significant relationship between *Toxocara* infection and development of asthma (Buijs et al., 1997; Chan et al., 2001; Hakim et al., 1997; Kanobana et al., 2013; Pinelli et al., 2008), especially in children, while some other studies have not found a significant association (Fernando et al., 2009; Sharghi et al., 2001).

Since asthma poses a substantial burden of morbidity and costs for families and healthcare systems and because there are conflicting data in the literature regarding the relationship between *Toxocara* infection and childhood asthma, we performed a systematic review and meta-analysis in an attempt to evaluate the available observational studies that investigate the association between *Toxocara* infection and development of childhood asthma.

2. Methods

This meta-analysis study was conducted based on the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines as described before (Shamseer et al., 2015; Stroup et al., 2000). Based on previously published article by Moher et al. (2009), “briefly, the PRISMA statement consists of a 27-item checklist and a four-phase flow diagram (Fig. 1). The aim of the PRISMA statement is to help authors improve the reporting of systematic reviews and meta-analyses. PRISMA may also be useful for critical appraisal of published systematic reviews”.

2.1. Search strategy and study selection

In September 2017, the electronic databases PubMed, Science Direct, Scopus, Web of Science (ISI), and Google scholar were searched by two trained investigators to identify studies assessing the association between *Toxocara* spp. infection and childhood asthma (Supplementary Fig. 1). Our search was performed using combinations of the following search keywords: “*Toxocara* seroprevalence”; “*Toxocara* seropositivity”; “*Toxocara* infection”; “toxocariasis”; “toxocarosis”; “*Toxocara* spp.”; “*Toxocara canis*”; “*Toxocara cati*”; “asthma”; “bronchial asthma”; “bronchial disorder”; “respiratory disorder”; “airway inflammation”; “wheeze”; “wheezing”; “allergy” and “allergic disorder”; with the Boolean operators “OR” and/or “AND”. We performed a hand search in reference lists of obtained papers and published reviews for further relevant literature. We restricted our search to English language and human subjects. Non-English papers with an English abstract were also included. We did not employ any time or geographic limitations. After duplicate removal; the initial title and abstract screening was performed by two independent researchers. We included studies that met the following inclusion criteria: (a) peer-reviewed original research articles with case-control; cross-sectional or cohort design at the baseline; (b) studies that used sera samples; and detected *Toxocara* spp. infection by serological assays; and (c) studies that presented an

acceptable definition childhood asthma. We excluded experimental studies; review or systematic reviews and studies that utilised same study population.

2.2. Data extraction and study quality assessment

A data extraction form was designed in an Excel sheet and the details of each article were extracted precisely for the following variables: the first author's last name, publication year, the start and end date of sampling, study design, country, matching criteria in case-control studies, age range or mean age of study population, number of the case and control subjects and of infected subjects in each groups, total sample size, number of cases with asthma and without asthma and number of infected subjects in cross-sectional studies. The above details were extracted by two researchers. In cases of disagreement, consensus was achieved through discussion and agreement with a third researcher. We used adjusted results if they were available. In order to assess the quality of each included study, we used the Newcastle–Ottawa Scale, as suggested by the Cochrane collaboration (Higgins and Green, 2011; Stang, 2010; Wells et al., 2015). Briefly, maximum of nine scores was defined for the following items including the subject selection criteria (0–4 points), comparability of subjects (0–2 points), and exposure (0–3 points). A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. Also, a maximum of two stars can be given for comparability. The papers with a total score of 0–3, 4–6, and 7–9 points were specified as the poor, moderate, and high quality, respectively.

2.3. Data synthesis and statistical analysis

In this study, all statistical analyses were conducted using Stata version 12 (Stata Corp., College Station, TX). The association between *Toxocara* seropositivity and childhood asthma was assessed through generate of the pooled odds ratio (OR) and 95% confidence intervals (CI) using the random effect model. OR and 95% CI was calculated for each study using two-by-two table. Heterogeneity between studies was assessed using Q-test and I^2 methods. I^2 values of 25%, 50% and 75% were considered as low, moderate and high heterogeneity, respectively. Subgroup analyses were performed to identify the sources of heterogeneity. Publication bias was assessed through Egger's publication bias methods for asymmetry. A *P*-value of less than 0.1 was considered statistically significant. Results are presented as forest plots and associations between an *Toxocara* infection seropositivity and childhood asthma is illustrated by an OR and 95% CI.

3. Results

3.1. Study characteristics

As shown in Fig. 1, the authors' electronic and manual searches yielded 2003 articles, 1973 of which were excluded due to duplicates removal and a review of the title and the abstract. The remaining 30 studies were evaluated in greater detail, and 13 were excluded for the reasons shown in Fig. 1. Finally, 17 studies fulfilled all inclusion criteria to be included in the meta-analysis (Angeles et al., 2010; Buijs et al., 1997; Buijs et al., 1994; Cadore et al., 2016; Chan et al., 2001; Cobzaru et al., 2012; Desowitz et al., 1981; Fernando et al., 2009; Ferreira et al., 2007; Figueiredo et al., 2005; Hakim et al., 1997; Kanobana et al., 2013; Mendonça et al., 2012; Mosayebi et al., 2016; Muñoz-Guzmán et al., 2010; Sharghi et al., 2001; Silva et al., 2017). Of these, 11 studies had a case-control design and six were cross-sectional. The main characteristics for included studies with case-control and cross-sectional design are presented in Tables 1 and 2, respectively. Most included studies reported seroprevalence of *Toxocara* spp. infection based on detection of IgG antibodies and only four studies additionally screened specific IgE antibodies for *Toxocara* infection. In studies with a

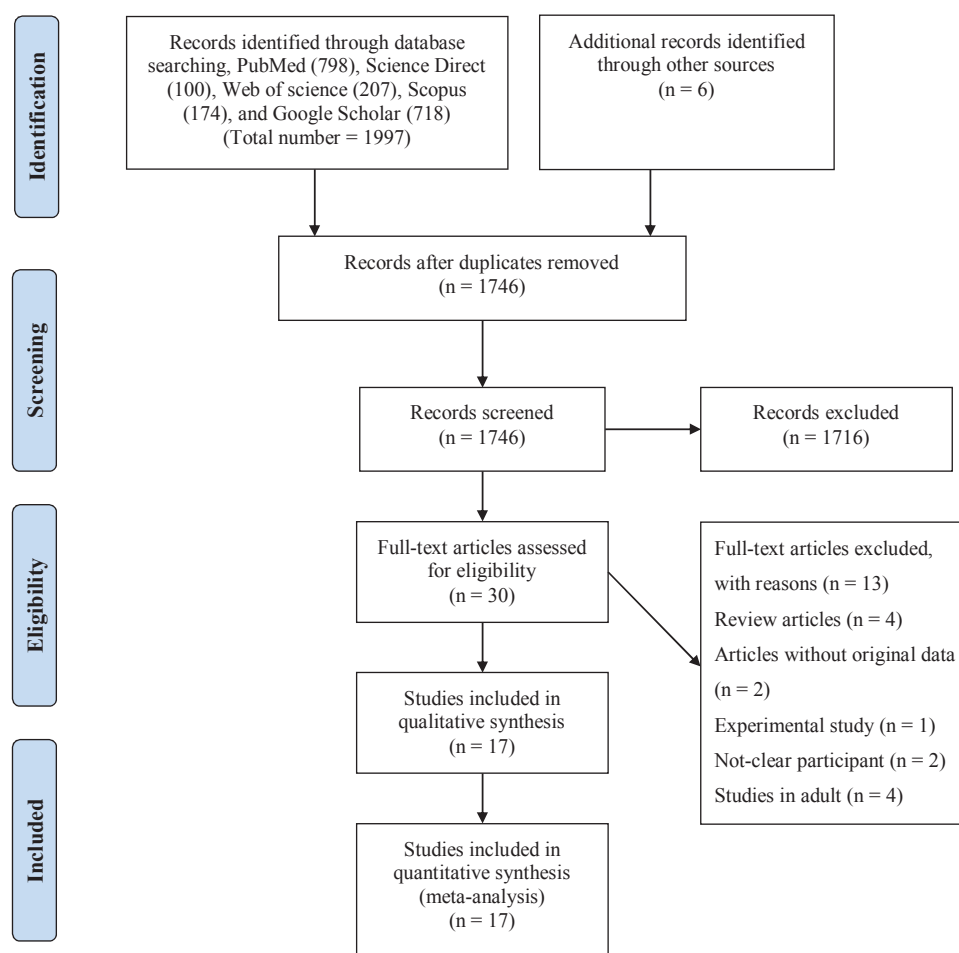


Fig. 1. Flow chart showing the process of study selection.

case-control design, the sample size of the cases and controls were 1139 and 1023, respectively. In this group, four studies (Angeles et al., 2010; Cobzaru et al., 2012; Desowitz et al., 1981; Muñoz-Guzmán et al., 2010) including 488 cases and 389 controls, additionally screened specific IgE against *Toxocara* spp. Cross-sectional studies had a total of 5469 participants, comprising 872 asthmatics and 4597 non-asthmatics children. Among the 11 studies with case-control design, three enrolled healthy children and eight enrolled hospital-based controls. The included studies were conducted in ten different countries from three continents (four in Asia, three in Europe and ten in America).

3.2. Seropositivity of *Toxocara* spp. among children with asthma and without asthma

Tables 1 and 2 provide a description of the key variables and results for all included studies. In studies with a case-control design, *Toxocara* infection seropositivity were reported in 24.8% (283/1139) v.s. 15.5% (129/1023) and 18.2% (89/488) v.s. 12.5 (49/389) for the IgG and IgE among cases and controls, respectively. In studies with cross-sectional design, the overall seroprevalence of *Toxocara* infection was 31% (1696/5469), and in the subgroups, 41.1% (376/872) and 28.7%

Table 1

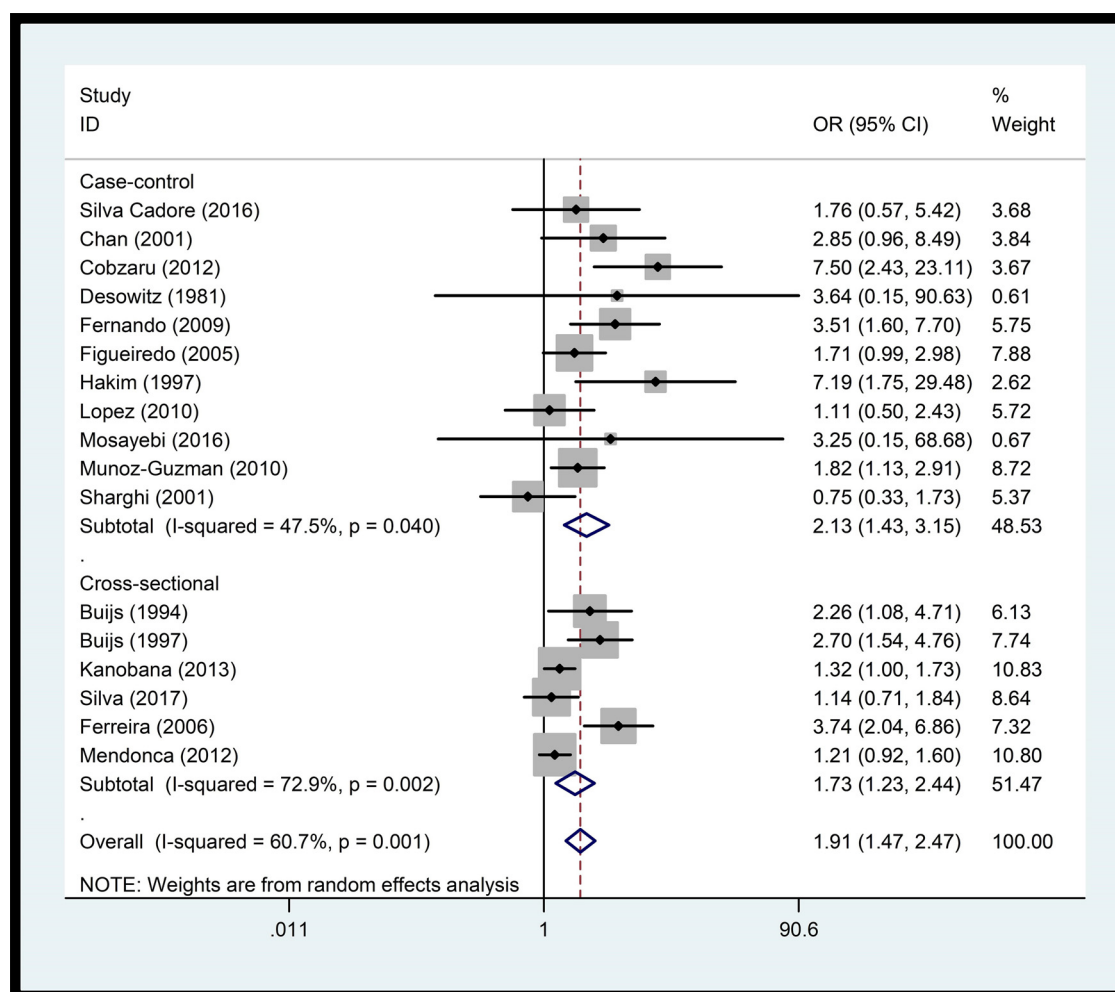
Summary of studies with case-control design investigating the association between *Toxocara* spp. infection and asthma.

Authors	Country	Implementation year	Matching	Age range Or Mean age* (years)	Asthmatic Patients (cases)		Control Group		Control population	Quality score
					Number	Infected (%)	Number	Infected (%)		
Desowitz et al., 1981	USA	1979–80	Age	1–18	80	1 (1.2)	96	0 (0.0)	HB ^a	6
Hakim et al., 1997	Malaysia	1996–7	Age	1–9	18	10 (55.5)	27	4 (14.8)	HB	5
Chan et al., 2001	Malaysia	1999	Age, sex	8.1*	66	14 (21.2)	58	5 (8.6)	HB	6
Sharghi et al., 2001	USA	1998–9	Age	5–12	95	8 (8.4)	229	25 (10.9)	HB	7
Figueiredo et al., 2005	Brazil	2000–1	Age	1–14	106	65 (61.3)	102	49 (48)	HB	6
Fernando et al., 2009	Sri Lanka	2006–7	Age, sex	5–12	100	29 (29)	96	10 (10.4)	HB	6
Muñoz-Guzmán et al., 2010	Mexico	2008–9	Age	4–12	285	88 (30.8)	152	30 (19.7)	HB	8
Angeles et al., 2010	Argentina	2008–9	Age	NA	47	26 (57.3)	53	28 (52.8)	HC ^b	8
Cobzaru et al., 2012	Romania	2010–1	Age	9.1*	76	20 (26.3)	88	4 (4.5)	HB	4
Silva et al., 2017	Brazil	2012–3	Age	6–12	156	20 (12.8)	52	4 (7.6)	HC	7
Mosayebi et al., 2016	Iran	2013–14	Age	5–15	110	2 (1.8)	70	0 (0.0)	HC	5

*mean age.

Table 2Summary of studies with cross-sectional design investigating the association between *Toxocara* spp. infection and asthma.

First author/year	Country	Implementation year	Age range	Total sample	Total infected	asthmatic children		Non-asthmatic children		Quality score
						Number	Infected (%)	Number	Infected (%)	
Buijs et al., 1994	Netherlands	1987–88	4–6	712	52	73	10 (13.6)	639	42 (6.5)	7
Buijs et al., 1997	Netherlands	1989–92	4–12	1379	114	94	17 (18)	1285	97 (7.5)	8
Ferreira et al., 2007	Brazil	2002–3	1–5	481	103	50	23 (46)	431	80 (18.5)	7
Mendonça et al., 2012	Brazil	1997–2005	4–12	1148	540	258	131 (50.7)	890	409 (45.9)	8
Kanobana et al., 2013	Cuba	2008–12	4–12	958	384	314	140 (44.5)	644	244 (37.8)	8
Silva et al., 2017	Brazil	2010	6–13	791	503	83	55 (66.2)	708	448 (63.2)	8

**Fig. 2.** Forest plot, pooled with random effects regarding the association between *Toxocara* infection and childhood asthma showing the OR and 95% CI by sub-groups.

(1320/4597) were seropositive in asthmatic and non-asthmatic children, respectively.

3.3. Results of meta-analyses

The results of the meta-analysis demonstrated a significant positive association between exposure to *Toxocara* infection and increased risk of childhood asthma (OR, 1.91; 95% CI, 1.47–2.47, Fig. 2). In general, heterogeneity ($\chi^2 = 40.69$; $I^2 = 60.7\%$, 95% CI 33–77) was evident among studies. In subgroup analyses, significant pooled ORs of positive association were observed in both studies with case-control (OR, 2.13; 95% CI, 1.43–3.15; $\chi^2 = 19.04$; $I^2 = 47.5\%$, 95% CI 0–74) and cross-sectional design (OR, 1.73; 95% CI, 1.23–2.44; $\chi^2 = 18.48$; $I^2 = 72.9\%$, 95% CI 38–88) (Fig. 2). Moreover, in four studies evaluating specific IgE and *Toxocara*, a pooled OR of 2.36 (95% CI, 0.93–5.98; $\chi^2 = 12.57$;

$I^2 = 76.1\%$, 95% CI, 34–91) was observed (Fig. 3).

To identify potential publication bias, we used Egger's test. In current study, there was not significant publication bias for studies with case-control ($P = 0.15$) and cross-sectional ($P = 0.08$) design (Fig. 4A and B). In addition, there was not significant publication bias ($P = 0.76$) for studies that reported specific IgE (Supplementary Fig. 2).

4. Discussion

We performed a systematic review and meta-analysis on the epidemiological literatures that evaluated the association between childhood asthma and *Toxocara* spp. infection. One of the important reasons for this work is this fact that *Toxocara* infection is widely distributed in the world and some epidemiological and casual evidences suggest that this cosmopolitan helminth with a significant link with poverty

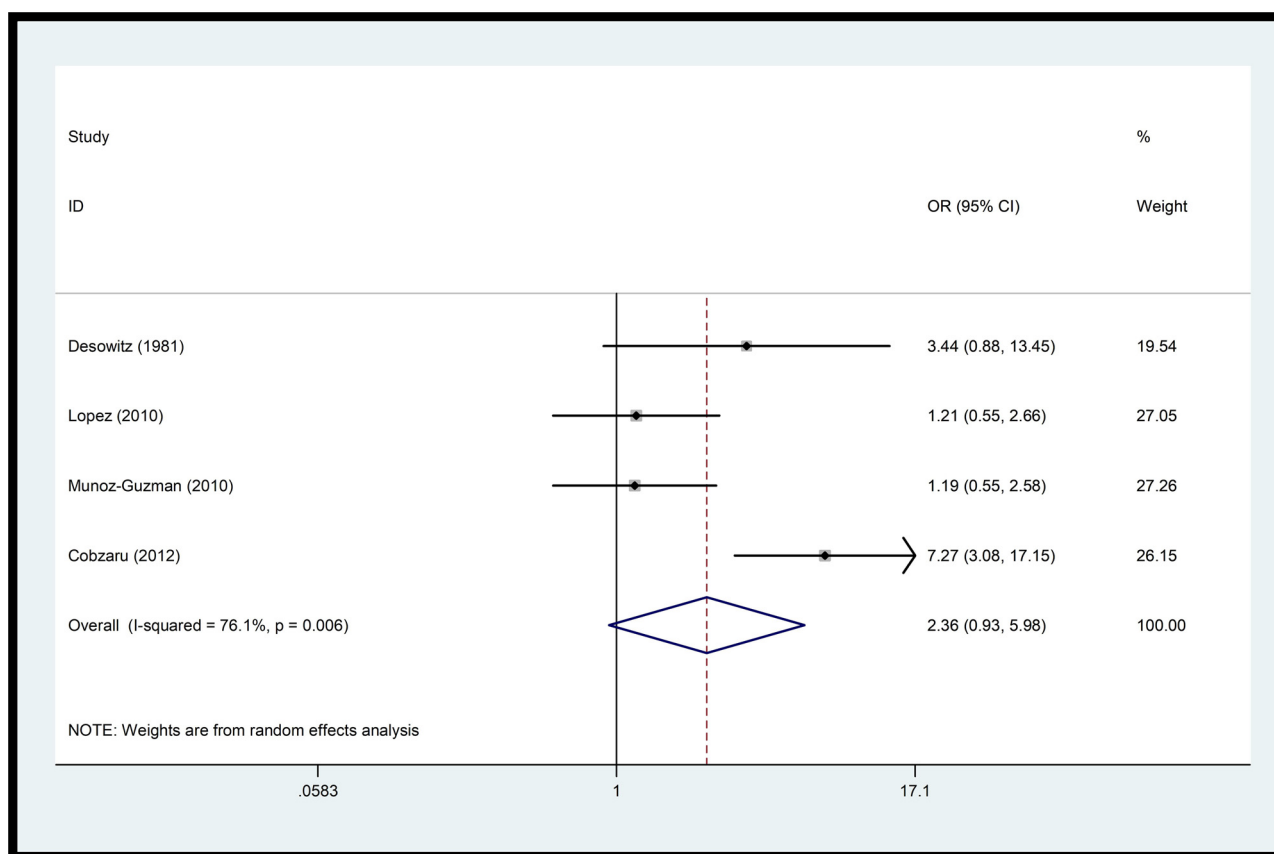


Fig. 3. Forest plots for the association between *Toxocara* infection and childhood asthma regarding the seropositivity for specific IgE antibody.

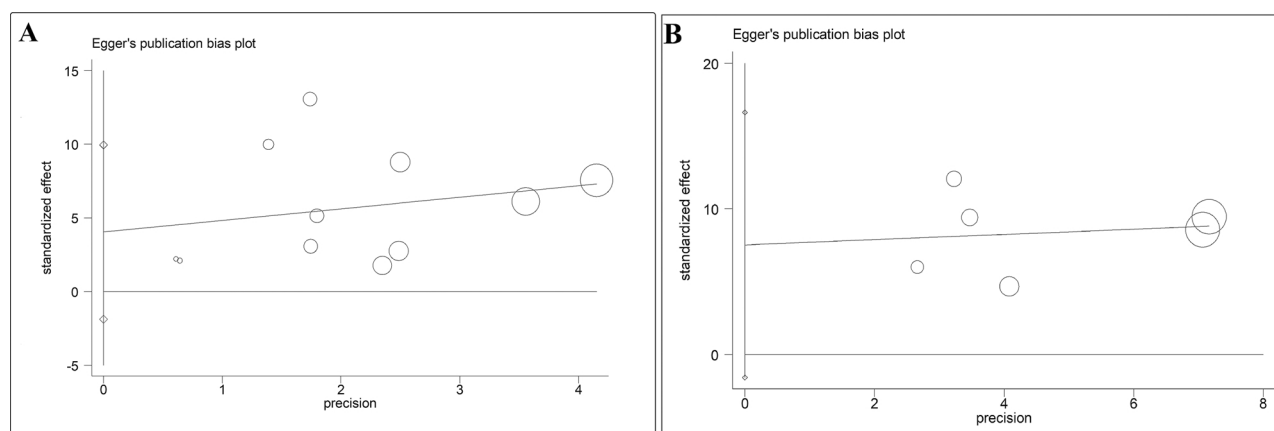


Fig. 4. Publication bias using Egger's plot. (A) Publication bias in studies with case-control design (B) Publication bias in studies with cross-sectional design.

(Holland, 2017) is a neglected risk factors for allergic disorders. Our study provides a strong evidence that *Toxocara* infection is an important risk factor for childhood asthma. The main finding for this study was a positive association (OR, 1.91; 95% CI, 1.47–2.47) between *Toxocara* seropositivity and increased prevalence of childhood asthma. Among the included studies, nine reported a non-significant (Angeles et al., 2010; Cadore et al., 2016; Chan et al., 2001; Desowitz et al., 1981; Figueiredo et al., 2005; Mendonça et al., 2012; Mosayebi et al., 2016; Sharghi et al., 2001; Silva et al., 2017), and eight reported a positive significant association related with *Toxocara* infection and childhood asthma (Buijs et al., 1997; Buijs et al., 1994; Cobzaru et al., 2012; Fernando et al., 2009; Ferreira et al., 2007; Hakim et al., 1997; Kanobana et al., 2013; Muñoz-Guzmán et al., 2010). Moreover, none of the studies reported a protective effect. The obtained scores in our

systematic review represents acceptable quality in included papers (Tables 1 and 2).

In last two decades there has been considerable interest in exposure to helminth infections including toxocariasis, as an environmental risk factor for allergic asthma. However, some of these studies showed protective effect by helminths. In a comprehensive meta-analysis study, Leonardi-Bee et al. (2006) have reported a small, nonsignificant increase in asthma risk (OR, 1.24; 95% CI, 0.98–1.57) for individuals infected with any helminths parasites. Furthermore, they findings demonstrated that infection with *Ascaris lumbricoides* was significantly related with increased risk of asthma (OR, 1.34; 95% CI, 1.05–1.71), while hookworm infection was associated with significantly (OR, 0.50; 95% CI, 0.28–0.90) reduced risk of asthma (Leonardi-Bee et al., 2006). A recently performed experimental study demonstrated that anti-

inflammatory protein-2 (AIP-2) secreted by hookworms is effective in suppression of airway inflammation in a mouse model of asthma (Navarro et al., 2016). Several factors include helminth species, acute or chronic infection, intensity of infection and host genetic may influence the association between helminth infections and allergic manifestations. It is assumed that current helminth infection may be more involved in induction of allergic asthma. Detailed reviews on this issue are available in valuable published articles (Cooper, 2008; Pinelli and Aranzamendi, 2012). The exact mechanisms for *Toxocara* infection to induce of asthma and other allergic disorder remains unclear. Although experimental studies have elucidated that infections with nematodes whose life cycle includes migration across pulmonary tissues to the development of larval stages (e.g. *Toxocara* spp. and *Ascaris suum*), are associated with diminished lung function, especially in accidental hosts like human (Pinelli et al., 2005; Pritchard et al., 1983). *Toxocara* larvae are unable to mature further in human body (accidental hosts) and migrate through different organs. Larval migration is associated with intensive immunological responses, resulting in allergic inflammation in involved tissues, including the lung (Cooper, 2008; Ma et al., 2017). Pulmonary inflammation usually occurs within 48 h post infection and can be continued up to two or three months (Pinelli et al., 2005). In a recent study, Pinelli et al. (2008) utilising an animal model have shown that previous infection with *T. canis* intensifies ovalbumin (OVA)-induced allergic airway inflammation in mice. Moreover, they reported an elevated levels of IgE antibody and eosinophil counts in bronchoalveolar lavage fluid, and also expression of IL-4 mRNA in lung tissue of pre-infected mice (Pinelli et al., 2008).

Human immunological responses to *Toxocara* infection seems to be main effectors to the development of allergic disorders. There is a wide range of molecules in *Toxocara* spp. that have a potential role in host-parasite interaction, including adhesion molecules, lectins, peptidases, and SCP/TAPS proteins (Gasser et al., 2016; Ma et al., 2017). Immune responses against *Toxocara* infection are mediated by CD4⁺ T-helper type-2 cells (Th2) through the induction of cytokines such as IL-4, IL-5, IL10, and IL-13, that can lead to an increase in the level of specific antibodies and eosinophilia, effective immune responses to parasite killing (Ma et al., 2017; Maizels, 2013). It seems that *Toxocara* excretory-secretory (TES) antigens are vigorous stimulators that induce Th2-associated immune responses and therefore contribute to airway hypersensitivity and inflammation, associating chronic *T. canis* infection with allergic disorder like asthma, allergic rhinitis, atopy, and urticarial (Cooper, 2008; Gavignet et al., 2008; Maizels, 2013; Mazur-Melewska et al., 2016; Yariktas et al., 2007).

This study has some important strengths and limitations. The main strengths of the study are comprehensive literature search, rigorous methodology, large sample size, defined clear inclusion and exclusion criteria, studies from different countries and continents (except Africa), defined matching criteria in case-control studies and subgroup analysis considering the type of studies. Nevertheless, there are some important limitations that are due to nature of the existing studies. First, selecting the controls is an important pitfall in case-control studies. As mentioned in our previous meta-analyses (Majidiani et al., 2016; Nourollahpour Shideh et al., 2017; Rostami et al., 2017), hospital controls might resemble cases more than healthy volunteers' controls, biasing OR towards the null. Furthermore, in three studies with healthy controls (Angeles et al., 2010; Cadore et al., 2016; Mosayebi et al., 2016), volunteers were from an undefined setting. Second, some studies used in house-ELISA and some other used commercial ELISA kit to identifying of *Toxocara* infection, therefore results of this study should be interpreted with regard to different cut-off values and also sensitivity and specificity that were applied in included studies. Third, as mentioned above a recent infection might be more involved in the pathogenesis of asthma than a past infection, but a single serological examination that was performed in all included studies might not be truly representative of a recent infection. Fourth, a relatively high prevalence of *Toxocara* spp. was observed across the African continent (Lötsch et al., 2017).

However, we have not found any paper on the association between *Toxocara* infection and asthma in Africa.

In conclusion, this meta-analysis provides evidence that children infected with *Toxocara* spp. are more at risk to development of asthma compared to non-infected children. More studies are needed to further investigate the impact of *Toxocara* spp. infection in inception or development of asthma in future. Moreover, we suggest further experimental studies to better understand the immunological and molecular mechanisms that underpin the association between *Toxocara* spp. infection and allergic asthma.

Specific author contributions

S. Aghaei, S.M. Riahi, I. Mohammadzadeh, M. Foroutan, M.R. Esmaeili Dooki, M. Javanian and A. Rostami, conceived the study; S. Aghaei, I. Mohammadzadeh, and M. Foroutan collected all data; A. Rostami, S.M. Riahi, and M.R. Esmaeili Dooki analyzed and interpreted the data; A. Rostami, S. Aghaei and M. Javanian drafted the manuscript; and all authors commented on the drafts of the manuscript and approved the final draft of the paper.

Conflict interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.actatropica.2018.03.022>.

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Supplementary figures

Number of identified article in different databases

1: Pubmed: 798 documents in overall

((("Toxocara"[MeSH Terms] OR "Toxocara"[All Fields] AND seropositivity[All Fields]) OR ("Toxocariasis"[MeSH Terms] OR "Toxocariasis"[All Fields] OR "toxocara"[All Fields] AND "infection"[All Fields]) OR "toxocara infection"[All Fields]) OR ("toxocariasis"[MeSH Terms] OR "toxocariasis"[All Fields] OR ("toxocariasis"[MeSH Terms] OR "toxocariasis"[All Fields] OR "toxocariasis"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "bronchial"[All Fields] AND "asthma"[All Fields]) OR "bronchial asthma"[All Fields]))

Results= 85

((("Toxocara"[MeSH Terms] OR "Toxocara"[All Fields] AND seropositivity[All Fields]) OR ("toxocariasis"[MeSH Terms] OR "toxocariasis"[All Fields] OR "toxocara"[All Fields] AND "infection"[All Fields]) OR "toxocara infection"[All Fields]) OR ("toxocariasis"[MeSH Terms] OR "toxocariasis"[All Fields] OR ("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND "Sci Public Policy"[Journal] OR "spp"[All Fields])) AND ((("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "asthma"[MeSH Terms] OR "asthma"[All Fields] OR "bronchial"[All Fields] AND "asthma"[All Fields]) OR "bronchial asthma"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR "respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields]) OR ("respiratory tract diseases"[MeSH Terms] OR "respiratory"[All Fields] AND "tract"[All Fields] AND "diseases"[All Fields]) OR "respiratory tract diseases"[All Fields] OR "respiratory"[All Fields] AND "disorder"[All Fields] OR "respiratory disorder"[All Fields] OR "respiration disorders"[MeSH Terms] OR "respiration"[All Fields] AND "disorders"[All Fields] OR "respiration disorders"[All Fields] OR "respiratory"[All Fields] AND "disorder"[All Fields]))

Results= 247

((("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND cnis[All Fields]) OR ((("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND cati[All Fields]) OR ("toxocariasis"[MeSH Terms] OR "toxocariasis"[All Fields] OR ("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND ("Sci Public Policy"[Journal] OR "spp"[All Fields])) AND ((("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR "asthma"[MeSH Terms] OR "asthma"[All Fields] OR "bronchial"[All Fields] AND "asthma"[All Fields]) OR "bronchial asthma"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR "respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields]) OR ("respiratory tract diseases"[MeSH Terms] OR "respiratory"[All Fields] AND "tract"[All Fields] AND "diseases"[All Fields]) OR "respiratory tract diseases"[All Fields] OR "respiratory"[All Fields] AND "disorder"[All Fields]) OR "respiratory disorder"[All Fields] OR "respiration disorders"[MeSH Terms] OR "respiration"[All Fields] AND "disorders"[All Fields] OR "respiration disorders"[All Fields] OR "respiratory"[All Fields] AND "disorder"[All Fields]))

Results= 233

((("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND cnis[All Fields]) OR ((("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND cati[All Fields]) OR ("toxocariasis"[MeSH Terms] OR "toxocariasis"[All Fields] OR ("toxocara"[MeSH Terms] OR "toxocara"[All Fields] AND ("Sci Public Policy"[Journal] OR "spp"[All Fields])) AND ((("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR "asthma"[MeSH Terms] OR "asthma"[All Fields] OR "bronchial"[All Fields] AND "asthma"[All Fields]) OR "bronchial asthma"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR "respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields]) OR "airway"[All Fields] AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields])) OR ("bronchial diseases"[MeSH Terms] OR "bronchial"[All Fields] AND "diseases"[All Fields]) OR "bronchial diseases"[All Fields] OR ("bronchial"[All Fields] AND "disorder"[All Fields]) OR "bronchial disorder"[All Fields] OR ("respiratory tract diseases"[MeSH Terms] OR "respiratory"[All Fields] AND "tract"[All Fields] AND "diseases"[All Fields]) OR "respiratory tract diseases"[All Fields] OR "respiratory"[All Fields] AND "disorder"[All Fields] OR "respiratory disorder"[All Fields] OR "respiration disorders"[MeSH Terms] OR "respiration"[All Fields] AND "disorders"[All Fields] OR "respiration disorders"[All Fields] OR "respiratory"[All Fields] AND "disorder"[All Fields]))

Results= 233

2: Science direct: 100 documents in overall

TITLE-ABSTR-KEY(*Toxocara* OR *Toxocariasis*) and TITLE-ABSTR-KEY(asthma or childhood asthma or wheezing). **Results=42**

TITLE-ABSTR-KEY(*Toxocara cati* or *Toxocara canis*) and TITLE-ABSTR-KEY(asthma or allergy or allergic disorder or wheezing). **Results=39**

TITLE-ABSTR-KEY(*Toxocara cati* or *Toxocara canis* or toxocariasis) and TITLE-ABSTR-KEY(bronchial disorder or respiratory disorder or airway inflammation or bronchial asthma). **Results=19**

3: Web of science: 207 documents in overall

You searched for:TOPIC: ((Toxocara or Toxocariasis) and (asthma or childhood asthma or wheezing))

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI

Results=94

You searched for:TOPIC: ((Toxocara cati or Toxocara canis or toxocariasis) and (bronchial disorder or respiratory disorder or airway inflammation or bronchial asthma))

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI.

Results=30

You searched for: TOPIC: ((Toxocara infection or Toxocara seropositivity or Toxocara seroprevalence) and (asthma or bronchial asthma or childhood asthma or allergy))

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI.

Results=83

4: Scopus: 174 documents in total

TITLE-ABS-KEY

((toxocara OR toxocariasis) AND (asthma OR childhood AND asthma OR wheezing))

Results= 144

TITLE-ABS-KEY

(((*Toxocara* AND cati OR *Toxocara* AND canis OR toxocariasis) AND (bronchial AND disorder OR respiratory AND disorder OR airway AND inflammation OR bronchial AND asthma))

Results=3

TITLE-ABS-KEY

((toxocara AND infection OR toxocara AND seropositivity OR toxocara AND seroprevalence) AND (asthma OR bronchial AND asthma OR childhood AND asthma OR allergy))

Results=27

5: Google scholar: 718 documents in total

(toxocara OR toxocariasis) AND (asthma OR childhood AND asthma OR wheezing)

Results=325

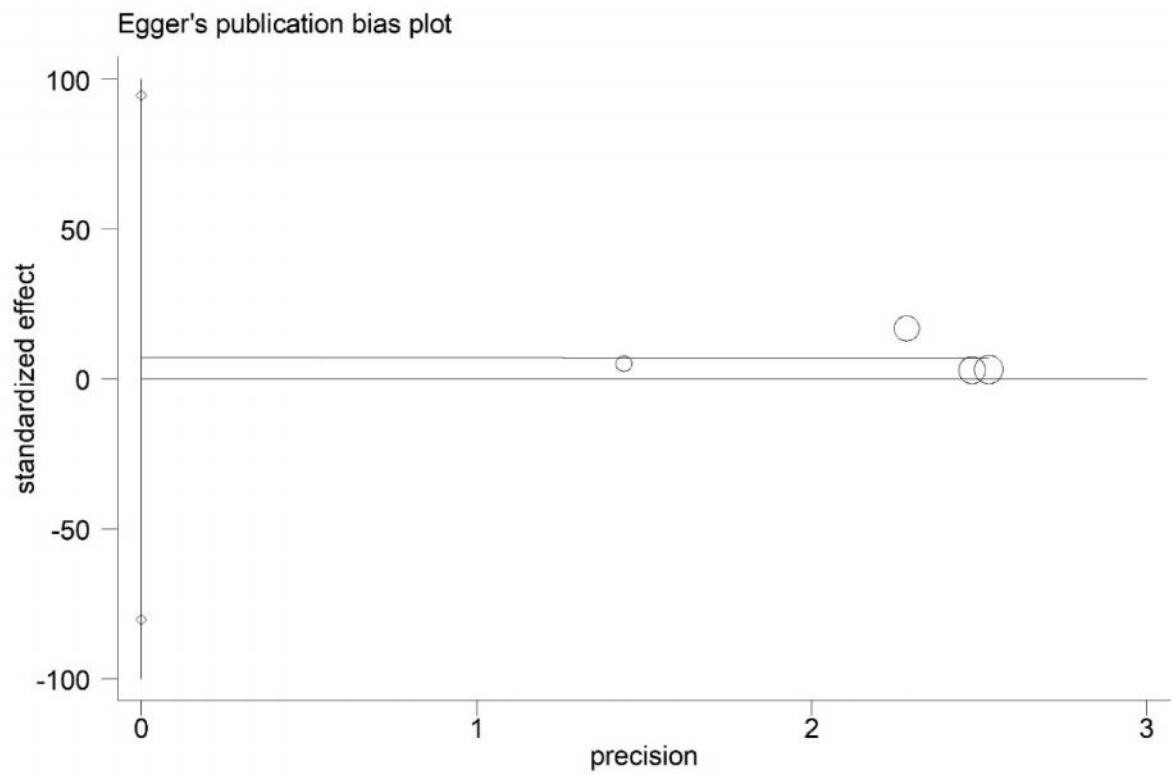
(Toxocara cati OR Toxocara canis OR toxocariasis) AND (bronchial disorder OR respiratory disorder OR airway inflammation OR bronchial asthma)

Results=170

(toxocara infection OR toxocara seropositivity OR toxocara seroprevalence) AND (asthma OR bronchial asthma OR childhood asthma OR allergy)

Results=223

Supplementary figure 1. search strategies in different databases to identify the eligible studies



Supplementary figure 2. Publication bias using Egger's plot in studies evaluating specific IgE.